Current Status, Prevention and Treatment of BK Virus Nephropathy

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ABSTRACT

All renal transplant recipients should undergo a regular screening for BK viral (BKV) viremia. Gradual reduction of immunosuppression is recommended in patients with persistent plasma BKV viremia for 3 weeks after the first detection, reflecting the presence of probable or suspected BKV-associated nephropathy. Reduction of immunosuppression is also a primary intervention in biopsy proven nephropathy associated with BKV (BKVN). Thus, allograft biopsy is not required to treat patients with BKV viremia with stabilized graft function. There is a lack of proper randomised clinical trials recommending treatment in the form of switching from tacrolimus to cyclosporin-A, from mycophenolate to mTOR inhibitors or leflunomide, or the additive use of intravenous immunoglobulins, leflunomide or cidofovir. Fluoroquinolones are not recommended for prophylaxis or therapy. There are on-going studies to evaluate the possibility of using a multi-epitope anti-BKV vaccine, administration of BKV-specific T cell immunotherapy, BKV-specific human monoclonal antibody and RNA antisense oligonucleotides. Retransplantation after allograft loss due to BKVN can be successful if BKV viremia is definitively removed, regardless of allograft nephrectomy.

KEYWORDS

BK virus nephropathy; BK virus-specific T-cell immunotherapy; monoclonal anti-BK virus antibodies; BK virus vaccine; immunosuppressive therapy; RNA antisense oligonucleotides; kidney transplantation

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INTRODUCTION

BKVN represents a severe infection, threatening function of the kidney graft, particularly during the first year after transplantation. Its occurrence is closely related to the level of attenuation of the recipient's immune system. In the absence of BK specific treatment options for advanced BKVN, active screening for BKV replication and subsequent immunosuppression adjustment represent essential measures in preventing the development of BKVN. Management during modification of immunosuppressive protocols as well as addressing the initial stages of replication associated with significant urinary BKV excretion remain not completely clear.

EPIDEMIOLOGY AND PATHOGENESIS OF BKVN

BKV is a polyomavirus, which traditionally causes nephropathy in renal allografts as a result of reactivation of latent BKV in renal tubular epithelium (1). Based on the amino acid sequence of the large T-antigen, polyomaviruses are divided into 4 genera with >70 species. BKV is an omnipresent, small (40–45 nm) DNA virus, consists of a capsid and a DNA double helix but lacks a lipid envelope. The large T-antigen is important for BKV replication, recognition by the cellular immunity components and virus oncogenicity. Genotype I and its subgroup I/b-2 (60–80%) are predominant, followed by the genotype IVa (10–20%) (2, 3). BKV was first reported in the 1970s (4). In the first months of life, maternal antibodies protect infants from BKV infection, and after their disappearance, BKV infection starts to occur, as demonstrated by 10% to 30% seropositivity in infants and 65% to >90% between 5 and 10 years of age (5). Primary BKV infection in immunocompetent patients is usually a subclinical event or associated with mild nonspecific symptoms, after which BKV persists in the kidney, peripheral-blood leukocytes and possibly the brain. Transmission is ongoing from person-to-person, foecal-oral transmission via wastewater is also possible. Furthermore, leukocyte-containing blood transfusion and transplacental transmission has been also reported (4, 6). BKV replicates itself in the nucleus of renal tubular proximal epithelial cells that are also the natural host cells (6). Daughter viruses are delivered to other cells to spread infection (7), which is followed by necrosis, inflammation and local tissue damage which enables the virus to penetrate into the intertubular space, peritubular capillaries and adjacent cells (8). About 5–15% of renal transplant recipients become viremic, and 20–40% become BK viruric, ureteral stenosis is rarer (9, 10). Only viremia has been related to BKVN (11). Graft failure has been observed in 50–80% of recipients who developed BKVN within 24 months from virus detection (12). Potential risk factors associated with BKVN development are the age of both the donor and the recipient, male gender, obesity, diabetes duration, delayed graft function (13), degree of HLA mismatches, ABO-discordance, the condition of retransplant, higher variability in mean tacrolimus levels, kidneys received from BKV seropositive donors and transplanted to BKV seronegative recipients as well as donors and recipients positivity in the serum of both BKV and cytomegalovirus (CMV) (14).

CLINICAL MANIFESTATIONS OF BKVN

BKV replication can be detected as early as 1 month after kidney transplantation and its overall accumulative rate increases steadily with time after transplantation, most frequently occurs during the first year after transplantation (in a range of six days to five years) when immunosuppression is at its most intense (11, 15). BKV has been associated with several clinical manifestations amongst them most prominently BKVN, ureteral stenosis and late-onset haemorrhagic cystitis, particularly in patients after bone marrow transplantation (16). Most frequently, we may observe only asymptomatic, acute or gradual creatinine elevation, the urinalysis corresponds to interstitial nephritis. However, the urine examination may be even completely normal (17). Early donor-specific antibody (DSA) formation in case of BKV viraemia has been reported in African-American graft recipients more commonly in the first 24 months after transplantation (18). Association between persistent BKV viraemia (≥140 days) and significant class II DSA de-novo formation has also been pointed out by Sawinski et al. (2015) (19). Collapsing glomerulopathy in regressing BKVN after immunosuppressive therapy reduction has also been documented, as well as co-occurrence of BKVN with cytomegalovirus glomerulitis in the first weeks after kidney transplantation (20, 21). Also, the association with malignancies remains a topic of ongoing discussion (16). Cases of BKV-positive urothelial bladder carcinoma developing 15 months after transplantation have been reported, as well as BKV-positive urothelial carcinoma of the graft 5 years after clinically successful BKVN therapy (22, 23). Unusual manifestations may include vasculopathy, retinitis, hepatitis, systemic lupus erythematosus, Guillain-Barré syndrome, cases of meningoencephalitis and interstitial pneumonitis (24). Metastatic clonal BKV spread from kidneys to other organs was not detected (25).

BKVN DIAGNOSTICS

Regular screening of BKV reactivation in asymptomatic patients is of paramount importance to prevent graft dysfunction. Prospective screening may be based on monitoring of decoy cells in urine; quantitative polymerase chain reaction (PCR)-BKV analysis of urine and peripheral blood is rather currently used (26).

PCR

The presence of viruria usually precedes BKV viraemia by 4 weeks and the development of BKVN with graft dysfunction by 8 weeks in average (27). PCR method analysing is the most sensitive marker of BKV reactivation, occurring in 23–73% of recipients. More than 95% of viral load in urine comes from BKV replication in uroepithelium and only less than 5% from tubular cell BKV replication (28).

Recently, high levels of BKV viruria (≥ 2.5 × 10^7 copies/ml) have been documented as a possible early marker of the BKV viraemia and BKVN development risk (29). The influence of persistent nephrotoxicity of calcineurin inhibitors (CI) on the higher incidence of significant BKV viruria (> 10^7 copies/ml) with more frequent transition to BKV viraemia and BKVN in the first year after transplantation has also been reported (30). Frequent PCR screening of viruria is currently a common method for early detection of BKV replication (31). Its importance is highest during the first year after transplantation, or within 2 years from the procedure (32). BKV viraemia affects 8–62% of kidney recipients with a maximum incidence of 3–6 months after transplantation (33). BKVN incidence during the first year is reported in a range of 1–10% (34). Plasma viraemia >10^4 copies/ml has a stronger positive predictive value for BKVN than viruria (35). However, less than 10^4/ml plasma copies have been demonstrated in up to 35% of BKVN patients (36). Todays, higher BKV prevalence is noted based on standardized detection. In one recent study, PCR testing for viremia or viruria indicated BKV positivity in 62% of patients (37). In the current study urinary cell mRNA profiling showed 86% sensitivity and 100% specificity (38). PCR negative cases have been reported sporadically (39).

ALTERNATIVE METHODS OF BKV REPLICATION DETECTION

PCR from saliva and oral cavity flush has similar efficacy in detection of BKV and John Cunningham virus (JCV) as the blood and urine analysis (40). The uptake of cylinder-like three-dimensional aggregates of polyomaviruses in urine in the electronmicroscopic examination, so-called Haufen bodies (HB), is accompanied by substantial BKV viraemia and provided 100% sensitivity and 99% specificity for detection of biopsy proven BKVN. Quantitative determination of HB and BKVN has also demonstrated very good correlation (41). Determination of BKV mRNA levels in urine using a cut-off limit of 6.5 × 10^5 BKV VP1 mRNAs/ng of RNA in urinary cells has shown 99% sensitivity and specificity for BKVN detection (42). Elevation in urinary exosomal BKV-micro RNA-B1–5p throughout the first 12 months post-transplantation precedes the development of PCR-BKV viraemia and subsequent manifestation of BKVN (43). Serology examination aimed at demonstration of BKV antibodies is not beneficial for detection of BKVN. In case of primary infection after transplantation they increase in the IgG class in at least 6 weeks after contact with the virus, but even in the intervals of up to 2 years (44).

CURRENT GUIDELINES FOR PRE-TRANSPLANT SCREENING OF BKV REPLICATION

Due to the absence of valid studies, pre-transplant donor screening of BKV viruria, virus genotyping or examination of VLP/Vp1 specific antibodies is not recommended. Similarly, recipient testing for VLP/Vp1 specific antibodies, neutralizing BKV antibodies (BKV subtypes), and the presence and function of BKV-specific T cells is not suggested within pre-transplant screening (45).

CURRENT GUIDELINES FOR POST-TRANSPLANT SCREENING OF BKV REPLICATION

BKV-DNA viraemia PCR monitoring is recommended in the post-transplant period to initiate preemptive therapy early and prevent the development of BKVN. Alternatively, urinary DC evaluation may be used when the urine finding of > 3 DC/HPF or BKV viruria > 10^7 copies/ml may be considered positive (45, 46). Testing should be performed monthly during the first year after transplantation for the first 9 months; afterwards, every 3 months up to 2 years after transplantation (47). Then, it is appropriate to test at an annual frequency for 5 years. Potential BKV replication should also be evaluated at any per-protocol or diagnostic biopsy, particularly in case of unclear dysfunction. Detection of BKV-DNA viraemia should be confirmed within the next 3 weeks by a repeated examination. In case of viraemia persistence and stable graft function compared to the previous examination, where the patient is not at a higher risk of acute rejection (AR), immunosuppressive therapy may be reduced without biopsy (45).

CURRENT GUIDELINES FOR GRAFT BIOPSY IN CASE OF SUSPECTED BKVN

Biopsy should be performed before reduction of immunosuppressive therapy in case of a high immunological risk or progressive graft dysfunction (48). Biopsy procedure should include collection of 2 samples of the renal tissue to capture the medullary part of the parenchyma. 10–30% of biopsy samples may be falsely negative in case of focal distribution of changes and predominance of medullary involvement within BKVN (45, 49). BKVN should be considered in cytopathic changes in tubular epithelial cells and confirmed with immunohistochemistry (SV40 +). Histological findings in demonstrated BKVN should be evaluated based on the AST-IDCOP 2013 guidelines together with the guidelines of Banff 2018 Study group (45, 48). The Banff 2018 kidney allograft biopsy classification schema applies a semiquantitative scoring system of 0, 1, 2, or 3 for scoring acute and chronic histological lesions within the kidney allograft (50, 51). In 2019 a consensus panel including viral infections associated with transplantation was established (51). However, a well-designed study failed to show clear relationship between any of the morphological histological features or categories and graft prognosis (49). Furthermore, another large study has demonstrated that graft loss in BKVN correlates with 3 clinical parameters only – transplant from a deceased donor, level of BKV viraemia, and the incidence of late AR (52). Multicenter retrospective study of 124 patients with BKVN found no correlation between Banff 2018 classification classes and risk of graft loss (53).

CURRENT GUIDELINES IN CASE OF BKVN AND AR COINCIDENCE

If AR and BKVN co-occurrence is suspected, we should search for the presence of rejection endarteritis, fibrinoid

vascular necrosis, glomerulitis or C4d deposition around the peritubular capillaries. Tubulitis and peritubular inflammation are not AR-specific and are also present in BKVN. Moreover, they may occur outside the region where BKVN was detected (54). C4d+ positivity may be detected in tubular basement membranes in isolated BKVN, but not in peritubular capillaries. Alloreactive and virus-reactive T cells co-occurrence is also common (55). Thus, anti-rejection therapy should be initiated in patients with biopsy proven AR, with persistent BKV viraemia (with or without histological verification of BKVN) as the first step. Only if there is a clinical and laboratory response to anti-rejection therapy after approximately 2 weeks, the second step should follow with reduction in immunosuppressive therapy (45).

CURRENT GUIDELINES FOR BKV VIRAEMIA AND BKVN THERAPY

Therapy of significant BKV viraemia and BKVN is based on reduction of immunosuppressive therapy. The diagnosis of BKVN is probable in case of demonstration of > 10^3 copies/ml of blood (2 measurements over 3 weeks) and presumptive in case of demonstration of > 10^4 copies/ml of blood (at least 1 measurement out of 2). BKV viraemia resolution may be expected in 80–100% of patients after reduction of immunosuppressive therapy, BKV viraemia recurrence in 10% of patients. Further reduction of immunosuppression is recommended in such a case (56, 57). If immunosuppressive therapy is reduced in already developed BKVN (biopsy proven), the effect on viraemia is usually substantially worse and further intervention is often required; function restitution may take longer and definitive failure of graft function is more frequent as well (45, 58). Immunosuppressant level targets should be < 6 ng/ml for tacrolimus, < 150 ng/ml for cyclosporine, < 6 ng/ml for sirolimus; mycophenolate should be administered in a half or lower dose. Complementary therapy based on conversion of tacrolimus to low-dose cyclosporine, CI to sirolimus or mycophenolate replacement with leflunomide may be considered. There are practically two options for immunosuppressive therapy reduction. In the first case, we initiate therapy with reduction of the CI dose by 25–50%; in the next step, MMF is reduced by 50% or then completely withdrawn. This approach could be particularly advantageous in the case of the current histological finding of CI nephrotoxicity (30). The second option is to start the treatment with reduction of MMF by 50%, followed by CI dose decrease by 25–50% in case of the persistence of virus replication, followed by withdrawal of MMF. The dose of prednisone should be < 10 mg/day in both cases. It is recommended to repeat testing every 2 weeks in this therapy until viraemia disappears; should viraemia persist, the management is individual – further reduction of immunosuppression is recommended with target tacrolimus levels of < 3 ng/ml and cyclosporine levels of < 100 ng/ml. mTORi for therapy of refractory or advanced BKVN is also possible. Supportive antiviral therapy may be considered in patients with persistent BKV viraemia and probable, presumptive or biopsy proven BKVN, despite adequately reduced immunosuppressive therapy (45).

SUPPORTIVE THERAPY OF BKVN

INTRAVENOUS IMMUNOGLOBULINS (IVIG)

IVIGs may contain antibodies against omnipresent BKV and JCV. However, the neutralising effect of these antibodies against all major BKV genotypes is not generally accepted (44). Possible effect of IVIG on strengthening of the overall antibody response may be expected in inadequate cellular reactivity (59). They are mostly administered in a dose of 0.1–2 g/kg with concomitant reduction of immunosuppressive therapy (45).

ALTERNATIVE PROCEDURES IN BKVN THERAPY

Conversion from tacrolimus to low-dose cyclosporine may be considered, taking advantage of the suppressive effects of cyclosporine for BKV replication and at the same time reducing mycophenolate levels. In a study by Chen et al., conversion from tacrolimus to low-dose cyclosporine was effective in BKVN therapy (59). A prospective observational study in patients with BKV viraemia and BKVN to evaluate the effect of this conversion on virus replication is currently ongoing (60). Cidofovir can inhibit polyoma viral DNA replication but is primarily excreted by the kidneys and is nephrotoxic. The lack of randomized studies have led to reluctance to adopt it widely. Prophylaxis with newer less toxic brincidofovir may yet prove effective (61).

