IgG4-related Systemic Disease in a Native American Man

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Abstract

IgG4-related systemic disease is a recently described entity that can elude even the most astute diagnostician. Patients with the disease, characterized by the infiltration of polyclonal IgG4-positive plasmacytes, can present with single or multi-organ involvement. Manifestations include dacryoadenitis, sialadenitis, thyroiditis, pneumonitis, retroperitoneal fibrosis, pancreatitis, sclerosing cholangitis, tubulointerstitial nephritis, prostatitis, and hypophysitis. We describe a biopsy-confirmed case with extensive multi-organ involvement, including hypophysitis, dacryoadenitis, retroperitoneal fibrosis and tubulointerstitial nephritis. By reporting this case, we hope to bring IgG4-related systemic disease to the attention of the broader medical community as it is an elusive disease that commonly responds to systemic corticosteroids.

Key words: IgG4-related systemic disease, IgG4

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Introduction

IgG4-related systemic disease is an immunoglobulin deposition disease characterized by infiltration of organs by IgG4-positive plasma cells. Manifestations include retroperitoneal fibrosis, dacryoadenitis, sialadenitis, thyroiditis, pneumonitis, pancreatitis, sclerosing cholangitis, tubulointerstitial nephritis, prostatitis, and hypophysitis (1, 2). Regardless of organ involvement, biopsy with review of histopathology and immunohistochemical staining for IgG4 are essential for diagnosis. When diagnosed, IgG4-related systemic disease can often be successfully treated with systemic corticosteroids (1). Here, we present an interesting case of IgG4-related systemic disease in a patient with multi-organ involvement. Following the case report we review the diagnosis and management of IgG4-related systemic disease.

Case Report

A 55-year-old Native American man was transferred to our inpatient medicine service for further evaluation of a 6-week history of 16 kg unintentional weight loss, intermittent fevers, headache, fatigue and right periorbital swelling. More recently, he complained of polyuria, dry mouth and intermittent diplopia. An exhaustive review of systems iden-

tified no other symptoms. Prior medical history included psoriasis, Raynaud's phenomenon, and primary hypothyroidism.

Upon admission, the patient had a temperature of 36.8 degrees Celsius, heart rate of 85 beats per minute, blood pressure of 92/60 mmHg, respiratory rate of 16 breaths per minute, and an oxygen saturation of 100% on room air. He appeared cachectic, and had a non-tender, right supraorbital swelling. His integument, cardiac, pulmonary, abdominal, neurologic, musculoskeletal and lymph node exams were normal. Genital exam revealed small, soft testicles.

Laboratory studies were significant for a white blood cell count of $6.9 \times 10^9/L$, a hemoglobin of 9.0 g/dL, mean corpuscular volume of 79.1 fL, a platelet count of $450 \times 10^9/L$, absolute reticulocyte count of $24.3 \times 10^9/L$, sodium of 150 mmol/L and serum osmolality of 296 mOsm/kg (275-295). Remaining electrolytes, aminotransferases, creatinine, bilirubin, glucose, and total protein were within normal limits. Urinalysis showed 4-10 WBCs, 4 mg/dL protein, and an osmolality of 66 mOsm/kg (300-800). Urine gram stain was negative. Peripheral smear was remarkable for microcytic, hypochromic red blood cells with rouleaux. A Cosyntropin stimulation test revealed adrenal insufficiency with cortisol levels of 2.5 mcg/dL at 0 minute, 12 mcg/dL at 30 minutes, and 13 mcg/dL at 60 minutes. Total and free testosterone levels were undetectable. Luteinizing hormone level was 0.4

Figure 1. MRI Head-Lacrimal and Pituitary Glands. A-Arrow: Mass-like enhancing enlargement of the right lacrimal gland with a mass effect on globe; B-Circle: Enlargement of pituitary and infundibulum with abnormal enhancing tissue extending over the posterior aspect of sella into the prepontine space.

Figure 2. CT Abdomen-Bilateral Renal Masses and Retroperitoneal Fibrosis. A&B-Circles: Enhancing renal masses that do not demonstrate arterial hyperenhancement; Arrows: Retroperitoneal fibrosis surrounding the aorta at different levels.

IU/L (1.8-8.6) and follicular-stimulating hormone was 1.8 IU/L (1.1-12.9). TSH was 40.4 mIU/L (0.3-5.0) with a free thyroxine level of 0.9 ng/dL (0.8-1.9). Blood and urine cultures were negative. HIV, CMV, EBV, Hepatitis B/C, Lyme, Anaplasma, Ehrlichia, Q Fever, Rickettsial, and fungal serologies were negative. QuantiFERON was negative. Erythrocyte sedimentation rate and c-reactive protein were both elevated at 90 mm/h and 99.7 mg/L, respectively. Anti-nuclear antibody titers were negative. Rheumatoid factor, tissue transglutaminase antibody, and cryoglobulins were negative. Angiotensin-converting enzyme levels were normal. P-ANCA was positive and myeloperoxidase antibody titer was elevated at 14.3 U/mL. Heavy metal and vitamin levels were unremarkable. Serum protein electrophoresis with im-

munofixation showed a polyclonal hypergammaglobulinemia, and urine protein electrophoresis with immunofixation was unremarkable.

