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Fatal outcome of a corticosteroid resistant IgG4-related autoimmune hepatitis and IgG4-primary sclerosing cholangitis

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Dear Editor,

A 33-year-old Arab woman with a five-year history of four admissions for cholangitis and/or biliary obstruction due to bile duct stenosis, which were found at different levels during each hospitalization, without any stones being observed. During one of the admissions, a brushing of one of the strictures revealed inflammatory infiltrate with plasma cells, although IgG4 positivity was not tested at that time. She was admitted again, presenting with jaundice three months after giving birth. Blood analysis revealed elevated levels of aspartate aminotransaminase 1064U/L, alanine aminotransaminase 1097U/L, gamma-glutamyl transferase 194U/L, alkaline phosphatase 284U/L, bilirubin 27mg/dL and prothrombin time of 19.3s. Magnetic

resonance-cholangiopancreatography revealed intrahepatic bile duct dilation with a stenosis in the common hepatic duct, not detected on endoscopic retrograde cholangiopancreatography. Additionally, diffuse signal abnormalities were observed in the liver parenchyma on T2 sequences. The serological tests showed IgG levels at 1710 mg/dL, IgG4 at 1140mg/dL, C4 at 9.1mg/dL and vitamin-D 3.77ng/mL. Tests for hepatitis A, B, C, E, Herpesviridae, syphilis, human immunodeficiency virus, antinuclear antibody, antimitochondrial antibody, anti-smooth muscle antibody, anti-liver-kidney-microsomal antibody, antineutrophil cytoplasmic antibodies, ceruloplasmin and genetic testing for hemochromatosis were negative. Methylprednisolone was initiated at a dose of 1mg/kg/day and an early liver biopsy showed moderate-severe interface hepatitis with IgG4-positive plasma cell infiltration (IgG4-PPC) of 8-20cells/HPF, hepatocellular ballooning and focal rosette formation, yielding 6 points of the simplified-score for autoimmune hepatitis (AIH). Contrast computed tomography and positron emission tomography revealed no signs of systemic disease, but showed peripheral heterogeneous and predominantly subcapsular contrast enhancement of the liver. From the outset, we maintained communication with the liver transplant unit at the reference center. Given the patient's stability, coupled with the robust hepatology unit at our hospital, it was mutually agreed to retain the patient in our facility. However, upon receiving the pathology report, and considering the lack of response after two weeks of corticosteroid treatment, along with the concurrent onset of blurred vision and confusion, albeit mild, it was determined that transfer was necessary. A cranial magnetic resonance showed no abnormalities and albumin dialysis was performed, leading to clinical and analytical improvement, thus postponing the need for liver transplantation. After ruling out infections, the patient received rituximab as a rescue treatment, but three days later, developed candida sepsis with rapid progression to multiorgan failure, ultimately resulting in death.

IgG4-related AIH is a rare subtype of AIH characterized by hepatic accumulation of IgG4-PPC and elevated serum IgG4 levels in the presence of AIH features[1]. Diagnostic criteria proposed include hepatic infiltration of IgG4-PPC ≥10/HPF, elevation of IgG4 ≥135mg/dL[2] and IgG4/IgG-ratio ≥5%[3]. The patient fulfilled both criteria and exhibited AIH features on liver biopsy. IgG4-AIH typically presents with severe histology, greater

portal inflammation, lobular hepatitis, plasma cell infiltration and rosette formation, although with similar fibrosis levels[3-4]. The imaging diagnosis is complex and its presentation heterogeneous, in our case with predominantly subcapsular enhancement of the hepatic parenchyma, although a case has been described where the image mimics a hepatic abscess[5]. It usually does not involve duct damage and its association with IgG4-related sclerosing cholangitis is infrequent, suggesting they may both be part of systemic IgG4-related disease. The treatment involves corticosteroids followed by maintenance with azathioprine, with response comparable to classic AIH, although normalization of alanine aminotransaminase typically occurs sooner[4]. Cases without corticosteroid response are not described.

