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A Comprehensive Guide to Typhoidal Anemia

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Abstract: Typhoid fever, caused primarily by *Salmonella* Typhi and Paratyphi, stands as a significant global health concern, with complications extending beyond the typical gastrointestinal manifestations. This review systematically examines the intricate relationship between typhoid fever and hematologic complications, collectively referred to as typhoidal anemia. Hematological abnormalities, including changes in blood profiles and bone marrow responses, are scrutinized, providing a comprehensive understanding of the disease's impact on physiological systems. Specific populations, such as immunocompromised individuals, sickle cell anemia patients, and children in resource-limited settings, reveal varied susceptibilities and outcomes. Complications, such as psoas abscess and secondary hemophagocytic lymphohistiocytosis, are explored, highlighting the multifaceted nature of the disease. The distinct contributions of *Salmonella* Typhi and Paratyphi to anemia are elucidated, shedding light on the pathophysiological mechanisms involved. Global prevalence and epidemiological variations offer valuable perspectives, underscoring the importance of regional nuances in disease manifestation. Challenges in accurate diagnosis and treatment limitations are acknowledged, emphasizing the need for continued research to enhance diagnostic precision and therapeutic strategies. Insights into long-term effects, prognosis, and the influence of host factors contribute to a holistic understanding of typhoidal anemia. The review concludes by identifying critical gaps in knowledge, advocating for ongoing research initiatives and heightened awareness campaigns. The synthesis of diverse findings provides a comprehensive overview of typhoidal anemia, underscoring the imperative of continued research and awareness for improved patient care and global public health.

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Introduction

Typhoid fever, caused primarily by *Salmonella enterica* serotypes Typhi and Paratyphi, it is a systemic infectious disease characterized by a range of symptoms, including persistent fever, abdominal pain, and gastrointestinal disturbances. Among the myriad complications associated with typhoid fever. Anemia emerges as a significant and clinically relevant aspect. This short review aims to synthesize findings from various studies, shedding light on the patterns, clinical implications, and underlying mechanisms of typhoidal anemia. Several clinical investigations have delved into the morbidity and mortality patterns of typhoid fever, revealing intriguing insights into the influence of age and gender on the prevalence and severity of associated anemia. A study was done by Butler et al. (1991) provides a foundational understanding of the interplay between typhoidal fever and anemia, forming a cornerstone for subsequent research in this domain. Beyond the conventional manifestations, typhoid fever has been associated with diverse hematological abnormalities. Notably, research by Anabire et al. (2018) and Ndako et al. (2020) explores the coexistence of anemia in patients with both malaria and typhoid, emphasizing the need for nuanced diagnostic approaches in regions with overlapping disease burdens. A unique case of pus abscess caused by non-typhoidal *Salmonella* in a patient with severe aplastic anemia is reported by Kuo et al. (2010), highlighting the potential for atypical presentations of typhoidal complications in individuals with underlying hematological disorders. Chronic typhoid fever has been explored as a natural model of secondary hemophagocytic lymphohistiocytosis (HLH) in murine studies. According to Brown et al. (2010) represents a valuable perspective on the chronicity of typhoidal infections and their implications for hematopoietic processes. The pediatric population has been a focus of investigation and this type of study provided that the correlation between clinical profiles, bone marrow responses and serum opsonization of *Salmonella* in children particularly those with sickle cell anemia (Hand and King, 1978; Landesman et al., 1982; Chow and Leung, 1986; James et al., 1997). Furthermore, different studies by various researchers from different parts of the world explored the intricate relationship between typhoidal infections and various forms of anemia, including autoimmune hemolytic anemia, sickle cell anemia, and anemia associated with underlying immunodeficiencies (Hook et al., 1957; Kaye and Hook, 1964; Barrett-Connor, 1972; Roux et al., 2010; Giannotta et al., 2021). The literature reveals that typhoidal anemia is a complex condition with various dimensions. It highlights the necessity for a thorough grasp of its epidemiology, clinical presentations, and related risk factors. Subsequent sections of this review will further explore specific facets such as diagnosis, treatment, and complications, building upon the groundwork established by these influential studies.

Pathophysiology

Typhoidal anemia, a common complication in 26–73% of patients with typhoid fever, particularly affects those with glucose-6-phosphate dehydrogenase (G6PD) deficiency. The underlying pathology often involves acute hemolysis triggered by the inflammatory response characteristic of typhoid fever, exacerbating red blood cell destruction. Furthermore, the increased inflammation leads to elevated levels of hepcidin, a peptide hormone that impairs iron absorption, consequently exacerbating the anemia. This results in a presentation consistent with anemia of chronic disease, featuring microcytic hypochromic red blood cells, alongside normal to increased ferritin levels (Mohamed et al., 2020; Fukushima et al., 2023).

Clinical manifestations

Typhoidal anemia manifests as a prominent clinical feature within the spectrum of typhoid fever, and understanding its distinctive characteristics is essential for comprehensive patient care. Classical manifestations include persistent fever, abdominal pain, and gastrointestinal disturbances (Butler et al., 1991). These symptoms are coupled with alterations in hematological parameters, including changes in red blood cell counts, hemoglobin levels, and other markers indicative of anemia. Other findings emphasize that children and individuals with sickle cell anemia may exhibit unique clinical profiles, warranting careful consideration in the evaluation of typhoidal anemia in these populations (Chow and Leung, 1986; James et al., 1997).

The progression and severity of anemia in the context of typhoidal fever

The progression and severity of anemia in the context of typhoidal fever unfold as a dynamic interplay between the infectious agent, the host's immune response, and potential complicating factors. Typhoidal fever caused by *Salmonella* Typhi and Paratyphi typically progresses through distinct stages. In the early phase, the bacteria invade the gastrointestinal tract, leading to bacteremia and systemic dissemination (Butler et al., 1991). Concurrently, the host responds

with an inflammatory cascade, releasing cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) (Barrett-Connor, 1972). This inflammatory milieu, along with the ability of *Salmonella* to invade the bone marrow and can disrupt hematopoiesis and contribute to anemia (James et al., 1997). The chronicity of infection, particularly in cases of persistent or untreated typhoidal fever, may further exacerbate the severity of anemia. Complications such as psoas abscess (Kuo et al., 2010), and the potential synergy with other pathogens (Roux et al., 2010), can compound the hematological challenges, leading to an escalation in the severity of anemia.

The symptoms or signs associated with typhoidal anemia

Persistent fever, a hallmark of typhoid fever, often accompanies typhoidal anemia (Butler et al., 1991). Additionally, patients may exhibit abdominal pain, gastrointestinal disturbances, and changes in bowel habits, contributing to the clinical picture of typhoidal anemia. Importantly, specific signs related to hematological abnormalities become evident, including fatigue, pallor, and weakness, suggestive of anemia's impact on oxygen-carrying capacity. The correlation between clinical symptoms and bone marrow responses, emphasizing the link between the systemic manifestations of typhoidal fever and underlying hematopoietic disruption (James et al., 1997). In pediatric populations and individuals with sickle cell anemia, unique clinical profiles may emerge (Chow and Leung, 1986) providing insights into anemia-associated symptoms in these specific groups. As typhoidal anemia progresses, complications such as psoas abscess (Kuo et al., 2010), may further contribute to the clinical complexity. Recognizing these specific symptoms and signs associated with typhoidal anemia is crucial for prompt diagnosis and targeted therapeutic interventions.

Epidemiology

An overview of the global prevalence on typhoidal anemia

The global prevalence of typhoidal anemia is a subject of significant concern, particularly given the widespread incidence of typhoid fever caused by *Salmonella* Typhi and Paratyphi. Butler et al. (1991) conducted a comprehensive review in Bangladesh, shedding light on the patterns of morbidity and mortality in typhoid fever based on a study of 552 hospitalized patients with diarrhoea. Other researchers contributed by exploring hematological abnormalities in patients with malaria and typhoid in the Tamale Metropolis of Ghana. Their study highlighted the intersectionality of typhoidal anemia with other infectious diseases, offering insights into the complex epidemiological landscape. The global prevalence of typhoidal anemia is also influenced by unique population dynamics, as evidenced by studies on children and individuals with sickle cell anemia (Chow and Leung, 1986; James et al., 1997). This collective body of research underscores the multifaceted nature of typhoidal anemia's prevalence on a global scale, necessitating ongoing efforts for comprehensive surveillance, diagnosis, and management.

Different incidences among different populations

The incidence of typhoidal anemia exhibits notable variations among different populations, reflecting diverse demographic and epidemiological factors. Different findings revealed that variations in the occurrence of typhoidal anemia across different age groups and genders (Butler et al., 1991; Anabire et al., 2018). Moreover, Anabire et al. (2018) investigation into hematological abnormalities in the Tamale Metropolis of Ghana emphasized regional disparities, suggesting that the incidence may vary based on geographic and environmental factors. Unique population dynamics also contribute to variations (Chow and Leung, 1986; James et al., 1997) highlighting the specific challenges faced by children and individuals with sickle cell anemia.

Demographic or geographic factors influencing the epidemiology

Demographic and geographic factors play pivotal roles in shaping the epidemiology of typhoidal anemia, reflecting the intricate nature of typhoid fever's prevalence. whose research in the Tamale Metropolis of Ghana revealed regional disparities in hematological abnormalities associated with typhoid fever. Environmental conditions, access to healthcare, and regional prevalence of typhoid fever contribute to these variations. Additionally, the global distribution of typhoid fever is influenced by socioeconomic factors, water sanitation practices, and healthcare infrastructure, creating distinct epidemiological patterns. The identification and understanding of these demographic and geographic factors are crucial for developing targeted interventions, public health strategies, and healthcare policies to mitigate the impact of typhoidal anemia (Chow and Leung, 1986; Butler et al., 1991; James et al., 1997; Anabire et al., 2018).

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Diagnosis

Outline the methods used to diagnose typhoidal anemia

Diagnosing typhoidal anemia involves a comprehensive approach, integrating clinical, laboratory, and imaging methods to provide a thorough assessment of the patient's condition. Clinical manifestations, play a crucial role in the initial diagnostic process (Butler et al., 1991). Persistent fever, abdominal pain, and gastrointestinal symptoms, coupled with characteristic signs of anemia such as fatigue and weakness, provide essential clinical clues. Laboratory investigations are instrumental in confirming the diagnosis, with blood tests assessing hematological parameters such as hemoglobin levels, red blood cell counts, and markers of inflammation. Findings of James et al. (1997) underscore the importance of bone marrow examination in correlating clinical symptoms with hematologic profiles, aiding in the identification of specific features associated with typhoidal anemia. Imaging techniques, including abdominal ultrasound or computed tomography (CT) scans, may be employed to detect complications such as psoas abscess, contributing to a comprehensive diagnostic approach. While no single test is definitive, the integration of clinical, laboratory, and imaging methods, as informed by the literature, enhances the accuracy of diagnosing typhoidal anemia and guides appropriate therapeutic interventions.

Challenges and limitations in accurately diagnosing anemia in the context of typhoidal fever

Accurately diagnosing anemia in the context of typhoidal fever poses several challenges and limitations, reflecting the complex nature of the disease and the intricacies involved in its assessment. Butler et al. (1991) highlighted the variability in clinical presentations, as symptoms of typhoid fever often overlap with other febrile illnesses. This overlapping symptomatology may lead to delays in diagnosis and complicate the differentiation of anemia specific to typhoidal fever. The reliance on laboratory parameters, such as hemoglobin levels and red blood cell counts, while essential, may not capture the dynamic nature of typhoidal anemia throughout the course of the disease. Additionally, the need for invasive procedures like bone marrow examination, as emphasized by James et al. (1997), presents practical challenges and is not always feasible in resource-limited settings. The diagnostic process may be further complicated by the coexistence of other infections, as demonstrated by Anabire et al. (2018), necessitating a comprehensive approach to differentiate the specific contribution of typhoidal fever to the overall anemic condition. These challenges underscore the importance of continuous research and the development of improved diagnostic tools to enhance the accuracy of identifying and characterizing anemia in the context of typhoidal fever.

Highlight any advancements or emerging diagnostic techniques

Advancements in diagnostic techniques for typhoidal anemia have been spurred by ongoing research efforts, aiming to address the challenges and limitations associated with traditional methods. Butler et al. (1991) discussed the importance of serological tests, such as the Widal test, in detecting specific antibodies against *Salmonella* antigens. However, the reliability of the Widal test has been questioned, prompting the exploration of molecular techniques. Polymerase chain reaction (PCR) assays targeting *Salmonella* DNA, as indicated by Anabire et al. (2018), offer enhanced sensitivity and specificity, providing a more accurate and timely diagnosis.

Treatment and management

Current approaches to managing typhoidal anemia

Current approaches to managing typhoidal anemia involve a multi-faceted strategy that combines antimicrobial therapy, supportive care, and addressing the underlying hematologic abnormalities. Butler et al. (1991) highlighted the significance of early and appropriate antibiotic administration to target the causative agents, *Salmonella* Typhi and Paratyphi, and mitigate the progression of typhoid fever. Antibiotics, such as fluoroquinolones and third-generation cephalosporins, have been pivotal in reducing the severity and duration of the infection. Additionally, supportive care measures, including intravenous fluids and nutritional support, are crucial to manage dehydration and malnutrition associated with prolonged fever. Hematological interventions may be required to address anemia directly. Transfusion of packed red blood cells, as indicated by studies on sickle cell anemia populations (Chow and Leung, 1986; James et al., 1997), can ameliorate the impact of anemia on oxygen-carrying capacity. Comprehensive management also involves monitoring for complications, such as psoas abscess, and addressing them promptly (Kuo et al., 2010). By integrating these therapeutic approaches, clinicians can optimize outcomes in individuals with typhoidal anemia, emphasizing the importance of a tailored and holistic management strategy.

Challenges in treatment and potential areas for improvement

Despite advancements in the management of typhoidal anemia, challenges persist, and opportunities for improvement exist within the current treatment landscape. According to Butler et al. (1991) highlighted the emergence of antibiotic resistance in *Salmonella* strains, posing a significant challenge to the effectiveness of antimicrobial therapy. This resistance complicates treatment choices and emphasizes the need for ongoing surveillance and the development of new therapeutic options. Additionally, the availability and affordability of certain antibiotics, especially in resource-limited settings, can limit access to optimal treatment. The potential for misdiagnosis, as discussed by James et al. (1997), further complicates the timely initiation of appropriate therapy. Addressing these challenges requires a concerted effort to enhance antimicrobial stewardship, promote the judicious use of antibiotics, and explore alternative treatment options. Advancements in diagnostic tools, such as molecular techniques (Anabire et al., 2018), can contribute to more accurate and rapid diagnosis, guiding tailored treatment strategies. Future research should focus on overcoming antibiotic resistance, improving access to effective therapies, and developing innovative diagnostic and therapeutic approaches to enhance the overall management of typhoidal anemia.

Complications and prognosis

Complications associated with typhoidal anemia

Typhoidal anemia is associated with several complications that can significantly impact the course of the disease and the overall health of affected individuals. Kuo et al. (2010) reported the development of a psoas abscess caused by non-typhoidal *Salmonella* in a patient with severe aplastic anemia, highlighting the potential for localized infections in the context of compromised hematopoiesis. Chronic complications, particularly in murine models, were investigated by Brown et al. (2010), who established a link between chronic murine typhoid fever and secondary hemophagocytic lymphohistiocytosis. This finding underscores the systemic impact of typhoidal anemia, with implications for immune dysregulation and secondary pathologies. Additionally, Ndako et al. (2020) investigated changes in hematological parameters in typhoid fever patients, emphasizing the potential for profound alterations in the blood profile. The study by Roux et al. (2010) shed light on how both hemolytic anemia and malaria parasite-specific factors can increase susceptibility to non-typhoidal *Salmonella* infection in mice, showcasing the complex interplay between infectious agents.

The long-term effects and prognosis for individuals with typhoidal anemia

The long-term effects and prognosis for individuals with typhoidal anemia can vary based on factors such as the severity of the infection, timely medical intervention, and the presence of underlying health conditions. Brown et al. (2015) highlighted that chronic murine typhoid fever can serve as a natural model of secondary hemophagocytic lymphohistiocytosis, suggesting that persistent infection may contribute to prolonged immune dysregulation. Chronic inflammation and immune system modulation may have implications for long-term health outcomes. Additionally, the study by Loomis et al. (2020) emphasized that CD4 T cell-deficient hosts may fail to control chronic non-typhoidal *Salmonella* infection, leading to exacerbated inflammation, chronic anemia, and altered myelopoiesis. These findings suggest that individuals with compromised immune function may experience prolonged and severe consequences of typhoidal anemia. The long-term effects may also be influenced by complications such as psoas abscess, as reported by Kuo et al. (2010), which can result in localized infections and potentially impact the musculoskeletal system. The prognosis for individuals with typhoidal anemia underscores the importance of early diagnosis, appropriate treatment, and monitoring for complications, all of which contribute to a more favourable long-term outcome.

Factors influencing the outcome of typhoidal anemia

The outcome of typhoidal anemia is influenced by a multitude of factors, reflecting the complex interplay between the host, the pathogen, and the effectiveness of medical interventions. Ndako et al. (2020) investigated changes in hematological parameters in typhoid fever patients, emphasizing that the initial blood profile may serve as a prognostic indicator. The severity of the underlying infection, as discussed by Butler et al. (1991), is a critical determinant, with prompt and appropriate antimicrobial therapy contributing significantly to a more favourable outcome. Immunocompromised individuals, as highlighted in studies by Roux et al. (2010) and Loomis et al. (2020), may experience exacerbated outcomes, emphasizing the importance of host factors in shaping the disease trajectory. Complications, such as pus abscess (Kuo et al., 2010), can further complicate the clinical course, influencing the overall prognosis. The accessibility and quality of healthcare, as well as regional variations in disease prevalence,

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can impact the timeliness of diagnosis and treatment. Understanding these multifactorial influences is essential for clinicians to tailor interventions, optimize care, and improve the overall outcomes for individuals grappling with typhoidal anemia.

Research gaps and future directions

Gaps in the current understanding of typhoidal anemia

Despite considerable research on typhoidal anemia, there are notable gaps in our current understanding that warrant further investigation. Butler et al. (1991) highlighted the need for more comprehensive studies elucidating the patterns of morbidity and mortality associated with typhoid fever across diverse demographic groups. Understanding how age, gender, and other factors influence the disease trajectory could provide critical insights into tailored intervention strategies. The study by James et al. (1997) underscored the importance of correlating clinical and hematologic profiles with bone marrow responses in typhoid fever, but further research is required to unravel the intricate mechanisms underlying hematologic alterations during the course of the disease. Additionally, while the role of *Salmonella* Typhi and Paratyphi in typhoidal anemia is well-established, there is a gap in understanding how other microorganisms or coexisting infections may contribute to the complex hematologic manifestations, as indicated by Anabire et al. (2018). Advancements in diagnostic techniques, such as molecular assays and imaging modalities, have been mentioned (Kuo et al., 2010), but further exploration of their accuracy and applicability in different settings is necessary. Bridging these gaps will enhance our understanding of typhoidal anemia, ultimately improving diagnostic precision, treatment strategies, and outcomes for affected individuals.

Suggest areas for future research to improve diagnosis, treatment, and prevention

To advance our understanding of typhoidal anemia and enhance diagnostic, treatment, and prevention strategies, several areas of future research can be explored:

Diagnostic innovations: Investigate and develop more reliable and rapid diagnostic tools for typhoidal anemia. Molecular techniques, such as advanced PCR assays, can be refined and validated for their sensitivity and specificity in different settings (Butler et al., 1991; Anabire et al., 2018).

Host-pathogen interactions: Explore the intricate host-pathogen interactions during typhoidal fever to uncover novel therapeutic targets. Understanding the immune response and hematologic changes, as highlighted by James et al. (1997) and Roux et al. (2010), can guide the development of targeted interventions.

Antimicrobial resistance: Investigate the emergence and mechanisms of antimicrobial resistance in *Salmonella* strains causing typhoidal fever. Strategies to combat resistance and alternative treatment options should be explored to ensure effective management (Butler et al., 1991).

Complications and co-infections: Examine the associations between typhoidal anemia and complications, such as psoas abscess, and explore potential co-infections that may contribute to hematologic abnormalities (Kuo et al., 2010; Anabire et al., 2018).

Immunocompromised populations: Focus on understanding the impact of typhoidal anemia in immunocompromised individuals, as demonstrated by Loomis et al. (2020), to tailor treatment approaches for this vulnerable population.

Epidemiological studies: Conduct large-scale epidemiological studies to assess the global prevalence of typhoidal anemia and investigate variations among different populations, considering demographic and geographic factors (Brent et al., 2006; Ndako et al., 2020).

Vaccine development: Support research on the development and evaluation of effective vaccines against typhoid fever. Robbins and Pearson (1965) indicated the normal response of sickle cell anemia patients to *Salmonella* vaccines, suggesting vaccination as a potential preventive strategy.

Public health interventions: Explore public health interventions to improve hygiene, sanitation, and water quality, which are essential components in the prevention of typhoid fever and, consequently, typhoidal anemia (Barrett-Connor, 1972; Brent et al., 2006).

By addressing these research avenues, scientists and healthcare professionals can contribute to a more comprehensive and nuanced understanding of typhoidal anemia, ultimately leading to improved patient outcomes and enhanced public health measures.

Conclusion

This comprehensive review on typhoidal anemia synthesizes key findings from various studies, providing a nuanced understanding of the hematologic complications associated with typhoid fever. The analysis reveals a clear association between typhoidal anemia and typhoid fever, as evidenced by patterns of morbidity and mortality in hospitalized patients, emphasizing the intertwined nature of these conditions. The review delves into the diverse hematological abnormalities observed in typhoid fever patients, shedding light on changes in blood profiles and bone marrow responses. Insightful investigations explore specific populations, elucidating susceptibilities and outcomes in immunocompromised individuals, sickle cell anemia patients, and children in resource-limited settings. Complications such as psoas abscess and secondary hemophagocytic lymphohistiocytosis are detailed, underscoring the multifaceted nature of the disease. Studies further highlight the distinct contributions of *Salmonella* Typhi and Paratyphi to anemia, deepening our understanding of the pathophysiological mechanisms involved. The review also touches upon the global prevalence and epidemiological variations, offering valuable perspectives from diverse populations. Recognizing challenges in accurate diagnosis and treatment limitations, the findings emphasize the importance of addressing these hurdles for improved patient outcomes. Insights into long-term effects, prognosis, and the influence of host factors contribute to a holistic understanding of typhoidal anemia. Finally, the review identifies critical gaps in knowledge, paving the way for future research to enhance diagnostic precision, treatment strategies, and preventive measures. In conclusion, this synthesis provides a comprehensive overview of typhoidal anemia, offering valuable insights that can inform clinical practice and guide future scientific inquiry.

The significance of ongoing research and heightened awareness regarding typhoidal anemia cannot be overstated. As this review underscores the intricate relationship between typhoid fever and hematological complications, continued research is paramount for deepening our understanding of the underlying mechanisms, diverse clinical manifestations, and long-term impacts of typhoidal anemia. This knowledge is crucial for refining diagnostic approaches, advancing treatment modalities, and ultimately improving patient outcomes. Furthermore, as the global prevalence and epidemiological variations of typhoidal anemia become clearer, there is a growing need for increased awareness among healthcare professionals, policymakers, and the public. Heightened awareness is vital for early detection, prompt intervention, and the implementation of preventive measures. By fostering a comprehensive understanding of typhoidal anemia, research and awareness initiatives contribute not only to individual patient care but also to public health strategies aimed at reducing the burden of this condition worldwide. As scientific inquiry progresses and awareness campaigns proliferate, the potential for effective management, prevention, and, ultimately, the eradication of typhoidal anemia becomes increasingly tangible.

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Modern Trends in Cancer Diagnosis and Treatment: Innovative Aspects

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Abstract: The study aims to analyse new methods in the treatment and diagnosis of cancer, as the prevalence of cancer has been growing rapidly over the past 10 years. This study examined and investigated the implementation of novel approaches in molecular diagnostics, precision medicine (focusing on the genetic and molecular characteristics of cancer), immunotherapy (including immune checkpoint inhibitors), radiation therapy (such as intensity-modulated radiation therapy, CyberKnife, brachytherapy, and proton therapy), nanotechnology, tissue engineering, and the application of artificial intelligence. According to the results of the study, it is worth noting that the use of these diagnostic and treatment methods has significant potential in the field of oncology. For example, molecular diagnostics can detect mutations in the cancer process and optimise treatment. Kosovo is actively considering the use of molecular biomarkers to inhibit cell growth, and Albania has introduced a new molecular classification that helps to predict the occurrence of complications. Genetic research in Kyrgyz Republic is studying the impact on the immune system of the tumour, apoptosis and treatment prognosis. Albania is also making parallels in the immune system of pregnancy and endometrial cancer to predict abnormal pregnancy and find new methods of cancer diagnosis and treatment. The problem of this study is the lack of empirical, clinical research and testing, and the toxicity of some diagnostic and treatment methods. Further research should focus on developing new methods of cancer treatment and diagnosis, as well as optimising and improving existing methods through empirical and clinical trials.

