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Immunoglobulin (Ig) G4–related disease is a rare disease that typically affects middle-aged adults, with an average age of onset of 50 to 60 years and male predominance.1,2 Owing to the growing recognition of IgG4–related disease, the true incidence remains unknown but has been estimated to be up to 1 in 100 000 per year.1 Clinical presentation varies widely and includes retroperitoneal fibrosis, sialadenitis or thyroiditis, or tumor-like lesions, most commonly in the orbit, salivary glands, pancreas, and lymph nodes. Multiorgan involvement is common; for example, extraophthalmic involvement is found in more than 70% of patients with IgG4–related disease involving the orbit.3 Patients may present with a constellation of symptoms depending on the affected site, related to the formation of these mass-forming lesions. They typically have elevated serum IgG4 levels and frequently respond well to immunosuppressive therapy. These patients may also have low serum levels of antinuclear antibody (ANA) and rheumatoid factor, though serum positivity for more specific autoantibodies is unusual.4 While clinical and serologic findings may suggest the diagnosis of IgG4–related disease, histologic confirmation continues to be the gold standard. These histologic features are well defined in adults, with criteria including a dense lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, an IgG4:IgG-positive plasma cell ratio greater than 0.4, and an organ–specific threshold for IgG4–positive plasma cell count per high-power field by immunohistochemical staining.5

However, in children, IgG4–related disease is limited to few case reports. Based on the existing literature, children present at a median age of 13 years with a slight female predominance and commonly show involvement of the orbit and pancreas.6 They typically respond to steroid or other immunosuppressive therapy, as with adults. Because of the sparse literature on pediatric IgG4–related disease, we sought to further characterize the spectrum of IgG4–rich lesions in patients younger than 18 years, with a focus on histologic features.

MATERIALS AND METHODS

With institutional review board approval, a retrospective search of the pathology database at our institution from 2011 to 2019 was performed for cases for which IgG4 immunohistochemical staining was performed. All patients were younger than 18 years at the time of diagnosis. Cases that showed more than rare IgG4–positive plasma cells were included in this study. The electronic medical record was reviewed for patient clinical history, serologic workup, and follow-up. Slides were reviewed for histologic features, IgG and IgG4 immunohistochemical stains, and other ancillary testing.

Clinicopathologic Characterization of IgG4-Rich Pediatric Head and Neck Lesions

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An IgG4/IgG plasma cell ratio was determined by counting the number of IgG4-positive and IgG-positive plasma cells, respectively, in a given high-power field and calculating the ratio. For cases in which they had not originally been performed, Grocott methenamine silver (GMS) staining, Ziehl-Neelsen acid-fast bacilli (AFB) staining, and in situ hybridization for κ and λ light chains were performed by using clinically validated procedures. Polymerase chain reaction (PCR)–based B-cell clonality screening for IgH and IgK gene rearrangements was performed on case 3 by using clinically validated procedures.

RESULTS

Between 2011 and 2019, a total of 20 cases were identified for which immunohistochemical staining for IgG4 was performed. Of these cases, 16 (80%) were reported as containing only rare or no IgG4–positive plasma cells. Of the 4 remaining cases with more than rare IgG4–positive plasma cells, 3 cases were orbital (all female) and 1 was in extrathyroidal neck soft tissue (male). Clinical features of these cases are summarized in Table 1. Patient age ranged from 10 to 15 years (mean, 12.1 years; median, 11.3 years). All patients had normal to mildly elevated serum IgG levels, and 2 patients (cases 1 and 4) had elevated serum IgG levels. All patients had positive serology findings for ANA, with titers ranging from 1:160 to 1:640 and speckled and/or homogeneous staining patterns. Two of 4 patients (cases 2 and 3) also had positivity for antineutrophil cytoplasmic antibodies (ANCA), specifically anti-myeloperoxidase (MPO) autoantibody. Other autoantibodies, including ssA, ssB, RNP, anti–ribonucleoprotein autoantibodies; ssA, anti–Sjögren syndrome-related antigen A autoantibodies; ssB, anti–Sjögren syndrome-related antigen B autoantibodies; SM, anti–smooth muscle antibody.

