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Case Series

Pathology Section

Immunoglobulin G4-related Disease: A Series of Four Cases

CHANDNI THOMAS[1], S DIVYA[2], JOY AUGUSTINE[3]

ABSTRACT

Immunoglobulin G4-related Disease (IgG4-RD) is an immune-mediated fibroinflammatory disease that affects multiple organs, resulting in tumefactive lesions and/or organ dysfunction. This chronic, multiorgan inflammatory process is characterised by the infiltration of IgG4-positive plasma cells and has a variable clinical presentation depending on the organ involved. The present case series discusses four cases (two males and two females) of IgG4-RD involving different sites in patients presented to present Institution. The authors reviewed four cases of IgG4-RD, including clinical details, biochemical, radiological, and histopathological features. The case series includes IgG4-RD masquerading as meningioma, IgG4-related sclerosing cholangitis, IgG4-RD of the thyroid gland, and IgG4-RD of the lacrimal gland. Since IgG4-RD has non specific clinical features, histopathological analysis and immunohistochemistry play a pivotal role in diagnosis. Despite its diagnostic difficulties, earlier recognition is crucial to prevent significant morbidity and extensive fibrosis leading to organ failure.

Keywords: Immunoglobulin G4-related sclerosing disease, Immunohistochemistry, Multiorgan

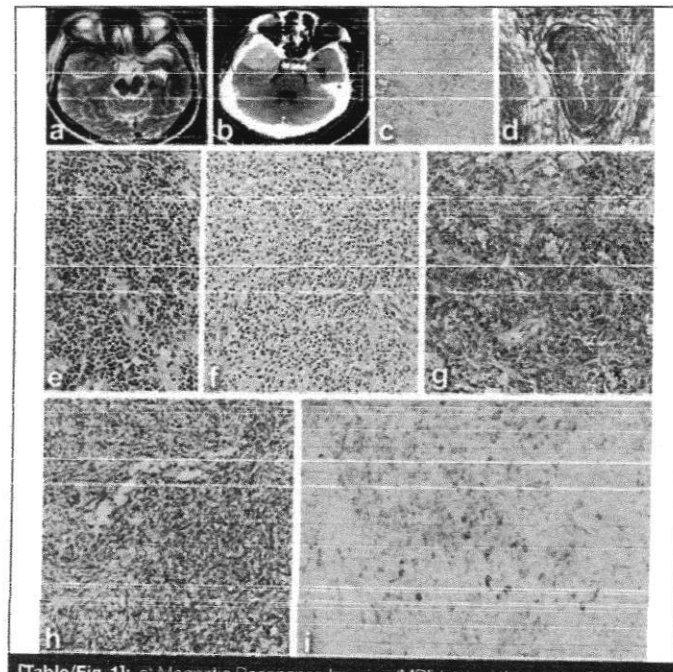
INTRODUCTION

Immunoglobulin G4-related Disease (IgG4-RD) is a systemic immune-mediated condition affecting any organ. It encompasses a spectrum of diseases that were considered independent disorders for past decades, such as type 1 Autoimmune Pancreatitis (AIP), retroperitoneal fibrosis, Mikulicz disease, Riedel thyroiditis, and hypertrophic pachymeningitis. It is characterised by tissue inflammation and fibrotic outcomes [1]. Based on organ involvement, four clinical phenotypes have been defined: i) Pancreaticobiliary disease; ii) Retroperitoneal fibrosis with or without aortitis; iii) Head and neck limited disease; iv) Mikulicz syndrome with systemic involvement [2-5]. Pancreatic, retroperitoneal, salivary, and lacrimal gland involvement represent the prototypical manifestations, but lesions in the head and neck are less specific, making the differential diagnosis challenging [6,7]. Dense infiltration of IgG4-positive plasma cells is seen in the involved tissues, with or without elevated plasma levels of IgG4 [8]. IgG4-RD is a fibroinflammatory condition with a broad variety of clinical spectrum. Hereby, the authors present just four cases, each of which presented with varied clinical symptoms and underwent systematic work-up to reveal the exact diagnosis.

