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CASE REPORT

Polyclonal hyperviscosity syndrome in IgG4-related disease and associated conditions

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Key Clinical Message

Polyclonal hyperviscosity syndrome (HVS) is rare and has been reported in various disorders of immune dysregulation and lymphoid hyperplasia. IgG4-Related Disease (IgG4-RD) is an emerging disorder often associated with exuberant hypergammaglobulinemia, and this review of seven cases establishes IgG4-RD as an important cause of polyclonal HVS.

Keywords

Hyperviscosity syndrome, IgG4 related disease, polyclonal hyperviscosity.

Introduction

IgG4-related disease (IgG4-RD) is a recently described fibro-inflammatory disease affecting nearly every organ system including lymph nodes, periorbital tissues, salivary glands, kidneys, lungs, breast, prostate, thyroid, lungs, meninges, large vessels, and pancreas [1]. It was first recognized as a systemic disease in 2003, with autoimmune pancreatitis as the canonical manifestation [2], and has garnered increasing international recognition since then. Despite the wide variety of organ manifestations, the histologic appearance: increased IgG4-positive plasma cells, lymphoplasmacytic and eosinophilic infiltrates, storiform fibrosis, and obliterative phlebitis, is consistent across diverse tissues and organs. Lymph nodes and bone marrow are the exceptions to this rule, where the lack of storiform fibrosis (not to be confused with myelofibrosis) and obliterative phlebitis produce more variable findings [3, 4]. The emergence of this entity has provided a unifying diagnosis for many patients with rare conditions previously thought to be unique, organ-specific diseases such as Mikulicz's disease [5], idiopathic retroperitoneal fibrosis [6], and lymphoplasmacytic aortitis [7].

The purpose of this study is to review seven cases of polyclonal hyperviscosity syndrome (HVS). Two of these (Cases 1 and 2) have histologically confirmed IgG4-RD and the rest (Cases 3 to 7) have many features of IgG4-RD. Most patients with IgG4-RD have elevated serum levels of polyclonal immunoglobulin G (IgG), including IgG4. In some cases, serum protein production is exuberant, thus it intuitively follows that some patients with IgG4-RD may be at risk of polyclonal HVS. Serum hyperviscosity is typically associated with monoclonal proteins in patients with B-cell lymphoma and myeloma. However, polyclonal expansion of immunoglobulins causing hyperviscosity has been described in diseases such as rheumatoid arthritis [8, 9], Sjögren's syndrome [10], and HIV [11, 12]. The level of polyclonal IgG necessary to cause symptomatic hyperviscosity varies greatly and depends on factors such as IgG subtype and tendency of the proteins involved to complex with other plasma proteins. For example, IgG1 is nonaggregating and causes an increase in serum viscosity in a linear fashion, with symptomatic HVS typically occurring at concentrations >120 g/L, whereas IgG3 has a tendency to polymerize *in vivo* and can cause HVS at concentrations of 30–40 g/L

[13]. As well, IgG can complex with other serum proteins such as IgM and IgA to cause HVS. Cases of polyclonal HVS are rare, and many have been published as diagnostic dilemmas with no discrete diagnostic assignment possible [14, 15].

Patients and Methods

Seven published cases of polyclonal HVS were reviewed. Cases 1–3 were from the authors' own institutions and thus underwent further review of pathology specimens. Cases 4–7 were identified from the literature and the features suggestive of IgG4-RD are described, but pathology review to definitely confirm IgG4-RD was not possible. Case 1 was previously published as the first case of confirmed polyclonal HVS due to IgG4-RD, and was also the first successful report of purine-analogue therapy in IgG4-RD [16]. This report updates his unique clinical course and ongoing therapy, including recent response to bendamustine therapy. Case 2 had been previously diagnosed with idiopathic hypereosinophilic syndrome when her case was published in 2010 [17], but a pathology review in 2013 demonstrated that she in fact had IgG4-RD. Case 3 is a case of systemic plasmacytosis with hyperviscosity [18], and the laboratory and pathology findings pertaining to IgG4-RD are provided here. We performed literature searches in Pubmed for "Polyclonal hypergammaglobulinemia" and "Hyperviscosity syndrome" and identified case reports of patients with features suspicious for IgG4-RD (Cases 4–7) [15, 19, 20]. We attempted to contact the authors to obtain further information and were able to do so for Case 7. Pathology review to definitively confirm or refute IgG4-RD was not possible in these cases. This study was not intended to be a systematic review of polyclonal HVS in IgG4-RD, but rather a presentation of selected cases which support the diagnostic reasoning of physicians evaluating such patients. As this study involved pathology review of two or fewer cases at the University of British Columbia and the University of Tokyo, and otherwise review of previously published data, ethics approval was not required by either institution.