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Introduction

The prevalence of cancer in the world has been growing rapidly over the past 10 years. According to the World Health Organization (2024), 20 million new cases of cancer and 9.7 million cancer-related deaths were registered worldwide in 2022. Many researchers study this problem by analysing existing data and conducting experimental studies in the field of innovative methods related to cancer. The detection rate of cancer has been steadily increasing over the past decade. Lung cancer is the most common cancer worldwide, accounting for 12.4% of all newly diagnosed cases, and it is also the leading cause of cancer-related deaths, contributing to 18.7% of all cancer fatalities. Breast cancer follows closely as the second most common cancer, making up 11.6% of new cases (World Health Organization, 2024). These statistics underscore the relevance and urgency of the present study, highlighting the importance of identifying new methods for diagnosing and treating the most prevalent and deadly forms of cancer.

Chamberlin et al. (2024) faced the problem of limited access to mammography and ultrasound in breast cancer screening, and in preparation for surgery, the use of mammography leads to inaccuracies on the operating table due to different positions of the patient during the examination and surgery. In this regard, researchers have developed a new method of diagnosis and treatment that includes magnetic resonance imaging (MRI) lying on the back to more accurately determine the location of the tumour in the breast, which preserves healthy tissue and avoid radical mastectomy. Shala et al. (2023) studied the treatment of brain tumours in paediatrics and found that the methods include surgery, chemotherapy and radiotherapy, but these methods still lead to severe side effects, poor prognosis, and low survival rates. In this regard, an innovative method of treatment with the use of herbal preparations was considered. Such a drug is quercetin, which affects tumour cells and metastases, in the form of apoptosis and autophagy. Apoptosis or "programmed cell death" is a process that occurs under the control of certain molecules, the correct functioning of which has a positive effect on the development of the tumour, in the form of its reduction. Furthermore, this study found that quercetin affects cell proliferation by reducing the vital functions of tumour cells, which leads to a decrease in migration and invasion.

Given the high prevalence of gastric cancer, Bilyalov et al. (2023) studied the relationship between heredity and gastric cancer detection. The study was conducted with 113 patients who were diagnosed for the first time, and the analysis was based on the identification of mutated genes responsible for the onset of gastric cancer in the next generation. Among the results, it is worth highlighting that 6.2% of patients had a pathological or potentially pathological genetic set, 3.5% of patients had heterozygous variants of the genetic set in the form of pathogenic/possibly pathogenic genes, and 2.7% of patients had heterozygous mutations in autosomal recessive inheritance. Thus, this study found that the prevalence of genetic inheritance of gastric cancer is high and corresponds to global statistics (Assumpção et al., 2020). Furthermore, due to the increase in the detection and mortality rate from lung cancer, Khan et al. (2023) reviewed the use of exosomal nanovesicles in the diagnosis and treatment of this disease. The progression of lung cancer depends on the coordination of cancer cells and immune cells in the microenvironment of the cancer process. Exosomes are membrane vesicles that are released under the influence of various processes and cells for cell-cell interaction in normal and pathological conditions, however, tumour cell exosomes have an individual composition of molecules that determines the nature of the tumour and also contain neoantigens, ribonucleic acid (RNA), deoxyribonucleic acid (DNA) and proteins. Tumour exosomes can also control the suppression and stimulation of the immune response, which leads to an impact on acquired and innate immune factors. In addition, they are involved in signal transduction, tumour and metastasis growth, angiogenesis and epithelial-mesenchymal transition. This study showed that exosomes can be used as biomarkers in lung cancer immunotherapy, helping to suppress the tumour's immune response, and thereby reducing tumour growth. However, the lack of data and research in this area slows down the process of studying the topic.

Dell'Acqua et al. (2020) conducted an empirical study on the use of intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer. During the year, 84 patients with squamous cell carcinoma who received IMRT were monitored. The study analysis addressed acute and early toxicity, time and intervals in treatment, life expectancy without colostomy removal and tumour response to the therapy used. The results of this study showed that the tumour response to treatment was positive with insignificant acute toxicity and justifies the use of IMRT as a standard of care for patients with anal cancer. Minervini et al. (2023) addressed the use of microRNAs as markers in the diagnosis of oral cancer at early stages. Previous studies have shown that microRNAs are significant biomarkers that help to detect smoking-related cancers at an early stage.

This study offers a unique contribution to the field of oncology by integrating a range of innovative diagnostic and treatment methods, including molecular diagnostics, precision medicine, immunotherapy, advanced radiation therapies, nanotechnology, tissue engineering, and artificial intelligence (AI). Unlike previous studies focusing on single approaches, this research highlights the synergy of these technologies to improve early cancer detection, personalized treatment, and patient outcomes. The study's novelty lies in its comprehensive application of genetic and molecular features for tailored therapies, with a focus on real-world settings in Kosovo, Albania, and the Kyrgyz Republic.

The study aims to explore innovative diagnostic and treatment methods for the early detection, effective treatment, and prevention of cancer, with a specific focus on improving patient outcomes, including survival rates and quality of life. The research seeks to assess how these advanced methods can enhance cancer care and contribute to better long-term health outcomes for patients.

Material and Methods

The scope of the study is defined by a focus on the most common and deadly cancers, such as stomach cancer, lung cancer, breast cancer, colorectal cancer, and endometrial cancer. The study pays special attention to patients with genetic predispositions to these cancers, as well as the application of innovative diagnostic and treatment methods in the context of different socioeconomic groups, in particular in developing countries such as Kyrgyzstan, Albania and Kosovo.

The main method of this theoretical research was a literature search in evidence-based databases and search engines such as PubMed, ScienceDirect, Scopus, and Google Scholar. The literature, in the form of empirical, theoretical, case studies and clinical cases, was selected for the period from 2020 to 2024. The following keywords were used to search for published studies: oncological diseases, cancer, diagnostics of malignant neoplasm, molecular diagnostics of cancer, genetic diagnostics of cancer, treatment of cancer, cancer immunotherapy, modulated radiation therapy of cancer, proton therapy of malignant process, brachytherapy of cancer, CyberKnife in the diagnosis and treatment of cancer, nanotechnology in the treatment of cancer, tissue engineering in the diagnosis and treatment of cancer AI in the diagnosis and treatment of cancer, Kyrgyz Republic, Albania, Kosovo. The literature search was conducted according to the selection criteria: relevance to the research topic, free access to reading, data published no later than 2020, and publications in English or Russian. The study selected 63 articles; however, if an article did not correspond to the topic, had unspecified data, was not published in English or Russian, or was not freely available, it was excluded from the lists for study. Upon completion of the selection, the list of references was narrowed down to 31 studies. This study examines innovative methods of cancer diagnosis and treatment in Kyrgyz Republic, Albania and Kosovo.

The study analyses the use of magnetic resonance imaging, immunotherapy, the study of genetic aspects of the immune system in the oncological process, and the use of passive radio wave radiometry in combination with AI in the diagnosis of breast cancer in Kyrgyz Republic. In addition, data on the introduction of genetic testing for hereditary gastric cancer, the use of immunotherapy for lung cancer, the use of molecular biomarkers for the treatment and diagnosis of cancer, and the ability of molecular diagnostics to detect malignant tumours in Kosovo were systematised. The use of intensity-modulated radiotherapy for the treatment of anal cancer, the identification of microRNAs for the early diagnosis of oral cancer, a comparative analysis of the immune system in pregnancy and endometrial cancer, and the introduction of a molecular classification for endometrial cancer in Albania were analysed.

The application of molecular diagnostics in the form of the ability to describe anatomical characteristics and determine the exact size, quantitative data, and composition at the cellular and molecular level is studied in detail. The use of liquid biopsies in genetic diagnostics, the use of combined immune systems, and the influence of inflammatory processes and cytokines in the treatment and diagnosis of cancer are reviewed and investigated. The comparison method was used to study intensity-modulated radiation therapy, magnetic resonance, proton, stereotactic, adapted radiation therapy, and the CyberKnife robotic radiation delivery system. Innovations in the use of nano/micromotors and magnetic nanoparticles for drug delivery and tumour destruction in the field of nanotechnology are considered. AI-assisted diagnostics were evaluated to speed up diagnostic processes (identifying mutations, the origin of tumours, adjusting the technical characteristics of diagnostic devices) and optimise treatment according to individual patient data.

Results and Discussion

The development of molecular diagnostics is improving the ability to detect cancer at an early stage and identify individual mutations, which helps to select

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the most effective treatment. The system for assessing tumour response to therapy may not accurately assess the effect of drugs due to poor tumour volume ratio, necrotic changes or tumour shrinkage, which may lead to a delay in detecting the effect. Molecular imaging can characterise a tumour not only anatomically, but also visualise its exact size, and quantitative data, and analyse it at the molecular, cellular, and subcellular levels. In addition, this method can be used to assess the response to treatment and clinical outcomes (Bai et al., 2023).

Molecular imaging is a method that visually outlines, characterises and measures the processes occurring in a tumour at the cellular and molecular level without resorting to invasive diagnostic methods. This method differs from the others in that it demonstrates the physiological process of molecules in a particular tissue or organ. Nuclear imaging is a type of molecular imaging used with radiotracers to assess the volume, number and biological appearance of a tumour. The advantages of this imaging method include high sensitivity and quantitative characteristics. For example, nuclear imaging and computed tomography, which can combine the anatomical structure and functioning of a tumour, can help correct cancer processes in the body more accurately. Photoacoustic imaging is one of the newer molecular imaging methods that generates an ultrasound signal based on photoacoustic action. When the laser pulses hit the tissue, they are partially absorbed and transformed into heat, which then creates an ultrasound signal and, consequently, an image. The method is highly accurate, making it clinically important for cancer diagnosis (Bai et al., 2023). Figure 1 shows the areas of application for molecular imaging. At the cellular level, probes bind to cell surface receptors, the nucleus, and targets in the cytoplasm. After the molecular probes are introduced into a living organism, the tumour response to therapy is assessed.

It is also worth noting a study on molecular imaging in gastric cancer. Scientists have studied the leucine-rich G-protein contained in the repeat receptor 5 and determined that it can be a marker of stem cells in gastric cancer. They also created a peptide probe that was used for molecular imaging of gastric cancer and found that the probe could be used to diagnose not only cancer but also metastases in the peritoneal zone (Kwak et al., 2021).

Histopathological factors and clinical presentation are the most common methods for determining the risks for the further management of a cancer patient. However, patients with stage II colorectal cancer need to optimise their treatment regimens, and in patients with stage III, the need for chemotherapy should be assessed to avoid unnecessary toxicity. In this regard, new genetic and epigenetic biomarkers were developed to help assess and plan the necessary therapy. New types of biopsy are also being developed, such as liquid biopsies, which are characterised by minimal intervention in the body and are based on the collection of blood or other human biological fluids and analysis of components derived from the cancerous tumour. However, there are some problems with this method, such as the small number of circulating cells, molecules or tumour DNA in the biological fluids. This way, a liquid biopsy will help analyse the tumour information in real-time, which will help to optimise treatment individually for each

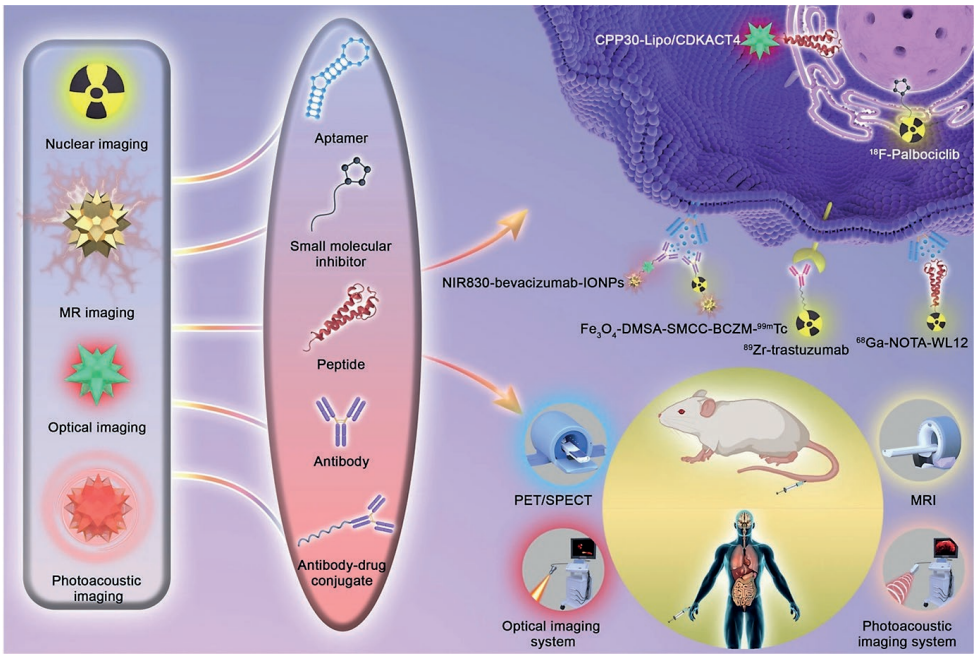

Figure 1: Areas of application for molecular imaging. Source: Bai et al. (2023).

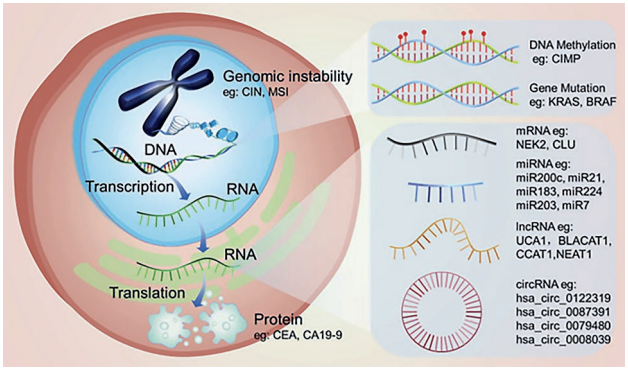

Figure 2: Types of epigenetic biomarkers. Source: Luo et al. (2021).

patient. Epigenetic biomarkers, which include DNA, microRNAs, lncRNAs and circRNAs, have been widely studied in oncology. Some of them have begun to be used in practice, such as a mutation in the proto-oncogene (KRAS), which is the only marker with the most proven effectiveness (Figure 2). However, the study of this topic is slowing down due to different types of samples, small sample size, selection of schemes with low efficiency and other reasons (Luo et al., 2021).

The development of immunotherapy in the field of oncology helps increase the body's immune response to tumours, which leads to an improvement in prognosis, outcomes, quality and duration of life. The use of immune cells to treat cancer is gaining momentum in this area. Combination therapies based on immune checkpoints, such as nivolumab and ipilimumab, have been used as first-line therapy for metastatic melanoma, with a nearly 60% improvement in progression-free survival rates of approximately 1 year. Furthermore, combinations of immune checkpoints with chemotherapy, antiangiogenics and other treatments were addressed (Yap et al., 2021). New small molecule agonists TLR7/8 can induce cytokines aimed at eliminating the inflammatory process, which contributes to increased cellular cytotoxicity. This method of treatment with small molecule agonists can increase the body's resistance to tumours, due to the effectiveness of monoclonal antibodies and the use of combining immunotherapy with other methods. In addition, the potential impact of inflammation and cytokines as markers for lung cancer in patients treated with immune checkpoint therapy, as well as their response to this treatment and prognosis, has been studied (Craig et al., 2024).

Radiotherapy has become more commonly used in the treatment of liver cancer, due to the good results achieved in this area. Radiation therapy includes optimised image guidance, treatment planning using precise methods, and motion control. These methods include intensity-modulated radiation therapy, magnetic resonance radiation therapy, proton radiation therapy, and stereotactic radiation therapy. Proton radiotherapy is based on reduced radiation exposure to normal tissues surrounding the tumour, which increases the dose to the tumour. Magnetic resonance radiotherapy delineates soft tissues more clearly than computed tomography.

In the regions of Kyrgyzstan, Albania and Kosovo, different methods of radiation therapy are used, each with its own characteristics and advantages. IMRT allows for more precise delivery of radiation to the tumour, reducing damage to surrounding healthy tissue due to the ability to control the shape and dose of the beam. This method is very effective in treating tumours in complex anatomical areas such as the head and neck, but has certain disadvantages, such as higher requirements for technical equipment and long treatment times. In Albania and Kosovo, IMRT is actively used to treat various types of cancer, such as prostate and breast cancer, but the limited availability of high-quality equipment may limit its use in some regions.

Proton therapy is the next stage in the development of radiation therapy, which reduces the dose of radiation to healthy tissues by using protons instead of X-rays. This method is especially useful in treating pediatric tumours and tumours located near important organs such as the brain or eyes. Proton therapy can also be used in the treatment of severe head and neck cancer, but it is expensive and technologically demanding, which limits its use in countries with limited access to appropriate equipment, such as Kyrgyzstan.

Stereotactic radiation therapy is another innovative technique that uses highly precise targeting of the tumour with multiple high doses of radiation, which allows for shorter treatment times and high efficacy in limited tumour areas. This method is particularly suitable for treating small tumours, such as those in the lung or liver, and is highly accurate when combined with computer and imaging technologies. However, its application requires expensive equipment and specialized knowledge, which limits its use in countries with low levels of medical funding, such as Kyrgyzstan.

As for AI tools in the diagnosis and treatment of oncology, their effectiveness varies in different regions depending on the level of technological equipment and data availability. In countries with advanced medical systems, such as Albania and Kosovo, AI is actively used for early cancer detection through the analysis of images such as mammograms, MRI, and computed tomography (CT) scans. AI can significantly improve diagnostic accuracy, reducing errors and improving early detection of tumours, which is critical for effective treatment. In Kosovo, for example, AI is

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also being used for personalized treatment planning, helping to develop optimal treatment regimens for each patient based on their genetic data.

In Kyrgyzstan, where medical technologies often have limited access, the use of AI in oncology is still in its infancy. However, in the future, with the development of technology and access to training programs, AI can become an important tool to support medical staff in diagnosing, planning treatment, and optimizing therapeutic processes, especially for early cancer detection, which is especially important in a country with limited resources for examinations.

Furthermore, in combination with online adaptive therapy, this method overcomes the problem of uncontrolled patient movements and reduces radiation doses to normal surrounding tissues (Zaki et al., 2023). In addition, adapted radiotherapy is used in oncology. Thus, the use of narrower fields significantly reduced the radiation dose by almost 60%. In this case, the doses directed to the tumour went beyond it to a lesser extent, which reduced the risks to the surrounding tissues (Nenoff et al., 2019). The use of CyberKnife, which is a robotic system for delivering radiation to the cancerous tumour zone, along with stereotactic image-guided radiation therapy, contributes to more accurate delivery of radiation doses to the required tumour zone. The use of such complex treatment improves target coverage, reduces risks to surrounding tissues, and improves the prognosis of the disease. In addition, CyberKnife has an advantage over brachytherapy, as patients complain of severe discomfort and have high risks associated with damage to other organs around the tumour (Gao et al., 2022; Posolenyk, 2024).

Nano/micromotors are created microscopic robots that convert energy into motion. In the field of oncology, such micro-robots can be used for drug delivery, tumour destruction or biomarker sensing (Figure 3). There are several types of micromotors: chemical, light, magnetic, and ultrasonic. However,

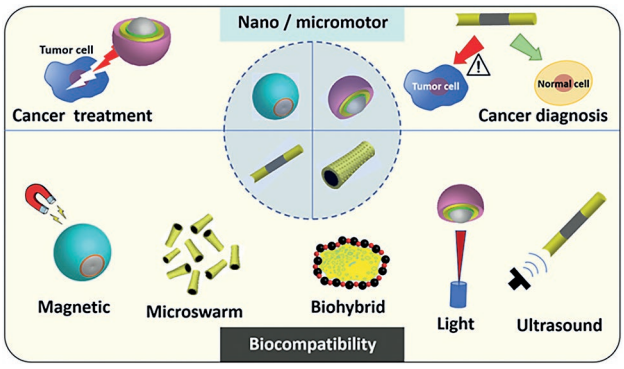

Figure 3: Micromotors used in oncology. Source: Zheng et al. (2024).

there are some problems in the study of this issue, which complicates the transition from laboratory to clinical trials. Micromotors are quite toxic, have harmful by-products, consume large amounts of toxic fuel and can cause an uncontrollable immune response from non-degradable components. Therefore, this method of diagnosis and treatment is still under development and animal testing, but has great potential (Zheng et al., 2024).

One of the primary concerns is the toxicity associated with these micromotors. Many of the materials used in their construction can be harmful, either due to their by-products or their degradation into toxic components. The fuel sources that power these micromotors can also be toxic, and the non-degradable components of these robots may trigger an uncontrolled immune response, further complicating their clinical use. Recent research is addressing these issues by focusing on reducing the toxicity of nano/micromotors. One avenue of improvement is the development of biocompatible materials that can minimize harmful interactions with the body. Chehelgerdi et al. (2023) highlight the importance of using biocompatible and biodegradable materials in the design of these micromotors. By employing such materials, the risk of an adverse immune response can be minimized, and the potential for the body to safely break down these robots after their use increases.

Research into the use of non-toxic fuels is being explored. Traditional fuels for nano/micromotors often involve chemical reactions that can produce harmful by-products, but alternative, safer fuels are being developed to mitigate these risks. Using non-toxic or minimally toxic fuels can significantly reduce the harmful effects associated with the operation of these micromotors, making them more suitable for clinical applications. Despite these advancements, the clinical implementation of nano/micromotors in oncology is still in the experimental phase. Most of the research is being conducted through animal testing, and many hurdles remain before these technologies can be safely used in humans. The progress in reducing toxicity and improving biocompatibility, as discussed by Chehelgerdi et al. (2023), provides a promising outlook for the future of nano/micromotors in cancer treatment. These innovations have the potential to revolutionize targeted therapy, offering a more precise, efficient, and less toxic treatment option for cancer patients.

Magnetic nanoparticles have garnered significant attention in the field of oncology due to their potential for targeted drug delivery and diagnostic applications. These nanoparticles are highly accessible and can be synthesized through various methods, including

thermal decomposition, polynomial synthesis, and hydrothermal synthesis. Magnetic nanoparticles offer several advantages, such as their ability to be controlled externally using magnetic fields, which makes them highly suitable for precise drug delivery to tumour sites and for enhancing diagnostic imaging. Liu et al. (2024), have highlighted the promising role of magnetic nanoparticles in improving the efficacy of anticancer treatments. Specifically, they have focused on their use in the delivery of autophagy-modulating compounds derived from Traditional Chinese Medicine. Autophagy, a process by which cells recycle damaged components, has been identified as a potential therapeutic target in cancer, as modulating this pathway can help induce cancer cell death and improve the effectiveness of anticancer treatments. Magnetic nanoparticles, when loaded with autophagy-modulating compounds, can be directed precisely to cancer cells, enhancing the localized effects of these compounds while minimizing off-target effects.

Authors provide insights into how magnetic nanoparticles can be designed to enhance the delivery of these compounds, ensuring that they reach the tumour site efficiently. The ability to control the nanoparticles using external magnetic fields allows for the fine-tuning of drug release, ensuring a more controlled and sustained therapeutic effect. This precision in targeting not only improves the effectiveness of the treatment but also reduces systemic toxicity, a significant challenge in traditional chemotherapy.

Challenges still remain in optimizing the use of magnetic nanoparticles for clinical applications. Issues such as biocompatibility, potential toxicity, and the stability of the nanoparticles within the body need to be addressed. Liu et al. (2024) emphasize the importance of using biocompatible materials for the synthesis of these nanoparticles, which can reduce the risk of adverse immune reactions. The development of more efficient synthesis methods that can scale up production while maintaining the nanoparticles' functionality is crucial for their future clinical use.

Developments in the field of tissue engineering make it possible to create artificial tissues and organs that can replace damaged tissue after cancer treatment. For example, using bone cancer as an example, tissue engineering methods are being developed to find biocompatible, tissue-specific and functional materials that will help restore bone and have an anti-cancer effect at the same time. Fourth-generation biomaterials have the properties of smart biomaterials, which have anti-infective and anti-tumour functions, which release active molecules and activate pathways necessary for fighting in the tumour microenvironment (Alromi et al., 2021; Ambrosio et al., 2021).

The use of nanomaterials, such as those described by Egwu et al. (2024), allows for better control over the drug release process and reduces the risk of harmful by-products. Nanomaterials can be designed to be biocompatible, biodegradable, and non-toxic, which significantly mitigates the risks of an immune response or tissue damage. These materials are often engineered to degrade in the body without releasing harmful substances, making them more suitable for clinical applications. Researchers are working on strategies to design these biomaterials with specific surface modifications that enable them to avoid immune system detection, thus reducing the likelihood of an immune response. This can be achieved through the use of hydrophilic coatings or by incorporating molecules that promote immune tolerance, further enhancing the safety profile of these materials.

As Egwu et al. (2024) discuss, the future of nanomaterials in drug delivery lies in their ability to combine effectiveness with minimal toxicity, allowing for a more targeted approach to treatment with fewer side effects. The ongoing advancements in fourth-generation biomaterials and nanomaterial-based drug delivery systems are set to play a crucial role in cancer therapy. By minimizing toxicity and providing controlled, localized delivery of therapeutic agents, these innovations hold the potential to significantly improve outcomes for cancer patients, particularly in the areas of tissue regeneration and tumour management.

In the clinical settings of Kyrgyzstan, Albania, and Kosovo, innovative cancer diagnostic and treatment methods have been increasingly integrated to enhance patient care. In Kyrgyzstan, for example, the use of passive microwave radiometry combined with AI has shown promise in diagnosing breast cancer. This approach, when combined with mammography and ultrasound, has improved the ability to identify pathological changes at early stages, thus enabling better prediction and prevention of malignancy. Additionally, AI assists in analysing microRNA biomarkers, contributing to the identification of conditions that could potentially develop into cancer.