CASE SERIES

Case 1

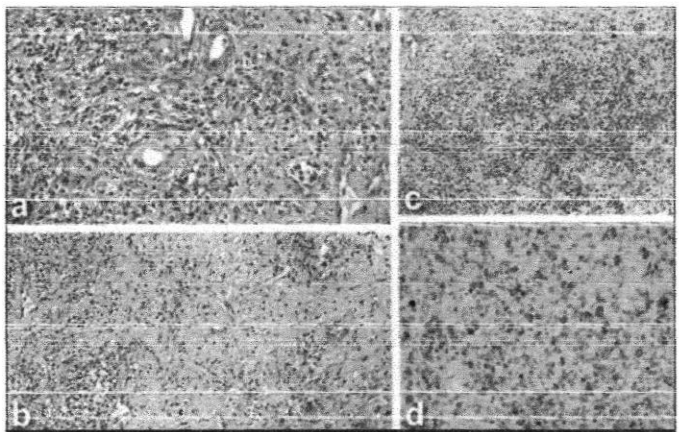
A 78-year-old male patient, diabetic and asthmatic, well controlled on bronchodilators and oral hypoglycemic agents, presented with a history of recurring generalised tonic-clonic seizures and headache for the past month. He also reported a fall at his home one month prior, resulting in a wound over his right forehead. Physical examination did not reveal any neurological deficits. Radiological examination showed a space-occupying lesion in the right temporal lobe, measuring about 41.3×40×39 mm, suggestive of meningioma. A Computed Tomography (CT) scan of the brain revealed extra-axial extension of the lesion with underlying bone erosion [Table/Fig-1a,b]. Preoperative work-up showed an elevated Erythrocyte Sedimentation Rate (88 mm in 1 hr, normal: ≤30 mm). Based on radiological and laborato investigations, the provisional diagnosis was meningioma. The pati underwent right fronto-temporoparietal craniotomy and excisi of the mass, following which the specimen was received in th pathology laboratory. Microscopy showed tissue with dense fibrosis. Some areas exhibited a storiform pattern. Blood vessels of varying calibre were noted, showing obliterated lumen with perivascular concentric fibrosis. Focally nodular lymphoid aggregates were seen. The entire tissue was infiltrated by eosinophils in sheets and, in some areas, by sheets of plasma cells and lymphocytes. Fibrosis was highlighted with Masson's trichrome stain [Table/Fig-1c-i]. The patient responded well to subsequent treatment with prednisolone 1 mg/kg and steroid-sparing immunosuppressive therapy. At the time of writing this report, the patient was symptomatically better with no focal neurological deficits.



[Table/Fig-1]: a) Magnetic Resonance Imaging (MRI) brain-right temporal space occupying lesion; b) CT brain- extra-axial lesion in temporal region; c) Tissue with dense fibrosis (Storiform pattern), H&E X100; d) Obliterative phlebitis (Masson's trichrome staining), H&E X400; e) Tissue with dense lymphoplasmacytic infiltrate, H&E X400; f) Sheets of eosinophils, (H&E X200); g) IHC: CD138 positivity-demonstrating the significant plasma cell infiltrate, X400; h) IHC: diffuse vimentin positivity, X400; i) IHC: IgG4 positive plasma cells, 400x. Immunohistochemical analysis showed significant CD138 positive plasma cell infiltrate and more than 30 IgG4 positive plasma cells/high power field, favouring the diagnosis. His preoperative serum IgG level was 0.58 g/L (normal range: 0.68-2.01 g/L). H&E: Haematoxylin and eosin; IHC: Immunohistochemistry

Case 2

A 59-year-old male patient, known to have chronic calcific pancreatitis and under treatment, presented with colicky abdominal pain for the past three days. An ultrasound of the abdomen showed hepatomegaly with ill-defined heterogeneous hypoechoic areas in the right lobe segment V-VIII and segment VII subcapsularly, suspicious of an evolving abscess. Prominent central biliary ducts were also found, suggestive of biliary obstruction. A Ultrasonography (USG)-guided liver biopsy was performed. Microscopy revealed liver tissue with architectural distortion. Hepatocytes showed mild nuclear atypia. Spotty necrosis and portal inflammation with severe interface hepatitis were noted. The inflammatory cells comprised plasma cells, neutrophils, and foam cells. Portal sclerosis was present with marked expansion of the fibrosed portal area [Table/Fig-2a-d]. These findings were suggestive of IgG4-related sclerosing cholangitis. He was treated with systemic steroids and showed symptomatic improvement after a one-month course.



