Türk Pediatri Arşivi
Turkish Archives of Pediatrics

Case Report / Olgu Sunumu

IgG4 related disease in a seven year old girl with multiple organ involvement: A rare presentation

Yedi yaşındaki kız olguda çoklu organ tutulumlu IgG4 ilişkili hastalık: Ender bir prezentasyon

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The known about this topic

Immunoglobulin G4 related disease (IgG4-RD) is a chronic, fibro-inflammatory condition that has been described mostly in late adulthood. Inflammatory bowel disease has rarely been reported in IgG4-RD.

Contribution of the study

This case represents a childhood onset IgG4-RD with multiple organ involvement including Inflammatory bowel disease.

Abstract

Autoimmune pancreatitis has been described as a pancreatic manifestation of immunoglobulin G4-related disease, which is characterized by typical histopathologic, radiologic, and clinical features. Immunoglobulin G4-related disease is usually accompanied by elevated serum immunoglobulin G4 level, and can involve multiple organ/systems. Immunoglobulin G4-related disease has rarely been reported in pediatric population. There are few reports of inflammatory bowel disease in association with immunoglobulin G4-related disease. We describe a 7-year-old girl who presented with pancreatitis and concurrent sclerosing cholangitis, and developed bloody diarrhea during follow-up. An endoscopic examination revealed inflammatory bowel disease, and later lacrimal gland involvement was also recognized. She was diagnosed as having immunoglobulin G4-related disease, and her clinical signs and symptoms improved dramatically after steroid treatment. Hence, awareness of the clinical picture is important and early diagnosis can prevent fibrosis and organ damage.

Keywords: Autoimmune pancreatitis, child, immunoglobulin G4-related disease

Öz

İmmünglobulin G4 ilişkili sistemik hastalık çocuk yaş grubunda ender görülür ve tipik histopatolojik, radyolojik ve klinik özellikler ile belirgindir. Birçok organ ya da sistem tutulumunun görülebildiği hastalıkta pankreas tutulumu otoimmun pankreatit olarak tanımlanmıştır. Hastalıkta serum immünglobulin G4 düzeyi genellikle yüksektir. Enflamatuvar bağırsak hastalığı birlikteliği ender bildirilmiştir. Pankreatit ve eş zamanlı sklerozan kolanjit tablosu ile başvuran yedi yaşındaki olgumuz izlemde gelişen kanlı dışkılama nedeniyle endoskopik olarak incelenmiş ve enflamatuvar bağırsak hastalığı saptanmıştır. Ayrıca lakrimal bez tutulumu saptanan hasta immünglobulin G4 ilişkili sistemik hastalık tanısı almış ve steroid tedavisi ardından hastanın semptom ve bulgularında dramatik iyileşme sağlanmıştır. İmmünglobulin G4 ilişkili sistemik hastalıkta farkındalık, erken tanıda ve hastalık ilişkili organ hasarının önlenmesinde önemlidir.

Anahtar sözcükler: İmmünglobulin G4 ilişkili sistemik hastalık, çocuk, otoimmun pankreatit

Cite this article as: Şahin Akkelle B, Tutar E, Ergelen R, Çelikel ÇA, Ertem D. IgG4 related disease in a seven year old girl with multiple organ involvement: A rare presentation. Turk Pediatri Ars 2020; 55(2): 191–4.

Introduction

Autoimmune pancreatitis (AIP) is an unusual form of pancreatitis associated with obstructive jaundice, hypergammaglobulinemia, and features of autoimmune disease (1). In 2003, immunoglobulin G4-related disease (IgG4-RD) was first recognized as a chronic inflammatory and fibrosing multi-system disease in patients with AIP (2). To date, type 1 AIP, which is characterized with lymphoplasmacytic inflammation and sclerosis, is defined as

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Received/Geliş Tarihi: 05.05.2018 **Accepted/Kabul Tarihi:** 02.08.2018