In Albania, there is a significant focus on molecular diagnostics, especially in the area of endometrial cancer. The introduction of molecular classification systems has helped improve the selection of patients for specific treatments, enhancing both prognosis and treatment efficiency. Research into the immune system's response during pregnancy and its similarities with endometrial cancer has also paved the way for new therapeutic insights. Furthermore, the identification of microRNAs for early oral cancer detection is helping clinicians in Albania adopt more

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proactive screening methods, ensuring that cancer is caught at a more treatable stage.

Kosovo has seen the implementation of genetic testing for hereditary gastric cancer, which has allowed for more accurate risk assessments and tailored treatment plans. The use of immunotherapy for lung cancer, particularly with immune checkpoint inhibitors, has improved survival rates, and molecular biomarkers are increasingly used to guide diagnosis and treatment. The ability of molecular diagnostics to detect malignant tumours early in their development has significantly improved, providing clinicians with valuable tools to personalize cancer treatments and monitor therapy responses more effectively. These innovations have enabled oncologists in Kyrgyzstan, Albania, and Kosovo to move toward more personalized, precise treatment approaches, improving early detection, enhancing treatment outcomes, and reducing unnecessary toxicities. These advancements are making a critical difference in patient care by providing more effective, less invasive options for diagnosing and treating cancer.

Over the past ten years, the application of AI in the field of oncology has achieved great results. With the help of training and the availability of extensive information in the field of medical research, as well as unlimited possibilities in computing, AI has great potential in the diagnosis and treatment of cancer in patients. This method makes it possible to detect oncology more accurately at an early stage, determine the classification, and molecular structure of the tumour, prognosis of the disease and treatment, create individual treatment regimens, as well as automate the process of radiation therapy and be involved in the invention of new drugs (Chen et al., 2021). AI can be used to analyse histopathological data, as well as CT, MRI, mammography, or photographs of suspicious lesions. The genetic profile data can be used to determine the classification of tumours more accurately and quickly using AI. In addition, the detection of cancer mutations and the origin of tumour cells using liquid biopsy is also possible with proper training and settings of AI. Characterisation of the microenvironment of cancer formation, formation of design, and physicochemical properties of drugs is also possible using this method (Bhinder et al., 2021; Soyka et al., 2024).

Temaj et al. (2024) conducted a study, which examines changes in genetic information and their impact on the cancer process. When a mutation occurs in a gene responsible for creating a protein, it can lead to cells malfunctioning and turning into cancerous cells. Up-frameshift-1 (UPF1) has protective functions that help remove incorrect proteins from cells and prevent their accumulation. In addition, lncRNAs also affect the way cells divide and grow. In this regard, UPF1 can be a biomarker for the diagnosis and treatment of cancer, and the combination of UPF1 and lncRNA can affect cell growth processes and provide prognoses in this area. As for immune checkpoint inhibitors, they are one of the main methods of cancer treatment, both mono- and complex therapy. However, the problem with this method is that the effect is achieved in only one-third of all patients. Thus, the effectiveness of this method is influenced by individual cancer cell data, levels of immune checkpoint ligands, and the extracellular matrix, which is a crucial link. A study by Fejza et al. (2023) confirmed that optimisation of the extracellular matrix has an important interaction with the immune system of different tumour types. Many molecules derived from the extracellular matrix are used as a marker that can detect tumours and have a positive effect on treatment.

The use of immunotherapy in paediatric oncology is successful, as the survival rate for children is about 80–90%. Optimisation of supportive care and the use of therapy based on the genetic characteristics of tumour cells are important factors in this area. Among the improvements and innovations, it is worth noting the classification of certain subgroups based on genetic data in the form of aneuploidy or translocation, as well as their interaction and response to treatment. One of the problems that arise during treatment is the occurrence of toxicity with negative outcomes. Therefore, the use of immunotherapy has promising possibilities in cases of high risk, relapse and certain genetic changes. Signalling pathways can be targeted to slow down or stop small molecules by monoclonal antibodies that can recognise cell surface antigens. Inotuzumab ozogamicin, used in immunotherapy, can interact with leukaemia cells and release a toxin that leads to the destruction of the pathological cell, while blinatumumab activates T cells that have a genetic programme capable of detecting leukaemia cells. However, this area of oncology still requires additional study and research (Graiqevci-Uka et al., 2023).

Scientists in Albania Bruno et al. (2024) and Gupta et al. (2024) conducted a review to improve classifications and determine the risk of complications of endometrial cancer. The existing characteristics of risk predictors are not able to predict the response to treatment and the occurrence of relapse in the future. Biomolecular classification can help improve the system of selecting patients for a particular type of treatment, and it also improves the likelihood of complications in women with endometrial cancer. Among the disadvantages of this method, it is worth noting the unclear differences in the case of relapse, so in the future, efforts should be directed

at optimising the classification and using it in complex diagnostics. Zub et al. (2022) and Betti et al. (2023) studied the immune system of endometrial cancer by comparing it to pregnancy. As such, the immune systems of pregnancy and endometrial cancer are similar, however, those factors that have a positive effect on pregnancy can have a negative impact on the oncological process of the uterus. For example, studying the immune response during pregnancy complications can help determine the immune system response to cancer. The availability of existing research and machine learning can improve oncology research. These data can be used both for the management of complicated pregnancies and for the diagnosis and treatment of endometrial cancer.

A group of scientists from Kyrgyz Republic Fisher et al. (2023) conducted a study on the use of passive microwave radiometry for the diagnosis of breast cancer, and in the future, to identify microRNAs of this disease. As such, a study found that the combined use of mammography, ultrasound, passive microwave radiometry, and AI microRNAs can identify conditions and pathological changes in the body that may turn into cancer in the future. The use of these methods as mono-diagnostics shows only a low probability of cancer in a patient, while the combination of all methods determines reliable signs of the oncological process. This method identifies patients at risk of malignant disease and prevents precancerous conditions. In addition, a study by Hussain et al. (2024) on circular RNAs and KRAS found that circRNAs are a type of RNA that plays a significant role in the control of certain processes in cancer. Other types of RNA have also been studied that have an impact on the functioning and signalling pathway of the KRAS gene in cancerous tumours and can increase the activity of the KRAS pathway, thereby enhancing the growth and spread of cancer cells. Therefore, circular RNAs may influence the tumour's immune response to treatment, apoptosis programming, and drug sensitivity. This makes this method important in the diagnosis and treatment of cancer. However, there are also problems in this area: the complexity of KRAS gene mutations and the lack of research to clearly understand the processes.

Statistics and innovation perspectives

Begolli et al. (2023) studied molecular diagnostics and immunochemical tools, gene expression microarrays, immunoassays and immunostaining, and reviewed new trends in diagnostics and future applications of carbohydrate sulfotransferases. The latter accelerates the synthesis of proteoglycans, which are responsible for physical contact and signal transmission between neighbouring cells in normal and pathological conditions. The study found that carbohydrate sulfotransferases are used in most cases in the diagnosis of inflammatory conditions, cancer and connective tissue diseases. Low activity was detected in congenital connective tissue diseases, but an increased response was found in oncological processes. Mutation of the gene for carbohydrate sulfotransferase 3 causes bone dysplasia and multiple joint dislocations inherited by autosomal recessive type, on the other hand, increased activity of carbohydrate sulfotransferases 11, 12 and 15 is an unfavourable prognostic factor in ovarian cancer, glioblastoma and pancreatic malignancy. In addition, hyperactivity of carbohydrate sulfotransferases 11 and 15 in vascular smooth muscle cells has been associated with severe lung conditions in patients with COVID-19. This progress in molecular diagnostics is similar to the present study and confirms the importance of studying issues in this area.

In addition, Sadeghnejad Barkousaraie et al. (2020) addressed deep neural network training to improve beam orientation in prostate cancer using intensity-modulated radiation therapy. Manual or protocol selection of beam orientation is quite time-consuming and can produce incorrect results. Many algorithms were developed to improve the choice of beam orientation due to its impact on treatment outcome, but these calculations are quite slow. In the course of the study, a new method for fast beam orientation selection using deep neural network training was proposed, which can quickly produce a plan using state-of-the-art column generation. The innovation proposed by the researchers is based on the structure of training, observation control, the structure of the neural network training process, and the ability to learn from anatomical features to plan the required beam orientations without using dosimetric information from the candidate beams. AI studies the possibility of simulating column generation and selects the beam orientation by accurately calculating the beam suitability. This study involved 70 patients with prostate cancer who were divided into 3 groups: 50 patients for neural network training, 7 patients for validation, and 13 patients for testing – for model formation and testing. Six contours were created for each patient: the planned target volume, body, bladder, rectum and both femoral heads. Using neural networks and supervised column generation, two sets of plans were created for each subgroup in the test set. The method took about 1.5 s to create a set of 5 beam orientations 300 s to calculate the dose-effect matrices for the 5 beams, and about 20 s to improve the fluence map. However, it took about 15 hours to

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perform all the final calculations of the dose-effect matrices for all beams. The average dose received by the organs ranged from 1 to 6%. The bladder had the lowest dose – 1.18%, the rectum – 2.4%, left and right femoral heads – 5.8 and 5.5% respectively, and the body – 0.1% between the generated treatment plans. The study results show that the developed method of fast beam orientation selection based on neural network training can calculate the beam orientation in a matter of seconds, which makes it suitable for clinical procedures. The training of neural networks is similar to the present study and confirms the importance of introducing innovative methods in the field of oncology to improve treatment prognoses and speed up diagnosis.

Alkhathami et al. (2022) studied the issue of breast cancer and serum levels of lncRNA, which is usually abnormal in malignant tumours. This study involved 100 patients with histologically confirmed breast cancer and 100 healthy patients. Blood was drawn with serum separation and RNA extraction, followed by analysis of lncRNA expression (androgen receptor negatively induced [ANRIL], taurine-regulated gene 1 [TUG1], urothelial cancer 1 [UCA1] and HIT). Increased expression results were observed in patients with breast cancer compared to healthy controls. The relative expression of UCA1 lncRNA was significantly increased in patients with rapidly developing stages compared to patients at the initial stage. In addition, the expression of TUG1 lncRNA in patients with early-stage cancer was higher than in patients with advanced cancer, and ANRIL lncRNA was upregulated in patients with positive status. Furthermore, lncRNA-HIT had the greatest role in the potential use as a candidate biomarker in patients with breast cancer. The findings of this study suggest that changes in lncRNA expression may be a significant biomarker in the prognosis of cancer. The data from the biomarker panel determines the severity and progression of the cancer process. The study also contributed to the improvement of knowledge of the molecular mechanism in the field of breast cancer. Among the limitations of the study was the analysis based on the determination of lncRNA in serum, rather than working with patient tissue. This study has similar results and prospects in the study of the cancer process, its diagnosis and treatment.

Conclusion

According to statistics, about 10 million cases of cancer are detected worldwide per year, which means that every 5 people suffer from cancer. In this regard, scientists are striving to study and optimise new approaches to the diagnosis and treatment of cancer. In this theoretical study, some promising types of cancer diagnosis and treatment were considered.

This study examined the development of molecular diagnostic methods that help identify individual mutations, which allows us to select the most effective treatment. In Kosovo, research using molecular imaging and immune checkpoint inhibitors is being actively conducted. Albania is introducing molecular values in the classification of endometrial cancer, which helps determine the likelihood of complications. The study also established that precision medicine plays an important role: the use of genetics and bioinformatics allows us to tailor treatment individually to each patient, considering the genetic and molecular characteristics of the tumour and the patient's response. Kyrgyz Republic is actively researching the genetic aspects of cancer and the impact on their immune system, apoptosis and response to treatment. In addition, immunotherapy, which includes immune checkpoint inhibitors, contributes to a more robust resistance to the cancer process, which improves the quality and duration of patients' lives. In Albania, a comparative analysis between the immune systems of endometrial cancer and pregnancy was applied, which leads to the potential for the management of complicated pregnancies and endometrial cancer.

The present study confirms that the study of new radiotherapy methods includes intensity-modulated radiotherapy, CyberKnife, proton and brachytherapy. The development of nanotechnologies using microparticles to deliver drugs to tumour cells can improve the effect of treatment and reduce side effects, while tissue engineering can create artificial tissues and organs to visualise the cancer process or restore damaged organs after treatment. In addition, research is being carried out using AI, which is used in medicine to help predict the risk of cancer, speed up diagnosis, adapt treatment and monitor the results of therapy. Limitations in the introduction of the latest methods of diagnosis and treatment of cancer are the lack of research, accessibility, information and experimental studies in this area.

To implement the latest methods of cancer diagnosis and treatment, it is important for clinicians to use molecular diagnostics and molecular imaging. Nuclear imaging and photoacoustic imaging allow for accurate assessment of tumours at the molecular level, which ensures early detection and monitoring of treatment effectiveness. Liquid biopsies, which allow for real-time tumour monitoring with minimal intervention, should become the standard of practice, despite certain limitations of this technique.

It is important to integrate genetic and epigenetic biomarkers to individualize treatment, in particular

to assess mutations such as mutation in the proto-oncogene in patients with colorectal cancer. Immune therapy, in particular checkpoint inhibitors, is a promising area and requires precise selection for each patient. Advanced radiotherapy techniques, such as proton therapy and intensity-modulated radiation therapy, should be implemented to improve treatment accuracy and reduce damage to healthy tissue. The use of artificial intelligence to analyse medical images and predict responses to therapy can optimize diagnostic and treatment processes.

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Correlation of Ki-67 Expression with the Stage of Disease in Patients of Colorectal Carcinoma

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Abstract: Colorectal carcinoma (CRC) is a multifactorial disease process with several factors influencing prognosis. CRC is associated with the expression of multiple cell proliferating markers such as Ki-67/MIB-1. This study was aimed to examine possible correlations between Ki-67 expression and the stage of colorectal carcinoma. This was a single centre prospective study including 93 patients who underwent surgery for colorectal carcinoma. Expression of Ki-67 was assessed by immunohistochemistry on formalin-fixed paraffin-embedded tumour tissue blocks. Categorical variables data were presented as number with corresponding percentage. Continuous data were analysed using parametric tests as applicable and categorical data using nonparametric tests. The level of significance $\alpha = 0.05$ and P-value < 0.05 was considered statistically significant. The average Ki-67 expression was 77.66% (SD [standard deviation] = 9.68%) with a range of 60 to 90%. Patients with nodal involvement and larger size had a higher Ki-67 expression. To assess statistical significance, the cut-off for Ki-67 expression was set at 70%. Of 66, 48 (72.7%) adenocarcinomas and 12/18 (66.66%) mucinous adenocarcinomas had Ki-67 expression above cut-off as compared to signet ring cell variety. Ki-67 expression in colorectal carcinoma signifies mitotic activity of the tumour. Thus, it could be used as an adjunct to the existing diagnostic arsenal to help overcome its limitation in gauging the functional status of tissues.

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Introduction

Colorectal carcinoma (CRC) is the most common malignancy of the gastrointestinal system (Kumar et al., 2015). As per Global Cancer Statistics 2020, it is third in terms of incidence, but second in terms of mortality (Kumar et al., 2015). CRC incidence rates have been steadily rising in the developing world (Sung et al., 2021). Previous studies have reported that its 5-year survival rate is about 64% (Li et al., 2020). However, the 5-year survival rate of metastatic CRC is only 12% (Li et al., 2020). Thus, it is very important to diagnose CRC at an early stage. Investigation into newer diagnostic markers and modalities are thus warranted.

CRC is a multifactorial disease process, and several factors influence the prognosis, including clinical, histopathological, and biological factors related to the TNM (tumour, node, metastasis) stage of the tumour. Therefore, investigations into the molecular mechanisms of CRC can lead to novel biomarkers, which can optimize diagnosis and/or treatment regimens.

Colorectal carcinoma is associated with the expression of multiple cell proliferating markers such as Ki-67/MIB-1, which have been linked to biological features and clinical behaviour of these tumours. The cell proliferation marker Ki-67 was identified as a nuclear nonhistone protein, found in perinucleolar region and nucleoplasm of dividing cells (Schlüter et al., 1993; Scholzen and Gerdes, 2000). Ki-67 labelling index (Ki-67LI): percentage of invasive cancer cell nuclei that are positive for Ki-67 immunostaining over total invasive cancer cell nuclei present in a histological sample – has become a routine practice in clinical pathology to estimate the growth fraction of a tumour (Melling et al., 2016). However, only a few studies exist on the prognostic role of Ki-67 in CRC and have produced contradictory results (Saleh et al., 2000).

Due to the paucity of definitive guidelines and inconsistent results in available literature further analysis into Ki-67 expression in CRC is needed. This study aimed to look for the correlation between Ki-67 expression and the grade of CRC.

Methods

Study design

This was a single centre prospective study conducted by the Department of Surgery from October 2019 to September 2021. We studied 93 cases of colorectal cancer which were included on accrual basis. The protocol was approved by the ethical review board of the institute (ethics number: LHMC/IEC/2019/76). According to the principles of the declaration of Helsinki 1975 and its later modifications, written, informed consent was obtained from all the participants.

Participants

The patients were selected from those attending the out-patient department at the hospital. The biopsy proven cases of colorectal carcinoma above the age of 18 years were included in the study. Exclusion criteria were: the patients who received chemotherapy/targeted immunotherapy, and also the cases with a history of other conditions with increased Ki-67 expression such as carcinoma breast and cervix were excluded from the study. Initially 96 patients were enrolled for the study, 2 patients had received neoadjuvant chemoradiotherapy while 1 patient had a history of carcinoma breast, and therefore, 3 total cases were excluded from the study.

Patients were clinically evaluated by detailed history during routine examination on initial contact. All the preoperative routine investigations were performed. Staging of disease was done using radiological and histopathological investigations.

Routine investigations include complete blood count, liver and renal function tests, serum electrolyte levels, blood total protein and albumin levels, electrocardiography, and chest X-ray.

Special investigations for diagnosis and planning of management include fecal occult blood test, carcinoembryonic antigen level, colonoscopy, biopsy and histopathological examination and contrast-enhanced computed tomography (CECT) of the abdomen. CECT chest was done in patients with findings of metastasis on chest X-ray. Disease was staged based on TNM staging system.

Patients meeting the inclusion criteria were given the standard treatment which includes surgery and chemotherapy. All surgeries were performed by the same team of two senior surgeons (including authors) and help from the third senior surgeon was taken in case of difficulty in the intraoperative period. Radical surgery, removing the tumour *en masse* with vessels first (medial to lateral) approach, was done in all the cases and R0 resection (microscopically negative resection margins) was achieved in all the operated cases. Chemotherapy was given based on the stage of the disease, and patient parameters.

Histopathological examination (HPE) (gross and microscopic) was performed on specimens collected in definitive surgery. Expression of Ki-67 was assessed by immunohistochemistry on formalin-fixed paraffin-embedded tumour tissue blocks. Representative tissue sections were examined for Ki-67 expression. Ki-67 labelling index was counted as fraction of the immunohistochemistry (IHC) positive nuclei observed

in viable tissue areas. All viable tissue areas (excluding the necrotic foci) in the representative sections were considered in this calculation.

The details and specifications of materials used for immunohistochemistry in the study were as follows

1) The VENTANA BenchMark XT autostainer
is composed of four main components that work together as a system comprised of the computer and its software, stainer assembly, automated fluidics assembly and waste bottle assembly. The Stainer assembly comprising of reagent carousel and various other parts performs processing of all slides which are identified by the system using unique bar codes.

2) Materials required
Poly-L-lysine coated slides, slide cradle, milk protein powder, any mild detergent, 100% alcohol, xylene, mounting medium

3) Labels and reporters
Antibodies used: ANTI: KI67, company: VENTANA, immunogen: Rabbit Monoclonal antibody, clone: SP6, type: ready to use, detection kit: Ultraview DAB IHC Detection Kit, control tissue: tonsil

Statistical analysis
Data was entered in excel sheets, compiled, validated and analysed using 27th (June 2019) version of SPSS software. Continuous variables were expressed as mean and standard deviations (SD). The presentation of the categorical variables was done in number and percentage (%). Continuous data were analysed using parametric tests as applicable and categorical data using nonparametric tests. The level of significance $\alpha = 0.05$ and P-value < 0.05 was considered statistically significant.

Results

A total of 93 diagnosed cases of CRC were included in this study. The average age of patients was 52.39 years (SD = 15.10) with a range of 53 years (27–80 years). There was a slight male preponderance in the study, with 48 (51.61%) male patients (Table 1).

The most common site of involvement was the recto-sigmoid region seen to be involved in 45 patients (48.39%) followed by right side involvement in 39 (41.94%).

Stage 3 disease was seen in 64.52% of the patients at the time of presentation. The most common stage was stage 3b seen in 36 patients (38.71%).

The average size (largest dimension) of the lesion was 5.54 cm (SD = 2.35 cm) with the maximum dimension of 11 cm seen in the study.

Adenocarcinoma was the most common histological subtype (70.97%) observed in the study, followed by mucinous adenocarcinoma (19.3%) and signet ring carcinoma (9.6%). Grade 1 (61.29%) disease was the most common occurrence at presentation followed by grade 2 (constituting 22.58%) and grade 3 lesions (16.13%). Nodal involvement was seen in 54 (58.06%) patients. Out of these 54 patients, only 3 patients had nodal status as N2, and N1 status was the more frequent occurrence.

Ki-67 expression analysis
The average Ki-67 expression was 77.66 (SD = 9.68%) with a range 60 to 90%. The Ki-67 percentage expression for the patients was assessed and

Table 1: General characteristics and tumour parameters

Parameter	Observation		
Age	<45 years	>45 years	
	33	60	
Site	right	left	rectosigmoid
	39	9	45
Stage	stage 1	stage 2	stage 3
	0	33	60
Node	positive	negative	
	54	39	
HPE type	adenocarcinoma	mucinous adenocarcinoma	signet cell
	66	18	9
Grade	grade 1	grade 2	grade 3
	57	21	15

HPE – histopathological examination

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correlated with different clinical and demographic parameters. For correlation with different parameters and to assess statistical significance, the cut-off for Ki-67 expression was set at 70%.

Patient age

Patient age was found to be positively correlated to Ki-67 expression with a correlation coefficient of R=0.23. However, the results were not significant statistically (P=0.2176). On dividing the data into subgroups according to level of Ki-67 expression, 39/60 (65%) patients of age > 45 years had 80–90% Ki-67 expression, as compared to just 3/33 patients of age < 45 years. This result was found to be statistically significant (chi-square, df 11.39, 2) (P=0.0034).

Patient gender

There was no significant difference between the two genders in terms of the Ki-67 expression (77.83 vs. 77.50%, P=0.9212).

Tumour site

There was no significant difference between the lesions based on site in terms of Ki-67 expression. The difference was not significant statistically (P=0.8587).

Disease stage at presentation

It was seen that the Ki-67 expression was slightly higher for the stage 2 patients (78.41%) compared to stage 3 (77.25%). The difference was not significant statistically (P=0.7555).

Lymph node status

Patients with nodal involvement had a higher Ki-67 expression (78.33%) compared to those with no nodal involvement (76.73%). But the P-value was not suggestive of any statistical significance (P=0.6658).

Tumour size

It was seen that as the size of the lesion increased, the Ki-67 expression percentage also increased. The correlation coefficient R was 0.21 suggestive of a positive correlation. The P-value for this analysis was 0.3361.

Table 2: Histopathological subtypes vs. KiLI

	Histopathological subtypes	
KiLI	**adenocarcinoma**	**mucinous**
60–70	18	6
70–80	18	0
80–90	30	12
>90	0	0
	chi-square, df 8.369, 4, P-value 0.079	

KiLI – Ki labelling index

Histopathological type

It was seen that the signet ring carcinoma was associated with a lower Ki-67 average expression (66.67%) compared to the adenocarcinoma (79.05%) and mucinous carcinoma subtypes (78.75%). The results were not significant statistically (P=0.1329).

But on using 70% expression value as cut-off, significant difference was noted. 48 out of 66 (72.7%) adenocarcinomas and 12 of 18 (66.66%) mucinous adenocarcinomas had Ki-67 expression above cut-off as compared to signet ring cell variety, all (9 out of 9) of which had expressions below the cut-off. These differences were found to be statistically significant (P-value – 0.0470, chi-square – 6.115) (Table 2).

Tumour grade

It was observed that the average Ki-67 expression was highest for the grade 1 patients (79.47%) and decreased as the grade changed to grade 3 (70.50%). The difference was not significant statistically (P=0.2256).

Subdividing the grade 1 tumour according to stage at presentation, it was noted that 27/39 (69.2%) stage 3 tumours had Ki-67 expression more than 70% as compared to 9/18 (50%) of stage 2 tumours. Within grade 2 tumours 9/9 of stage 3 tumours had Ki-67 expression above 70% as compared to 9/12 (75%) of stage 2 tumours. This difference was not statistically significant. Similar analysis on grade 3 tumours however yielded a statistically significant difference.

Table 3: Tumour stage vs. KiLI

	Grade 1 tumours		Grade 2 tumours		Grade 3 tumours
KiLI	stage 2	stage 3	stage 2	stage 3	stage 2
<70%	9	12	3	0	0
≥70%	9	27	9	9	3
	P-value 0.4192 chi-square 0.6525		P-value 0.3496 chi-square 0.8750		P-value 0.0253 chi-square 5

KiLI – Ki labelling index

All 12 of stage 3 tumours in our study had less than 70% Ki-67 expression as compared to higher expression in the single stage 2 tumour (Table 3).