A head magnetic resonance image was obtained, revealing an enhancing right lacrimal gland mass and heterogeneous enlargement and infiltration of the pituitary and infundibulum (Fig. 1). Review of the referring hospital's computed tomography of the chest, abdomen and pelvis showed mediastinal lymphadenopathy, hilar lymphadenopathy and bilateral renal masses with retroperitoneal fibrosis (Fig. 2).

Review of the renal mass biopsy performed by the referring hospital revealed chronic tubulointerstitial nephritis. A lacrimal gland biopsy performed at our institution showed chronic sclerosis, parenchymal destruction, fibrosis, and

Figure 3. Lacrimal Gland Biopsy (40× magnification). A-Hematoxylin and eosin stain showing sclerosis of the glandular parenchyma with lymphoplasmacytic infiltrate; B-IgG4 immunoperoxidase staining reveals >10 cells/hpf.

Figure 4. Head to Toe. Reported organ involvement in IgG4-related systemic disease.

lymphoplasmacytic infiltrate. Serum total IgG levels were elevated at 1,800 mg/dL (600-1,500) with a normal IgG4 level of 127 mg/dL (8-140). Of note, however, the patient had been started on physiologic doses of hydrocortisone one week prior to the measurement of IgG levels. Because of our clinical suspicion for IgG4-related systemic disease, the patient's lacrimal (Fig. 3) and renal biopsies were reviewed with immunohistochemistry staining for IgG4 and showed >30 IgG4-positive cells/high-powered field.

Discussion

Based on the current literature describing the disease, the patient was diagnosed with IgG4-related systemic disease, a

condition resulting from the excessive infiltration of polyclonal IgG4-positive plasmacytes into one or more organs. Interestingly, P-ANCA was positive in our patient, which could be suggestive of vasculitis. However, P-ANCA is not 100% specific and was interpreted as a false positive since the patient's overall clinical picture, radiographic findings and pathology were inconsistent with vasculitis.

Typically, the mean age of presentation is mid 50s to early 60s and patients usually have a history of allergic rhinitis or bronchial asthma (3). Males are more likely to be affected than females (4) and the disease is noted to be more severe in males and it is likely to include pancreas and renal involvement (3). Most cases include autoimmune pancreatitis; however, there are documented instances in addition to the present case, where IgG4-related systemic disease has occurred without pancreatic or biliary involvement (4, 5). Other documented manifestations include retroperitoneal fibrosis, pancreatitis, sclerosing cholangitis, hepatitis, tubulointerstitial nephritis, xerophthalmia from lacrimal gland infiltration, xerostosis from salivary gland infiltration, hypophysitis, thyroiditis, abdominal aortic aneurysm, lymphadenopathy, breast masses, prostatitis, rash, pericarditis, pulmonary masses and pulmonary interstitial disease (Fig. 4) (1, 6-21).

IgG4-related systemic disease is a diagnostic challenge. Serum IgG and IgG4 levels are variable in patients with the disease. Although elevated serum IgG4 is associated with this condition the serum IgG4 level cannot, by itself, include or exclude the diagnosis of IgG4-related systemic disease (22). Imaging findings in IgG4-related systemic disease are not specific for the disease either, and radiologic involvement may or may not result in symptoms.

Histopathology and immunohistochemical staining for IgG4 are the most valuable diagnostic tools in IgG4-related systemic disease. Histopathology typically shows fibrosis, sclerosis, glandular architecture destruction, obliterative phlebitis, and lymphoplasmacytic infiltration. In the absence of histopathologic features consistent with other disease and in the presence of >10 IgG4+ plasma cells/high-powered

field, IgG4-related systemic disease should be strongly considered (2, 6).

At the forefront of the treatment of IgG4-related systemic disease are systemic corticosteroids. No standardized regimen exists, however, most case reports and series describe treatment with 30-60 mg (0.6 mg/kg/day) of prednisolone per day for 1-2 months with a subsequent decrease in dose by 5 mg per week (23, 24). Response to steroids is rapid and dramatic, but there is a 30-40% relapse after discontinuation of steroids (23). To prevent relapses, a maintenance dose of 5 mg per day should be continued for at least 6 months and discontinued within 3 years of therapy initiation (24). After discontinuation of corticosteroids, recurrent symptoms should prompt another course of corticosteroids alone or possibly in combination with other immunosuppressive therapy (23). Patients should be monitored clinically, and serial imaging every 3-6 months of affected organs, as well as measurement of serum IgG4 levels, can be considered to ensure treatment success or facilitate early intervention for relapse.

Conclusion

The present patient was initially started on prednisone 60 mg per day for one month, along with pituitary replacement therapy. On follow-up, the patient gained 10 kilograms, was no longer anemic, and reported feeling back to his baseline. Repeat imaging showed resolution of radiologic abnormalities, including the pituitary abnormalities; however, to date, he continues to require hormone replacement for panhypopituitarism. This case highlights the need for expanding the differential diagnosis of multisystem organ disorders as prompt recognition and treatment may lead to remission of disease and prevent significant morbidity.

