Manifestations of IgG4-related kidney disease – diagnosis and treatment

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IgG4 – related disease is a newly recognized entity that may affect different organs. Its pathogenesis and etiology are not well-known yet. In kidneys, the most common form of the disease is IgG4-tubulointerstitial nephritis. Other manifestations of IgG4-RKD are membranous glomerulonephritis and retroperitoneal fibrosis. Typical for the disease are infiltrates consisting of lymphocytes and IgG4(+) plasmocytes in kidneys accompanied by storiform fibrosis. High serum IgG4 concentrations and specific radiological abnormalities together with characteristic histopathological findings are necessary to establish diagnosis. Glucocorticosteroids are the first-line therapy. A good response to such treatment represents another significant feature of the disease.

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Manifestacje IgG4-zależnej choroby nerek – diagnostyka i leczenie

Słowa kluczowe:
- IgG4-zależna choroba nerek
- IgG4-zależna nefropatia
- cewkowo-śródmiąższowe zapalenie nerek
- zwłóknienie zaotrzewnowe

Choroba IgG4- zależna to nowa jednostka chorobowa manifestująca się zajęciem różnych organów. Jej patogeneza oraz etiologia nie zostały dotychczas dobrze poznane. W nerkach najczęściej przybiera postać IgG4-zależnego cewkowo-śródmiąższowego zapalenia nerek. Inne manifestacje to nefropatia błoniasta oraz zwłóknienie zaotrzewnowe. Typowe dla choroby są nacieki składające się z limfocytów i plazmocytów IgG4(+) oraz włóknienie o charakterystycznym typie ‚storiform fibrosis'. Wysokie stężenie IgG4 w surowicy i specyficzne nieprawidłowości w badaniach obrazowych, wraz ze zmianami w badaniu histopatologicznym są wymagane do postawienia rozpoznania. Lekami pierwszego rzutu są glikokortykosteroidy, a dobra odpowiedź na terapię jest znamienną cechą choroby.

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Introduction

IgG4-related disease (IgG4-RD) is a systemic inflammatory disorder with multiple organ involvement. It presents as a tumefactive lesions in different sites or organ enlargement. The most significant feature is infiltration consisting of marked IgG4-positive plasma cell (IgG4+PC) in affected tissues [1]. This new entity was first described in relation to the pancreas (autoimmune pancreatitis - AIP); however, it has been shown that many other organs/tissues such as: lacrimal glands, salivary glands, kidneys, lungs, thyroid gland, retroperitoneum, the aorta may also be affected by the disease [2,3,4,5].

The characteristic feature of the IgG4--related disease is hypergammaglobulinemia, elevated serum IgG4-level and IgG4--positive plasma cells in affected organs with coexisting fibrosclerosis [4]. The diagnosis of IgG4-related disease relies on the clinical data and presence of typical radiological and, above all, histological findings [6]. Contrast-enhanced CT and MRI are the most recommended methods for diagnosing IgG4-RD, in particular, IgG4--RKD [7].

Renal involvement in IgG4-RD is referred to as IgG4-related kidney disease (IgG4-RKD) and accounts for approximately 15% of cases [7]. The most common manifestation of IgG4-RKD is IgG4-related tubulointerstitial nephritis (IgG4– TIN) [2,8]. AIP often accompanies IgG4-related TIN; however, some cases without AIP have also been reported [9]. IgG4-RKD may also take the form of membranous nephropathy anty-PLA2R(-) and is the most common glomerular lesion associated with IgG4--RD [1,10,11]. Another manifestation of IgG4-RKD is retroperitoneal fibrosis, which often causes hydronephrosis leading to acute kidney injury (AKI).

Epidemiology

The epidemiology of the disease is not very well-known yet. The majority of patients reported in the literature are from Japan, but the condition has been described all over the world [12].

The average age of the patients with IgG4-RKD is 65 years, and 73-87% are men [2,13,14].

Pathophysiology

The pathophysiology of the IgG4-RD is complicated and not entirely explored yet. Genetic studies have revealed that predisposition to IgG4-RD, as well as to its remission after treatment with steroids, may be related to several human leukocyte an-

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tigens (HLA) and non-HLA haplotypes/genotypes. Also, several autoantibodies have been identified in patients suffering from IgG4-RD. Among them, the most common were autoantibodies against lactoferrin and carbonic anhydrase II [15].

Recently, attention has been paid to the immune reaction associated with T-helper suggesting that this type of immune response is dominant in IgG4-RD. Interleukin 10 (IL-10) and transforming growth factor-β(TGF-β) are also considered to be important in the development of the disease, in particular, in an IgG4 class switch and fibroplasia [15].

