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Abdominal aortic aneurysm as an IgG4-related disease

M. Prucha ,* P. Sedivy,† P. Stadler,† P. Zdrahal,† P. Prokopova,‡ L. Voska§ and L. Sedlackova*

*Department of Clinical Biochemistry, Haematology and Immunology, Na Homolce Hospital, †Department of Vascular Surgery, Na Homolce Hospital, ‡Department of Pathology, Na Homolce Hospital, and §Department of Clinical and Experimental Pathology, IKEM, Prague, Czech Republic

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Correspondence: M. Prucha, Department of Clinical Biochemistry, Haematology and Immunology, Na Homolce Hospital, Prague, Czech Republic.
E-mail: miroslav.prucha@homolka.cz

Summary

The objectives of this study were to evaluate patients with aortic abdominal aneurysm (AAA) with regard to immunoglobulin (Ig)G4-related disease (IgG4-RD). IgG4-RD represents a recently defined condition comprised of a collection of disorders characterized by IgG4 hypergammaglobulinemia, the presence of IgG4-positive plasma cells in organs affected with fibrotic or sclerotizing changes and typical histopathological features. It was identified as a possible cause of vasculitis in large vessels. Studies have been published on a possible association between inflammatory aortic or cardiovascular disease and IgG4-RD. We examined 114 patients with AAA requiring surgery in order to identify findings which are characteristic of IgG4-RD. Aneurysm samples from seven patients showed histopathological features consistent with IgG4-RD and the presence of $IgG4^+$ plasma cells. Only two of these seven patients showed elevated IgG4 serum levels higher 1·35 g/l. In five of the patients, the concentration of serum IgG4 was lower than 1·20 g/l, with the number of $IgG4^+$ plasma cells being higher than 50/high-power field. These findings were consistent with AAA being a heterogeneous group of inflammatory diseases with different pathogenesis.

Keywords: aortic abdominal aneurysm, diagnostic value, histopathology, IgG4, IgG4-related disease

Introduction

Abdominal aortic aneurysm (AAA) is a serious disease associated with high mortality [1]. Its etiopathogenesis is known to be multi-factorial [2–4]. AAA is a chronic inflammatory disease characterized by inflammatory infiltrates in the vascular wall, degeneration and elastin fragmentation. The inflammatory process affects the entire vascular wall, leading to extracellular matrix degradation. The only therapeutic decision is surgical aneurysm removal or the use of a stent graft. So far, no pharmacotherapy has been developed that effectively treats AAA. With regard to risk factors, elimination of smoking has been the only approach shown to reduce aneurysm progression and rupture. Immunological mechanisms are important pathogenetic factors involved in AAA development. A localized inflammatory response in AAA is characterized by the presence of monocytes, macrophages, T and B lymphocytes and polymorphonuclear cells. The effects of cytokines and leukotrienes, together with adhesive molecule dysregulation, lead to erosions in the vascular smooth muscle, extracellular matrix degeneration and neovascularization [5–8]. Until recently, AAA has been presented exclusively as a consequence of the atherosclerotic process affecting the aorta [9]. However, transcriptomic studies have shown that this is not always the case [10]. AAA may result from aortitis or periaortitis, that are syndromes of IgG4-related disease (IgG4-RD). IgG4-RD represents a recently defined condition comprised of a collection of disorders characterized by IgG4 hypergammaglobulinemia and the presence of IgG4-positive plasma cells in organs affected with fibrosis or sclerosis [11]. IgG4-RD may affect virtually any organ – salivary glands, periorbital tissue, kidneys, lungs, meninges, aorta, prostate, pericardium and skin. However, its histopathology is consistent

irrespective of organ system, showing a large lymphoplasmacytic infiltrate enriched in IgG4-positive plasma cells [12]. In 2012, IgG4-RD was identified as a possible cause of vasculitis of large vessels [13]. Two forms of large vessel disease may exist in IgG4-RD, a primary vasculitis and a secondary form of vascular involvement characterized by periaortic or periarteritic involvement [14]. Recently, studies have been published on a possible association between inflammatory aortic or cardiovascular disease and IgG4-related disease [15,16]. In our study we investigated patients with AAA with regard to the possible etiopathogenesis of the condition as IgG4-RD.

Materials and methods

Patient selection

The study was designed as a retrospective cohort study. This study was approved by the institutional review board of the Na Homolce Hospital and all subjects provided informed, written consent. We examined a total of 114 patients from 2015 to 2016 with AAA requiring surgery in order to identify findings which are characteristic for IgG-RD. The demographic and clinical characteristics of patients are shown in Table 1. Clinical assessment of each case, including a thorough history and physical examination, followed by investigations including basic hematological and biochemical tests, was performed. Baseline demographics, including age and gender data, were also collected with regard to lipid metabolism parameters – cholesterol and triglycerides – and the presence of diabetes (DM), hypertension (HT), coronary heart disease (CHD) and smoking. In all patients we measured the levels of IgG and IgG1–IgG4 by turbidimetry.