Discussion

Ki-67 immunostaining patterns have been found to correlate well with tumour growth fraction and S phase fraction in various human malignancies; however, correlation with clinicopathologic parameters has been inconsistent (Scholzen and Gerdes, 2000). Some studies showed a significant correlation of Ki-67LI with clinically important prognostic pathologic parameters in colorectal carcinomas such as tumour differentiation, metastatic disease, and local invasiveness, whereas other studies showed no such correlation (Saleh et al., 2000; Melling et al., 2016). This lack of correlation is owing to the considerable heterogeneity of colon carcinoma (Saleh et al., 2000).

In the present study, Ki-67LI with a cut-off of around 70% yielded meaningful results. This cut-off is towards the higher side according to existing literature where cut-offs range from 5 to 62% (Scopa et al., 2003; Yoshimura et al., 2003).

We found a statistically significant higher expression of Ki-67 in tumours of patients > 45 years age as compared to those < 45 years (P=0.0034). Our finding of a positive correlation of Ki-67 expression with the increasing age of the patient (R=0.23) is similar to what has been reported previously by various authors (Lin et al., 2008; Li et al., 2016). This finding however is contradictory to our hypothesis in the sense that classically CRC in younger patients is known to be aggressive and thus further study is required to better analyse the correlation.

Our results found no statistically significant correlation between the site of lesion and Ki-67 expression. This again is in concordance with results in available literature (Melling et al., 2016). Carcinomas involving the rectosigmoid region were found to have a higher Ki-67 expression as compared to the other sites. This finding was not statistically significant. This finding has not been observed earlier by other authors and requires further evaluation.

We did not get any statistically significant difference in Ki-67 expression between TNM stage 2 and stage 3 tumours. Stage 2 tumours had slightly higher Ki-67 expression as compared to stage 3 tumours (average 78.41% vs. 77.25%). A large study on 1,800 patients reported the same finding with statistically significant results, whereas another study reported that high Ki-67 expression is associated with a higher tumour stage (Melling et al., 2016; Gayyed et al., 2021). Although overall results of the present study did not reveal any major trend, looking into various subgroups revealed the correlation between high Ki-67 and higher stage at presentation.

A positive correlation was observed between the tumour size and Ki-67 expression in our study (R=0.21), signifying that tumours with a higher mitotic rate tend to present with a bulkier disease. This result is in line with the previous reports (Saleh et al., 2000; Nussrat et al., 2011). In an existing study on colorectal adenomas, it has been reported that higher Ki-67 correlates well with size even in the case of adenomas (Nussrat et al., 2011).

In our study, we found that adenocarcinomas and mucinous adenocarcinomas had higher Ki-67 expression as compared to signet ring cell type. This difference was also found to be statistically significant (P=0.047) with 72% and 66% of adenocarcinomas and mucinous adenocarcinomas, respectively having Ki-67 expression > 70%, as compared to none of signet ring subtype. Similar findings could not be found in the existing literature.

Tumours having less aggressive morphology but the higher stage at presentation were also found to have higher Ki-67 expression. This again might signify the value of Ki-67 expression as a marker of aggressive tumour behaviour in CRC and its ability to identify low-grade tumours with advanced stage and aggressive behaviour (Ma et al., 2010).

We also observed that 9/12 tumours with poor morphology (histopathological grade 3) had lower Ki-67 expression. Despite this, these tumours had a higher stage at presentation. (All 9 signet ring carcinomas in our study were grade 3, stage 3 tumours. All nine also had very low Ki-67 expression of below 70%.) This again signifies that poor histological grade does not necessarily mean higher mitotic activity within the tumour. These tumours are aggressive due to some other reason (like poor cellular cohesiveness) than higher mitotic index which needs further evaluation by a larger and detailed study.

Analysis of tumour grade revealed a negative correlation between the grade of tumour and Ki-67 expression. One study reported a statistically significant positive correlation (P=0.0007) (Saleh et al., 2000). Another previous study reported the opposite finding, but their result also was not statistically significant (P=0.21) (Gurzu et al., 2007). Another study reported a statistically significant positive correlation between Ki-67 and higher dysplasia grades (Stromar and Jakic-Razumovic, 2014).

Though our results were not statistically significant, we observed that a large proportion of these low-grade tumours also had a higher stage at presentation (48/72 of grade 1 and 2 tumours were stage 3 at presentation). This might be due to the difference

between mitotic activity and morphological grading of tumours and requires further evaluation with a larger study. One study in the literature search found a positive correlation between these two parameters, yet another reported results similar to our finding (Saleh et al., 2000; Ma et al., 2010). Another study failed to find any correlation (Melling et al., 2016). Higher Ki-67 expression in tumours with low HPE grade but the higher stage at presentation was found to be correlating. Advanced tumour stage at presentation despite low histopathological grade might signify that histopathological grading alone does not present the complete picture. High Ki-67 expression if considered separately indicates aggressive tumour behaviour (Scholzen and Gerdes, 2000). Using it as an adjunct in histopathology analysis might help risk-stratify patients in a better way. Histopathological grading only tells about the morphology of tumours, and regular staining studies can't detect the mitotic rate of tumour tissues (Scholzen and Gerdes, 2000). Measuring Ki-67 expression thus is important and can detect highly mitotic tumours with dormant morphology.

It was seen that the Ki-67 expression was slightly higher for the stage 2 patients (78.41%) compared to the stage 3 (77.25%). The difference was not significant statistically (P=0.7555). These observations might have occurred due to the small study population and also the fact that stage 3 patients constituted 64.5% (60/93) of the group. But as mentioned previously within the subgroups classical adenocarcinoma and grade 1 tumours higher stages were observed to be correlated to high Ki-67LI.

Lymph node involvement was also noted to be positively correlated with Ki-67 expression. This observation though statistically non-significant is in line with multiple previous studies (Ishida et al., 2004; Martins et al., 2015).

Our study though providing valuable insights is limited by a small sample size. Larger studies are thus needed to verify and standardise the hypothesis.

Conclusion

Finally, we conclude that rather than using it as a blanket all or non-prognostic marker, Ki-67 expression in CRC should be used as an adjunct to standard histopathology, as it measures the growth fraction of the neoplasm and reflects progression of the tumour. Existing standard diagnostic protocols are limited by morphological features of the tumour specimen. Morphological features classically used to describe aggressive tumours are not necessarily present in all mitotic tissue. Thus, using Ki-67 as a marker signifying cell division provides additional information, over and above the morphological features characteristic of malignant behaviour. This can help by identifying tumours which have seemingly less aggressive morphology, but are physiologically rapidly dividing. This subset of tumours would be labelled as less aggressive variants if only morphology is relied upon. This information might prove helpful to devise aggressive management protocols and prognostic criteria for the tumours having higher Ki-67 expression.

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Navigating the Risks of Dental Aspiration in Older Adults: A Case Study of Prompt Diagnosis and Intervention

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Abstract: Foreign body aspiration is a significant cause of respiratory distress in geriatric patients, often leading to severe complications if not promptly identified and treated. Dental materials account for approximately 15–20% of foreign body aspirations in adults, with symptoms that can include dyspnea, localized wheezing, and, in some cases, cyanosis and pneumonia. We report the case of a 60-year-old man who aspirated a dental crown, resulting in shortness of breath. A computed tomography scan revealed the crown lodged in the left main bronchus. The patient underwent successful bronchoscopy for foreign body removal and experienced a full recovery without complications. Neurological conditions, such as epilepsy or Parkinson's disease, increase the risk of aspiration, particularly in elderly patients, in which symptoms may be misdiagnosed due to their nonspecific presentation. While the right bronchus is more commonly affected due to anatomical structure, foreign body aspiration in the left bronchus also warrants attention. This case underscores the importance of rapid imaging and bronchoscopy to reduce the risk of morbidity and mortality from aspiration events. Increased awareness and timely intervention are essential for improving patient outcomes in cases of dental and other foreign body aspirations in older populations.

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Introduction

Foreign body aspiration is a common cause of respiratory distress, particularly among geriatric patients, and can be life-threatening (Lin et al., 2014). Dental aspiration accounts for approximately 15–20% of all foreign body cases in adults. Symptoms may include reduced vesicular breath sounds, localized wheezing, pneumonia, dysphonia, dysphagia, asphyxia, cyanosis, dyspnea, fatigue, fever, hypertension, and tachycardia. Dental aspiration can cause airway obstruction, and in severe cases, asphyxia death and cardiac impairment (Xu et al., 2023).

These symptoms may mimic other respiratory diseases such as pneumonia or bronchitis, or even an exacerbation of an underlying geriatric disease (Lin et al., 2014). Clinical presentation on elderly patients may be obscure, probably due to its nonspecific symptoms and history, delay on bronchoscopy intervention and other reasons. Identification and removal of foreign body is of utmost importance to avoid complications as: pneumonia, hemoptysis and granulation tissue (Lin et al., 2014). A long time dental foreign body in the bronchus can result in tissue changes like edema, pressure necrosis, inflammatory response, increased bronchial wall vulnerability. Due to the radiopaque nature of dental materials, suspected cases of dental aspiration should be promptly evaluated with a chest X-ray or computed tomography (CT) scan (Xu et al., 2023).

Here, we report the case of a 60-year-old man with shortness of breath after accidental dental crowning resolved with bronchoscopy.

Case report

A 60-year-old man presented to the emergency department with sudden-onset shortness of breath following the accidental aspiration of a dental crown approximately 10 minutes prior. His medical history included systemic arterial hypertension and diabetes mellitus, both of which were under regular treatment. On physical examination, the patient was alert and hemodynamically stable, with a blood pressure of 144/87 mm Hg, a heart rate of 99 beats per minute, and an oxygen saturation level of 93% on room air. Despite his complaints of dyspnea, pulmonary and cardiac auscultations were unremarkable, with no wheezing, stridor, or abnormal heart sounds detected.

CT scan of the chest was promptly performed, revealing the presence of a foreign body – a tooth crown – lodged in the left main bronchus (Figure 1). This finding corroborated the patient's clinical history and provided clear localization of the aspirated object. Given the risk of airway obstruction and potential complications such as atelectasis, infection, or bronchial injury, immediate intervention was deemed necessary.

The patient was taken for urgent bronchoscopy under sedation, during which the dental crown was successfully retrieved from the bronchial lumen without any complications. Post-procedure, the patient reported significant relief of his symptoms. Following a brief period of observation to ensure stability and absence of any respiratory or procedural complications, he was discharged home in good condition. He was advised to follow-up with his dentist for further evaluation and management of his dental prosthesis.

Informed consent for the publication of this case report and accompanying images was obtained from the patient.

Discussion

Neurologic injuries affecting the airways, seen in conditions such as Parkinson's disease, seizures, and altered mental states caused by alcohol, drugs, and sedatives, as well as during dental procedures and trauma resulting in loss of consciousness, are the most frequent causes of foreign body aspiration in adults (Jeon et al., 2021). Some of traumatic event's causes are: maxillofacial trauma, oral surgery with general anesthesia, adenotonsillectomy, dental extraction and endotracheal intubation (Xu et al., 2023).

Patients with epilepsy are predisposed to aspiration because of impaired cognition, seizures, suppression of cough and swallowing reflexes by sedatives and laryngeal function (Xu et al., 2023). Specially in geriatric patients, the incidence of foreign body aspiration increases with advancing in age, and aspiration can cause life threat (Lin et al., 2014). Foreign body in the airways of elderly people are frequently diagnosed as a result of pneumonia condition or respiratory failure needing to be removed rapidly (Ishimoto et al., 2021). The incidence of foreign body aspiration is particularly higher in long-term residential mental health facilities (Kim, 2014).

Although the right bronchus is more commonly affected (60% of cases), healthcare professionals should also be vigilant for foreign bodies in the left bronchus, which occur in 40% of cases (Jeon et al., 2021). The right main bronchus is more predisposed to foreign body impaction because it is larger and has a more direct continuation of the trachea compared to the left main bronchus. The angle between the right bronchus and the trachea is approximately 20–25°, whereas the angle for the left bronchus is about 40–50° (D'Addio et al., 2022). Health professionals must be alert to

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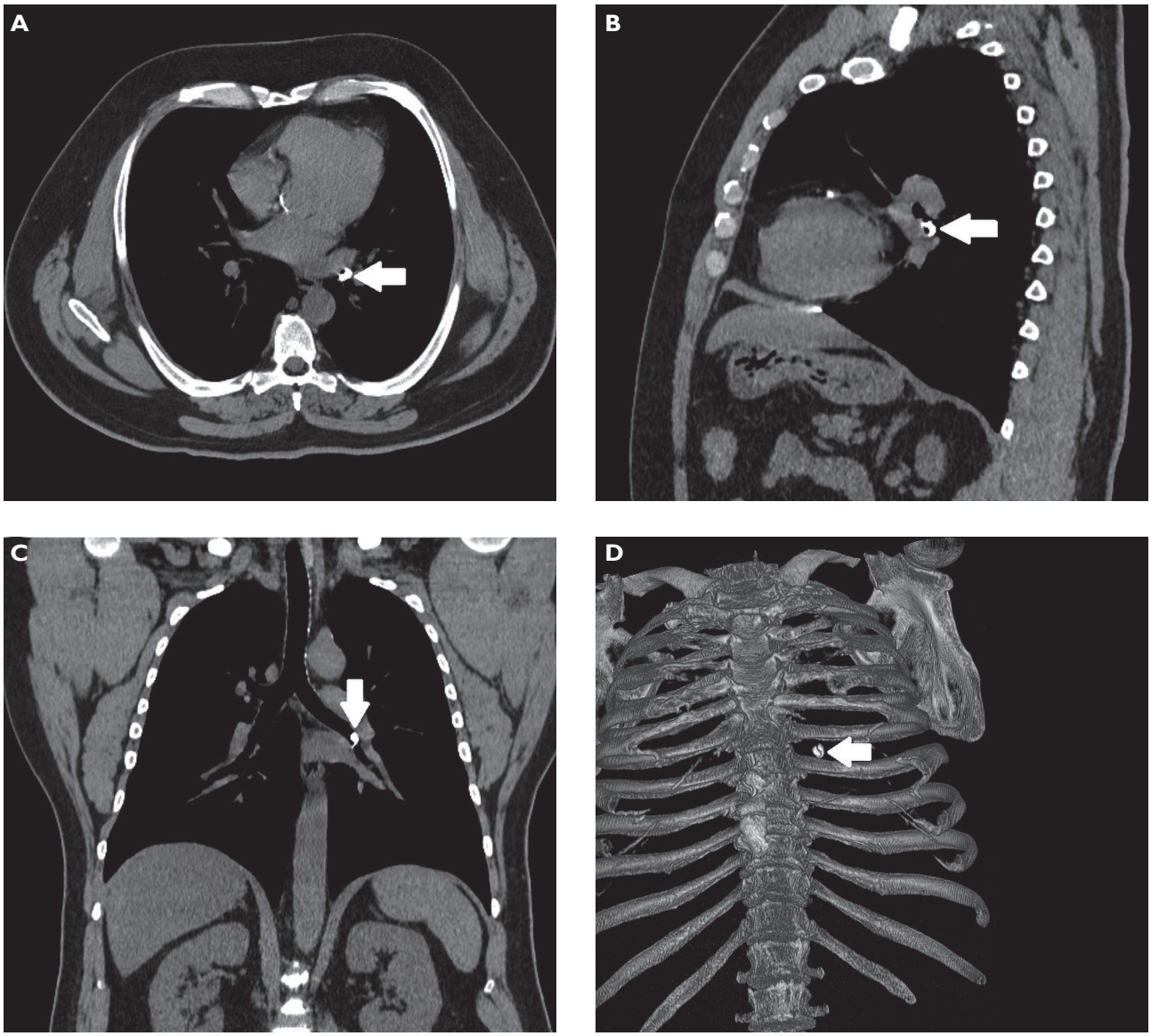

Figure 1: Computed tomography in the axial (A), sagittal (B) and coronal (C) sections, in addition to 3D reconstruction (D) demonstrating a dental crown in the left main bronchus (white arrows).

cases of foreign body in the left bronchus, even if this is not the most common (Bittencourt and Camargos, 2002).

CT scan reveals a foreign body as a dense structure within the bronchial lumen. Additionally, secondary changes such as volume loss, bronchiectasis, and hyperlucency due to air trapping are clearly visualized on a thoracic CT scan (Keny and Kakodkar, 2016). Fortunately, due to the prompt treatment of the patient in this case, none of these complications occurred. Bronchoscopy is the preferred method for diagnosing and removing airway foreign bodies because it is easy to use and typically requires only minimal general anesthesia. The bronchoscopy significantly reduces the mortality rate from aspiration from 50% to less than 1% (Jeon et al., 2021).

Conclusion

Foreign body aspiration, particularly of dental materials, poses a serious risk in geriatric patients, as it can mimic other respiratory conditions and lead to complications if not promptly identified and treated. This case of a 60-year-old man who aspirated a dental crown highlights the critical role of early imaging and intervention in preventing severe outcomes. Despite the left bronchus being less commonly affected than the right, this case reinforces the importance of vigilance in all bronchi, as swift diagnosis and bronchoscopy can prevent further complications such as pneumonia, tissue damage, and respiratory failure. Given that dental aspiration may occur during routine procedures and in patients with predisposing neurological conditions, health

professionals must consider foreign body aspiration in cases of unexplained respiratory symptoms. Prompt bronchoscopy remains the gold standard for foreign body removal, significantly reducing mortality and morbidity. This case underscores the need for increased awareness and preparedness in managing dental aspiration cases, especially in high-risk groups, to optimize patient outcomes.

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Subacute Sclerosing Encephalitis in an Adult with Congenital HIV Infection – Case Report

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Abstract: Subacute sclerosing panencephalitis (SSPE) is the result of a chronic infection of the central nervous system caused by a mutated measles virus. We present a case of SSPE in a 19-year-old female with congenital HIV-infection. The patient has been using antiretroviral therapy regularly since she was 4 years old. At the age of 15, she contracted measles of moderate severity. At the age 17, she had the HIV viral load < 20 copies/ml and the CD4 count 420 cells/μl. Three years after measles, bilateral necrotizing retinitis developed, and five months later, myoclonic seizures of the left limbs. Symptoms progressed gradually, with fever, generalised seizures, and lost consciousness. She was hospitalized in department for treatment patient with HIV-infection. Magnetic resonance imaging of the brain revealed massive areas of the altered signal without clear contours in both hemispheres of the brain, which captured the white and grey matter of the fronto-parietal, temporal-occipital lobes. The electroencephalography showed the flashes of slow-wave paroxysmal activity of the brain in the delta range, mainly in the fronto-parietal area. In the cerebral spinal fluid, anti-measles IgG was detected at a titre of 3738,408 U/ml, and in the blood – 9.4 U/ml. A diagnosis of SSPE was established. Supportive, corticosteroids and anticonvulsant treatment were ineffective. Patient died 10 months after the onset of the disease. Therefore, measles at any age in a person with congenital HIV-infection poses a risk of developing SSPE.

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Introduction

Subacute sclerosing panencephalitis (SSPE) is a severe, fatal nervous system lesion associated with the measles virus. It is caused by a mutated measles virus that constantly replicates in the cells of the nervous system. It is accompanied by damage to the white and grey matter of the brain, sometimes the thalamus, brainstem and spinal cord. The largest number of cases of SSPE was registered in children who contracted measles under age of 5. The frequency is 1:1,367 if children were affected under 5 years old, and 1:609, if they were under 12 months old. SSPE may occur after median latency period 9.5 years (2.5–34 years) at a median age of 12 years (3–35 years). Men get sick more often than women by 2.4 time (Wendorf et al., 2017). The incidence of SSPE in the world varies from 0.2 to 40 cases per million population per year and depends on the measles vaccination coverage in different countries (Alexander et al., 2020). Vaccination shortages in US (United States) led to an increase in measles incidence to 120 per million in 2019, the highest level since 2001 (Phadke et al., 2020). During COVID-19 epidemic in the UK (United Kingdom), the number of people vaccinated against measles-mumps-rubella in 2020 was 19.8% lower compared to 2019 (McDonald et al., 2020).

The pathophysiology of the disease is not fully understood, but there is evidence that the virus that causes SSPE is a hypermutated measles virus. Compared to the wild-type strain mutations involve the matrix protein (M), hemagglutinin (H), nucleocapsid (N) and membrane fusion protein (F) genes. The mutated protein F plays an exceptional role in the spread of the virus in nerve cells. The definitive receptor for the penetration of the virus into the nerve cell is unknown, perhaps it is a neurokinin-1 receptor (substance P is the mediator of the neurokinin-1 receptor), which are densely represented in interneuron synapses (Watanabe et al., 2019). It is suggested that presentation of cell adhesion molecule 1 (CADM1) and CADM2 on neuronal membrane may promote membrane fusion and the spread of measles virus (MeV) in cells. However, the exact mechanism of neuronal infection and virus spread in nervous tissue remains unknown (Shirogane et al., 2021; Takemoto et al., 2022).

Inadequate cellular immune response plays a crucial role in pathogenesis. This leads to the survival of the virus in the cells of the nervous system despite the strained humoral immunity. There is a lack cytokines of cellular immunity such as INF, IL-2, Il-10, Il-12, and excess levels of IL-4 and IL-1b, which stimulate factors of humoral immunity. Therefore, premature switching of the cellular immune response to the humoral one leads to a loss of the ability to eradicate the virus from the nerve cells (Hübschen et al., 2022).

Pathological examination of the brain reveals numerous glial nodules in the grey and white matter of the hemispheres, in brainstem and cerebellum ("nodular panencephalitis") with focuses of demyelination in subcortical formations (leukoencephalitis). Perivascular lymphomonocytic infiltration, damage and degenerative changes of neurons, and proliferation of glia were revealed. Apoptosis and oxidative stress may contribute to early neuronal damage, while lipid peroxidation and impairment glutamate transport can cause subsequent neurodegeneration (Kramarev et al., 2018). Clinical manifestations appear on average 6 years after infection with the measles virus. The disease progresses relentlessly and ends in death. It usually lasts from 6 months to 2–3 years. The clinical course of the disease includes 4 stages:

- stage I – personality changes, failure at school, strange behaviour;
- stage II – massive, repetitive, and frequent myoclonic jerks, seizures and dementia;
- stage III – rigidity, extrapyramidal symptoms, and progressive lack of unresponsiveness;
- stage IV – coma, vegetative state, autonomic failure, and akinetic mutism (Kramarev et al., 2018).

The literature describes the development of necrotizing retinitis against the background of subacute sclerosing panencephalitis. In most cases, retinitis with loss of vision joins later, already in the advanced stages of the disease (Fisher et al., 2015; Rana et al., 2023). Initially, one-sided damage to the eyes is possible, but the process quickly becomes bilateral and after 2 months ends with retinal atrophy of both eyes (Agarwal et al., 2017). In young adults, the disease does not progress as quickly as in children, but is also characterized by behavioural changes, cognitive deficits, and progressive neurological symptoms (Martins et al., 2018).

Electroencephalography (EEG) shows characteristic changes: periodic discharges of slow, spike-end waves of high amplitude every 3–8 seconds, which are replaced by short periods of reduced activity. EEG has diagnostic value in the myoclonic phase. The first type of EEG is characterized by periodic complexes consisting of bilateral, symmetrical, synchronous, high-voltage (200–500 mV) bursts of polyphasic, stereotyped delta waves. These complexes are regular with an interval of 4–10 seconds and correspond to myoclonic jerks. The second type of EEG is less common and is characterized by periodic slow giant delta waves combined with rapid spike activity. Type III is periodic, characterized by a long spike wave of discharge interrupted by giant delta waves. This type

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is characterized by rapid progression of the disease (Garg et al., 2022).

Neuroimaging in SSPE is not specific. In the early stages of the disease, brain magnetic resonance imaging (MRI) is usually normal. The first manifestations of a diffuse hyperintense signal occur in the white matter of the posterior parts of the cerebral hemispheres, especially in the parietal-occipital and posterior temporal regions, and later it moves to the frontal lobe, corpus callosum, and basal ganglia. Early involvement of grey matter in the pathological process is observed. The pathological process ends with cerebral atrophy. The final diagnosis requires the demonstration of elevated titres of antibodies against measles in the cerebrospinal fluid (CSF) (Garg et al., 2019).

Many drugs have been used to treat and stabilize the course of the disease, but without evidence in randomized clinical trials. Ribavirin, inosine pranobex, or intravenous human immunoglobulin were used. The combination of inosine pranobex and intrathecal administration of alpha interferon gave the best effect in relieving the symptoms of the disease (Sliva et al., 2019; Papetti et al., 2022).

Cases of subacute sclerosing measles panencephalitis in HIV-infected patients are described infrequently, mostly in children with congenital HIV infection. Moreover, children suffered from measles in early childhood. For example, a case of SSPE in a 17-year-old boy with congenital HIV infection and effective antiretroviral therapy (ART), who contracted measles at the age of 1.5 years. The disease developed rapidly and ended fatally 12 weeks after the onset (Sivadasan et al., 2012). There is an opinion that clinical course of SSPE depends on the degree of HIV-associated immunosuppression (Muthusamy et al., 2015).

During 2017–2018, the many incidences of measles occurred in countries of EU (European Union). For example, there were 8,274 cases in Romania, 4,885 cases in Italy, and 919 cases in Germany. In Ukraine at that time (until September 2018), 30,744 people fell ill including 18,136 children and 12,608 adults. Complications from the nervous system in the form of meningitis, meningoencephalitis, and delayed damage to the CNS (central nervous system) by the measles virus occurred in 1/1,000 patients (Prokopiv et al., 2019). According to medical records in one of retrospective study in Ukraine, 15.1% patients did not receive any dose of measles vaccine, 26.5% received 1 dose at childhood age, 15.9% had 2 doses, and in 42.5% of cases vaccination information was missing (Pryshliak et al., 2020). Since 2014, less than half of Ukrainian children have been vaccinated against measles. According to UNICEF in Ukraine, the number of children under year old, which vaccinated against measles, does not exceed 42% (Andreychyn, 2020). Therefore, the main reason of measles outbreaks in Ukraine in recent years was the low level of vaccination.

