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RESEARCH ARTICLE

AN OVERLAPPING CASE OF IGG4-RELATED DISEASE AND SYSTEMIC LUPUS ERYTHEMATOSUS

Jarti Mariama[1], Aharbil Fatima Ezahra[1], El bouatmani Mouna[1], Nacir Oussama[1], Lairani Fatima Ezzahra[1], Ait Errami Adil[1], Oubaha Sofia[2], Samlani Zouhour[1] and Krati Khadija[1]

1. Gastroenterology Department at Mohamed VI Universal Hospital of Marrakesh, Morocco.
2. Laboratory of Physiology, University Cadi Ayyad, Marrakesh, Morocco.

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Abstract

Immunoglobulin G4-related disease (IgG4-RD) is a rare newly discovered systemic immune-mediated fibroinflammatory disease of unknown etiology that can affect multiple organs. Involvement of the pancreas and biliary tract is the most common and well described in the literature. It shares certain similarities with cholangiocarcinoma. IgG4 sclerosing cholangitis (IgG4-SC) is an immune-mediated process that results in inflammation and fibrosis of the pancreatobiliarytract. Although IgG4-SC is predominantly associated with autoimmune pancreatitis, IgG4-SC as its own entity can be difficult to diagnose. Our case is presenting the fact that systemic lupus erythematosus and autoimmune pancreatitis (AIP) and IgG4-related sclerosing cholangitis, revealed by jaundice with cholestasis disease can be present in the same patient with multiple overlapping features making accurate diagnosis challenging. There are still significant gaps in our understanding, particularly in terms of pathogenesis and factors that influence therapy response. Further observational and interventional research is needed to better manage this disease.

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Introduction:-

The discovery of IgG4-related disease (IgG4-RD) has transformed the management of pancreatic and biliary autoimmune diseases, which are characterised by fibro-inflammatory attacks that can involve one or more organs in a synchronous or metachronous manner [1,2]. The diagnosis of IgG4-SC is ultimately based on characteristic biopsy findings, although an elevated serum IgG4 level is required. Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease characterised by the formation of numerous autoantibodies and immune complexes leading to systemic organ involvement. More than 90% of cases of SLE occur in women, often starting in the childbearing years [4].

IgG4-SC is morphologically characterised by dense lymphoplasmacytic infiltration, particularly of IgG4þ plasma cells and CD4þ T cells, extensive fibrosis in the bile duct walls and obliterative phlebitis, and in contrast to PSC, patients with IgG4-SC often have elevated serum IgG4.

Corresponding Author:- Jarti Mariama
Address:- Gastroenterology Department at Mohamed VI Universal Hospital of Marrakesh, Morocco.

The pancreatic involvement of IgG4 disease was the earliest reported and is therefore the most studied. It usually presents as a chronic pseudotumour, but acute manifestations have also been reported. IgG4-RD can be mimicked by a variety of conditions, including pancreatic adenocarcinoma.

Biliary involvement is most commonly associated with pancreatic involvement, although isolated sclerosing cholangitis has been observed in some cases. It shares some similarities with cholangiocarcinoma.

IgG4-RD biliopancreatic involvement is known to be steroid sensitive with a significant risk of relapse or cortico-resistance. Immunomodulatory therapies such as thiopurines, methotrexate and rituximab have been shown to be necessary in some cases [3].

The main purpose of this case is to illustrate the different clinical and paraclinical aspects of this disease, as well as the challenges involved in its management.

Case:

A 38-year-old male patient with history of recurrent pancreatitis, he was referred to our department for acute epigastric pain andcholestatic jaundice evolving for one month with hair loss, joint pains for approximately last 3 yearsassociated with asthenia and weight loss. The clinical examination revealed generalized jaundice with right upper quadrant tenderness.

Initial labs showed cholestasis with elevated bilirubin (120.4 mg/L), conjugated bilirubin (102 mg/l), GGT (640U/l), ALP (787U/l), and cytolysis (AST: 77U/l, ALAT: 140U/l)Lipasemia was elevated to 190 U/l, Abdominal CT showed a body enlarged pancreas. MRCP revealed a normal common bile duct and dilated and stricture of multiple intrahepatic bile ducts with an enlarged pancreas

Serology for viral hepatitis and autoimmune laboratory testing came back negative. The serum level of IgG4 was raised to 2.04 g/l. Extensive workup revealed elevated anti-nuclear antibody (ANA) and elevated total immunoglobulin G (IgG) levels, and anti-dsDNA levels.

We first suspected an acute flare of chronic pancreatitis. The autoimmune origin was the most probable, given the absence of alcoholism, biliary stones, and metabolic abnormalities.

We finally retained the diagnosis of overlapping IgG4 sclerosing cholangitis with autoimmune pancreatitis related disease and lupus erythematosus. Corticosteroid therapy at 0.6 mg/kg/day of prednisolone was started for four weeks, then tapered to 5 mg/two weeks. After three months of corticosteroid therapy, jaundice disappeared, but the patient kept asthenia with cytolysis and cholestasis. The decision was to add azathioprine at a dose of 2 mg/kg/day and to maintain corticosteroid therapy at a dose of 5 mg/day After three months of azathioprine, the patient developed cirrhosis with ascitic decompensation and he died of hepatic encephalopathy.

