Ormond's Disease – 26 Years of Experience at One Centre

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Abstract: Ormond's disease is a systemic autoimmune disease with serious complications. We present our retrospective analysis of 83 patients diagnosed with and treated for idiopathic retroperitoneal fibrosis (Ormond's disease) in our department from 1997 to 2023. In this retrospective study, we analysed the diagnostic approaches, the clinical history and surgical and immunosuppressive therapies, and their subsequent effects on our patients. Patients with established disease activity were given immunosuppressive treatment, using corticosteroids alone or in combination with azathioprine, in patients with exacerbation of the disease mycophenolate mofetil. Three patients with Ormond's disease and systemic complications (IgG4-related disease) were treated with rituximab. In the entire cohort, 83 patients received immunosuppressive therapy; the next 5 patients did not receive this treatment because they did not present inflammatory activity from the disease. In these 83 patients, computed tomography showed that immunosuppressive treatment resulted in partial or complete regression of the inflammatory infiltrate. Out of the 83 patients, 10 patients experienced disease exacerbation 7 and 24 months after the immunosuppressive treatment was discontinued. The follow-up ranged from 24 months to 26 years.

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Introduction

Ormond's disease – idiopathic retroperitoneal fibrosis (IRF) – is a relatively rare disease with an unclear aetiology, characterised by chronic periaortitis and retroperitoneal fibrosis (RF). The inflammatory process affects the infrarenal part of the abdominal aorta and the iliac arteries. Moreover, infiltrates encasing the ureters and the inferior vena cava are also commonly found. Its incidence is 1.3 in 100,000 people (van Bommel et al., 2009). A subset of patients with Ormond's disease has immunoglobulin G4-related disease (IgG4-RD). The course of the disease is associated with the incidence of complications, the most serious of which are renal failure and aneurysm of the abdominal aorta or the iliac arteries. Thanks to further advances in medicine and diagnostics, therapeutic strategies are gradually changing. Improved results from pharmacotherapy regimens lead to a greater emphasis on early comprehensive medical therapy with corticosteroids and immunosuppressive or immunomodulatory drugs. In this retrospective study, we describe the clinical outcomes of 83 patients diagnosed with and treated for Ormond's disease in our department.

Patients and Methods

Patients and setting

Between 1997 and 2023, our department, in collaboration with the Department of Urology and the Department of Vascular Surgery, investigated 135 patients suspected to have Ormond's disease. Ultimately, 83 patients were diagnosed with and subsequently treated for this disease. Patients with RF that had been medically induced, caused by cancer, or exacerbated by other disease were excluded from the analysis. Ormond's disease was diagnosed based on a comprehensive clinical examination using biochemical, immunological, and microbiological tests, and imaging methods – ultrasound, computed tomography (CT), positron emission tomography (PET)/CT, and CT/arteriography. Laboratory screening included a biochemistry panel, screening for hepatitis B and C; the serum levels of IgG, specifically the IgG1-IgG4 subclasses; and the erythrocyte sedimentation rate (ESR). Patients were also examined for the presence of antinuclear antibodies, extractable nuclear antibodies, and antibodies to double-stranded DNA. RF was considered if a soft-tissue density surrounded the infrarenal aorta or iliac vessels on contrast-enhanced CT and/or on histological confirmation. Disease activity was confirmed by a PET/CT scan in all patients upon the initiation and discontinuation of immunosuppressive therapy. In 45 patients (54%), a biopsy was performed percutaneously using a biopsy needle under CT navigation, whereas in 3 patients, laparoscopy was used to collect the sample. The diagnosis of IgG4-RD in 28 patients was confirmed by subsequent histological examination: the presence of at least one characteristic histopathological feature, >30 $IgG4^+$ plasma cells per high power field, and an $IgG4^+/IgG^+$ plasma cell ratio cut-off of >40%.

Treatment

All medical and surgical treatments for IRF were reviewed. The medications used included glucocorticoids, azathioprine, mycophenolate mofetil, and rituximab. The first-line treatment was a combination of corticosteroids and azathioprine or corticosteroids alone. Mycophenolate mofetil therapy was subsequently used in 5 of these patients with exacerbations of the disease. Rituximab was used in three patients with systemic clinical manifestations associated with IgG4-RD and exacerbations of IRF after finishing of the corticosteroids therapy. Where indicated, surgical procedures were applied, namely ureteral stenting, nephrostomy, stenting of arteries.

