CLINICAL VIGNETTE

The Diagnosis and Clinical Manifestations of IgG4-Related Disease

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Clinical Case

A 37-year-old female with a history of autoimmune hemolytic anemia and splenectomy presented to her ophthalmologist complaining of ocular irritation, which she attributed to contact usage. She was noted to have proptosis on examination. MRI of the orbits revealed enlargement of the lacrimal and parotid glands bilaterally. Parotid ultrasound showed bilateral submandibular gland enlargement with multiple focal hypoechoic and cystic areas. A right submandibular gland core needle biopsy was performed, which showed lymphocytic sialadenitis. There was no fibrosis and obliterative phlebitis. IgG4 immunohistochemical staining showed 50 IgG4+ plasma cells/HPF and a 40% IgG4+/IgG+ plasma cell ratio.

Lab work revealed an elevated white blood cell count of 10.75 x 10E3/uL and platelet count of 569 x 10E3/uL. C-reactive protein was elevated at 1.9 mg/dL with a sedimentation rate of 19 mm/hr. ANA performed by immunofluorescence method was positive at 1:160 (homogenous pattern), but all additional sub-serologies (i.e. dsDNA, Sm, RNP, SSA, SSB) were negative. IgG4 was elevated at 183 mg/dL (reference range: 1-123 mg/dL).

The patient was diagnosed with IgG4-related disease (RD). She was started on prednisone 40 mg daily with rapid improvement of both her clinical and laboratory parameters. However, over the next two to three months, the patient developed recurrence of glandular enlargement when the prednisone dose was tapered to less than 10 mg daily. Given refractory symptoms, she received one course of rituximab (1 g times two doses, administered intravenously approximately 15 days apart).

Discussion

IgG4-RD was first recognized as a distinct disease entity in 2003 when common pathologic features were noted to be present in a number of extra-pancreatic disease manifestations. The exact prevalence of this disease is unknown, and its pathogenesis is poorly understood. Given the heterogeneous presentation and multi-organ involvement of this disease, diagnosis can be difficult (Table 1). It can be often mistaken for malignancy, infection, or other autoimmune conditions. A multi-specialty approach is often required for diagnosis, and careful investigation is required to rule out mimickers.[1]

In 2019, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) developed and validated new classification criteria.[2] These have demonstrated high specificity (98%) and sensitivity (85%). As with all classification criteria established for rheumatological diseases, these criteria are not intended for diagnosis, and are designed to facilitate the recruitment of patients for research studies. Nonetheless, classification criteria can have utility in the clinical setting when evaluating a patient for a rheumatic disease.[3] These criteria have three steps. Step 1 consists of the entry criteria with the patient having characteristic clinical or radiological involvement of an organ characteristically involved in IgG4-RD (e.g. pancreas, salivary glands, bile ducts, orbits, kidney, lung, aorta, retroperitoneum, pachymeninges, thyroid) or classic inflammatory and histopathologic involvement of an organ. Step 2 consists of exclusion criteria, and step 3 is considered only if the patient meets entry criteria and does not have exclusion criteria. During this final step, numerical weight is given to clinical, serologic, radiographic, and pathologic features, and patients with ≥ 20 points fulfill the criteria.

These classification criteria emphasize that clinical, serologic, radiographic, and pathologic information need to be assessed together when evaluating for IgG4-RD. High serum IgG4 concentrations can be useful for screening for the disease in the appropriate clinical scenario, but are neither sensitive nor specific for the disease. Tissue biopsy is typically the gold standard for diagnosis. Classic histopathologic features are: lymphoplasmacytic infiltrate rich in IgG4+ plasma cells, storiform fibrosis, and obliterative phlebitis. These criteria also have exclusion criteria, emphasizing the importance of ruling out other disease processes that can present similarly to IgG4-RD.[2]

In regards to management, prednisone is the initial treatment for all symptomatic patients with evidence of active disease. The dosage of prednisone is adjusted based on body weight and severity of symptoms. In general, a steroid-sparing agent is added when glucocorticoids cannot be tapered due to persistently active disease. While medications such as azathioprine, mycophenolate mofetil, methotrexate, tacrolimus, and cyclophosphamide have all been used with variable success, B cell depletion with rituximab has been found to be the most efficacious.[4,5]

Table 1: Clinical Manifestations of IgG4-RD

Constitutional	Weight loss Fatigue Fever
Musculoskeletal	Arthralgia Enthesopathy
Ophthalmologic	Dacroadenitis Orbital myositis Scleritis
Salivary Glands	Submandibular, parotid, and/or sublingual gland disease Xerostomia
Ear, Nose, Throat	Allergic rhinitis Nasal polyps Chronic sinusitis Nasal obstruction Inflammation or mass lesions of the pharynx or hypopharynx Tracheal inflammation
Thyroid Gland	Thyroiditis
Lymphadenopathy	Involvement of the cervical, supraclavicular, submandibular, axillary, hilar, mediastinal, para-aortic, retroperitoneal, and/or inguinal lymph nodes can occur
Vascular	Aortitis (can be complicated by aneurysms or dissection)
Lungs	Bronchovascular bundle thickening Pulmonary nodules Ground-glass opacities Pleural thickening Interstitial lung disease
Kidneys	Tubulointerstitial nephritis Membranous glomerulonephropathy
Gastrointestinal	Pancreatitis Sclerosing cholangitis Cholecystitis
Other	Retroperitoneal fibrosis Hypertrophic pachymeningitis Hypophysitis Fibrosing mediastinitis Sclerosing mesenteritis Rash

Conclusion

IgG4-RD is an immune-mediated disease that often has a heterogeneous presentation and multi-organ involvement. Many other conditions can mimic IgG-RD, and it is vital to differentiate between these diagnoses given that this can greatly alter management. Glucocorticoid therapy is the mainstay of treatment, although refractory patients may require additional steroid-sparing agents.

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