Histological assays

A biopsy sample was taken from the aneurysm pouch from the place with the largest dilation, established macroscopically, in each patient during surgery. Subsequently, histopathological examination was performed, as well as the examination of the presence of IgG4-producing plasma cells. The positive histopathological features include a dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis. A density of 50 IgG^+ plasma cells per high-power field (HPF) and an $IgG4^+/IgG^+$ ratio of at least 0·50 was required to establish the diagnosis in accordance with international consensus criteria on the pathology of IgG4-RD [17].

Results

In the group of 114 patients, an increased IgG4 level of more than 1·35 g/l was present in four patients. In two of these patients immunohistochemistry showed 30 to 50 $IgG4^+$ plasma cells/HPF, but histopathological findings were negative with regard to IgG4-RD (without the presence of storiform fibrosis and obliterative phlebitis). In a further two patients, IgG4 levels exceeded 1·35 g/l and more than 50/$IgG4^+$ plasma cells/HPF were found in the histological preparation. In addition, there were positive histopathological features (storiform fibrosis, dense lymphoplasmacytic infiltrate and obliterative phlebitis) that confirmed IgG4-RD. In a further five patients, more than 50 $IgG4^+$ plasma cells/HPF were found in the aneurysm samples, as well as histopathological findings indicative of IgG4-RD. However, serum IgG4 levels were within a normal range in these five patients. Table 2 shows an overall summary of the results. Figures 1 and 2 show typical histopathological features in one of them. In these seven patients, in whom aneurysm tissue met the histopathological criteria of IgG4-RD, we found no further inflammatory affects of another system or organ suspected of IgG4-RD. In another 13 patients an increased number of $IgG4^+$ plasma cells were present, with more than 30 $IgG4^+$ and fewer than 50 IgG^+ plasma cells/HPF; however, IgG4 serum levels were lower than 1·35 g/l and no IgG4-RD histopathological features were found (e.g. storiform fibrosis, obliterative phlebitis).

Discussion

Abdominal aortic aneurysm is a disease with an unclear etiopathogenesis, although immunological mechanisms undoubtedly play an important role in its development. Aortitis and/or periaortitis are considered to be IgG4-RD. The findings of AAA and perianeurysmal fibrosis, usually described as 'inflammatory aneurysm', are considered one of the manifestations of retroperitoneal fibrosis [18]. Studies on the possible involvement of humoral activities and/or the role of IgG4 antibodies and IgG4-producing plasma

Table 1. Demographic and clinical characteristics of patients

					Cholesterol (mmol/l)	TGL (mmol/l)				
	n	M	F	Age (mean)	Mean 95% CI	Mean 95% CI	DM	HT	IHD	Smoking
Patients	114	91	23	69	5·41 5·32–6·08	1·85 1·62–2·12	23	102	58	108

CI = confidence interval; TGL = triglycerides; DM = diabetes mellitus; HT = hypertension; IHD = ischemic heart disease.

Table 2. Immunoglobulin (Ig)G4 in serum, IgG4/high-power field (HPF) in patients fulfilling criteria of IgG4-RD

Patient	Sex	Age	IgG4⁻ serum (g/l)	IgG4⁺/HPF	Histopathology
1	Male	69	0·55	86	Positive
2	Male	59	0·45	81	Positive
3	Male	68	0·77	51	Positive
4	Male	66	1·87	169	Positive
5	Male	61	2·41	72	Positive
6	Male	64	0·11	84	Positive
7	Male	60	0·47	53	Positive

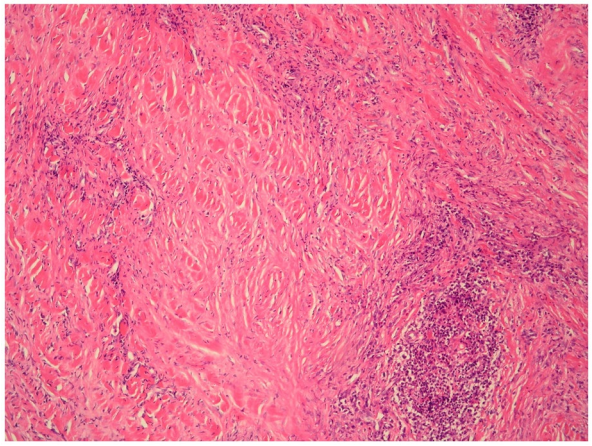

Fig. 1. Typical histopathological features of lymphoplasmatic infiltrate and storiform fibrosis.

