Is Pediatric IgG4-Related Disease Distinct from its Adult Counterpart?

A Single Center Case Series

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BACKGROUND

IgG4-related disease (IgG4-RD) is a poorly understood and rarely diagnosed fibro-inflammatory condition in pediatrics. While myriad presentations of this disease have been described in the adult literature for centuries, only recently has this disease been recognized as a clinical entity in pediatrics. Indeed, consensus as to best practices in the diagnosis and treatment of pediatric IgG4-RD has not yet been established. This case series describes the patients diagnosed with and treated for IgG4-RD at a major pediatric referral center between 2012 and 2019. It includes an accounting of therapeutic modalities employed and outcomes observed.

PURPOSE

The purpose of this series was to describe the presentations, treatments, and outcomes of IgG4-RD diagnosed at a large, pediatric institution.

METHODS

Retrospective chart review identified 4 patients who presented for evaluation by Pediatric Rheumatology for IgG4-RD at Texas Children's Hospital from January 2012 to May 2019. Records of these patients' initial presentation, subsequent workup, therapeutic approach, and eventual outcomes were reviewed. Median age at presentation was 13.2 years (range 4 – 15.3). 3 patients were female. 2 patients were Hispanic, one was African-American, and one was Caucasian. 3 patients presented with IgG4-related ocular disease, while one presented with sialadenitis. Median duration of symptoms at time of diagnosis was 2 months (range 0 – 9). 3 of the 4 patients met the criteria for "histologically highly suggestive of IgG4-RD" by the consensus criteria outlined by Deshpande, et al (2012). The patient not satisfying criteria did not meet secondary to inadequate IgG4 per HPF but did satisfy the requirement of >40% IgG4 to IgG ratio. 3 of the 4 patients met the newly proposed ACR/EULAR IgG4-related disease classification. The patient not satisfying criteria did not meet secondary to too few inclusion points.

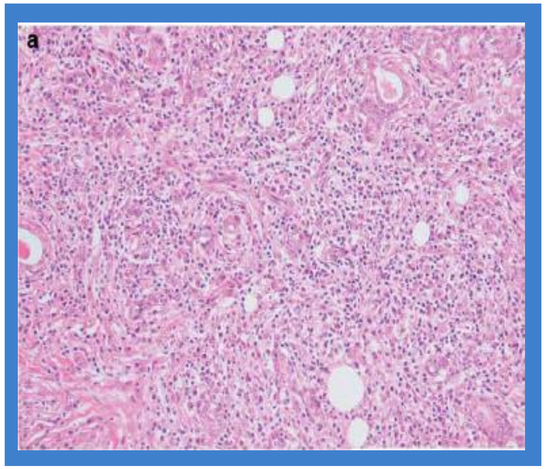

Fig 1: IgG4-related sialadenitis. Extensive infiltration of salivary glands by lymphocytes and plasma cells.[1]

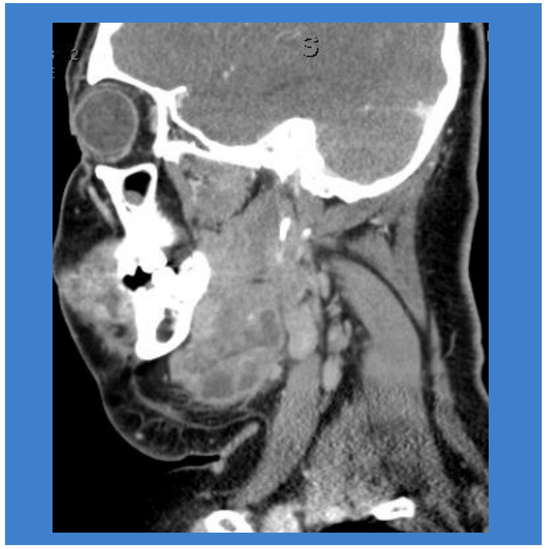

Fig 2: Sialadenitis in patient diagnosed with IgG4-RD

Table 4 The 2019 American College of Rheumatology/European League Against Rheumatism classification criteria for IgG4-RD