It has also been shown that B cell-activating factor of the tumor necrosis factor family (BAFF) and a proliferation-inducing ligand (APRIL) have significance in B cell function and antibody production. Kiyama et al. revealed that serum BAFF and APRIL levels are elevated in patients with IgG4-RD and that the levels of both correlate with clinical activity [16].

Clinical and laboratory features

Organ-specific symptoms occur frequently and usually are associated with mass-forming localized or systemic lesions. IgG4-RKD should be suspected in patients with an impaired renal function associated with tubulointerstitial nephritis or nephrotic range proteinuria in the course of IgG4-related membranous glomerulonephropathy (MGN). Nephrologists should also be alert to symptoms such as the abdomen and flank pain which may suggest retroperitoneal fibrosis [7,17].

The typical laboratory feature of IgG4-RD is hypergammaglobulinemia. The most important blood test finding is elevated serum IgG4 level. However, about 20% of patients have normal serum IgG4 levels. Besides, an elevated serum IgG4 level is not unique to IgG4-RD and might also be present in other diseases (e.g., asthma, pemphigus, atopic dermatitis, and multicentric Castleman's disease). Also elevated serum IgE level and peripheral eosinophilia seems to have significance in this disorder and are probably related to the allergic predisposition of the disease. Hypocomplementemia, with decreased serum C3 or C4, is another distinct feature of IgG4-RD [7,13,14,18]. In one study from Japan, Muraki et al. measured serum complement level in 44 patients with AIP. It appeared that only 36% of patients had decreased serum C3 or C4 and 17% of them had a CH50 of less than 30U/ml [19]. However, compared to general IgG4-RD patients, hypocomplementemia more frequently occurs in IgG4-RKD patients (above 50% of patients) [14]. In some cases of IgG4-RKD, C3 and C4 levels are extremely low, which is reminiscent of active stage of systemic lupus erythematosus. Complement might also be useful as a biomarker of IgG4-TIN remission [1]. Recently, it has been shown that elevated circulating plasmablasts might also become an important and valuable biomarker of the disease, even if the serum IgG4 concentration is normal [20].

IgG4-TIN patients may also present decreased renal function (58,5%) [13]. Kidney failure is usually accompanied by mild proteinuria, leukocyturia and mild hematuria [2]. Patients with coexisting

membranous glomerulonephritis (MGN) often present with the nephrotic range of proteinuria like in idiopathic MGN patients. However, they do not have antibodies against phospholipase A2 receptors in their circulation, which is characteristic for idiopathic MGN [10,21]. In patients with RPF, kidney function may be slightly impaired or even normal with the normal urinalysis [22].

Radiologic features of IgG4-related kidney disease

Computer tomography is most relevant and useful radiographic imaging method that is recommended in IgG4-RD and, in particular, in IgG4-RKD. However, due to a necessity of using contrast during the scan, it is essential to qualify patients with impaired renal function carefully [13]. Characteristic features of the disease in CT are multiple round or wedge-shaped, low-density lesions. Rarely, a solitary lesion may also appear. Another feature observed in patients with severe renal failure, which was a contraindication for the administration of contrast medium, is bilateral renal swelling. The intraluminal surface of the urinary tract is usually smooth [13,23]. Retroperitoneal masses with unilateral or bilateral hydronephrosis may be found in IgG4-related RPF patients [22]. Solitary lesions are not very common, but if encountered, it is important to consider a differential diagnosis of the malignant tumor. If the risk of malignancy is high, it often leads to nephrectomy [24].

Other modalities used to identify renal lesions are gallium scintigraphy, magnetic resonance imaging, and fluorodeoxyglucose positron emission tomography. MRI is imaging method that might improve the lesion detection in early stages of the disease. On T2-weighted MR images, renal parenchymal nodules are hypointense with a progressive enhancement pattern on dynamic contrast-enhanced images. Typically lesions are bilateral and multiple. Diffusion-weighted MR imaging (DWI) is considered to be most useful for detecting IgG4-RKD, its sensitivity is 100%. Besides, MRI is an alternative for patients with renal function impairment and contraindication to contrast-enhanced CT [1,23,25].

FDG-PET and gallium scintigraphy are other imaging methods used to screen the whole body and determine the extent of the systemic organ involvement. PET/CT is also an important imaging method, which enables detecting a larger number of lesions than CT or ultrasonography by providing a comprehensive view of the organs involved in the disease. 18F-FDG PET/CT may also help to choose the biopsy site or to guide the recanalization of ureteral obstruction. It is also relevant to monitor treatment of the disease. A good response to steroid therapy confirm the diagnosis and rule out possible malignancies [1,23,26].