| Case No. | Location | Patient Age, y/Sex | Symptom Duration | Serum IgG, mg/dL (Normal Range) | Serum IgG4, mg/dL (Normal Range) | Serum ANA | Serum ANCA | Other Serologic Markers | Additional Clinical Findings |
|----------|----------|-------------------|-----------------|-------------------------------|---------------------------------|-----------|------------|-------------------------|-----------------------------|
| 1        | Orbit, bilateral | 11/F | 5 y | 851 (748–1398) | 263 (1–168) | Positive (1:160, speckled) | Negative | Elevated IgE (2160 IU/mL; normal 0–257) | Negative ssA, ssB | Pulmonary nodules, asthma |
| 2        | Orbit, right | 15/F | 3 wk | 1060 (697–1042) | 171 (1–291) | Positive (1:640, homogeneous, speckled) | Positive (perinuclear, 1:80) | Negative MPO | Negative PR3 | N/A |
| 3        | Orbit, right | 10/F | 1 mo | 1350 (748–1398) | 119 (1–121) | Positive (1:160, speckled) | Positive (1:20; perinuclear) | Negative ssA, ssB, RNP, anti-cardiolipin | N/A |
| 4        | Extrathyroidal neck soft tissue | 11/M | 1 mo | 1470 (748–1398) | >330 (1–168) | Positive (1:160, speckled) | Negative | N/A | N/A |

Abbreviations: ANA, antinuclear antibody; ANCA: antineutrophil cytoplasmic antibodies; MPO, anti–myeloperoxidase autoantibody; N/A, not applicable; PR3, anti–proteinase 3 autoantibody; RNP, anti–ribonucleoprotein autoantibodies; ssA, anti–Sjögren syndrome-related antigen A autoantibodies; ssB, anti–Sjögren syndrome-related antigen B autoantibodies; SM, anti–smooth muscle antibody.

### Table 1. Clinical Features of Pediatric Cases With Increased Immunoglobulin (Ig) G4–Positive Plasma Cells

| Case | Location | Patient Age, y/Sex | Symptom Duration | Serum IgG, mg/dL (Normal Range) | Serum IgG4, mg/dL (Normal Range) | Serum ANA | Other Serologic Markers | Additional Clinical Findings |
|------|----------|-------------------|-----------------|-------------------------------|---------------------------------|-----------|-------------------------|-----------------------------|
| 1    | Orbit, bilateral | 11/F | 5 y | 851 (748–1398) | 263 (1–168) | Positive (1:160, speckled) | Elevated IgE (2160 IU/mL; normal 0–257) | Negative ssA, ssB | Pulmonary nodules, asthma |
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An IgG4/IgG plasma cell ratio was determined by counting the number of IgG4–positive and IgG–positive plasma cells, respectively, in a given high-power field and calculating the ratio. For cases in which they had not originally been performed, Grocott methenamine silver (GMS) staining, Ziehl-Neelsen acid-fast bacilli (AFB) staining, and in situ hybridization for κ and λ light chains were performed by using clinically validated procedures. Polymerase chain reaction (PCR)–based B-cell clonality screening for IgH and IgK gene rearrangements was performed on case 3 by using clinically validated procedures.