Case Series

A summary of key Clinical and Laboratory features is presented in Table 1 and Histological Findings, Treatment, and Outcomes in Table 2.

Case 1

This man presented at age 41 with hyperviscosity due to IgG4-RD, as previously described and was extraordinarily refractory to treatment [16]. He eventually responded to fludarabine and rituximab, which was a novel observation in IgG4-RD, but relapsed 1 year later with rising IgG, IgG3, and IgG4 levels. At relapse, treatment with cyclosporine, single agent rituximab, and bortezomib with dexamethasone, yielded no significant response. He was therefore given six cycles of bendamustine 70 mg/m^2 day 1 and 2 and rituximab 375 mg/m^2 day 1, monthly which produced an excellent remission at the time of this report with normalization of his total protein, IgG, and IgG subclass levels. The highly elevated IgG3 level in this patient was likely a major contributor to his HVS. The severe, refractory, progressive nature of his disease exemplifies the need for clinical trials to determine optimal therapy in these patients.

Case 2

This woman presented at age 21 with HVS, episodic angioedema, lymphadenopathy, and eosinophilia, which, after extensive investigation, was thought to be due to idiopathic hypereosinophilic syndrome (HES) [17]. Of note, her case had been reviewed by numerous clinicians and pathologists who are world experts in eosinophilia and lymphoproliferative disorders before this diagnosis was agreed upon. However, her initial workup did not include staining of pathology specimens for IgG4 or serum IgG4 levels. Recent review of her bone marrow biopsy and submandibular lymph node specimen, revealed morphology and IgG4 staining consistent with IgG4 related disease (Fig. 1). Since the initial report, the patient relocated to Asia and was lost to follow up. We have not been able to obtain serum IgG4 levels, but review of her serum protein electrophoresis and immunofixation gels show a large polyclonal, polytypic IgG band in the fast gamma region, where IgG4 is typically located (Fig. 2). Moreover, diagnosis of IgG4-RD requires demonstration of appropriate clinical findings in addition to histologic findings but not necessarily elevated serum IgG4, so this case meets diagnostic criteria for IgG4-RD. She sustained an excellent remission on azathioprine from Nov 2007 to April 2009 (after which she was lost to follow up), which has rarely been reported in IgG4-RD [21].

Case 3

This woman presented at age 49 with chronic erythematosus plaques on her skin and was found to have minor lymphadenopathy and splenomegaly, elevated serum IL-6 levels, polyclonal hypergammaglobulinemia, and fundoscopic findings indicating HVS [18]. She was diagnosed with systemic plasmacytosis based on the clinical findings and histopathology of the skin and

Table 1. Summary of clinical and laboratory features.

