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REVIEW ARTICLES

IgG4-related disease and isolated retroperitoneal fibrosis: a narrative review

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ABSTRACT

Background: Retroperitoneal fibrosis (RPF) can occur due to many etiologies and is categorized into idiopathic and secondary. Etiologies of secondary RPF include medications, autoimmune disease, malignancy, and IgG4-related disease (IgG4-RD). Although IgG4-RD usually involves multiple systems synchronically including the pancreas, aorta, and kidneys, it can present with isolated RPF without involvement of other organ systems. Caution must be exercised in these instances as the diagnosis should be confirmed based on specific clinical, radiographic, and histopathologic criteria. Such confirmation can affect the work-up and therapeutic approach as treatment with corticosteroids can lead to remission, both clinically and radiographically.

Keywords: Immunosuppressants; Lymphocytes; Primary care rheumatology; Soft tissue rheumatism; Radiology.

INTRODUCTION

Immunoglobulin G4-related disease (IgG4-RD) has recently emerged as a clinical entity. It has been labelled as a diverse constellation of symptoms affecting a wide range of organs. It is characterized by elevated serum IgG4 levels, infiltration of IgG4 positive cells manifesting as mass forming lesions with fibrosis and good response to corticosteroids[1].

In the early 2000s, elevated levels of IgG-4 were increasingly linked to autoimmune pancreatitis. However, the same patients also had extra pancreatic manifestations raising the possibility of a systemic pathology[2]. In 2012, Umehara *et al.* formally defined the comprehensive diagnostic criteria for IgG4-RD as follows: (i) clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs; (ii) hematological examination showing elevated serum IgG4 concentrations (> 1350 mg/L); and (iii) histopathologic examination showing marked lymphocytic and plasmocytic infiltration and fibrosis, as well as infiltration of IgG4+ plasma cells at a ratio of IgG4/IgG cells > 40% and > 10 IgG4+ plasma cells/high-power field. Diagnosis being definite with three out of three criteria, probable with criteria one and three and possible with criteria one and two[3]. Commonly affected organs include the pancreas, lacrimal and salivary glands, in addition to retroperitoneal fibrosis, which is becoming of increasing interest[4,5].

Retroperitoneal fibrosis (RPF) is a rare clinical disorder characterized by the formation of fibro-inflammatory masses surrounding retroperitoneal structures, most commonly the abdominal aorta, iliac arteries, and ureters[6]. This can lead to an array of symptoms including abdominal pain, renal insufficiency and ureteral obstruction[7]. RPF was mainly divided into two types: idiopathic RPF (IRPF) and secondary RPF, with the latter being associated with drugs, infections, or malignancies.

The association between retroperitoneal fibrosis and IgG4 disease was established largely following studies exploring extra pancreatic manifestations in patients with autoimmune pancreatitis, noting abundant infiltration of IgG4-positive plasma cells in both their pancreatic and retroperitoneal lesions[8]. As such, retroperitoneal fibrosis is now regarded as a typical lesion of IgG4 related disease[9].

Epidemiology

Given the relatively recent recognition of IgG4-RD about two decades ago, the epidemiology is insufficiently described in literature and most literature is restricted to Japan. However, some demographic characteristics are generally identified. IgG4-RD is more commonly

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seen to affect men with a male: female ratio of 3:1[10]. Another review of 69 articles reports male: female ratio to be as high as 8:3[11]. This is particularly interesting as it contradicts the general observation of predilection of autoimmune diseases for females. While significant demographic features were observed, in the cohort study by Massachusetts General Hospital Centre for IgG4-RD, there were no significant differences noticed in terms of disease severity, serum IgG4 levels and organ involvement[12].

There is paucity of data on prevalence and incidence. One nationwide survey conducted in Japan by Uchida *et al.* reports an incidence of 0.28–1.08/100, 000 people[13]. Uchida *et al*. also reports male: female ratio of 1:0.77 and mean age of onset as 58.8 years. Another study from Japan reported a prevalence of about 62 patients with IgG4-RD per million people[14]. However, due to heterogeneity of data between different countries, it is not possible to accurately estimate the prevalence and incidence on a wider scale. Several other studies have also analyzed that IgG4-RD commonly affects people between the fifth and seventh decade of life[11,15,16].

Isolated Retroperitoneal Fibrosis with IgG4-RD (IgG4-RD RPF) is an uncommon clinical manifestation of IgG4-RD. About 9.6-27% of the IgG4-RD patients will develop IgG4-RD RPF[17]. A recent study including 132 Chinese cohort population of IgG4-RD RPF patients reports male predominance and mean age of onset of 54.8 years[18]. A review of 52 cases of IgG4-RD RPF reports male: female ratio of 3.3:1.0[19]. Another two-center study of 27 patients with retroperitoneal fibrosis, conducted in Korea, reports 59.3% of patients with presumed idiopathic retroperitoneal fibrosis had IgG4-RD RPF. Most of them (62%) were male and the mean age was 59.7 ± 13.6 years[20]. In addition to the previously mentioned cohorts, multiple cases of IgG4-RD manifesting as isolated RPF were reported[21].

