

◆ CASO CLÍNICO

Autoimmune cholangitis associated to IgG4 related sclerosing disease

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Summary

The IgG4-related sclerosing disease is characterized by the presence of plasmatic IgG4 positive cells and T-lymphocytes infiltration in different organs. We herein report a case of cholestasis due to autoimmune cholangitis associated to IgG4 disease. A 40-year-old woman with a history of pruritus, anosmia, Sjögren's syndrome and diabetes, was referred for a pancreatic tumor. Alkaline phosphatase was 24-fold upper limit of normal (ULN), gamma-glutamyl transpeptidase 21-fold ULN, aspartate aminotransferase 3-fold ULN, alanine aminotransferase 2-fold ULN, cholesterol 408 mg/dL, bilirubin normal, gamma-globulin 3.92 g/dL, IgG4 4.6 g/L, antinuclear antibody positive (1/320), and antimitochondrial antibodies negative. Ultrasound scan (US) showed a mass in the pancreatic head and thickening of the gallbladder and the bile duct walls. Dilatation and strictures of the main pancreatic duct and intrahepatic bile ducts were detected by MR cholangiopancreatography. Liver biopsy showed chronic inflammatory lesions, ductal damage (autoimmune cholangitis) (METAVIR A2, F2) and IgG4 bearing plasmatic cells. A cervical lymph node showed IgG4 bearing plasmatic cells. After 2 weeks of treatment with meprednisone, ursodeoxycholic acid and insulin, pruritus and anosmia disappeared. After eleven months of treatment imaging studies showed disappearance of the pancreatic tumor, atrophy of the body and the pancreatic tail and normal biochemical parameters, except for alkaline phosphatase 2-fold ULN. The

final diagnosis of our patient was autoimmune hepatitis with cholangitis associated to IgG4 systemic disease.

Key words. IgG4, Autoimmune cholangitis, Autoimmune pancreatitis, Cholestasis.

Colangitis autoinmune asociada a enfermedad esclerosante relacionada a IgG4

Resumen

La enfermedad esclerosante relacionada a IgG4 se caracteriza por la presencia de células plasmáticas IgG4 positivas e infiltración de linfocitos T en varios órganos. Presentamos una colestasis debida a colangitis autoinmune asociada a enfermedad por IgG4. Una mujer de 40 años con prurito, anosmia, síndrome de Sjögren y diabetes, fue derivada por un tumor pancreático. La fosfatasa alcalina (FAL) era 24 veces mayor que el valor superior normal (VSN), la gamma glutamil transpeptidasa 21 veces mayor que el VSN, la aspartato aminotransferasa 3 veces mayor que el VSN, la alanino aminotransferasa 2 veces mayor que el VSN, el colesterol 408 mg/dl, la bilirrubina normal, la gamma-globulina 3,92 g/dl, la IgG4 4,6 g/l, los anticuerpos antinucleares positivos (1/320) y los anticuerpos anti-mitocondriales negativos. La ecografía mostró una masa en la cabeza pancreática, un engrosamiento de la pared vesicular y del colédoco, y dilatación y estenosis del conducto de Wirsung y de la vía biliar intrahepática que se confirmaron mediante colangiorresonancia. La biopsia hepática demostró lesiones inflamatorias crónicas, daño ductal (colangitis autoinmune) y plasmocitos IgG4 positivos (también presentes en un ganglio cervical). Después de 2 semanas de tratamiento

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con meprednisona, ácido ursodeoxicólico e insulina, el prurito y la anosmia desaparecieron. Luego de once meses de tratamiento desapareció la tumoración pancreática y se observó atrofia del cuerpo y cola del páncreas. El laboratorio fue normal excepto la fosfatasa alcalina que permaneció elevada 2 veces por encima del VSN. El diagnóstico final de nuestra paciente fue colangitis autoinmune asociada a enfermedad IgG4 sistémica.

Palabras claves. Colangitis autoinmune, pancreatitis, autoinmune, colestasis.