POSSIBILITIES OF IMMUNOTHERAPY IN THE TREATMENT OF BKVN

BKV SPECIFIC T CELL IMMUNOTHERAPY

Failure of BKV-specific T cell to control viral replication due to IS overdose results in reactivation of BKV infection (62). A phase II clinical trial showed that administration of BKV-specific T cells manufactured from a patient's stem cell donor or unrelated donors could reduce symptomatic infection and BK viral load effectively in HSCT and solid organ transplant recipients. Virus-specific T cells therapy in this study was safe with no infusional toxicity, de novo graft-versus-host disease, or graft rejection (63). A phase II of multicentre, randomized, double-blind, placebo-controlled trial of adoptively transferred multivirus-specific T cells in kidney transplant recipients with either high or low levels of BK viraemia is also currently underway. Its results are expected in 2023 (64).

ANTIBODIES IN THE TREATMENT OF BK VIRUS

A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of MAU868 for the treatment of BK viraemia in kidney transplant recipients is currently being conducted (65). MAU868 is a human monoclonal antibody (IgG1), which binds to viral capsid protein VP1 and blocks the binding of the virus to the host cell surface. It could be the first effective therapy for BKV infection. Final results of the study are expected in 2023 (66).

BKV VACCINE DEVELOPMENT

Administration of a multi-epitope VLP vaccine, which is associated with a significant response in the form of antibody production that neutralizes all 5 BKV serotypes, appears promising (67). A prospective phase II multicenter study to evaluate the tolerability and safety of BD03, a DNA vaccine administered intramuscularly for the prevention of CMV and BKV reactivation in kidney transplant recipients, is currently in progress (68).

RNA-BASED THERAPY (HYBRIDIZE'S THERAPEUTICS)

A direct acting anti-viral therapy is designed to target the viral mRNA, work intra-cellular and protect the cells from within and therefore provides for low off-target effects. RNA antisense oligonucleotides discontinues the splicing process, preventing viral synthesis and replication (69). Clinical studies to prevent severe disease from BK virus (BKV) infections in immunocompromised patients are expected to start within two years (70).

SUMMARY

BKVN represents a severe complication, threatening function of the kidney graft, particularly during the first year after transplantation. But we have to bear it in mind in every deterioration of function. Its incidence is likely to increase with the increasing number of retransplants and incompatible transplants. Active screening for BKV replication in the post-transplant period represents an essential prophylactic procedure in prevention of the graft damage considering the absence of BKV-specific antiviral therapy. It allows for initiation of preemptive reduction of immunosuppressive therapy in case of demonstration of significant BKV viraemia, thus preventing the development of nephropathy. This approach appears to be effective for reduction of early graft loss due to BKVN, despite a higher risk of alloimmune activation and AR. Post-transplantation screening of BKV replication is also suitable in organ recipients during non-renal transplants considering possible BKV reactivation affecting their own kidney. Non-specific antiviral therapy is utilised in patients with clinically manifest BKVN with graft dysfunction progressing over a few weeks or months despite maximum immunosuppressive therapy reduction. Retransplantation is delayed in patients with BKVN-induced graft failure until BKV viraemia resolution. General nephro-ureterectomy of the original transplanted kidney is not recommended in the absence of BKV replication. Research on multi-epitope anti-BKV vaccination, BKV-specific T cell or antibody mediated immunotherapy or the development of BKV specific antivirals and direct acting anti-viral therapy is of much importance. If shown to be safe and effective, this therapy could be a true game changer in transplantation medicine with the potential to prevent kidney transplant patients from developing graft rejection and organ loss due to BKV.

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Primary Duodenal Melanoma: Challenges in Diagnosis and Management of a Rare Entity

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ABSTRACT

Primary melanoma of the duodenum is an extremely rare, aggressive and life-threatening malignant neoplasm. Published data regarding the effectiveness of current treatment strategies is limited, and our knowledge relies mostly on sporadic case reports. The diagnosis of primary duodenal melanoma is challenging and is based on the patient's medical history and findings from physical examination and radiological and endoscopic imaging as well as proper and careful pathological examinations of the tumor. Despite the many advances in cancer treatment, the prognosis for patients with this type of melanoma remains extremely poor. Delayed diagnosis at advanced disease stage, the general aggressive behavior of this neoplasm, the technical difficulty in achieving complete surgical resection, along with the rich vascular and lymphatic drainage of the intestinal mucosa, all have a negative impact on patients' outcome. In the present review, we aimed to collect and summarize the currently available data in the literature regarding the pathogenesis, clinical features, diagnosis, management and long-term outcomes of this rare, malignant tumor, in order to expand knowledge of its biological behavior and investigate optimal therapeutic options for these patients. Additionally, we present our experience of a case involving a 73-year-old female with primary duodenal melanoma, who was successfully treated with complete surgical resection.

KEYWORDS

primary duodenal melanoma; diagnosis; management; outcome; treatment; prognosis

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INTRODUCTION

Malignant gastrointestinal (GI) melanomas, primary or metastatic, are exceedingly rare, representing just 1–3% of all malignant neoplasms located along the GI tract (1). In the absence of a screened primary cutaneous lesion, differentiation between the primary and metastatic nature of a malignant melanoma (MM) can be highly challenging to establish (2, 3). In the case of secondary localization, the metastatic site can vary greatly throughout the entire length of the GI tract; nonetheless, the most frequent metastatic site is the small bowel (4). Primary mucosal melanoma is an unusual oncologic entity, accounting for only 1% of all melanomas, being epidemiologically and molecularly distinct from the cutaneous subtype. It occurs less commonly in the small intestine and presents high malignant potential, with an estimated 5-year overall survival rate of 25%, regardless of stage (5–7). Specifically, it has been demonstrated that the primary sites of MMs originating from the GI tract were mainly the oropharynx and nasopharynx (32.8%), anal canal (31.4 %) and rectum (22.2%), while small intestine tumors accounted for only 2.3% of GI melanomas(8). Primary melanoma of the duodenum (PMD) is shown to be extremely aggressive and life-threatening. It is associated with dismal prognosis, possibly due to its insidious anatomical localization and lack of symptoms in early stages, resulting in extensive disease at the time of diagnosis (9, 10). Due to its rare occurrence, real-world data on the efficacy of existing treatments are scarce, and as there are no specific recommendations, our current knowledge relies mostly on sporadic case reports.

In this review, we aimed to summarize the limited existing evidence concerning the pathogenesis, clinical features, diagnosis and management of this infrequent but difficult malignancy in the adult population, in order to enhance the knowledge of its biological behavior and highlight the optimal treatment approach for the patients. Additionally, we describe our related clinical experience in a case of PMD successfully treated by surgical resection.

CASE PRESENTATION

A 73-year-old female patient presented to our emergency department with a five-day history of moderate epigastric pain accompanied by multiple episodes of emesis and melena. At presentation, she was hemodynamically stable but with signs of mild dehydration. Physical examination revealed a mildly distended abdomen with tenderness to palpation, especially in the epigastrium. On auscultation, bowel sounds were normal, with no sign of bowel obstruction. Laboratory evaluation revealed mild anemia (hemoglobin of 8.8 g/dL; reference range: 12.0–15.0 g/dL). Her past medical history was unremarkable. Abdominal computed tomography (CT) performed on admission revealed a large mass at the level of the third portion of the duodenum, with significant dilation of the stomach and first and second portions of the duodenum (Figure 1). Upper endoscopy confirmed a duodenal obstruction (Figure 2). A biopsy and histological examination of the lesion indicated MM (Figure 3).

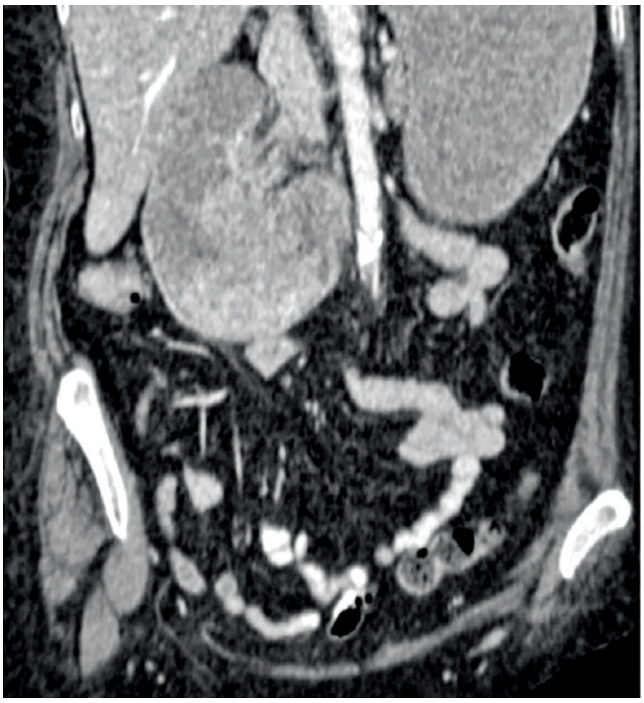

Fig. 1 Abdominal computed tomography revealed a large mass at the level of third portion of the duodenum with a significant dilation of stomach and first and second portions of the duodenum.

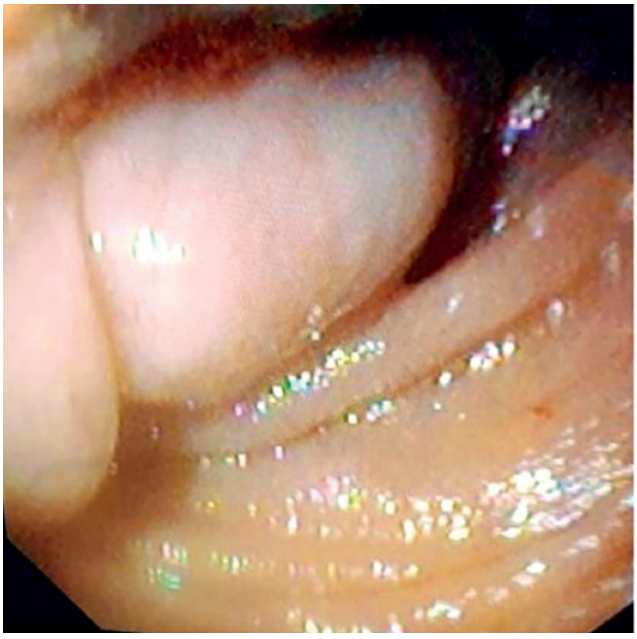

Fig. 2 Upper endoscopy confirmed a subtotal obstructing duodenal mass.

Accordingly, the patient underwent exhaustive systemic evaluation including cutaneous, retina, nasal and oral cavity examination as well as a colonoscopy, which did not detect a primary melanoma lesion. Therefore, the lesion was categorized as a PMD. After optimization of the patient's condition, a Whipple's procedure was performed. Her postoperative course was uneventful and she was discharged on postoperative day 10. At 3-year follow-up, the patient remains disease-free. Informed consent was given by the patient for publication of this case.

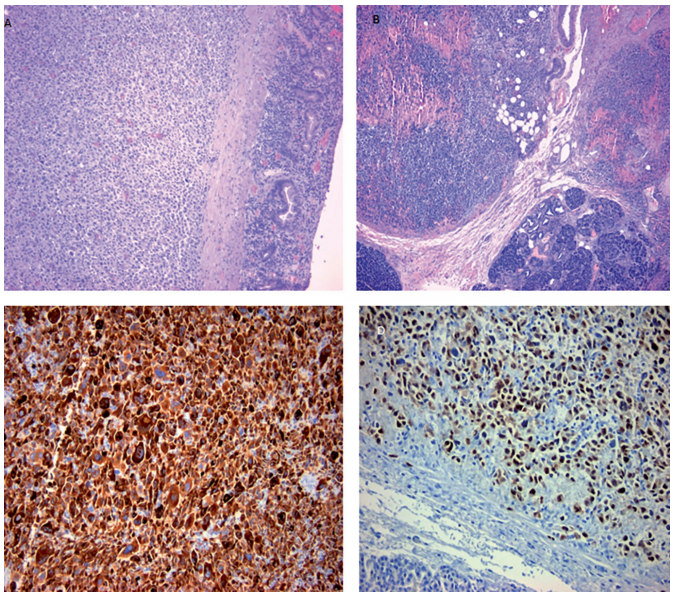

Fig. 3 Biopsied sections showed a pleiomorphic tumor infiltrating adjacent organs. A: Duodenum (hematoxylin & eosin, 200×); B: Pancreas (hematoxylin & eosin, 200×); C–D: By immunohistochemistry, the cells were positive for S100 (C; 400×) and SOX10 (D; 400×).

PATHOGENESIS

PMD is a particularly rare tumor with unclear etiology. Several theories have attempted to describe its pathogenesis in the past, but determination of its exact origin remains problematic and controversial. One hypothesis proposes that although melanocytes are not normally contained within the small and large bowel, they can be sporadically found in the mucosa epithelium of the alimentary tract and in the lymph nodes, leading to the development of primary melanomas at these sites (11). Another theory suggests that these neoplasms may arise from Schwann cells related to the autonomic innervation of the gut (12). Others have postulated that GI melanomas might originate from melanoblastic neural crest cells that migrate into the GI mucosa *via* the umbilical-mesenteric canal during embryogenesis, where they differentiate into amine precursor uptake and decarboxylation cells (13). Subsequently, amine precursor uptake and decarboxylation cells may potentially transform into neoplastic cells and produce tumors such as gastrinomas, carcinoids and melanomas (13). Furthermore, it has been presumed that melanoblasts normally exist in the small intestine and might behave as precursors to MM. Other researchers disagree with the presence of primary melanomas in the small intestine and maintain that these lesions represent metastasis from unknown or regressed primary cutaneous tumors (1, 14–16).

CLINICAL PRESENTATION

Clinical presentation of MM originating in the duodenum involves a broad spectrum of clinical features and is often elusive, as it varies between patients depending on the extent of disease (3, 10, 17, 18). Remarkably, in most cases, no specific early symptomatology has been reported The tumor becomes noticeable only when its growth presses on neighboring structures or invades surrounding tissue, or when metastasis has occurred (6, 19, 20). Since diagnosis is frequently delayed, a high index of suspicion is required to reveal its incidence. Its symptoms generally include abdominal pain, intestinal obstruction, hematemesis, melena, vomiting, weakness, weight loss, anemia, loss of appetite, constipation, malabsorption, perforated bowel, jaundice and palpable abdominal mass, which are typically identical to those of other types of duodenal tumors (3, 17, 21, 22). In comparison to duodenal adenocarcinoma, which presents more frequently with obstructive jaundice, most patients with PMD initially present with abdominal pain, anemia, upper GI hemorrhage or a palpable abdominal mass (3, 18, 21).

From the year 2000 until today, a total of only 12 cases of PMD have been reported in the literature, seven of which concerned males with a median age at diagnosis of 56.5 years-old (Table 1). No risk factors have been confirmed, possibly because PMD develops on surfaces that are not exposed to ultraviolet light (23). A detailed and accurate history often reveals several episodes of intermittent midepigastric pain, sometimes associated with vomiting and nausea, while fatigue, weakness and weight loss have also been recorded. According to the published cases, the majority of patients presented to hospital with abdominal pain (n = 8). Five patients were referred with upper GI hemorrhage, such as melena or hematemesis, and five mentioned weight loss; six out of 12 patients were diagnosed with anemia. Furthermore, as illustrated in Table one, six patients described feelings of fatigue or weakness and five reported occasional episodes of vomiting, while two patients displayed jaundice attributable to an obstructive tumoral mass in the ampulla of Vater.

A thorough physical examination may demonstrate epigastric sensitivity, a palpable, firm abdominal mass (two cases), or lymphadenopathy that indicates extensive disease. The pre-existence or coexistence of a primary lesion must also be excluded at this time (3). In our review, all patients had negative ophthalmological, otorhinolaryngeal and dermatological examination findings for other primary locations of melanoma.