DOI: 10.14744/TurkPediatriArs.2019.83435

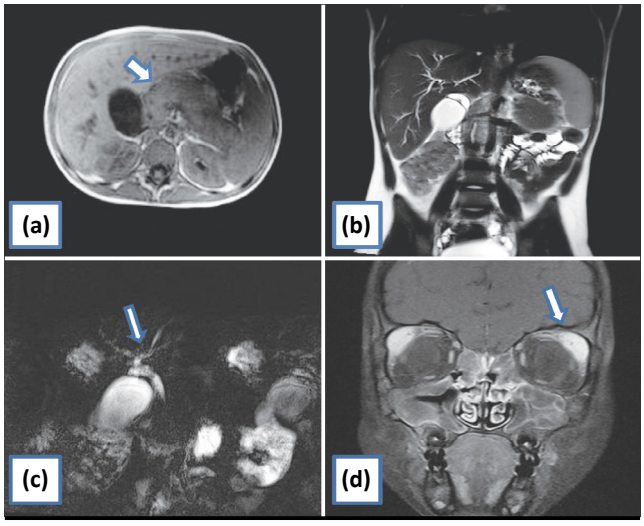

Figure 1. The magnetic resonance imaging and magnetic resonance cholangiopancreatography findings of the patient. (a) (T1W MRI) Diffuse enlargement of pancreas and capsule like rim. (b) (T2W MRI) Mild dilatation of intrahepatic bile ducts. (c) (MRCP) Narrowing at the bifurcation of the common hepatic duct. (d) (MRI) Enlarged lacrimal glands with contrast enhancement

a pancreatic manifestation of IgG4-RD. This condition may also influence the biliary system, kidneys, retroperitoneum, mesentery, thyroid gland, salivary/lacrimal glands, preorbital tissues, meninges, lymph nodes, lungs, and blood vessels (3). The pathologic findings are characterized by lymphoplasmacytic infiltrates, fibrosis, and the presence of abundant IgG4-positive plasma cell infiltration of the affected organs, which is often associated with raised serum IgG4 levels. Since 2011, the International Consensus Diagnostic Criteria (ICDC) based on histology, imaging, serology, organ involvement, response to therapy and clinical profiles has been used for the diagnosis of AIP (4).

Herein, we describe a seven year old girl who represented with type 1 AIP, sclerosing cholangitis, inflammatory bowel disease (IBD), and lacrimal gland involvement, and was diagnosed as having IgG4-RD.

Case

A seven year old girl was referred to our hospital with abdominal pain and nausea, which started two weeks ago, and she also described mild pruritus in the last week. There was slight jaundice, epigastric tenderness, and hepatomegaly on physical examination. Laboratory investigations revealed hypertransaminasemia and marked elevation in alkaline phosphatase and gamma-glutamyl transpeptidase, while total bilirubin, direct bilirubin, lipase and pancreatic amylase were slightly increased.

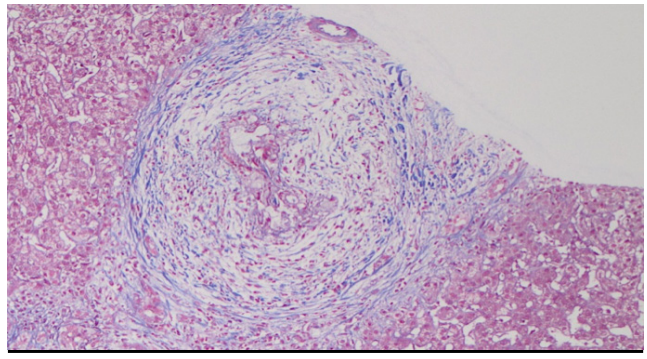

Figure 2. Histopathologic findings of liver biopsy (lymphoplasmacytic inflammation around the portal bile ducts with periportal fibrosis and mild bridging necrosis), (H&E, X200)

Acute-phase reactants such as white blood cell count, platelet count, C-reactive protein, and erythrocyte sedimentation rate were markedly elevated, which were compatible with a systemic inflammation. Viral hepatitis serology was negative.

