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Case Report

Autoimmune pancreatitis: The Last Puzzle Piece of IgG4-Related Disease

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Abstract

Immunoglobulin G4-related systemic disorder (IgG4-RD) is an under-diagnosed fibro-inflammatory disorder with unknown etiology and multiorgan involvement. IgG4-RD manifestations consist of lymphadenopathy, extrapancreatic bile duct lesions, lacrimal and salivary gland lesions, hypothyroidism, retroperitoneal fibrosis, and kidney mass. We report the case of a 46-year-old patient, with moderate persistent asthma and chronic hyperplastic rhinosinusitis, who presented at emergency department because of obstructive jaundice due to a mass in the pancreatic head. The pathology of the surgical specimen disclosed lymphoplasmacytic inflammation with fibrosis of intra and inter-lobular septs and ducts ectasia and abundant infiltration of plasmacytes, most of whom being IgG4-positive (> 200/hpf). These findings were consistent with the diagnosis of IgG4-RD. The patient's medical history suggests pancreatitis is the last piece of the jigsaw puzzle that initiated years before with swelling of submandibular glands and and enlarged lacrimal glands.

Introduction

IgG4-related disease (IgG4-RD) is an emerging immune-mediated disorder with the capability of involving any organ [1]. The cardinal feature of IgG4-RD is the abnormal swelling of single or multiple organ that could also be suspected for malignancy. The disease may have a wide spectrum of manifestations with involvement of different organs such as: pancreas (autoimmune pancreatitis), bile ducts (sclerosing cholangitis), major salivary glands (Mikulicz disease and Kuttner tumor), eye (orbital tumor), lung and pleura (interstitial pneumonia), kidney (tubulointerstitial nephrosis), retroperitoneum (retroperitoneal fibrosis and Ormond disease) and lymph nodes [2]. The peculiar pathology features of IgG4-RD are lymphoplasmacytic infiltration and storiform fibrosis, which are often associated with elevated levels of serum IgG4.

Case Presentation

A 46-year-old man at the emergency department in September 2013 presented with mild-moderate epigastric pain with back irradiation for 2-3 weeks, and jaundice. Increased levels of serum bilirubin (181.26 µmol/L; normal range:2-18 µmol/L), conjugated bilirubin (152.2 µmol/L; normal range: ≤ 7 µmol/L), alkaline phosphatase (722 U/L; normal range: 40-120 U/L), gamma glutamyl transferase (723 U/L; normal range: 8-61) and pancreatic amylase (131 U/L; 12-52 U/L) were found. An abdominal ultrasound showed dilatation of the extra and intrahepatic biliary tract and a distended gallbladder with biliary sludge. There was no evidence of gallstones, but the pancreatic head was enlarged. A high-resolution CT showed a bulky pancreatic head (39.8 mm of maximal diameter) with a thick walled common bile duct (CBD), proximal biliary dilatation and distended gallbladder. The main pan-

creatic duct was mildly dilated, and there were no pancreatic stones, calcifications or peripancreatic fluids. Endoscopic retrograde cholangiopancreatography (ERCP) showed tight distal CBD stricture with a dilated proximal system, that needed dilatation, sphincterotomy, and placement of stent that significantly improved bilirubin level. During the procedure we obtained non-informative brush cytology from the CBD. The endoscopic ultrasound revealed a 4-cm hypoechoic heterogeneous pancreatic head lesion with no invasion of nearby vascular structures, but the pancreatic needle biopsy showed atypical epithelial ductal cells. The patient received a pancreatico-duodenectomy. However, the suspected cancer was not confirmed by surgical specimen pathology, which showed lymphoplasmacytic tissue infiltration and predominant IgG4-positive plasma cells (> 200/hpf) (Figure 1, panels A and B) with fibrosis of the intra- and inter-lobular septs, ducts ectasia, and hyperplastic insular cells. The findings are consistent with chronic type 1 autoimmune pancreatitis [3].