DIAGNOSIS

As this type of neoplasm is rare and no typical early symptoms or signs are evident, diagnosis is invariably reached late during the disease course (6, 19). Difficult anatomical localization demanding visual detection and frequent amelanotic presentation pose a challenge to clinicians (7). Definite diagnosis relies on the combination of clinical examination, endoscopic and radiological imaging findings and careful histologic investigation with the use of proper immunohistochemical stains (9, 10). Initially, a potential metastatic spread should be excluded; although, primary or secondary origin of GI melanomas can be difficult or even impossible to establish, giving rise to much controversy (2, 3, 24, 25). Indeed, the primary site may regress

Tab. 1 Characteristics and management of reported cases with primary duodenal melanoma.

Year; Author	No of cases	Sex	Age (years)	Primary symptom	Systemic exploration for melanoma	Diagnosis-Radiogical-Biomarkers	Distant metastasis	Management	Adjuvant chemotherapy	Pathologic examination / LN+	Stains	Follow-up(months)	Recurrence	Melanoma related death	Survival
Kilambi 2017	1	M	35	Abdominal pain, weight loss	Negative	U/S, Upper GI endoscopy, CT, EUS-FNA, PET	No	Pancreaticoduodenal resection & Colectomy	Yes temozolamide	MM / Yes	HMB-45(+), S-100 protein(–)	32	No	No	Alive at 32 months
Jain 2015	1	M	35	Abdominal pain, vomiting	Negative	U/S, PET	No	Resection	Yes chemoradiotherapy	MM / Not known	HMB-45(+), S-100 protein(+)	Not known	Not known	Not known	Not known
Suganuma 2013	1	M	67	Anemia, Fatigue, dyspnea	Negative	EGD, EUS-FNA, GBS, PET, CT	Yes Stomach, left adrenal gland	Distal duodenojejunectomy, partial gastrectomy, left adreanalectomy	Yes Dacarbazine, vincristine, nimustine	AMM / No	HMB-45(–), S-100 protein(+), Melan A(+)	36	No	No	Alive at 36 months
Bendic 2013	1	M	52	Abdominal pain, hematemesis, jaundice, weakness	Negative	Upper GI endoscopy, CT, US	No	Whipple	No	AMM/ Yes	S-100(+), Melan-A(+), Vimentin(+)	6	Yes	Yes	Died at 6 months
Li 2012	1	M	60	Abdominal pain, melena, vomiting	Negative	Upper GI endoscopy, GBS, CT	No	Tumor resection	No	MM/ Yes	HMB-45(+), S-100 protein(+), vomiting-Melan-A(+), Vimentin(+)	46	No	No	Alive at 46 months
Korkolis 2008	1	M	55	Abdominal pain, massive upper GI hemorrhage, anemia	Negative	Upper GI endoscopy, CT	No	Pancreaticoduodenal resection	Yes Interferon	MM/ Yes	HMB-45(+), S-100 protein(+), Melan-A(+), Vimentin(+)	14	No	No	Alive at 14 months

Year; Author	No of cases	Sex	Age (years)	Primary symptom	Systemic exploration for melanoma	Diagnosis-Radiogical-Biomarkers	Distant metastasis	Management	Adjuvant chemother-apy	Pathologic examination / LN+	Stains	Follow-up(months)	Recurrence	Melanoma related death	Survival
Houissa 2001	1	F	78	Abdominal pain, weakness, weight loss, loss of appetite anemia	Negative	Upper GI endoscopy, CT, U/S	Yes Stomach, esophagus, liver	Palliative	No	MM/Yes	HMB-45(+), Melan-A(–),	1	Not known	Yes	Died at 1 month
Flechon 2002	1	F	33	Jaundice, pruritus, vomiting	Negative	Upper GI endoscopy, CT, EUS-FNA, U/S	Yes, pancreas, interpancreaticoduodenal region	Pancreaticoduodenal resection	No	MM/Yes	HMB-45(+), S-100 protein(+), Melan-A(+), Vimentin(+)	2	Yes	Yes	Died at 2 months
Zhou 2020	1	F	58	Bone pain, fatigue	Negative	Upper GI endoscopy, CT, MDP	Yes Liver and bone	Palliative	No	MM/Not known	HMB-45(+), S-100 protein(+)	1	Not known	Yes	Died at 1 month
Anvari 2018	1	M	68	Fatigue, weakness, lethargy, weight loss, anemia	Negative	Upper GI endoscopy, CT	Yes Gallbladder, adrenal glands, mesenteric lymph nodes	Palliative chemotherapy (temozolamide)	No	MM/Yes	S-100 protein(+), Melan-A(+),	Not known	Not known	Yes	Died quickly
Surjan 2020	1	F	40	Abdominal pain, anorexia, weight loss, vomiting, melena, anemia	Negative	Upper GI endoscopy, CT	No	Pancreaticoduodejunal resection	Yes cisplatin-temozolamide	MM/No	HMB-45(+), S-100 protein(+), Melan-A(+),	36	No	No	Alive at 36 months
Coban 2013	1	F	63	Abdominal pain, melena, hematemesis, fatigue, weakness, vomiting, weight loss, anemia	Negative	Upper GI endoscopy, CT	No	Palliative	No	MM/Not known	HMB-45(+), S-100 protein(+),	1	Not known	Yes	Died at 3 weeks

AMM: Amelanotic malignant melanoma; CT: Computed tomography; EGD: Esophagogastroduodenoscopy; EUS-FNA; Endoscopic ultrasound-guided fine needle aspiration; GBS: Gastrointestinal barium study; GI: Gastrointestinal; HMD-45: Human melanoma black-45; LN+: Positive lymph nodes; Melan-A: Melanoma antigen; MM: Malignant melanoma; PET: Positron emission tomography; U/S: Ultrasound.

spontaneously without receipt of appropriate treatment, or it can be too small to be detected by conventional clinical and laboratory investigation techniques (26).

Several criteria have been suggested to distinguish whether a lesion is a PMD or a metastasis from another primary site. A biopsy-proven melanoma from the intestine at single focus, no evidence of disease in any other organs (including skin, eye and lymph nodes outside the region of drainage at the time of diagnosis) and presence of intramucosal lesions in the overlying or adjacent intestinal epithelium, may be required to support the diagnosis (4, 14). These criteria are based on the hypothesis that a metastatic melanoma would generally be multifocal. However, primary GI melanomas may present as single or multiple lesions. At least two cases have been described in the literature with primary diffuse upper GI tract melanoma with masses involving the stomach and duodenum, most likely through local hematogenous metastasis (22, 27–29). In addition, five cases with metastases to other organs have been reported, which is consistent with the aggressive behavior of mucosal melanomas (9, 22, 27–29). Even if these cases do not fulfill the above criteria, current data suggest that they are primary melanomas. Consequently, the criteria may need to be revised in order to establish a proper diagnosis.

A plethora of imaging studies has been used for the preoperative diagnosis of PMD. Since patients mostly present to the hospital with vague abdominal symptoms, transabdominal ultrasonography is typically the first diagnostic tool, as (18, 21), as it could detect a large mass arising from the region of the duodenum or dilatation of the main or intrahepatic bile ducts due to obstruction of the ampulla of Vater (18, 22). Barium examination can improve intestinal imaging but is not appropriate for extraintestinal findings (10, 29). CT allows for better visualization of the duodenum and can define extraluminal and metastatic disease, although the reported sensitivity of CT for detection of intestinal melanoma is only 60–70% (30–32). Sensitivity and specificity are higher with 18-fluorodeoxyglucose whole-body positron emission tomography imaging (FDG-PET), which can offer a dual advantage by excluding other primary tumors and by staging the disease (21, 33). The most valuable diagnostic procedure is the esophagogastroduodenoscopy, as the presence of an ulcerative pigmented lesion is a pathognomonic finding, and biopsies can also be obtained at the same time (9, 32). However, endoscopic appearance may be deceptive since PMD can also present as multiple nodular lesions or as a non-pigmented lesion (18, 27, 28, 31). Indeed, in our review, two cases of amelanotic melanoma were described that complicated the diagnosis (18, 31). In addition to demonstrating the lesion and tissue acquisition, endoscopic ultrasonography is able to assess the status of the vessels entering into the mass, the layer of the duodenal wall from where the tumor originates, and the extraluminal extent (18, 22, 29). In our study, upper GI endoscopy, CT and abdominal ultrasound were the most frequently used modalities, followed by PET, endoscopic ultrasound-guided fine needle aspiration and GI barium study (Table 1).

Careful differential diagnosis is essential, as GI melanomas mimic other neoplasms, such as carcinomas, lymphomas and neuroendocrine or GI stromal tumors (10, 19, 32). Definite diagnosis of PMD is confirmed by pathological examination and several immunohistochemical markers, such as human melanoma black-45, S-100 protein, melanoma antigen (referred to as Melan-A) and vimentin (10, 20). Of note, regarding published PMD cases, seven out of 12 patients had positive lymph nodes after pathological analysis. Finally, findings from laboratory investigations are usually unremarkable, apart from anemia and abnormal hepatic biochemistry caused by the obstruction of bile ducts or metastatic disease to the liver (22, 27, 31).

STAGING

Currently, there is no universal staging system for mucosal melanomas, including PMD. However, a simplified staging system can be utilized, which was firstly applied for melanomas of the head and neck (34). Specifically, stage I involves clinically localized disease, stage II is defined as regional lymph node metastases and stage III describes the presence of distant metastatic disease (3). Nevertheless, further studies are necessary in order to establish an accurate staging system that could determine prognosis and suggest preferable and more efficient treatment, thereby improving survival.

TREATMENT

Curative surgical resection remains the gold standard treatment in patients with PMD, although its hidden and atypical presentation prevents early diagnosis, making the process challenging, morbid or even impossible (1, 3). Whether open or laparoscopic, the procedure must involve wide local excision of the neoplasm with negative margins accompanied by a subtended wedge of the mesentery to remove regional lymph nodes (3, 26). Consequently, cautious patient selection for surgery is fundamental, taking into consideration findings from imaging studies that indicate the extent of disease and patient's performance status and preference, in order to precisely predict postoperative morbidity and benefits (3, 20). With regard to the reviewed case reports, eight cases underwent surgical resection and four received palliative treatment due to metastatic disease, poor patient condition or non-acceptance of the surgical approach. The most frequent intervention was pancreaticoduodenectomy with regional lymphadenectomy (five cases). Two patients underwent tumor resection only, while one case was subjected to a distal duodenojejunostomy along with partial gastrectomy and left adrenalectomy in order to achieve complete disease excision (Table 1). In all reported cases, patient outcome was good after surgery, and no postoperative complications were recorded.

According to the published cases, two patients suffered from obstructive jaundice caused by tumors involving the ampulla region. One patient was treated with percutaneous transhepatic biliary drainage and the other underwent a pancreaticoduodenectomy (22, 31).

Published data on systemic adjuvant therapy in patients with PMD are limited, and there are no definite guidelines supporting this choice, as no improvement in the OS rate has been shown (8). The only available evidence originates from a phase II randomized trial of interferon *vs.* chemotherapy, including temozolamide and cisplatin, which showed progression-free survival in patients with resected mucosal melanoma and significantly elevated OS rates in the second group (35). However, further clinical trials with a larger patient population are needed, in order to advance adjuvant chemotherapy in accordance with general recommendations. In this context, adjuvant therapy with temozolamide alone, temozolamide-cisplatin, interferon or dacarbazine-nimustine hydrochloride-vincristine was administered to five patients with PMD with prolonged progression-free survival (Table 1) (18, 19, 21, 29, 32).

Currently, cancer immunotherapy is a hot topic that has a recognized role in cutaneous and non-cutaneous melanoma postoperatively or later in disease evolution, with substantial effects on survival (36, 37). Nevertheless, compared with skin melanomas, mucosal melanomas differ biologically; they have a lower mutational burden, less immunogenicity, and have reduced expression of programmed death-ligand 1, all of which could possibly weaken the efficacy of immunotherapy (38–40). Although there are no randomized clinical trials indicating the effectiveness of immunotherapy in patients with PMD, existing evidence illustrates that in metastatic or unresected mucosal melanomas, combination therapy with programmed cell death protein 1 and cytotoxic T-lymphocyte antigen 4 antibodies or concomitant radiotherapy and immunotherapy may be of particular benefit to OS (7, 40, 41). That being the case, broader clinical trials are warranted to clarify the role of immunotherapy on mucosal melanomas.

GI melanomas also have distinct mutational and molecular profiles compared with cutaneous subtypes (40, 42, 43). Specifically, mutations in the proto-oncogene B-Raf are rare in GI melanomas (less than 5%), whereas mutations in the proto-oncogene c-KIT are more frequent (40, 42, 43). Some clinical trials demonstrated an improved response in patients with advanced mucosal melanomas that received either c-KIT or B-Raf inhibitors, depending on the tumor's gene mutations, but further investigation is necessary (44, 45).

PROGNOSIS

Despite the many advances in cancer treatment over the past few decades, the prognosis for patients with primary GI melanomas remains extremely poor, with a median OS of up to 17 months after curative surgical intervention (8). Commonly delayed diagnosis at advanced stages, the general aggressive behavior of these neoplasms and the technical difficulty in achieving complete surgical resection, along with the rich vascular and lymphatic drainage of the intestinal mucosa, are all considered major determinants of prognosis (5, 46, 47). Microinvasion or distant metastasis have already occurred at the time of diagnosis, and current therapies are unable to offer definite treatment outcome (6, 18). According to our results, the median OS was 10 months and the longest reported survival was 46 months. Notably, no recurrence was recorded during the follow-up period of three patients (32, 36 and 36 months, respectively), who underwent surgery and received adjuvant therapy postoperatively (temozolamide, dacarbazine/vincristine/,nimustine and cisplatin/temozolamide, respectively) and of one patient (follow-up period of 46 months), who refused chemotherapy after tumor resection, choosing to use Chinese traditional medicine treatment instead (10, 18, 19, 29) (Table 1). The limited number of included cases and restricted follow-up data may significantly affect the results, and prognosis cannot be accurately calculated. Larger clinical trials are required to determine the precise morbidity and mortality of PMD. The rare nature of the disease and highly malignant potential with low survival rates pose challenges to this task.

CONCLUSION

In conclusion, PMD is a very rare, aggressive oncologic entity of the alimentary tract with an extremely devastating prognosis. As its clinical manifestation is not specific, detection of this neoplasm remains particularly demanding and definite diagnosis depends on the combination of detailed history, thorough clinical examination, advanced imaging modalities and cautious histological investigation. Differential diagnosis between primary and secondary origin of the tumor is crucial since complete surgical resection can be achieved in the case of PMD, which could lead to a significant increase in OS, contrary to patients with secondary duodenal melanoma. In the literature, however, this subject remains controversial. Given the absence of significant knowledge about this malignancy, management of PMD is unclear. A methodical, multimodal and individualized approach is required, including surgical and non-surgical options, to achieve long-term survival (> 2 years) in these patients. Although complete surgical resection is the treatment of choice, the impressive advancements in systemic therapies may open up new avenues with adequate therapeutic effect, especially in the context of advanced unresected disease. Further research is needed to understand the underlying and complex pathogenetic nature of this neoplasm in order to target it specifically and design preferable and more efficient strategies.

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Sexual Behavior of Men Who Have Sex with Men and Its Relationship to Sexually Transmitted Infections during an Outbreak of the Human Monkeypox Virus

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ABSTRACT

Background: There is a high frequency of monkeypox (MPOX) and sexually transmitted infections (STIs) in men who have sex with men (MSM).
Aim: To identify the sexual behavior of MSM during the MPOX infection period.
Methods: We conducted an observational study of cases and controls were carried out.
Results: A total of 171 participants were considered, two heterosexual male controls (MSW) were included for each case of MSM with a consecutive selection of people who attended the STI prevention and control center from January to July 2022.
The results revealed that the mean number of sexual partners reported in the last year was higher in cases (4.2) compared to controls 1.9 ($p < 0.05$). The related conditions for MSM to acquire some type of STI were sexual intercourse under the influence of alcohol (OR 2.42; 95% CI: 1.11–3.96), forgetting to use a protection method (condom) (OR 3.16; 95%: 1.73–7.48) and sexual intercourse with casual couples (OR 1.4; 95% CI: 1.01–2.16).
Conclusion: Our findings demonstrated a link between the sexual behavior of men who have sex with men and the high prevalence of sexually transmitted infections during the human monkeypox virus outbreak.