Histopathological features of IgG4-related kidney disease: IgG4-TIN

Characteristic histopathological features of IgG4-RKD are fibrosis and prominent IgG4-positive plasma cells. Lesions consist of lymphocytes (mostly T cells) intermingled with plasma cells. Occasionally, numerous infiltrating eosinophils may be found. However, they dominate in a minority of cases. It is crucial to remember that numerous IgG4 plasma cells are typical but not specific finding for the diagnosis of IgG4-TIN and may also be present in patients with lupus nephritis, necrotizing glomerulonephritis, diabetic nephropathy, MGN, and idiopathic TIN [27].

The distinctive distribution of kidney parenchymal lesions is very characteristic of IgG4-RKD. The margins of lesions in an interstitium are well defined so that there is a clear demarcation between affected and unaffected areas. Another feature found in IgG4-TIN is an extension of cell infiltration into and beyond renal capsule [6,9,13,28]. Granulomatous lesions, neutrophil infiltration, severe tubulitis, severe peritubular capillaritis, and necrotizing angiitis are not typical of IgG4-TIN, so if found in biopsy material, it is highly likely to rule out IgG4-RKD [28].

Storiform or bird's eye fibrosis is another distinctive feature of the disease [2,6,13,14]. Typical for this kind of fibrosis is its swirling pattern, in which irregular fibrosis surrounds nests of inflammatory cells. Comparing to non-IgG4-related TIN, in IgG4-TIN fibrosis is more severe, and its severity may vary in different areas. In one study storiform fibrosis was defined as a pattern of fibrosclerosing inflammation consisting of inflammatory cells that infiltrated into dense collagen fibers, creating a characteristic pattern resembling arabesque in the renal interstitium [28]. Some authors compare storiform to spokes of a cartwheel, in which the spindle cells (fibroblasts and myofibroblasts) are typically buried within the lymphoplasmacytic infiltrate [6]. The interstitial fibrosis may be divided into different stages depending on its severity, starting with the stage without fibrosis, through mild to severe fibrosis.

Deposits consisting of immunoglobulin and complement have also been detected by immunofluorescence microscopy in the tubular basement membrane and interstitium in IgG4-TIN patients [9,14].

Glomerular lesions

Membranous glomerulonephritis (MGN) is the most common manifestation of glomerular diseases associated with IgG4-RKD and accounts for approximately 7% of cases. MGN may coexist with IgG4-TIN or occurs without deposits in the interstitium [10,29–32]. A distinctive feature of IgG4-MGN are granular deposits of IgG, C3, fibrinogen, kappa and lambda chain along the glomerular capillary walls that can be seen by immunofluorescence microscopy. In some cases C1q deposits are prominent. Of all the IgG subclasses dominating is IgG4. However, it may be accompanied by other

IgG subclasses. In certain cases, deposits in tubular basement membrane may coexist [29–32]. In contrast to primary MGN, an anti-M-type phospholipase A2 receptor antibody is undetectable in IgG4-related MGN. Anti-PLA2R antibodies do not participate in the pathogenesis of IgG4-RD [11].

One study evaluated 20 Japanese patients and found out that except for MGN which was most common glomerular lesion other possible glomerular lesions were Henoch-Schonlein purpura nephritis, IgA nephropathy, membranoproliferative glomerulonephritis, and focal and segmental endocapillary hypercellularity [33].

Retroperitoneal fibrosis

Ormond's disease (idiopathic retroperitoneal fibrosis) is another manifestation of IgG4-RKD. Chronic periaortitis and retroperitoneal fibrosis are characteristic for the disease. The inflammatory process includes part of the abdominal aorta and the iliac arteries. The inflammatory tissue extends into retroperitoneum and may encase the ureters and inferior vena cava. It can lead to hydronephrosis and renal injury [22].

Typical clinical manifestation is uropathy. Characteristic symptoms are: back, flank or abdominal pain, often accompanied by constipation. Men may also suffer from testicular pain. Other non-specific symptoms are: fatigue, anorexia, weight loss and appear due to an inflammatory condition. In the laboratory test, typical findings are elevated inflammatory markers.

CT and MRI are the most important imaging methods. An irregular soft-tissue peri- aortic mass, irregular but well-delimited, which extends between the renal arteries and iliac vessels or even further is a representative image for the disease. It is usually located anterior and lateral to the aorta.

Histopathological findings are typical for IgG4-RD patients: IgG4-positive plasma cells and lymphocytes infiltrates, ''storiform'' fibrosis and obliterative phlebitis [22,34].