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### RESULTS

Between 2011 and 2019, a total of 20 cases were identified for which immunohistochemical staining for IgG4 was performed. Of these cases, 16 (80%) were reported as containing only rare or no IgG4–positive plasma cells. Of the 4 remaining cases with more than rare IgG4–positive plasma cells, 3 cases were orbital (all female) and 1 was in extrathyroidal neck soft tissue (male). Clinical features of these cases are summarized in Table 1. Patient age ranged from 10 to 15 years (mean, 12.1 years; median, 11.3 years). All patients had normal to mildly elevated serum IgG levels, and 2 patients (cases 1 and 4) had elevated serum IgG levels. All patients had positive serology findings for ANA, with titers ranging from 1:160 to 1:640 and speckled and/or homogeneous staining patterns. Two of 4 patients (cases 2 and 3) also had positivity for antineutrophil cytoplasmic antibodies (ANCA), specifically anti-myeloperoxidase (MPO) autoantibody. Other autoantibodies, including ssA, ssB, and ribonucleoprotein (RNP) autoantibody, showed negativity in all tested patients. One patient (case 1) also had a clinical history significant for longstanding pulmonary nodules, asthma, and elevated serum IgE levels. No other systemic findings were noted in these 4 patients on rheumatology workup; chest imaging including computed tomography scan was negative in cases 2 and 3.

Several common histologic features were seen in the biopsies obtained from these patients (Table 2). In all cases, a prominent and dense plasmacytic infiltrate was seen (Figure 1, A). All 4 cases at least focally contained small vessels with concentric but nonstoriform perivascular fibrosis without oblitative phlebitis (Figure 1, B). An eosinophilic infiltrate was found in association with the plasma cell infiltrate in all 4 cases, ranging from scattered eosinophils to clusters and microabscesses (Figure 1, C and D). In addition, 3 of 4 cases (cases 2, 3, and 4) had a prominent histiocytic infiltrate without granuloma formation (Figure 1, E). GMS and AFB stains showed negativity for fungi and acid-fast bacilli in all cases, including the patient with a longstanding history of pulmonary nodules (case 1). Four years before the orbital biopsy, this patient received targeted lung wedge biopsies, which showed eosinophilic pneumonia, only rare plasma cells, and negative staining for microorganisms. In 3 of the cases (cases 1, 2, and 4), CD1a and/or Langerin staining was performed to rule out Langerhans cell histiocytosis that highlighted only scattered histiocytes. In 3 of 4 cases (cases 1, 2, and 3), there was lymphoid follicle formation with germinal centers (Figure 1, F).

Immunohistochemical staining for IgG and IgG4 was performed on all 4 cases. Cases had IgG4–positive plasma cell counts ranging from 60 to 110 per high-power field, all above the respective adult location cutoffs (Figure 2, A). The calculated IgG4/IgG ratio ranged from 0.5 to 0.9 (Figure 2, A and B).

Owing to the dense plasmacytic infiltrate, in situ hybridization for κ and λ was performed in 1 case (case 3) to rule out a possible clonal plasma cell proliferation. This case showed κ light-chain restriction in the infiltrating plasma cells, with a κ:λ ratio of approximately 7.5:1 (Figure 2, C and D). PCR-based testing for IgH and IgK gene rearrangements detected a clonal B cell population in the submitted tissue. In situ hybridization for κ and λ was performed retrospectively in cases 1, 2, and 4 but did not show light-chain restriction (κ:λ ratios ranging from 1–2:1).

As a result of the histologic findings, patient 1 was given rituximab for presumed IgG4–related disease with marked improvement in preauricular and eyelid swelling (9 month follow-up). Patient 2 did not have signs or symptoms of...
systemic vasculitis despite her positive ANCA finding; she was given high-dose systemic steroids for her mild symptoms and is currently not taking steroids, without worsening of her eye swelling (16 month follow-up). Patient 3 also did not have signs or symptoms of systemic vasculitis despite her positive ANCA finding; she was given high-dose systemic steroids with taper following resection of the eye swelling/mass and has had no recurrence to date (32 month follow-up). Three months after the left-sided neck biopsy that showed increased IgG4-positive plasma cells, patient 4 developed infection of the left-sided neck mass. The neck mass resection specimen, which included skin and thyroid tissue, showed chronic inflammation, fibrosis, and foreign-body giant cell reaction with histologic features suggestive of inflamed branchial cleft sinus. Given the history of increased IgG4-positive plasma cells on his previous biopsy, IgG and IgG4 immunohistochemical staining were performed and showed 90 IgG4-positive plasma cells per high-power field and an IgG4/IgG ratio of up to 0.5, equivocal for the diagnosis of IgG4-related disease. He continues to have elevated serum IgG4 levels and mild persistent lymphadenopathy but is otherwise asymptomatic and has not been treated for rheumatologic disease (11 month follow-up).

