54-Year-Old Man With Severe Prostatism, Palatal Mass, and History of Pancreatitis

Kathryn B. Bollin, MD; Meaghan L. Khan, MD; and Steven W. Ressler, MD

A 54-year-old man with a history of benign prostatic hypertrophy, hypothyroidism, and well-controlled insulin-dependent diabetes mellitus secondary to idiopathic pancreatitis presented to our internal medicine consultation clinic. He complained of a lump in the hard palate, dry mouth present for 2 years, and bilateral submandibular gland swelling for which he had been evaluated by an otolaryngologist. A previous biopsy of the hard palate mass had demonstrated florid reactive lymphoid hyperplasia with fibrosis, polyclonal plasmacytosis and increased IgG4-positive plasma cells. He also complained of obstructive urinary symptoms and was found to have a very large and nodular prostate on digital rectal examination. The prostate-specific antigen level was 0.13 ng/mL (reference range, 0-3.2 ng/mL), and results of urinalysis were unremarkable. A computed tomographic scan of the chest from an outside facility showed a mass in the right middle lobe in addition to bilateral renal lesions. Suspicion for a common link among his current symptoms and previous diagnoses was raised.

1. Which of the following is the most likely unifying diagnosis?
   a. Multiple myeloma
   b. Amyloidosis
   c. Metastatic prostate cancer
   d. IgG4-related sclerosing disease (IgG4-RSD)
   e. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes)

   Multiple myeloma is associated with proliferation of plasma cells in the bone marrow, and although ectopic groupings of these cells can occur, this distribution of lungs, kidneys, pancreas, and hard palate would be unusual. Amyloidosis can affect many organs, including heart, liver, lungs, kidneys, and, rarely, pancreas. Amyloid deposition can also be seen in various soft tissues and on prostate biopsy, but it would not be the primary disease in the setting of plasma cells. A prostate-specific antigen level of 0.13 ng/mL would not be consistent with metastatic prostate cancer in this setting, and involvement of the hard palate would be unusual. IgG4-RSD involves lymphoplasmacytic infiltrates with notable IgG4-concentrations in various organs and soft tissues and is consistent with this patient’s presentation. Typical manifestations include autoimmune pancreatitis with or without involvement of kidneys, liver, biliary tree, gallbladder, prostate, retropertioneum, lungs, and thyroid and salivary glands, although numerous other areas of involvement have been reported in the literature. POEMS syndrome is also a plasma cell disorder, but typically it is characterized by a monoclonal plasma cell population on biopsy. Organ involvement with POEMS more characteristically involves the liver and spleen.

The patient had become insulin dependent since his episodes of “idiopathic pancreatitis” 12 years earlier. We hypothesized that he likely had autoimmune pancreatitis (AIP) related to IgG4-RSD.

2. Which one laboratory test would have been most helpful in differentiating AIP from idiopathic pancreatitis?
   a. Peripheral antineutrophil cytoplasmic autoantibody
   b. Sedimentation rate and C-reactive protein
   c. Serum IgG4
   d. Carcinoembryonic antigen
   e. Carbohydrate antigen 19-9

   The presence of peripheral antineutrophil cytoplasmic autoantibody in the serum can be associated with primary sclerosing cholangitis, primary biliary cirrhosis, and chronic active hepatitis, but it is not helpful in diagnosing AIP. Sedimentation rate and C-reactive protein are nonspecific and may be elevated in any inflammatory condition of the pancreas. Serum IgG4 levels are commonly elevated with AIP along with total serum IgG. An elevated IgG4 subclass level would have been helpful in diagnosing AIP in this patient and could have changed his treatment. In fact, an elevated serum IgG4 level is part of the major diagnostic criteria set forth in both the Mayo Clinic and the Japanese guidelines for diagnosing AIP.1–3 Carcinoembryonic antigen and carbohydrate antigen 19-9 are elevated in various intra-abdominal malignancies and inflammatory conditions and would not be specific to AIP.