KEYWORDS

monkeypox; sexually transmitted infections; men who have sex with men; sexual behavior

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INTRODUCTION

Monkeypox (MPOX) is a zoonotic virus that belongs to the Poxviridae family, transmission occurs through direct contact with respiratory secretions and skin lesions of infected people (1). The first reported case of MPOX was in the Democratic Republic of the Congo in 1970 which affected people who have been in close contact with animals since 1990. The cases were due to direct contact with affected people, causing a progressive increase in the frequency of cases (2).

This virus remained endemic in some African countries, until May 2022 when other continents received notices of MPOX cases. On July 26, 2022, the World Health Organization (WHO) decreed MPOX as a Public Health Emergency of Importance (1). Due to the global increase in cases and even though it is not a sexual disease, this increase was for the most part concentrated among men who have sex with other men transmission (MSM) (3), because sexual contact and prolonged exposure to the affected person increases the risk of transmission through the exchange of fluids and respiratory secretions.

The United States notified about three thousand settlements between May and June 2022 rapidly increasing in people infected by the MPOX, the median age reported was 35 years, 99% were MSM and with a history of sexual contact for three weeks before the onset of symptoms. Among the most common clinical manifestations were: skin rashes associated with fever, chills and rectal pain. Skin rashes were frequent in the genital region, arms, face, and legs (4). The number of patients was increasing and until December 2022, around 84,000 cases were reported worldwide, arising in 110 countries, and in Peru approximately 3,600 cases were reported, and is the South American country with the highest number of reported cases (5).

MPOX infection is a current public health problem, due to its high morbidity rates and associated complications. The findings of the studies agree that MPOX mainly affects MSM with a history of sexual contact before the development of the disease. The objective of this study was to identify the sexual behavior of MSM during the period of MPOX infection and to understand the relationship with sexually transmitted infections (STIs).

METHODS

POPULATION AND STUDY DESIGN

The present control-case study was conducted on 57 MSM cases and 114 controls of non-MSM participants. All participants were male residents of Peru. A total of 171 participants were recruited to the study between January and July 2022, due to privacy concerns the participant-driven sampling (PDM) method was used (6), this recruitment started with 20 people who attended for the first time the control program of sexually transmitted infections (STIs) of the Carrion Hospital in the study period. Initially, each participant was called a seed who had to freely invite two contacts to be able to participate in the study, each of the new participants who entered the study referred by the seeds, had to invite another two friends until reaching 57 MSM and 114 non-MSM participants. The inclusion criteria were males over 15 years old, answering the questionnaire, and agreeing to be tested for HIV and other STIs. Sex workers were excluded. The sample size was calculated using the proportions method, considering a sample power of 0.90, a bilateral probability of type I error of 0.05 for a proportion of MSM and STIs of 60% in cases (7) and a proportion of MPOX in MSM of 88% (8) and a case to control ratio of 1 : 2.

PROCEDURES

After agreeing to participate in the study, the participants responded to a previously structured, anonymous, and validated survey, which evaluated sexual behavior and the most frequent conditions associated with risk behaviors for STIs. Subsequently, each participant was given counseling on HIV and STIs, and samples for HIV, hepatitis B, Hepatitis C, and syphilis were screened using the immunochromatography method (rapid test).

STATISTICAL ANALYSIS

For the analysis, the statistical program STATA version 14.0 for Windows (STATA Corp, College Station, TX, US) was used. Categorical variables were compared using the Chi-square estimator or Fisher's exact test, as appropriate. Student's t-test was used for numerical variables, in addition to the mean and standard deviation (SD). Finally, the multivariable logistic regression model was performed to estimate the risk factors for STIs in MSM. The variables with a value of $p < 0.10$ from the univariate model were included in the multivariate model using the backward method, the odds ratio (OR) and their confidence interval values (95% CI) were calculated, and the level of significance set was 0.05. The potential confounding variables included in the model were age, and comorbidities.

ETHICAL ASPECTS

This study was approved by the institutional committee of the Hospital Daniel Alcides Carrion number 24-2022. In addition, the study obtained the informed consent of each participant, and her information was kept confidential, respecting her identity.

RESULTS

Of a total of 171 enrolled participants, the mean age was 37 (16–70) years, the MSM participants were relatively younger with a mean age of 31 (16–65) years, and the most frequent group was between 16 and 24 years (42.6%). Trade was the most frequent labor activity (45/171; 26.5%). The diagnosis of HIV infection was positive in 101 patients (101/171; 59.1%) of which 52 (91.2%) belonged to the MSM group and 46 (40.3%) participants in the group of men who have sex only with women (MSW).

Among the 171 participants, 104 (61.4%) were also diagnosed with other STIs, 54 (94.7%) were MSM, and

50 (43.8%) patients were MSW (p < 0.001). The most STI frequently identified was syphilis in 41 (39.1%) people. The second most frequent was genital herpes, which was present in 24 (22.9%) participants.

In terms of the number of sexual couples in the past year, the average number of couples was 2.7 (0 to 30) in the total participants, 4.2 (1 to 30) was the average in the MSM group, and 1.9 (0 to 10) in the MSW group. The average number of sexual couples during the last 5 years was 6.7 (1 to 100), MSM participants had an average of 12.7 (1 to 100) couples and in the MSW the average was 3.7 (1 to 20).

More than half of the participants (91/171; 66.4%) had sexual intercourse while under the influence of alcohol, of which 30 participants (83.3%) were MSM, and 61 (60.4%) were MSW, the consumption of drugs during intercourse was reported by 5 (3.7%) participants (Table 1).

Less than half of the patients (76/171, 44.4%) reported that they did not use condom during sexual intercourse, of which 28 people were from the MSM group (28/57, 49.1%). More than half of the participants (87/171, 50.9%) forgot to use a condom at some time, it was observed that 56% were in the MSM group and 40.4% localized in the MSW group. The average number of times they forgot to use a condom in the last month was 3.2, higher in the MSM group (p = 0.036).

Most of the patients surveyed went to nightclubs (114/171, 66.7%), which represented 45 (78.9%) of the MSM patients and 69 (60.5%) participants of the MSW group (p = 0.017). The average number of times per month that they went to nightclubs was 1.4 in total, which includes

Tab. 1 Characteristics of the study population according to the sexual behavior of men.

Characteristic	Total n = 171 (%)	MSM n = 57 (%)	MSW n = 114 (%)	p-value*
Age (years): mean (age range)	37 (16–70)	31 (16–65)	40 (18–70)	0.008
16–24	51 (30.5%)	23 (42.6%)	28 (24.8%)	0.013
25–39	55 (32.9%)	19 (35.2%)	36 (31.8%)	
> 39	61 (36.5%)	12 (22.2%)	49 (43.4%)	
Occupation				
Businessman	45 (26.5%)	24 (42.8%)	21 (18.4%)	0.017
Student	24 14.1%)	5 (8.9%)	19 (16.7%)	
Farmer	24 (14.1%)	4 (7.1%)	20 (17.5%)	
Builder	13 (7.6%)	4 (7.1%)	9 (7.9%)	
Driver	13 (7.6%)	1 (1.8%)	12 (10.5%)	
Public office	18 (10.6%)	7 (12.5%)	11 (9.6%)	
HIV POSITIVE	101 (59.1%)	52 (91.2%)	49 (42.9%)	< 0.001
STIs	104 (61.4%)	54 (94.7%)	50(43.8%)	< 0.001
Type of STI				
Syphilis	41 (39.1%)	27 (49.1%)	14 (28%)	0.250
Herpes	27 (25.8%)	13 (23.6%)	14 (87%)	
Gonorrhea	23 (21.9%)	9 (16.4%)	14 (28%)	
Condyloma acuminatum	12 (11.4%)	9 (16.4%)	3 (5.6%)	
Proctitis	3 (2.9%)	3 (5.5%)	0 (0%)	
Number of sexual partners last year (average and range)	2.7 (0–30)	4.2 (1–30)	1.9 (0–10)	< 0.001
Number of sexual partners last 5 years (average and range)	6.7 (1–100)	12.7 (1–100)	3.7 (1–20)	< 0.001
Sex under the influence of substances				
None	41 (29.9%)	1 (2.8%)	40 (39.6%)	< 0.001
Alcohol	91(66.4%)	30 (83.3%)	61 (60.4%)	
Drugs	5(3.7%)	5 (13.8%)	0 (0%)	
Rape victim	23(14.5%)	18 (36%)	5 (4.6%)	< 0.001
Use a condom during sexual intercourse				
Yes	77 (45.1%)	21 (36.8%)	56 (49.1%)	0.247
No	76 (44.4%)	28 (49.1%)	48 (42.1%)	
Sometimes	18 (10.5%)	8 (14.1%)	10 (8.7%)	
Have you ever forgotten to use a condom?	87 (50.9%)	32 (56.1%)	46 (40.4%)	<0.032
Times you forget to use a condom per month (average)	3.2	3.5	2.8	0.036

Characteristic	Total n = 171 (%)	MSM n = 57 (%)	MSW n = 114 (%)	p-value*
Do you go to a night club or a brothel?	114 (66.7%)	45 (78.9%)	69 (60.5%)	0.017
How many times a month do you go to a night club or brothel? (average)	1.4 (0.1–16)	2.4 (0.5–15)	1.1 (0.1–16)	0.035
How did you get STI?				
Does not know	14 (15.5%)	6 (11.5%)	8 (21.1%)	0.095
With your stable partner	25 (27.8%)	21 (40.3%)	4 (10.5%)	
In a brothel	3 (3.3%)	1 (1.9%)	2 (5.3%)	
With an occasional partner	33 (36.7%)	17 (32.7%)	16 (42.1%)	
With street sex worker	8 (8.9%)	4 (7.7%)	4 (10.5%)	
Rape victim	2 (2.2%)	1 (1.9%)	1 (2.6%)	
Transmitted STI to another person				
Yes	54 (57.5%)	31 (56.4%)	23 (58.9%)	0.485
No	40 (42.6%)	24 (43.6%)	16 (41.1%)	
Average (range)	2.28 (0–8)	2.8 (0–8)	1.6 (0–5)	0.0487
Comorbidity	64 (37.4%)	24 (42.1%)	40 (35.1%)	0.405
Type of comorbidity				
Gastritis	13 (20.3%)	2 (8.3%)	11 (27.5%)	0.252
Diarrhea	14 (21.8%)	7 (29.2%)	7 (17.5%)	
Tuberculosis	10 (15.6%)	5 (20.8%)	5 (12.5%)	

* Fisher's exact test was used to calculate the p-value in the case of categorical variables, and Student t test for numerical variables. MSM: Men who have sex with men; MSW: Men who have only sex with women (Heterosexual men); STI: sexually transmitted infection.

2.4 (0.5 to 15) on average in MSM participants and 1.1 (0.1 to 16) in MSW participants (p = 0.035). The history of rape was reported in 23 (14.5%) of the total participants, 18 (36%) in the MSM group while 5 (4.6%) people were in the MSW (p < 0.001)

Less than half of the people (33; 36.7%) mentioned that some occasional partner was the one who transmitted the STI or HIV to them, another 25 (27.8%) participants mentioned that their stable partner was the one who infected them with the STI and less frequent it was those who answered that they do not know where they acquired the infection (14; 15.5%). In question, how many people you infected with an STI, the average number of infected people by the participants was 2.28 (0 to 8), in terms of frequency this average was higher in MSM people 2.8 (0 to 8) while in the MSW group the average number of people to whom the infectious agent was transmitted was 1.6 (0 to 5) P = 0.048. Most patients reported some comorbidity, the most frequent being diarrhea 14 (21.8%) followed by gastritis 13 (20.3%). Participants belonging to the MSM group have approximately 5 times more risk of suffering from STIs (95% CI: 1.89–14.81) than the group of MSW.

The evaluation of the variables that are associated with STIs in the multivariate model in MSM participants showed that for participants who reported more than 5 partners the OR was 10.24 (CI95%: 1.42–23.52) compared to those who had less than 3 sexual partners in 5 years. Sexual intercourse under the alcohol influence showed OR 2.41 (95% CI: 1.11–3.96). Forgetting to use a condom was 3.16 times more likely to contract an STI, including HIV (95% CI: 1.73–7.48). Participants who have sex with a casual partner have a 1.4-fold increased risk of contracting an STI (95% CI: 1.01–2.16). The variables that did not show a significant relationship with the risk of contracting an STI in the multivariate model were age, going to nightclubs, and having sex with sex workers (Table 2).

Tab. 2 Analysis of the sexual behaviors associated with the risk of sexually transmitted infection in men who have sex with men.

Variable	Crude model		Fitted model	
	OR crude	IC 95%	OR fitted	IC 95%
Age years*				
15 a 24	1.47	0.69–3.12		
25 a 39	3.03	1.37–6.65	3.37	0.88–12.84
Number of couples in the last 5 years (terciles)				
3–5	3.65	1.68–7.94	2.45	0.62–9.66
> 5	17.2	5.61–52.79	10.24	1.42–23.52
Intercourse under the influence of alcohol	14.64	5.21–41.11	2.41	1.11–3.96
Forget to use condom	6.94	2.77–17.36	3.16	1.73–7.48
Go to the nightclub	3.38	1.73–6.55	1.19	0.336–4.21
Eventual sexual partner	1.7	1.14–3.19	1.4	1.01–2.16
Go to a sex worker	1.3	0.26–5.45		

* Compared to over 39 years; **Compared to vaginal. Adjusted for age. OR, odds ratio; 95% CI, 95% confidence interval. MSM: Men who have sex with men; MSW: Men who have sex only with women.

DISCUSSION

In this retrospective study, the sexual behavior of MSM participants during the monkeypox (MPOX) period 2022 in Huancayo-Peru was updated, since intimate physical contact during sexual activities is highly involved in the transmission of MPOX infection (9, 10). In addition, community transmission of MPOX is emerging disproportionately among men who have sex with men and is consistent with data reported by some studies (11, 12).

The purpose of this study was to examine the sexual behavior of MSM participants, identify the risk for STIs, and thus contribute to the development of disease control programs during the human monkeypox period. The average age of the MSM participants was 31 years, this age is like those affected by MPOX in MSM (13). Young population is the most affected by the activities of their age and their higher-risk sexual behavior.

HIV and other STIs were more frequent in MSM. In the context of MPOX, the studies reported that most patients with MPOX also have HIV or were found with pre-exposure prophylaxis (14), and other STIs such as herpes (15). The number of HIV cases were high in patients diagnosed with MPOX has raised the alarm worldwide, this leads the Centers for Disease Control and Prevention to publish recommendations for the prevention and treatment of MPOX in patients with HIV infection (16).

The high number of STIs diagnosed in the participants was surprising, this association is also frequent in other studies where more than two-thirds of MSM patients had been diagnosed with STIs in the last six months and almost half of them in the last month, in the MPOX period, this coincidence has also been observed in cohort studies that found high rates of STIs among MSM with MPOX infections (9, 17), so the suggestion to perform HIV and STI screening in patients recently diagnosed with MPOX or vice versa (16).

Participants who have more than 5 sexual partners are 10.24 times more likely to acquire an STI compared to those who have less than 3 partners. It is known from other studies that young men prevalence is to have multiple sexual partners (18), especially MSM who have an average of three partners in 6 months (19), like what was found in this study of four couples per year.

