Scholars Journal of Medical Case Reports
Abbreviated Key Title: Sch J Med Case Rep
ISSN 2347-9507 (Print) | ISSN 2347-6559 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Gastroenterology

IgG4-Related Disease: A Case Report and Diagnostic Challenges

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DOI: https://doi.org/10.36347/sjmcr.2024.v12i10.005 | **Received:** 20.08.2024 | **Accepted:** 29.09.2024 | **Published:** 01.10.2024

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Abstract **Case Report**

IgG4 disease, also known as IgG4 autoimmune polyexocrinopathy, is a new entity that includes type 1 autoimmune pancreatitis. It has the capacity to affect various organs such as the central nervous system, salivary glands, thyroid, lungs, pancreas, bile ducts, liver, digestive tract, kidneys and prostate, resulting in symptoms specific to the organ affected. It is a rare disease. It is most common in men over the age of 50. Diagnosis is based on histological features such as the presence of a dense lymphoplasmacytic infiltrate in the affected organ, serum IgG4 elevation in more than 80% of cases, IgG4 positivity on immunohistochemistry, fibrosis of the organ and obliterating venulitis. It is sensitive to corticosteroid therapy, which entails a significant risk of relapse when corticosteroid treatment is stopped, necessitating recourse to immunomodulators. We describe the case of a 53-year-old female patient who was admitted to our institution for an aetiological work-up of chronic epigastric pain resembling pancreatic involvement, revealing IgG4 disease.

Keywords: IgG4 - PAI type1 – Corticotherapy.

INTRODUCTION

IgG4 disease (ML-IgG4), also known internationally by the consensus term IgG4-Related Disease, is an anatomical and clinical entity. It has long been identified by various organ specialists under different names such as Mikulicz syndrome, Riedel's thyroiditis and retroperitoneal fibrosis. The incidence and prevalence of IgG4 disease remain unknown due to its rarity. It should also be noted that diagnostic criteria have evolved significantly in recent years, and studies in this field are somewhat heterogeneous. Most research comes from Asian countries such as Japan and South Korea, and focuses on programmable artificial intelligence (PAI). The prevalence of IAP has been estimated at 6% of so-called idiopathic pancreatitis in Asia. This figure is probably underestimated due to a lack of diagnosis. In Japan, the prevalence has been estimated at 0.82/100,000 inhabitants. The disease was first identified in patients with autoimmune pancreatitis (AIP) in the early 2000s [1]. IgG4-associated disease has subsequently been described as affecting virtually all organs. The main organs involved are the pancreas and biliary tract, salivary and lacrimal glands, mediastinal lymph nodes and retroperitoneum, lungs, kidneys and inflammatory aortic disease [2]. It is more common in men over the age of 50. Clinical manifestations are usually sub-acute, in the form of slowly progressive damage to one or more organs. Diagnosis may be made by chance through the discovery of radiological abnormalities (e.g. adenopathies) or histopathological features [3]. It is frequently correlated with an increase in serum IgG4 levels above 1.35g/L. The histopathological appearance is characterised by a sometimes pseudotumourous enlargement of the organs affected, attributable to lymphoplasmacytic infiltration with a predominance of IgG4-positive plasma cells, as well as progressive fibrosis and lesions of obliterating thrombophlebitis. It responds favourably to corticosteroid therapy, but presents a non-negligible risk of relapse if this treatment is discontinued, which may necessitate recourse to immunomodulators such as thiopurines (azathioprine or 6-mercaptopurine), methotrexate and more recently rituximab, which can also be used as an inducing treatment. The aim of this research is to present a unique case of ML-IgG4 based on clinical and radiological criteria, as well as on the response of the patient to the treatment.