Positron emission tomography–computed tomography (PET-CT) showed areas of hypermetabi-
bolic uptake in the following organs: submandibular glands, thyroid, bilateral central bronchioles, pancreas, prostate, and 2 local areas in the kidneys. These findings, combined with typical histopathologic and serum findings, confirmed the diagnosis of IgG4-RSD.4

3. Which of the following should be initial treatment for IgG4-RSD in this patient?
   a. Rituximab
   b. Plasmapheresis to decrease circulating IgG4
   c. Bortezomib
   d. No treatment at this time
   e. Corticosteroids

Rituximab is a monoclonal antibody that triggers lysis of CD20+ B cells. It has been reported to be effective for second-line therapy for various manifestations of IgG4-RSD when first-line therapy has failed.3 Plasmapheresis has not been reported in the literature to date as a treatment option. Bortezomib, a proteasome inhibitor that is cytotoxic to plasma cells, has indications for the treatment of multiple myeloma and mantle cell lymphoma. There are some initial reports of its use as a second-line therapy for IgG4-RSD.5,6

Withholding treatment has been entertained in some cases of AIP, especially when there are no symptoms, because occasional cases of spontaneous remission occur.7 However, this patient has experienced significant morbidity from this disease in the form of pancreatic endocrine dysfunction, hypothyroidism, and very problematic lower urinary tract symptoms. As such, treatment to prevent further complications of this fibroinflammatory process would be indicated. Oral corticosteroids are clearly indicated for symptomatic pancreatic or biliary disease and are the generally accepted therapy for extrapancreatic manifestations, particularly when symptomatic.

Treatment was initiated with oral prednisone at 40 mg daily. Adjustments to the patient’s insulin regimen were made, and follow-up computed tomographic imaging at 6 weeks showed significant reductions in the affected areas of the lung, pancreas, salivary and thyroid glands, prostate, and kidneys. However, at 10 months of treatment, after efforts to taper prednisone, he was found to be cushingoid and complained of worsening symptoms of prostatitis. It was felt that alternative treatment was in order for refractory disease. A chemotherapeutic regimen with CyBORG-D (cyclophosphamide, bortezomib, dexamethasone) was started. Shortly thereafter the patient began experiencing relief from obstructive urinary symptoms, although he had headaches and neuropathic pain affecting his hands and feet. An electromyelogram showed a new mild sensory polyneuropathy.

4. Which one of the following is the most likely cause of the patient’s peripheral neuropathy?
   a. IgG4-related peripheral neuropathy
   b. Diabetic peripheral neuropathy
   c. Bortezomib
   d. Cyclophosphamide
   e. Dexamethasone

No specific neuropathy has yet been well described with IgG4-RSD. Diabetes is associated with various neuropathies, and corticosteroid use may worsen blood glucose control and end-organ complications. However, our patient’s diabetes had been well-controlled before treatment. Bortezomib is associated with predominantly sensory peripheral neuropathy in up to half of all patients treated; this effect often limits ongoing therapy with this drug. The temporal association with bortezomib treatment makes this the more likely culprit than diabetes. Cyclophosphamide is not typically associated with neuropathy. Dexamethasone can be associated with central nervous system effects, including euphoria, insomnia, and depression, and long-term use rarely is associated with pseudotumor cerebri. However, dexamethasone is not typically associated with neuropathy, although proper blood glucose management is necessary, particularly in patients with diabetes.

Although our patient was initially responsive to 40 mg of prednisone daily, his symptoms worsened when the dosage was tapered over 10 months to 10 mg. We then treated with 3 cycles of bortezomib (provided under compassionate use), which improved the obstructive urinary symptoms but caused a severe peripheral neuropathy. Fourteen months after making the diagnosis of IgG4-RSD, we transitioned treatment to rituximab, which has been successful in patients with IgG4-RSD refractory to immunosuppressive agents, such as methotrexate, azathioprine, 6-mercaptopurine, and mycophenolate mofetil. Rituximab is an anti-CD20 B lymphocyte-depleting antibody. With depletion of B cells, the pool of IgG4-bearing plasma cells is eliminated, likely inhibiting the fibroinflammatory process in IgG4-RSD.5 Now, 5 months after completion of 4 cycles of rituximab, our patient’s urinary symptoms are negligible and the IgG4 level is 121 mg/dL (reference range, 2.4-121 mg/dL). He receives follow-up care by a neurologist for persistent peripheral neuropathy controlled with nortriptyline and methadone, and he continues to receive follow-up care for IgG4-RSD in our hematology clinic.
5. Disease remission in patients with AIP most consistently correlates with which one of the following?
   a. Glucocorticoid therapy
   b. Normalization of serum IgG4 concentration
   c. Radiologic remission
   d. Use of nonsteroidal immunosuppressive agents
   e. Age at onset