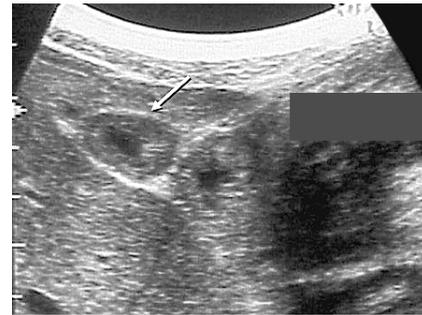
Case report

A 40-year-old woman presenting clinical and biochemical cholestasis and a pancreatic head tumor on the computed tomography scan (CT) was referred to our surgical department with the presumptive diagnosis of a pancreatic cancer. She referred weakness, pruritus, dry eyes and anosmia for more than a year. Diabetes and Sjögren's syndrome had been diagnosed and the latter confirmed by histology. She denied taking medicines, alcohol or herbal remedies and presented submaxilar, axilar and other superficial lymph nodes. Biochemistry showed raised alkaline phosphatase (AP) 24-fold upper limit of normal (ULN), gamma-glutamyl transpeptidase (GGT) 21-fold ULN, aspartate aminotransferase (AST) 3-fold ULN, alanine aminotransferase (ALT) 2-fold ULN, cholesterol 408 mg/dL, conjugated bilirubin 0.37 mg/dL, serum gammaglobulin 3.92 g/dL, with IgG1 19 g/L (normal value 4.9 -11.4 g/L), IgG2 6.80 g/L (normal value 1.50-6.4 g/L), IgG3 2.00 g/L (normal value 0.20-1.10 g/L) and IgG4 4.6 g/L (normal value 0.08-1.40 g/L), albumin 2.99 g/dL, alfa-2 1.03 g/dL. The antinuclear antibody (ANA) was positive (1:320, homogeneous), antimitochondrial antibodies (AMA) and smooth muscle antibody were negative. Serologic markers for hepatitis A, B and C, cytomegalovirus, Epstein-Barr virus, anti-HIV and HCV RNA by PCR were negative. Prothrombin time was 100%, hemoglobin 9,5 g/dL and platelet count 290,000 per mm³. An ultrasound scan (US) showed a hypoechoic mass in the head of the pancreas with significant thickening of the gallbladder wall and the main bile duct wall (Figure 1). CT scan showed similar findings. The main pancreatic duct was dilated and irregular (Figures 1 and 2). Magnetic resonance

Figure 1. Pancreatic head tumor and main pancreatic duct strictures.



Figure 2. Thickening of the gallbladder wall.



cholangiopancreatography (MRCP) showed irregular dilation of the main bile duct, the intrahepatic bile ducts and the main pancreatic duct. A liver biopsy was performed, showing florid duct lesions and portal inflammation. Bile duct injury was segmental, affecting small sized interlobular bile ducts, in association with infiltration by mature lymphocytes. The basement membrane was disrupted. The injured bile duct was surrounded by inflammatory infiltrate predominantly composed of lymphocytes, plasma cells with positive immunofluorescence for IgG4, some histiocytes, and a variable number of eosinophils. The biopsy also showed an irregularly distributed and relatively dense portal infiltrate composed of lymphocytes and plasma cells, with periportal interface hepatitis (METAVIR A2, F2) (Figures 3 and 4). The IgG4 bearing plasmatic cells (up to 10 high power field) suggested the diagnosis of autoimmune cholangitis related to IgG4 (Figure 5). A cervical lymph node biopsy also showed IgG4 bearing plasmatic cells and follicular hyperplasia. After 2 weeks of treatment with 0.5 mg/kg/day of meprednisone, 1,200 mg of ursodeoxycholic acid (UDCA) (30 mg/kg/day) and insulin, the AP dropped to 4-fold ULN and GGT to 4-fold ULN, with disappearance of pruritus and

Figure 3. Panoramic view (HE, 100x). Portal tract with interfase hepatitis.