Discussion:

Systemic lupus erythematosusis a chronicautoimmunediseasewith a variable clinicalpresentation and can affect any part of the body. The mostcommonpresentationis a mixture of skin, musculoskeletal, haematological and fatigue symptomswith positive serologies. The diagnosis of systemic lupus erythematosusshouldbebased on a combination of clinical and immunologicalfindings. [4]

IgG4 diseaseis a recentlydiscovered immune-mediateddisorderaffecting multiple organsystems. Itsepidemiologyisstillpoorlydescribed. In Japan, the prevalenceisestimated to be 1/600,000 and the annual incidence is 0.28-1.08/100,000 population [5]. The characterisation of thisentity has been the subject of an international consensus adopted in 2012 [6], and several diagnostic criteria have been defined, rangingfrom the JapaneseComprehensive Diagnostic Criteria (CDC) [7] to the ACR/EULAR classification criteria in 2019 [8]. Otherorgan-specificcriteria have been suggested.

Pancreaticdiseasewas the first described manifestation. It results in an enlargedpancreaswith progressive parenchymal destruction due to the progression of fibrosis [6]. The meanage of diagnosisis 60 yearswith a male predominance [9]. The clinicalpresentationisoften progressive, rarely acute, withjaundice in 75% of cases and

pruritus, steatorrhea and diabetessuggesting exocrine and endocrine pancreaticinsufficiency in over 60% of cases [10]. Radiologicalfindingsinclude an enlargedpancreaswithlack of lobulation and stenosis of the pancreatic duct.is seen. The dilation can sometimesbelocalised, raising the possibility of cancer. Echo-endoscopy can show similarabnormalities and allowpancreatic biopsies [11]. Histologyis the gold standard of diagnosis. Characteristicpathologicalfindings are lymphoplasmacyticinfiltrateswithprominent IgG4+ plasma cells, storiformfibrosis and obliterativephlebitis.

In daily practice, itis hard to obtain a representativesample of the pancreasusing fine needlesthrough a transparent approach or guided by echoendoscopy. The serum IgG4 levelis of great importance in establishing the diagnosis; athreshold of 135 mg/dl has been maintained for the positive diagnosisbecauseitdifferentiatesbetweenpancreatic cancer and chroniccalcifyingpancreatitis; this has a sensitivity of 90% and a negativepredictive value of 96%, but the specificity and positive predictive value are low at 60% and 34% respectively [12].

It accounts for 96% of AIP cases in Japan and at least 80% in the West. Pancreaticlesionsaccount for 41% of IgG4-RD sites [8]. The diagnosisdilemma has led international groups to develop a set of diagnostic criteriathatincludeclinical, radiological, histological, biological and therapeuticresponses. In our case weused the International Consensus Diagnostic Criteria (ICDC) to establish the diagnosis of IgG4 pancreatitis [11].

IgG4-related cholangitisis the second mostfrequent type of IgG4 diseaseafterpancreaticdisease, occurring in 83% of cases. Severalcriteria have been established for the diagnosis of IgG4 cholangitis, the mostcommonlyusedbeing the Japanesecriteriapublished in 2012 [14]. The prevalenceis 10% according to an American series of 125 patients and 6% according to anotherJapaneseseries of 235 patients [15].

IgG4 cholangitisisusuallypresentedwithjaundice, cytolysis and cholestasis. Imaging oftenrevealsbiliarystenosiswiththickening. The extrahepatic bile ducts are mostcommonlyinvolved. Isolatedintrahepaticinvolvementis possible but rare. A radiological classification has been established, individualising four formsbased on the degree of biliarystenosis. Thesefeatures are not unique to IgG4 cholangitis [16].

Elevated IgG4 levels are an essential but inconsistent diagnostic criterion. A threshold of 135 mg/dl seems to beuseful to distinguish IgG4 cholangitisfrompancreatic cancer and primarysclerosingcholangitis (PSC). However, a threshold of 182 mg/dl with a specificity of 96.6% has been suggested to differentiate CS-IgG4 fromcholangiocarcinoma [16]. A new quantitative PCR test thatmeasures the IgG4/IgG RNA ratio has recently been recommended to differentiate IgG4 diseasefrompancreaticobiliarymalignancies. However, more researchisneeded to confirmthis test on a largerscale [17].

Histopathologically, IgG4 cholangitis has the samecommonhistologicalcharacteristics as IgG4-RD, includinglymphoplasmacyticinfiltrateswithprominent IgG4+ plasma cells, storiformfibrosis and obliterativephlebitis. However, thesecriteria are hard to demonstrate in the case of intrahepaticinvolvement [18].

IgG4-RD is a corticosteroid-sensitive disease with a 97% to 100% response rate. Western teams initiate at 0.6 to 0.8 mg/kg/day for four weeks, then taper by 5 mg every two weeks for three to six months. To limit the risk of relapse, most Japanese teams maintain low-dose corticosteroids (2.5 to 5 mg/day) for three years [18]. Monitoring is clinical, radiological and biochemical. In the event of a relapse, after withdrawal of corticosteroids [18].

Immunosuppressive drugs are recommended in addition to corticosteroids. Azathioprine is the most commonly used, although the level of evidence is low. Rituximab is a very promising treatment for the management of disease relapse and maintenance of remission [3].

Conclusion:-

IgG4-SC is a rare disease often affecting elderly people, but should be considered especially when there is clinical concern for PSC and/or cholangiocarcinoma,

The purpose of this case is to focus on the current status of biliary and pancreatic IgG4-RD, as well as the challenges in diagnosing and managing it. We also want to remind specialists that they should rule out pancreatic or biliary cancers first to avoid unnecessary surgery for a steroid-sensitive disease.

Conflicts of Interest:
The authors declare that there is no conflict of interest regarding the publication of this paper.

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