Case	1	2	3	4	5	6	7
Reference	Wong et al. 2013[16]	Chen et al. 2010[17]	Noda et al. 2011[18]	Boulanger et al. 2006[19]	Hadler et al. 1977[15]		Simon et al. 2002[20]
Age (years)	41	21	49	14	59	63	41
Gender	Male	Female	Female	Female	Female	Female	Female
Ethnicity	Chinese	Chinese	Japanese	Algerian	African American	African American	Mexican
Clinical Presentation	Polyclonal hyperviscosity syndrome	Polyclonal hyperviscosity syndrome	Polyclonal hyperviscosity syndrome	Polyclonal hyperviscosity syndrome	Polyclonal hyperviscosity syndrome	Polyclonal hyperviscosity syndrome	Polyclonal hyperviscosity syndrome
	Chronic lacrimal hyperplasia	Lymphadenopathy Salivary gland hypertrophy	Erythematous skin plaques	Lymphadenopathy	Weight loss	Mass in inferior cul-de-sac	Xerophthalmia
	Salivary gland hypertrophy	Hepatomegaly	Lymphadenopathy	Splenomegaly	Splenomegaly	Diffuse lymphadenopathy	Xerostomia
	Lymphadenopathy	Episodic angioedema	Splenomegaly	Anemia	Salivary gland hypertrophy	"Striking" parotid gland hypertrophy and dry mouth	Lymphadenopathy
	Coronary artery aneurysmal disease			Proteinuria and microscopic hematuria		Hepatosplenomegaly Ascites, pleural effusions and edema	Hepatic infiltration on CT scan
Eosinophils (giga/L, normal < 0.8)	3.9	10.6	0.5	Normal	Not available	Not available	Not available
Total IgG (g/L, normal < 15)	52.1[1]	77.4	67.7	117	40.35	5.7 (IgG precipitin)	61.90, "increased gamma fraction" on serum electrophoresis
IgG4 (g/L, normal < 1.25)	26.9[1]	n/a[2]	4.23	124	Not available	Not available	Not available
Other immunoglobulins	IgM 5.35 g/L[1]	IgM 2.6 g/L	IgM 2.24 g/L	IgM 0.24 g/L	IgM 2.75 g/L	IgM 2.15 g/L	IgM 18 g/L
	IgA 1.53 g/L[1]	IgA 1.4 g/L	IgA 10.26 g/L	IgA 0.5 g/L	IgA 7.65 g/L	IgA 2.90 g/L	IgA 6.82 g/L
	IgE 1445 μg/L[1] (<430)	IgE 912 μg/L (<430)	IgE 912 μg/L (<430)	IgE 1375 kUI/L (< 100)			
	IgG1 20.2 g/L[1]			IgG1 1.2 g/L			
	IgG2 25.1 g/L[1]			IgG2 0.58 g/L			
	IgG3 16.3 g/L [1]			IgG3 0.084 g/L			
Autoimmune serology	RF > 900 IU/mL (0-15)	RF 246 IU/mL ANA, ENA, ANCA	RF 47 IU/ml ds-DNA 28.0 (<10)	RF negative ANA negative	Not available	Not available	RF 586, ANA 1:80, anti DNA, anti-SSA/ro, anti-SSB/La, anti-Mt,

(*Continued*)

Table 1. Continued.

	ANA, ENA, ANCA negative C3/C4 normal	negative C3/C4 normal	IU/ml Cardiolipin IgG 26 U/ml (<10) Jo-1 19.2 index (<17.9) ANA, SS-A, SS-B negative				anti-smooth negative
Cytokines and C-reactive protein (CRP)	IL-5 43.2 (< 3.5 pg/mL) IL-6 7.3 (<17.4 pg/mL) CRP 2 mg/L	IL-5 9.8 pg/mL	IL-6 45.9 pg/mL (<4 pg/mL) CRP 14 mg/L	CRP 1 mg/L IL-2, IL-4, IL-7, IL-13, MIP-1α, RANTES, hGH levels normal	Not available	Not available	Not available
Viscosity (normal 1.4-1.8)	Unmeasurable before PLEX, 9.7 after PLEX	22.1	3	Not available	12.5	12.1	13

[1]After plasmapheresis (PLEX) – unmeasurable prior to plasmapheresis

[2]IgG subclasses were not done but subsequent review of serum protein electrophoresis and immunofixation gels show a large polyclonal, polytypic IgG band in the fast gamma region, where IgG4 is typically located (Figure 2)

lymph node showing heavy lymphoplasmacytic infiltration [18]. This patient did in fact have a moderately elevated serum IgG4 levels of 4.23 g/L (Table S1) and a subsequent review of the lymph node specimen revealed IgG4-positive cells comprising 10% of IgG-positive cells (Fig. 3). The skin specimen showed only scant IgG4 positive plasma cells. While these findings do not meet diagnostic criteria for IgG4-RD, where an IgG4/IgG plasma cell ratio of > 40%, among other criteria, are required [3, 22], they do suggest an overlap between the pathophysiology of hypergammaglobulinemia in systemic plasmacytosis and IgG4-RD. She responded initially to treatment with oral steroids but subsequently died of sudden unexplained cardiopulmonary arrest.