There are few long-term prognostic data about patients with extrapancreatic IgG4-RSD; however, several studies have contained follow-up for patients with AIP. While some patients with AIP enter spontaneous remission, others progress to systemic disease and even death from organ failure. Glucocorticoids have most consistently correlated with remission rates and shorter duration to remission.\(^5\) Whereas monitoring of serum IgG4 concentrations and radiologic changes is helpful, correlation with disease remission is less certain. It is recommended that nonsteroidal immunosuppressive agents be reserved for patients with either intolerance to glucocorticoids or recurrent or refractory disease. Long-term follow-up of these patients is insufficient to identify effects on remission. There are no data evaluating age at onset with disease remission.

DISCUSSION

IgG4-RSD is a clinicopathologic entity characterized by infiltration of various organs by IgG4-positive plasma cells and T lymphocytes. Its discovery stems from observational and clinical research of patients with AIP such that AIP is now considered a pancreatic manifestation of IgG4-RSD.\(^4\,^8\) The mechanism of disease has yet to be discovered, and the specific role of IgG4 antibodies is unclear. Their role may be pathogenic or perhaps protective against an antigen-mediated chronic inflammatory process.

Clinical features of IgG4-RSD include a male predominance, with a mean age at diagnosis of 66.5 years.\(^7\) Initial presenting symptoms are specific to site of organ involvement and often involve compromise in exocrine or endocrine function.\(^9\) The spectrum of disease ranges from single organ involvement, such as the pancreas or within the hepatobiliary tract, to multiple sites, as in our patient. Typical organ disease includes autoimmune pancreatitis, sclerosing cholangitis, saladenitis, thyroiditis, interstitial pneumonia, tubulointerstitial nephritis, prostatitis, aortitis, colitis, retroperitoneal fibrosis, and lymphadenopathy.\(^4\,^10\,^11\)

The diagnosis depends on obtaining a tissue sample and identifying the histologic triad of lymphoplasmacytic infiltrate, sclerosis, and obliterator phlebitis. Three patterns of histologic morphology are seen in extranodal sites, likely representing various stages in the fibroinflammatory process: pseudolymphomatous, mixed, and sclerosing. Staining for IgG4 will support the diagnosis and distinguish between IgG4-RSD and lymphoma.\(^1\)\(^1\) A baseline serum IgG4 concentration should be measured because this, in addition to serial imaging and symptom management, is helpful in monitoring treatment response. Higher serum concentrations of IgG4 are seen in patients with greater organ involvement, and discovery of the disease in a single organ should prompt investigation for multiorgan involvement.\(^1\)\(^1\) PET-CT was helpful in demonstrating the scope of disease in this patient and shed light on the probable causes of his previous pancreatitis and more recent hypothyroidism. Furthermore, the clinical and serologic improvement in this patient largely correlated with improvements on serial PET-CT imaging. At present, there is a paucity of literature on the utility of PET-CT for diagnosing and managing this disease.\(^1\)\(^2\)

Confirming the diagnosis is essential so that treatment can be administered before development of organ failure from the fibroinflammatory process. Establishing the diagnosis is also important to avoid surgical morbidity, as often the masses, or pseudotumors, can be difficult to distinguish from malignancies.\(^2\,^5\)

The clinical symptoms of IgG4-RSD typically improve with systemic corticosteroid therapy, but in refractory cases nonsteroidal immunosuppressant or chemotherapeutic agents are required to induce and maintain remission. Although remarkable strides have been made in understanding this disease, long-term prognosis remains unclear.

Correspondence: Address to Steven W. Ressler, MD, Department of Consultative Medicine, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259 (ressler.steven@mayo.edu).

REFERENCES

1504-1507.
8. Khosroshahi A, Stone JH. A clinical overview of IgG4-related
IgG4-related disease: historical overview and pathology of
10. Bateman AC, Deheragoda MG. IgG4-related systemic scleros-
ing disease - an emerging and under-diagnosed condition.
11. Cheuk W, Chan JK. IgG4-related sclerosing disease; a critical
appraisal of an evolving clinicopathologic entity. Adv Anot
positron emission tomography in the evaluation of distribution
and activity of systemic lesions associated with autoimmune

CORRECT ANSWERS: 1. d, 2. c, 3. e, 4. c, 5. a