Clinical manifestations

IgG4-RD is a fibroinflammatory disorder characterized by IgG4-positive plasma cells infiltrating various organs. The classic presentation comprises the subacute development of a mass in the affected organ or diffuse enlargement of an organ as a sequela of inflammatory cell infiltration and associated fibrotic response. Some hallmark organ manifestations include autoimmune pancreatitis, sclerosing cholangitis, retroperitoneal fibrosis, aortitis, pachymeningitis, and glandular enlargement[22].

RPF is one of the most commonly encountered and characteristic phenotypic manifestations of IgG4-RD. IgG4-RD accounts for about 30 to 60 percent of cases of retroperitoneal fibrosis and can be the sole manifestation[23]. RPF is an inflammatory process involving the retroperitoneal region, which can compress one or both ureters in over 60% of cases, and the abdominal vasculature, including the aorta and inferior vena cava[24]. RPF in IgG4-RD is particularly likely to involve the infrarenal aorta and iliac arteries and, unlike other autoimmune disorders, often lacks concomitant fevers and arthralgia.

The fibrosclerotic retroperitoneal tissues encase and compress visceral organs leading to damage and dysfunction simultaneously or successively[19]. The most common presenting symptom among patients with RPF is a pain in the lower back and abdomen, which is present in over 90 percent of patients.[25] Pain is usually dull and poorly localized and often has features of nocturnal exacerbation. Some patients may have flank pain that radiates to the inguinal region. Other common symptoms include malaise, anorexia, weight loss and lower extremity oedema.

The involvement of the kidneys and the ureters can present as back pain, flank pain, urinary frequency, urgency, dysuria, and acute renal failure[26]. Urine output is variable and may be reduced, normal or increased due to concentration defects in obstructive uropathy[26]. More than 50% of patients may have elevated BUN and creatinine at presentation[25,26]. About 8 to 30% of patients may have unilateral or bilateral kidney parenchymal atrophy stemming from slowly progressive ureteral obstruction due to renal artery compression leading to ischemia. Ultrasound often reveals hydronephrosis with or without bilateral encasement of renal vessels by peri-iliac fibrotic tissue and such encasement of renal arteries can be responsible for renovascular hypertension in these patients[26].

Vascular involvement can have various presentations depending on the predominant involvement of venous or arterial structures. IgG4-related aortitis and arteritis can lead to the genesis of inflammatory aneurysms, presenting as pulsatile mass, low-grade fever, back pain, or even aneurysm rupture. When the arterial circulation of the lower extremities is affected, it can cause claudication.[26] Similarly, abdominal pain due to mesenteric ischemia from compression of the mesenteric arteries can occur. Involvement of inferior vena cava and iliac veins presents as lower extremity oedema, thrombophlebitis, or deep vein thrombosis. Hydrocele and varicocele are also commonly seen resulting from compression of retroperitoneal testicular vessels[24,25].

Sclerosing mesenteritis is one of the rarer manifestations of RPF of clinical significance. It presents as abdominal pain, diarrhea, intestinal obstruction or chylous ascites[19]. Fulminant presentations have been primarily due to complications of intestinal obstruction and mesenteric vascular occlusion.

Histopathology

Histopathology remains essential in confirming the diagnosis of IgG4-RD, especially with its potential to affect a wide array of organ systems, mimicking other diseases. As more cases were being reported over the years, multiple histopathologic criteria that rely on immunologic stains and ancillary studies, in addition to conventional histopathology examination were proposed. The major criteria include:

A. Peri-vascular dense lymphoplasmacytic infiltration with B-cells, T-cells, plasma cells and occasionally eosinophils. A ratio of more than 40% of $IgG4^+$ of all IgG^+ plasma cells was suggested, although minor organ-specific differences in the ratio were noted in previous studies. B-cells tend to cluster, forming lymphoid aggregates or less commonly, ectopic germinal centers.

B. Obliterative or non-obliterative endo-phlebitis which tend to affect veins more commonly than arteries, with a predilection for small and medium-sized vessels.

C. Swirling or "cartwheel"-like pattern of fibrosis, which can resemble neoplasms of the mesenchyme in long-standing fibrosis[27].

These criteria were suggested during an international symposium conducted in Boston, MA, USA in November 2011, with contribution from rheumatologists, pathologists, and gastroenterologists[28,29]. Pathology plays a crucial role not only in confirming IgG4-RD but also in ruling out a co-existing infectious process or more sinister diseases such as malignancies. As mentioned in the 2019 ACR/EULAR classification criteria, the presence of neutrophil-predominant infiltrates, necrosis or granulomatous inflammation warrants consideration of other pathologies and puts the diagnosis of IgG4-RD into question[30].

