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Case Report

IgG4-Related Disease and Monoclonal Gammopathy: Case Report

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Abstract

Background: IgG4-related disease (IgG4-RD) is a progressive, chronic, atypical presenting clinical entity characterized by an elevated serum IgG4 level, leading to an immune-mediated fibroinflammatory condition affecting various organs.

Case Summary: We present the case of a patient with clinical manifestations compatible with chronic pancreatitis due to the time of evolution. Physical examination revealed submaxillary, axillary, and inguinal lymphadenopathy and pain on abdominal palpation. Laboratory tests showed eosinophilia and a hepatocellular pattern in the liver profile. Immunofixation showed a monoclonal IgG lambda band with IgG4 values of 1183 mg/dl. To confirm the diagnosis of autoimmune chronic pancreatitis associated with IgG4-related sclerosing cholangitis, imaging tests were performed, which showed intrahepatic and extrahepatic cholestasis associated with pancreatic parenchymal alterations compatible with this entity. Subsequently, upon initiating glucocorticoid therapy, the patient evolved favorably.

Conclusion: ER-IgG4 is a rare condition that causes inflammation and scarring in various organs. It is hard to diagnose and often mistaken for other diseases. The pancreas and biliary tract are frequently affected.

INTRODUCTION

IgG4-related disease (IgG4-RD), initially described in the pancreas, is of autoimmune origin, and can affect any organ in a localized or multisystem fashion [1]. It is histopathologically characterized by inflammation with a dense lymphoplasmacytic infiltrate, obliterative phlebitis and stromal fibrosis [2]. Traditionally, the diagnosis was based on histopathologic findings. Currently, the diagnosis is based on the 2019 ACR/EULAR classification criteria [3]. IgG4-RD has been associated with various clinical conditions and polyclonal gammopathies. We present a case of pancreatic-hepatic-biliary IgG4-RD associated with eosinophilia.

CASE PRESENTATION

Peruvian male patient, 71 years old, farmer, with no previous comorbidities, presented disease 1 year ago with severe abdominal pain in the upper hemiabdomen, without irradiation, which worsened with food intake; in addition, the patient had progressive hyporexia and sometimes nausea. The abdominal pain persisted and increased in frequency and intensity. Three months before admission, the patient noticed sporadic episodes of steatorrhea and choluria. Due to the persistence of symptoms and weight loss of 20kg, the patient was admitted to the hospital. At the initial examination the patient was thin and pale; lymphadenopathies were found in the submaxillary region of 1 cm, axillary of 1.5 cm and inguinal of 3 cm, which were nontender, soft, mobile, and not attached to deep tissues; and the abdomen was painful on palpation in the epigastrium and right hypochondrium. The initial laboratory tests are listed in Table 1. Due to the patient's symptoms, the possibility of chronic pancreatitis was raised, and a complete tomography was performed, showing intra- and extrahepatic biliary tract with diffuse wall thickening, gallbladder with thickened walls, pancreas with diffuse volume increase predominantly in the head and uncinate process with peripancreatic inflammatory changes and lamellar collections were evidenced. Due to the imaging findings and the altered hepatic profile suggesting a hepatocellular picture associated with intrahepatic and extrahepatic cholestasis, a magnetic cholangioresonance (MRI) was performed, showed foci of stenosis in the intrahepatic biliary tract with fusiform configuration, asymmetric thickening of the walls of the distal common bile duct, gallbladder wall with diffuse thickening , without evidence of gallstones, loss of normal lobulation of the pancreas; in addition in both kidneys with multiple patchy areas of low signal on T2 in the periphery of the renal cortex up to 2.3 cm in size, bulging the renal capsule and showing late contrast enhancement. Endoscopic ultrasound was also performed and