Case report

Female, 19 years old, was born on January 14, 2004. The HIV infection was diagnosed in the girl at the age of 2 years (2006), through index testing after the diagnosis of HIV infection in her mother. At the age of 4 years, on August 3, 2008, she started ART with scheme AZT+3TC+LPV/rtv. In 2019, at the age of 15, she suffered from measles, of moderate severity. In 2019, the CD4 count was 280 cells/μl, and HIV viral load (VL) was < 20 RNA copies/ml. In 2020, the ART regimen was replaced by TNF+3TC+DTG. On March 29, 2022, the CD4 count was 420 cells/μl and VL < 20 copies/ml. In April 2022, visual disturbances appeared, there was no fever. She was hospitalized at the Ivano-Frankivsk Regional Clinical Infectious Disease Hospital, where the diagnosis was established: HIV infection, clinical stage II. Ophthalmologist (March 30, 2022) – neuroparalytic mydriasis, neuroretinitis of both eyes.

Blood tests for infectious agents: DNA of Epstein-Barr virus (EBV), *Toxoplasma gondii*, herpes simplex virus 1 or 2 type (HSV 1/2), cytomegalovirus (CMV), a-*Borrelia burgdorferi* IgM, IgG were negative. Chest X-ray, abdomen ultrasound, general clinical and biochemical tests were without specifics changes. Neurologist (March 31, 2022) – no focal neurological symptoms were detected. MRI of the brain (March 31, 2022) – no pathological changes in the signal of the brain substance were detected.

She was examined twice at the Institute of Eye Diseases in Odesa, Ukraine. The diagnosis was the same and the treatment was unsuccessful. Her health gradually worsened, irritability and personality disorders appeared, her memory and academic performance at the university deteriorated.

In September 2022, in the 5th month of the onset of retinitis, twitching in the left hand and the left corner of the mouth and dysmetria of the left hand appeared. She was observed by a neurologist. Tendon reflexes were brisk on both sides symmetrically. No pathological foot reflexes were found. Stato-coordinator tests were satisfactory. The diagnosis was established – symptomatic epilepsy with focal motor seizures with awareness (left-sided myoclonus?). On September 9, 2022, levetiracetam 500 mg twice a day was prescribed.

EEG was performed three times with the conclusion: outbursts of slow-wave paroxysmal activity in the

delta range with an amplitude of 300 μV, mainly in the fronto-parietal area with a transition to the temporal and occipital areas, which coincided with involuntary muscle contractions of the left limbs. The condition improved somewhat, myoclonus decreased, but there was crying, a change in mood. The neurologist regarded this as a side effect of levetiracetam and added lamotrigine 50 mg 2-time a day, but there was no effect. On November 10, 2022, clonazepam 1 mg twice a day was additionally introduced into the treatment regimen. In relation to myoclonus, the condition improved significantly but temporarily. However, the patient's condition gradually worsening, generalized convulsions appeared. In December 2021, the body temperature periodically rose to 40.0 °C, the convulsions did not stop, the disturbance of consciousness increased. In December 2022, severe stiffness of the left limbs and spasm of the muscles of the right half of the face, tonic convulsions of the limbs, severe hyperthermia (up to 40.0 °C) with pronounced oiliness and sweating of the skin appeared. She was hospitalized on January 21, 2023 – in the Communal non-commercial enterprise "Center of Infection Diseases of Ivano-Frankivsk Regional Council". During hospitalization, the patient's condition was severe, she was unconscious with readiness for convulsions, her body temperature was 38 °C.

A preliminary diagnosis was established: HIV infection, clinical stage IV. Meningoencephalitis is probably toxoplasmic. Signs of retinal degeneration. Symptomatic epilepsy. Oropharyngeal candidiasis. Bilateral pneumonia? Tuberculosis?

Trial antitoxoplasmosis therapy was prescribed: dalacin 600 mg 4-times a day, TMP/SMX-480 4 tablets 3-times a day. Also, fluconazole 200 mg per day, and dexamethasone 16 mg daily intramuscularly for 7 days, then 12 mg for 5 days, after that 8 mg. Sibazon was prescribed as an anticonvulsant.

Blood analysis for infectious agents (January 21, 2023): CMV DNA, HSV 1/2 DNA, EBV DNA, *Toxoplasma gondii* DNA, *Mycobacterium tuberculosis* DNA were negative. Blood ELISA tests (January 22, 2023): a-CMV IgG – 9.42 (with a norm 0.8–1.0), and a-CMV IgM, anti-*Toxoplasma gondii* IgG and IgM, anti-HSV 1/2 IgG and IgM, a-*Chlamydia trachomatis* IgG and IgA, anti-HBsAg, anti-HCV total Ig, antibodies to *Treponema pallidum* were negative. In blood D-dimer was 300 ng/ml (N < 250 ng/ml) (on January 24, 2023). The HIV viral load was determined to be ≤ 20 copies/ml and CD4 T-cells count was 218 cells/μl (January 21, 2023). Complete blood count (CBC) on 21.01.23 and 30.01.2023 were normal.

CSF (22.01.2023): volume – 0.5 ml, colourless, transparent, Pandey's test – negative, cytosis – 4 per μl, lymphocytes – 76%, segmented cells – 24%. PCR examination of CSF: DNA CMV, EBV, and human herpes viruses (HHV) – 1, 2, 3, 6, 7 types, MBT (*Mycobacterium tuberculosis*), *Toxoplasma gondii* were negative. Bacteriological examination of CSF – culture without growth. Microscopy for cryptococcus was negative, no cryptococcal antigen was detected.

Chest X-ray twice (at 21.01.2023 and 23.01.2023) – no pathology was found. Abdominal ultrasound (23.01.2023) – moderate diffuse changes in the liver and pancreas were found. Ultrasound of the heart (23.01.2023) – no pathologies were detected.

Ophthalmologist (01.23.2023) – anisocoria, neuroretinitis of both eyes. Neurologist (01.23.2023) – meningoencephalitis? Symptomatic epilepsy. MRI of the brain is recommended.

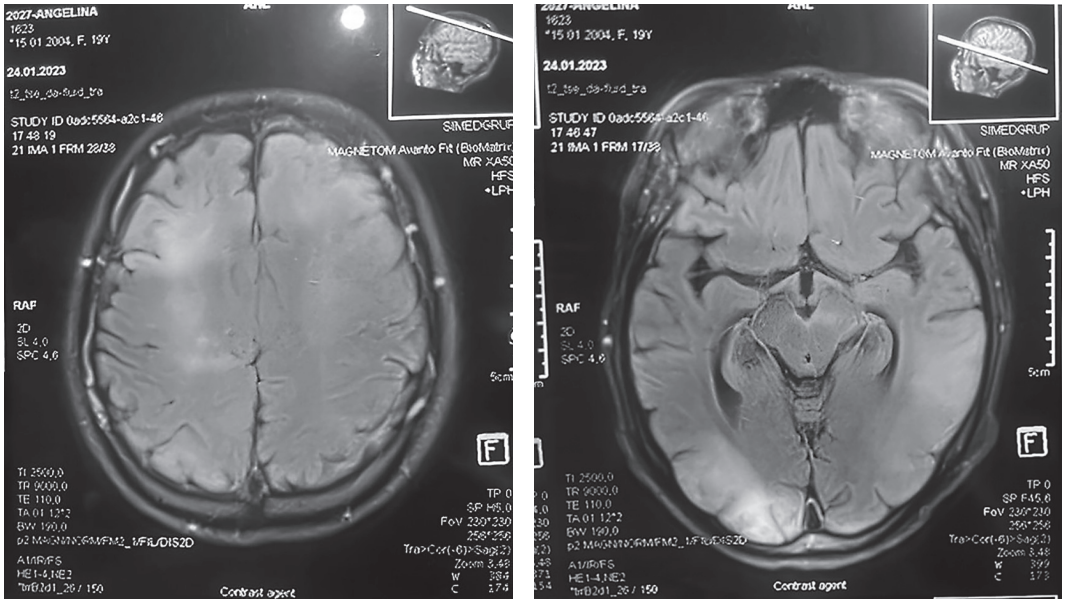

Figure 1: Brain magnetic resonance imaging of a 19-year-old perinatal HIV-infected female with subacute sclerosing panencephalitis.

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MRI of brain (24.01.23): in both hemispheres, at the level of the fronto-parietal, temporal-occipital lobes, there are massive areas of the changed signal without clear smooth contours, which capture the white and grey matter of the brain, mostly weakly hyperintense. There is a weakly hypertense signal in the T2 and T2 TIRM modes, in the diffusion-weighted imaging (DWI) mode, slightly hypointense in the T1 mode. After intravenous contrast in the T1 mode, the presence of a slight contrast enhancement along the course of the gyri in the parietal-occipital area on the left side is noted. The middle structures are not displaced. In the right maxillary sinus, there is content up to 0.45 cm thick. Conclusions: MRI signs are more consistent with encephalitis in large hemispheres of the brain. Progressive multifocal leucoencephalopathy? Slightly pronounced left-sided maxillary sinusitis (Figure 1).

Anti-measles IgG was detected in CSF – 3738,408 U/ml and in the blood – 9.4 U/ml (01.02.2023).

Against the background of treatment, the patient's condition remained serious. Coma I-II. No positive dynamics were noted. The patient died on 02.02.2023.

Final diagnosis: HIV infection, III clinical stage. Subacute sclerosing panencephalitis, severe course. Symptomatic epilepsy. Neuroretinitis of both eyes, retinal degeneration, neuroplastic mydriasis. Oropharyngeal candidiasis.

Discussion

The special contingent of children with congenital HIV infection in Ukraine is quite significant. By the end of 2022, 3,334 children with congenital HIV infection were registered in Ukraine (Center for Public Health Kyiv, 2023).

According to the vaccination schedule, when the level of CD4+ T-cells is < 200 μl, live vaccines cannot be administered to HIV-infected children (Ministry of Health Protection of Ukraine, 2022). Therefore, many HIV positive children in country may not be vaccinated with measles, mumps and rubella vaccine (MMR).

After measles the insufficiency of cellular immunity in HIV-infected people can contribute to the replication of the mutated measles virus in the CNS (Hübschen et al., 2022). In patients using ART HIV replication in glial cells of the brain can continue despite aviremia in the blood and cause locally immunodeficiency in the brain (Wahl and Al-Harthi, 2023).

On the basis of the described case of the disease, it is possible to establish a risk of SSPE in persons who contracted measles in adolescence. This risk persists regardless of the number of CD4+ T-lymphocytes and the regular use of ART, because of all patient's cases describing in the literature regularly received ART (Sivadasan et al., 2012; Muthusamy et al., 2015). It is likely that the majority of childhood HIV-infected patients were vaccinated with MMR at 12 month or 6 years old, although reliable vaccination data are often not available (Muthusamy et al., 2015). In the reported case the possibility of vaccination the child at the age of 12 months also cannot be excluded, because of at that time the child was not diagnosed with HIV. So, there was no contraindication for MMR vaccination.

This patient suffered with measles at the age of 15 years, and 3 years later SSPE developed. On admission to the hospital the diagnosis of toxoplasmosis encephalitis was incorrect but acceptable at that time because of unknown etiology of brain lesion. Diagnosis of the IV stages of HIV was also incorrect, but corresponded to hypothetical toxoplasmosis encephalitis. Antitoxoplasma treatment was carried out 10 days and cancelled due to ineffectiveness.

The clinical picture of this case of the disease had its own characteristic. The disease began with severe chorioretinitis, marked loss of vision in both eyes and paralytic mydriasis. Other clinical manifestations were typical: personality disorders, loss of cognitive abilities, deterioration of academic performance, myoclonus, and in the terminal period loss of consciousness, comatose state and fatal outcome. The patient's disease lasted 10 months. The correct diagnosis of SSPE was established at the final stage of the disease, 4 days before death, because of lack of vigilance of physicians to such a pathology. The EEG study which registered a pathological delta rhythm and bursts of activity corresponding to myoclonus was quite informative. A confirmatory study was the detection of intrathecal antibodies to the measles virus in high titres.

Conclusion

Individuals with congenital HIV-infection are at risk for SSPE if they have a history of measles-like illness at any age. For the timely diagnosis of SSPE, it is necessary to conduct an examination of the cerebrospinal fluid and blood for the detection of intrathecal antibodies to the measles virus.

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Solitary Fibrous Tumour of the Spine: Case Report and Histopathological Review

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Abstract: Solitary fibrous tumour (SFT) is an uncommon type of spindle cell tumour that affects soft tissues. Due to the rarity of spinal SFTs, they are often overlooked by healthcare providers, leading to frequent misdiagnosis. The clinical signs of spinal SFT are not specific and can vary based on tumour size and location. Typically, the main symptom is localized pain, which can be associated with limb numbness and other symptoms caused by pressure. Computed tomography scan was used to assess the extent of tumour involvement in the spinal canal and to identify any affected tissues. Magnetic resonance imaging is the most sensitive imaging method, and it is usually similar to disc extrusion or sequestered disc fragments. Surgical removal is the primary treatment for spinal SFT, and additional therapies, such as chemotherapy and radiotherapy, are considered for cases in which the tumour is not fully resected or inoperable.

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Introduction

Solitary fibrous tumour (SFT) is a rare spindle cell soft tissue tumour. To date, fewer than 100 cases have been reported, predominantly in adults (range of 10–83 years; median of 51.5 years). The incidence was slightly higher in men than in women (56.4% vs. 43.6%). The rarity of spinal SFTs often leads clinicians to overlook their existence, resulting in misdiagnosis (Lang et al., 2018). SFTs can occur in various parts of the body, with 24.5% of them located in the central nervous system.

Among spinal locations, the thoracic spine is the most prevalent (56%), followed by the cervical spine (31%), and lumbar spine (13%) (Zhang et al., 2019; Verla et al., 2020). These tumours are mesenchymal in nature and may originate from dendritic mesenchymal cells, sharing a similar NAB2-STAT6 DNA fusion pattern with haemangiopericytoma (Lang et al., 2018).

Herein, we report the case of a 30-year-old male patient reporting of numbness in his legs, particularly on the left side, over the past year. Informed consent was obtained from the patient.

Case report

A 30-year-old male presented with a year-long history of progressive numbness in his legs, which appeared to be more pronounced on the left side. The symptoms had gradually worsened over time, prompting him to seek medical attention. Despite this, he did not report any significant motor deficits. Upon physical examination, there were no signs of weakness, and he was able to perform movements such as dorsiflexion on both sides with full strength. The sensory examination, however, revealed reduced perception of vibration sensation in the left leg when compared to the right leg, suggesting a sensory

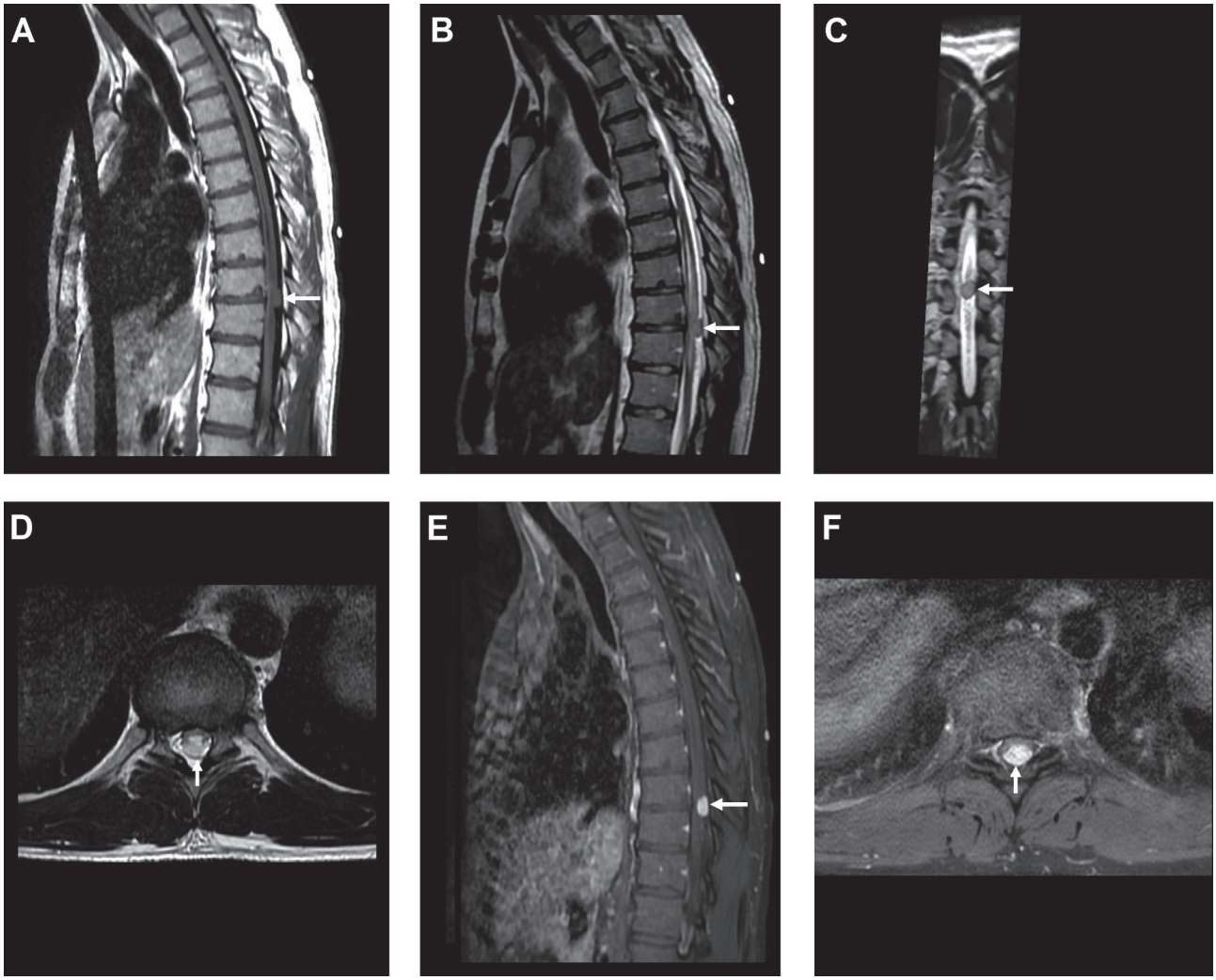

Figure 1: Thoracic spine magnetic resonance imaging. Sagittal T1 weighted-image (A); T2 weighted-image (B); coronal T2 weighted-image (C); axial T2 weighted-image (D); sagittal (E) and axial (F) T1 FAT SAT with contrast. Intradural extramedullary enhancing tumour located dorsally to the spinal cord at the T9-10 level (white arrows), with spinal cord infiltration and spinal cord edema/pre syrinx.

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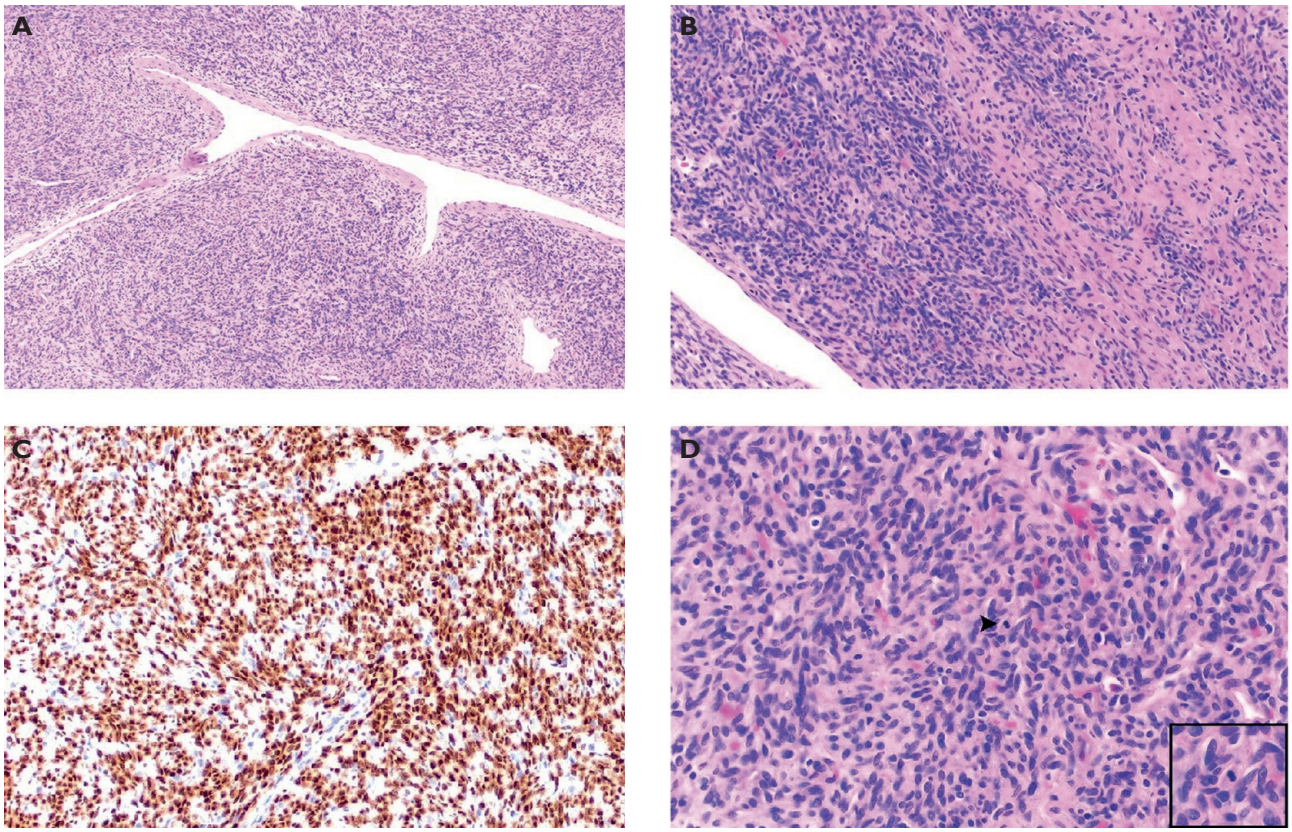

Figure 2: Histologic sections of solitary fibrous tumour. A) The tumour is composed of ovoid spindled cells and has scattered, thin-walled, dilated vessels with a "staghorn" appearance (haematoxylin [H] and eosin [E] stain, 200× magnification). B) The tumour shows regions of variable cellularity. Within regions of higher cellularity, the tumour cells are haphazardly arranged (left). Whereas in regions of lower cellularity, there is dense collagen deposition (right) (H and E, 200× magnification). C) Nuclear expression of STAT6 within the tumour cells (STAT6 immunohistochemical stain, 200× magnification). D) Haphazardly arranged tumour cells with a mitotic figure (arrowhead). The inset image on the right highlights the mitotic figure with greater magnification (H and E, 400× magnification).

disturbance. Despite this sensory loss, the patient was still able to walk independently without any assistance, and there were no abnormalities noted in his motor coordination.

Further neurological evaluation revealed hyperactivity of the deep tendon reflexes, particularly in the lower extremities, which suggested an upper motor neuron involvement. The absence of motor weakness and the patient's ability to ambulate independently were reassuring, but the sensory findings warranted further investigation into the cause of his symptoms.

To determine the underlying pathology, the patient underwent magnetic resonance imaging (MRI) of the spine. The imaging revealed an intradural extramedullary enhancing tumour located at the dorsal aspect of the spinal cord between the T9 and T10 vertebral levels (Figure 1). This location and the characteristics of the tumour raised concerns about a mass effect on the spinal cord or nerve roots, which could account for the sensory changes observed.

The tumour was subsequently surgically excised through a posterior approach. The operation proceeded without complications, and a biopsy was taken for further histopathological analysis. The results from the biopsy confirmed the diagnosis of a solitary fibrous tumour (SFT), classified as central nervous system (CNS) World Health Organization (WHO) grade 2. Molecular analysis revealed the presence of an NAB2-STAT6 gene fusion (NAB2-exon4:STAT6-exon2), a characteristic genetic alteration frequently seen in solitary fibrous tumours (Figure 2). This fusion is often associated with the pathogenesis of SFTs and provides valuable information for both diagnosis and potential therapeutic strategies.

Postoperatively, the patient experienced significant improvement in his sensory symptoms, with gradual restoration of vibration sensation in the left leg. Follow-up care, including regular MRI surveillance, will be necessary to monitor for any recurrence of the tumour. The patient's motor function remained intact, and he continued to walk independently, with no further deficits observed during his recovery.

Discussion

The clinical manifestations of spinal SFT are nonspecific and may vary depending on the location and size of the lesion. The primary symptom is often localized pain, which may be accompanied by limb numbness and other pressure-related symptoms. Although spinal SFTs are typically found in the intradural extramedullary area, they can also occur extradurally or intramedullary and are often accompanied by exophytic growth (Lang et al., 2018).

