A 48-year-old man with a history of chronic rhinosinusitis, gastroesophageal reflux disease, and diet-controlled non–insulin-dependent diabetes mellitus presented to our pulmonary consultation clinic with chronic dry cough, dyspnea, fatigue, and anorexia of 4 months’ duration. The patient was taking montelukast, 10 mg once daily, and fluticasone nasal spray twice daily. Physical examination revealed normal vital signs with an oxygen saturation of 95% while the patient breathed room air in addition to scattered fine lung crackles on auscultation bilaterally. Prior work-up done by the patient’s primary care physician revealed a white blood cell count of 8.0 × 10^9/L, hemoglobin level of 16 g/dL, platelet count of 220 × 10^9/L, serum sodium level of 143 mmol/L, serum potassium concentration of 4.7 mmol/L, creatinine level of 1.0 mg/dL, and erythrocyte sedimentation rate (ESR) of 5 mm/h, all of which were within the reference range. Pulmonary function tests were also obtained before presentation and revealed a forced expiratory volume in the first second of expiration of 68% of predicted, a forced vital capacity of 75% of predicted, a forced expiratory volume in the first second of expiration to forced vital capacity ratio of 82%, and a diffusing capacity of the lungs for carbon monoxide of 73%. Chest computed tomography (CT) revealed bilateral hilar lymphadenopathy and extensive bilateral micronodular opacities. Transbronchial lung biopsy revealed noncaseating granulomas.

1. Which one of the following would be inconsistent with the patient’s presentation?
   a. Tuberculosis
   b. Sarcoidosis
   c. Histoplasmosis
   d. Polyarteritis nodosa (PAN)
   e. Blastomycosis

Tuberculosis can have a presentation similar to our patient’s and in addition can cause lung granulomas. Granulomas seen in tuberculosis are typically caseating granulomas, but tuberculosis should be considered in the differential diagnosis in this case. Common presenting symptoms in patients with sarcoidosis include cough, dyspnea, fatigue, malaise, and fevers. Pulmonary imaging often reveals abnormalities. Bilateral hilar adenopathy is a classic finding on chest radiography and high-resolution CT. In sarcoidosis, the histopathologic feature is noncaseating granuloma. Histoplasmosis can present with fatigue, cough, and shortness of breath. Morphological findings in biopsy specimens from patients with histoplasmosis include caseating and noncaseating granulomas. PAN is a systemic necrotizing vasculitis that typically affects medium-sized arteries. PAN can affect virtually any organ but has a striking tendency to spare the lungs, making it the least likely explanation for this patient’s findings. Blastomycosis can present with features similar to the other options and can cause caseating and noncaseating granulomas.

Further testing revealed negative results of fungal serologies, histochemical stains negative for fungal and mycobacterial organisms, and negative results on anti–proteinase 3 antineutrophil cytoplasmic antibody and anti–myeloperoxidase antineutrophil cytoplasmic antibody testing. Sarcoidosis was initially diagnosed, and prednisone treatment was initiated. The patient subsequently had...
development of multiple ecchymoses and petechiae, and immune thrombocytopenia was diagnosed, which was successfully treated with prednisone. Four months after prednisone treatment, he was hospitalized for abdominal pain and was found to have acute pancreatitis. Abdominal imaging revealed diffuse “sausage-shaped” pancreatic enlargement with a featureless border and effacement of the lobular contour.

Subsequently, the patient returned to the clinic with new bilateral upper eyelid swelling, dry eyes, and worsening sinusitis. On physical examination, he had enlarged lacrimal glands bilaterally. Follow-up abdominal CT revealed multifocal lobulated masslike lesions in both kidneys bilaterally.

2. In light of the findings thus far, which one of the following is the most likely diagnosis?
   a. Sarcoidosis
   b. Disseminated tuberculosis
   c. Granulomatosis with polyangiitis
   d. Disseminated fungal infection
   e. IgG4-related disease (IgG4-RD)

   The abdominal CT findings at the time the patient was diagnosed with acute pancreatitis are typical of autoimmune pancreatitis (AIP). Ocular involvement in sarcoidosis is well documented; sarcoidosis can involve the orbit, anterior and posterior segments of the eye, conjunctiva, lacrimal glands, and extraocular muscles, which may explain this patient’s symptoms. However, it would be unlikely for sarcoidosis to cause AIP and idiopathic thrombocytopenic purpura (ITP). Similarly, it would be unusual for tuberculosis to cause AIP or ITP, making this option unlikely. Although granulomatosis with polyangiitis can cause recurrent sinusitis in addition to renal involvement, it would be unlikely to cause the kidney masses seen on CT; it is also unlikely to result in AIP or ITP. Likewise, disseminated fungal infections are not typically associated with AIP or ITP. IgG4-related disease is an immune-mediated disorder that can involve multiple organs. It typically causes AIP, chronic sinusitis, and tumorlike swelling of involved organs, as observed in this case. As a result, IgG4-RD is the most likely cause in this case.