Table 1. Pre-treatment and post-treatment laboratory tests

	Before Therapy		After therapy	Reference ranges
Hemoglobin	8.2	9.2	10.4	>13mg/dL
Platelet count	243 000	202000	305 000	150 000 – 450 000
Eosinophils	2288	1990	880	0-500
Creatinine	0.64	0.58	0.44	0.74-1.35mg/dL
Albumin	1.59	1.74	2.37	3.4-5.4g/dL
AST	122	166	128	8-33IU/L
ALT	88	83	71	29-33IU/L
Alkaline phosphatase	477	701	699	20-140IU/L
CRP	1.86	1.04	0.65	<0.3mg/dL
Serum IgG4	1183	2400	-	<140mg/dL
Protein-to-creatinine ratio	11.06	13.67	7.57	<0.2
ANA	Negative	-	-	
ANCA	Negative	-	-	
Iron	65.99	-	-	12.5-32.2umol/L
Iron saturation	55.12	-	-	15%-50%
Ferritin	1363	-	-	30-300ng/mL
LDH	166	-	-	105-333IU/L

showed thickening of the gallbladder wall, diffuse thickening of the entire biliary tract including the common hepatic and common bile ducts. These imaging findings were consistent with IgG4-RD. On the other hand, the images incidentally showed renal lesions compatible with tubulointerstitial nephritis, which is usually present in IgG4-RD. Another important incidental finding was lung lesions: mild interstitial pattern, reticular opacities in the right upper lobe, apical pleural thickening and mediastinal adenopathies; all of which have been described in IgG4-RD.

Because of the anemia and hypereosinophilia, hematologic studies were performed to rule out a malignant neoplasm. Because of the anemia, an upper endoscopy was performed, which revealed atrophic pangastritis, and a lower endoscopy was normal. Due to the finding of hypereosinophilia, parasitosis, allergies and hematologic malignancies were excluded. Due to the elevated globulin levels, an electrophoretic proteinogram was performed showing a monoclonal increase in gamma globulins and a monoclonal IgG lambda band in immunofixation. A dosage of immunoglobulins was performed, which showed a significant increase of IgG4 from 1183 mg/dl (NV: 11 - 157 mg/dl). The marked elevation of IgG4 in combination with the clinical and imaging findings made the diagnosis of IgG4-RD very likely, but other pathologies with similar findings and IgG4 elevation had to be excluded.

The patient underwent a bone marrow aspiration and biopsy, which revealed adequate cellularity for age, no neoplastic cells and no infiltration of other cells. Flow cytometry showed no neoplastic cells or pathologic lymphoid cells. Autoimmunity studies were also performed and were all negative. Additionally, peripheral blood was tested for the FIP1L1/PDGFRA fusion gene by PCR, which was negative. Finally, an inguinal lymph node biopsy was performed which showed hyperplasia of lymphoid follicles with a germinal center with tingled bodies surrounded by mature lymphocytes without concentric arrangement. The interfollicular area was expanded by lymphoid cells. Immunohistochemistry showed IgG4 > 60%. With these findings and in the absence of oncohematologic and/or autoimmune disease, a diagnosis of multisystemic hepato-pancreato-biliary phenotypic IgG4-RD was made, in addition to pulmonary and renal involvement, all associated with IgG lambda monoclonal gammopathy. The initiation of corticosteroid therapy was decided. At the follow-up visit one month after starting treatment, the patient reported general improvement, no pain, no hyperbilirubinemia, appetite, and weight gain.

DISCUSSION

IgG4-RD is an immune-mediated systemic fibroinflammatory disease characterized by elevated IgG4 levels in blood and tissues. It is characterized by a dense lymphoplasmacytic infiltrate with a predominance of IgG4-positive plasma cells, usually accompanied by storiform fibrosis, phlebitis obliterans, and in certain cases with the presence of eosinophils, all of which can lead to fibrosis and organ failure [2]. Onset is usually subacute, and nearly half of the patients are asymptomatic. Four phenotypes have been described: hepatobiliary-pancreatic disease (31%), retroperitoneal fibrosis with or without aortitis (24%), disease limited to the head and neck (24%), and Mikulicz syndrome with systemic involvement (22%) [4]. The diagnosis is one of exclusion, and patients usually have a history of non-specific symptoms and repeated visits to medical services prior to diagnosis [4]. Timely diagnosis and appropriate treatment are among the determinants of the disease prognosis. An important clue in the evaluation of patients with suspected IgG4-RD is multisystem involvement, as evidenced clinically, laboratory, or imaging studies. Clinically, our patient presented with a chronic history of intermittent abdominal pain with episodes of choluria associated with weight loss (Figure 1).

