IgG4 Sclerosing Cholangitis and Post Infantile Giant Cell Hepatitis: A Case Report of an Extraordinary Co-presentation

Maha M El-Sabaawy1, Eman Abdel-Sameea1, Ayat R Abdallah2, Ahmed El-Refaey1, Mervat Soltan1 and Nemine Ehsan1

Department of Pathology, National Liver Institute, Menoufia University, Egypt

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Abstract

Background: Giant cell hepatitis is rarely described in adults; referred to as post infantile giant cell hepatitis (PIGCH). Most reports have mentioned PIGCH's association with systemic lupus erythematosus, autoimmune hepatitis, lymphoma, and leukemia. However, links with other medical disorders are still evolving.

Reports of primary sclerosing cholangitis (PSC) presenting as IgG4-SC has been typically described in association with other IgG4-related disorders, most frequently autoimmune pancreatitis. However, some cases of isolated IgG4-SC have been reported. Herein; we report a case of IgG4-SC presented by PIGCH.

Case description: A 29-year-old gentleman presented with two month jaundice and biochemical evidence of acute hepatitis. He reported no history of drug exposure, had no gall bladder or pancreatic disease, nor prior similar attacks. The work up revealed negative serology for viral hepatitis. Markers of autoimmune liver disease were negative except for pANCA, and serum levels of pancreatic enzymes, copper and ceruloplasmin were normal, and urinary copper was normal.

Results: Abdominal sonography and MRCP showed normal pancreas and biliary tract. ERCP showed that the common bile duct had a single short narrowed segment with thickened walls. Histological examination of colonoscopic biopsies taken from the terminal ileum and colon demonstrated no pathological alterations. Liver histology showed evidence of parenchymal extinction with extensive giant cell transformation, ductular proliferation, cholestasis, and positive IgG4 staining, a picture suggestive of PSC and PIGCH.

Discussion: In this case, we did not test for serum levels of IgG4, and resorted to immune-staining of liver tissue, as this is the hallmark for diagnosing IgG4-SC. Histopathological features and, more definitely, the positive IgG4 immunostaining were present in the liver tissue, which were crucial in diagnosing this case as IgG4-SC (IAC).

Conclusion: This case presented with both IgG4-SC and biopsy proven PIGCH, and had a favourable outcome with biliary drainage and immuno-suppression therapy

Keywords: Pancreatobiliary system; Abdominal ultrasound, Cholangiopathy; Immunosuppressive agents; Liver cirrhosis

Introduction

Primary sclerosing cholangitis (PSC) is characterized by chronic inflammation of the extrahepatic and/or intrahepatic bile ducts along with obliterative fibrosis and ultimately, liver cirrhosis [1,2]. Multidisciplinary team cooperation is essential for proper diagnosis of PSC [2]. Immunoglobulin G4-related disease (IgG4-RD) is a chronic, systemic, multiorgan, inflammatory and sclerosing disease [3]. IgG4 associated sclerosing cholangitis (IgG4-SC) - as a variant of PSC - had been correctly reclassified as IgG4-RD-SC) [4]. Being characterized by a favorable response to glucocorticoids and immunosuppressive agents makes the distinction between IgG4-SC and PBC mandatory [5]. The diagnostic value of IgG4 serum levels is questioned as about 40% of IgG4-RD patients have normal serum levels [4,5]. Interplay between IgG4 positive tissue immunostaining, along with both clinical and cholangiographic features of cholangiopathy, is required for proper diagnosis [5]. Histopathological discrimination between IgG4-SC and cholangiocarcinoma is essential; however, this is not usually easy with the difficulty in the endoscopic transpapillary bile duct biopsy [6].

PIGCH is a histological description with unspecified etiology that clinically presents by disturbed liver function [7]. It represents a rare form of acute liver injury that can progress to fulminant hepatic failure, occasionally even necessitating liver transplantation [8]. The multinucleated giant hepatocytes are the discriminative histopathological feature of PIGCH [9]. Autoimmunity and infection are the two pathognomonic milestones of PIGCH [10].

Case Presentation

A 29-year old male accountant presented to the National Liver Institute’s hospital with two month jaundice associated with itching, nausea and vomiting that have been gradually increasing, with no fever. The patient had no history of prior medical problems. Clinical examination revealed jaundice and a mildly enlarged liver. Laboratory investigations confirmed the diagnosis of acute hepatitis (Table 1, Figures 1 and 2). Abdominal ultrasound and MRCP demonstrated normal images for the gall bladder and pancreatobiliary system. He was negative for hepatitis B surface antigen (HBsAg) anti-hepatitis B core (Hbc)-IgG, anti-Hbc-IgM, anti-EBV-IgM, anti-CMV-IgM, anti-EBV-IgM, anti-CMV-IgM, anti-

*Corresponding author: Maha Elsabaawy, Department of Hepatology, National Liver Institute, Menoufia University, Egypt, Tel: 020482223216; E-mail: maha.ahmed@liver.menofia.edu.eg

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HIV-Ab, and anti-HSV-IgM), and polymerase chain reaction (PCR) for HCV-RNA. Serum ferritin and urinary copper were within normal ranges. Antinuclear antibody (ANA), ant-smooth muscle antibody (ASMA) anti-mitochondrial antibody (AMA) and anti-liver-kidney microsomal antibody (anti-LKM-1) were negative, and perinuclear anti-neutrophil cytoplasmic antigen (p-ANCA) was positive (1/120). Serum levels of alpha-fetoprotein, carcinoembryonic antigen and CA19-9 were within normal ranges.