Case 4

One paper published shortly before the discovery of IgG4-RD describes two patients with a syndrome of polyclonal IgG4 gammopathy with lymphadenopathy and nephropathy [19]. One of these patients was a 14-year-old Algerian female with hyperviscosity syndrome and markedly elevated polyclonal IgG and IgG4 levels (Table S1) requiring plasmapheresis. She responded to cyclophosphamide and prednisone, and then relapsed while on prednisone but subsequently had a sustained remission to hydroxychloroquine. Lymphadenopathy and renal involvement are common in IgG4-RD, although IgG4-RD does not typically respond to antimalarials [23].

Cases 5 and 6

A 59-year-old female and 63-year-old female with multiorgan disease that defied discrete diagnosis were reported in 1977 [15]. These patients had lymphadenopathy and HVS due to polymerizing IgG. Although they were positive for rheumatoid factor, neither had the typical erosive arthritis seen in rheumatoid arthritis. Their course and multisystem involvement were more suggestive of a lymphoproliferative disease reminiscent of the "pseudo-lymphoma" of Sjögren's syndrome. The authors concluded: "rather than argue that a diagnosis of Sjögren's syndrome is justifiable in these two patients, we prefer to postulate that they share with Sjögren's syndrome a common immunopathogenesis for hyperviscosity and lymphoproliferation."

Case 7

Like patients 1, 2, 5, and 6, this patient had features of atypical Sjögren's [20], which is now known to overlap considerably with IgG4-RD [24]. She presented with HVS

Table 2. Summary of histologic findings, treatment, and outcomes.

Case	Organ	Pathological findings	IgG4+ plasma cells (cells/hpf), IgG4+/IgG ratio[1]	Treatment and Outcome	Differential Diagnosis[2]
1	Lacrimal glands	Lymphoplasmacytic infiltrate, peri-ductal fibrosis	96/hpf 56%	Plasmapheresis Failed Steroids, azathioprine, Pegylated interferon alpha 2a Partial response to Rituximab *Fludarabine* and Rituximab (1 year remission) Failed Bortezomib *Bendamustine* and Rituximab given x 6 cycles Oct 2013→ remission	*IgG4 RD confirmed*
	Jugulo-digrastric lymph node	Reactive follicular hyperplasia	> 120/hpf > 80%		
	Bone marrow	Lymphoplasmacytic infiltrate and eosinophilia	> 120/hpf > 80%		
2	Salivary gland	Lymphoplasmacytic infiltrate with reactive follicular hyperplasia, peri-ductal fibrosis, acinar atrophy, scattered eosinophils (Figure 2)	137/hpf 58%	Plasmapheresis Good response to Prednisone	*IgG4 RD confirmed*
	Bone marrow	Polyclonal plasmacytosis and eosinophilia (Figure 2)	98/hpf 63%	Sustained response to azathioprine as steroid sparing agent	
3	Skin	Dense lymphoplasmacytic infiltrate and dermal fibrosis, mostly B cells, and peri-follicular T cells, no light chain restriction, HHV-8 negative.	Sparse IgG4+ cells	Plasmapheresis Response to prednisone	Systemic Plasmacytosis
	Lymph node	Enlarged interfollicular areas with densely packed polyclonal plasma cells	80/hpf 10%	Died of cardiopulmonary arrest.	
4	Cervical lymph node	Massive polytypic interfollicular plasma cell infiltration with normal germinal centers, B and T clonality negative by PCR.	Not available	Plasmapheresis, Steroids and IV cyclophosphamide,	IgG4 RD vs. other lymphoproliferative disorder
	Bone marrow	Normal	Not available	Relapsed on prednisone 0.15 mg/kg/day	
	Kidneys	Enlarged glomerular capillaries filled with plasma-like material and prominent podocytes containing large hyaline cytoplasmic droplets. Lymphoplasmacytic infiltrate in renal interstitial tissue	Not available	Response to hydroxychloroquine, IgG4 down to 4.6 g/L, pt lost to follow up	

(*Continued*)

Table 2. Continued.