Radiology

Multiple modalities were utilized for the evaluation of IgG4-RPF, and these include computed tomography (CT), magnetic resonance imaging (MRI), and fluorodeoxyglucose-labelled positron emission tomography (PET). These modalities can be used to both evaluate the initial burden of the disease and to monitor response to treatment[31]. Unlike involvement of other organs such as the pancreas, IgG4-RPF was not found to have specific radiologic features. Comparison between IgG4-RPF and idiopathic RPF did not demonstrate a predilection for a specific site or pattern of involvement. Periaortic, peri-iliac, and periureteral were the most frequently involved sites, with the formation of masses or pseudotumors in most of the cases. Other sites involved include retrocaval, retrovesicular and perirectal. Accompanying features observed which may or may not be related to IgG4-RD include abdominal aortic aneurysms and lymphadenopathy[32]. Extension of the disease from the retroperitoneal space to the renal capsule and parenchyma was observed before, which can clinically manifest as tubulointerstitial nephritis. In these instances, CT can detect hypodense nodules in the cortex, diffuse patchy involvement associated with renal enlargement or rim-like enhancing lesions in the capsule. However, these findings are not specific for IgG4-RD[17]. Due to the absence of specific radiographic features of IgG4-RPF, imaging alone cannot be used to confirm the disease, but rather to assess the extent, look for other organ involvement and as a follow-up method after treatment is initiated[33].

Treatment, follow-up, and prognosis

First line treatment of IgG4-RD is glucocorticoids. Prednisolone or prednisone is given at an induction dose of 30-40 mg/day, or 0.4-0.6 mg/kg/day for 3-4 weeks followed by tapering and maintenance therapy[17,27]. In IgG4- RPF moderate to high-dose glucocorticoids are needed[18]. Prednisone is started at 1 mg/kg/day for 1 month (maximum dose 80 mg) and tapered by 0.5 mg/kg in the second month and 0.25 mg/kg in the third and fourth month to continue tapering for 6-12 months[34]. Good response is typically seen due to the glucocorticoid receptors seen in fibro/myofibroblasts, CD4-positive T cells and IgG4-positive plasma cells. In fact, diagnosis should be doubted if there is no response to glucocorticoids[17].

Even though there is a good initial response to glucocorticoids, 33% have relapses of the disease.[35] In those cases, a second trial of high-dose prednisone can be done[34]. In glucocorticoid-resistant or recurrent disease Rituximab is second-line therapy[18,36]. As well as to avoid corticosteroid toxicity and in patients with immediate organ-threatening disease[36]. Rituximab is given at the dose of 375 mg/m2 a week for 4 consecutive weeks or 1g x2 given 2 weeks apart. It has shown sustained remission of 12 months[34].

Other drugs that can be used include tamoxifen, mycophenolate, azathioprine, and medroxyprogesterone[36]. It has been shown that methotrexate and mycophenolate are efficacious in relapsing RPF where long-term therapy is needed[34]. In the retrospective study of 132 patients by Wang *et al*, tamoxifen and immunosuppressants such as cyclophosphamide, mycophenolate mofetil and methotrexate were used as glucocorticoid-sparing agents or remission-maintenance drugs[18]. It is important to acknowledge lack of randomized controlled trial evidence for some of the treatments outlined, with reliance on case series and clinical experience in many of the instances.

Surgery should be considered in selected cases. It is mostly used in patients with compressive or infiltrative masses involving tubular anatomical structures causing

obstruction. In the case of ureteral involvement by RPF, ureteral stenting or ureterolysis is used[27]. In RPF associated with aortic aneurysm surgical follow-up is recommended for intervention planning[34].

Monitoring for treatment response includes measuring C-Reactive Protein (CRP), erythrocyte sedimentation rate (ESR) and renal function every 4-8 weeks. However, CRP and ESR values don't correlate with treatment response as relapse can happen with normal values. Imaging can also be monitored every 3-6 months once the disease is stable and then annually[34,36]. Imaging modalities that can be done at the end of treatment include MRI, CT, and F-FDG-PET. F-FDG-PET can be used to assess for residual metabolic activity which can guide follow-up and subsequent therapeutic choices[34]. In the retrospective study of 27 cases of idiopathic RPF by Choi *et al,* systemic glucocorticoids were given with 100% response rate and to monitor for remission or recurrence, imaging was used to measure the retroperitoneal mass. It was also noted that four patients with IgG4-related RPF who discontinued systemic steroids relapsed at 14 months, which necessitated repeat courses of corticosteroids[20]. It is worth mentioning however, that this number of patients is small and is therefore a limitation for accurate assessment of prognosis and rate of relapse.

The relationship between serum IgG4 level and treatment response or relapse has not been well established however Wang et al saw that higher serum IgG4 level was seen in the group of patients with no response and with relapse[18].

CONCLUSION

IgG4 related disease is a fibroinflammatory disorder characterized by infiltration of IgG4 into multiple organ systems and sites. The retroperitoneum is one of the commonly involved sites leading to retroperitoneal fibrosis. IgG4-RPF can occur in isolation or in the context of diffuse systemic disease. As more cases of idiopathic RPF are being attributed to IgG4-RD, it is essential for practicing internists, rheumatologists, and surgeons to be well aware of the epidemiology, clinical presentations and therapeutic options of IgG4-RPF.

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