Diagnostic criteria

The diagnosis of IgG4-RKD is based on clinical, serological and histopathological criteria. Among clinical symptoms, kidney damage with abnormalities in urinalysis or urine markers or with impaired kidney function with either hypergammaglobulinemia, hypocomplementemia or elevated serum IgE level usually occur. The major serological feature is serum IgG4 level ≥ 135 mg/dl. Typical radiological finding in kidneys is a presence of multiple low-density lesions. It can also present as a single solitary mass; however, such a manifestation of the disease is relatively rare. Other cases include diffuse kidney enlargement or hypertrophic lesion of a renal pelvic wall. The most important are histologic findings in the kidney. To diagnose the disease, a presence of dense infiltration of lymphocytes and IgG4-positive plasma cells [≥10/high power field (HPF) and/or IgG4/IgG-positive plasma cells [≥40%] is required. Another criterium is a presence of storiform or bird's eye fibrosis. A presence of lymphoplasmacytic infiltration (IgG4-positive plasma cells ≥10/high power field (HPF) and/or IgG4/IgG-positive plasma cells ≥40%) in the histopathology of extra-renal organs is also one of the criteria. The confirmation of the diagnosis by biopsy is strongly recommended. It is also crucial to exclude malignancies and other IgG4-RD mimics. The diagnosis cannot be based entirely on the number of IgG4-positive plasma cells or serum concentrations of IgG4 alone because they are neither sensitive nor specific for the disease [6,13,35].

Treatment

The first line therapy for IgG4-RKD is glucocorticosteroids. They are used to induce remission in all patients with active disease who have not been previously treated and have no contraindications to such therapy. Good response to glucocorticosteroids is a distinctive feature of the disease and is used to confirm the diagnosis.

The recommended initial prednisolone dose oscillates between 30-40 mg/day [35]. The response may be seen after 2-4 weeks and may refer to clinical improvement, serologic remission (decrease in serum IgG4 concentration), and reduction of radiologic abnormalities [35,36]. When a response to therapy is evident, it is suggested to gradually taper the dose of glucocorticosteroids (5-10 every 1-2 weeks) and discontinue 3-6 months after starting therapy or to use of low-dose glucocorticoid maintenance treatment for up to 3 years [1,35,36]. In the study Mizushima et al. evaluated six IgG4-related TIN patients receiving renal biopsies before and after corticosteroid therapy. All clinical data and histopathological findings were assessed before and after treatment. They found out that elevated serum creatinine levels rapidly improved after corticosteroid therapy in four patients. All patients have achieved significant improvement in radiological as well as histological findings: infiltrated area diminished, fibrosis became evident in the renal interstitium and number of IgG4-positive plasma cells decreased even at the beginning of therapy [37].

However, prolonged steroid therapy pose a high risk of adverse side-effects to patients, so in some cases with incomplete response to treatment, the combination of glucocorticoids and a steroid-sparing immunosuppressive agent (such as azathioprine, mycophenolate mofetil, methotrexate, cyclosporine) is recommended from the start of therapy. Nonetheless, the efficacy of these drugs has not been demonstrated [7,35)].

In patients who are resistant to glucocorticosteroids, are unable to taper these medications, the disease is frequently recurrent and steroid-sparing immunosuppressive (disease-modifying antirheumatic drugs (DMARDs) are ineffective the use of rituximab is recommended [38,39]. In one study ten patients with IgG4-RD were treated with rituximab (RTX) (2 infusions of 1000 mg, 15 days apart). After treatment, they evaluated clinical, serological and radiological improvement by assessing the ability to discontinue treatment with steroids and other immunosuppressive drugs, by measurements of serum IgG levels and different IgG subclasses, and by comparing radiological images before and after treatment. RTX therapy was effective in patients with active inflammation, who did not respond well to steroids and DMARDs [39].

In IgG4-RKD cases, particularly these associated with membranous nephropathy when glucocorticosteroids are ineffective, and proteinuria with impaired renal function persist, the use of immunosuppressants should be taken into consideration. One study reported two Japanese patients with IgG4-TIN and associated MGN with proteinuria. In both cases, they did not respond to steroid treatment, and proteinuria was resolved only after the administration of mizoribine [32].

Conclusion

The most common renal manifestation of IgG4-related kidney disease is IgG4--TIN. Among glomerular lesions that accompany IgG4-TIN most frequently occurs membranous nephropathy; however, other glomerular lesions may also appear. Retroperitoneal fibrosis as a manifestation of the disease should be suspected when patient experience symptoms such as abdominal and flank pain or when hydronephrosis or acute renal injury occurs. The disease is diagnosed based on serological, radiological and histopathological findings. The biopsy sample is the most important for diagnosis. IgG4-positive plasma cells and lymphocytes infiltrate, ''storiform'' fibrosis are typical histopathological findings. Hypergammaglobulinemia, elevated IgG4 serum concentrations, and hypocomplementemia are typical for IgG4-RKD. However, they are not specific for the disease, so the differential diagnosis is mandatory.

The first line therapy is glucocorticosteroids. Other medications include immunosuppressive drugs such as rituximab, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine. Further studies and randomized controlled trials are necessary to understand the pathophysiology of the disease better and to assess therapy best.

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