Alcohol consumption before sexual intercourse is twice as likely to acquire an STI and makes MSM participants make impulsively and unconsciously decisions, leading a risk during drunken state of conscious. This variable has not yet been studied in patients with MPOX infection and STI risk. The results also showed that homosexual men are less likely to use condoms, which is like studies from the United States and China, which found that MSM is more likely to have sex without a condom compared to heterosexuals (20), this may be due to the widespread idea that condom use is only to prevent pregnancy.

Active sexuality is related to MPOX infection (21, 22); in this study, sexual intercourses with casual partners were more likely to acquire some STI, similar to that reported by another study (23). It seems that the group of MSM attends more frequent entertainment sites to meet couples. The sum of all these common conditions in MSM people makes them the group most affected by MPOX (10, 24). Interestingly, based on what was found in this study, it seems that going to nightclubs and having sex with sex workers are not risk factors to acquire some type of STI this can be explained by the people who go to these centers generally use condoms.

Our study has some limitations. First limitation concerns the compilation of the data, there may be some data that has not been reported by the participants. Furthermore, no cases of MPOX were diagnosed in this study. Another challenge of the study has been pinpointing exact sexual behavior, as most participants are fearful of intimate information and do not always openly disclose their homosexual behavior. In addition, sexual intercourse under the influence effects of alcohol makes it difficult for the participants to report actual sexual behavior.

CONCLUSION

Sexual behavior of men who have sex with men was characterized by a greater number of sexual partners, nonuse of condoms, sexual relations under alcohol effects and with casual partners, which may explain the high prevalence of sexually transmitted infections in this human group evaluated during the human monkeypox virus outbreak. These results emphasize that urgent educational prevention actions are required in these group of people and demonstrate a link between the sexual behavior of MSM participants and the high frequency of STIs.

CONTRIBUTORS

RM and MM designed the study, analyzed the data, and drafted the manuscript. SC and LZ contributed to the questionnaire design and collected the data. CN undertook the statistical analysis. All authors reviewed the final manuscript prior to submission. RM is the guarantor of this paper.

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COMPETING INTERESTS

None declared.

ETHICS STATEMENTS

The participants signed the Informed Consent for their inclusion in the study, maintaining the confidentiality of the data.

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Performance Characteristics and Utility of the Standard Q COVID-19 Antigen Test for Emergency Admissions to Healthcare Facilities

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ABSTRACT

This study evaluated the performance of the COVID-19 Ag-RDT compared to the real-time reverse transcription-polymerase chain reaction (rtRT-PCR) for SARS-CoV-2 detection and its use among patients referred for emergency admission.

A total of 120 nasopharyngeal swabs were collected from patients referred for emergency admission and immediately preceded for testing to the Unit of Clinical Microbiology. Out of 60 Ag positive tests, 53 (88.3%) were confirmed by rtRT-PCR, while 7 (11.7%) tested negative (false positives). Out of 60 Ag negative tests, 56 (93.3%) were confirmed negative by rtRT-PCR, and 4 (6.7%) were positive (false negatives). Ct value comparison was performed for 53 samples that were positive by both methods: 8 (15.1%) isolates had Ct value up to 20; 37 (69.8%) 21 to 30 and 8 (15.1%) 31 to 40, respectively. The sensitivity of the analyzed rapid Ag test was 92.9%, and specificity 88.9%. The accuracy of the Ag test was 90.8%.

This study has shown that rapid Ag tests can be used in emergency admissions to healthcare facilities. However, rtRT-PCR should be considered after negative antigen test results in symptomatic patients, and after positive antigen test results in asymptomatic persons.

KEYWORDS

SARS-CoV-2; rapid antigen test; RT-PCR; emergency admission

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INTRODUCTION

Since its first notification, SARS-CoV-2 has spread around the world in a very short time, besides many attempts to control the disease. Laboratories have been constantly increasing the number of tests performed, and there was a need to shorten the time to obtain results. This is especially related to patients who require hospital admission, since early detection of positive patients is of particular importance for preliminary rapid triaging, timely isolation, and limiting the spread of the virus in hospital settings (1).

Therefore, the control strategy in hospitals is based on the availability of fast and reliable diagnostic tests that aim at early detection of virus in respiratory materials (2).

Until today, the reverse transcription-polymerase chain reaction (RT-PCR) assay was the gold standard in the diagnosis of SARS-CoV-2 infection since such an assay has excellent sensitivity and specificity. However, these assays are often too slow to inform patient placement in emergency departments (EDs) and require specialized instruments and educated and trained personnel (3). Isolation rooms are often limited in capacity, requiring the cohorting of COVID-19-positive patients. Due to all the above, options for additional non-PCR-based testing such as rapid antigen-based diagnostic tests (Ag-RDT) are receiving increasing attention and are being widely implemented in national test strategies. In principle, such assays are supposed to provide rapid and reliable information on the SARS-CoV-2 infection status, e.g. in emergency departments (ED) or other health care facility settings. They could help to improve the flow of patients through the ED into "COVID-19-positive" cohorts and reduce pressure on limited hospital isolation rooms (4, 5).

In the interim guidance of September 11, 2020, WHO has presented this option as a new technology for COVID-19 detection that is simpler and faster to perform than the currently recommended nucleic acid amplification tests (6).

This document has been updated to incorporate new findings concerning test performance across Ag-RDT brands and sample types. These tests have become a useful tool since they provide faster results in situations when PCR capacity is limited. Upper respiratory specimens or saliva are used for testing to detect SARS-CoV-2 proteins (e.g., nucleoproteins) and results are obtained within 30 minutes (7).

Although these tests could be used in diagnostic algorithms for emergency admissions to healthcare facilities, their performance data, especially from asymptomatic persons, is still limited.

This study evaluated the performance characterization of the SARS-CoV-2 Ag-RDT compared to the real-time reverse transcription-polymerase chain reaction (rtRT-PCR) for SARS-CoV-2 detection and its utilization among patients referred for emergency admission to the Clinical Center of the University of Sarajevo (CCUS), Bosnia and Herzegovina.

MATERIAL AND METHODS

The study was conducted from November 2020 to February 2021. The nasopharyngeal swab samples were collected in a Citoswab Collection and Transport Kit (nal von Minden, GmbH, Moers, Germany) containing 3 ml of the virus transport medium (VTM) from patients referred for emergency admission and immediately proceeded for testing to the Unit of Clinical Microbiology situated at the Clinical Center of the University of Sarajevo, Bosnia and Herzegovina.

All patients were screened by using the Ag-RDT SARS-CoV-2 test (Standard Q COVID-19 Ag test; SD Biosensor, Inc. Gyeonggi-do, Republic of Korea) for the early detection of potential infection. The 350 µl of the specimen from VTM was tested by Ag-RDT in a Class II Microbiology Safety Cabinet and according to the manufacturer's instructions. In principle, mouse monoclonal anti-SARS-CoV-2 antibody is coated on the test line region, and mouse monoclonal anti-Chicken IgG antibody is coated on the control line region. Mouse monoclonal anti-SARS-CoV-2 antibodies conjugated with color particles are used as detectors for the SARS-CoV-2 antigen device. During the test, SARS-CoV-2 antigen in the specimen interacts with monoclonal anti-SARS-CoV-2 antibody conjugated with color particles, making an antigen-antibody color particle complex. This complex migrates on the membrane via capillary action until the test line, where it will be captured by the mouse monoclonal anti-SARS-CoV-2 antibody. A colored test line would be visible in the result window if SARS-CoV-2 antigens are present in the specimen. If SARS-CoV-2 antigens are not present in the specimen, then no color appears in the test line. The control line should always appear if the test procedure is performed properly and the test reagents of the control line are working.

Ag-RDT test was compared with PhoenixDX SARSCoV-2 Multiplex rtRT-PCR test (Procomcure Biotech; Thalgau, Austria) performed simultaneously (within two hours after the sample was received in the laboratory), using Applied Biosystems 7500 Realtime PCR System (Thermo Fisher Scientific, Waltham, MA, USA), to assess its performance characteristics.

The PhoenixDx SARS-CoV-2 Multiplex test is based on rtRT-PCR technology for the qualitative detection of the RNA genome of SARS-CoV-2 from the patient sample. Nucleic acids were extracted from 200 µL of VTM using a fully automatic system, Nextractor NX-48, utilizing the NX-48 Viral NA Kit (Genolution, Seoul, Republic of Korea) according to the manufacturer's instructions. Samples were eluted in 50 µL of elution buffer. The isolated nucleic acids (RNA) were immediately used for rtRT-PCR.

External controls (positive and negative) were included in the kit and processed in the same way with each run. The PhoenixDx SARS-CoV-2 Multiplex master mix contains detection probes for the two SARS- CoV-2 ORF1ab and N genes (FAM-labeled) and one for the internal RNaseP (HEX/VIC labeled). Each reporter dye is measured at defined wavelengths, which enables simultaneous detection and discrimination of the amplified coronavirus targets. The total of 20 ml of RT-PCR reaction mix contained the kit-specific RT Enzyme mix (1 ml), the SARS-CoV-2 Multiplex mix (15 ml), and 4 ml of nucleic acids (RNA) of the sample, positive or negative control, respectively. The rtRT-PCR program was set up as follows: reverse transcription (50 °C, 5 minutes), initial denaturation (95 °C,

5 minutes), and amplification (40 cycles of the steps: 95 °C, 5 seconds, and 60 °C, 30 seconds—data collection step). Positive Ct value for virus-specific targets considered to represent the positive SARS-CoV-2 result with or without the presence of internal RNase P signal.

Descriptive statistics used for data analysis included mean, median, mode, standard deviation, minimum, maximum, count, and confidence level. Performance of the Ag-RDT test compared to rtRT-PCR was evaluated by sensitivity, specificity, accuracy, positive and negative likelihood ratio, prevalence, and positive and negative predictive values (PPV, NPV).

RESULTS

The SARS-CoV-2 Ag-RDT test (Standard Q COVID-19 Ag test; SD Biosensor, Gyeonggi-do, Republic of Korea) was compared with the PhoenixDX SARS-CoV-2 Multiplex rtRT-PCR test (Procomcure Biotech; Thalgau, Austria) using the ABI 7500 Realtime PCR System.

A total of 120 nasopharyngeal swabs from patients for emergency admission were analyzed (Figure 1).

Comparison of Ag-RDT and rtRT-PCR results showed the difference in rtRT-PCR Ct values (Table 1). Actually, the mean Ct value for Ag-RDT positive results was 24.85 ± 4.24 (STDEV), while the higher Ct values were observed for Ag-RDT negative results (mean 31.25 ± 2.22 STDEV). Ag-RDT positivity was more prevalent in persons at the mean age of 58 years. Persons with negative Ag-RTD tests showed a slightly lower mean age (52 years). Although the days of onset of symptoms were not available for all tested persons, the mean of 4 days of Ag-RDT testing was recorded regardless of Ag-RDT result.

According to the presence of COVID-19 symptoms among patients admitted to the emergency hospital department, 26/60 (43.33%) of Ag-RDT positive persons were symptomatic and 34/60 (56.67%) of them were asymptomatic (Table 2). The Ag-RDT positivity of 25/26 (96.15%) symptomatic persons was confirmed by rtRT-PCR. Among COVID-19 asymptomatic persons, 28/34 (82.35%) of Ag-RDT positive results were confirmed by rtRT-PCR. The 56/57 (98.25%) of Ag-RDT and rtRT-PCR negative patients, had no COVID-19 signs. These patients were tested as a preventive measure upon entry to the Clinical center. All 3/3 (100.00%) symptomatic patients with Ag-RDT negative test were positive by rtRT-PCR assay.

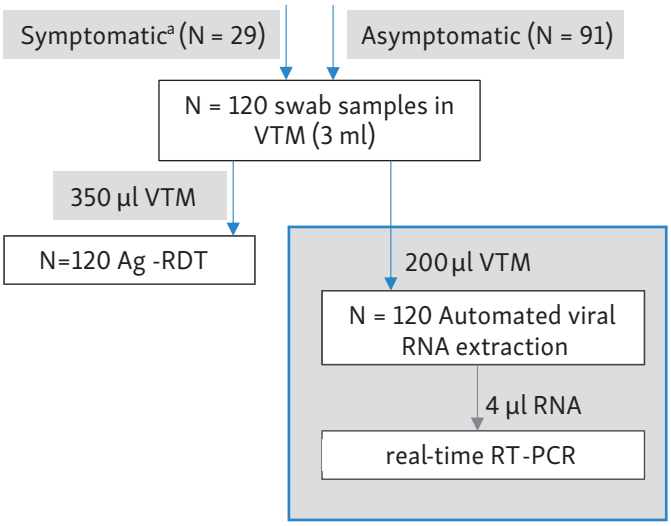

Fig. 1 Flowchart of the study.
[a] Symptoms were linked to the COVID-19.

Performance characteristics of the Ag-RDT assay are summarized in Table 3. Namely, Ag-RDT positive tests were confirmed by rtRT-PCR in 53/60 (88.33%) samples, while 7/60 (11,67%) tested rtRT-PCR negative (false positives). Ag-RDT negative results matched rtRT-PCR in 56/60 (93.33%) cases, except for 4/60 (6.67%) samples that tested Ag-RDT negative and rtRT-PCR positive (false negatives). The sensitivity of Ag-RDT was 92.98% and the specificity was 88.95%.

Tab. 1 Comparison of Ag-RDT and commercial rtRT-PCR assay.

	Age (years)[a]		**Real-time RT-PCR (Ct value)**		**Testing after onset of symptoms (days)**[b]	
*Ag-RDT test result**	*Ag-RDT (+)*	*Ag-RDT (-)*	*Ag-RDT (+)*	*Ag-RDT (-)*	*Ag-RDT (+)*	*Ag-RDT (-)*
Mean	58.83	52.02	24.85	31.25	4.19	4
Median	63	57	24	32	3	4
Mode	57	55	22	32	1	N/A
Standard Deviation	20.60	21.87	4.24	2.22	5.19	N/A
Minimum	1	7	15	28	0	4
Maximum	89	91	34	33	20	4
Confidence Level (95.0%)	5.32	5.65	1.17	3.53	2.36	N/A
Total number of respondents	*60*	*60*	*53*	*4*	*21*	*1*

Legend: * Data were divided based on Ag-RDT test results (positive +; negative –); [a] Age statistics of respondents participated in the study, provided in years. The columns give the brief insight into the age structure of the study population along with testing results and days after onset of symptoms (where available); [b] Number of days after onset of symptoms when Ag-RDT testing was performed. Results are shown for respondents with available data; N/A: Data not available. Statistics for the given parameters could not be calculated on the basis of one symptomatic person in whom the Ag-RDT test was negative upon admission, on the fourth day after the onset of symptoms; Ag-RDT: Standard Q COVID-19 Ag test (SD Biosensor, Gyeonggi-do, Republic of Korea); real-time RT-PCR: PhoenixDX SARS-CoV-2 Multiplex rtRT-PCR test (Procomcure Biotech; Thalgau, Austria).

Tab. 2 Concordance of Ag-RDT and commercial Real-time RT-PCR test with the presence of COVID-19 symptoms of patients in emergency hospital admission.

		COVID-19 Symptoms		
		Yes	*No*	*Total*
Ag-RDT (+)		26 (43.33%)	34 (56.67%)	60 (100.00%)
	w/ Real-time RT-PCR (+)	25 (96.15%)	28 (82.35%)	53 (88.33%)
	w/ Real-time RT-PCR (–)	1 (3.85%)	6 (17.65%)	7 (11.67%)
Ag-RDT (–)		3 (5.00%)	57 (95.0%)	60 (100.00%)
	w/ Real-time RT-PCR (–)	0 (0.00%)	56 (98.25%)	56 (93.33%)
	w/ Real-time RT-PCR (+)	3 (100.00%)	1 (1.75%)	4 (6.67%)

Legend: Ag-RDT test results (positive +; negative –); Real-time RT-PCR test results (positive +; negative –); Ag-RDT: Standard Q COVID-19 Ag test (SD Biosensor, Gyeonggi-do, Republic of Korea); real-time RT-PCR: PhoenixDX SARSCoV-2 Multiplex rtRT-PCR test (Procomcure Biotech; Thalgau, Austria).