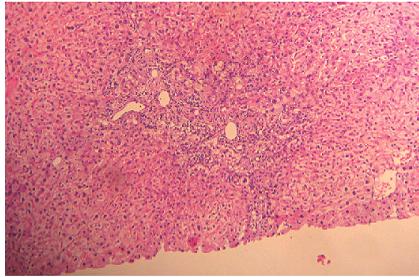


Figure 4. Portal tract with lymphoplasmacytic cell infiltration and biliary duct damage (HE 400x).

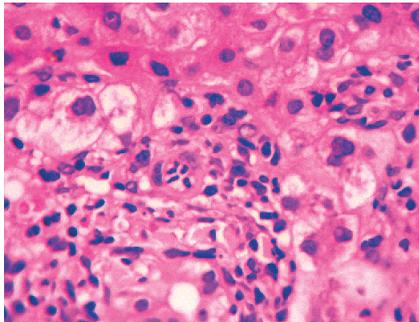
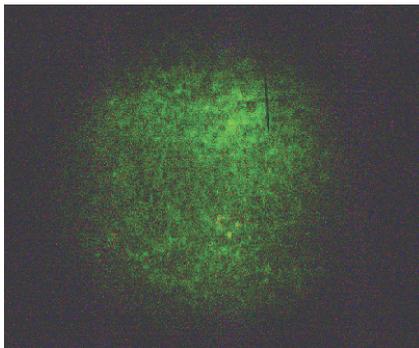


Figure 5. Plasmatic cell bearing IgG4 (immunofluorescence) in a portal tract.



anosmia. The pancreatic head tumor size showed a diameter reduction from 4 x 4 cm to 1.5 x 1.5 cm. After 11 months of treatment, the AP fell to 1.5-fold ULN. AST, ALT and GGT were within the normal range and imaging showed the resolution of the pancreatic tumor and the atrophy of the body and pancreatic tail. Gallbladder wall thickening disappeared but the main bile duct wall thickening remained unchanged. (Figures 6 and 7). ANA became negative, gammaglobulin levels became normal and MRCP showed a normal pancreatic duct.

Figure 6. Posttreatment US: disappearance of the gallbladder thickening wall and persisting thickening of the main bile duct.

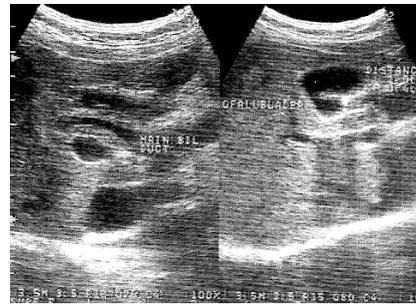


Figure 7. Posttreatment US: dilation of the main pancreatic duct and atrophy of the pancreatic body.



Discussion

We report a case of autoimmune cholangitis associated to IgG4 related sclerosing disease with involvement of other target organs including pancreas, salivary glands and lymph nodes. Raised serum IgG4 and IgG4 bearing plasma cells infiltrates have a high sensitivity and specificity for the diagnosis of autoimmune pancreatitis and associated diseases, including autoimmune hepatitis (AIH) and sclerosing cholangitis. In our case, clinical, serological, radiological and histological criteria of autoimmune cholangitis, including abundant IgG4-bearing plasma cells in liver and in lymph nodes, associated to pancreatic and extrapancreatic manifestations, fulfilled the diagnostic criteria of an IgG4 systemic related disease.¹

Autoimmune liver diseases include AIH, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). Clinical features, disease courses and response to therapy are quite different in typical patients with these entities. Some patients present clinical, histological and biochemical features of both

