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Case Report

IgG4 Sclerosing Cholangitis: Entity Rarely Described in Children

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Abstract

IgG4-related sclerosing cholangitis (IgG4-SC) is known in the adult patients as a steroid-responsive biliary disease, frequently associated with autoimmune pancreatitis; The diagnosis of IgG4-SC may be difficult to differentiate from primary sclerosing cholangitis (PSC) or cholangiocarcinoma; This entity is been described in the absence of pancreatic implication. It is defined by high level of serum IgG4 in contrast to primary sclerosing cholangitis. It's morphologically characterized by dense lymphoplasmacellular infiltration, particularly IgG4+ plasma cells and CD4+ T cells and extensive fibrosis in bile duct. In patients with IgG4-related sclerosing cholangitis, response to steroid therapy is high; in patients with PSC corticosteroid therapy is unsuccessful. An Early recognition of IgG4-SC can save patients from potential harmful and unnecessary surgical interventions. In the literature, cholangiocarcinoma in patients with IgG4- related sclerosing cholangitis was not described, whereas cholangiocarcinoma develops in up to 10-30% of patients with PSC. We present the case of a 3 years old child with features of sclerosing IgG4 cholangitis with asymptomatic elevation in liver enzymes, bile duct strictures on imaging, characteristic pathology findings, elevated serum IgG4, without signs of pancreatic involvement, and excellent response to corticosteroids. Pediatric gastroenterologists and hepatologists, as well as pediatric hepatopathologists, need to be aware of IgG4-SC as a disease entity.

Keywords

IgG4 Level, Cholangitis, Steroid, Lymphoplasmacytic Infiltration, Child

1. Introduction

IG4 sclerosing cholangitis is the biliary manifestation of a steroid-responsive multisystem fibroinflammatory disorder in which the affected organs show a characteristic lymphoplasmacytic infiltrate rich in IgG4-positive cells. [1]

There is a clinical observation of a 3-year-old boy, the clinical, biological, radiological, histological, therapeutic and evolutionary characteristics of this entity very rarely described in the pediatric field [12].

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2. Clinical Case

A 3-year-old child presented in December 2021 to the pediatric gastroenterology department for intermittent cholestatic jaundice evolving for 1 year with enormous abdominal distension of progressive installation without pain or digestive hemorrhage and noted no symptoms. associated lung. During the interrogation with the family we did not find any notion of consanguinity; the mother was followed for cholelithiasis programmed for a possible cholecystectomy, there is no evidence of autoimmunity or similar cases in the family. The physical examination on admission found a child weighing 12 kg (at least two standard derivations from normal), the body mass index was 12, 24 Kg/m2 (at the 93rd percentile) with a height of 99 cm (i.e. minus two standard leads compared to normal); generalized jaundice with diffuse scratching lesions; the liver extended 7 cm below the right costal edge with a hepatic arrow of 10.4 cm, a splenomegaly of 4 cm below the left costal edge, we did not note collateral venous circulation, nor ascites and no signs mucocutaneous hemorrhages. The rest of the clinical examination was unremarkable. no ascites and no mucocutaneous haemorrhagic signs.

Liver tests during his initial evaluation found obvious cytolysis with alanine aminotransferase (ALT) at 300 U/L (normal 7 – 45 U/L), aspartate aminotransferase (AST) at 394 U/L (normal 8 – 50 U/L), albumin level 35 g/l, total bilirubin 50 mg/l With direct fraction 35mg/l, alkaline phosphatase 622 U/L (normal 169 – 372 U/L), an elevated gamma-glutamyl transpeptidase (GGT) level of 441 U/L (normal 6 – 29 U/L). Analysis of coagulation factors revealed a prothrombin level of 63% with a normal level of factor V (89% activity). The initial blood count had objectified a hemoglobin level at 11.9 g/dl, normal white blood cells at 5740/mm 3 and thrombocytopenia at 85000/mm 3.

Faced with this picture of clinical and biological cholestasis. An exhaustive etiological assessment was requested. The serological profile of autoimmune hepatitis was requested, in particular, anti-nuclear antibodies are negative, anti-smooth muscle antibodies negative, anti-endoplasmic reticulum of liver and kidney (anti-LKM 1 and 3) negative, negative anti cytosol antibodies, negative anti-soluble antigen (anti-SLA), ANCA were positive supplemented by protein electrophoresis showing no abnormalities; A sweat test was negative; a copper balance returning to normal. The metabolic assessment comprising the dosage of lactates, pyruvates with chromatography of amino and organic acids was strictly normal.

His serum IgG4 level was markedly elevated at 2.9 g/l (normal values 0.01 -0.54 g/l). Lipasemia was normal at 26 IU/l. In view of these results, the possibility of IgG4 cholangitis was strongly suggestive.

