CLINICAL VIGNETTE

Type 1 Autoimmune Pancreatitis with Systemic Lymphadenopathy: An IgG-Related Disease

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Case Vignette

A 75-year-old Asian male with hypertension, recently diagnosed Type 2 diabetes mellitus, and history of latent TB, presented with 3 months of fatigue associated with anorexia, 35 pound weight loss and bilateral non-tender inguinal lymphadenopathy. He developed postauricular lymphadenopathy two years prior, which was biopsied with normal pathology. He denied gastrointestinal symptoms including nausea, vomiting, diarrhea, or abdominal pain. His diabetes was diagnosed, around the time of symptom onset, with initial rx with metformin, which was switched to linagliptin.

Physical exam revealed a fatigued male with normal vital signs and multiple bilateral enlarged, non-tender inguinal lymph nodes. His exam was otherwise unremarkable.

Initial Labs:

CBC: WBC 4.05 (lower limit of normal 4.16), H/H 10.6/33.9, MCV 93.1, and Platelet 140.

Ferritin 1128, Iron 17 with 32 % saturation, B12 and erythropoietin levels were normal. Comprehensive metabolic panel was remarkable for eGFR of 51 with Cr 1.35. ESR was elevated at 86 with CRP of 1.5. A1C was 6.4%, improved from 7.2% and Urine Alb/CR ratio was elevated at 235 mcg/ml. Due to his significant lymphadenopathy, unintentional weight loss and lab abnormalities, CT scans of chest, abdomen, and pelvis were ordered, as well as referrals to Hematology- Oncology and Gastroenterology.

Chest CT scan showed mediastinal lymphadenopathy.
CT abdomen/pelvis demonstrated:

- Diffuse uniform enlargement of pancreas with surrounding hypo-attenuating halo, strongly suggestive of autoimmune pancreatitis;
- Inhomogeneous nephrograph with patchy well-defined hypoattenuating cortical lesions; multiple bilateral borderline external iliac and common iliac lymph nodes;
- Prominent non-enlarged para-aortic lymph nodes.

The constellation of pancreatic, renal, lymph node finding raised suspicious for IgG 4-related disease and Total IgG level was elevated at 5340 mg/dl with marked IgG4 elevation at 2410 mg/dl (nl 1-123 mg/dl). CA 19-9 level was normal. Peripheral smear showed normochromic, normocytic anemia with normal white cells and adequate platelets. Inguinal lymph node biopsy showed inter-follicular expansion with numerous plasma cells, but no atypical plasma cells. Immunohistochemistry showed increased IgG4 plasma cells with at least 40% IgG4: IgG ratio, supportive of IgG4- related disease. There was no evidence of lymphoma. Upper endoscopy was normal and colonoscopy showed several tubular adenomas.

The patient was diagnosed with IgG4-related disease with autoimmune pancreatitis and lymphadenopathy. His linagliptin was discontinued and he was started on prednisone 40 mg daily for 4 weeks, followed by 5mg/week taper, with improvement in inguinal lymphadenopathy and constitutional symptoms. Subsequent abdominal MRI demonstrated resolution of both pancreatic enlargement and retroperitoneal lymphadenopathy as well as interval decrease in perinephric haziness.

However, after tapering off prednisone, he developed fatigue with recurrent lymphadenopathy and repeat imaging showed recurrence of autoimmune pancreatitis. IgG4 which decreased from 2410 mg/dl initially to 1110 mg/dl during prednisone therapy, increased to 1920 mg/dl. Prednisone was restarted, and he was referred to rheumatology for further management. Due to multiple organ involvement and recurrence off prednisone, he was started on rituximab with a slow prednisone taper with complete resolution of symptoms. IgG4 decreased to 701 mg/dl, creatinine improved to 1.04 mg/dl with eGFR 69 ml/min/1.73 m2, and his cell counts and inflammatory markers normalized.

Discussion

IgG4-related disease (IgG4-RD) is an autoimmune multi-organ fibroinflammatory disorder. Prior to the established terminology of IgG4-RD to encompass multiple systems as a collective group, each organ lesion was described independently as separate disease entities. Organ systems involved include the CNS, lacrimal/salivary glands, thyroid gland, lung, pancreas, bile ducts, kidney, prostate, retroperitoneum, skin, lymph nodes, and arteries.[1] In 2000 IgG4 related disease was recognized as a unified disease process with multi-organ involvement that shared many characteristic findings.[2,3] Clinical manifestations vary depending on organ involvement.

Patients exhibit focal or diffuse organ swelling with high IgG4 plasma cell infiltrate and fibrosis with a "storiform" (whorled) pattern on histology. IgG4-RD generally responds well to corticosteroid therapy.[2-4] At this time, the underlying pathophysiology and long-term prognosis are still not clearly understood.[2] This discussion will focus on Type 1 autoimmune pancreatitis with lymphadenopathy as a presentation of IgG4-RD.

Autoimmune pancreatitis is a rare but increasingly recognized form of pancreatitis. There are currently two subtypes based on the international consensus diagnostic criteria (ICDC). Type 1 AIP, also known as Lymphoplasmacytic Sclerosing Pancreatitis (LPSP), is a subset of IgG4-related disease. Type 2 AIP is Idiopathic Duct-Centric Pancreatitis (IDCP) or AIP with granulocytic epithelial lesion (GEL).[5] The pathophysiology for AIP is currently unknown but likely involves a significant autoimmune process. This is supported by increased autoantibodies, lymphoplasmacytic infiltration on histology, hypergammaglobulinemia, and the predictable response to steroid.[5,6]