Computed tomography (CT) can be used to assess the extent of SFT involvement within the spinal canal and to determine any involvement of surrounding tissues (Zhang et al., 2019). However, MRI remains the most sensitive imaging modality, often demonstrating radiographic similarities to disc extrusion or sequestered disc fragments on T1- and T2-weighted imaging (displaying low signal intensity). Nevertheless, avid contrast enhancement is typically observed, indicating a well-circumscribed homogeneous lesion (Kim et al., 2020; Verla et al., 2020). Given its nonspecific clinical and radiographic features, spinal SFTs may resemble other pathologies, such as schwannoma, meningioma, and osteosarcoma (Verla et al., 2020). Biopsy or surgical resection is essential for accurate diagnosis (Lang et al., 2018).

Histopathologically, typical SFTs exhibit clear tumour cell boundaries with an uneven distribution of cell-rich and cell-sparse areas. Immunohistochemically, SFTs tend to express mesenchymal and vascular endothelium-related antigens, including CD34, CD99, vimentin, and bcl-2, and typically show negative staining for EMA, SMA, GFAP, and S-100. Moreover, recent studies have identified STAT6 as a characteristic tumour marker for SFT diagnosis, and the combination of STAT6 with CD34, CD99, and bcl-2 aids in the differential diagnosis of related lesions (Zhang et al., 2019).

The primary treatment for spinal SFT is complete surgical excision, with adjuvant therapies like chemotherapy or radiotherapy, considered for incomplete resections or inoperable cases (Kim et al., 2020). Approximately 10–20% of SFTs show invasive or malignant features, leading to recurrence or metastasis (Lang et al., 2018; WHO Classification of Tumours Editorial Board, 2021). Consequently, long-term follow-up is recommended for all SFTs (WHO Classification of Tumours Editorial Board, 2021). Although benign SFTs have a favourable prognosis, with a 5-year survival rate of approximately 100%, studies indicate that 63% of patients with malignant SFTs experience recurrence following surgery and succumb within two years (Lang et al., 2018).

Conclusion

SFT of the spine is a rare entity with fewer than 100 cases reported, making early diagnosis challenging. Its clinical presentation is often nonspecific, with symptoms such as localized pain or limb numbness, which can mimic other spinal conditions. Diagnosis relies heavily on imaging modalities like MRI, but histopathological analysis and immunohistochemistry, particularly markers such as CD34 and STAT6 are essential for confirmation. Complete surgical resection remains the primary treatment approach, with a generally favourable prognosis for benign cases. However, long-term follow-up is crucial due to the risk of recurrence, even in low-grade tumours, and the potential for distant metastasis in higher-grade cases. This report underscores the importance of considering SFT in the differential diagnosis of spinal tumours and highlights the need for awareness among clinicians to prevent misdiagnosis.

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Imaging Features of Prostate Sarcoma: A Case Report

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Key words: Prostate sarcoma – Prostate tumour – Imaging – Radiology – MRI

Abstract: A 54-year-old man presented to our clinic complaining of painful ejaculation. The patient underwent various imaging modalities, including ultrasound, transrectal ultrasound, prostate magnetic resonance imaging and positron emission tomography/computed tomography that detected a voluminous mass originating from the prostate. Histological examination diagnosed a prostate sarcoma, a rare mesenchymal tumour. This case offers an opportunity to evaluate a rare subtype of prostate cancer and to describe its main imaging features with an educational approach.

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Introduction

Prostate sarcoma is a rare malignancy arising from the mesenchymal tissues of the prostate gland. It accounts for about 0.1% of all prostate malignancies and typically arises in adults with an average age of 50 to 60 years (Ehat et al., 2023). The exact aetiology of prostate sarcoma remains obscure, although some cases have been associated with genetic predispositions, prior radiation therapy, and exposure to certain chemicals (Girling et al., 2007).

Patients with prostate sarcoma often present with nonspecific symptoms, such as urinary frequency, urgency, haematuria, and obstructive voiding symptoms. In advanced stages, patients may experience pelvic pain, lower back pain, weight loss, and constitutional symptoms indicative of systemic involvement. The insidious onset and lack of specific symptoms often lead to delayed diagnosis and advanced disease at presentation (Jaouani et al., 2023).

No reliable tumour markers for prostate sarcoma have been identified, with serum prostate-specific antigen (PSA) values usually normal due to the non-epithelial origin of these tumours (Arham et al., 2024).

Diagnosis of prostate sarcoma relies on a combination of clinical evaluation, imaging studies, and histopathological analysis. Transrectal ultrasound (TRUS), magnetic resonance imaging (MRI), and computed tomography (CT) scans are commonly employed to assess the extent of local invasion and detect distant metastases. Definitive diagnosis is established through prostate biopsy, with histopathological examination revealing characteristic features of sarcomatous tissue (Andreou et al., 2013).

Prostate sarcomas encompass a diverse group of histological subtypes. In children, the most common tumour type is a prostatic rhabdomyosarcoma (42% all prostatic sarcomas). In adults, leiomyosarcomas are most common (25% of all cases). Other types of prostatic sarcomas include sarcomatoid carcinoma; malignant fibrous histiocytoma; phyllodes tumour (also known as cysto-sarcoma phyllodes); undifferentiated stromal sarcoma of the prostate. Histological examination typically reveals spindle-shaped or pleomorphic cells with varying degrees of differentiation. Immunohistochemical analysis plays a crucial role in confirming the diagnosis and identifying specific markers associated with different subtypes (Andreou et al., 2013; Phuong et al., 2023).

Prostate sarcoma is associated with a poor prognosis, with five-year survival rates ranging from 20 to 40% depending on the histological subtype and stage of disease at presentation. Factors associated with worse outcomes include advanced age, large tumour size, high-grade histology, presence of metastases, and incomplete surgical resection. Despite aggressive multimodal therapy, local recurrence and distant metastases frequently occur, contributing to significant morbidity and mortality (Qin et al., 2023).

Treatment typically involves a multidisciplinary approach, including urologists, oncologists, radiotherapist, and radiologists. Surgical resection with wide margins remains the cornerstone of treatment for localized disease, although achieving negative surgical margins can be challenging given the propensity for local invasion. Adjuvant radiation therapy may be employed to improve local control and reduce the risk of local recurrence (Hodotsuka et al., 2023).

Case report

A 54-year-old male patient presented to our department complaining of painful ejaculation for a couple of years. He did not report haematuria, and he had no significant past medical history. Laboratory tests including PSA were within normal ranges. A trans-abdominal prostate ultrasound (US) was performed (Figure 1).

The US findings necessitated a specialist urological evaluation. The patient underwent a transrectal US (TRUS) examination (Figure 2).

A prostate MRI (1.5T) performed before and after contrast administration was necessary to better characterize the mass, evaluate its relationships with surrounding structures and exclude their infiltrations. The protocol included multiplanar T1-weighted, T2-weighted, diffusion-weighted imaging (DWI) with apparent diffusion coefficient (ADC) mapping, 3D chemical shift imaging (CSI) sequences (Figures 3–5).

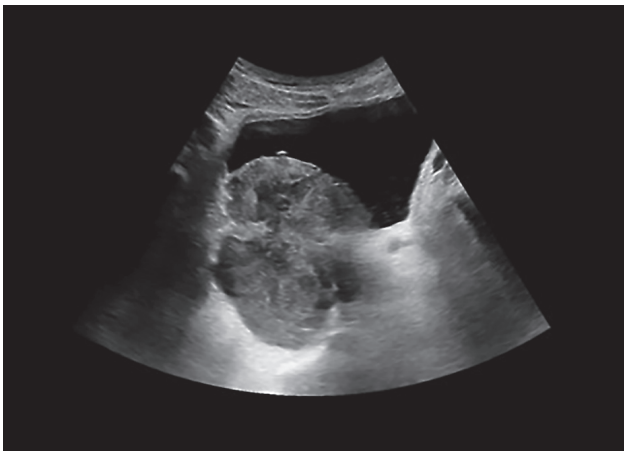

Figure 1: Prostate ultrasound image showing a prostate significantly increased in size (about 7 cm) due to the presence of a voluminous mass in the apical area, with mixed echogenicity, which imprinted and compressed the posterior bladder wall.

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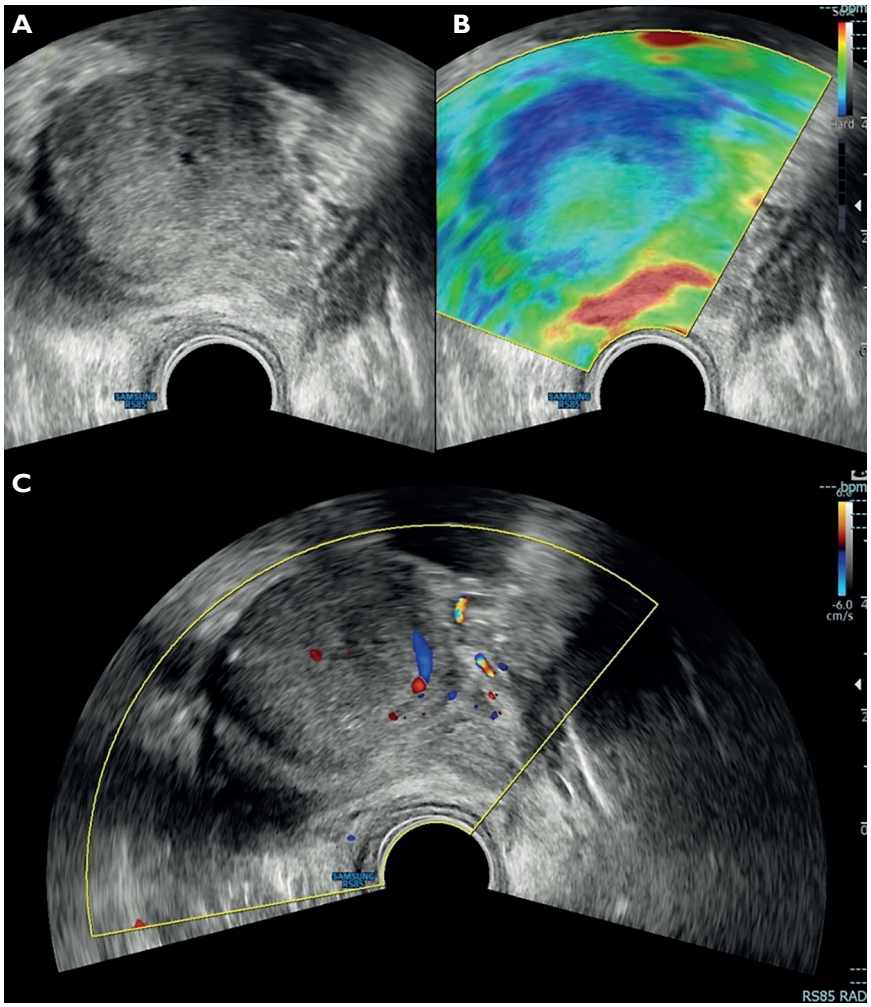

Figure 2: (A–C) Transrectal ultrasound confirmed the presence of a voluminous prostatic mass (A), with solid component showing intense blue colour on elastographic evaluation (B) and intralesional vascularization on colour Doppler evaluation (C), highly indicative of malignancy.

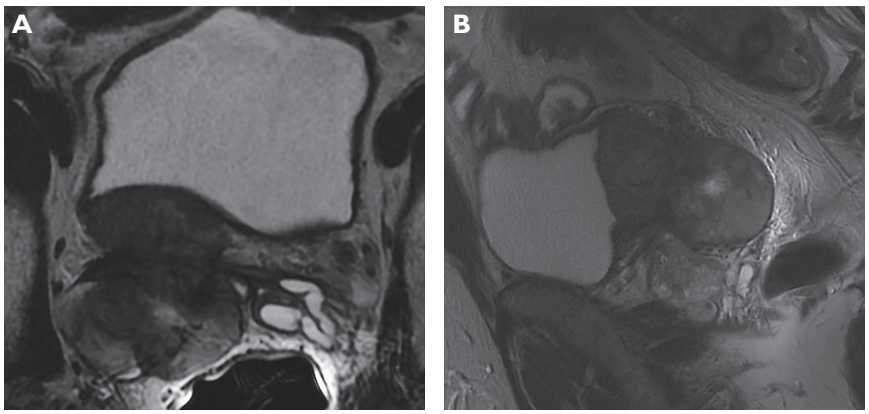

Figure 3: Axial (A) and sagittal (B) magnetic resonance imaging T2-w sequences showed a well-demarcated, heterogeneous lesion, mainly hypointense, arising from the central part of the apex and responsible of bladder compression.

The MRI examination findings revealed a heterogeneous mass, with an estimated diameter of 8×7×6 cm, arising from the prostate apex causing bladder compression, without clear infiltrative aspects. A more in-depth evaluation was requested with biopsy. The histological examination diagnosed a high-grade pleomorphic spindle cell malignant mesenchymal neoplasm, showing morphological and immunophenotypic characteristics (smooth muscle actin + multifocal; desmin –; caldesmon –;

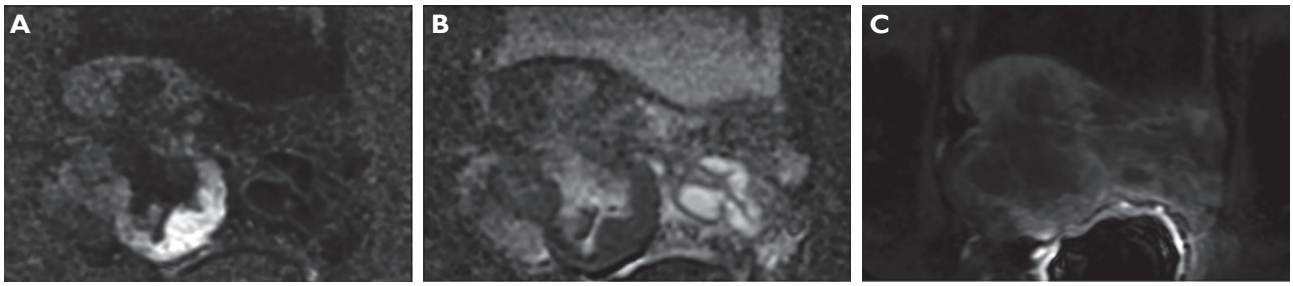

Figure 4: 1.5 magnetic resonance imaging: axial diffusion weighted imaging (A) and apparent diffusion coefficient map (B) image showed the presence of areas of diffusive restriction; axial post-contrast (C) image showed a peripherical enhancement surrounding the necrotic/colliquative central areas.

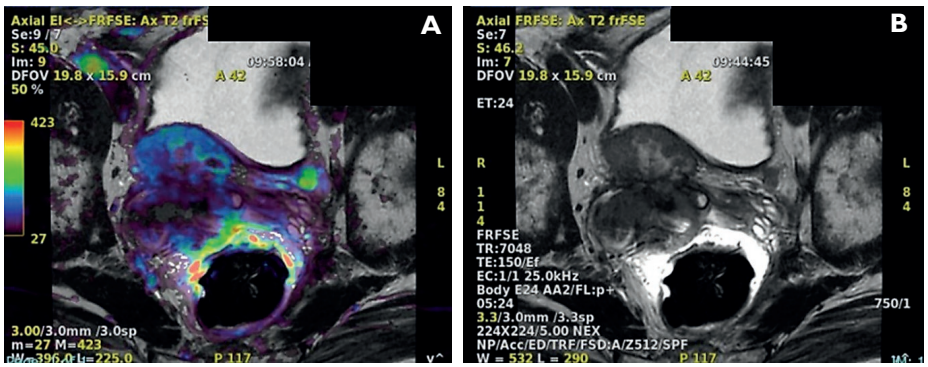

Figure 5: 3D-CSI 1.5 magnetic resonance imaging: coloured parametric maps (A) superimposed to T2-weighted image (B).

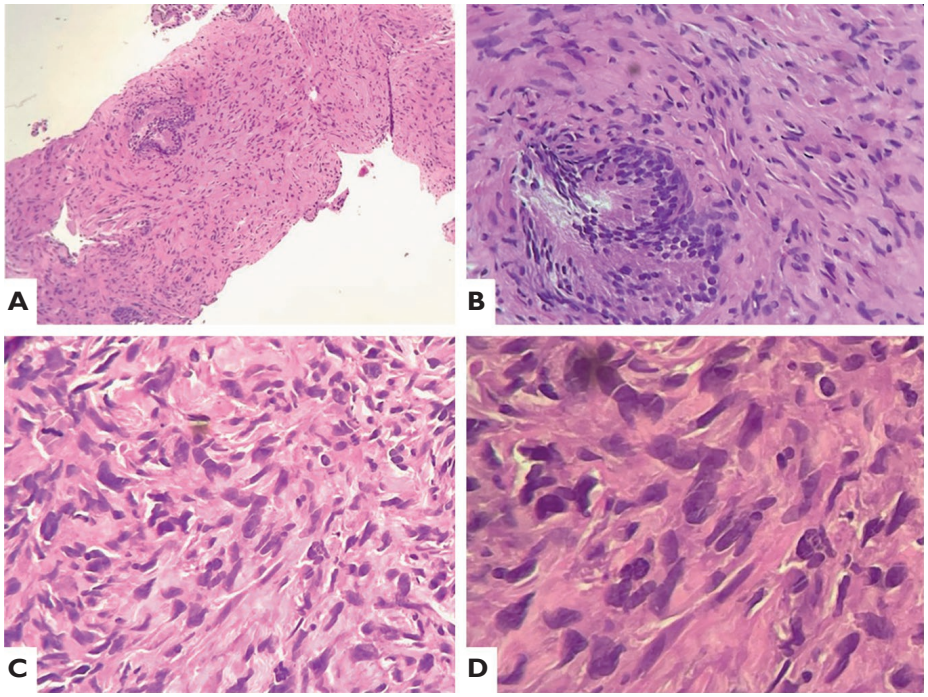

Figure 6: Proliferation of stromal cells that surrounds normal prostatic glands without destroying them (A, B). The proliferation is composed of fused and pleomorphic mesenchymal cells with areas of necrosis (not shown) with evident mitotic activity (C, D).

myogenin –; MDM2 –; H3K27me expression preserved; S100 –; cytokeratin MNF116 –) were consistent with the diagnosis of undifferentiated pleomorphic sarcoma, G3 according to French Federation of Cancer Centres Sarcoma Group (FNCLCC), which confirmed the presence of prostate sarcoma (Figure 6).

The patient underwent a positron emission tomography (PET)/CT with 18 F-FDG in order to exclude the presence of metastasis: the investigation

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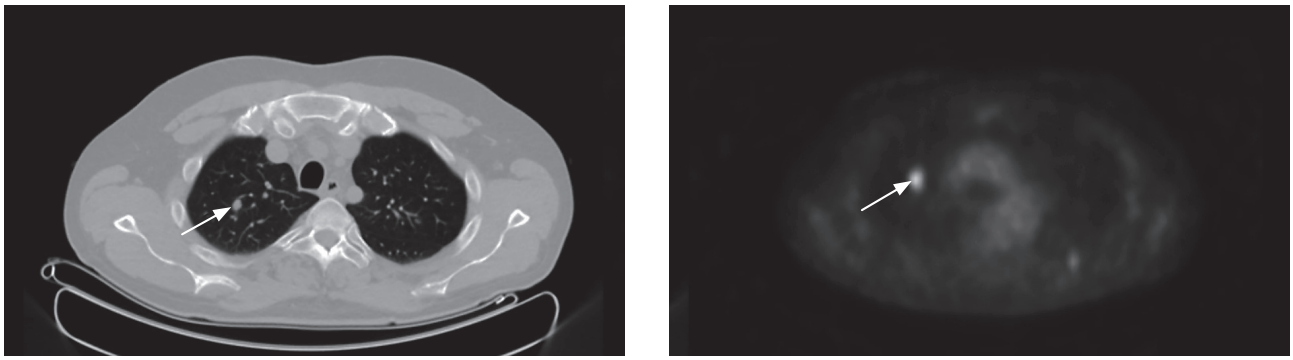

Figure 7: Axial thorax positron emission tomography/computed tomography image showing a pulmonary nodule (arrow) in the apical segment of the right upper lobe with hyper uptake of the 18 F-FDG, referable to secondaries.

revealed the presence of multiple and ubiquitous nodular lesions in both lung fields that showed hyper uptake of the radiotracer (Figure 7).

Treatment and patient management required a multidisciplinary approach and involved a combination of surgery to obtain clear margins, radiation therapy to control local extension, and chemotherapy to address systemic risks. However, imaging at six months revealed progression of lung metastases, prompting a change in the chemotherapy regimen. Regular follow-up with MRI and PET/CT continues to monitor disease status.

Discussion

Imaging techniques play a pivotal role in the detection, characterization, and staging of prostate sarcoma, aiding clinicians in making informed decisions regarding treatment strategies and patient care. Several imaging modalities are used in the global assessment of the neoplasm, each offering unique advantages and limitations (Andreou et al., 2013) (Table 1).

Imaging findings of prostate sarcoma may vary depending on the histologic subtype and stage of the disease. However, typically, prostate sarcoma presents as a heterogeneous mass within the prostate gland, often with irregular margins and areas of necrosis or haemorrhage. Prostate sarcomas generally are large at the time of diagnosis, with an average size of about 8 cm. Tumour shape varies from well-defined, roundish or lobular masses to irregular, ill-defined lesions (Luo et al., 2024).

In the reported case, the patient underwent US, TRUS, MRI and PET/CT examinations. In particular, prostate MRI represents the gold standard for the prostate evaluation since it provides a high soft tissue contrast resolution necessary to determine the site of origin of the tumour, its local extent, the presence of local adenopathy, aiding in planning surgical resection. The main imaging features on MRI examination are described in Table 2 (Yang et al., 2023).

The prostate MRI performed in our department revealed the presence of a voluminous heterogeneous mass in most sequences, indicating the presence of necrotic contextual areas. In particular, this was confirmed by the T1-w performed before and after contrasting medium administration. Necrosis and cystic change in these types of tumours are common, because of their high malignancy and rapid growth. The DWI and ADC sequences showed area of restricted diffusion, as expression of the

Table 1: Main role of each imaging modality

Imaging modality	Role	Advantages
TRUS	To provide an initial evaluation and detection of prostate abnormalities.	real-time images
CT	To evaluate lesion extension, lymph node involvement, and distant metastases.	detailed multiplanar images
MRI	To delineate tumour margins, assess local invasion, and detect lymph node metastases.	high soft tissue contrast
PET/CT	To detect distant metastases and assess treatment response.	To combine metabolic and anatomical imaging.

TRUS – transrectal ultrasound; CT – computed tomography; MRI – magnetic resonance imaging; PET/CT – positron emission tomography/CT

Table 2: Typical signal intensity of prostate sarcoma on magnetic resonance imaging sequences

MRI sequence	Signal intensity
T1-w	heterogeneous low signal mass
T2-w	heterogeneous intermediate to high signal mass
CE-T1	heterogenous contrast enhancement
DWI/ADC	mostly impeded diffusion, with high signal intensity at higher b values and low diffusion coefficient
Spectroscopy	marked increase in choline/citrate ratio

MRI – magnetic resonance imaging; DWI – diffusion weighted imaging; ADC – apparent diffusion coefficient

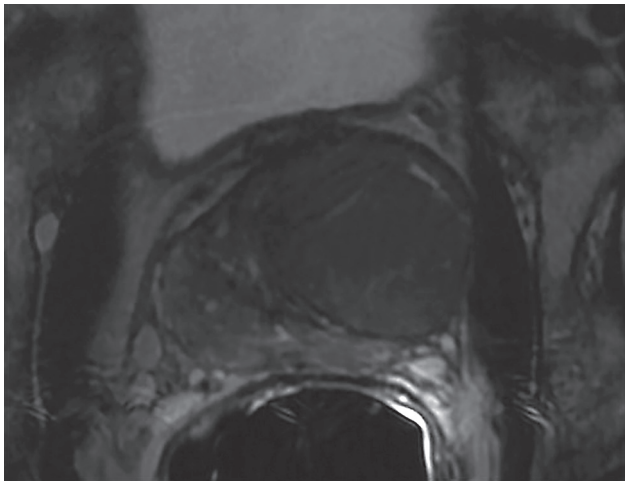

Figure 8: T2-w 1.5 magnetic resonance imaging of the prostate apex showed the presence of a capsule (low signal intensity complete line).

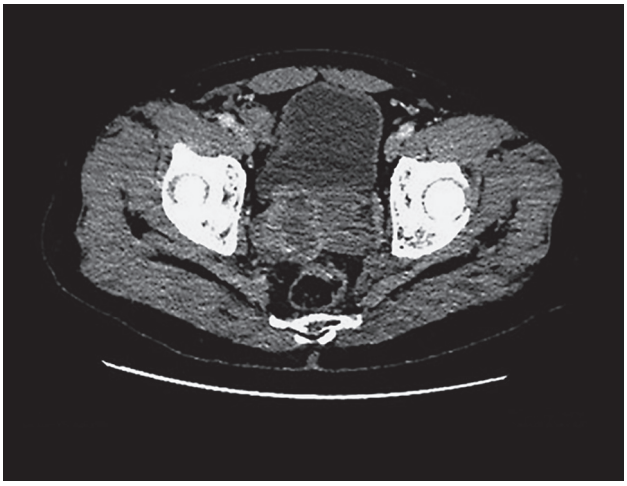

Figure 9: Axial computed tomography scan showed a prostate heterogeneous mass with hypodense areas suggesting contextual necrosis.

hyper cellularity of the prostate lesion. Spectroscopy generally shows a marked increase in the ratio of choline/citrate, according to the imaging features presented in this case (Wang et al., 2023; Nitta et al., 2024).