Tab. 3 Performance characteristics of Ag-RDT evaluated by commercial real-time RT-PCR.

Real-time RT-PCR	**Ag-RDT**				**Performance characteristics of Ag-RTD**	
		Positive	Negative	*Total*	Sensitivity:	92.98%
	Positive	53	4	57	Specificity:	88.89%
	Negative	7	56	63	Accuracy:	90.83%
	Total	60	60	120	Positive likelihood ratio:	8.368
					Negative likelihood ratio:	0.07895
					Prevalence:	47.5%
					PPV:	88.33%
					NPV:	93.33%

Legend: PPV – positive predictive value; NPV – negative predictive value; Ag-RDT: Standard Q COVID-19 Ag test (SD Biosensor, Gyeonggi-do, Republic of Korea); real-time RT-PCR: PhoenixDX SARSCoV-2 Multiplex rtRT-PCR test (Procomcure Biotech; Thalgau, Austria).

The probability that a person with a positive screening test (Ag-RDT) truly has the disease (PPV) was 88.33%, while the probability that someone with a negative screening test (Ag-RDT) truly doesn't have the disease (NPV) was 93.33%. The accuracy of the Ag-RDT test was determined by the ratio of correct results (rtRT-PCR positive at the same time) to all the results of the Ag-RDT. It was 90.83%. Both positive and negative likelihood ratios describe the value of a test. The possibility that the person with the disease would test positive for Ag-RDT was 8.368 (positive likelihood ratio) and that the healthy person would test negative was 0.07895 (negative likelihood ratio), respectively. The prevalence of SARS-CoV-2 infection as determined by rtRT-PCR positives (true positives, N = 57) in a total group (N = 120) was 47.5% (Table 3).

DISCUSSION

Rapid and accurate identification of SARS-CoV-2 is crucial for emergency admissions to healthcare facilities, since the patients may be asymptomatic carriers, and if not promptly identified, could spread the infection within the hospital. The RT-PCR test is the gold-standard diagnostic for SARS-CoV-2 infection, but the results are often delayed and not suitable for the emergency department (ED) timing. Due to their quick performance and the timeliness of their results the rapid antigen test (RAT) could overcome the limitations of RT-PCR testing and improve the risk management of infection and transmission in the ED (8).

To examine the performance and utility of RAT in emergency hospital admissions, a study was conducted from November 2020 to February 2021 at the Clinical Center of the University of Sarajevo, Bosnia and Herzegovina. These data provide the first quantitative analysis of the performance characteristics of a rapid antigen detection kit when applied to an emergency department in our country.

120 patients referred for emergency admission and required hospitalization was tested with both a RAT and RT-PCR. The prevalence of SARS-CoV-2 infection as determined by rtRT-PCR positives (true positives, N = 57) in a total group (N = 120) was 47.5%. In SARS-CoV-2 positive patients, the RAT was positive in 88.33% of cases (53/60), while a false-positive RAT was in 11.67% (7/60) with a negative RT-PCR. Overall, the sensitivity and specificity of Ag-RDT in our study were 92.98% and 88.95% respectively, and the accuracy was 90.83%.

The average sensitivity reported in symptomatic individuals from 37 evaluations was 72.0% (95% CI: 63.7–79.0%), while that in asymptomatic individuals from 12 evaluations was 58.1% (95% CI: 40.2–74.1%) (9). The SD Biosensor RAT (Inc., Republic of Korea) manufacturer reported a higher sensitivity (96.52%; 95% CI: 91.33–99.04%) obtained in prospective, randomized, single-blinded studies conducted in Brazil and India in symptomatic and

asymptomatic individuals (SARS-CoV-2 Rapid Antigen Test Package Insert 2020-08, V 1.0).

WHO recommends the use of Ag-RDTs that meet minimum performance requirements of ≥ 80% sensitivity and ≥97% specificity (7). According to Centers for Disease Control and Prevention (CDC, 2021) the sensitivity of 69.86% indicates that RAT should not replace real-time RT-PCR in the diagnosis and surveillance of SARS-CoV-2 infection (10).

In our study, the mean Ct value for Ag-RDT positive results was 24.85 ± 4.24 (STDEV), while the higher Ct values were observed for Ag-RDT negative results (mean 31.25 ± 2.22 STDEV). After the acute phase when the viral load decreases, the use of Ag-RDTs might lead to high rates of false negatives, suggesting that the tests should be replaced by a combination of molecular and serological tests (11).

Ag-RDT was confirmed by rtRT-PCR in 96.15% (25/26) of symptomatic, and 82.35% (28/34) of COVID-19 asymptomatic persons. In the group of symptomatic persons, the performance of the RAT seems to be high enough to propose its use as an initial screening test directly upon arrival in triage. In this group, a positive RAT may accelerate the management of the infected patient.

A high percentage of our patients (98.25%) with Ag-RDT and rtRT-PCR negative results had no COVID-19 signs. In case of a negative test, the subsequent clinical management may depend on the degree of clinical suspicion. However, a negative RAT in patients with low clinical suspicion cannot completely exclude the presence of SARS-CoV-2 infection (8, 12).

The accuracy of the Ag-RDT test largely depends on the specificity of monoclonal antibodies. However, relatively high predictive values (our study showed PPV 88.33% and NPV 93.33% respectively), ease of use, low cost, and short turnaround time (15 ~ 30 minutes) give it an advantage to be used for triage of COVID-19 patients in areas such as ED. In countries with limited resources, it could be more suitable compared to more sensitive but expensive "on demand" Real time PCR platforms.

CONCLUSIONS

This study has shown that the use of RAT to assess the risk of infection directly in triage should be considered in emergency admissions to healthcare facilities. The short time to results might have a key role in the early placement of SARS-CoV-2-positive patients into COVID-19 units, reducing the risk of cross-transmission in the emergency department. However, rtRT-PCR should be considered after negative antigen test results in symptomatic patients, and after positive antigen test results in asymptomatic persons.

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Association of Giant Cell Arteritis with Papillary Thyroid Carcinoma

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ABSTRACT

Previous studies suggest that there may be an association between cancer and autoimmune diseases. We describe the case of a 59-year-old patient who did not have any significant diseases in the last year. She had new onset of fever of unknown aetiology, headache, fatigue and night sweats. We used laboratory methods to rule out infectious diseases. Significant laboratory findings reported increased signs of inflammation and anti-nuclear antibody (ANA) positivity. Positron emission tomography/computed tomography (PET/CT) imaging showed the origin of the patient's difficulties, arteritis, with increased metabolic activity in the aortic wall and other arteries. Doppler ultrasonography of the arteries did not show pathology in the temporal arteries but found accelerated blood flow in the superior mesenteric artery (AMS). Another finding from PET/CT was a tumour in the thyroid gland, later verified histologically as papillary thyroid carcinoma (PTC). We investigated the link between rheumatological disease and papillary carcinoma, applying similar therapy, corticosteroids and immunosuppressants.

KEYWORDS

giant cell arteritis; thyroid gland; papillary thyroid carcinoma; corticosteroids; fever; PET/CT; vasculitis

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INTRODUCTION

Giant cell arteritis (GCA) is one of the primary systemic vasculitis affecting medium and large arteries. GCA's clinical manifestations include general non-specific symptoms (fever, night sweats, fatigue, weight loss). Classification criteria are age greater than or equal to 50 years at disease onset, new onset of headaches, decreased pulsation and tenderness of the temporal arteries, elevated erythrocyte sedimentation rate greater than or equal to 50 mm/hour, and abnormal temporal artery biopsy (1, 2). The diagnosis is based on having at least 3 of these 5 criteria met (2).

Furthermore, the diagnosis can be confirmed by imaging or histology (3). Because of non-specific symptoms, the diagnosis can be delayed. This report describes our clinical case of a patient whose symptoms were non-specific. We were looking for cases associated with GCA and papillary thyroid carcinoma (PTC), but none have been reported to date. We present a case of a middle-aged woman who had GCA concomitantly with PTC.

CASE REPORT

In April 2021, a 59-year-old patient was admitted to our hospital after a previous investigation of fever of unknown origin. Since February 2021, the patient has had a headache, night sweats, fever over 39 °C, small and large joint pain, and lost over 10 kg of weight from February to April 2021. She took ibuprofen as an analgesic and antipyretic multiple times per day without results. Before we admitted the patient to our hospital, she was treated by a general practitioner (GP) and in her local hospital. GP treated her with two broad-spectrum antibiotics, but the treatment was ineffective. Afterwards, the GP sent her to her local hospital, that further investigated the cause of her symptoms. The hospital provided laboratory tests, microbiology (blood culture) and immunology, radiology tests, X-ray of the chest, ultrasonography (USG) of the abdomen, computed tomography (CT) of the head and chest and transoesophageal echocardiography (TEE). However, the results of the tests presented no new findings. Because of the patient's headaches, the neurologist performed an examination but did not find any source of pain. She was given another broad-spectrum antibiotic, but the fever remained while headaches and joint pain worsened. The local hospital reached out to us for consultations, and we recommended that the patient undergoes positron emission tomography/computed tomography (PET/CT). After the PET/CT, the patient was admitted to our hospital in April with her complete medical history.

On admission, her temperature was 35.8 °C, her heart rate was regular at 110/minute, her respiratory rate was 16/minute, and her blood pressure in the supine position was 116/78 mmHg. Her height was 178 cm, and she weighed 78 kg. She reported that she is subfebrile every evening. A physical examination was performed with palpation of the mass in the thyroid gland. Laboratory findings were as follows: C-reactive protein (CRP) 148.9 mg/l, leukocytes 9.68 × 10^9/l, erythrocytes 3.44 × 10^{12}/l, haemoglobin 91 g/l, erythrocyte sedimentation in the first hour was higher, 120 mm/h. The free tetra-iodothyronine (fT4) 17.2 pmol/l and thyroid-stimulating hormone (TSH) 1.02 mU/l were normal. The antineutrophil cytoplasmic antibodies (ANCA) were negative, ANCA myeloperoxidase (MPO) 1.33 U/ml, ANCA proteinase 3 (PR3) 1.13 U/ml, IgG 14.5 g/l, IgG4 0.19 g/l, rapid plasma reagin (RPR) negative, Treponema pallidum hemagglutination assay (TPHA) negative. The anti-nuclear antibodies (ANA) were positive. Creatine level was normal.

PET/CT showed 18F-fluorodeoxyglucose (18F-FDG) uptake in the aortic wall, subclavian arteries, carotid arteries, common iliac arteries, internal iliac arteries, and left lobe of the thyroid gland. We diagnosed her with GCA because she had increased sedimentation, new onset of headaches, pathological findings on PET/CT and was over 50 years old. We also investigated temporal arteries, but there was no sensitivity or decreased pulsation. Doppler ultrasonography of the arteries did not show pathology in the temporal arteries, but it showed flow acceleration in the proximal part of AMS 200–250 cm/s.

Since we had laboratory findings with signs of inflammation (high CRP, sedimentation) and the results from PET/CT showed inflammation of arteries and no pathological findings in temporal arteries, we did not perform a biopsy of the temporal artery. We started treating the patient's vasculitis with an initial dose of 32 mg/day of methylprednisolone. The patient also had eye and vision examinations. The fundus examination did not show a sign of ischemia, but automated perimetry revealed abnormalities in visual fields in temporal halves. Because of that, we started treatment with a dose of 500 mg/day of methylprednisolone for four days. The corticosteroid treatment promptly resolved the patient's symptoms, which she already had before coming to our hospital.

While she was treated for her vasculitis, we also focused on the mass in the left lobe of her thyroid gland revealed on PET/CT. Thyroid gland USG showed a mildly hypoechoic nodule 12 × 15 × 15 mm with calcifications. USG-guided fine-needle aspiration biopsy was performed and revealed suspicion for papillary thyroid carcinoma (Bethesda V). Immediately after the last dose of methylprednisolone, total thyroidectomy was performed, with no postoperative complications. Histology confirmed the classical variant of PTC, 21 × 19 × 12 mm, with dystrophic calcifications, one site of vascular invasion and no capsular invasion. The patient was discharged home with corticosteroid therapy (methylprednisolone), which we tapered from 16 mg/day to the final dose of 6 mg/day. Two months postoperatively, she received radioactive iodine (131-I) remnant ablation using 3700 MBq (100mCi) activity. The investigation before 131-I ablation revealed a moderate postoperative residuum of thyroid tissue (24-hour iodine neck accumulation of 8.9 % and serum thyroglobulin (TG) level of 18.65 ng/ml in hypothyroidism). Post-therapeutic whole-body scintigraphy and single photon emission CT (SPECT) of the neck and mediastinum, combined with low dose CT (SPECT/CT) confirmed a small residuum of the right lobe of the thyroid, together with one metastatic lymph node close to the right sternoclavicular joint. No distant metastases were found. She was classified as T2N1MO, stage II, and intermediate risk according to American Thyroid Association

(ATA). Subsequently she was treated with levothyroxine (dose adjusted to TSH suppression) and followed up using USG and serum levels of TG and autoantibodies against TG (TG-Ab). There was an excellent treatment response, with no USG signs of relapse and TG level below 0.2 ng/ml (and negative TG-Ab) with suppressed TSH and 0.44 ng/ml (i.e. below 1.0) with non-suppressed TSH. As there was no active residual cancer, while the vasculitis symptoms (joint pain) reoccurred after several months, we conclude that the symptoms were not paraneoplastic.

We added methotrexate to therapy, but the effect was temporal. We then increased the dose of oral methylprednisolone from 6 mg/day to 16mg/day for 7 days. Now she has a dose of 8mg/day of methylprednisolone with a satisfying effect.

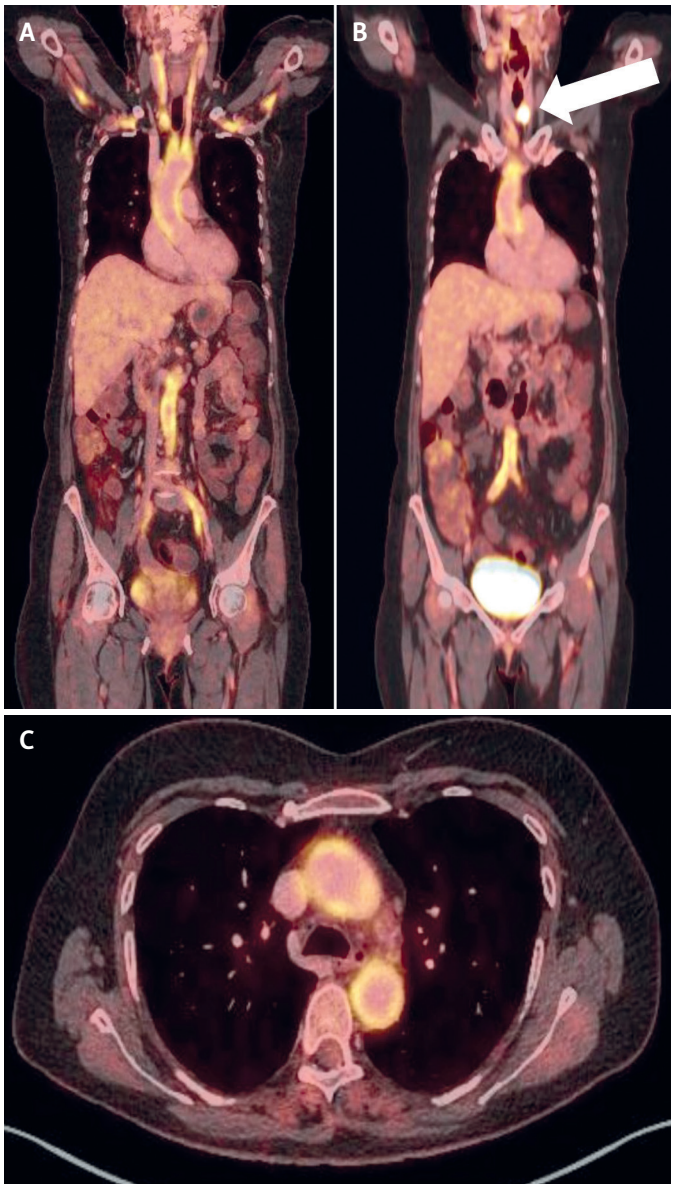

Fig. 1 PET/CT performed before patient was admitted to our hospital (with permission of Multiscan, s.r.o. database).
A: An uptake of ^{18}F-FDG in the aortic wall, subclavian arteries, carotid arteries, common iliac arteries, internal iliac arteries; B: An uptake of ^{18}F-FDG in the left lobe of the thyroid gland in the left lobe of the thyroid gland. Arrow points to a tumour in the thyroid gland; C: Axial view.

