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IgG4-related disease: a rheumatologist's perspective

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ABSTRACT

Objective. *Given that the clinical features of several IgG4-related diseases (IgG4-RD) can mimic those of autoimmune disorders, the aim of this study was to find possible distinguishing characteristics that would help us identify such cases from the pool of patients in a rheumatology clinic.*

Methods. *From our clinic's medical records, we identified patients who fulfilled the recently published diagnostic criteria for IgG4-RD. We recorded their presenting features, co-morbid conditions, laboratory, radiologic and histologic findings as well as their treatment and outcome.*

Results. *We identified 11 cases of IgG4-RD: 4 cases of IgG4-related autoimmune pancreatitis (AIP), 5 cases of IgG4-related retroperitoneal fibrosis (RPF)/ periaortitis, 2 cases of IgG4-related sialadenitis and one of IgG4-related interstitial nephritis. 5 out of the 11 patients had been diagnosed with an autoimmune disease, namely rheumatoid arthritis (RA), Sjogren's syndrome (SS) and antiphospholipid syndrome (APS). 3 out of 11 patients were subsequently diagnosed with neoplastic disorders. All patients with IgG4-related AIP had raised CRP levels at presentation. Presenting features of RPF/periaortitis patients were constitutional symptoms, abnormal renal function, hypertension and back pain. Patients with IgG4-related sialadenitis had clinical features mimicking SS. The majority of patients had a favourable response to steroids.*

Conclusion. *We present common IgG4-RD presentations in the setting of a rheumatology clinic. Increased awareness may avoid delay in diagnosis.*

Introduction

IgG4 related disease (IgG4-RD) is a newly recognised fibro-inflammatory disease characterised by elevated serum IgG4 levels (>135mg/dl) and infiltration of the affected organ(s) by IgG4+ plasma cells and lymphocytes. IgG4-RD can affect one or more organs and has a wide spectrum of clinical manifestations with a favourable response to treatment with glucocorticoids (1). Several manifestations of IgG4-RD such as autoimmune pancreatitis (AIP), sialadenitis, interstitial nephritis and retroperitoneal fibrosis (RPF) are shared with autoimmune diseases and can be a reason for referral to rheumatologists for further evaluation. Additionally, the concomitant occurrence of IgG4-RD with systemic autoimmune/rheumatic disorders remains a possibility. In this context, it is important to recognise features of IgG4-RD in a rheumatology/ autoimmune diseases setting. Hence, we conducted a retrospective study of patients with IgG4-RD followed in our clinic. We identified 11 patients, four with IgG4-related AIP, five with IgG4-related RPF/periaortitis, two with IgG4-related sialadenitis and one with IgG4-related interstitial nephritis.

Patients and methods

Patient selection

All patients were seen between 2009 and 2013 in the Autoimmune diseases/ Rheumatology clinic of the Department of Pathophysiology, University of Athens Medical School or in Euroclinic Hospital in Athens, Greece.

Identification of patients

To identify patients diagnosed with IgG4-RD, we used our institutions' medical record databases at the Department of Pathophysiology, School of Medicine, University of Athens and at the Department of Rheumatology, Euroclinic Hospital, Athens, from 1 January 2009 to 30 June 2013. All medical records were reviewed to confirm the diagnosis of IgG4-RD, according to the recently published classification criteria: **a.** characteristic diffuse/localised swelling or masses in single or multiple organs, **b.** elevated serum IgG4 (≥135 mg/dL) **c.** marked lymphocyte and plasmacyte infiltration, fibrosis and infiltration by IgG4+plasma cells (ratio of IgG4+/ IgG+ cells >40% and >10 IgG4+ plasma cells /hpf) on tissue biopsies.

Depending on the presence of one or more of the above criteria, diagnosis of IgGRD can be classified into either possible (a+b), probable (b+c) and definite (a+b+c) (2).

Data collection

The following variables were recorded in all patients included in the study: age

Table I.