Case	Organ	Pathological findings	IgG4+ plasma cells (cells/hpf), IgG4+/IgG ratio[1]	Treatment and Outcome	Differential Diagnosis[2]
5	Salivary glands	Dense infiltration of small lymphocytes with no distortion of underlying exocrine gland structure	Not available	Plasmapheresis	IgG4 RD vs. other autoimmune or lymphoproliferative disorder
	Bone marrow	Erythroid hyperplasia	Not available	Response to chlorambucil and prednisone	
6	Initial lymph node biopsy	Benign lymphoid hyperplasia	Not available	Plasmapheresis	IgG4 RD vs. other autoimmune or lymphoproliferative disorder
	Parotid gland	Dense infiltration of lymphocytes with fibrosis of the underlying exocrine gland	Not available	Failed azathioprine with progressive weight loss, massive pleural effusions, dry eyes and mouth then hyperviscosity Response to plasmapheresis, chlorambucil and prednisone	
	1st Liver biopsy	Chronic aggressive hepatitis	Not available		
	2nd Liver biopsy (after steroids)	Mild postnecrotic cirrhosis and minimal inflammation	Not available		
	Bone marrow	Erythroid hyperplasia	Not available		
	Pleural fluid and pleural biopsy	Lymphocytic exudate, mesothelial hyperplasia	Not available		
	2nd lymph node (supraclavicular)	Pleomorphic lymphocytic and histiocytic infiltrate	Not available		
7	Lymph nodes	Normal	Not available	Plasmapheresis	Atypical Sjögren's syndrome vs. IgG4 RD
	Bone marrow	Normal	Not available	Response to Prednisone 50 mg/day	
	Liver	Portal inflammation, fibrosis, and biliary duct neoformation	Not available		
	Lip	Changes consistent with Sjogren's syndrome	Not available		

[1]For most tissues, a diagnosis of IgG4-RD requires an IgG4/IgG ratio of >40%; the number of IgG4+ cells required varies by tissue type[3]
[2]This differential diagnosis is the opinion of the authors of the present study.