The patient will continue with regular check-ups at our hospital's rheumatology and endocrinology outpatient clinic.

DISCUSSION

As mentioned, no case report has been published with a patient treated simultaneously for GCA and PC of the thyroid gland. On the other hand, other interesting cases connect rheumatology and endocrinology. We used the database PubMed and studied a total of ten cases that included patients with rheumatological diseases and papillary carcinoma of the thyroid gland (see table) (4–13). The cases consisted of three men and seven women aged 31 to 69 years and tumour sizes from 19 to 40 mm. We compared our treatment procedure with the previously studied cases (4–13) and found similarities. Seven patients were treated with corticosteroids (4–8, 10, 13), and six of them had corticosteroid treatment before thyroidectomy (5–8, 10, 13). Only four patients had a fever (5–7, 13). It is known that GCA can exhibit non-specific symptoms, including fever of unknown origin (FUO) (14). Many case reports described patients examined for the aetiology of FUO, followed by PET/CT examinations that showed the cause of FUO (15–17). Our case was similar as we did not know the origin of the symptoms, and PET/CT helped us with the diagnosis.

Some cases reported that thyroidectomy resolved all rheumatic symptoms. These findings suggest that thyroid carcinoma caused paraneoplastic syndrome, demonstrated as rheumatic symptoms (9, 10). Thus, we can conclude that thyroidectomy was a crucial moment in therapy. It was unclear if PCL induced rheumatic manifestation in patients in other cases (4, 7, 13). Our patient's symptoms resolved for some time after treatment with corticosteroids. Unfortunately, after several months, when the patient had a lower dose of corticosteroids than at the beginning of treatment, the symptoms returned. This finding excludes the possibility that the symptoms were paraneoplastic. If the patient's symptoms would rapidly progress, we would consider changing the therapy to biological therapy, e.g., interleukin-6 inhibitors (tocilizumab) (18).

PTC, the most common thyroid malignancy, is associated with an excellent prognosis. Overall survival is more than 90% (19). A study was published in 2019 that studied the tumour volume doubling time (TVDT) in a group of 196 with a median patient age of 51 years. The findings of the study uncovered that 71.8% had a TVDT of five years or more (20). Another study was published in 2017 with similar results with intrathyroidal tumours ≤1.5 cm in a group of 291 patients with the median patient age 52 (21). Therefore, it is not necessary to rush with providing thyroidectomy. However, the endocrinology department at our hospital could perform a thyroidectomy in a very short time.

CONCLUSION

In conclusion, the relationship between rheumatology diseases and PTC is still unclear, and further studies are

Tab. 1 Overview of published case reports of patients with connective tissue diseases and papillary thyroid carcinoma.

Age	Sex	Size of PTC	Fever	Therapy	Disease	Corticosteroid therapy before thyroidectomy	Reference
31 years	Female	35 mm	no	Corticosteroids, azathioprine	Polymyositis	no	(1)
64 years	Female	20 × 20 mm	yes	Corticosteroids	Polymyalgia rheumatica	yes	(2)
59 years	Female	not specified	yes	Corticosteroids, cyclophosphamide	Granulomatosis with polyangiitis	yes	(3)
68 years	Male	not specified	yes	Corticosteroids	Still's disease	yes	(4)
69 years	Male	not specified	yes	Corticosteroids	Granulomatosis with polyangiitis	yes	(5)
55 years	Female	19 × 8 mm	no	without corticosteroid therapy	Paraneoplastic vasculitis	no	(6)
64 years	Female	35 mm	no	Corticosteroids	Panuveitis	yes	(7)
46 years	Female	40 mm	no	Azathioprine	Granulomatosis with polyangiitis	no	(8)
51 years	Male	40 mm	no	not specified	Cutaneous and renal vasculitis	No	(9)
32 years	Female	not specified	yes	Corticosteroids	Still's disease	yes	(10)

needed. A convincing association has not been found between PTC and rheumatic diseases, which does not necessarily mean that there is no association. In some patients, the connection between PTC and rheumatological disease is based on paraneoplastic symptoms, which was ruled out in our patient. So far, only a few cases with similar concomitant diseases have been published, and further investigation is required.

ABBREVATIONS

^{18}F-FDG – ^{18}F-fluorodeoxyglucose
AMS – superior mesenteric artery
ANA – anti-nuclear antibody
ANCA – antineutrophil cytoplasmic antibodies
CRP – C-reactive protein
CT – computed tomography
fT4 – free tetra-iodothyronine
FUO – fever of unknown origin
GCA – giant cell arteritis
GP – general practitioner
MPO – myeloperoxidase
PET/CT – positron emission tomography/computed tomography
PTC – papillary thyroid carcinoma
RPR – rapid plasma reagin
TEE – transoesophageal echocardiography
TSH – thyroid-stimulating hormone
TPHA – Treponema pallidum hemagglutination assay
TVDT – tumour volume doubling time
USG – ultrasonography

CONSENT

We obtained signed informed consent in the Czech language from the patient to publish a case report and pictures from imaging examinations.

CONFLICT OF INTEREST

None.

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Successful Pregnancy Outcome after Amnioreduction Treated Acute Polyhydramnios Caused by Duodenal Atresia

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ABSTRACT

The aim of our manuscript is to report of a successful perinatal outcome after treatment of acute polyhydramnios caused by duodenal atresia.

A 34-year-old G3P1 was referred due to polyhydramnios in the 30th week of pregnancy. Ultrasound revealed polyhydramnios, amniotic fluid index (AFI) 28, and a double bubble sign that indicated duodenal atresia and dilatated oesophagus. In the 32nd week of gestation, the volume of amniotic fluid increases, AFI 35, along with symptoms of dyspnea and abdominal pain. Due to the clinical picture and the early gestational age, it was decided to perform an amnioreduction. In the 36th week of gestation cesarean section was performed. The baby was taken for exploratory laparotomy and found to have a simultaneous complete duodenal atresia and annular pancreas with associated dilated the first portion of the duodenum and the stomach. A side-to-side duodenoduodenostomy via single-layer hand-sewn anastomosis was performed over a transanastamotic feeding tube (TAFT). The postoperative course was uneventful. Amnioreduction is useful and safe in the treatment of acute polyhydramnios caused by duodenal atresia and thus has a significant role in prolonging gestation until fetal maturity.

KEYWORDS

polyhydramnios; pediatric surgery; invasive ultrasound; antenatal care

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INTRODUCTION

Congenital duodenal obstruction (CDO) is a frequent cause of intestinal obstruction, representing up to 60 percent of all cases of neonatal intestinal obstructions, and occurs in approximately one infant per 10,000 births (1). Early prenatal diagnosis of CDO is not possible, due to underdeveloped gastric emptying, which prevents dilatation of the duodenum. Duodenal atresia is rarely recognized until 20 to 24 weeks of pregnancy when the characteristic "double bubble" ultrasound sign and polyhydramnios become apparent (2, 3).

The average time of prenatal diagnosis of CDO has been reported late in pregnancy at around 30 weeks of gestation (ranging from 20 to 38 weeks of gestation). Polyhydramnios can be a sign of high bowel atresia due to the lack of re-absorption of amniotic fluid, and presence of polyhydramnios varies from 30% to 80% (2, 3). Prenatal detection of CDO with polyhydramnios and "double bubble" sign is present in 45% of cases on antenatal ultrasound examination (2, 3). Chromosomal defects, mainly trisomy 21, are found in 30% of cases of CDO (2, 3).

Polyhydramnios represents an excessive accumulation of amniotic fluid, when the amniotic fluid index is greater than 25 or the volume of one pocket of amniotic fluid is greater than 8, and its prevalence ranges from 1–2% (4).

Sometimes polyhydramnios can be associated with a negative perinatal outcome; fetal anomalies and chromosomopathies, fetal anemia, maternal diabetes and infections, premature birth, but it can also be idiopathic (4).

Amnioreduction is a widely accepted treatment for polyhydramnios in twin to twin transfusion syndrome before laser ablation of vascular anastomoses, but its use in the treatment of acute polyhydramnios in singleton pregnancies has rarely been published (4, 5). To the best of our knowledge, in our country so far one case report has been published regarding a successfully performed amnioreduction before the placement of an emergency cerclage, after which the pregnancy was extended for 17 weeks and ended with a successful neonatal outcome (6).

The aim of our manuscript is to report of a successful perinatal outcome after treatment of acute polyhydramnios caused by duodenal atresia.

CASE REPORT

A 34-year-old G3P1 was referred to the Clinic due to polyhydramnios in the 30th week of pregnancy. Ultrasound revealed polyhydramnios, amniotic fluid index (AFI) 28, and a double bubble sign that indicated duodenal atresia and dilatated oesophagus (Figure 1A and 1B). The patient was hospitalized and monitored. In the 32nd week of gestation, the volume of amniotic fluid increases, AFI 35, along with symptoms of dyspnea and abdominal pain. On figure 1C we show how the foetus regurgitates amniotic fluid from mouth (Figure 1C). Due to the clinical picture and the early gestational age, it was decided to perform an amnioreduction. With this procedure, 1700 ml of amniotic fluid is evacuated and sent for cytogenetic analysis, after which an orderly cytogenetic finding was obtained (Figure 1D),

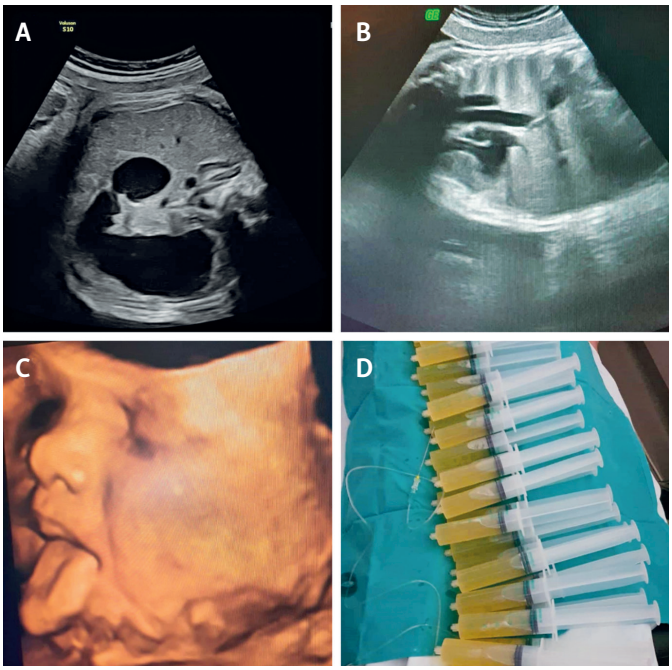

Fig. 1 A: Double bubble sign at ultrasound that indicated duodenal atresia; B: Oesophageal dilatation; C: The fetus regurgitates water, D: Amnioreduction of 1700 ml of amniotic fluid.

after which the AFI was reduced to 22. Fifteen days later, polyhydramnios develops again, the amnioreduction was repeated, and 1600 ml of amniotic fluid was evacuated. In the 36th week of gestation, AFI was 30, and the fetus was in breech presentation. Course of antenatal corticosteroids as respiratory distress syndrome prophylaxis was administered. Cesarean section was performed 48 hours later and delivered female newborn with birth weight and lenght 3350/52, and Apgar score in first and fifth minute 7 and 10. Postpartum diagnostic work-up confirmed the antenatal diagnosis by abdominal radiograph with barium contrast depicts the double-bubble sign of duodenal atresia (Figure 1A).

After correcting dehydration and electrolyte imbalance the baby was taken on day two for exploratory laparotomy through a right subcostal approach and found to have a simultaneous complete duodenal atresia and annular pancreas (Figure 2B) with associated dilated the first portion of the duodenum and the stomach. A side-to-side duodenoduodenostomy via single-layer hand-sewn anastomosis was performed over a transanastamotic feeding tube (TAFT). A nasogastric tube was placed in the stomach for proximal decompression.

The postoperative course was uneventful, enteral nutrition through TATF was introduced on the second postoperative day and achieved on full feeds on a postoperative day 5. The baby was discharged in stable condition and kept in regular follow-up.

DISCUSSION

In our case, duodenal atresia in the presence of polyhydramnios was detected in the 30th week of pregnancy, when it is most often detected (2, 3).

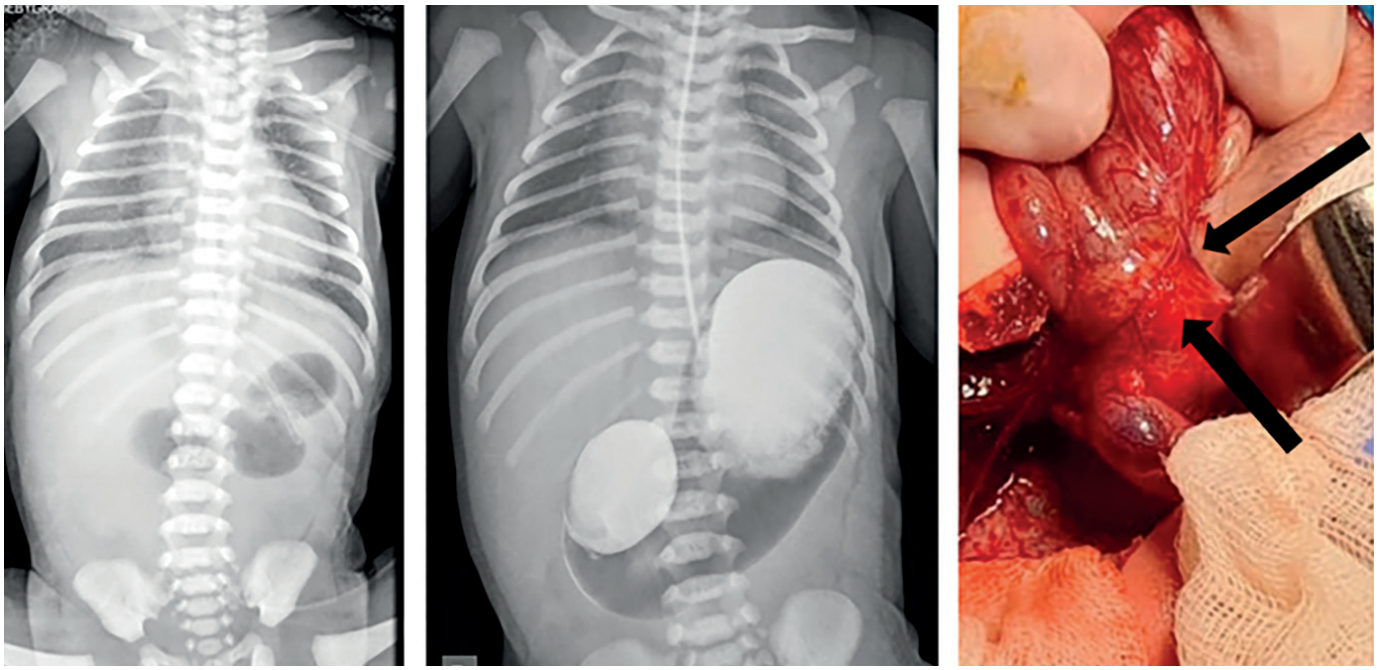

Fig. 2 A: The abdominal radiograph with barium contrast depicts the double-bubble sign of duodenal atresia; B: Intraoperative finding of duodenal atresia (the atretic part of the duodenum is under the surgeon's fingers, and the annular pancreas is at the level of the right Farabef hook.