   The overall impression was that the patient’s presentation is likely secondary to IgG4-RD, and additional tests were obtained to confirm the diagnosis.

3. Which one of the following tests will be the criterion standard in confirming the diagnosis?
   a. Serum IgG4 measurement
   b. Serum angiotensin-converting enzyme (ACE) level
   c. Biopsy for histopathologic analysis and immunohistochemical staining
   d. ESR and C-reactive protein (CRP) measurement
   e. Blood plasmablast concentrations

   Whenever IgG4-RD is suspected, serum IgG4 levels should be measured, and isolated elevated levels are a major aid in diagnosis. However, serum IgG4 testing has poor specificity and low positive predictive value given that multiple non—IgG4-RD conditions are associated with elevated serum IgG4 levels. Serum ACE level can be elevated in patients with sarcoidosis. However, serum ACE elevation is not seen in IgG4-RD, and it has limited utility as a diagnostic test for sarcoidosis because of its poor sensitivity and specificity. International consensus guidelines outline the histopathologic and immunohistochemical features that support the diagnosis of IgG4-RD, and in the proper clinical setting, these histopathologic and immunohistochemical features can be viewed as diagnostic. According to the international consensus guidelines, diagnostic confirmation by biopsy is strongly recommended for the exclusion of malignancies and other IgG4-RD mimics. The ESR and CRP are nonspecific and can be elevated in any inflammatory condition. Blood plasmablast concentration may be a better biomarker than serum IgG4 levels. Plasmablasts are a potentially useful biomarker for diagnosing IgG4-RD, assessing response to treatment, and determining the appropriate time for re-treatment. However, measurement of
plasmablasts, particularly IgG4 plasmablasts, is not widely available for routine testing.

In our patient, serum IgG4 levels were measured and were elevated at 1200 mg/dL (reference range, 2.4-121.0 mg/dL). The ESR and CRP were within normal limits. Biopsies were obtained from the left orbital lacrimal gland and surrounding soft tissue nodules. Biopsy results in our patient were negative for malignancy but revealed IgG4+ plasma cell infiltrates in addition to storiform fibrosis and obliterative phlebitis. Additionally, the patient had an elevated IgE level of 350 kU/L (reference range, <214 kU/L) and eosinophilia (eosinophil count of 1.2 × 10^9/L). The biopsy findings, elevated serum IgG4 level, and the patient’s clinical presentation were sufficient to diagnose IgG4-RD.

4. Which one of the following is the most appropriate initial treatment for this condition?
   a. Glucocorticoids
   b. Azathioprine
   c. Methotrexate
   d. Rituximab
   e. No treatment is warranted at this time

Glucocorticoids are the first-line agent for remission induction in patients with active, untreated IgG4-RD unless contraindicated. Azathioprine, methotrexate, mycophenolate mofetil, and 6-mercaptopurine have all been used as corticosteroid-sparing agents in the treatment of IgG4-RD. However, the efficacies of these agents have not been evaluated in prospective trials, and there are few data overall to support the effectiveness of corticosteroid-sparing agents in the treatment of IgG4-RD. Data from retrospective studies suggest that treatment with rituximab is effective for remission induction in IgG4-RD. Rituximab is typically used for remission induction in patients who do not respond to corticosteroids and in patients in whom corticosteroids are contraindicated. Given that our patient had been taking corticosteroids for almost 2 years for presumed sarcoidosis and the dosage could not be decreased below 10 mg/d because of persistent dyspnea and pulmonary infiltrates and the recent episode of AIP, ITP, and multiorgan involvement, proceeding with no treatment will be inappropriate.

A regimen of prednisone, 40 mg/d, was initiated, with inadequate response. Treatment was switched to intravenous rituximab, 1000 mg in 2 doses 2 weeks apart for remission induction.