Step	Categorical assessment or numerical weight
Step 1. Entry criteria	
Characteristic* clinical or radiological involvement of a typical organ (eg, pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges or thyroid gland (Riedel's thyroiditis)) OR pathological evidence of an inflammatory process accompanied by a lymphoplasmacytic infiltrate of uncertain aetiology in one of these same organs	Yes† or No
Step 2. Exclusion criteria‡: domains and items§	Yes or No¶
Clinical	
Fever	
No objective response to glucocorticoids	
Serological	
Leucopenia and thrombocytopenia with no explanation	
Peripheral eosinophilia	
Positive antineutrophil cytoplasmic antibody (specifically against proteinase 3 or myeloperoxidase)	
Positive SSA/Ro or SSB/La antibody	
Positive double-stranded DNA, RNP or Sm antibody	
Other disease-specific autoantibody	
Cryoglobulinemia	
Radiological	
Known radiological findings suspicious for malignancy or infection that have not been sufficiently investigated	
Rapid radiological progression	
Long bone abnormalities consistent with Erdheim-Chester disease	
Splenomegaly	
Pathological	
Cellular infiltrates suggesting malignancy that have not been sufficiently evaluated	
Markers consistent with inflammatory myofibroblastic tumour	
Prominent neutrophilic inflammation	
Necrotizing vasculitis	
Prominent necrosis	
Primarily granulomatous inflammation	
Pathologic features of macrophage/histiocytic disorder	
Known diagnosis of the following:	
Multicentric Castleman's disease	
Crohn's disease or ulcerative colitis (if only pancreatobiliary disease is present)	
Hashimoto thyroiditis (if only the thyroid is affected)	
If case meets entry criteria and does not meet any exclusion criteria, proceed to step 3.	
Step 3. Inclusion criteria: domains and items¶	
Histopathology	
Uninformative biopsy	0
Dense lymphocytic infiltrate	+4
Dense lymphocytic infiltrate and obliterative phlebitis	+6
Dense lymphocytic infiltrate and storiform fibrosis with or without obliterative phlebitis	+13
Immunostaining**	0–16, as follows: Assigned weight is 0 if the IgG4+:IgG+ ratio is 0%–40% or indeterminate and the number of IgG4+ cells/hpf is 0–9.11. Assigned weight is 7 if: (1) the IgG4+:IgG+ ratio is ≥41% and the number of IgG4+cells/hpf is 0–9 or indeterminate or (2) the IgG4+:IgG+ ratio is 0–40% or indeterminate and the number of IgG4+ cells/hpf is ≥10 or indeterminate. Assigned weight is 14 if: (1) the IgG4+:IgG+ ratio is 41%–70% and the number of IgG4+ cells/hpf is ≥10 or (2) the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is 10–50. Assigned weight is 16 if the IgG4+:IgG+ ratio is ≥71% and the number of IgG4+ cells/hpf is ≥51.
Serum IgG_4 concentration	
Normal or not checked	0
>Normal but <2× upper limit of normal	+4
2–5× upper limit of normal	+6
≥>5× upper limit of normal	+11
Bilateral lacrimal, parotid, sublingual and submandibular glands	