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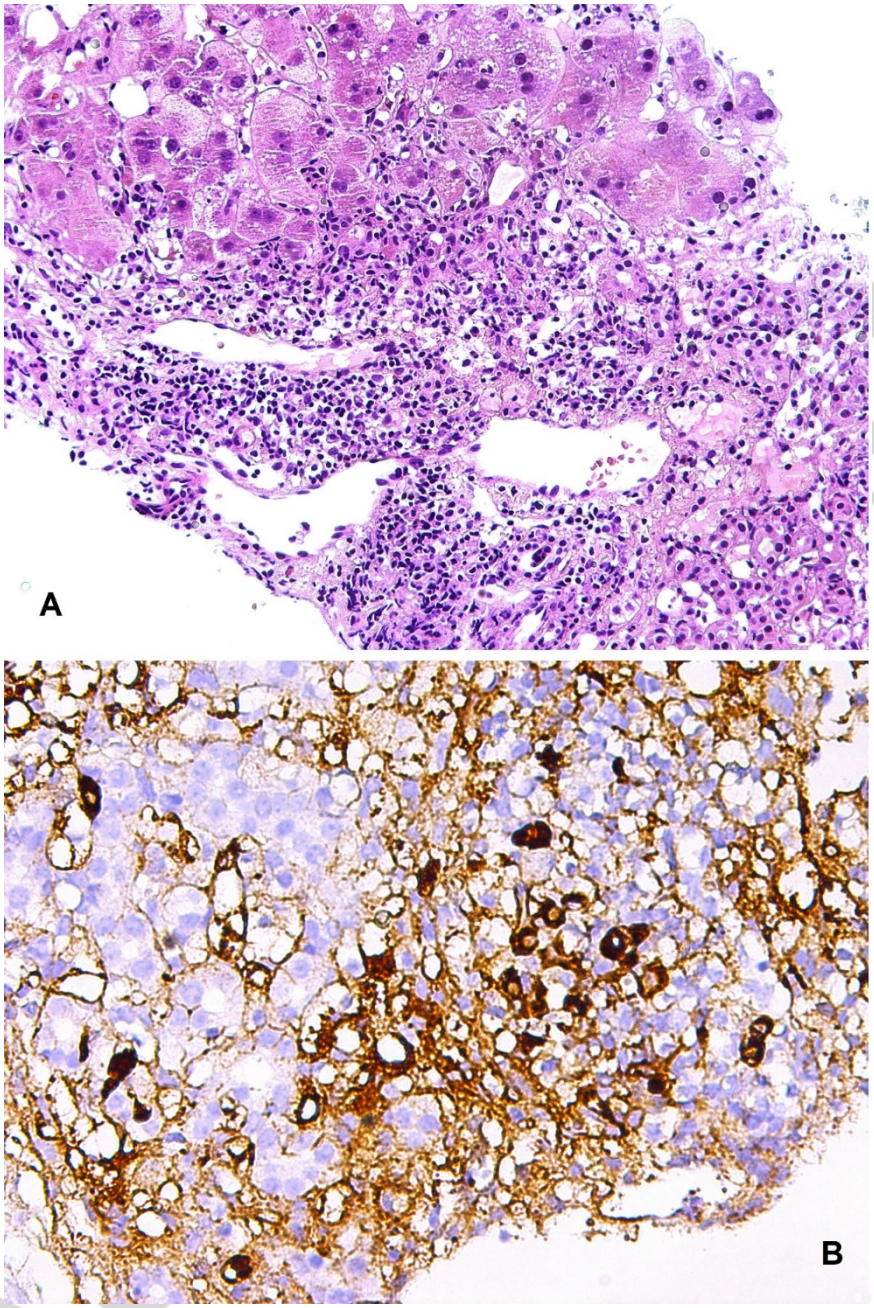

Figure 1. A. The liver biopsy revealed moderate to severe interface hepatitis upon hematoxylin staining. **B.** There were numerous IgG4-positive portal plasma cells