### Results

Histopathological examination revealed moderately disturbed lobular architecture by fibrous expansion of the portal tracts exhibiting moderate bile ductular proliferation with accompanying portal tract edema with moderate to marked mixed inflammation (lymphoplasmacytic and neutrophils) exceeding the limiting plates with the numerous IgG4 positively stained plasma cells both in bile ducts and liver tissue. There was moderate bile duct proliferation with marked intracellular and intracytoplasmic cholestasis. Parenchyma showed lobular disarray with loss of trabecular arrangement of hepatocytes that was totally replaced by giant cell transformation. This picture favored the diagnosis of IgG4-SC with cirrhosis and giant cell hepatitis (Figures 3-7). By the second week, laboratory data showed peaking of liver enzymes both hepatocellular and cholestatic with persistence of hyperbilirubinemia. The patient received antihistaminics and phototherapy for itching. ERCP showed a short segment of thickened CBD (Figure 8) with dilatation of the intrahepatic biliary radicles, further supporting the diagnosis of SC, but warranted exclusion of cholangiocarcinoma. Biopsy from thickened segment of the common bile duct (CBD) was technically unfeasible, and a precut followed by a 10 French plastic stent insertion were done. Colonoscopy was normal and histopathological examination of biopsies taken from the colon and terminal ileum demonstrated no pathological alterations.

### Table 1: Laboratory data.

| Test                  | 2 weeks Before Admission | On Admission | Week 1 | Week 2 | Week 3 | Week 4 | After ERCP | On Discharge | 1 month later |
|-----------------------|--------------------------|--------------|--------|--------|--------|--------|------------|--------------|---------------|
| Total bilirubin (mg/dL) | 14.8                     | 34.75        | 24.1   | 24.5   | 22.7   | 18.8   | 11.6       | 5.2          | 2.1           |
| Direct bilirubin (mg/dL) | 13.2                     | 29.35        | 22.5   | 23.8   | 20.1   | 16.3   | 9.8        | 4.3          | 2             |
| Total Protein (gm/dL)  | --                       | 8.7          | 5.8    | --     | 5.6    | 5.5    | 5.9        | 6            | 6.1           |
| Albumin (gm/dL)        | --                       | 3.8          | 3.1    | 3.5    | 3.5    | 2.9    | 2.9        | 3.1          | 3.9           |
| AST (IU/L)             | 169                      | 208          | 178    | 204    | 176    | 171    | 157        | 76           | 44            |
| ALT (IU/L)             | 499                      | 156          | 109    | 187    | 105    | 90     | 101        | 82           | 43            |
| ALP (IU/L)             | --                       | --           | 156    | 137    | 161    | 149    | 123        | 152          | 133           |
| GGT (IU/L)             | 122                      | 47           | 39     | 37     | 43     | 38     | 64         | 64           | 63            |
| Urea (mg/dL)           | 16                       | 14           | --     | --     | --     | --     | --         | 15           | 18            |
| Creatinine (mg/dL)     | 1.2                      | 0.6          | 0.9    | --     | --     | --     | --         | 0.7          | 0.5           |

GGT: Gamma-Glutamyl Transpeptidase; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase.
The patient improved further in both general condition and laboratory investigations. Endosonography (EUS) showed no abnormality, and biopsies taken from the distal common duct showed no evidence of malignancy.

One year later the patient had normal liver tests, and liver stiffness measurement by Fibroscan showed the presence of cirrhosis (stiffness was 11 kPa). Repeat examination of terminal ileum and colonic tissues revealed absence of features of inflammatory bowel disease.

**Discussion**

PSC is a chronic cholestatic disorder with significantly increased risk of cholangiocarcinoma (CCA) that demands constant vigilance [11]. The heterogeneous presentation characterizing PSC involves at least four variants: “Classical” PSC (involving the intrahepatic or extrahepatic biliary tree or both), small-duct PSC, PSC/autoimmune hepatitis (AIH) overlap syndrome, and the IgG4 associated cholangitis (IgG4-SC) or immune associated cholangiopathy (IAC) [12].

The diagnosis of IAC can be challenging because of paucity of related scientific work and lack of high level evidence of management [4].

IAC is a distinguished variant of PSC, characterized by elevated serum IgG4 and infiltration of IgG4-positive plasma cells in bile ducts and liver tissue, with notable association with autoimmune pancreatitis (AIP) [13].

