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CLINICAL VIGNETTE

IgG4 Related Disease: A Clinical Challenge

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Introduction

IgG4 related disease (IgG4-RD) is often missed by clinicians. Recognition of the disease has recently started to improve although, the exact prevalence remains unclear.[1] This disease still has not been assigned its own ICD 10 code. The lack of a code hinders epidemiologic studies. As an immune mediated fibroinflammatory condition, that can affect multiple organs, it can be categorized in several systems. It frequently masquerades as lympho-proliferative neoplasm, plasma cell dyscrasia or other autoimmune conditions. We describe a patient with this condition. His clinical presentation and disease course illustrate the challenges clinicians face in making the right diagnosis. This is followed by a brief review, highlighting clinical clues that can help direct us to the right diagnosis.

Case History

SF is a 78-year-old male presented initially with 5-10 lb. weight loss, eosinophilia and small peripheral adenopathy. He had diabetes mellitus, hypertension, and hyperlipidemia but otherwise had been active. CT scan showed 1-1.5 cm mediastinal adenopathy, subcentimeter submandibular and cervical nodes. SPEP showed monoclonal gammaglobulinemia, 0.7gm/dl. Bone marrow biopsy was unremarkable and submandibular gland aspirate revealed only sialadenitis. The patient was then lost to follow-up for one year.

During that time he developed bilateral lacrimal gland swelling and continued weight loss. He also noted progressive enlargement of submandibular glands and cervical adenopathy. Repeat CT PET scan showed diffuse hypermetabolism in lacrimal glands, cervical, submandibular, hilar and retroperitoneal nodes. Lacrimal gland biopsy by ophthalmology revealed granulomas with multinucleated giant cells. AFB and fungal stains and cultures were unremarkable. Excisional biopsy of his left submandibular gland showed features highly suggestive of IgG4 Related Disease: presence of extensive chronic lymphoplasmacytic inflammation with fibrosis of the submandibular gland, and marked increased IgG4plasma cells. Repeat SPEP showed a band-like pattern in the upper gamma region consistent with IgG4. IgG4 level was elevated at 1245.

His clinical presentation including eosinophilia, hypergammaglobulinemia, swelling in lacrimal glands, salivary glands and lymph nodes, high IgG4 level with characteristic histopathology findings were diagnostic of IgG Related Disease.

Patient was started on prednisone 0.6mg per kg with gradual slow taper. He experienced excellent clinical response, with weight gain, and resolution of adenopathy, and lacrimal gland swelling. His IgG4 level decreased to 246 after 2 months. After 6 months treatment, his prednisone has been tapered to 2.5 gm daily and remains asymptomatic with complete resolution of lacrimal gland, lymph nodes and submandibular gland swelling.

Discussion

IgG4 related disease, is an immune related fibro-inflammatory disorder that could involve many different organ systems.[2] Initial diagnosis could easily be missed by hematologists, as its clinical presentation tends to mimic lymphoproliferative disorders, plasma cell dyscrasia and/or autoimmune conditions.

As in our case the initial presentation of adenopathy, “monoclonal gammopathy” and eosinophilia lead to the impression of possible lymphoma.

Serum IgG4 typically runs in the fast gamma region on the serum protein electrophoresis, though typically polyclonal, high IgG4 levels can be mistaken as monoclonal gammopathy. Histologic diagnosis can also be misinterpreted if obtained with aspiration only.

As in our case only after excision biopsy of the submandibular gland and discussion with pathology, regarding possible IgG4RD, was the typical pattern identified. Repeat SPEP showed band like pattern in the upper gamma region consistent with IgG4, which was previously confused as M spike. Confirmatory IgG4 level was marked elevated. The subsequent response to steroids served to confirm the diagnosis.

It is useful to consider the clinical symptoms and presentations that could guide us to consider IgG4-RD. It is important to remember that IgG4-RD can affect almost any organ.[2] The most recognizable forms include: autoimmune pancreatitis, orbital disease, salivary gland involvement and retroperitoneal fibrosis. Adenopathy is also common, present in 30-60% of patients in large series. Weight loss, present in 40-50%, may indicate exocrine pancreatitis from autoimmune pan-

creatitis, resulting in malabsorption. The clinical course tends to be subacute or chronic, with progressive enlargement of nodes, lacrimal glands and/or mass in kidney, lung or pancreas. Certain combinations of symptoms strongly suggest IgG4 Related Disease. For example, sclerosing cholangitis typically occurs together with pancreatitis. Major salivary gland- parotid or submandibular involvement together with lacrimal enlargement is strongly suggestive of IgG4 RD. Retroperitoneal fibrosis, one of the more recognizable subsets of IgG4RD can also involve the aorta and iliac arteries, and chronic fibrotic changes involving the ureters can result in hydronephrosis. The most common kidney involvement is tubulointerstitial nephritis. Pulmonary involvement is diverse, ranging from lung nodules, hilar adenopathy, pleural thickening, alveolar interstitial opacities presenting with cough and sob. Though infrequent, any other organs can be involved, including stomach, liver, nasopharyngeal, ovary, and prostate.[2]