DISCUSSION

This represents the largest series of pediatric IgG4-related disease to date. A large retrospective literature review identified 25 cases of pediatric IgG4-related disease but did not review or confirm the histologic findings seen in those cases. We performed additional literature review and identified a total of 53 cases of IgG4-related disease in children, that is, patients younger than 18 years (Table 3). Including the cases described in this series, the median age of presentation for patients with IgG4-related disease was 13 years (age range, 22 months–17 years), with a slight female predominance (female to male ratio, 30:23; 57% female).

Pediatric IgG4-related disease frequently involves the orbital region (20 of 53 reported cases [38%]). The female predominance is slightly more pronounced than that seen in pediatric IgG4-related disease cases as a whole (female to male ratio, 15:5 [75% female] orbital; female to male ratio, 30:23 [57% female] overall). In contrast to pediatric IgG4-related disease cases as a whole, most patients with orbital involvement do not have concomitant elevation in serum IgG4. In pediatric patients with IgG4-related disease of any site, 16 of 49 (33%) had normal serum IgG4 levels, while 11 of 19 cases with orbital involvement (58%) had normal serum IgG4 levels. By comparison, in adults, orbital IgG4-related disease presents at a median age of about 50 years with a slight male predominance, less marked than seen at other sites. Patients typically present with elevated serum IgG4 levels; normal serum IgG4 levels are reported in only a minority (0%–37%) of patients with adult orbital disease. Disease in adults is usually bilateral, and patients present with eyelid swelling. Extraorbital involvement is seen in at least 70% of adult patients, with frequent involvement of the salivary glands and lymph nodes. Pediatric patients with orbital disease typically present with orbital swelling but only rarely have bilateral involvement (3 of 20 total cases [15%], including cases in this series) and infrequently have extraorbital disease (4 of 20 total cases [20%]). In our series, 2 of the 3 patients with orbital involvement had normal serum IgG4 levels. Extraorbital

### Table 2. Summary of Histologic Features of Immunoglobulin (Ig) G4–Rich Pediatric Head and Neck Lesions

| Case No. | Dense Plasma Cell Infiltrate | Epithelial Infiltrate | Concentric Fibrosis | Storiform Fibrosis | Other Findings |
|----------|-----------------------------|----------------------|--------------------|-------------------|----------------|
| 1        | Present                     | Present (perivascular) | Present (perivascular) | Absent | Present Absent Present (periductal, periglandular) |
| 2        | Present                     | Absent                | Present (perivascular) | Present | Absent Present (microabscesses) |
| 3        | Present                     | Absent                | Absent              | Present (clusters) | Present |
| 4        | Absent                      | Absent                | Absent              | Absent            | Absent |

Abbreviation: N/A, not applicable.
involvement was not identified in any of our patients; 1 patient (case 1) had a lung biopsy 4 years before her orbital biopsy that showed eosinophilic pneumonia but no plasma cell accumulation. Thus, the clinical features in pediatric patients with orbital IgG4-related disease as a whole and in our cohort are distinct from those in adults, with more frequently normal serum IgG4 levels and uncommon bilateral and extraorbital involvement.