OBSERVATION

The patient in question was M.F, 53 years of age, whose history included a cholecystectomy 11 years previously. She was admitted to our clinic for assessment

of the aetiology of chronic epigastralgia of pancreatic origin evolving in a context of apyrexia and altered general condition. Clinical examination revealed only epigastric tenderness, with no tenderness or contractures. Laboratory tests showed normal liver function tests and pancreatic enzymes. Pancreatic MRI revealed a swollen, globular appearance of the head of the pancreas, with a poorly defined lesion formation measuring 30 x 25 mm, blending into the pancreatic parenchyma with a signal and enhancement identical to those of the pancreas, and containing small millimetre-sized cystic-like formations with a T2 hypersignal not enhanced by Gadolinium. There was another lesion formation caudal to the pancreas with the same characteristics, with more marked infiltration of peri-pancreatic fat opposite the tail of the pancreas. The 2nd-line work-up revealed an increase in gamma globulins to 3.8 times normal, with IgG4 at 5 g/l. An oesophago-duodenal fibroscopy and echoendoscopy were performed, with the following findings: erythematous antifundial gastritis and, on echoendoscopy, a heterogeneous hypertrophic pancreas, especially at the head, with multiple hyperechoic images with shadow cones; visualisation of the Wirsung in its corporo-caudal part with an irregular, non-dilated appearance. On the basis of these findings: elevation of IgG4 and the radiological appearance, the diagnosis of IgG4 autoimmune pancreatitis was accepted and the patient was put on corticosteroid therapy at a dose of 40 mg/d. The course of treatment was favourable, with disappearance of the clinical symptoms and normalisation of the IgG4 level on day 19. The patient has now been off corticosteroids for 8 months without relapse.

DISCUSSION

The association between sclerosing pancreatitis (or type I autoimmune pancreatitis) and high IgG4 levels was first described in 2001 [1]. Since then, a growing number of inflammatory diseases have joined this new entity, called IgG4-related disease (MLIgG4) [2, 3]. MLIgG4 therefore brings together inflammatory disorders of various organs under a common nosological umbrella, in a similar way to sarcoidosis. The clinical, paraclinical and histopathological features of ML-IgG4 were the subject of an international consensus adopted in 2011 [4, 5]. It may affect one or more organs, either synchronously or at a later stage, in the form of a mass or diffuse enlargement of the affected organs. The histopathological appearance is one of lymphoplasmacytic infiltration and progressive fibrosis. The organs most commonly affected are the pancreas, bile ducts, salivary glands, lacrimal glands, mediastinal lymph nodes, retroperitoneum, aorta, lungs and kidneys [6]. Multiple organ involvement occurs in 60-90% of cases [7]. In our patient, the involvement was of the pancreas. Clinical manifestations are usually subacute, in the form of slowly progressive involvement of one or more organs. Sometimes the patient is asymptomatic. The diagnosis may be made by chance through the discovery of characteristic radiological (e.g. adenopathy) or histopathological abnormalities. Allergic-type laboratory abnormalities (elevated serum total IgE levels and circulating eosinophil cell count) may be associated in around 40% of cases [8]. The clinical presentation of PAI has contributed to a better understanding and description of ML-IgG4. Pre-auricular type 1 is widespread in Asia (more than 90% of cases in Japan), whereas it accounts for less than 20% of cases in the West. On average, 80% of patients are over 50 years old, and the vast majority are male (80%). The diversity of clinical manifestations can be attributed either to direct involvement of the pancreatic gland, such as jaundice caused by compression of the main bile duct in its retro-pancreatic portion, the pseudotumour form, acute pancreatitis (although less frequent), and exocrine or endocrine pancreatic insufficiency; or frequent extra-pancreatic involvement (in more than 60-70% of cases), such as jaundice caused by specific lesions of the bile ducts, dry syndrome or retroperitoneal fibrosis. In our study, acute pancreatitis was the most common presentation of the disease. The likelihood of ML-IgG4 is increased by elevated serum IgG4 levels, allergic symptoms and fibrotic processes [7]. In addition to clinical examination, diagnosis is therefore based on paraclinical data combining immunoglobulin assays (serum IgG4 ≥1.35g/l), imaging and, above all, the histopathological appearance of tissue samples. Carruthers *et al.*, studied the diagnostic utility of serum IgG4 levels in ML-IgG4 [9]. Despite a sensitivity of 90% and a negative predictive value of 96% for the diagnosis of ML-IgG4, its specificity (60%) and positive predictive value (34%) are low, as other conditions may be associated with an increase in IgG4 [9, 10]. A threshold of 135mg/dL appears to be useful in distinguishing ML-IgG4 from pancreatic cancer and Primary Sclerosing Cholangitis (PSC). However, it has a lower specificity for distinguishing ML-IgG4 from CC [10]. Ohara *et al.*, [11] established a threshold to distinguish ML- IgG4 from CC using serum levels measured in nine Japanese centres. A threshold of 182 mg/dl has a specificity of 96.6% and a threshold of 207 mg/dl has a higher sensitivity and specificity to distinguish CC types 3 and 4 from ML-IgG4. Our patient had a serum IgG4 level in excess of these two thresholds, reinforcing the diagnosis of ML-IgG4.