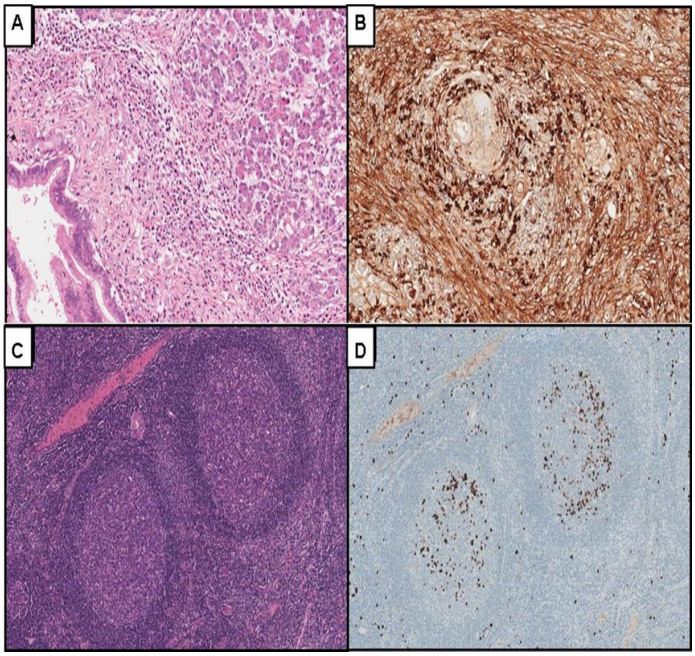

Figure 1. PANEL A: pancreatic ducts with abundandt fibrotic tissue containing plasma cells (purple staining) (H&E, 20x magnification). PANEL B: Immunohistochemical reaction of pancreatic tissue with anti-IgG4 antibodies highlight plasma cells localized between fibrotic bundles around pancreatic ducts (20x magnification). PANEL C: Hematoxylin and eosin stain (H&E) (10x magnification) of lymph-node showing follicles with germinal center hyperplasia. PANEL D: Immunohistochemical reaction of a lymph node with anti-IgG4 antibodies highlight plasma cells inside and around germinal centers (10x magnification).

The peri-pancreatic, peri-portal, and retro-duodenal lymph nodes showed reactive lymphoid hyperplasia with no evidence of malignancy. The serum IgG4 level was 840 mg/dL, which is well above the upper limit of normal (135 mg/dL).

The patient's medical history suggests pancreatitis is the last piece of the jigsaw puzzle that initiated in 2002 when the patient developed swelling of submandibular glands with reactive lymphadenopathy that resolved spontaneously. The pathologic examination of a submandibular lymph node revealed prominent follicular hyperplasia with rare germinal centers and no granuloma. The patient also suffered from chronic rhinosinusitis with nasal polyps and eosinophilic refractory asthma that requires frequent oral corticosteroids. The patient had three treatments in the last year. In 2010, the patient had enlarged lachrymal glands and nonspecific chronic dacryoadenitis identified by pathologic examination of a biopsy sample. The recent diagnosis of autoimmune pancreatitis and the previously reported submandibular salivary gland enlargement, lymphadenitis, and dacryoadenitis are all manifestations of the same IgG4 related disease (IgG4-RD). A re-evaluation of the lymph node biopsy confirmed this hypothesis and showed a high number of IgG4 plasmocytes (Figure 1, panels C and D). When last seen, 10 months after surgery, the patient was not receiving specific treatment except for topical nasal fluticasone and bronchial salmeterol/fluticasone. A whole body positron emission tomography with the glucose analogue 2-18F-fluoro-2-deoxy-D-glucose (FDG) showed no significant FDG uptake, which suggests no disease recurrence [4] and the serum IgG4 level was normal (85 mg/dl).

Discussion

The clinical and histological features of this case are characteristic of IgG4-RD. The disease is an under diagnosed fibro-inflammatory disorder with unknown etiology and multiorgan involvement. Our patient had involvement of the lachrymal gland, salivary glands, and lymph nodes at different times. It is possible that the slow disease course is due to the frequent systemic glucocorticoid treatments for severe chronic rhinosinusitis with nasal polyps, which may be also interpreted as one of the manifestation of IgG4-RD as suggested elsewhere [5,6] . The disease responds to therapy with glucocorticoids [7] and relapses following therapy discontinuation. IgG4-RD is an emerging immune-mediated disorder, which may have a wide spectrum of manifestations which had been previously considered as unrelated conditions, like Type-1 autoimmune pancreatitis and IgG4-related sclerosing cholangitis, Mikulicz disease, Riedel thyroiditis or orbital pseudotumor. The diagnosis of IgG4-RD is based upon biopsy findings demonstrating the characteristic histopathology. Serum IgG4 elevated levels are a significant aid in diagnosis, although they are not diagnostic. Organ involvement may be identified through a careful history, physical examination, routine laboratory testing, and selected imaging studies. Awareness of the disease is needed to ensure early diagnosis, aimed at preventing severe organ damage and irreversible tissue fibrosis.

References

1. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet. 2015, 385(9976): 1460-1471.

2. Islam AD, Selmi C, Datta-Mitra A, Sonu R, Chen M et al. The changing faces of IgG4-related disease: Clinical manifestations and pathogenesis. Autoimmun Rev. 2015, 14(10): 914-922.

3. Hart PA, Zen Y, Chari ST. Recent Advances in Autoimmune Pancreatitis. Gastroenterology. 2015, 149(1): 39–51.

4. Ebbo M, Grados A, Guedj E, Gobert D, Colavolpe C et al. Usefulness of 2-[18F]-fl uoro-2-deoxy-D-glucose-positron emission tomography/computed tomography for staging and evaluation of treatment response in IgG4-related disease: a retrospective multicenter study. Arthritis Care Res (Hoboken). 2014, 66(1): 86–96.

5. Van Zele T, Gevaert P, Holtappels G, van Cauwenberge P, Bachert C. Local immunoglobulin production in nasal polyposis is modulated by superantigens. Clin Exp Allergy. 2007, 37(12):1840-1847.

6. Lü J, Liu HG. [Expression and significance of IgG4 in inflammatory disease of nasal cavity and paranasal sinuses]. Zhonghua Bing Li Xue Za Zhi. 2013, 42(6): 386-391.

7. Masaki Y, for the All-Japan Team for the Prospective Treatment Study of IgG4-RD. A trial of corticosteroids for IgG4-related disease. Second International Symposium on IgG4-related Disease & Associated Conditions, Honolulu, HA, USA, February 16–19, 2014.