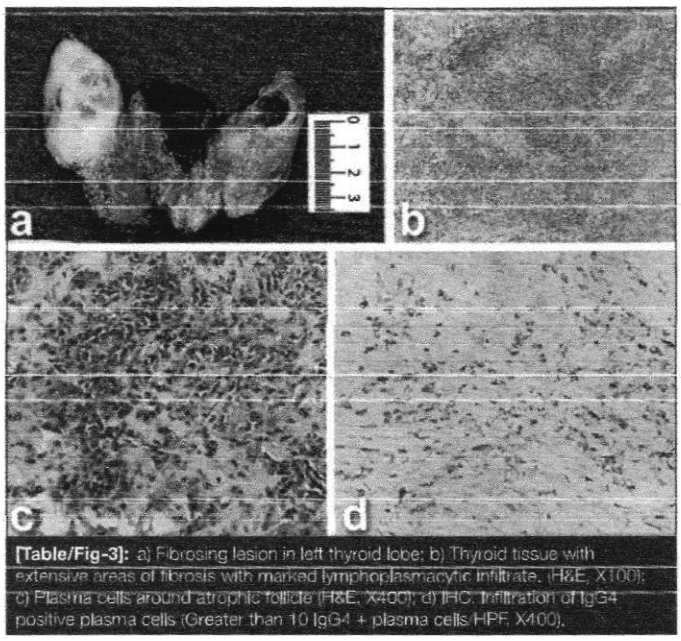
[Table/Fig-2]: a) Portal inflammation (H&E, X400); b) Periductal fibrosis (H&E, X100); c) Marked lymphoplasmacytic infiltration (H&E, X200); d) IHC: Infiltration of IgG4 + plasma cells (Greater than 10 IgG4 + plasma cells/HPF, X400).

Case 3

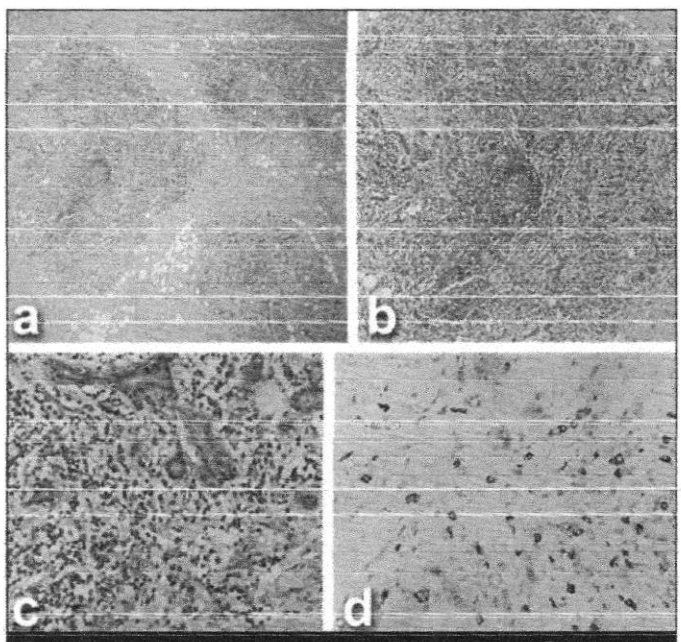
A 56-year-old female patient with diabetes, asthma, and dyslipidemia presented with an enlarged thyroid with a nodule in the left lobe for the past six months. Ultrasound scanning suggested a multinodular goiter {Thyroid Imaging Reporting and Data System (TIRADS-IV)}. She underwent total thyroidectomy with level IV lymph node dissection. Grossly, the thyroid revealed a grey-white solid-cystic lesion in the left lobe of the thyroid, towards the upper pole, measuring 3.5×2.7×1.7 cm [Table/Fig-3a]. Microscopic examination of both lobes of the thyroid showed extensive areas of fibrosis with marked infiltration of chronic inflammatory cells composed of sheets of plasma cells and lymphocytes [Table/Fig-3b]. Dense and broad collagenous fibrous bands were noted, separating the thyroid parenchyma into nodules. Atrophic follicles and folliculolysis [Table/Fig-3c] were noted, along with foci of granuloma composed of foreign body giant cells and epithelioid histiocytes around the colloid. Thick-walled blood vessels of varying calibers, some having obliterated lumens with perivascular fibrosis, were also seen. Lymph nodes showed reactive changes only. With these histological features, a diagnosis of Riedel thyroiditis/IgG4-RD was suggested, and IgG4-positive plasma cells were identified using the IgG4 immunohistochemical marker [Table/Fig-3d].

