

Case Report

Immunoglobulin G4-related disease - diagnostic dilemma and importance of clinical judgement: a case report

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Received: 16 September 2020

Accepted: 13 October 2020

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ABSTRACT

Immunoglobulin G4 (IgG4)-related disease is a multi-organ, immune-mediated, fibro-inflammatory disorder characterized by tumefactive masses in the affected organs. Incidence and prevalence of IgG4-related disease (RD) are not clearly known and have slight male preponderance. It often involves multiple organs at the time of presentation or over the course of disease mimicking malignancy, Sjogren's syndrome, antineutrophil cytoplasmic antibodies associated vasculitis, infections. A thorough workup is needed to rule out these mimickers. A 33-year-old gentleman presented to us with history of progressive swelling in the right peri-orbital region for four years. On evaluation, abdominal imaging was notable for the sausage-shaped pancreas and hypoechoic nodules in bilateral kidneys. Histological examination of right lacrimal gland revealed lymphoplasmacytic infiltrate and storiform fibrosis. Serum IgG4 levels were normal, and immunostaining was negative. A diagnosis of IgG4-RD was suggested because of multi-organ involvement, classical radiological and histopathological features. Awareness about IgG4-RD, an under-recognized entity is essential, as it is treatable, and early recognition may help in a favourable outcome. Appropriate use of clinicopathological, serological and imaging features in the right clinical context may help in accurate diagnosis. Elevated serum IgG4 levels and biopsy are not mandatory for the diagnosis.

Keywords: IgG4-RD, Dacryoadenitis, Sausage pancreas, Storiform fibrosis

INTRODUCTION

IgG4-related disease (IgG4-RD) is a multi-organ, immune-mediated, fibro-inflammatory disorder characterized by tumefactive masses with dense lymphoplasmacytic infiltrate rich in IgG4+ cells and elevated serum IgG4 levels frequently.¹⁻³ IgG4-RD was recognized as a distinct entity in the year 2003.^{4,5} Several conditions which were previously described as idiopathic fibrosing disorders are now included in the IgG4-RD spectrum. Incidence and prevalence of IgG4-RD are not clearly known. Unlike other autoimmune diseases, IgG4-RD has shown slight male preponderance, but it varies depending on the organ affected.

It often involves multiple organs at the time of presentation or over the course of disease mimicking malignancy,

Sjogren's syndrome, antineutrophil cytoplasmic antibodies (ANCA) associated vasculitis, and infections. A thorough diagnostic workup to rule out these mimickers is vital, as management plan and outcome changes depending on the diagnosis. The disease can affect any organ, but specific organs like the pancreas, kidney, major salivary glands, orbit and lacrimal glands, lungs, thyroid gland, meninges, aorta and retroperitoneal organs seem to be more often affected.⁶ Integration of clinical history and thorough physical examination, serological, radiological and pathological features may contribute in deciding whether to classify a patient as having IgG4-RD or not.⁶

In this case report, we describe a 33-year-old gentleman who presented to us with history of right peri-orbital swelling for four years. He was subsequently diagnosed to have IgG4-RD. Although many diagnostic criteria have

been proposed, none of them can clearly distinguish IgG4-RD. This case is reported to highlight the importance of clinical judgement in diagnosis of IgG4-RD, a chameleon.

CASE REPORT

A 33-year-old gentleman presented to us in February 2018 with a history of progressive swelling in the right peri-orbital region for four years and, a history of fatigue and intermittent giddiness for one year. The swelling was insidious in onset, progressively increasing in size and painless (Figure 1 and 2). His past medical history was notable for diabetes mellitus for four years for which he is on oral hypoglycaemic drugs and insulin. General examination revealed a mobile, rubbery, non-tender enlarged lymph node in the right submandibular region. Ophthalmological examination was notable for visual acuity of 6/24 in the right eye and 6/9 in the left eye, pulsatile proptosis and macular oedema in the right eye.



Figure 1: Right peri-orbital swelling.



Figure 2: Right eye proptosis with conjunctival congestion.