Continued

Table 4 Continued

Step	Categorical assessment or numerical weight
No set of glands involved	0
One set of glands involved	+6
Two or more sets of glands involved	+14
Chest	
Not checked or neither of the items listed is present	0
Peribronchovascular and septal thickening	+4
Paravertebral band-like soft tissue in the thorax	+10
Pancreas and biliary tree	
Not checked or none of the items listed is present	0
Diffuse pancreas enlargement (loss of lobulations)	+8
Diffuse pancreas enlargement and capsule-like rim with decreased enhancement	+11
Pancreas (either of above) and biliary tree involvement	+19
Kidney	
Not checked or none of the items listed is present	0
Hypocomplementemia	+6
Renal pelvis thickening/soft tissue	+8
Bilateral renal cortex low-density areas	+10
Retroperitoneum	
Not checked or neither of the items listed is present	0
Diffuse thickening of the abdominal aortic wall	+4
Circumferential or anterolateral soft tissue around the infrarenal aorta or iliac arteries	+8
Step 4. Total inclusion points	
A case meets the classification criteria for IgG4-RD if the entry criteria are met, no exclusion criteria are present, and the total points is ≥20	

*Refers to enlargement or tumour-like mass in an affected organ except in (1) the bile ducts, where narrowing tends to occur, (2) the aorta, where wall thickening or aneurysmal dilatation is typical and (3) the lungs, where thickening of the bronchovascular bundles is common.
†If entry criteria are not fulfilled, the patient cannot be further considered for classification as having IgG4-RD.
‡Assessment for the presence of exclusion criteria should be individualised depending on a patient's clinical scenario.
§If exclusion criteria are met, the patient cannot be further considered for classification as having IgG4-RD.
¶Only the highest weighted item in each domain is scored.
**Biopsies from lymph nodes, mucosal surfaces of the gastrointestinal tract and skin are not acceptable for use in weighting the immunostaining domain.
††'Indeterminate' refers to a situation in which the pathologist is unable to clearly quantify the number of positively staining cells within an infiltrate, yet can still ascertain that the number of cells is at least 10/hpf. For a number of reasons, most often pertaining to the quality of the immunostain, pathologists are sometimes unable to count the number of IgG4+ plasma cells with precision yet even so, can be confident in grouping cases into the appropriate immunostaining result category.
hpf, high-power field; IgG4-RD, IgG4-related disease.

Fig 3: 2019 ACR/EULAR classification criteria for IgG4-RD

TREATMENTS/OUTCOMES

All 4 patients received treatment with oral and/or IV steroids. 3 patients received steroid-sparing therapy: 2 patients were treated with methotrexate, 1 with mycophenolate. All 3 of the patients receiving steroid sparing therapy also received rituximab. All of these patients were subsequently considered in remission after receipt of rituximab. One patient was noted to have recurrent transient thyroiditis with positive thyroglobulin and TPO antibodies, but thyroid disease was not the presenting feature for IgG4-RD. Malignancy (Hodgkin's lymphoma) was diagnosed in the patient treated with rituximab and mycophenolate, approximately 23 months after initial presentation. The patient with sialadenitis had clinical/imaging evidence of resolution of IgG4 sialadenitis but was subsequently diagnosed with granulomatosis with polyangiitis. The patient not receiving steroid-sparing therapy was recently diagnosed and evaluation remains ongoing.

CONCLUSION

IgG4-RD remains a rare diagnosis in pediatrics, especially when compared with adults. While classification criteria with excellent specificity and sensitivity have been developed for adult disease, it remains to be seen whether these criteria are entirely applicable to pediatric IgG4-RD. Moreover, treatment regimens suggested in adult IgG4-RD rely heavily on glucocorticoids, which may be both inadequate and unacceptable secondary to morbidity with long-term use. Additional research is needed to better define pediatric IgG4-RD, develop and validate classification criteria, and determine optimal therapeutic regimens.

REFERENCES

1. Deshpande V, Zen Y, Chan JK, Yi EE, Sato Y, Yoshino T, et al. Consensus statement on the pathology of IgG4-related disease. *Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc*. 2012;25(9):1181-1192.

2. Wallace ZS, Naden RP, Chari S, Choi H, Della-Torre E, Dicaire JF, et al. The 2019 American College of Rheumatology/European League Against Rheumatism Classification Criteria for IgG4-Related Disease. *Arthritis & rheumatology (Hoboken, NJ)*. 2020;72(1):7-19.