The patients had hypergammaglobulinemia (serum IgG 2 710 mg/dL, upper limit of normal for age <1 682 mg/dL), and a significant elevation in serum IgG4 level (143 mg/dL, N: 1.0–108.7 mg/dL) was observed. Antinuclear antibody (ANA) and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) were positive by indirect immunofluorescence test, whereas liver kidney microsome type 1 antibody (anti-LKM-1), anti-mitochondrial antibody (AMA), anti-smooth muscle antibody (ASMA) were negative. Magnetic resonance imaging (MRI) of the abdomen revealed hepatomegaly with a heterogeneous parenchyma of the liver and a diffuse enlargement of the pancreas, surrounded by a capsule-like rim, and it was compatible with autoimmune pancreatitis (Fig. 1). Further radiologic investigation with magnetic resonance cholangiopancreatography (MRCP) confirmed a narrowing at the bifurcation of the common hepatic duct and mild dilatation of intrahepatic bile ducts (Fig. 1). The histopathologic examination of liver biopsy showed lymphoplasmacytic inflammation around the portal bile ducts with periportal fibrosis and mild bridging necrosis (Fig. 2). Furthermore, immunostaining of the liver biopsy revealed intense IgG, but only scarce IgG4 (+) plasma cells (8 plasma cells/high-power field). The patient was given ursodeoxycholic acid 15 mg/kg/day treatment.

During follow-up, the patient reported bilateral orbital edema around the upper orbital rim and the eyelid with no pain or erythema. Orbital MRI demonstrated enlarged lacrimal glands with contrast enhancement (Fig. 1). On the second month of admission, the patient developed

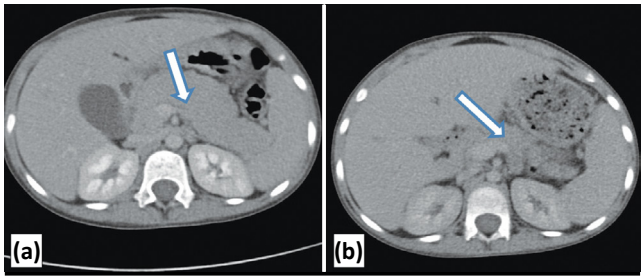

Figure 3. Radiologic imaging of the pancreas before and after the treatment (resolution of pancreatic enlargement after treatment). (a) Diffuse enlargement of pancreas at diagnosis. (b) Complete resolution of pancreatic enlargement after treatment

bloody diarrhea and underwent an ileo-colonoscopy. All colonic segments were erythematous and scattered exudative lesions were more pronounced in the distal colon. A histopathologic examination of the colonic biopsies demonstrated lymphoplasmacytic inflammation in lamina propria, cryptitis, destruction of crypts, and vasculitis. Hence, both the endoscopic and the pathologic findings were consistent with IBD, favoring ulcerative colitis. Upper GI tract endoscopy revealed erosions in the duodenum, and histopathology confirmed duodenitis with patchy lymphoplasmacytic inflammation and focally enhanced gastritis.

The patient was investigated for tuberculosis and missing vaccines were completed before commencing long-term immunosuppressive therapy. Later on, treatment with intravenous methylprednisolone 1.5 mg/kg/day, oral mesalazine 60 mg/kg/day was initiated. Methylprednisolone was gradually tapered to 4 mg/day over 10 weeks. Her signs and symptoms improved dramatically, and follow-up imaging of the abdomen at the second week of treatment demonstrated complete resolution of pancreatic enlargement (Fig. 3). The initial peak of total IgG (3 350 mg/dL) and IgG4 (177 mg/dL) levels improved to 1790 mg/dL and 77 mg/dL, respectively 2 weeks later. At the 3rd month of treatment, serum ESR and CRP levels improved and returned to normal. The patient has been asymptomatic while using 4 mg/day methylprednisolone treatment, and laboratory examinations have been normal during the last 12 months of follow-up. A written informed consent of the patient is obtained.

Discussion

Immunoglobulin G4-related disease is a chronic, fibroinflammatory condition that can involve multiple organ/systems. It has been described mostly in late adulthood. However, there are few reports of IgG4-RD in pediatric population. Clinical manifestations vary depending on the involved organs. The most common presenting symptoms in patients with IgG4-RD might be nonspecific abdominal pain, obstructive jaundice, and weight loss, as in our patient.