Figure 1. Histologic features in cases of IgG4-positive plasma cell-rich lesions. A, An infiltrate of dense, confluent plasma cells was seen in all cases. B, Nonstoriform perivascular fibrosis was seen around small vessels in all biopsies. C and D, A significant eosinophilic infiltrate was seen in all cases, ranging from scattered eosinophils (C) to microabscess formation (D). E, Prominent histiocytosis without granuloma formation was seen in most cases. F, Most cases exhibited prominent lymphoid follicle formation with occasional germinal centers (hematoxylin-eosin, original magnifications ×400 [A through E] and ×200 [F]).
As with IgG4-related disease at other sites, a dense lymphoplasmacytic infiltrate and fibrosis are commonly described histologic features in orbital disease; however, storiform fibrosis and obliterative phlebitis are seen in only 10% of adult cases. Germinal centers and a mild to moderate eosinophilic infiltrate are commonly described. For the lacrimal gland, consensus diagnostic criteria have established a location-specific cutoff of greater than 50 to 100 IgG4-positive plasma cells per high-power field, IgG4:IgG-positive plasma cell ratio greater than 0.4, and the presence of at least 1 characteristic histologic feature (dense lymphoplasmacytic infiltrate, fibrosis, or obliterative phlebitis) highly suggestive of IgG4-related disease. Historically, all reported cases of pediatric IgG4-related disease had at least focally dense plasma cell infiltrate, a minority (8 of 25 [32%]) showed obliterative phlebitis, and storiform fibrosis was seen in 15 of 26 cases (58%). In the current series, all cases showed a dense plasmacytic infiltrate and perivascular fibrosis but lacked storiform fibrosis and obliterative phlebitis. All cases met previously described criteria for IgG4:IgG ratio and IgG4-positive plasma cell counts for location. Eosinophilic and histiocytic infiltrates have been described in previous series, consistent with our finding of histiocytic infiltrates in 3 of 4 cases, at least rare eosinophils in all 4 cases, and eosinophilic microabscess formation in 3. Of note, eosinophilic microabscesses were seen in the lacrimal gland lesion from a patient with previous clinical history of elevated serum IgE level and asthma (case 1), suggesting a role for allergic reaction in the development of IgG4-related disease. Late-onset asthma has been described in adult patients with elevated serum IgG4 levels and orbital involvement, though the nature of the association between asthma and IgG4-related orbital disease remains unclear in these patients. The histiocytic infiltrate in our patients was not consistent with Langerhans cell histiocytosis (negativity for CD1a and Langerin), and clinical workup was negative for systemic involvement, other than in the patient with a prior history of pulmonary nodules (case 1). In all cases, the microbiologic workup was negative and no discrete granulomas were seen, ruling out infectious etiologies for the histiocytic proliferation. An unusual finding in our series was light-chain restriction in 1 case, detected both by in situ hybridization for κ and λ light chains and by PCR analysis. Of note, this patient did not have an elevated serum IgG4 level; serum light chains were not assessed. In adults, light-chain

Figure 2. Immunohistochemical stains for immunoglobulin (Ig) G4 (A) and IgG (B) showed a dense infiltrate of IgG4-positive plasma cells, with up to 110 IgG4-positive plasma cells per high-power field (A) and IgG4:IgG ratios of greater than 0.5 in all cases. In case 3, in situ hybridization for κ (C) and λ (D) light chains showed κ light-chain restriction, with a κ:λ ratio of 7:1 (original magnification ×400 [A through D]).
restriction, even in the context of IgG4-predominant plasma cells, is most commonly associated with plasma cell dyscrasia. Serum light-chain restriction has been reported in a few cases of adult IgG4-related disease, particularly but not invariably in the context of renal insufficiency. In that study, serum light-chain restriction was seen in the context of IgG4-related disease but not in other autoimmune diseases such as systemic lupus erythematosus and Sjögren syndrome. Histologic light-chain restriction was not described. This patient did not have a history of renal insufficiency and is unlikely to have a plasma cell dyscrasia given her age; in addition, orbital swelling responded to resection and immunosuppressive therapy, which would be unusual for a plasma cell dyscrasia. Thus, tissue light-chain restriction and clonal plasma cell proliferation may be a feature of IgG4-related disease in some children, and its presence should not rule out IgG4-related disease as a potential etiology for mass-forming plasma cell-rich lesions in children and young adults.