Blood investigations revealed leucocytosis with mild eosinophilia (Total white blood cell i.e. WBC count – 13,460 with 7% eosinophils), and poorly controlled diabetes (fasting blood glucose – 361 mg/dl, hemoglobin (Hb) A1C – 9.8%). Thyroid-stimulating hormone (TSH) was 6.42 μ IU/ml, free thyroxine (T4)-1.16 ng/dl and anti-TSH receptor antibodies were negative. Ultrasound whole abdomen revealed a well-defined hypochoic focal pancreatic lesion measuring 3.9 \times 2.5 \times 2.9 cm. Magnetic resonance imaging (MRI) brain and orbit was done elsewhere as per patient preference, and it revealed

proptosis of the right eye with gross enlargement of right extraocular muscles, nodular infiltrates in the right lateral rectus muscles and enlarged lacrimal gland.

Contrast-enhanced computed tomography (CECT) abdomen (Figure 3 and 4) revealed a diffuse reduction of pancreatic parenchymal volume around the body and tail. Pancreas appeared sausage-shaped, and there were hypoenhancing nodules in bilateral kidneys. Ultrasound neck revealed multiple sub-centimetric lymph nodes in both the cervical regions and a lymph node measuring 3 \times 2.1 cm in the right submandibular region. He underwent cervical lymph node biopsy, and it did not show any malignant changes; non-specific reactive changes were present.



Figure 3: CECT abdomen showing sausage shaped pancreas.



Figure 4: CECT abdomen showing hypodense lesions in kidney.

Incision biopsy of right lacrimal gland was performed elsewhere as per patient's choice, and the histopathological examination (HPE) revealed dacryoadenitis with dense lymphoplasmacytic infiltrate, storiform fibrosis and scattered eosinophils. Serum antinuclear antibodies (ANA), anti-double-stranded deoxyribonucleic acid (dsDNA), ANCA and extractable nuclear antigens immunoglobulin G (ENA IgG) were negative. Human leukocyte antigen (HLA) B-27 was detected. With a high index of suspicion for IgG4-RD, HPE samples were sent for immunohistochemistry (IHC).

Serum IgG4 levels were within normal limits, and IHC revealed the polyclonal nature of plasma cells with IgG4+

plasma cells about 1-3/hpf. Although serum IgG4 levels were not elevated and IHC was negative, a diagnosis of IgG4-RD was suggested because of multi-organ involvement, classical radiological and histopathological features. We started him on oral prednisolone, and he showed significant improvement with a reduction in the size of right eye swelling and improvement in the visual acuity in 3-months outpatient follow up. He was advised to continue oral steroids to taper over the next 12 weeks.

DISCUSSION

IgG4-related disease can virtually affect any organ in the body, and about 60-90% of the patients will have multiple organ involvement at the time of diagnosis, like in our patient who had lacrimal gland, pancreatic and renal involvement.⁷ The exact etiopathogenesis is still unclear. An unknown trigger may result in aberrant T helper-2 immune response resulting in hypereosinophilia, excess IgE production and T regulatory cell-mediated interleukin-10 production which in turn induces class switching of IgG4 and transforming growth factor resulting in fibrosis and IgG4+ plasma cell infiltrates in affected organs.¹ The clinical presentation and severity of the disease depend on the organs involved.

The most typical presentation of IgG4-RD is sub-acute mass lesion resulting in the enlargement of the affected organ, and most often it is detected incidentally on HPE of surgically resected samples for suspected malignancy. IgG-RD should be suspected if mass lesions with insidious onset are present in typical organs like pancreato-hepato-biliary system, kidneys, lacrimal glands, major salivary glands, lungs and retroperitoneum. Tumefactive mass lesions may result in simple swelling of affected organ or obstruction (obstructive jaundice, obstructive uropathy), or organ dysfunction or even acute conditions like pancreatitis, aortic dissection, pachymeningitis.¹ Lymph node enlargement has been reported in about 25-60% of the patients mimicking lymphoproliferative disorders.⁸ Table 1 describes a few of many clinical manifestations of IgG4-RD.^{1,9}