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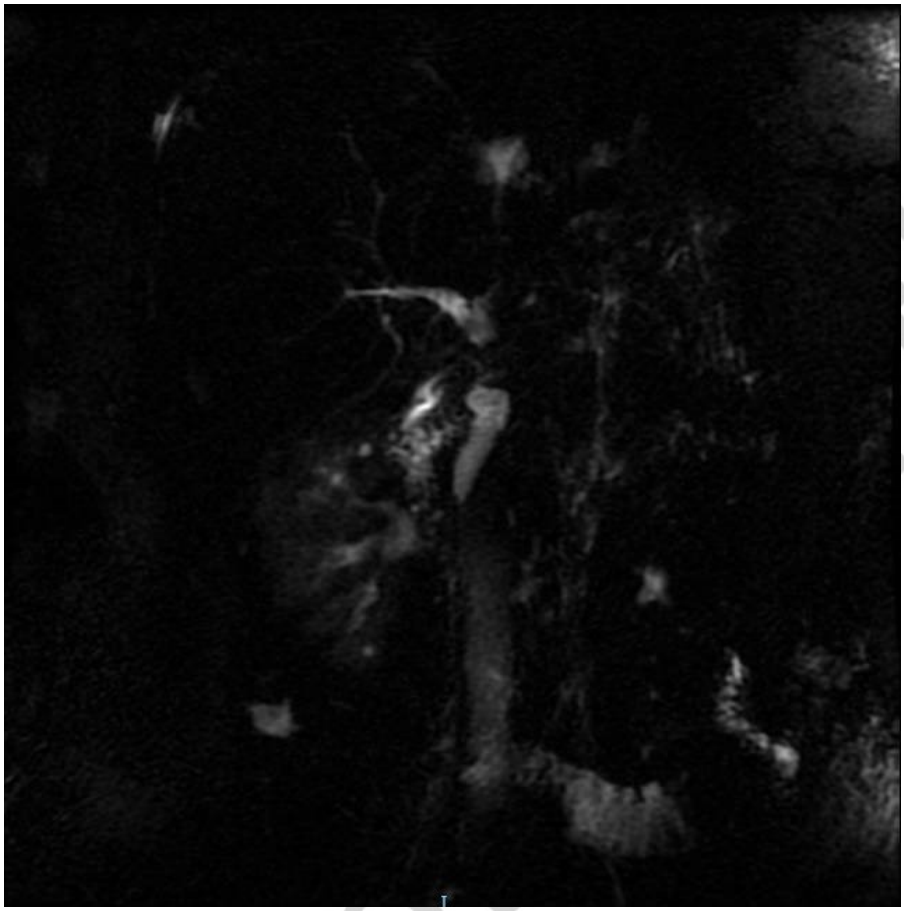
identified through immunohistochemical staining for IgG4.



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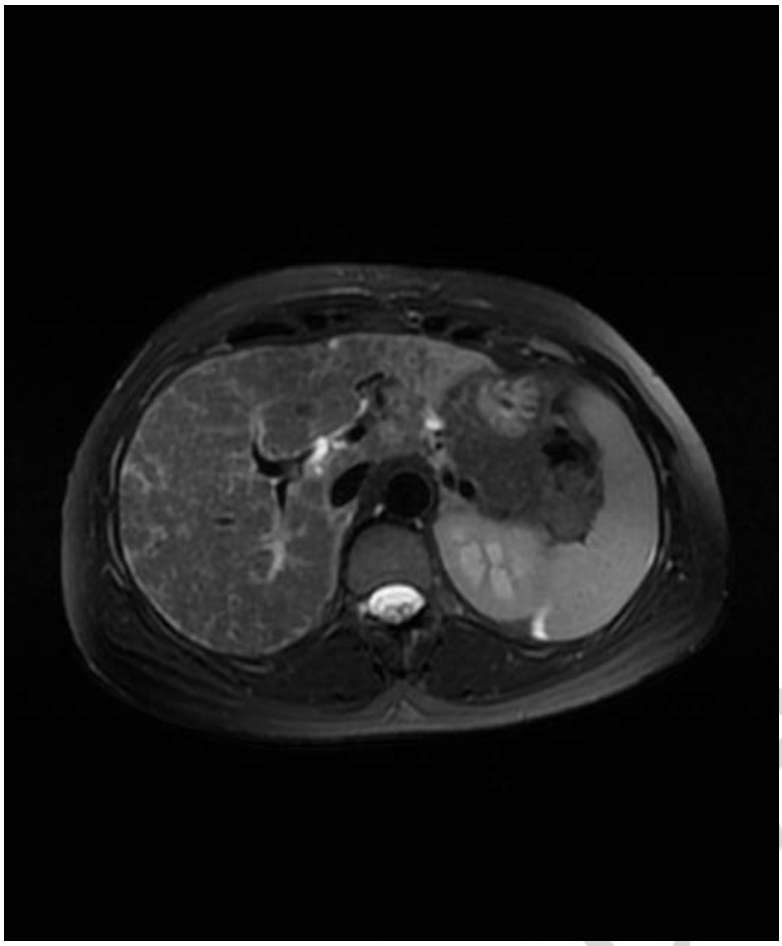

Figure 2-3. In the cholangio-RMI images, a slight dilation of the common bile duct of 8 mm is observed, without identifying stones or masses. A stenosis of the common hepatic duct of unspecified origin is observed with slight dilation of the intrahepatic bile duct.