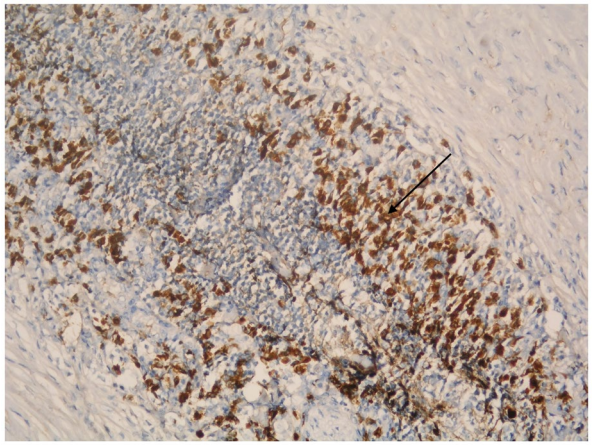

Fig. 2. Using immunohistochemistry for immunoglobulin (Ig)G4, the majority of the IgG⁺ plasma cells expressed IgG4.

cells in some thoracic aortic aneurysm (TAA) and AAA cases have been published [19,20]. The pathogenic role of IgG4 antibodies is poorly understood [21]. Therefore, it was also the focus of our study. In our group of AAA patients, we detected an increased number of IgG4⁺ plasma cells, higher than 50/HPF in seven patients. Characteristic histopathological findings corresponding with an IgG4-RD were found in all seven patients. Only in two of these seven patients were IgG4 serum levels higher than 1·35 g/l. This finding is consistent with the results of studies that indicate that serum IgG4 is not a good predictive marker for IgG4-RD [22]. In another 13 patients an increased number of IgG4⁺ plasma cells were present, with more than 30 IgG4⁺ and fewer than 50 IgG⁺ plasma cells/HPF; however, IgG4 serum levels were lower than 1·35 g/l and no IgG4-RD histopathological features were found. Also, no other clinical symptomatology for IgG4-RD affecting another organ or system was present in these patients. Even so, our study suggested that some patients indicated for surgery due to AAA were consistent with IgG4-RD. Our results are in line with those of Raparia *et al.*, who established that inflammatory aortic aneurysm (IAA) may be an aortic manifestation of the IgG4-related sclerosing disease. They evaluated the expression of IgG4 in both IAA study cases and arteriosclerotic aortic aneurysm control cases [23]. Italian researchers presented the case report of a patient who suffered an acute myocardial infarction, and periaortitis found during subsequent revascularization revealed IgG4-associated disease on histopathological examination [24]. However, it should be noted that the patient had been diagnosed with and treated for retroperitoneal fibrosis in the past. Japanese authors presented a case of IgG4-associated periaortitis accompanied by AAA where histopathological and clinical findings differed from those established in patients with aneurysm due to arteriosclerosis [25]. A recent study has shown periaortitis and periarteritis in 65 of 179 patients with IgG4-RD [26]. The authors divided them into five types according to the localization of the disorder. The evidence that AAA may be an example of an IgG4-RD in some patients has both diagnostic and therapeutic consequences. Concerning the etiopathogenesis of IgG4-RD, the use of corticosteroids and/or other immunosuppressive drugs has to be considered in the treatment of these patients. It is only possible to establish a definitive diagnosis of IgG4-related periaortitis or periarteritis by means of histopathology. Imaging methods are not sufficiently reliable for diagnosing purposes or as indicators of the risks of aneurysm rupture. For isolated periaortitis or periarteritis, we depend on histopathological findings obtained during surgery or positron emission tomography–computed tomography (PET/CT), the diagnostic yield and accuracy of which are very high [27,28]. Our study confirmed that an elevated IgG4 serum level is not a reliable parameter for diagnosing IgG4-RD; nor is the finding of positive IgG4⁺ plasma cells, the number of which can very variable. The most reliable

parameter and the 'gold standard' for diagnosis is a typical histopathological finding. A great challenge for the future is finding a biomarker that would already select patients with IgG4-RD during the growth of the aneurysm. The treatment with corticosteroids and/or other immunosuppressive drugs to stop the growth of aneurysm could be used in such patients. The patients would thus avoid extremely exacting surgery. We would like to continue searching for such biomarker in further studies.

Conclusion

In seven of 114 patients, histology of the aneurysm tissue met the definition for IgG4–RD. In five of these, the concentration of serum IgG4 was lower than 1·35 g/l. These findings support the claim that some patients with AAA meet the criteria of IgG4-RD. IgG4 levels are not a good predictive marker in patients with AAA for identifying patients with IgG4-RD.

The subject of further research is an effort to find a marker that allows us to identify patients early with IgG4-RD AAA origin. This would allow the use of anti-inflammatory–immunosuppressive therapy to prevent the progression of AAA and the need for its surgical solution.

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Disclosures

None.

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