Our patient had lacrimal and extraocular muscle involvement manifesting as proptosis, and diabetes secondary to pancreatic involvement. He also had asymptomatic renal involvement with normal function. Constitutional symptoms and pain are rare in IgG4-RD; fatigue may be present, especially if multiple organs are involved as seen in our case. About 30-40% of these patients may give the history of allergies, asthma, eczema and food allergy.¹⁰

Though IgG4 levels are generally increased in these patients, it is neither necessary nor sufficient to classify a case as IgG4-RD. IgG4 levels may be increased in many other mimicking diseases; moreover, its role in pathogenesis is in question. Monitoring serum IgG4 levels may help in assessing disease severity, but it is not the lone determinant of disease activity. IgG4 levels were normal

in our patient. Low complements levels may be observed in some patients, especially with renal involvement. Extensive autoimmune workup may be needed to rule out other autoimmune mimickers. Some of these patients may have non-specific markers like antinuclear antibodies, rheumatic factor; our patient had weakly positive RA factor.¹¹

Given multi-organ involvement in a significant number of patients, a thorough chest and abdominal imaging may be needed in these patients. Presence of sausage-shaped pancreas and periaortitis affecting infrarenal aorta is strongly suggestive of IgG4-RD.⁶ Our patient had sausage-shaped pancreas with a hypoechoic rim which was an essential diagnostic clue in the given clinical context.

The major histological features of IgG4-RD are dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis. Eosinophils may be present, and fibrosis may predominate in chronic cases. The extent to which these features are present is different in different organs; typical storiform fibrosis is rarely seen in lymph nodes whereas obliterative phlebitis is rare in lacrimal glands, salivary glands, lymph nodes and kidneys. Obliterative arteritis and focal neutrophilic infiltration may be seen in the lungs.² Irrespective of serum IgG4 levels, presence of IgG4-positive plasma cells on immunostaining is pathognomonic of IgG4-RD. But our patient had normal serum IgG4 levels and negative IHC, which made the case more complicated. IgG4-RD is a great mimicker and needs a thorough workup to rule out many closely related diseases. Table 2 shows mimickers of IgG4-RD and differentiating features.

Multi-organ involvement, typical histopathological and radiological features, negative autoimmune, malignant and infectious disease workup made us to arrive at a diagnosis of IgG4-RD, even in the absence of specific serological and IHC features. A good response to steroid therapy is also in favour of IgG4-RD. In fact, as per the 2019 American college of Rheumatology/European league against rheumatism (ACR/EULAR) classification criteria for IgG4-related disease, neither biopsy nor elevated serum IgG4 levels are required for classifying a case as IgG4-RD. On applying these latest criteria retrospectively, our patient fulfilled the "entry criteria" and did not have any of "exclusion criteria" and, his score was 34 as in Table 3. A score of more than 20 is required for classification of IgG4-RD as per 2019 ACR/EULAR criteria. This confirms that our clinical judgment was accurate even prior to the evolution of these criteria and prompt treatment helped in a favourable outcome.

HLA-B27 was detected in our patient. A retrospective study on Egyptian patients has reported the presence of sacroiliitis and coexistence of HLA-B27 in 60% of IgG4-RD patients.¹² There are a few more case reports of sacroiliitis and HLA-B27 positivity in IgG4-RD patients. It is unclear whether this spondyloarthropathy (SpA) and IgG4-RD are related or unrelated. Most of these patients

could not be classified as SpA as per EULAR criteria. It is important to note that about 6% of the population in North India have HLA-B27.¹³ Our patient did not have any symptoms related to SpA. Further studies are needed to see if HLA-B27 positivity in IgG4-RD increases the risk of sacroiliitis, or it is an incidental finding. Steroids are the

mainstay of treatment for IgG4-RD. Very limited data is available regarding steroids sparing drugs like azathioprine, mycophenolate mofetil, cyclophosphamide, methotrexate and leflunomide. Biologics like rituximab, bortezomib and abatacept are also tried in the treatment of IgG4-RD, and these have shown promising results.

Table 1: Clinical manifestations of IgG4-RD.