Case 4

A 53-year-old female patient presented with painless swelling of the left eyelid, which she noticed a year ago and has gradually enlarged to its present size. On examination, the swelling was firm and non tender. She was not on any routine medications. She



[Table/Fig-3]: a) Fibrosing lesion in left thyroid lobe; b) Thyroid tissue with extensive areas of fibrosis with marked lymphoplasmacytic infiltrate. (H&E, X100); c) Plasma cells around atrophic follicle (H&E, X400); d) IHC: Infiltration of IgG4 positive plasma cells (Greater than 10 IgG4 + plasma cells/HPF, X400).



[Table/Fig-4]: a) Lacrimal gland shows broad bands of fibrosis (H&E, X100); b) Dense inflammatory cell infiltration surrounding atrophic acini (H&E, X200); c) Prominent plasma cell infiltration (H&E,X400); d) IHC: Infiltration of IgG4 + plasma cells (Greater than 10 IgG4 + plasma cells/HPF X400).

was evaluated at a peripheral hospital and clinically diagnosed with lymphoma, following which she was referred to hospital. Excision was done, and authors received a firm, nodular mass measuring 2×2×1 cm; the cut section of which was homogenous and grey-white. Microscopy showed markedly fibrosed lacrimal glands with extensive fibrosis and acinar atrophy. Fibrosis surrounded the ductular elements. Prominent plasma cell infiltration was noted, admixed with lymphocytes and eosinophils focally [Table/Fig-4a-c]. The plasma cells were positive for IgG4 immunohistochemical staining [Table/Fig-4d]. With these features, a possibility of IgG4-RD was suggested. She was treated with systemic steroids for a short while and was symptomatically better afterwards.

DISCUSSION

ImmunoglobulinG4-related Disease (IgG4-RD) was recognised as a distinct entity during the past decade. It is characterised by the infiltration of one or more target organs by IgG4-positive plasma cells and lymphocytes. Autoimmiune Pancreatitis (AIP), which was first described in 1995, was found to be associated with elevated

levels of IgG4 in 2001 [9]. Later, it was postulated by Kamisawa T et al., that IgG4-RD is a systemic condition affecting many extra-pancreatic organs such as bile ducts, gall bladder, retroperitoneum, kidneys, breasts, prostate, lungs, and skin [10].

IgG4 constitutes less than 5% of the total immunoglobulins in healthy individuals and is associated with both autoimmune and allergic diseases [11]. The presence of elevated IgG4 in the serum is a weak diagnostic feature for IgG4-RD, as up to 50% of patients with IgG4-RD have normal levels, as in one of present cases [12]. However, the cut-off level for IgG4 of 135 mg/dL has a positive predictive value for IgG4-RD [13].