Pt/Sex	Age	IgG4-RD type	Presenting features	Associated conditions	CT/MRI findings	↑CRP	IgG4 serum levels (mg/dl)	Biopsy findings	Treatment	Follow-up/Outcome
1/M	79	AIP	Epigastric/ back pain amylasemia	HT	enlarged pancreas*	no	737	-	CS	Remission at 1.5 years
2/M	62	AIP	Epigastric pain amylasemia	Seropositive** RA, Type 2 DM	enlarged pancreas	yes	170	-	CS, AZA, anti-CD20	Remission at 2 years
3/M	62	AIP	Epigastric pain amylasemia	Seropositive** RA, APS***, Hepatitis C	enlarged pancreas	yes	285	-	CS	Remission at 4 years
4/M	59	RPF	Anorexia, malaise, New onset HT, ARF	Multinodular goiter, HT, Peripheral neuropathy	Periaortic soft tissue, hydronephrosis (left)	yes	313	-	CS	Remission at 1.5 years
5/M	77	RPF	ARF	Type 2 DM, IHD, Castelman's disease	Periaortic soft tissue, hydronephrosis (BL)	no	338	-	CS, CYC D-Pen	Died at 6 years
6/M	65	RPF	Back pain	HT, Nephrolithiasis, Renal carcinoma	Periaortic soft tissue	no	280	-	CS	Remission at 13 years
7/M	60	RPF	Abdominal pain, New onset HT		Periaortic soft tissue	no	290	-	CS	Remission at 1 year
8/M	80	RPF, AIP	Fatigue, low grade fever	HT Nephrolithiasis	Periaortic soft tissue enlarged pancreas	yes	280	-	CS	Remission at 1 year
9/M	36	Sialadenitis	Dry mouth, SGE	-	-	no	304	SG: IgG4+/IgG plasmacytic ratio >40%	-	Lost to follow up
10/F	71	Sialadenitis	Dry mouth, SGE	SS****, gastric MALT lymphoma	-	no	286	SG: IgG4+ /IgG plasmacytic ratio >40%	-	Stable at 1 year
11/F	64	Interstitial nephritis	Arthralgias, Recurrent pyelonephritis	SLE, APS***, nephrolithiasis	-	no	250	Kidney: IgG4+ /IgG plasmacytic ratio >40%	-	Stable at 6 years

*rim-like contrast enhancement; **positive titers of rheumatoid factor and antibodies against citrullinated peptides; ***high titers of IgG anticardiolipin and anti-β2GPI antibodies in more than 2 occasions; ****positive titers of anti-Ro/SSA and anti-La/SSB antibodies. APS: Antiphospholipid syndrome; ARF: Acute renal failure; AZA: Azathioprine, BL: bilateral; CS: Corticosteroids; CYC: Cyclophosphamide; DM: Diabetes mellitus; D-Pen: D-Penicillamine; IHD: Ischaemic heart disease; HT: Hypertension; MALT: Mucosa associated lymphoid tissue; RA: Rheumatoid arthritis; SG: Salivary gland; SGE: Salivary gland enlargement; SS: Sjögren's syndrome; SLE: Systemic lupus erythematosus.

at study entry, age at diagnosis, sex, associated conditions, clinical symptoms at presentation and follow-up and all pertinent laboratory investigations including CT, MRI and results of biopsies of the organ involved. Additionally, information on treatment regimens, response to treatment, presence and number of relapses and follow-up were recorded according to documentation by the treating physician.

Results

Patients and diagnosis

Eleven out of 2910 new patients seen in a period of 3.5 years in our clinics fulfilled the diagnostic criteria for IgG4-RD (incidence rate per year: 0.1%). All patients were exclusively Caucasian of Greek origin and predominantly male (82%) with a median age of 64 (range 36–80) years at diagnosis. The median duration of follow-up for 10 patients was 21 (range 12–156) months. One out of 11 patients was lost at follow-up. Comorbid conditions included: diabetes mellitus 2 in 2 patients (18.1%); hypertension in 4 patients (36.4%); nephrolithiasis in 3 patients (27.3%), hepatitis C in 1 patient (9.1%) and peripheral neuropathy with multinodular goiter in 1 patient (9.1%). Seven patients (64.6%) were current or past smokers. Autoimmune disease was present in four patients (36.4%): Case 2 had longstanding rheumatoid arthritis (RA), Case 3 had RA/ antiphospholipid syndrome (APS), Case 10 had Sjögren's syndrome (SS) and Case 11 had lupus/APS. Three out of 11 patients (27.3%) were diagnosed with neoplastic disorders (1 mucosa-associated lymphoid tissue lymphoma (MALT), 1 Castleman's and 1 renal cancer) diagnosed within 3 months, 6 years and 12 years, respectively.