Region	Clinical manifestations
Head and neck region	Hypertrophic pachymeningitis, hypophysitis, orbital inflammatory pseudotumour, dacryoadenitis, sinusitis, sialoadenitis, fibrosing thyroiditis (Riedel thyroiditis)
Mediastinum	Tracheobronchial stenosis, pulmonary or pleural nodules, interstitial lung disease, pleural effusion, pericarditis, paravertebral mass
Pancreato-hepato-biliary	Type-1 autoimmune pancreatitis, sclerosing cholangitis, cholecystitis, IgG4-RD hepatopathy and hepatic pseudotumours
Renal	Tubulointerstitial nephritis, membranous glomerulonephritis
Retroperitoneum	Idiopathic retroperitoneal fibrosis (Ormond disease), periaortitis, obstructive uropathy
Lymph nodes	IgG4 related lymphadenopathy
Others	Sclerosing mesenteritis, mastitis, prostatitis

Table 2: A few of many great mimickers of IgG4-RD and differentiating features.

Region	Differential diagnosis	Differentiating features
Pancreato-hepato-biliary disease	Pancreatic malignancy	Increased serum IgG4 levels twice the upper limit of normal and sausage shaped pancreas on imaging in IgG4 RD
	Primary sclerosing cholangitis	Simultaneous presence bile duct and pancreatic disease and involvement of extra biliary organs seen in IgG4-RD
	Cholangiocarcinoma	Higher levels of serum bilirubin and CA19-19 in cholangiocarcinoma
Head and neck disease	Sjogren's syndrome (SS)	Female preponderance, normal IgG4 levels and positive anti-SSA or anti-SSB in SS
Chest	Sarcoidosis	Presence of granuloma in sarcoidosis Elevated ACE levels in sarcoidosis Cutaneous disease more common in sarcoidosis
	Lymphoma	Fever may be present and rapid progression across tissue planes seen in lymphoma
ANA associated vasculitis (AAV)		Fever, very high CRP and eosinophilia $>3000/\text{mm}^3$ are in favour of AAV Positive MPO-ANCA/PR3-ANCA and necrotizing granuloma favour AAV
Infections		Fever, rapid progression and positive blood cultures favour infection
Generalized lymphadenopathy	Sarcoidosis	Modest lymph node enlargement, lack of constitutional symptoms and remarkable response to steroids favour IgG4-RD
	Multicentric castleman's disease	
	Tuberculosis	
Orbit and eye disease	Thyroid eye disease	IgG4-RD specific histopathological features are helpful
	Sarcoidosis	
	Granulomatosis with polyangitis	
	Idiopathic orbital inflammation	
	Lymphoproliferative diseases	
Retroperitoneal region	Retroperitoneal fibrosis of other causes	Presence of extra peritoneal lesions and specific HPE features favour IgG4-RD
	Aortitis and periaortitis	Infra renal periaortitis extending into iliac vessels is strongly suggestive of IgG4-RD

Table 3: The 2019 ACR/EULAR classification criteria for IgG4-RD in our patient.

Criteria	In our patient	Weighted score
Histopathology	Dense lymphoplasmacytic infiltrate with storiform fibrosis	+13
Immunostaining	IgG4+cells were 1-3 cells/hpf	0
Serum IgG4 concentration	No significant abnormality detected	0
Bilateral lacrimal and salivary gland involvement	Our patient had unilateral lacrimal gland involvement	0
Chest	Normal	0
Pancreas and biliary tree	Sausage shaped pancreas with hypoechoic rim	+11
Kidneys	Hypoechoic cortical nodules in both kidneys	+10
Retroperitoneum	No significant abnormality detected	0
Total score		34

CONCLUSION

Awareness about IgG4-RD, an under-recognized entity, is essential as it is treatable, and early recognition may help in a favourable outcome. Appropriate use of clinicopathological, serological and imaging features in the right clinical context may help in accurate diagnosis. Elevated serum IgG4 levels and biopsy are not mandatory for the diagnosis. Steroids are the mainstay of treatment, but relapses are common and needs close follow up.

ACKNOWLEDGEMENTS

The authors would like to thank the family of the patient for their assistance in preparing the manuscript.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

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Cite this article as: Chandrasekaran J, Machiraju PK. Immunoglobulin G4-related disease - diagnostic dilemma and importance of clinical judgement: a case report. Int J Res Med Sci 2020;8:4144-8.