Imaging techniques play a key role also in staging prostate sarcoma, taking into account the size of the tumour, the extent of invasion, lymph node involvement and the presence of distant metastases at sites such as bone, lung, or liver. It is important to assess local invasion, as prostate sarcoma tends to invade surrounding structures, such as seminal vesicles, bladder, or rectum, indicative of locally advanced disease. Given the usual large size of the pelvic mass at the time of detection, it is important to distinguish its prostatic origin from the bladder which may be mistakenly considered the origin. In the reported case, the tumour was responsible for a mass effect on the surrounding structures, in particular on the bladder, and the presence of a complete pseudo-capsule was decisive in excluding the involvement of the perilesional tissue (Jaouani et al., 2023) (Figure 8).

The patient underwent a total-body PET/CT to detect distant metastases, such as pulmonary. Prostate sarcoma did not present CT features able to characterize the neoplasm. However, it confirmed the

Table 3: Main differences between prostate sarcoma and prostate adenocarcinoma

Feature	Prostate sarcoma	Prostate adenocarcinoma
Epidemiology	before 50 years old	after 50 years old
PSA level	normal	increased
Tissue/zone involved	mesenchymal tissue, in and around the prostate	glandular tissue, almost of the peripheral zone
Local invasion	common	rare at diagnosis
Metastasis	lung and liver; osteolytic bone lesion	osteoblastic bone lesion

PSA – prostate-specific antigen

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presence of a large prostate mass with heterogeneous attenuation for the presence of necrosis/cystic areas and heterogeneous enhancement (Andreou et al., 2013) (Figure 9).

In the differential diagnosis it is important to distinguish prostatic sarcoma from prostate adenocarcinoma, as they are characterized by different management and prognosis. Imaging features can be helpful in differentiating, considering the zone involved, the presence and type of local invasion/metastases. In particular, the prostate adenocarcinoma arises in the glandular peripheral zone, while the prostate sarcoma was evident in the central zone. In addition to these differences, it should be considered the epidemiology, and the serum PSA value which is usually normal in prostate sarcoma due to the non-epithelial origin of the sarcomatous tumour (Rojas-Jiménez et al., 2013) (Table 3).

In the reported case, as confirmed by histology which represent any case the definite diagnosis, the main features were compatible with a prostate sarcoma.

Conclusion

Prostate sarcomas pose significant diagnostic challenges due to their rarity, heterogeneity, and propensity for rapid progression. Knowing the imaging features of prostate sarcoma may assist in the characterization of a prostate lesion and in the differential diagnosis with adenocarcinoma. Tumour invasion may be difficult to assess accurately without high-quality imaging, and it is essential to avoid misinterpreting these areas of mass effect as infiltration. Multidisciplinary collaboration among urologists, oncologists, and radiologists is essential to optimize patient management and improve clinical outcomes.

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Pancreatic Fistula after Laparoscopic Radical Nephrectomy

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Key words: Laparoscopy – Complication – Pancreatic fistula – Renal tumours – Diagnosis

Abstract: Laparoscopy is widely used technique for renal tumours in the world. After laparoscopy, some complications can occur in the follow-up. Pancreatic fistula incidence is 2.1% after left laparoscopic radical nephrectomy. This complication is very rare after right laparoscopic nephrectomy. I reported a case of pancreatic fistula which was misdiagnosed after surgery and managed conservatively.

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Introduction

Intraoperative pancreatic trauma is an uncommon complication during laparoscopic nephrectomy (Bozkurt et al., 2017). This complication usually occurs in laparoscopic radical left nephrectomy and laparoscopic left adrenalectomy with an incidence of 2.1 and 8.6% respectively (Varkarakıs et al., 2004). Most of the patients are diagnosed on postoperative period. Herein, I present a case of delayed diagnosed pancreatic fistula after laparoscopic right radical nephrectomy.

Case report

A 42-year-old woman admitted to our hospital with right flank pain of 4 months duration. Physical examination and laboratory tests were unremarkable. Ultrasonography revealed 5 cm solid mass in the upper pole of the right kidney. Computed tomography was consistent with the diagnosis of renal cell carcinoma (Figure 1). The patient was informed about partial vs. radical nephrectomy. She elected to undergo a transperitoneal laparoscopic right radical nephrectomy. No bleeding occurred in peri-operative and postoperative period. After 2 days, the surgical drain was removed. She subsequently developed mild abdominal distension. Ultrasonography revealed 6.5 cm collection. General surgical consultation recommended conservative management. The patient was discharged on the 5th post-operative day.

The patient presented with abdominal pain and distension on the 15th post-operative day. Laboratory results were as follows: white blood cell (WBC) 8,650×10^{6}/l, C-reactive protein (CRP) 379 mg/dl, creatinine 1.91 mg/dl. Computed tomography showed a 10.5 cm collection in the operation field (Figure 2). Percutaneous drainage was performed, and 3,000 ml liquid was evacuated, and a drain was left indwelling. The drainage fluid amylase level was 3,548 U/l and the patient was diagnosed as pancreatic fistula.

Antibiotic therapy was regulated (ceftriaxone 1 g 2×1 iv and metronidazole 500 mg 2×1 iv), somatostatin analogues was given, oral diet without fat was started and drainage decreased to less than 50 ml/24 hours after 10 days. After 2 weeks there was no drainage and ultrasonography confirmed resolution of the collection, and the drainage catheter was removed. The subsequent post-operative course was uneventful. To the best of my knowledge, this is the first report of pancreatic fistula after right laparoscopic radical nephrectomy in the literature.

Discussion

The general incidence of pancreatic fistula is 0.2% following laparoscopic urological surgeries (Varkarakıs et al., 2004). There are five degrees of pancreatic fistula according to the severity. Grade 1: minor contusion without ductal injury; Grade 2: major contusion or tear (>3 cm) without ductal injury; Grade 3: distal transection or proximal tear with ductal injury; Grade 4: transection or proximal tear of pancreas with ductal injury; and Grade 5: disruption of pancreatic head or pancreaticoduodenal disruption. Grade 4 and 5 injuries usually occur in right sided surgery because of anatomic relation of the right kidney with duodenum and pancreas. To the best of my knowledge, this is the first report of pancreatic fistula after laparoscopic right nephrectomy in the literature.

Several mechanisms can be associated with pancreatic fistula during laparoscopic nephrectomy. Pancreatic fistula may occur during a difficult,

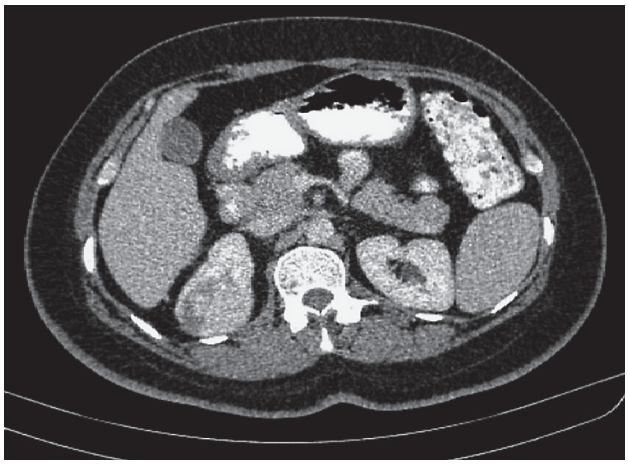

Figure 1: Renal tumour image on computed tomography.

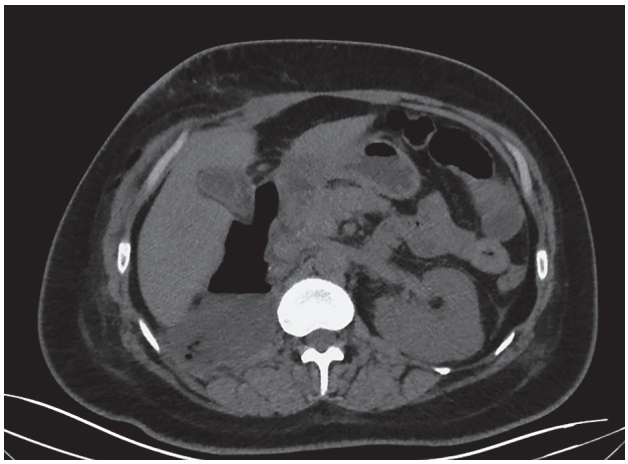

Figure 2: Collection of the pancreatic fluid.

dissection, use of the gastrointestinal anastomosis (GIA) stapler and specimen morcellation (Varkarakıs et al., 2004). In this case I believe the injury occurred while using the GIA stapler for pedicle control.

The diagnosis is usually suggested by abdominal pain associated with elevated serum amylase levels and confirmed by abdominal computed tomography scan (Varkarakıs et al., 2004). In some case the patient is asymptomatic, and the diagnosis is delayed. In this study, the patient had minimal abdominal distention which delayed the diagnosis.

Treatment options are conservative treatment, percutaneous drainage, surgical drainage and invasive modalities including endoscopic sphincterectomy, prosthetic restoration and open surgery (Bozkurt et al., 2017).

Conservative treatment involves discontinuing oral intake, antibiotic therapy and somatostatin analogues. Most fistulas close after drainage and further surgical procedure is seldom necessary. The drains should be left in the surgical bed until the drainage is less than 50 ml/day and fluid amylase levels have returned to the serum levels (Varkarakıs et al., 2004).

Ceylan et al. (2013) reported a case of pancreatic fistula after nephrectomy treated with endoscopic retrograde cholangiopancreatography with pancreatic stent. In the current study, the patient was treated with conservative treatment and percutaneous drainage.

In conclusion, pancreatic fistula is very rare complication after laparoscopic right nephrectomy. This complication should be considered after nephrectomy. Early diagnosis and treatment expedite recovery.

To the history of Dr. Mustafa Kanbay.

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Exploring the Intriguing Consequences of Trauma – Pseudoaneurysm of the Tibial Arteries

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Key words: Pseudoaneurysm – Tibial arteries – Saphenous vein – Blood vessel graft

Abstract: Aneurysms are commonly managed by vascular surgeons, primarily affecting proximal arteries in the lower limb. In contrast, pseudoaneurysms often occur in the infrapopliteal region (Nair and Suhania, 2021), with anterior tibial artery involvement being particularly rare. It is even more uncommon for both the anterior and posterior tibial arteries to be affected simultaneously. Here, we present a case of a 21-year-old man who sustained vascular trauma to his right calf and presented one month later with difficulty in ambulation. A diagnosis of pseudoaneurysm involving both the anterior and posterior tibial arteries was made, and he successfully underwent reversed saphenous vein graft interposition for both arteries.

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Introduction

Aneurysms are frequently managed by vascular surgeons, typically occurring in the proximal arteries of the lower limb, such as the femoral and popliteal arteries, compared to the smaller distal vessels. Pseudoaneurysms are more common in the infrapopliteal region and occur when all three layers of the arterial wall are injured, leading to blood extravasation contained within a fibrous capsule.

Pseudoaneurysm of the anterior or posterior tibial artery is rare and usually results from trauma or iatrogenic injury. Many reports discuss pseudoaneurysms of either the anterior or posterior tibial artery. However, to the best of our knowledge, there are no reported cases of pseudoaneurysm involving both arteries in the same limb simultaneously. Here, we describe our experience in successfully managing such a case following a stab injury.

Case report

A 21-year-old gentleman was assaulted by a group of tugs and sustained a stab wound over his right calf. Post trauma, he sought treatment at a nearby health facility and underwent toilet and suturing and before being discharged. Since discharge, he experienced progressive swelling in the right calf, which became increasingly painful and eventually limited his ability to walk.

On physical examination, patient appeared clinically pale and tachycardic. Examination of the lower limb noted that there was swelling from the foot extending till the knee. He was unable to extend his knee due to pain. There were no skin changes, the surrounding skin felt warm, and the wound over the calf was well healed with no discharge seen. Distal pulses (posterior tibia artery [PTA] and dorsalis pedis artery [DPA]) were not palpable in view of the gross swelling. However Doppler ultrasound revealed biphasic wavelength over the right PTA and DPA.

A computer tomography angiography (CTA) demonstrated contrast extravasation from mid part of right anterior tibial artery into anterior compartment of the right leg, with pooling of extravasated contrast measuring approximately 3.1×2.2×2.9 cm (anterior posterior×width×craniocaudal). There is also a saccular dilatation arising from mid part of the right posterior tibial artery (PTA), which is filled with contrast on arterial phase, likely representing a pseudoaneurysm (Figure 1). Presence of intramuscular collections were observed within anterior, superficial posterior and deep posterior compartments of the right leg, which have layering of various densities within.

The patient subsequently underwent mid PTA and ATA (anterior tibial artery) reversed saphenous vein graft (RSVG) interposition. Intraoperatively there was mid PTA pseudoaneurysm of 6 cm in size with a 2 cm arterial defect, requiring evacuation of 500 cc of blood clots. The pseudoaneurysm sac was resected and RSVG was anastomosed via end-to-side anastomosis (ETSA) fashion to the proximal and distal PTA. As for the ATA, there was a mid-ATA pseudoaneurysm of 4 cm, also containing 500 cc of blood clots with visible puncture site of 1 cm. Pseudoaneurysm was resected and RSVG anastomosed via end to side fashion to the

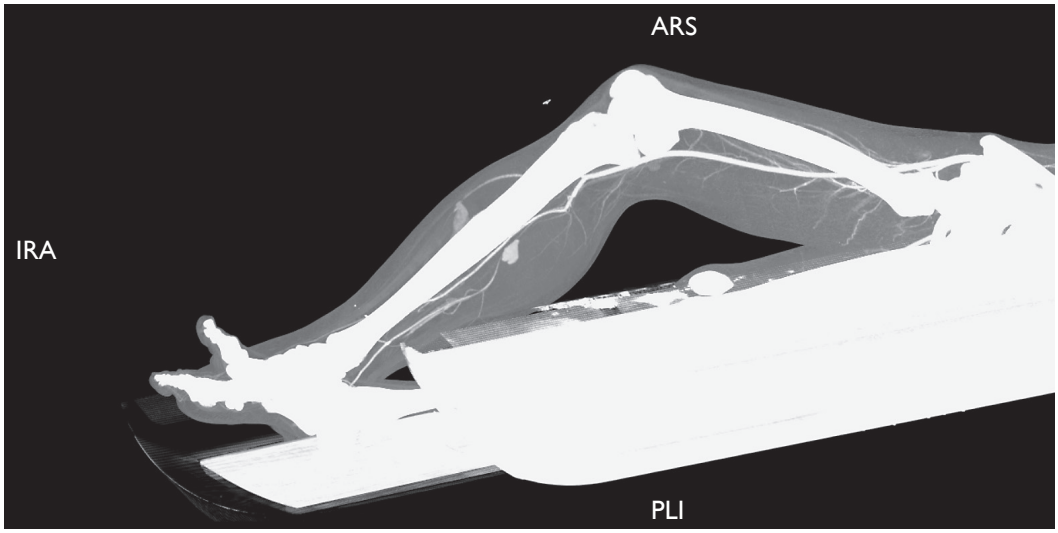

Figure 1: Computed tomography angiogram of lower limb in maximum intensity projection showing a saccular dilatation from mid part of right posterior tibial artery and contrast extravasate from mid part of right anterior tibial artery with pooling of contrast suggestive of active bleeding.

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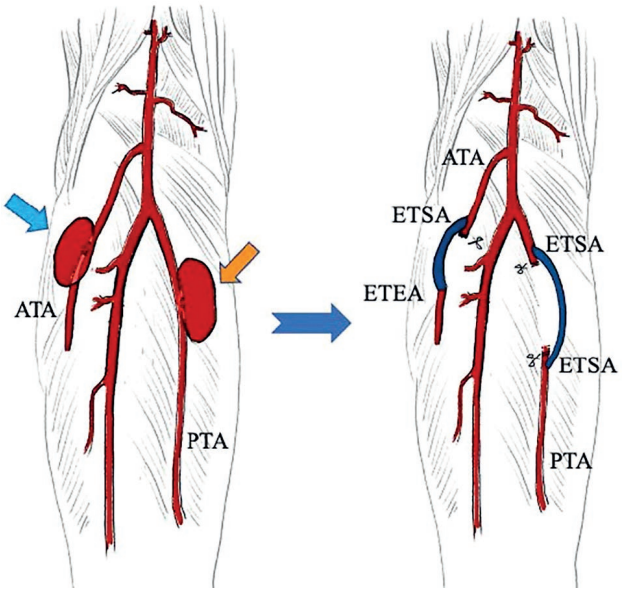

Figure 2: A schematic diagram of the lower limb showing the pseudoaneurysm of the right posterior tibial artery (PTA) and anterior tibial artery (ATA) and the anastomosis of the PTA and ATA using saphenous vein graft from the same leg. The left arrow shown PTA pseudoaneurysm; the right arrow shown ATA pseudoaneurysm; ETSA – end-to-side anastomosis; ETEA – end-to-end anastomosis.

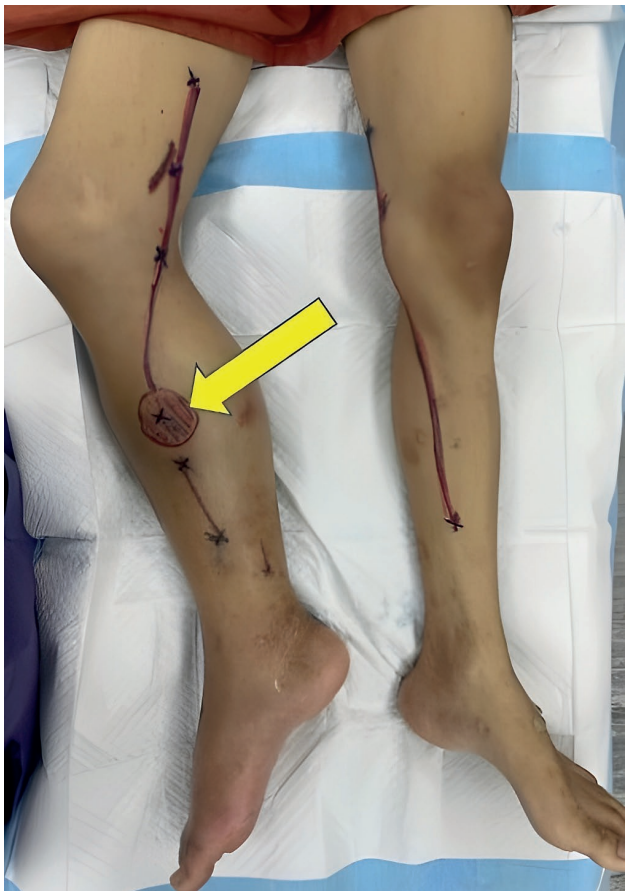

Figure 3: Right lower limb is generally more edematous and in flex position compared to the left. Arrow shown posterior tibial artery pseudoaneurysm.

proximal ATA with end-to-end anastomosis (ETEA) fashion over the distal ATA (Figures 2–6). Doppler signal of DPA and PTA were biphasic preoperatively and remained so postoperatively.

Post operatively patient recovered well and was discharged home one week after surgery. On interval follow-up, patient demonstrated good functional recovery, with unremarkable vascular examination of lower limb.

Discussion

Pseudoaneurysm is a localized arterial injury, with or without the involvement of the adventitia. It is characterized by damage to all three layers of the arterial wall, leading to blood extravasation. This extravasation is contained by the surrounding connective tissues, which form a cavity that remains connected to the arterial lumen via a neck, allowing continuous leakage into the pseudoaneurysm. The most common site of pseudoaneurysm in the lower limb is the anterior tibial artery (Suri et al., 2011; Tonogai et al., 2017; Eilersen and Strøm, 2021) while pseudoaneurysms of the posterior tibial artery are rare, with only a few cases reported in the literature (Sagar and Button, 2014; Gangadharan et al., 2015; Liu et al., 2020; Beijers et al., 2024).

The causes of pseudoaneurysms are typically traumatic, iatrogenic, or inflammatory. Trauma-related pseudoaneurysms have increased due to road traffic accidents and violent assaults. Both Suri et al. (2011) and Tonogai et al. (2017) describe pseudoaneurysms related to trauma and iatrogenic factors, particularly during lower limb surgeries. Sharp hardware used in surgical procedures can cause traction injuries to arterial structures, resulting in pseudoaneurysm formation. In our case, the patient sustained a stab wound to the right medial calf. However, despite the superficial nature of the injury and absence of deep penetration, the patient developed both PTA and ATA pseudoaneurysms. We speculate the ATA pseudoaneurysm may have developed spontaneously, as almost the same case as described in Al-Zoubi et al. (2017).

The clinical presentation of pseudoaneurysms depends on their size. Symptoms can range from being asymptomatic, with spontaneous regression, to the opposite end of the spectrum, where the pseudoaneurysm progressively enlarges, causing swelling, throbbing pain, paresthesia, neuralgia, or even ischemia.

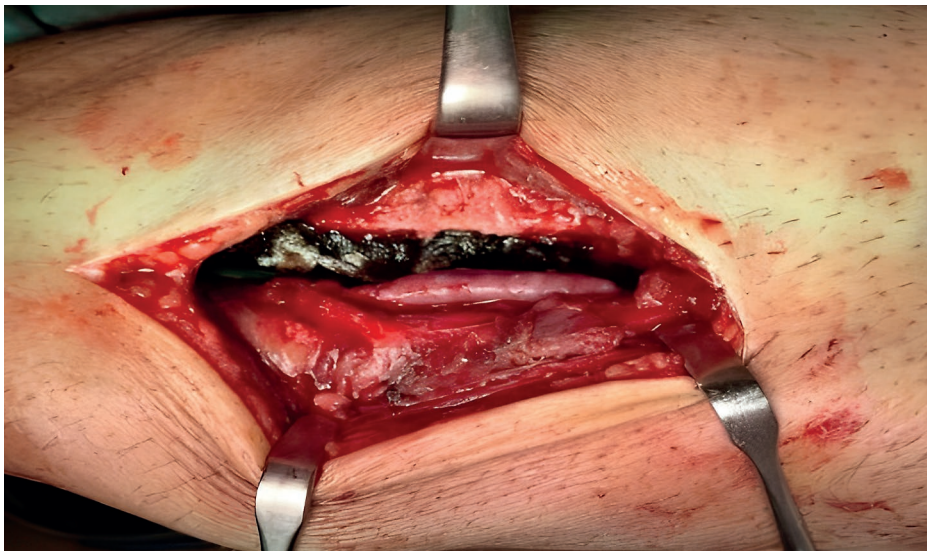

Figure 4: Anterior tibial artery pseudoaneurysm post reversed saphenous vein graft anastomosis.

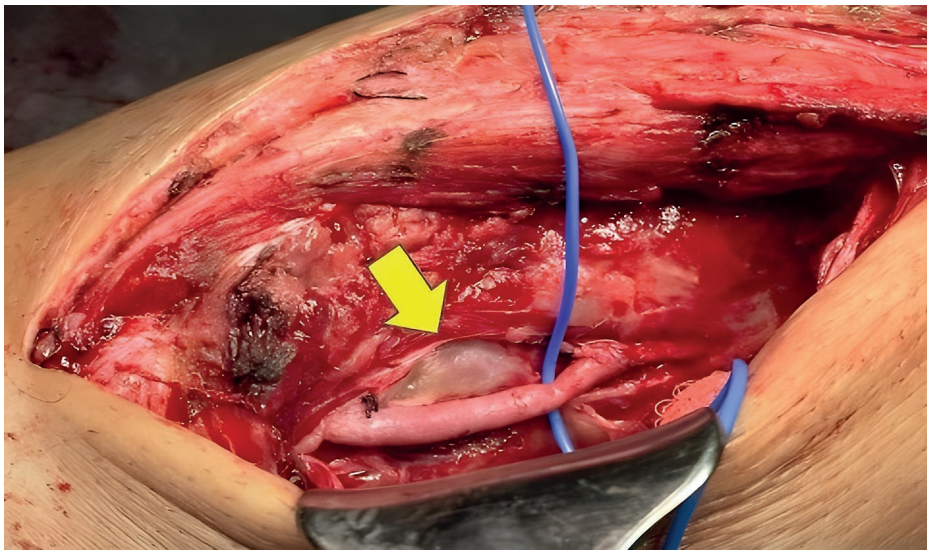

Figure 5: Posterior tibial artery pseudoaneurysm with proximal and distal artery control. Arrow showing site of pseudoaneurysm.

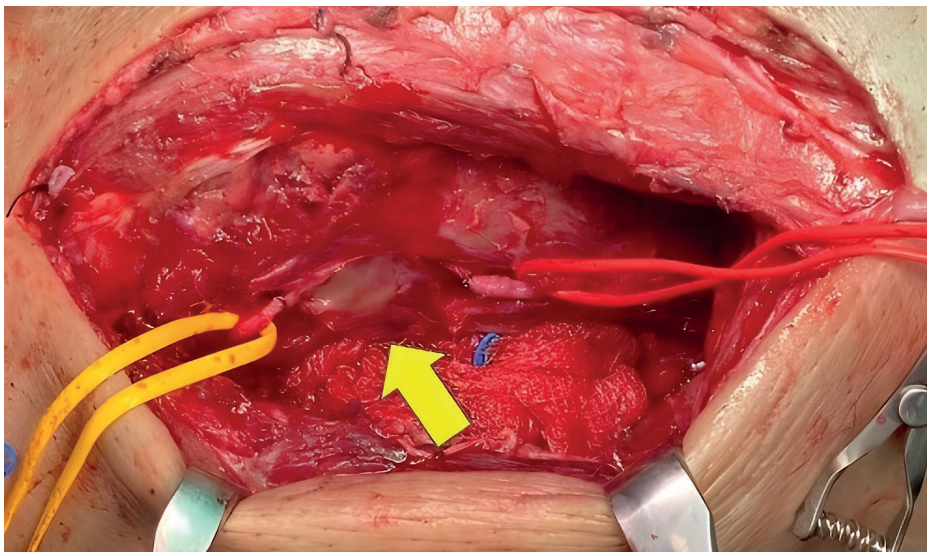

Figure 6: Posterior tibial artery pseudoaneurysm post reversed saphenous vein graft anastomosis. Arrow showing site of pseudoaneurysm.