ML-IgG4 is a disease that is highly sensitive to corticosteroid therapy. As a result, corticosteroids remain the first-line treatment for this condition, even though most of the information gathered was based on retrospective studies, particularly in the case of autoimmune pancreatitis. The International Consensus for the Treatment of Autoimmune Pancreatitis [6], sets out the indications and treatment regimen. Treatment is indicated in symptomatic patients with pancreatic involvement (e.g. obstructive jaundice, abdominal pain) or other organ involvement (e.g. jaundice secondary to narrowing of the bile ducts), but also in patients who are asymptomatic but have a persistent pancreatic mass on

imaging, or patients with IgG4 cholangitis with persistent liver dysfunction [6]. Corticosteroid therapy is the mainstay of induction treatment, with a very high response rate [6], but its regimen varies from school to school, and the Japanese authors with the most experience in this condition suggest the following treatment consensus [6], prednisolone at a dose of 0.6 to 1mg/kg per day for two to four weeks. After this initial dose, the dosage should be reduced by 5 to 10mg/day every 1 to 2 weeks until a daily dose of 20mg is reached, followed by a gradual reduction of 5mg every 2 weeks until the disease is stopped. Treatment for complete remission should generally last 12 weeks. Many Japanese experts recommend the use of low-dose glucocorticoid maintenance therapy (2.5 to 7.5mg/day) for a maximum of 3 years, with discontinuation of maintenance therapy planned in cases of radiological and serological improvement [11]. This treatment regimen was initiated in our patient with good clinical and biological improvement. In the event of corticosteroid dependence, or especially in the event of side-effects in patients who may already have osteoporosis or diabetes, immunosuppressants or other treatments may be used: Rituximab, Azathioprine (2 to 2.5mg/kg per day), Mycophenolate mofetil (750mg per day) [6]. These are the two most commonly used immunosuppressants. Because of the high rate of recurrence, particularly in cases of biliary involvement, monitoring is recommended. Factors predictive of relapse include remarkably high serum IgG4 levels (such as > x4 UNL) before treatment and persistently high levels after steroid treatment; the presence of diffuse enlargement of the pancreas, proximal cholangitis and multi-organ involvement [6]. Monitoring is as follows: liver function tests (transaminases, alkaline phosphatases and total/conjugated bilirubin) and serum IgG4 every 3 months for 2 years and pancreatic and biliary MRI every year for 2 years.

CONCLUSION

IgG4 disease is a recently identified systemic autoimmune disorder affecting several organs, with characteristic histological features such as an IgG4-rich lymphoplasmacytic infiltrate, fibrosis and obliterative venulitis. It is more common in Asia, but accounts for 20-30% of autoimmune pancreatitis in the West. Despite the presence of normal serum immunoglobulins and recurrent manifestations of benign acute pancreatitis, chronic inflammatory bowel disease is observed in 20-30% of cases. Recent advances have made it possible to diagnose the disease more accurately, limiting the need for unnecessary surgery. However, much remains to be learned about the pathophysiology, specific biomarkers, long-term evolution, and optimal use of diagnostics such as pancreatic biopsy by echo-endoscopy. An international consensus is needed to improve patient management, particularly during relapses and the early stages of the disease.

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