The validity of serum IgG4 as a diagnostic marker for IgG4-SC (IAC) has been repeatedly questioned. Many studies have shown associations between elevated serum IgG4 and non-IgG4 disorders as cholangiocarcinoma, pancreatic carcinoma, inflammatory bowel disease and systemic lupus erythematosus (SLE). In addition, IgG4 levels have been found within the normal range in up to 40% of patients having typical histopathological diagnosis of IgG4-SC, and one half of those with elevated IgG4 do not meet IAC diagnostic criteria [14].

In this case, we did not test for serum levels of IgG4, and resorted to immune-staining of liver tissue, as this is the hallmark for diagnosing IgG4-SC. Histopathological features and, more definitely, the positive IgG4 immunostaining were present in the liver tissue, which were crucial in diagnosing this case as IgG4-SC (IAC). Infiltration of IgG4 positive plasma cells and the presence of periportal fibro-inflammatory nodules were evident in the present case, and were previously reported as features suggestive of IgG4-RD-SC. Ductopenia and periductal concentric fibrosis, typical of the prototype PSC, were absent in this case [15].

Additional sensitive but less specific markers of IAC include hyper gamma-globulinemia (observed in 50% of patients), antinuclear antibodies (40–50%), rheumatoid factor (20%), and eosinophilia (15–25%) [16]. Autoantibody against SS-A (Ro) or SS-B (La), antimitochondrial antibody, and antineutrophilic cytoplasmic antibody (ANCA) are all exceptional (<5%) in IAC [17]. Therefore, the positive P-ANCA reported in this case pointing to PSC does not exclude the possible presence of IgG4-SC.

Comprehensive histopathological analysis showed that 23% of liver explants of PSC patients had increased immunohischemical staining of IgG4 periductal plasma cells, with corresponding histopathological features of classic PSC. Some authors have stated that combined histological findings and positive immunostaining are not enough to diagnose IgG4-SC [18]. Therefore, other diagnostic tools as serum markers and radiologic studies are essential, not only for IAC diagnosis, but also for ruling out the possibility of cholangiocarcinoma, especially in patients’ presenting with hilar cholangiopathy [19].
ERCP had displayed superior results over the less invasive MRCP in recognition of early or single large duct PSC. The MRCP views in these conditions might not be the most advantageous [1] which might explain normal MRCP in this case.

Valchou et al., in their study of IAC cases, found 43% of cases presenting with isolated extrahepatic bile duct involvement, and only 5% with intrahepatic bile duct involvement, while the copresentation was evident in 52%, and in 20% only the intra-pancreatic portion of the common bile duct was involved [20]. Isolated strictures of the distal common bile duct also are common [21]. Placement of a temporary endoscopic biliary stent or percutaneous biliary drainage was performed in 26 patients (59%) to relieve jaundice [20]. According to the findings of the ERCP, the present case belongs to the group of isolated CBD stricture and placement of a plastic stent was successfully undertaken.

Type 1 autoimmune pancreatitis (AIP) is part of the IgG4-RD that often affects multiple organs including the pancreas, bile ducts, salivary glands, kidneys and lymph nodes [22]. The isolated IgG4-SC without the mutually described AIP has been reported in a small number of cases. It has been reported that AIP is absent in 10% of IAC cases [23,24]. A recent report described a series of six Japanese cases of IAC without clinically manifest AIP [25] and the current case is similar to the cases in this report.

Patients with IgG4-RD respond beneficially to corticosteroid therapy, especially when given at early stages. A good initial therapeutic response to corticosteroids is characteristic, particularly in those whose excessive tissue fibrosis has not yet supervened [20]. Without treatment, IgG4-SC may be self-limited, or it may asymptptomatically progress and lead to biliary cirrhosis [20].

Despite the proposed mutual autoimmune background for both ailments, the association between AIC and inflammatory bowel disease is still blurred, with a few scattered understudied studies. Ravi et al. had detected inflammatory bowel disease in 6% of patients with proved autoimmune pancreatitis, while in Zamboni et al. the incidence heightened to 17% [26,27].

PIGCH is rare histopathological description that has been reported basically in connection to serious medical disorders [10]. Whereas its pathogenesis remains unsettled; amalgamated mononuclear hepatocytes versus nuclear proliferation without cell division have been proposed as the pathogenic basis [28].

In most of the time PIGCH presents as self-limited acute hepatitis but it can be chronic or progressively fulminant [29]. However, the background etiology is the main determinant of the outcome after one or repeated attacks of PIGCH.

This case presented with prolonged cholestasis and acute hepatitis, along with combined histological features of both PIGCH and IAC. In absence of PIGCH related etiologies previously mentioned in the literature, the concurrent occurrence of GCH in this case could be attributed to the existence of IAC. Apart from this case, only a few cases of PIGCH presenting simultaneously with classic type PSC/ autoimmune hepatitis overlap cases have been reported [9,30,31].

Conclusion

This case presented with both IgG4-SC and biopsy proven PIGCH, and had a favourable outcome with biliary drainage and immuno-suppression therapy.

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