Follow-up and outcomes

Patients in the study were followed-up regularly during the treatment of their disease (via medical record review) and then at least once per year for the next 5 years. The primary outcome was the reduction of clinical symptoms, extubation of the obstructed ureters, and reduction of soft tissue mass, followed by the absence of inflammatory activity on a PET/CT scan. The secondary end-points included monitoring the biochemical parameters of renal function, the IgG4 concentration, and reaching normal values of inflammatory biomarkers.

The patients were monitored at regular intervals of 2–4 weeks during the first 4 months when biochemical and immunological parameters were monitored. After inflammatory markers became insignificant, this interval was extended to 2 months. Follow-up CT or PET/CT scans were performed after the first 6 months and then as needed. The follow-up range was 24 months to 26 years.

Results

We investigated 135 patients between July 1997 and June 2023 who were suspected to have IRF. We excluded 52 patients: 5 patients without activity of the disease, 34 patients did not have Ormond's disease, 8 patients had an inflammatory abdominal

aortic aneurysm, and 5 patients had a cancerous retroperitoneal mass. Our final study population included 83 patients, 55 (66%) of whom were men and 28 (24%) of whom were women. All patients had imaging findings consistent with Ormond's disease. The diagnosis was confirmed by biopsy in 48 cases (58%). Fifty-three patients presented with clinical symptoms of ureteric obstruction with hydronephrosis, renal insufficiency (17 patients), or renal failure (5 patients). Thirty patients had periaortitis, with aneurysms of the aorta and/or iliac arteries present in 12 of these patients. After laboratory testing, 22 patients were positive for antinuclear antibodies, without evidence of specificity for extractable nuclear antibodies. None of the patients tested positive for antibodies to double-stranded DNA. Other autoimmune diseases were present in 25 patients, in which 14 had autoimmune thyroiditis, 2 had vasculitis, and 9 had Sjogren's syndrome. The IgG4 concentration was examined in 52 patients; 28 had an elevated IgG4 serum concentration. The IgG4 serum concentration was within the normal range in all patients after receiving immunosuppressive therapy. Hydronephrosis was found in 32 patients; 18 patients showed impairment of one ureter and 14 patients had impairment of both ureters. In 7 patients, despite an initial diagnosis of renal insufficiency, subsequent surgical intervention and immunosuppressive therapy resulted in the recovery of renal function. The standard surgical solution involved the insertion of stents, and a nephrostomy was performed on 3 patients. In all 83 patients, CT showed that immunosuppressive treatment resulted in partial or complete regression of the inflammatory infiltrate. After termination of the immunosuppressive therapy, 32 ureters were extubated successfully. Eight patients presented an abdominal aortic aneurysm, and 6 patients had iliac artery aneurysms. Surgical treatment was indicated for aneurysms in 4 patients prior to the deployment of immunosuppressive therapy. In 1 patient with an aneurysm, surgical treatment was not indicated after the initial diagnosis, but 4 months after termination of immunosuppressive treatment, the size of the aneurysm had increased, and surgery was required. Four patients who underwent surgery for aneurysms were subsequently given standard immunosuppressive treatment, with no exacerbation of the disease for 6 months after its termination.

83 patients received immunosuppressive therapy; the next 5 patients did not show inflammatory activity from the disease, so they did not receive this treatment. The 83 treated patients received a combination of corticosteroids with azathioprine, corticosteroids or mycophenolate mofetil alone. Out of the 83 patients, 10 patients (12%) experienced disease exacerbation 7 and 24 months, respectively, after the immunosuppressive treatment was discontinued. There was no difference in the success of therapy between the IgG4-associated and non-IgG4-associated groups of patients with Ormond's disease.

The follow-up period ranged from 24 months to 26 years. Out of the total number of 83 patients, 80 are still alive. One patient died of an acute abdominal event, and 2 patients died of cancer.