5. Which one of the following is correct about IgG4-RD?
   a. Decreased eosinophil count can be seen in the peripheral blood
   b. Breast involvement is not a feature of this disorder
   c. Complement levels are typically elevated in this disease
   d. Retroperitoneal fibrosis is a known subset of this disorder
   e. Skin involvement is not a feature of this disease

Patients with IgG4-RD may have eosinophilia in the peripheral blood rather than eosinopenia. Breast involvement in IgG4-RSD has been described as both inflammatory pseudotumors within breast tissue and IgG4-related sclerosing mastitis. Serum complement levels are typically decreased rather than increased in IgG4-RD. Retroperitoneal fibrosis can result from infections, radiation, drugs (such as ergot alkaloids), malignancy, and trauma. “Idiopathic” retroperitoneal fibrosis is a rare event. In recent years, it has become clear that in a subset of patients with idiopathic retroperitoneal fibrosis, the disorder is in fact occurring in the setting of IgG4-RD. Skin involvement has been described in IgG4-RD in the form of cutaneous pseudolymphoma.

The patient was followed up in the clinic 3 months after remission induction and had notable improvement in his symptoms. Follow-up CT confirmed an excellent response to treatment with complete resolution of the orbital pseudotumors and the kidney masses.

DISCUSSION

IgG4-related disease is an increasingly recognized multiorgan immune-mediated condition. This entity includes a constellation of
disorders that share particular pathologic, serologic, and clinical features. It typically affects middle-aged and older men, with a male to female ratio of 3:1 in contrast to other autoimmune diseases. Clinical presentation depends on the organs affected, and manifestations of IgG4-RD are recognized in nearly every organ system.

IgG4-RD includes, but is not limited to, type 1 autoimmune pancreatitis, IgG4-associated cholangitis, chronic sclerosing sialadenitis (Küttner tumor), bilateral, symmetrical, painless swelling of the lacrimal and salivary glands (Mikulicz disease), chronic sclerosing dacryoadenitis, and inflammatory orbital pseudotumors, retroperitoneal fibrosis, aortitis, fibrous variant of Hashimoto thyroiditis in addition to Riedel thyroiditis, IgG4-related sclerosing mastitis, pulmonary inflammatory pseudotumors and interstitial pneumonias, inflammatory pseudotumors of the kidney, hyophysitis, IgG4 pachymeningitis, prostatitis, cutaneous pseudolymphoma, localized and generalized lymphadenopathy, and constrictive pericarditis.

Currently there is no pathognomonic test to diagnose IgG4-RD. However, the presence of unexplained enlargement or swelling of one or more organs or tissue organs, peripheral eosinophilia, hypergammaglobulinemia, elevated serum IgE levels, and hypocomplementemia should raise the suspicion for IgG4-RD. Elevated IgG4 levels are a major aid in diagnosis. However, elevated levels are not sufficient for the diagnosis of IgG4-RD. Additionally, blood plasmablast measurement is helpful for diagnosis and assessing response to treatment. However, measurement of plasmablasts, particularly IgG4 plasmablasts, is not widely available for routine testing.

According to the international consensus guidelines, the results of clinical assessment, laboratory evaluation, and imaging studies are often insufficient to distinguish IgG4-RD from malignancy and other IgG4-RD mimics, and diagnostic confirmation by biopsy is strongly recommended. The presence of typical histopathologic features, including the existence of numerous IgG4+ plasma cells within affected tissue, is the criterion standard for the diagnosis of IgG4-RD. Findings of storiform fibrosis and obliterator phlebitis heighten diagnostic specificity, but clinicopathologic correlation is always essential. Therefore, to confirm the diagnosis of IgG4-RD, a combination of clinical, laboratory, appropriate radiologic studies, and histopathologic findings is required.

Our patient initially had noncaseating granulomas on biopsy, and hence sarcoidosis was diagnosed. Although an unusual finding, the presence of granulomas should not preclude a diagnosis of IgG4-RD in the appropriate clinicopathologic context. This interesting case should remind readers that sarcoidosis is a diagnosis of exclusion even in the presence of biopsy features compatible with sarcoidosis.

For remission induction, glucocorticoids are the first-line agent. Rituximab can be used in patients who do not respond to glucocorticoids or in whom glucocorticoids are contraindicated. According to the international consensus guidance statement on the management and treatment of IgG4-RD, following successful induction, certain patients benefit from maintenance therapy. This can be achieved by low-dose glucocorticoids or rituximab.

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Correspondence: Address to Eva M. Carmona, MD, PhD, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (carmona.eva@mayo.edu).

REFERENCES


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