AIH and PBC, the so called "overlap syndrome" or "autoimmune cholangiopathy".² Some authors agree to the term "autoimmune cholangitis" as a variant of PBC or an AMA negative PBC with ANA positive or features of PBC with AIH overlap. Therefore, the overlap syndrome might be a complex entity including different subsets of patients not yet well defined. From a practical point of view, it is difficult to develop diagnostic criteria of all the possible variants of these autoimmune liver diseases and the therapeutic implications of these variants.³ The AIH international scoring system has a very good sensitivity to exclude AIH in patients with chronic liver diseases but does not allow unmasking AIH/overlap syndromes or AIH with other liver diseases.⁴⁻⁷ The presence of other autoimmune diseases or autoantibody markers together with negative viral hepatitis markers should warn physicians for the possible presence of AIH either as "pure" AIH or in association with other liver disorders (AIH/overlap syndromes or AIH with other concurrent other liver diseases). In these cases, liver histology becomes necessary for the diagnosis and must always be included in the work-up of these patients. Our case had an AIH international score index of 15, and this was the limit reported in some publications as found in patients with AIH/overlap syndromes or AIH with other concurrent liver disorders.^{4,7} The presence of AIH associated to IgG4 can explain some cases of these overlap syndromes and the features of the case we report may be an example. Our patient had ANA-positive, AMA-negative, severe cholestasis with histological and clinical features of autoimmunity (AIP, AIH and PBC) and IgG4 bearing cells in the liver and the lymph nodes. US, CT and MRCP alterations were also typical.⁸ The presence of IgG4 could explain some cases of these autoimmune disorders. In our patient the excellent response of cholangitic lesions to steroids and other immune modulators, different from the negative response of PSC to these drugs, supports the diagnosis of a different entity.

Patients with overlapping features of AIH and PSC may be more common than it is currently assumed.^{9,10} Overlap of PSC and AIH occurs in about 50% of pediatric cases and in 10% of adult cases. The presence of IgG4 bearing cells in liver and the involvement of other organs such as pancreas, salivary glands and lymph nodes may rule out this type of association. On the other hand no typical characteristic of PSC (small or large bile ducts) was

seen in the liver biopsy of our patient. The possibility of a different inflammatory pancreatic disease (AIP) was first described in 1961.¹¹ A disease complex of chronic pancreatitis, sclerosing cholangitis, and Sjogren's syndrome was first described in 1984 and was considered a probable well-defined entity with an autoimmune cause similar to that occurring in PBC.¹² The coexistence of pancreatitis and other autoimmune diseases has been reported on the basis of the presence of raised immunoglobulins¹³ and AIP was the first described disease associated to IgG4 raised levels. Other organs may be involved in this entity not restricted to the pancreatic disease.¹⁴ Metachronic and synchronous lesions in other organs may be found as we report in this case.¹³⁻¹⁴ Imaging of AIP showed typical lesions such as irregular narrowing of the main pancreatic duct, swelling of the pancreatic parenchyma, bile duct lesions and marked wall thickening of the gallbladder and the main bile duct on US or CT (Figure 1).⁸ These lesions can be attributable to autoimmune cholangitis of intrahepatic bile ducts, the most frequent liver lesion associated to AIP. All these lesions may improve dramatically or disappear with steroids used as the first therapeutic option¹⁵⁻¹⁶ and this response is another typical characteristic of IgG4 associated disease. Besides sclerosing cholangitis, the liver may be involved in AIH associated to IgG4 bearing cells, with or without AIP.¹⁷⁻¹⁸ The importance of recognizing the primary lymph node involvement in the lymphadenopathic form of IgG4-related sclerosing disease relies on the excellent response to steroid treatment of this entity and on the differential diagnosis from lymphoma.¹⁹ The case we report presented an autoimmune cholangitis with a dramatic improvement in clinical, biochemical and radiological features with a treatment with steroids and UDCA. IgG4 related autoimmune cholangitis is another possible association of this systemic disease. Patients with AIH exhibit findings that suggest concurrent PSC, PBC, or a cholestatic syndrome in the absence of PSC and PBC. Overlap syndromes lack codified clinical or pathological definitions, and they do not have a distinctive etiology or pathophysiology. Designations are arbitrary and imprecise, and the clinical phenotypes of patients with the same overlap designation are commonly different.²⁰ In summary we present a patient with severe cholestasis, biliary duct lesions and AIH associated to IgG4 systemic disease.

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