Amnioreduction was performed on two occasions, in which the amniotic fluid was reduced by 1700 ml and 1600 ml, which correlates with literature recommendations that no more than 2000 ml to 2500 ml should be removed (4). Amnioreduction in our case prolonged the duration of pregnancy by 4 weeks, it was also performed without potential complications such as placental abruption and premature prelabour rupture of fetal membranes (4, 5).

Dickinson et al. in their retrospective study of all singleton pregnancies receiving amnioreduction for polyhydramnios concluded that amnioreduction has a useful role in the management of polyhydramnios, that complications are uncommon and delivery typically occurs near term (4).

Dickinson et al. found that median gestation when the first amnioreduction was performed was 31 weeks, median amniotic fluid volume removed was 2100 ml, median duration from amnioreduction to delivery was 26 days, median gestation at delivery was 36.4 weeks. In 4.1% of procedures, an unplanned preterm birth occurred within 48 hours of the procedure (4). The final diagnosis in neonates from this study was gastrointestinal malformations (21%), idiopathic (20.3%), chromosomal (15.2%), syndromic (13.7%) and neurologic (8%) (4).

The prognosis for duodenal obstruction is highly dependent on the presence or absence of associated anomalies. In isolated duodenal obstruction, the survival rate is >95%; there is a wide variation in mortality rate in complicated cases, dependent on the nature of the associated anomalies (2, 3). Duodenal obstruction is associated with a high rate of prematurity, possibly because of polyhydramnios, and an increased rate of unexpected fetal demise (2, 3).

Congenital duodenal obstruction (CDO) may be either partial or complete, extrinsic or intrinsic, or even both. Important intrinsic causes of CDO include duodenal atresia, stenosis, and webs, while extrinsic CDO may be caused by the annular pancreas, malrotation, or preduodenal portal vein (2). An association between duodenal atresia (DA) and the annular pancreas has only occasionally been found simultaneously (7–11), including in our present case.

CONCLUSION

Amnioreduction is useful and safe in the treatment of acute polyhydramnios caused by duodenal atresia and thus has a significant role in prolonging gestation until fetal maturity. Prenatal ultrasound recognition of duodenal atresia allows the multidisciplinary approach of obstetricians, neonatologists, pediatric surgeons, and anesthesiologists to surgically correct it in time and enable an optimal neonatal outcome.

CONFLICT OF INTEREST

The authors have nothing to disclose and no conflict of interest to declare. No funding source was involved in this study and there are no financial or other relationships that could be perceived to influence the manuscript.

ETHICAL APPROVAL

These is case report, for which there is no requirement of our institution to seek permission of the Ethics Committee to publish a paper. We obtained a required patient's family permission.

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Gallstone Ileus in Octogenarians: Is Cholecystectomy Really Needed?

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ABSTRACT

Gallstone ileus is an uncommon complication of cholelithiasis and occurs when a gallstone migrates through a cholecystoenteric fistula and impacts within the gastrointestinal tract. Surgical intervention remains the treatment of choice, which consists of a full-thickness incision of the visceral wall and removal of the impacted gallstone. In this paper we present the treatment approach of 6 cases of gallstone ileus in octogenarians. In our cohort, intestinal obstruction was resolved through an enterotomy or gastrotomy and lithotomy/stone extraction in every patient. No cholecystectomies were undertaken. Despite the fact that gallstone ileus is diagnosed in small percent of patients suffering from gallstone disease, it accounts for a large proportion of intestine obstruction in patients older than 65 years old. Since accurate diagnosis and timely intervention are vital, providers should be familiar with the diagnostic approach and the treatment of this clinical entity.

KEYWORDS

gallstone ileus; bowel obstruction; intestinal obstruction; treatment

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INTRODUCTION

Gallstone ileus is a rare complication of cholelithiasis that occurs when a gallstone migrates from the gallbladder through a cholecystoenteric fistula, subsequently becoming impacted within the gastrointestinal tract. It is characterized by mechanical obstruction of the bowel and often presents with abdominal distention, vomiting and fever. In the elderly, dehydration, shock, or peritonitis may complicate the clinical presentation (1). Although endoscopic management has been successful in up to 30% of reported cases (2), surgical treatment is warranted in the majority cases (1). Surgical management consists of two components: resolution of acute small bowel obstruction with removal of the impacted gallstone, followed by elective evaluation of the gallstone disease and inflammatory fistulisation (1, 2).

Since Courvoisier published the first series of 131 cases, reporting a mortality rate of 44% in 1890, gallstone ileus remains a rare morbid complication of gallbladder inflammation (3), with the issue of optimal surgical approach and timing of the procedure being still debated. The rarity of the disease, compounded by the scarcity of patient-level data represent a challenge in devising accurate evidence-based management protocols, especially regarding the biliary disease component. Herein, we present the diagnostic and treatment modalities of 6 cases of octogenarian patients suffering from bowel obstruction caused by impacted gallstones.

CASE SERIES

CASE 1

An 83-year-old female patient presented to the emergency department due to complaints of vomiting and abdominal pain which began three days before her admission to our hospital. Physical examination revealed epigastric tenderness. Her past medical history included diabetes, abdominal aortic aneurysm, and atrial fibrillation. One month before presentation, she complained about an atypical right upper quadrant pain and low-grade fever. Computed-tomography (CT) scan with intravenous and oral contrast of the abdomen demonstrated marked gastric dilation and a solid mass of approximately 3.5 cm in size, embedded in the third part of the duodenum (Figure 1a). Exploratory laparotomy via a supraumbilical midline incision was decided upon, whereby duodenotomy, lithotomy and gallstone extraction followed by defect closure were performed. A low-output fistula occurred during the postoperative period, which was managed conservatively, with the patient being discharged in good clinical condition after removal of the drain on postoperative day 25. The patient died of congestive heart failure 18 months after surgery.

CASE 2

An 81-year-old male patient, with a personal history of diabetes mellitus, atrial fibrillation and chronic obstructive lung disease presented to the emergency department because of dyspnea, abdominal pain and vomiting starting two days ago. Physical examinations revealed right upper quadrant tenderness and crackles on the right lower lung fields. Four months prior to this episode he had experienced pain in the right upper quadrant of his abdomen. CT scan with IV and oral contrast demonstrated distention of stomach and jejunum due to obstruction from an impacted gallstone with air bubbles present within the gallbladder (Figure 1b). The patient underwent laparotomy, with the stone was removed through a 3-cm enterotomy. The length of postoperative stay was prolonged due to aspiration pneumonia; however, the patient was discharged on postoperative day 10 with his thereafter course being uneventful. Two years after the procedure, the patient is alive but reports frequent hospitalization due to exacerbation of chronic obstructive pulmonary disease.

CASE 3

An 85-year-old woman, with a history of hypertension, came to the emergency department due to vomiting and abdominal pain. The patient reported a similar episode of severe back pain relieved by rest and analgesics a few months prior to presentation. Contrast-enhanced CT scan revealed stomach dilation and a solid mass impacted in the first part of the duodenum, as well as air into the gallbladder and the biliary tree (Figure 1c). Via midline laparotomy, the gallstone was palpated and was maneuvered into the stomach where it was retrieved via gastrotomy. The patient had an uneventful postoperative course and was discharged on postoperative day 10. The patient remains in good health two years postoperatively.

CASE 4

An 80-year-old male patient visited the emergency department because of vomiting and abdominal pain. Physical examination revealed abdominal distention and tenderness. His medical history included chronic obstructive pulmonary disease and aortic valve replacement. Approximately sixty days prior to his admission he had experienced an atypical epigastric pain. CT scan with IV contrast showed a mass causing ileal obstruction with air present within the gallbladder (Figure 1d). Eventually, the patient was taken to the operating theatre and underwent an exploratory laparotomy. The site of obstruction was identified by palpation and the gallstone was retrieved after an enterotomy which was subsequently closed. The patient recovered uneventfully and was discharged on postoperative day 10. Four years after the operation the patient is still alive without presenting any symptoms associated with residual gallstone disease.

CASE 5

An 88-year-old female patient with a history of hypertension and dementia presented to the emergency department with fever, abdominal pain, and vomiting. Due to an episode of cholangitis 3 months ago, she underwent endoscopic retrograde cholangiopancreatography. Impacted gallstones into the common bile duct (CBD) that were

removed and CBD double-stenting after a sphincterotomy were performed. Abdominal distention, tenderness and jaundice (bilirubin 4 mg/dl) with increased number of inflammatory markers (WBC 16700/mm3 and CRP 150 mg/dl) needed emergency management. Computer tomography showed ileal obstruction caused by a solid mass plus air in the gallbladder and the biliary tree (Figure 1e). She underwent open surgery, and the stone was located and removed. The patient's post-operative period was complicated by surgical site infection (SSI) however, the patient was discharged on postoperative day 6. Twelve months after the operation she remains in good condition without any biliary-associated complaints.

CASE 6

This is a case of an 82-year-old female patient who presented to the emergency department with complaints of vomiting and abdominal pain. Abdominal examination revealed tenderness, but no distention. Her past medical history included atrial fibrillation, a transient ischemic attack and dementia. A CT scan with IV and oral contrast was performed, that showed jejunal obstruction (Figure 1f) and air in the gallbladder. The abdomen was explored through a midline incision. After the obstruction was identified an enterotomy, lithotomy and defect closure were performed. The patient was uneventfully discharged on postoperative day 8, however he died 6 months later due to an ischemic stroke.

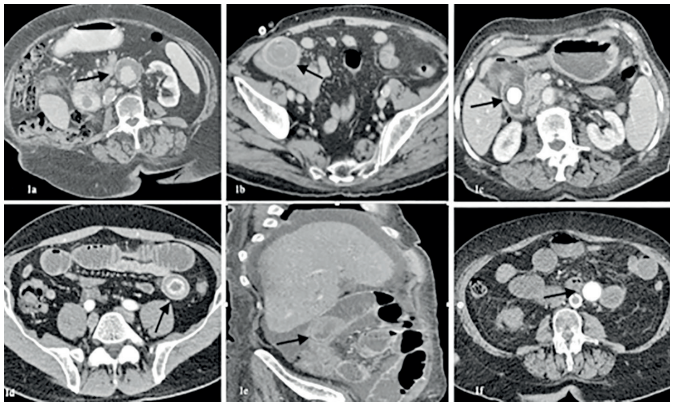

Fig. 1 CT scan with IV and oral contrast showing (a) a solid mass in size of 3.5 cm embedded in the 3rd part of the duodenum (white arrow) in case 1, (b) a gallstone impacted in the jejunum in case 2, (c) a solid mass impacted in the first part of the duodenum, as well as air into the gallbladder and the biliary tree in case 3, (d) a solid mass obstructing the ileum in case 4, (e) ileal obstruction caused by a solid mass in case 5, (f) jejunal obstruction in case 6.

DISCUSSION

Gallstone ileus is diagnosed in 0.3–0.5% of patients suffering from gallstone disease (4). Accounting for almost one fourth of intestine obstructions in patients older than 65 years old, accurate diagnosis and timely intervention are warranted (5). Two possible pathogenetic pathways of a cholecystoenteric fistula have been previously described. The first entails the formation of a fistula between gallbladder wall and an adjacent hollow viscera, while the second involves migration of gallstones through the common bile duct and the ampulla of Vater after endoscopic sphincterotomy (3).

The possible sites of obstruction include the ileum (60%), the jejunum (15%), the stomach (15%), and the colon (5%) (6). Plain abdominal x-ray and abdominal computed tomography (CT) with intravenous and oral contrast are the diagnostic modalities best used in acute setting (5). The classic radiological findings, called Rigler's triad consisting of pneumobilia or contrast medium within the biliary tract, small bowel obstruction and an ectopic gallstone in the bowel are present in one-third of patients (2, 7).

Surgical management consists of a full-thickness incision of the visceral wall and removal of the impacted gallstone. In cases of duodenal impaction, gently pushing the gallstone to the stomach allows for an easier and safer retrieval. Synchronous impacted gallstone removal, cholecystectomy and fistulectomy can be urgently performed during a single operation (3). Although a planned cholecystectomy following the resolution of acute small bowel obstruction is a feasible option, this is not recommended in older fragile patients (3, 4). It is well worth noting that spontaneous closure of inflammatory cholecystoenteric fistulas in asymptomatic patients has been recorded (8). Synchronous gallbladder carcinoma as an incidental finding is another possibility that should be taken into consideration (9, 10).

Laparoscopic resolution of gallstone ileus is feasible, albeit with a high risk of conversion due to exacerbated small bowel distention and risk of bowel content spillage in the abdominal cavity following enterotomy for stone extraction (11). Other minimal invasive methods such as endoscopic lithotomy, lithotripsy or extraction have been previously described as alternatives to cholecystectomy in fragile patients, however, data on the efficacy of such approaches remain, as yet, limited (3).

Intestinal obstruction was resolved through an enterotomy or gastrotomy and lithotomy/stone extraction in every patient in our cohort. Postoperative mortality is considerable when synchronous cholecystectomy is undertaken and should be factored in when contemplating the optimal surgical approach in elder patients (3). In the present case series follow-up symptoms of cholecystitis, cholangitis and recurrent ileus did not recur, with two registered mortalities being attributable to non-biliary causes (Table 1).

Although omitting cholecystectomy appears to be safe in frail patients, this observation cannot be generalized due to the small number and the narrow demographic range of included cases. Nevertheless, long-term postoperative outcomes regarding biliary-associated complications appear to be low, thus justifying a more conservative approach with regard to the biliary disease component.

CONCLUSION

Gallstone ileus is a rather rare complication of cholecystitis. Surgical treatment of gallstone ileus consists of removal of the impacted gallstone to resolve bowel obstruction in

Tab. 1 Characteristics of patients with gallstone ileus in our series.

Patient	Gender	Age	Comorbidities	CCI	Symptoms of RUQ inflammation preoperatively	Biliary interventions preoperatively	CT findings	Operation	Morbidity	Length of postoperative stay	Postoperative mortality	Mortality
1	F	83	Diabetes, atrial fibrillation	7	RUQP, fever	None	Bouveret's syndrome, air into the gallbladder, gastrographin into the gallbladder	Duodenotomy and lithotomy	Leakage	25	No	18 months
2	M	81	Diabetes, atrial fibrillation, chronic obstructive pulmonary disease	8	RUQP	None	Jejunal obstruction, air into the gallbladder	Enterotomy and lithotomy	Pneumonia	10	No	No
3	F	85	Hypertension	5	Back pain	None	Bouveret's syndrome, air into the gallbladder, pneumobilia	Gastrotomy and lithotomy	No	10	No	No
4	M	80	Chronic obstructive pulmonary disease, metallic aortic valve	6	Epigastric pain	None	Ileum obstruction, air into the gallbladder	Enterotomy and lithotomy	No	10	No	No
5	F	88	Hypertension, dementia	7	RUQP, fever, jaundice	ERCP	Ileum obstruction, air into the gallbladder, pneumobilia	Enterotomy and lithotomy	SSI	6	No	No
6	F	82	Atrial fibrillation, transient ischemic attack, dementia	7	None	None	Jejunal obstruction, air into the gallbladder	Enterotomy and lithotomy	No	8	No	6 months

the acute setting. While cholecystectomy may be contemplated, it is not recommended in older, frail patients. In our case series, intestinal obstruction was resolved through an enterotomy or gastrotomy and lithotomy/stone extraction in every patient with no patient subsequently developing biliary-related adverse events, despite the omission of cholecystectomy. Nevertheless, larger patient series are still necessary to corroborate the safety of leaving the gallbladder in situ, following an episode of gallstone ileus.

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