Clinical, laboratory, histopathological findings and follow-up

Table I lists the various IgG4-RD diagnoses according to the organ involved together with clinical presentation, relevant laboratory findings, histopathological results (where available), treatment regimens and outcome at follow-up. AIP (n=4), periaortitis/RPF (n=5), sialadenitis (n=2) and interstitial nephritis (n=1) were the 4 major IgG4-RD manifestations referred to our rheumatology clinic. Presenting features in RPF patients included new onset hypertension, constitutional symptoms (anorexia, malaise, fatigue, low grade fever) along with raised levels of inflammatory markers (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)), acute renal failure in two patients and low back pain in one. Oral dryness and enlarged salivary glands were the presenting symptoms in two cases of IgG4-related sialadenitis. One of those also fulfilled the diagnostic criteria for SS and was complicated by gastric MALT lymphoma. Finally, in case 11, recurrent urinary tract infections secondary to nephrolithiasis were

the main presenting features of IgG4-related interstitial nephritis in the background of SLE-secondary APS.

All patients had IgG4 levels above the upper normal limit of 135mg/dl as defined by the diagnostic criteria (2) (mean ± SD 321.2±144.4, range 170–737 mg/dl).

Imaging and histopathological findings are displayed in Table I. On the basis of the previously diagnostic criteria, 2 patients (cases 9 and 10) fulfilled the criteria for definite IgG4RD, 1 patient (case 11) for probable IgG4RD, while the remaining of patients (cases 1-8) were diagnosed with possible IgG4RD.

Discussion

To the best of our knowledge, this is the first case series of IgG4-RD patients diagnosed in the setting of rheumatology/autoimmune diseases clinic. Given that several features of IgG4-RD are similar to those occurring in patients with autoimmune diseases and that there is a previously reported association of IgG4-RD with autoimmune disorders (3), we aimed to identify and describe the IgG4-RD cases from the pool of patients followed in our clinic. Whist IgG4-RD was first recognised in Japan, from where the majority of currently available information with regards to IgG4-RD is derived (2), it seems that similar cases are not uncommon in other parts of the world, though they often remain unrecognised. Although the clinical spectrum of IgG4-RD is quite extensive, the major presenting clinical features highlighted in the present report which might be of interest to rheumatologists include AIP, RPF/periaortitis, IgG4-related sialadenitis and interstitial nephritis. These manifestations are shared with autoimmune diseases and respond well to treatment with steroids (4). The second observation was that one third of our patients with IgG4-RD had a history of other autoimmune diseases such as RA, APS or SS. Finally, the concomitant presence of malignancy was also noted in our series, in accordance with recently reported links between neoplastic disease and IgG4-RD (5), though associations of malignancies with retroperitoneal fibrosis have been also reported (6).