The authors state that they have no Conflict of Interest (COI).

References

1. Neild GH, Rodriguez-Justo M, Wall C, Connolly JO. Hyper-IgG4 disease: report and characterisation of a new disease. *BMC Med* **4**: 23, 2006.
2. Chari ST. Diagnosis of autoimmune pancreatitis using its five cardinal features: introducing the Mayo Clinic's HISORT criteria. *J Gastroenterol* **42** Suppl 18: 39-41, 2007.
3. Masaki Y, Dong L, Kurose N, et al. Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. *Annals Rheum Dis* **68**: 1310-1315, 2009.
4. Kamisawa T, Okamoto A. IgG4-related sclerosing disease. *World J Gastroenterol* **14**: 3948-3955, 2008.
5. Tanabe T, Tsushima K, Yasuo M, et al. IgG4-associated multifocal systemic fibrosis complicating sclerosing sialadenitis, hypophysitis, and retroperitoneal fibrosis, but lacking pancreatic involvement. *Intern Med* **45**: 1243-1247, 2006.
6. Björnsson E, Chari ST, Smyrk TC, Lindor K. Immunoglobulin G4 associated cholangitis: description of an emerging clinical entity based on review of the literature. *Hepatology* **45**: 1547-1554, 2007.
7. Cheuk W, Yuen HK, Chu SY, Chiu EK, Lam LK, Chan JK. Lymphadenopathy of IgG4-related sclerosing disease. *Am J Surg Pathol* **32**: 671-681, 2008.
8. Chung H, Watanabe T, Kudo M, Maenishi O, Wakatsuki Y, Chiba T. Identification and characterization of IgG4-associated autoimmune hepatitis. *Liver Int* **30**: 222-231, 2010.
9. Kasashima S, Zen Y, Kawashima A, Endo M, Matsumoto Y, Kasashima F. A new clinicopathological entity of IgG4-related inflammatory abdominal aortic aneurysm. *J Vasc Surg* **49**: 1264-1271, 2009.
10. Kitagawa S, Zen Y, Harada K, et al. Abundant IgG4-positive plasma cell infiltration characterizes chronic sclerosing sialadenitis (Kuttner's tumor). *Am J Surg Pathol* **29**: 783-791, 2005.
11. Miyagawa-Hayashino A, Matsumura Y, Kawakami F, et al. High ratio of IgG4-positive plasma cell infiltration in cutaneous plasmacytosis—is this a cutaneous manifestation of IgG4-related disease? *Hum Pathol* **40**: 1269-1277, 2009.
12. Shigemitsu H, Koss MN. IgG4-related interstitial lung disease: a new and evolving concept. *Curr Opin Pulm Med* **15**: 513-516, 2009.
13. Sugimoto T, Morita Y, Isshiki K, et al. Constrictive pericarditis as an emerging manifestation of hyper-IgG4 disease. *Int J Cardiol* **130**: e100-e101, 2008.
14. Wong S, Lam WY, Wong WK, Lee KC. Hypophysitis presented as inflammatory pseudotumor in immunoglobulin G4-related systemic disease. *Hum Pathol* **38**: 1720-1723, 2007.
15. Yoneda K, Murata K, Katayama K, et al. Tubulointerstitial nephritis associated with IgG4-related autoimmune disease. *Am J Kidney Dis* **50**: 455-462, 2007.
16. Yoshimura Y, Takeda S, Ieki Y, Takazakura E, Koizumi H, Takagawa K. IgG4-associated prostatitis complicating autoimmune pancreatitis. *Intern Med* **45**: 897-901, 2006.
17. Zen Y, Kasahara Y, Horita K, et al. Inflammatory pseudotumor of the breast in a patient with a high serum IgG4 level: histologic similarity to sclerosing pancreatitis. *Am J Surg Pathol* **29**: 275-278, 2005.
18. Zen Y, Kitagawa S, Minato H, et al. IgG4-positive plasma cells in inflammatory pseudotumor (plasma cell granuloma) of the lung. *Hum Pathol* **36**: 710-717, 2005.
19. Takeda S, Haratake J, Kasai T, Takaeda C, Takazakura E. IgG4-associated idiopathic tubulointerstitial nephritis complicating autoimmune pancreatitis. *Nephrol Dial Transpl* **19**: 474-476, 2004.
20. Umemura T, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K. Immunoglobulin G4-hepatopathy: association of immunoglobulin G4-bearing plasma cells in liver with autoimmune pancreatitis. *Hepatology* **46**: 463-471, 2007.
21. van der Vliet HJ, Perenboom RM. Multiple pseudotumors in IgG4-associated multifocal systemic fibrosis. *Ann Intern Med* **141**: 896-897, 2004.
22. Morselli-Labate AM, Pezzilli R. Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: A systematic literature review and meta-analysis. *J Gastroenterol Hepatol* **24**: 15-36, 2009.
23. Chari ST. Current concepts in the treatment of autoimmune pancreatitis. *JOP* **8**: 1-3, 2007.
24. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. *Gut* **58**: 1504-1507, 2009.