In the laboratory tests, there was an alteration of the mixed hepatic profile with predominance of cholestasis. Therefore, a cholangioresonance was performed, and showed increased volume and loss of normal pancreatic lobulation, stenosing lesions in the biliary tract, asymmetric thickening of the common

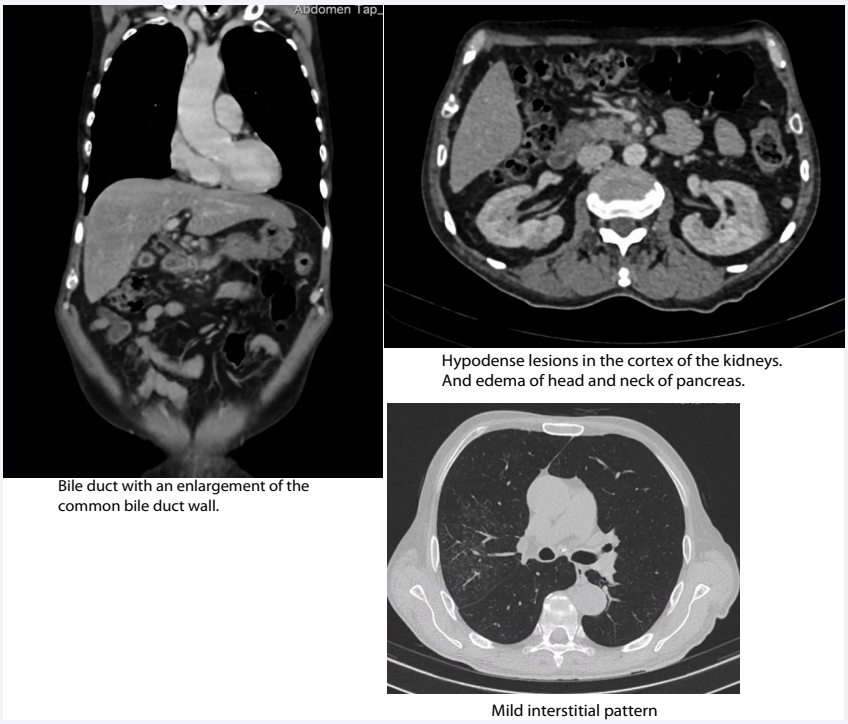
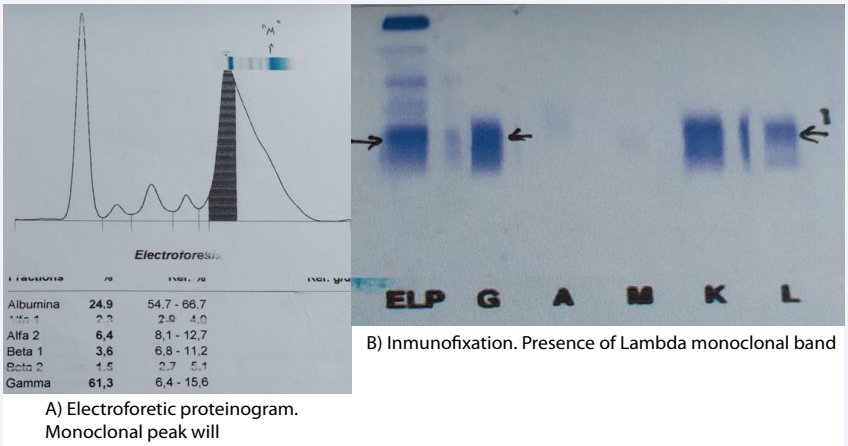


Figure 1 A. CT coronal section, B. CT abdominal axial section C. CT with contrast pulmonary window.



Data Supplements:

bile duct. The finding of increased pancreatic volume with loss of its lobulated borders is called "sausage pancreas", this is caused by periductal fibrosis which causes narrowing of the pancreatic duct and, in some cases, of the common bile duct [5]; all this can cause an extensive sclerosis that ends up altering the architecture of the pancreas [5]. These features are consistent with autoimmune pancreatitis type 1, which is usually associated with IgG4- related sclerosing cholangitis [5]. In addition, cholangioresonance revealed: intrahepatic bile duct stenosis with fusiform configuration and asymmetric thickening of the walls of the distal common bile duct; uncommon findings [5-7]. The literature describes that both intrahepatic and extrahepatic segments may be affected as a result of fibrosis, with focal or diffuse thickening of the bile duct wall, often associated with stenosis and dilatation [5-7]. Similarly, the diagnosis of bile duct strictures must be based on their location: hilar strictures may be confused with Klatskin's tumors, while distal common bile duct strictures may be caused by chronic pancreatitis, pancreatic cancer, or cholangiocarcinoma [8]. Based on the findings in our patient, the differential diagnosis proposed was primary sclerosing cholangitis (PSC), a chronic inflammatory disease of the intrahepatic and extrahepatic bile ducts characterized by progressive fibrosis and stenosis of the ducts. However, multiple segmental stenosis and biliary dilatation are usually visualized on cholangioresonance in patients with PSC, findings different from those found in our patient [9,10]. IgG4- RD affects the