Type 1 AIP, as an IgG4-RD, is characterized by massive infiltration of the lymphoplasmacytic cells without granulocytes in the pancreas, abundant IgG4-positive plasma cells, storiform or swirling fibrosis, and peri-venular infiltration with lymphoplasmacytic cells which often leads to obliterative phlebitis.[5] It accounts for 80% of autoimmune pancreatitis cases. Type 1 AIP predominantly affects elderly males, with a mean age of 63 years and a male to female ratio of 3-5:1.[5,7] Type 2 AIP manifests most commonly as recurrent acute pancreatitis in younger individuals with concurrent inflammatory bowel disease.[5] Type 2 AIP is not part of the IgG4-RD. The serum IgG4 level is normal and histologically the granulocyte epithelial lesion consists of intraluminal and intraepithelial neutrophils rather than the IgG4 plasma cells.[8]

Clinical presentations of Type 1 AIP are variable. Common symptoms are obstructive jaundice, mild abdominal pain, back pain, weight loss, and fatigue. Patients may have new-onset diabetes mellitus. Type 1 AIP may be associated with extra-pancreatic lesions that are part of IgG4-RD. The biliary tree is the most commonly involved site and manifests as sclerosing cholangitis. However, sialadenitis, retroperitoneal fibrosis, interstitial lung disease, tubulointerstitial nephritis, and lymphadenopathy are also reported.[9] These entities have shared histopathologic findings, frequently co-exist, and all respond favorably to steroid treatment.

Serum IgG4 concentrations of greater than 135 mg/dl have 97% overall accuracy, with 95% sensitivity and 97% specificity for Type 1 AIP.[10] While elevated serum IgG4 levels have greatest diagnostic value, they are not disease-specific, as elevations can occur in 5% of the normal population and in 10% of patients with pancreatic cancer and rarely other conditions including allergies, parasitic infections and pemphigus vulgaris.[10] Patients with biliary involvement may have abnormal liver enzymes.

On CT scan, 40-60% of patients with AIP exhibit diffuse morphological pancreatic parenchymal enlargement with a capsule-like low-density rim, while other findings include focal enlargement, normal pancreas or mixed patterns.[5] MRI demonstrates a capsule-like rim that is hypo-intense on both T1-T2 weighted images.[5] EUS findings are similar to CT findings. On ERCP, features suggestive of AIP include pancreatic duct strictures longer than 1/3rd of the duct, lack of upstream dilatation from stricture, multiple strictures, and side branches arising from a segment with stricture.[5]

Concomitant lymphadenopathy is a common finding in patients with IgG4-RD. It is occasionally characterized by systemic lymphadenopathy, polyclonal hyperimmunoglobulinemia, and positivity for various autoantibodies.[1] Most patients with systemic IgG4-related lymphadenopathy are significantly older with mean age of 68 years old.[1] IgG4-RD lymphadenopathy can be classified into two types based on the infiltrative patterns of IgG4 positive cells: the interfollicular plasmacytosis and intragerminal center plasmacytosis.[1] The percentage of the IgG4 +/ IgG+ plasma cells is greater than 40%, with mean of 62% compared to 9.9% of in other reactive lymphadenopathy conditions.[11]

The most commonly used criteria for the diagnosis of Type 1 AIP is the "HISORt" criteria proposed by the Mayo Clinic. The criteria are based on 5 cardinal features: diagnostic histology; characteristic imaging on CT and /or pancreatography; elevated serum IgG4 level on serologic testing; other organ involvement; and response of pancreatic and extra-pancreatic manifestations to glucocorticoid therapy.[12,13] At least one of the criteria is needed to diagnose Type 1 AIP.

Early treatment is necessary to prevent progression to chronic fibrosis. Unless there are contraindications, corticosteroids are the first-line agent in all active and symptomatic patients with untreated AIP as they lead to clinical remission in 99% of type 1 AIP and 92% of type 2 AIP.[14] Steroids are administered over 4 weeks then tapered. The relapse rate of type 1 AIP is 30-50 %.[15] Restarting steroids can induce remission of relapsing disease, however alternative treatment with steroid-sparing agents or rituximab is typically used.[2,3,5] In cases with low disease activity isolated to the pancreas, steroids can be tapered off within 3 months without steroid maintenance with complete radiological remission and normalized IgG4 level.[2] Maintenance therapy with low-dose steroids or rituximab is recommended with patients with Type 1 AIP. These patients show diffuse enlargement of the pancreas, delayed imaging remission, persistently high level IgG4 > 2 x upper limit of normal after treatment, or involvement of two or more other organs.[15]

Case Course

Our patient presented with anorexia, unintentional weight loss, fatigue, and inguinal lymphadenopathy initially concerning for a malignancy such as lymphoma or pancreatic cancer. His postauricular lymphadenopathy two years prior may have been

a sentinel event of type 1 AIP, as well as his newly diagnosed diabetes. CT showed a classic appearance of diffuse, uniform pancreatic enlargement with surrounding hypo-attenuating halo. Serum IgG4 was nearly 20 times the upper limit of normal. His lymph node biopsy was consistent with IgG4-RD. Rapid improvement with corticosteroids further validated the diagnosis of IgG4-RD with Type 1 AIP and lymphadenopathy. Unfortunately, the patient's condition relapsed after completion of the steroid course, but went into remission with resumption of steroids and initiation of rituximab. At this time, the patient is doing well under routine surveillance every 3-6 months.

Conclusion

IgG4-RD is a multi-organ autoimmune inflammatory syndrome characterized by organ swelling due to lymphoplasmacytic infiltrates and sclerosis, high serum IgG4 level, and increased IgG4+ plasma cells in the involved tissue that respond well to corticosteroid treatment. Clinical presentation is related to specific organ involvement. As IgG4-RD can mimic other concerning conditions including malignancy, it is important to keep this diagnosis in mind to avoid unnecessary procedures. Prompt treatment is crucial to prevent consequences of uncontrolled inflammation.

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