Other diseases may have similar presentations: Castleman disease, Rosai-Dorfman disease, malignant lymphoma, hypereosinphilic syndromes, plasma cell myeloma, vasculitis and other malignancies.

Lab abnormalities are common, but non-specific, including: high IgG4 levels, elevated 84%, greater than 135 mg/dl. Eosinophilia, polyclonal hypergammaglobulinemia, elevated IgE, presence of ANA, RF, hypocomplementemia. PET scan typically shows hypermetabolism in the involved organs. The patterns on CT and MRI, may help to distinguish IgG4RD with malignancy such pancreatic cancer or cholangiocarcinoma; diffuse infiltrative pattern as opposed to solitary mass.

Histopathology is key in the diagnosis of IgG4RD: Dense lymphoplasmacytic infiltration with storiform fibrosis, obliterative phlebitis and abundant infiltration IgG4- positive plasma cells. Adequate tissue sampling and IgG4 staining are required to fully appreciate the pathologic features. Pathology alone is insufficient to confirm the diagnosis unless correlated with characteristic clinical findings, along with elevate IgG4 concentration.

The comprehensive diagnostic criteria for IgG4 RD include:[3]

1. Clinical examination showing characteristic diffuse/ localized swelling or masses in single or multiple organs.
2. Elevated serum IgG4 concentration, greater or equal to 135 mg/dl.
3. Histopathological evidence shows:
   Marked lymphocyte and plasmacyte infiltration and fibrosis
   Infiltration of IgG4+ plasma cells: IgG4+/IgG+cells > 40% and >10 IgG4+ plasma cells/HPF

Steroids are the first line of therapy with overall response of over 90% and complete response in two thirds of the patients. The IgG4-RD Responder index score[4] help identify patient at high likelihood of relapse to steroid taper and may benefit from long term steroid maintenance. Other immunosuppressive agents used in rheumatology may have a role in remission maintenance. Rituximab is reserved for relapse and is highly effective in salvage, but response is typically short lived. Emerging therapies include anti-CD19 antibodies, fludarabine or bendamustine.

Summary

Our case illustrates several pitfalls in diagnosis of IgG4 RD. The subacute clinical presentation in an elderly male with weight loss, eosinophilia, adenopathy and submandibular salivary gland enlargement is a typical presentation. But the submandibular gland aspirate biopsy was nondiagnostic, showing sialadenitis only. His initial SPEP was mistakenly interpreted as monoclonal. Tissue obtained on aspirate is inadequate for histopathologic diagnosis. Serum IgG4 typically runs in the fast gamma region on the serum protein electrophoresis, though typically polyclonal, high IgG4 levels can be mistaken as monoclonal gammopathy.

The patient was then lost to follow-up. When he reappeared, one year later, he had marked swelling in his lymph nodes, lacrimal, parotid and submandibular glands. Lacrimal gland biopsy by ocular specialist showed “non caseating granuloma”. The presence of granuloma can detract pathologists from making a correct diagnosis of IgG4RD. Though rarely found, granulomas can be an unusual histologic feature for this disease.[5] Because of clinical concern for possible IgG4-RD, excision biopsy of his submandibular gland was then performed. On discussion with pathology, stain for IgG4 on the tissue confirmed the characteristic pattern for IgG4RD. Serum IgG4 level was markedly elevated. Clinical trial of prednisone 0.6 mg/kg was then given with impressive clinical response, further confirming the diagnosis. The patient continues to improve with weight gain, resolution of adenopathy, salivary gland and nodal swelling. He is now tapered to only 2.5 mg daily.

In summary IgG4 RD is an important condition for clinicians, especially hematologists, to recognize. The presentation of adenopathy, weight loss, eosinophilia and hypergammaglobulinemia can lead to erroneous diagnosis of neoplastic disease. IgG subclass measurements can frequently guide us to the correct diagnosis. Confirmation requires histology, an adequate biopsy specimen and discussion with the pathologist.

Once the appropriate diagnosis is made, treatment response is frequently gratifying.

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