All 4 patients in our series had elevated ANA levels and 2 of 4 had positive ANCA serologic titer, specifically anti-MPO in both cases. In adults, overlap syndromes between ANCA-associated vasculitis and IgG4-related disease have been described. In children, this phenomenon is less well studied. In both cases in this series with positive ANCA serologic titer, female patients presented with an approximately 1-month history of orbital swelling. Clinical features did not suggest a systemic vasculitis in either case. ANCA positivity, particularly p-ANCA, has been described in 38% (5 of 13) of pediatric cases with reported results for ANCA, including patients with and without orbital involvement. Histologically, orbital mass biopsies from both cases in our series exhibited perivascular inflammation, either lymphocytic (case 2) or neutrophilic/eosinophilic (case 3). Histiocytic infiltrates were a prominent feature in 1 case (case 2); however, there was no evidence of granulomatous inflammation or necrosis as might be seen in ANCA-associated disease. Thus, although these cases may still represent concomitant or unusual initial presentations of ANCA-associated vasculitis or a potential overlap syndrome, the clinical and histologic features do not currently support an ANCA-related process. It is unclear whether these cases represent examples of an overlap syndrome between IgG4-related disease and ANCA-associated vasculitis, whether pediatric patients with IgG4-related disease may have concomitant ANCA serologic titer without ANCA-associated vasculitis, or whether these patients actually have ANCA-associated vasculitis with a misdiagnosis of IgG4-related disease.

The patients in this series were treated with rituximab (case 1), high-dose steroids (cases 2 and 3), or surgical resection without systemic therapy (case 4). All 4 patients had resolution of their symptoms and no recurrence to date (clinical follow-up range, 9–32 months). Prior reports of pediatric IgG4-related disease almost universally use high-dose glucocorticoids as first-line therapy, with immunosuppressive therapy (mycophenolate mofetil, azathioprine, methotrexate, or rituximab) given in refractory cases. There is a single case report of a patient with lacrimal IgG4-related disease treated with partial debulking only, who remained symptom-free after 18 months. It is unclear whether these relatively rare cases of apparently self-resolving IgG4-related disease represent true disease, a distinct clinically benign subtype, or a different disease process. However, this suggests that not all cases of...
apparent IgG4-related disease may require immunosuppressive therapy. Our findings are consistent with previous case reports of IgG4-related disease in children in terms of clinical, serologic, and histologic features. Only a minority of pediatric IgG4-rich lesions show the pathognomonic features of storiform fibrosis and obliterator phlebitis described in adult IgG4-related disease, though these are also not universally seen in adult orbital IgG4-related disease. Instead, prominent features include perivascular fibrosis, eosinophilic and histiocytic infiltrates, and lymphoid follicle formation, which are still supportive of a fibroinflammatory process. Although the lesions evaluated all showed IgG4 counts and IgG4/IgG ratios above the accepted histologic criteria, only 2 of our 4 patients presented with elevated serum IgG4 levels. Our series and literature review highlights a striking feature of normal serum IgG4 levels in pediatric patients with orbital involvement. Thus, a normal serum IgG4 level should not rule out a consideration of IgG4-related disease, particularly in patients presenting with orbital disease. In addition, pediatric orbital IgG4-related disease is less commonly bilateral and extraorbital than in adults. These distinct features raise the possibility that pediatric orbital IgG4-related disease may represent a clinicopathologic diagnosis distinct from both adult IgG4-related disease and nonorbital pediatric IgG4-related disease. Unusual features in our series included positivity for other serum autoantibodies and intralesional light-chain restriction, raising the possibility of overlapping autoimmune and clonal proliferative conditions. Overall, these features make pediatric IgG4-related disease challenging to diagnose by the existing adult criteria. Additionally, given the rarity of the disease in children and reports of self-resolving lesions, they raise the possibility of the a different entity from the systemic fibroinflammatory disease described in adults. Thus, additional characterization of pediatric IgG4-related disease may prove useful for the timely diagnosis and effective treatment of this entity in the pediatric population.

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