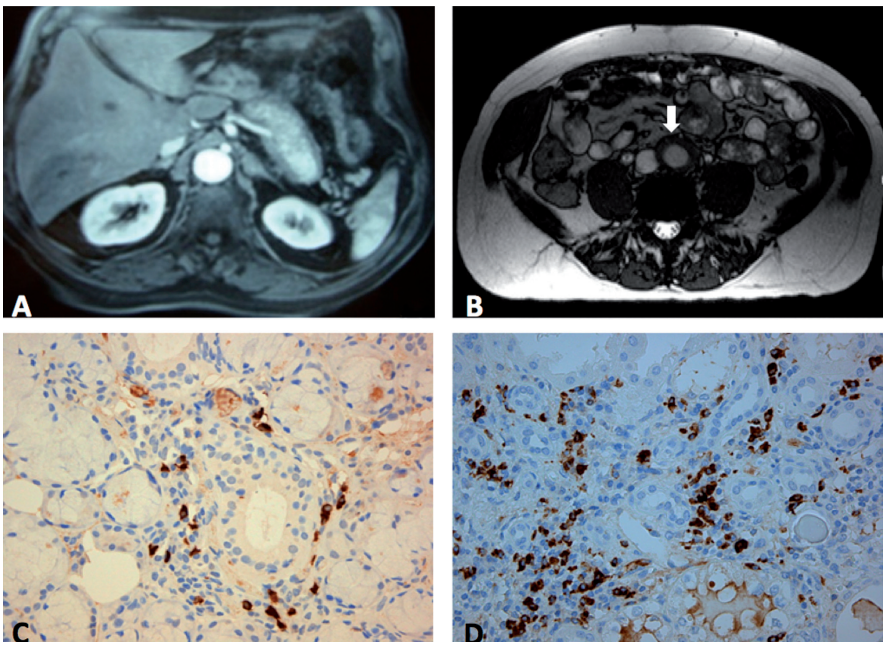

Fig. 1.

A. CT scan of the pancreas of case 1 showing diffuse swelling of the pancreas with a rim-like enhancement.

B. MRI scan of case 4 showing soft tissue surrounding the lower part of the abdominal aorta (arrow) strangulating both ureters.

C. Immunocytochemical stain for IgG4 performed on the salivary gland biopsy of case 9. IgG4+ plasma cells (brown staining), are present in the lymphocytic infiltrate surrounding the salivary duct, with an IgG4/IgG ratio >40%. Original magnification (Envision x 60).

D. Immunocytochemical stain for IgG4 performed on the kidney biopsy of Case 11. IgG4+ plasma cells in the interstitium (brown staining) are >10 per high power view. Original magnification (Envision x 60).

In the present report, AIP – the first disease entity found to be associated with high levels of IgG4 antibodies – (7) occurred in 4 out of 11 patients. The diagnosis is based on the presence of typical imaging of the pancreatic parenchyma by CT or MRI together with raised IgG4 levels or evidence of other organ involvement with IgG4-RD and favourable response to steroids (8). Two out of 4 AIP cases had an underlying diagnosis of longstanding seropositive RA with one of those (case 3) also having a diagnosis of APS manifested with multiple ischemic infarcts and raised titers of antiphospholipid antibodies. Despite the fact that IgG4RD pathogenesis has not been entirely elucidated, both autoimmune and allergic immune responses have been reported as potential contributors. Since polyautoimmunity -the co-occurrence of more than one autoimmune disease in the same individual- is increasingly recognised (9), it is tempting to suggest that IgG4RD can be associated with autoimmune diseases due to shared underlying pathogenetic mechanisms. Whether the shift from Th1/Th17 responses-typically seen in many autoimmune diseases including rheumatoid arthritis- to predominantly Th2 responses characterising IgGRD, is due to exogenous or endogenous signals during disease course, remains to be explored (1). All four of our patients with IgG4-related AIP showed an excellent response to treatment with steroids.

Chronic periaortitis/RPF was the second most frequent IgG4RD manifestation noted in our case series (10). Periaortitis/RPF presents with pain in the lower back, abdomen or flanks, constitutional symptoms, new onset hypertension and acute renal failure together with laboratory evidence of a systemic inflammatory response (11) can be a cause of referral to rheumatologists with a presumable diagnosis of systemic vasculitis. In a histopathological study of biopsies from RPF patients, 58% had numerous IgG4 plasma infiltrates suggesting that a proportion of idiopathic RPF cases are part of the IgG4-RD spectrum (12).