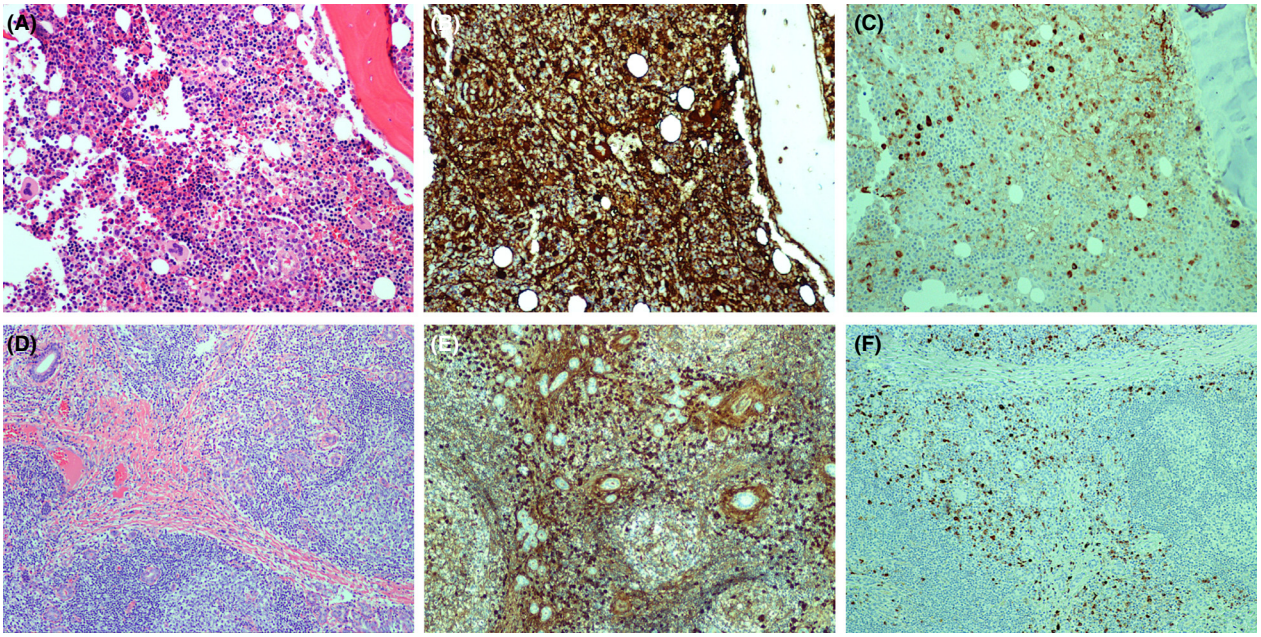

Figure 1. Bone marrow and right submandibular gland specimens from Case 2. (A) Bone marrow H & E showing plasmacytosis and eosinophilia. (B) Bone marrow IgG stain. (C) Bone marrow IgG4 stain, showing 98 IgG4+ plasma cells/hpf and IgG4/IgG ratio 63%. (D) Right submandibular salivary gland H & E showing heavy lymphoplasmacytic infiltrate with reactive follicular hyperplasia, peri-ductal fibrosis, acinar atrophy, and scattered eosinophils. (E) Right submandibular salivary gland IgG stain. (F) Right submandibular salivary gland IgG4 stain showing 137 IgG+ plasma cells/hpf and IgG4/IgG ratio 58%.

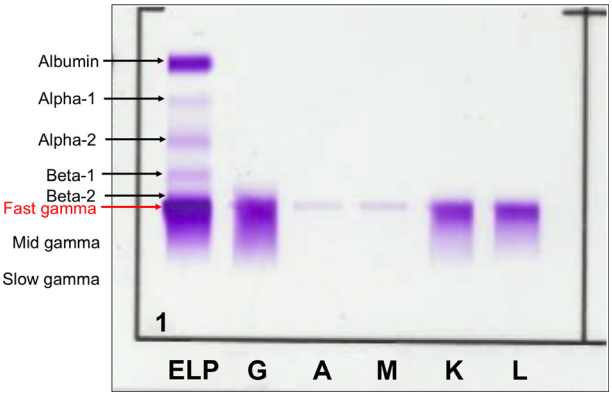

Figure 2. Immunofixation gel from case 2 showing a very dense polyclonal polytypic IgG band in the fast gamma region.

with a prodrome of xerophthalmia and xerostomia for 8 months, with a positive rheumatoid factor but low titer ANA 1:80 and negative anti-SSA/ro and anti-SSB/La. A lip biopsy showed "changes consistent with Sjögren's" but histological details were not provided. The patient developed hepatic infiltration with portal inflammation, fibrosis, and biliary duct neoformation. Although hepatobiliary abnormalities have been described in Sjögren's syndrome, the authors of this case report were not fully convinced that the changes in this case were attributable to Sjögren's (personal communication with Dr. A. Lazo-Langner October 2013). Hepatobiliary involvement is very common in IgG4-RD, but the hypothesis of IgG4-RD as a unifying diagnosis in this case could not be confirmed or refuted without a pathology review, which was not possible.

Discussion

This case series demonstrates that IgG4-RD very likely accounts for a subset of patients with polyclonal HVS, and also provides insight into a number of related issues. While the small number of cases in this rare condition makes it impossible to estimate the prevalence of hyperviscosity in IgG4-RD there are still a number of practical learning points for clinicians. First, IgG4-RD should be considered in the differential diagnosis for patients with polyclonal hypergammaglobulinemia and lymphoid hyperplasia. The largest study of moderate to marked polyclonal hypergammaglobulinemia (defined at gamma globulins >30 g/L) proposed six diagnostic categories: liver disease, connective tissue diseases, chronic infections, hematologic disorders, nonhematologic malignancies, and "other" [25]. None of the patients in that cohort were described as having hyperviscosity

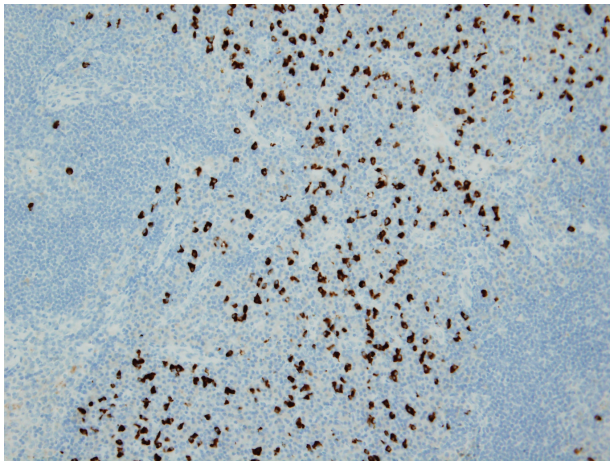

Figure 3. Inguinal lymph node specimen from Case 3, IgG stain (80 IgG+ plasma cells/hpf, IgG4/IgG ratio 10%).

syndrome. Although IgG4-RD certainly has features of autoimmune or connective tissue disease, it also has features of a lymphoproliferative disorder and represents a unique entity. We propose that a seventh category, "IgG4-RD and associated conditions", be considered in the diagnostic approach to polyclonal hypergammaglobulinemia.