kidney in approximately 7 to 24% of cases. Tubulointerstitial nephritis is the most common manifestation. Eighty percent usually have EMT lesions (hypodense, bilateral, and multiple lesions) predominantly in the cortex, and MRI usually shows lesions in the renal cortex with hypointense nodules on T2 [10]. Clinical presentation may include elevated creatinine, hematuria, proteinuria, and hypocomplementemia. However, asymptomatic presentation and incidental radiologic findings are also common, as in the case of our patient [11]. Between 15-35% of all patients with IgG4-RD have a thoracic involvement. Isolated thoracic involvement is about 10%. Most cases are found incidentally, as in the case of our patient. Up to 7 types of tomographic lesions have been described. Our patient had bilateral opacities, an interstitial pattern, and mediastinal nodules, all of which have been described in case series reports [12]. Hypereosinophilia is usually caused by allergic, parasitic, and oncohematologic diseases that have been excluded in the patient. Hypereosinophilia is a common finding in IgG4-RD, 20 to 40% of cases have eosinophilia and 50 to 80% have eosinophilic infiltrate in tissues, but it is very rare for peripheral blood eosinophilia to be >3000/uL and is an exclusion criterion according to the 2019 ACR/EULAR classification criteria [3]. The highest value in our patient was 2288. Hypergammaglobulinemia, eosinophilia, elevated IgE levels, and hypocomplementemia have also been reported as findings associated with IgG4-RD [1]. Excisional lymph node biopsy was performed and showed follicular hyperplasia. This is the most common of the 5 patterns described in IgG4-RD [12]. It is characterized by the presence of prominent follicular hyperplasia with benign features, well-formed mantle zones, and numerous macrophages in the germinal centers [13]. Plasma cells are present in follicular and extrafollicular areas with eosinophilic tissue infiltrate. It is important to note that obliterative phlebitis and stromal fibrosis are usually not found in the lymph nodes [12]. The finding of monoclonal gammopathy in IgG4-RD may be supported by polyclonal IgG4 migration in patients with high serum IgG4 levels [14]. This is characteristically manifested on immunofixation by a focal band connecting the beta and gamma fractions; a sign that the underlying process is IgG4-RD. It has also been described that the strong preference of IgG4 polyclonal antibodies for IgG4-kappa or IgG4-lambda may further simulate a monoclonal appearance on immunofixation analysis [14]. This was the case in our patient, where a monoclonal IgG4-lambda band was detected. However, the detection of this focal band could be mistaken for monoclonal gammopathy, which could lead to further unnecessary invasive diagnostic testing and delay the diagnosis. In fact, this finding could be mistaken for clonal proliferative processes such as multiple myeloma, Waldestrom's macroglobulinemia, and light chain amyloidosis [14].

There are numerous diagnostic criteria for this disease, which may vary depending on the organ involved; the most common and widely used are the ACR/EULAR 2019 criteria with high specificity [3]. Histopathology is not necessarily needed to evaluate the ACR/EULAR criteria, but a score of 20 or higher is mandatory [3]. Accordingly, an ACR/EULAR score of 40 points was achieved.

CONCLUSION

ER-IgG4 is a multisystemic fibroinflammatory disease with involvement of almost every organ. The diagnosis is difficult and by exclusion. The most common involvement is the pancreas and biliary tract. The ACR/EULAR 2019 criteria may help in diagnosis. Early treatment can prevent fibrosis and organ dysfunction.

AUTHOR CONTRIBUTIONS

Diego Pinto and Blanca Solis contributed to writing and revising the work, ensuring its intellectual quality and relevance, and approved the final version for publication. Bruno Portella also participated in revising the work, verifying its accuracy and integrity in all aspects. Jorge Huaringa conceived and designed the case study, critically reviewed the work for intellectual quality and relevance, and approved the final version for publication.

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