Lastly, 2 cases of IgG4 related sialadenitis and 1 with tubulointerstitial nephritis were also identified in our series. IgG4-related sialadenitis includes Mikulicz's disease and was initially thought to be part of the spectrum of SS characterised by swelling of any of the lacrimal, parotid, submandibular sublingual glands and some minor salivary glands (13). The almost equal male to female sex ratio, the milder sicca symptomatology as well as the favourable response to steroid therapy are the main features that differentiate IgG4-RD sialadenitis from SS (14). In a recent study from our group, a subset of SS patients were also found to display raised serum IgG4 levels and an increased prevalence of IgG4-related clinical features (autoimmune cholangitis, AIP and interstitial nephritis), lower rates of ANA positivity and higher IgG2 and IgE levels (Mavragani *et al*., *Arthritis Care Res*, in press). These patients may benefit from early intervention with steroid treatment leading to improvement of salivary gland function. In addition to the salivary gland, the kidney is another common target organ in both IgG4-RD and SS. Compared with other types of tubulointerstitial nephritis (TIN), IgG4-related TIN is often associated with extra-renal lesions such as sialadenitis, pancreatitis and lymphadenitis (15).

In conclusion, in the present case series we described 11 Greek patients with IgG4-RD referred to our autoimmune disease clinics. Given that IgG4-RD emerges as a great imitator of autoimmune disorders, has an increased prevalence amongst these patients and a favourable response to steroids, early identification and diagnosis by rheumatologists is of pivotal importance. Additionally, the evolution of autoimmune diseases from one form to another, as exemplified by our cases, highlights the importance of close follow-up during the course of the patient's disease. Raised IgG4 levels do not always equate with IgG4-RD and normal IgG4 levels do not exclude the diagnosis, whilst the possibility of underlying malignancy – potentially facilitated by cytotoxic therapies – should always be considered.

References

1. MAHAJAN VS, MATTOO H, DESHPANDE V, PILLAI SS, STONE JH: IgG4-Related Disease. *Annu Rev Pathol* 2014; 9: 315-47.
2. UMEHARA H, OKAZAKI K, MASAKI Y *et al*.: Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012; 22: 21-30.
3. MASAKI Y, SUGAI S, UMEHARA H: IgG4-related diseases including Mikulicz's disease and sclerosing pancreatitis: diagnostic insights. *J Rheumatol* 2010; 37: 1380-5.
4. KHOSROSHAHI A, STONE JH: Treatment approaches to IgG4-related systemic disease. *Curr Opin Rheumatol* 2011; 23: 67-71.
5. YAMAMOTO M, TAKAHASHI H, TABEYA T *et al*.: Risk of malignancies in IgG4-related disease. *Mod Rheumatol* 2012; 22: 414-8.
6. PEIXOTO RD, AL-BARRAK J, LIM H, RENOUF D: Gastroesophageal cancer and retroperitoneal fibrosis: Two case reports and review of the literature. *World journal of gastrointestinal oncology* 2013; 5: 68-70.
7. HAMANO H, KAWA S, HORIUCHI A *et al*.: High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; 344: 732-8.
8. KAMISAWA T, CHARI ST, GIDAY SA *et al*.: Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. *Pancreas* 2011; 40: 809-14.
9. ROJAS-VILLARRAGA A, AMAYA-AMAYA J, RODRIGUEZ-RODRIGUEZ A, MANTILLA RD, ANAYA JM: Introducing polyautoimmunity: secondary autoimmune diseases no longer exist. *Autoimmune Dis* 2012; 2012: 254-319.
10. MITCHINSON MJ: Chronic periaortitis and periarteritis. *Histopathology* 1984; 8: 589-600.
11. KERMANI TA, CROWSON CS, ACHENBACH SJ, LUTHRA HS: Idiopathic retroperitoneal fibrosis: a retrospective review of clinical presentation, treatment, and outcomes. *Mayo Clin Proc* 2011; 86: 297-303.
12. ZEN Y, ONODERA M, INOUE D *et al*.: Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. *Am J Surg Pathol* 2009; 33: 1833-9.
13. DELLE SEDIE A, BALDINI C, DONATI V, MOSCA M: Mikulicz's disease: a long-term follow-up case report. *Clin Exp Rheumatol* 2012; 30: 596.
14. GEYER JT, DESHPANDE V: IgG4-associated sialadenitis. *Curr Opin Rheumatol* 2011; 23: 95-101.
15. SAEKI T, NISHI S, IMAI N *et al*.: Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. *Kidney Int* 2010; 78: 1016-23.