Second, many patients with IgG4-RD have peripheral blood eosinophilia, which can be quite pronounced, as in Case 2. Current guidelines for diagnosis and management of eosinophilic disorders recommend exclusion of secondary causes of eosinophilia, evaluation for lymphocyte-variant HES and bone marrow biopsy to exclude systemic mastocytosis as well as cytogenetic studies for clonal abnormalities [26]. Ultimately, many patients with persistent peripheral blood eosinophilia are labeled with idiopathic eosinophilia or idiopathic hypereosinophilic syndrome, which are diagnoses of exclusion. IgG4-RD is a discrete, well-defined entity which should be ruled in or out in these patients with serum IgG4 levels and histological examination of pathology specimens. It should be noted that mild elevations of serum IgG4 are nonspecific [22]. Ultimately, diagnosis of IgG4-RD requires histological confirmation, and even cases with extremely elevated serum IgG4 such as Case 4, must not be classified as IgG4-RD without appropriate histological findings. Tissues from involved organs such as minor salivary glands and pancreatic tissue are generally more reliable than lymph node or bone marrow [3].

Third, distinguishing IgG4-RD from "associated conditions" such as atypical Sjögren's and the hyper-IL-6 syndromes is a diagnostic challenge. Early studies in IgG4-RD demonstrated that many patients previously diagnosed with atypical Sjögren's are better classified as IgG4-RD [24]. Similarly, the overlap between IgG4-RD and the cluster of diseases known as hyper-IL-6 syndromes is increasingly apparent. The hyper-IL-6 syndromes include common diseases such as rheumatoid arthritis, and rare conditions such as idiopathic plasmacytic lymphadenopathy, multicentric Castleman disease, and systemic plasmacytosis. They are associated with elevated IL-6, CRP, and other acute phase reactants. Whereas IgG4-RD is a "fibroinflammatory" disease, the inflammation is typically localized to particular organs and marked elevations in systemic acute phase reactants are observed in less than 10% of patients [27]. This distinction is illustrated by the disparity in IL-6 and CRP levels between Case 1 and Case 3 in this study (Table 1). Increased serum IgG4 and increased IgG4-positive plasma cells in tissue may be present in the hyper-IL-6 syndromes, particularly in systemic plasmacytosis [28] (e.g. Case 3 in this report), although not typically to the same degree as in IgG4-RD [29]. This overlap in clinical, laboratory, and histological features highlights the importance of adhering to standard diagnostic criteria for IgG4-RD.

Fourth, the variable response to treatment in these cases warrants comment. Case 1 clearly has severe, refractory disease illustrating the need to explore more intensive therapies in patients with this disease. To our knowledge, this is the only published case where fludarabine and bendamustine have been used successfully. In contrast, Cases 2 and 4 in this study sustained a prolonged response to milder immunosuppressives including low dose steroids and antimalarials. This variability suggests that polyclonal HVS is due to heterogeneous pathophysiological processes. To date, most of the reports on treatment in IgG4-RD have focused on medications used in autoimmune diseases, most notably corticosteroids [30] and rituximab [31], but lymphoma [16] and myeloma [32] therapies can also be considered in refractory disease.

The discovery of IgG4-RD and its myriad organ manifestations represents a milestone in our understanding of polyclonal hypergammaglobulinemia, hyperviscosity syndrome, and eosinophilia. It exemplifies the importance of continuous learning in clinical practice in order to develop diagnostic expertise [33]. Clinicians must actively incorporate new knowledge on emerging diseases such as IgG4-RD into diagnostic and therapeutic practice, particularly when evaluating rare conditions such as polyclonal HVS.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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