The primary diagnostic tools are CTA and, ideally, magnetic resonance imaging (MRI) of the lower limb. Prompt intervention is essential upon diagnosis to prevent further enlargement of the pseudoaneurysm and avoid potentially life-threatening complications.

There is no universally accepted treatment strategy for pseudoaneurysms, and management depends on factors such as size, location, symptoms, and clinical findings. While endovascular treatments have become increasingly popular for pseudoaneurysm management, traditional open repair remains a crucial option, particularly for ruptured, infected, large, or complex pseudoaneurysms (Sagar and Button, 2014; Gangadharan et al., 2015). In our case, open surgery was chosen due to the presence of dual PTA and ATA pseudoaneurysms. Additionally, the patient had significant calf swelling that required tissue decompression, and the open approach allowed for extensive exploration and meticulous repair of both the ATA and PTA. Given that the patient was young and relatively stable at the time of presentation, we decided to proceed with saphenous vein grafting for both arteries.

To the best of our knowledge, the simultaneous occurrence of anterior and posterior tibial artery pseudoaneurysms is extremely rare, with limited literature addressing the management of this pathology. Most reports focus on isolated anterior or posterior tibial artery pseudoaneurysms, and while their management is generally similar, there are no established guidelines specific to such cases.

In young patients like our patient with peripheral arterial pathologies, efforts are directed toward preserving as much of the arterial structure as possible. This approach has a significant impact on the patient's long-term outcomes and quality of life. Moreover, preserving arterial integrity is beneficial in the event of future peripheral arterial disease, which may require further interventions.

Conclusion

The presence of aneurysm of both ATA and PTA is a rare presentation. The management dilemma of endovascular approach versus open intervention has not been clearly delineated. The open surgery method has benefited the patient in terms of proper exploration and meticulous repair of both pseudoaneurysm of the ATA and PTA and tissue decompression.

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Adequacy of the Zetaplasty Technique for Closing Extensive Oroantral Communication

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Key words: Maxillary sinus – Surgery oral – Oral surgical procedures – Oral fistula

Abstract: A buccosinusal fistula consists of a permanent communication between the oral cavity and the sinus. For the treatment of this complication, three modalities can be highlighted: sliding of the vestibular flap, palatal flap, or graft of cheek adipose tissue. Each of these treatment forms has disadvantages, which led to the development of the zetaplasty technique. Patient C.M., a 57-years-old male, sought the Surgery Clinic of the Federal University of Alfenas for the treatment of a broad buccosinusal communication. After anesthesia, a perilesional incision followed by an extended incision anteriorly to expose the alveolar ridge for regularization. Additional relief incisions were executed to mobilize the vestibular and palatal flaps. The proposed technique aims to obtain relief incisions in the vestibular and palatal areas from the freshened wound margins, allowing the sliding of the flaps in the zetaplasty technique. There has been no need for surgical re-intervention up to the present moment.

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Introduction

The continuities between the maxillary sinus and the oral cavity are defined as the rupture of the bone lamina interposed between the dental roots and the maxillary cavity, concomitantly with the perforation of the surrounding sinus membrane. According to the characteristics of the opening site, communicating processes are classified in the literature as perforations of the maxillary sinus (recent and simple opening of the antrum, with bloody tissue on the margins of the lesion and favourable prognosis) or oroantral communications (also proposed as a fistula oroantral) (Rey Santamaría et al., 2006; Khandelwal and Hajira, 2017).

Bucosinusal communications are processes of doubtful prognosis. They are conditions in which the margins of the lesion are already epithelized by a mucous tissue generated during the healing process from the proliferation of tissues adjacent to the lesion. This process takes about three weeks, and thereafter there is no spontaneous regression of the case (Gonty, 1995).

The main etiology for oroantral communications are accidents related to the extraction of upper premolars and molars (Khandelwal and Hajira, 2017). Risk factors for the appearance of oroantral communications are the presence of divergent roots in the vicinity of edentulous spaces requiring extraction, pneumatization of the maxillary sinus, destruction of the sinus floor by periapical lesions, inadequate handling of instruments and large cystic lesions (Peterson et al., 2000).

Research demonstrates a greater involvement of males from the third decade of life, the age at which extractions of missing teeth usually begin (Freitas et al., 2003; Person et al., 2005; Park et al., 2019; Bereczki-Temistocle et al., 2022). On the other hand, Marzola (2005) reports a higher incidence in the 16–30 age group in his bibliographic review.

Gregori and Campos (2004) points out as important factors the deficiency of the surgical planning of extractions, mainly when there is pneumatization in the antrum, osteolytic pathological processes, roots with laceration, ankylosis, hypercementosis, manual inability, anatomical position occupied by unerupted teeth, maxillofacial trauma – facial, intraosseous cysts and infectious complications of molar extractions.

As systemic pathologies, the etiological factors are: bisphosphonates therapy (Esen and Akkulah, 2021) and tuberculosis (Ries Centeno, 1991; Rey Santamaría, 2006). Finally, osteoporosis and osteopenia can also be indicated, although there are no publications directly correlating these two processes with the continuities. Correlated articles point to evidence that obviously requires further studies for confirmation. Furthermore, the fact that osteoporosis is diagnosed in a part of the skeleton does not mean that it is present in all other bones (Esen and Akkulah, 2021).

If the oroantral communication is smaller than 2 mm in diameter, the most indicated treatment is clot stabilization and preservation at the extraction site. Additional soft tissue flap lifting is not required. Sutures are made to reposition the soft tissues and gauze is kept for 1 to 2 hours over the suture. The communication must be diagnosed and treated immediately to ensure better prognosis, avoid maxillary sinusitis and if the communication is equal to or greater than 3 mm in diameter, a surgical procedure must be performed to close the communication (Khandelwal and Hajira, 2017).

Case report

Patient C.M., male, 57-years-old, Caucasian, rural farmer, with a history of uncontrolled arterial hypertension, was referred for evaluation and treatment of oroantral communication established two months ago, after extraction of five right posterior upper teeth. According to the patient, some of these teeth were mobile and others quite destroyed. The extractions were performed by a dentist at a municipal public service office without radiographs. The patient had been using amoxicillin and nimesulid since the day of dental extractions and had been smoking cigarettes since the age of 18, with an average consumption of 10 cigarettes per day.

On clinical examination, an extensive epithelialized oroantral communication is observed (Figure 1).

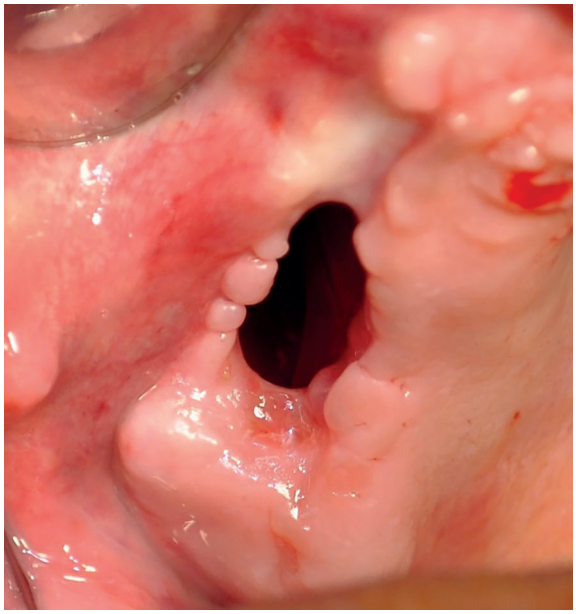

Figure 1: Clinical aspect of extensive oroantral fistula.

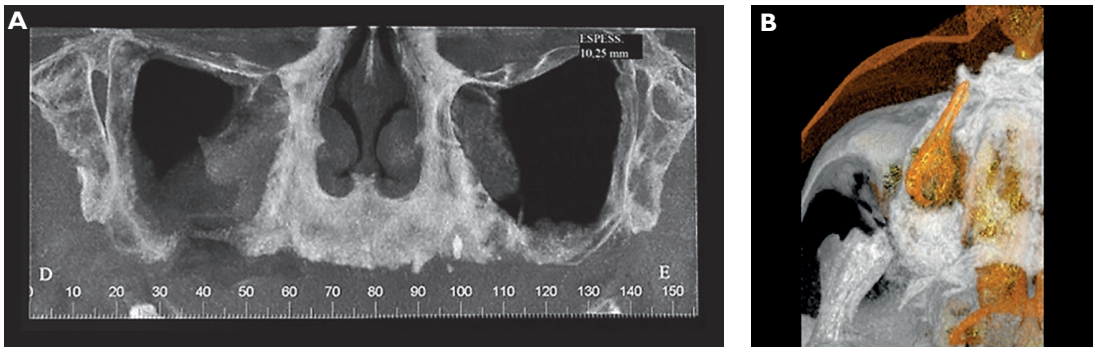

Figure 2: A) Panoramic view of the jaws. Observe the oroantral communication on the right side. B) Axial section of the right maxilla. Note extensive oroantral communication.

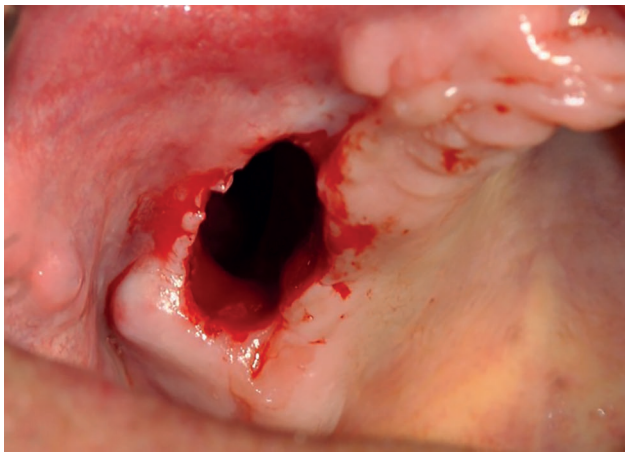

Figure 3: Elliptical incision for sharpening the edge of the wound (removal of oroantral fistula epithelium).

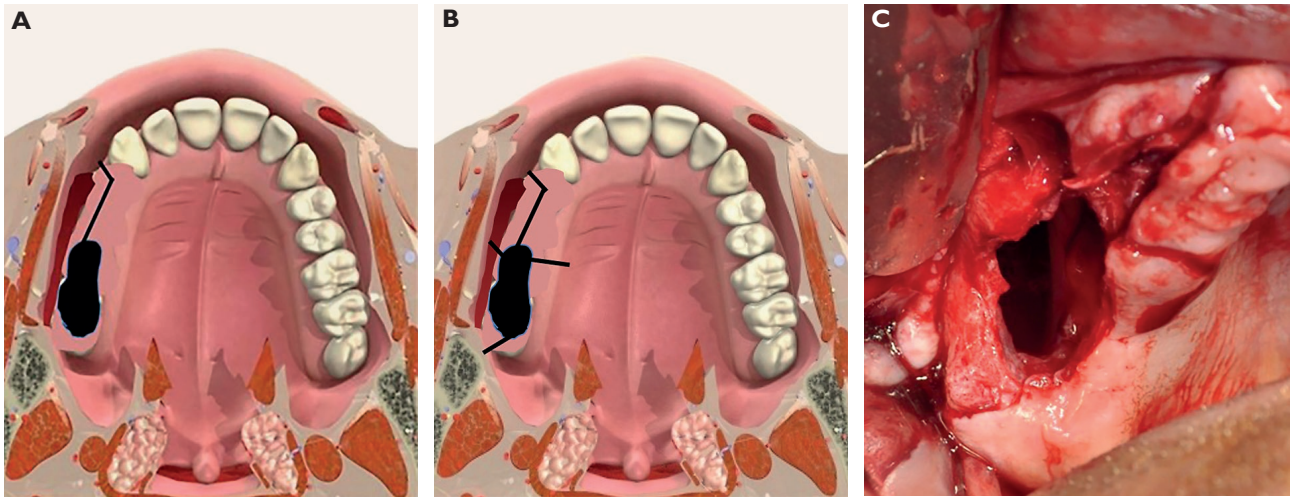

Figure 4: A) Schematic drawing of the linear anterior incision starting from the wound margin. B) Buccal and palatal relief incisions for mobilization of flaps in schematic drawing. C) Clinical aspect of buccal and palatal incisions.

The internal epithelium of the communication was slightly reddish. There were no reports of pus taste. The upper alveolar ridge has contour irregularities, as well as the lower alveolar ridge. The tomographic exam allows observing extensive oroantral bone continuity between the mouth and sinus (Figure 2).

Under local anesthesia (3% prilocaine with 0.03 IU/ml felypressin + 2% lidocaine) and intraoperative clinical monitoring, surgical access began with an elliptical incision to debride the edge of the wound (Figure 3). From the incision extended to the anterior, it was possible to regularize the alveolar ridge

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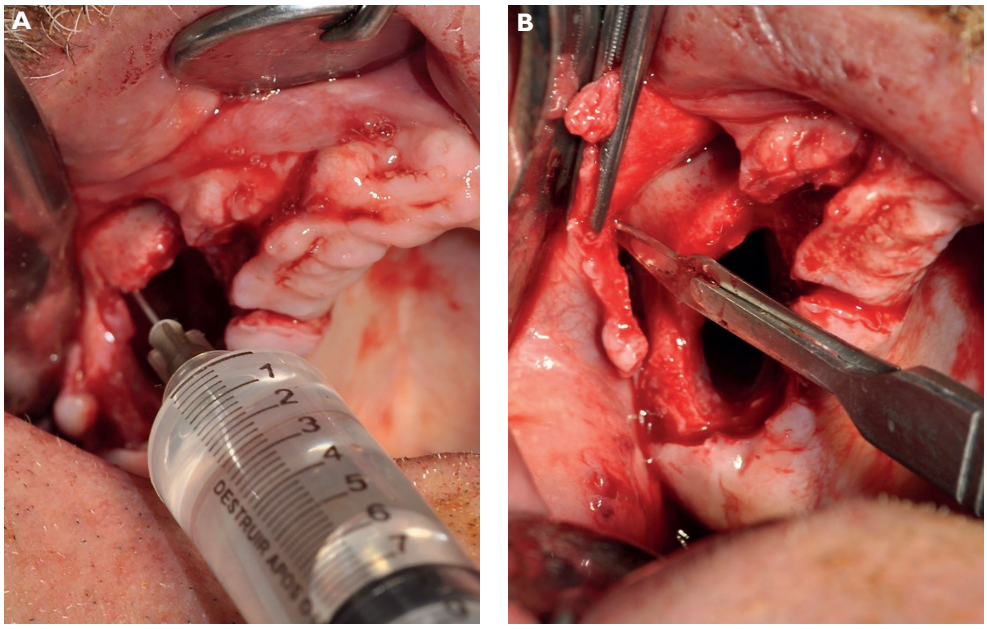

Figure 5: A) Irrigation with 0.5% metronidazole solution. B) Internal incision in the periosteum in the buccal flap.

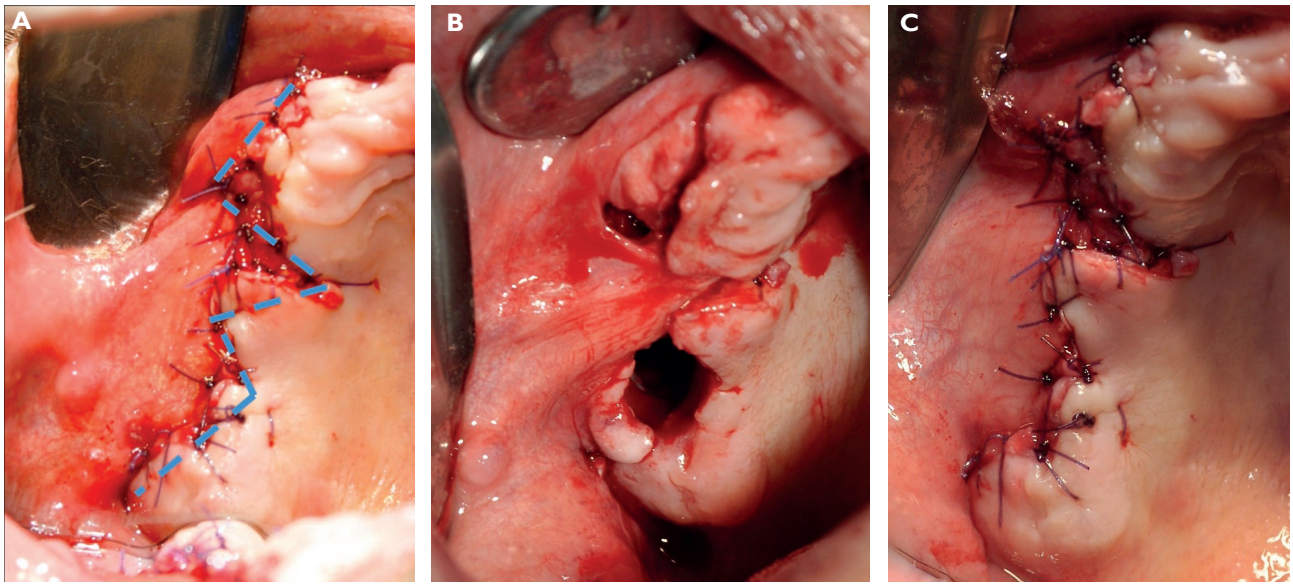

Figure 6: A) First stitch of suture shifting the buccal flap to the palate. B) Alternating buccal and palatal sutures for wound closure. C) Sliding of the flaps following the concept of the zetaplasty technique.

in this area with an alveolotomy and bone files. Thus, in addition to the anterior extension of the incision (Figure 4A), other relief incisions were made to mobilize the buccal and palatine flaps (Figure 4B). The technique aims to obtain, from the debrided wound margins, relief incisions in the vestibular and palatal areas to enable flap sliding (Figure 4C), following the concept of the zetaplasty technique.

Before starting the closure of the wound, in order to reduce the risk of infection, irrigation with 0.5% metronidazole was performed (Figure 5A).

As the vestibular flap was tight for the beginning of wound closure, internal incisions in the periosteum were made (Figure 5B). The first suture aimed to slide the vestibular flap towards the palate (Figure 6A). To achieve this, poliglecaprone 3-0 suture was used. This suture is absorbable and maintains its tensile strength for a long period (around 15 to 20 days). Then, alternating sutures of V and P flaps were performed until complete closure of the wound, as shown in Figure 6B and C.

The first follow-up for clinical observation occurred at 7 days. There were no complaints of pain or signs of infection. After 2 weeks (Figure 7A), the suture was removed. Clinical and radiographic follow-up was performed at 3 months and 1 year (Figure 7B).

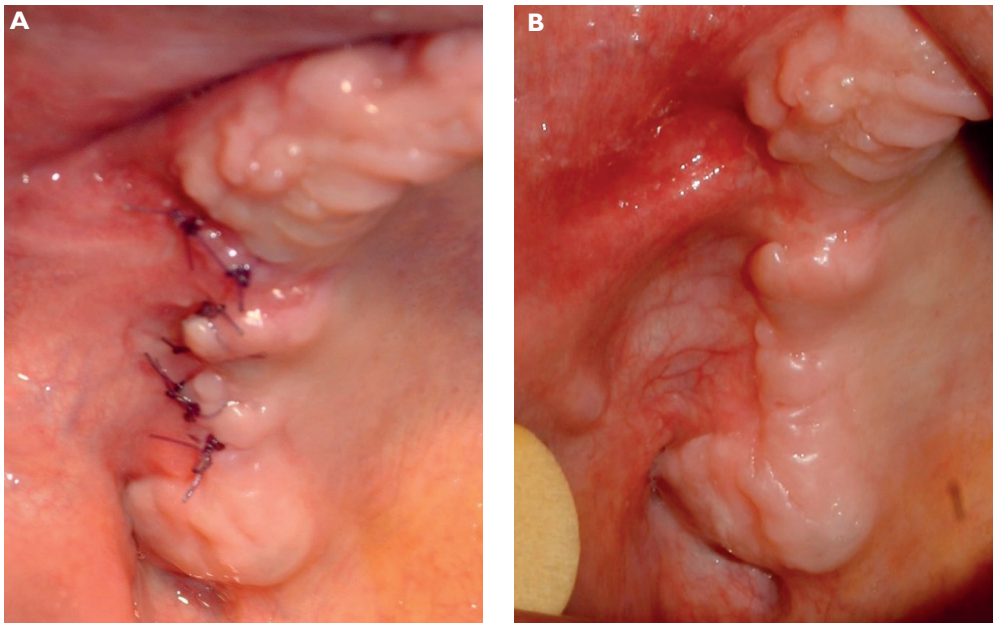

Figure 7: A) 14-day clinical follow-up. B) 1-year clinical follow-up.

Radiographic analysis shows no shadows and there are no complaints from the patient.

Discussion

The most frequent cause related to the establishment of oroantral perforation and consequent fistula formation is due to the deficiency (or even lack) of planning in the extraction of posterior-superior teeth, mainly upper molars (Gregori and Campos, 2004; Person et al., 2005; Galletti et al., 2016). This was demonstrated in the present clinical case, since not even radiographic analysis was performed to plan the extractions. Adequate planning, considering the pneumatization of the maxillary sinus or the close contact with the roots of the teeth to be extracted, leads the good professional to perform primary closure of the wound in the face of sinus perforations detected during the extraction session.

The best treatment for oroantral communication is to prevent it from occurring by performing a good planning and careful observation of the case, both radiographically and clinically. Radiographic analysis allows visualization of the existence of pneumatized maxillary sinus, divergent or dilacerated roots to determine the risk of perforating or fracturing the maxillary sinus floor during tooth extraction. If perforation occurs, the type of treatment to be performed will depend on the size of the communication, the presence of preoperative infectious processes such as sinusitis, periodontal disease or periapical lesions, and the presence of dental fragments or other foreign bodies introduced into the maxillary sinus (Peterson et al., 2000).

Several authors propose surgical techniques to close the oroantral communication, however, these techniques do not always have satisfactory results (Hanazawa et al., 1995). Among the options of sliding flaps for the case in question, the buccal sliding flap may be the most common and simple procedure, but this type of treatment can cause loss of depth of the buccal sulcus and decrease in attached gingiva (Graziani, 1995; Peterson et al., 2000; Konate et al., 2021). The palatal sliding flap has the advantage of a greater thickness and irrigation, providing a flap with sufficient size and mobility. However, it causes discomfort and pain in the region of exposed bone tissue, in addition to increasing the risk of infection (Kwon et al., 2020).

The pedicled buccal fat pad graft is not a new technique, as mentioned by Tideman et al. (1986), and was another treatment option for the case due to the size of the fistula being larger than 3 mm. The buccal fat pad has easy surgical access and considerable mobility, allowing for its traction and positioning over the fistula. The process of epithelialization is evident in the oral cavity on the seventh postoperative day and is complete in the 3rd or 4th week through a process of metaplasia. This process occurs similarly in the membrane of the maxillary sinus (Mannelli et al., 2019).

In the case in question, considering the size of the communication, we observed that the amount required for the use of the pedicled buccal fat pad graft could cause some facial asymmetry and post-operative complications related to excessive edema

and bleeding. We opted for the simultaneous manipulation of the vestibular and palatal flaps, slid using the zetaplasty technique described here.

Zetaplasty is recommended in frenectomies and cheiloplasties. The zetaplasty technique used here for the closure of the oroantral communication was an adaptation of the principles of flap sliding to optimize the closure of a wound without requiring extensive tissue dissection.

The fact that the patient is a smoker worsens the prognosis of the proposed treatment because smoking is a risk factor for oral surgeries, which can lead to complications related to poor wound healing (Bereczki-Temistocle et al., 2022). As smoking is a significant extrinsic factor that affects both the rate and quality of wound healing, increasing the risk of postoperative wound complications such as infection, dehiscence, and necrosis (Ahn et al., 2008), the authors sought an appropriate technique for closing the buccal sinus communication. Wounds need adequate blood supply to receive the various nutrients, chemicals, and cells required in the complex wound healing process, especially in the closure of buccal sinus communications. Smoking leads to hypoxia as a result of reduced blood flow to the skin and decreased oxygen-hemoglobin concentration due to competitive binding of carbon monoxide with heme molecules in red blood cells (Campanile et al., 1998). The technique employed in this case report, using small pedicled flaps, vestibular and palatal, for complete closure of the fistula, provided lower risks of tissue dehiscence and necrosis, especially in patients like this. Clinical and radiographic observation allowed for the observation of a good resolution of the presented case.

Conclusion

Therefore, the presented case showed that there was a high possibility that the communication was caused by the absence of adequate planning and improper maneuvers during tooth extraction. The choice of surgical treatment modality was based on the extent of the communication. It is believed that the sliding flap technique by zetaplasty presented in this study was effective in resolving the case, as to date, there has been no need for surgical reintervention.

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