On the radiological level, the ultrasound had shown an appearance of an enlarged liver with a hepatic arrow at 10.4 cm with regular contours and homogeneous echostructure, supplemented by a Bili-MRI objectifying a discreet enhancement of the head of the pancreas which is mentioned as physiological, without dilation of the intra or extra hepatic bile ducts and absence of individualization of image of stenosis or dilation of the bile ducts.

Histology had objectified an aspect of sclerosing cholangitis with an inflammatory infiltrate comprising lymphocytes, plasma cells and eosinophilic polynuclear cells with absence of availability of an immunostaining of IgG 4 (Figures 1, 2).

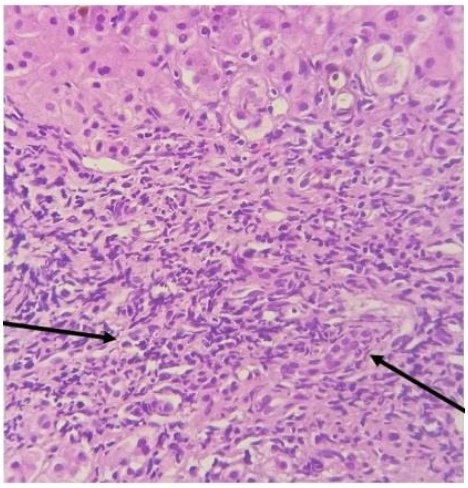

Figure 1. *Histological image stained with hematein eosin (Magnification x40) which shows the portal inflammatory infiltrate mainly lymphoplasmacytic associated with destruction of bile ducts.*

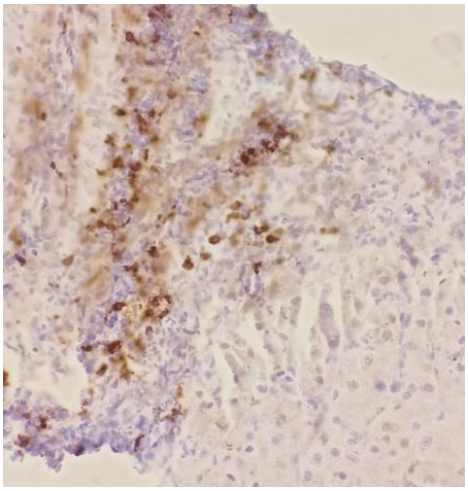

Figure 2. *Immunohistochemical study with CD138 Magnification x 40) highlighting the presence of plasma cells taking on a membrane stain.*

An IgG4 disease extension assessment was requested, in particular a chest CT scan which had shown a micronodular infiltrate with centrilobular bronchiolar distribution in the left basal region, this confirmed the pulmonary extension of the disease, all the more so it was not reported. Associated pulmonary symptoms (Figure 3). The ophthalmological examination came back normal.

Faced with this clinical, biological and histological picture

strongly suggestive of IgG4 cholangitis; the patient was put on corticosteroids at a rate of 1 mg/kg/day associated with ursodeoxycholic acid at a dosage of 15 mg/kg/day with the addition of an immunosuppressive treatment based on azathioprine aimed at cortisone sparing.

In eight months of treatment, there was a clear regression of hepato-splenomegaly, complete disappearance of jaundice with on the biological level the ASAT went from 458 U/L to 150 U/L and the ALAT from 362 U/L to 120 U/L. Total bilirubin decreased from 80 mg/dl to 40 mg/dl.

Prednisone was gradually reduced over 6 months and maintained at a low dose (0.1 mg/kg/day). Azathioprine and ursodeoxycholic acid were kept without detectable side effects. There is in the table below the biological evolution since the initial presentation and also the treatments received (table 1).

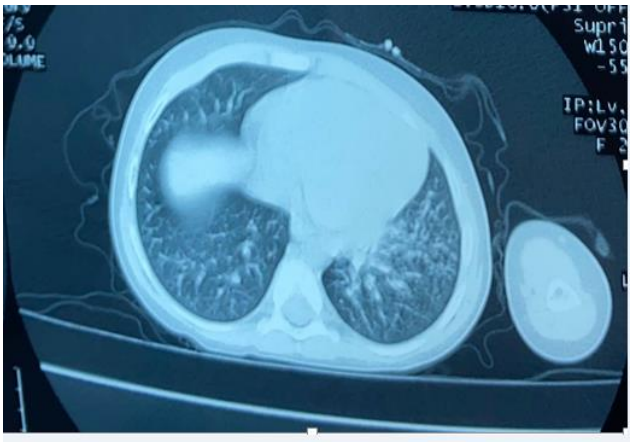

Figure 3. *Micronodular infiltrate with centrilobular left basal bronchiolar distribution.*

Table 1. *Biological monitoring of the patient with the various treatments received.*