Discussion

Disease diagnosis

IRF has an unclear aetiology. The term covers several common diseases – chronic periaortitis, inflammatory abdominal aortic aneurysm, and perianeurysmal RF. There is a general consensus that IRF is an autoimmune disease. The reported autoantigen is an atherosclerotic plaque (Parums, 1990). Some patients with Ormond's disease meet the definition of IgG4-RD (Khosroshahi et al., 2013). One of the complex and very important issues to be addressed in the diagnosis of RF involves distinguishing between the infectious and non-infectious aetiology of the inflammation. The emergence of a retroperitoneal or para-aortal infiltrate may also be induced by an infectious aetiology. Given the use of immunosuppressive therapy, the failure to recognise this difference may have fatal consequences for the patient. Potential causative agents may include viruses (e.g., hepatitis), mycobacteria, *Staphylococcus aureus*, and *Salmonella* (Sekar, 2010; Cartery et al., 2011). In our patient cohort, we did not observe differences in clinical symptomatology in patients meeting the histological criteria of IgG4-RD compared with patients without evidence of IgG4-RD. In most patients with IgG4-RD, the IgG4 serum concentration did not correlate with positive histological findings based on biopsy. This agrees with our findings in patients with abdominal aortic aneurysm (Hao et al., 2016; Prucha et al., 2019). We tried to establish a histological diagnosis for all patients by performing CT guided biopsy or, in three cases, laparoscopically. In other cases, obtaining a sample was associated with excessive risk to the patients due to the location or time constraints. In these instances, the laboratory results and imaging findings were correlated to confirm the diagnosis. The other possibility of diagnosis IgG4-RD and activity of the disease is the investigation of circulating plasma blasts but require flow cytometry facilities and are not disease-specific (Iaccarino et al., 2022).

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A simple CT scan with contrast is not sensitive enough to detect disease activity. We have good experience using PET/CT: we perform it routinely at the beginning of the diagnostic process, followed by a second examination after 6 months of therapy. Subsequently, we perform PET/CT as needed for each patient. In 5 patients, we did not detect metabolic activity in the infiltrate at the time of the examination, although 2 patients had signs of chronic renal insufficiency, and 1 patient had a unilaterally functional kidney. We did not start drug therapy in all of these patients, and the disease did not become active over the next few years. Therefore, it proves that a small number of patients may experience spontaneous recovery of disease activity (Williams et al., 2013).

Negative parameters of inflammation correlated with inactivity demonstrated by PET/CT. The clinical symptoms are non-specific in patients with Ormond's disease. There is no specific laboratory parameter for diagnosis or a biomarker to predict disease recurrence. The responsiveness of the disease to systemic corticosteroid therapy with a decrease in inflammatory parameters can be considered to confirm the diagnosis. Differentiating Ormond's disease from oncological disease is sometimes problematic (Sica et al., 2019). Hence, if possible, a biopsy should be performed to confirm the diagnosis. If the biopsy under CT guidance does not lead to an unequivocal verification and there are clinical doubts about the nature of the disease, then it is necessary to perform an operative revision and collect a representative sample for histological verification. We have repeatedly dealt with a situation where a patient was sent to us with suspicion of RF and a biopsy proved they had cancer.

From the point of view of laboratory parameters, Ormond's disease is characterised by positivity for inflammatory markers. However, these parameters are non-specific. Imaging methods (CT and PET/CT) provide great help in the diagnosis (Peisen et al., 2020). IRF can manifest as chronic periaortitis. This nosological unit describes several diseases with inflammatory involvement of the aorta – IRF, inflammatory aneurysm of the abdominal aorta, and perianeurysmal RF. We described inflammatory aneurysm of the abdominal aorta as part of IgG4-RD several years ago (Laco et al., 2013; Prucha et al., 2019). In these patients, however, the resulting abdominal aortic aneurysm is primarily treated surgically due to the practical impossibility of performing a biopsy and subsequent histological examination. It is worth noting that in the past 12 years, when we have been following patients with abdominal aortic aneurysm, there has not been a recurrence of the disease in any case after surgery. Perianeurysmal RF manifests as dilatation of the aorta and the presence of a fibrotic process that affects the adjacent organs (e.g., the ureters).