Human Leukocyte Antigen (HLA) and non HLA genes seem to play important roles in the pathogenesis of IgG4-RD. Studies have reported higher frequencies of HLA serotypes DRB1 0405 and DQB1 0401 in AIP. Single nucleotide polymorphisms (including Cytotoxic T-Lymphocyte Antigen (CTLA4) and tumour necrosis factor-alpha promoter genes) in non HLA genes were also linked to AIP [8]. The expression of Th2 cytokines (IL-4, IL-5, IL-13) and regulatory cytokines (IL10, TGF-beta) was found to be elevated in AIP and IgG4-related tubulointerstitial nephritis [14]. Increased production of IL-4, IL-5, IL-13 contributes to peripheral eosinophilia and elevated IgE levels. Increased production of IgG4 is caused by IL-10 and can lead to fibrosis by increasing the expression of the fibrotic cytokine, Transforming Growth Factor-beta (TGF-β). Expanded CD4+ effector/memory T cells with a cytolytic phenotype were found in IgG4-RD patients [8].

The diagnosis of IgG4-RD is made with an understanding of clinical, imaging, serological, and pathological details [15]. The original 2011 comprehensive diagnostic criteria for IgG4-RD or its revised 2020 version and the consensus statement on IgG4-RD pathology for diagnosis [Table/Fig-5] [17] are widely used in clinical practice nowadays [7,16]. Many problems have arisen with these criteria, including the difficulty in obtaining biopsy samples from some patients (AIP or retroperitoneal fibrosis) and the limited sensitivity and specificity of serum IgG4 concentrations. Such problems have been addressed by organ-specific criteria for IgG4-RD [17]. Patients with a possible or probable diagnosis of IgG4-RD could be re-diagnosed by organ-specific criteria, and patients who fulfilled at least one of the organ-specific criteria can be diagnosed with definite IgG4-RD [18].

The assessment ideally starts with a complete history and physical examination. Laboratory investigations and appropriate radiology evaluation will follow, depending on the site involved. Plasma IgG4 level should be checked. Enumeration of circulating plasmablasts is beneficial, especially in cases with normal serum IgG4 levels. Though elevated levels are seen in various inflammatory conditions, significant elevation (>2000 cells/mL) was observed in IgG4-RD [19]. Complement levels have shown correlation with the disease activity in cases of renal IgG4-RD [20].

Histopathology is the current "gold standard" for diagnosis. Combined with immunohistochemistry, it is a definitive cornerstone in evaluation. The present first case contributes to the few published cases in the literature of intracranial IgG4-related pseudo-tumours that masquerade as meningioma. Goulam-Houssein S et al., have described supratentorial meningioma-like lesions [9]. Authors' last case adds to the cases of orbital pathology of this disease spectrum and is the most frequent ophthalmic manifestation of the disease.

1. Clinical and radiological features
One or more organs show diffuse or localised swelling or a mass or nodule characteristic of IgG4-RD. In single organ involvement, lymph node swelling is omitted.
2. Serological diagnosis
Serum IgG4 levels greater than 135 mg/dL.
3. Pathological diagnosis
Positivity for two of the following three criteria:
• Dense lymphocyte and plasma cell infiltration with fibrosis.
• Ratio of IgG4-positive plasma cells/IgG-positive cells greater than 40% and the number of IgG4-positive plasma cells greater than 10 per high power field.
• Typical tissue fibrosis, particularly storiform fibrosis, or obliterative phlebitis.
Diagnosis:
Definite: 1+2+3
Probable: 1+3
Possible: 1+2

[Table/Fig-5]: The 2020 Revised Comprehensive Diagnostic (RCD) criteria for IgG4-RD [17].

CONCLUSION(S)

The IgG4-related disease is a multiorgan chronic inflammatory process with a widely varied clinical picture. Early recognition and therapy are important to prevent serious irreversible tissue damage. Hence, a multidisciplinary approach for case work-up with a high index of suspicion on morphological features is crucial to reveal the diagnosis.

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PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
2. Associate Professor, Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
3. Professor and Head, Department of Pathology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Chandni Thomas,
Junior Resident, Department of Pathology, Amala Institute of Medical Sciences, Thrissur-680001, Kerala, India.
E-mail: chandnithomaz@gmail.com

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Betsy

Dr. BETSY THOMAS
MD, FRCOG, DNB, MICOG
PRINCIPAL
AMALA INSTITUTE OF MEDICAL SCIENCES
AMALA NAGAR, THRISSUR-680 555

AMALA INSTITUTE OF MEDICAL SCIENCES THRISSUR