	AST (U/l)	ALT (U/l)	TB (mg/l)	BC (mg/l)	LIPASE (U/l)	IgG4 (U/l)	Prednisone	Azathioprine	Ursodeoxycholic acid
At initial presentation	458	362	80	60	17	2.7	1m/kg/d	-	15mg/kg/d
6 weeks after diagnosis	382	295	73.7	50.5	12	-	1m/kg/d	1.5mg/kg/d	15mg/kg/d
10 weeks after diagnosis	292	235	48	29	20	2.6	1m/kg/d	1.5mg/kg/d	15mg/kg/d
6 months after diagnosis	242	136	42	23	23	2.6	0.5m/kg/d	1.5mg/kg/d	15mg/kg/d
8 months after diagnosis	150	120	41	21	16	2, 5	0.1mg/kg/d	1.5mg/kg/d	15mg/kg/d

3. Discussion

IgG 4 cholangitis is the biliary manifestation of a steroid-responsive multisystem fibroinflammatory disorder, within the touched organs are infiltrated by IgG4-positive lymphoplasmacytic cells. The pathophysiological mechanism is unclear. If we untreat the patient, the disease could causes fibrosis and irreversible organ destruction. It is an entity described mainly in adults; it is an entity of biliary disease not recognized by pediatricians. There are currently only three pediatric cases that have been reported in the literature. This pathology is mostly observed in men during the fifth and sixth decades of their lives and presents as cholestatic jaundice, weight loss and mild abdominal discomfort. It is associated with autoimmune pancreatitis in 90% of cases [1, 3, 4].

The mode of revelation in the patient was cholestatic jaundice associated with abdominal distension dating back to the age of 1 year with failure to thrive.

Faiz Karim did a systematic review on IgG4 disease in pediatrics. Of a total of 740 articles, 25 cases of pediatric IgG4 disease were reported. The median age of the children was 13 years old, 64% of the patients were girls. IgG4-related orbital disease was at 44% and type 1/IgG4 autoimmune pancreatitis was at 12%, thoses are the main causes of this disease. Less commonly, other manifestations such as pulmonary manifestations with a single case of cholangitis has been identified. Almost all cases have been proven histologically. Prednisone was the optimal treatment who gives a favorable clinical response in 83% of cases. The maintenance treatment with steroid-sparing agents was recommended in 43% of cases. Rituximab gave good results in five cases, while mycophenolate mofetil, azathioprine and methotrexate were successful in 50% of cases [2, 9, 10].

In the patient of this case, azathioprine was used as a steroid-sparing agent in order to be able to reduce the doses of corticosteroids and avoid side effects. The clinical evolution was good but on the biological level one always announces the persistence of a less important cytolysis compared to the initial presentation.

The treatment of IgG4 cholangitis is mainly based on corticosteroids. There is no recommendations on the dosage of prednisone, but in most of cases a dose of 1 to 2 mg/kg/day should be suitable and adjusted according to the aggressive-

ness of the disease. Prednisone treatment is quickly effective, it must be continued for 2 to 6 weeks after commencement. According to previous studies, particularly in adults, approximately 25% of patients experience disease relapse despite maintenance treatment with prednisone, hence the need for the use of steroid-sparing agents such as mycophenolate mofetil, azathioprine and methotrexate. Recently, evidence of the serum IgG4, when elevated, can be used to monitor disease activity after initiation of therapy, but the role of serum IgG4 as markers of disease activity has been fully defined [5, 6, 11].

Patients with IG4 cholangitis are likely to develop autoimmune pancreatitis and warrant close follow-up. Screening in children with suspected overlap syndrome may be indicated, particularly for patients with pancreatic involvement and/or no evidence of inflammatory bowel disease and may identify a subset of patients who respond better to immunosuppression. [7, 8, 13].

4. Conclusions

IgG4-associated cholangitis is a fibro-inflammatory disease that is an entity rarely described in pediatrics, which must be part of the differential diagnosis of all unexplained biliary strictures since it is a pathology that responds to immunosuppressive treatments unlike other forms of cholangitis.

Diagnosis can be made on the basis of histology or after a trial of steroids in a patient with a high documented clinical suspicion and a good clinical, biological and radiological analysis. Although the initial response to steroids is excellent, relapses are common after early discontinuation of steroids. imunomodulatory drugs can maintain long-term remission.

Abbreviations

SC	Sclerosing Cholangitis
PSC	Primary Sclerosing Cholangitis

Author Contributions

Dalal Ben Sabbahia: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Halima Msaaf: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Resources, Writing – original draft Writing – review & editing

Meriem Atrassi: Resources, Supervision, Visualization

Sara Moukhlis: Data curation, Funding acquisition, Resources

Nissrine Bennani: Formal Analysis, Methodology, Validation

Abdelhak Abkari: Supervision, Validation

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Conflict of Interest

The authors declare no conflicts of interest.

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