Therapy

There is not a consensus regarding how to treat Ormond's disease (Vaglio and Maritati, 2016; Tanaka and Masumori, 2020; Gianfreda et al., 2023; Vianello et al., 2023). The first-line treatment often involves systemic corticosteroids alone or in combination with other immunosuppressants. In our cohort, 42 patients received a combination of corticosteroids with azathioprine, and 41 patients received corticosteroids alone. The starting dose was not higher than 60 mg of prednisone or 48 mg of methylprednisolone. The patients received the starting dose for 12–16 weeks, followed by gradual tapering to 5 mg over 2 weeks. In the case of using azathioprine, we used a dose of 2×50 mg/day with a reduction after 3 months. In 7 patients, we stopped after 4–12 weeks due to elevated liver test results. The results of the therapy did not differ between the groups that did and did not receive azathioprine. When patients received corticosteroids and azathioprine, we were able to stop corticosteroids more quickly. On the other hand, long-term use of corticosteroids caused hyperglycemia in 27 patients, necessitating the initiation of oral antidiabetic drugs. In 16 patients, these drugs could be discontinued after the therapy ended.

Out of the 83 patients, 10 (12%) experienced disease exacerbation between 7 and 24 months after the discontinuation of immunosuppressive treatment. This result aligns with the findings of Kermani et al. (2011). Mycophenolate mofetil therapy was successfully used in 5 patients with disease exacerbations.

We treated 3 patients with repeated exacerbations and systemic complications (IgG4-RD) using rituximab. For all three patients, we implemented a treatment regimen that included maintenance therapy six months after initiation. None of the three patients experienced disease exacerbation during the two years following the start of treatment. Additionally, no significant hypogammaglobulinemia occurred in any of these patients. Rituximab is currently considered safer and more effective than corticosteroids, taking into account their side effects.

A Boston study included 26 patients with retroperitoneal fibrosis (Wallwork et al., 2018). Of these, 19 were evaluated as retroperitoneal fibrosis associated with IgG4-RD, while 7 were classified as idiopathic retroperitoneal fibrosis. All patients were treated with rituximab. A total of 19 (73%) received rituximab as monotherapy, while the rest received it in combination with glucocorticoids.

Radiographic evaluations were conducted in 25 patients, with 22 (88%) showing radiographic improvement (reduction in infiltrate size). Among the 10 patients with ureteral stents and/or percutaneous nephrostomy, stents or nephrostomies could be removed in 4 (40%). This study confirmed the effectiveness of rituximab monotherapy for patients with retroperitoneal fibrosis, regardless of whether the fibrosis was associated with IgG4-RD or idiopathic. However, the study does not provide long-term follow-up data post-treatment.

The second retrospective study evaluating the benefits of rituximab specifically for patients with idiopathic retroperitoneal fibrosis was published in Canada (Boyeva et al., 2020). In all ten patients, regression of fibrotic infiltrate size was confirmed via imaging studies. However, the authors of this study highlighted unresolved questions. While maintenance therapy with rituximab prevents relapses, the optimal duration of therapy remains unclear.

A nationwide French study analysed 156 patients registered in their database, of whom 33 were treated with rituximab (Ebbo et al., 2017). A clinical therapeutic response was observed in 29 out of 31 evaluated patients (93.5%). During a median follow-up of 24.8 months, the disease relapsed in 13 out of 31 patients with therapeutic response, with a median interval of 19 months from the last rituximab application. This study was the first to evaluate maintenance therapy and demonstrated the absence of relapses with consistent use of maintenance therapy. Therefore, the authors strongly recommend maintenance therapy, emphasizing its benefits despite the increased risk of infections due to rituximab-associated hypogammaglobulinemia. However, the optimal duration of this therapy remains an open question.

Following the success of rituximab in treating lymphoproliferative diseases, other anti-CD20 monoclonal antibodies, such as ofatumumab and obinutuzumab, have been introduced. As of 2024, only one publication describes the use of ofatumumab in retroperitoneal fibrosis (Hanazono et al., 2022).

Conclusion

Ormond's disease (IRF) involves serious complications including renal insufficiency or failure and aneurysm of the abdominal aorta or iliac arteries. Its diagnosis and treatment are based on an interdisciplinary approach. In recent years, the possibilities of therapy have expanded significantly, which had improved the quality of life of patients and has reduced the development of serious complications.

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