The International Association of Pancreatology (IAP) defined cardinal features for the diagnosis of AIP (4). These are radiologic imaging of pancreatic parenchyma or pancreatic ducts, serologic tests, involvement of other organs, histopathology of pancreas, and the response to steroid treatment.

In this case, abdominal MRI revealed diffuse enlargement of the pancreas with a capsule-like rim, which was consistent with the definition of the ICDC for AIP.

A positive serologic marker *per se* is not sufficient for the diagnosis of AIP. Elevated serum IgG4 levels have been accepted as the best serologic criteria for AIP, and fold elevation of IgG4 above the upper limit of normal strongly suggests AIP (4). The sensitivity and specificity of serum IgG4 levels higher than 140 mg/dL for diagnosis of AIP has been reported as 76% and 93%, respectively (5). However, normal serum IgG4 level does not exclude IgG4-RD. Furthermore, serum IgG4 level could be within the normal range in almost 40% of patients with AIP. Response to steroid treatment is one of the diagnostic criteria for AIP, and achievement of normal serum level of IgG4 is expected. Elevations in serum ANA and IgG titers have also been reported in 37–76% of patients with AIP (6), as in our patient.

Multi-organ involvement has been reported in 60–92% of patients with IgG4-RD. Extrapancreatic organ involvements may be diagnosed by histologic examination of the tissues, by imaging (bile ducts, retroperitoneal fibrosis) methods or by clinical manifestations (4). IgG4-related sclerosing cholangitis (IgG4-SC) is the biliary manifestation of IgG4-RD (7). Sclerosing cholangitis was diagnosed by both imaging and histopathologic examination of the liver tissue in our patient. Immunostaining of the liver biopsy in our patient revealed only scant IgG4 positive cells, which might be explained by the sampling error due to the patchy involvement of the liver tissue or concurrent milder elevation of serum IgG4 level (143 mg/dL) prior to the peak value (177 mg/dL) at the time of liver biopsy. Periorbital lacrimal glands have been reported as one of a common extrapancreatic organ, involved in adult and pediatric reports. Lacrimal gland involvement in our patient presented with bilateral orbital swelling, and confirmed with MRI. Noninfectious bloody diarrhea, which was later diagnosed as ulcerative colitis, also developed in our patient. Although IBD is more commonly associated with type 2 rather than type 1 AIP, it can be associated with both forms of AIP (4). Ravi et al. (8) reported that four of a

total 71 patients with AIP had concurrent IBD, and three of them were diagnosed as having ulcerative colitis. In another study, 6% of patients with IgG4 related cholangiopathy had concurrent IBD (9). At admission, antinuclear cytoplasmic antibody (ANCA) positivity had anticipated the development IBD in our patient.

Type 1 AIP (lymphoplasmacytic sclerosing pancreatitis) is defined as the prototypic manifestation of systemic IgG4-RD. Nevertheless, the current ICDC for AIP does not require an invasive procedure such as a pancreas biopsy, and therefore type 1 AIP was diagnosed in our case without a pancreas biopsy (4).

In this case, a rapid response to steroid treatment with clinical, laboratory, and radiologic improvement (Fig. 1) confirmed the diagnosis of IgG4-RD. However, relapse is very common in IgG4-RD. It has been reported that maintenance of low-dose steroid treatment was associated with a lower relapse rate compared with the cessation of steroid therapy. On the other hand, there are other publications stating a relapse rate of 25% in patients with AIP who were on maintenance with low-dose steroid treatment (10).

The diagnosis of IgG4-RD in our patient was based on imaging, serologic and laboratory findings consistent with autoimmunity, other organ involvement, and confirmed with the response to the steroid therapy.

In conclusion, this case represents a combination of AIP, sclerosing cholangitis, IBD, and lacrimal gland involvement in a child who eventually had the diagnosis of IgG4-RD. There are scarce data regarding IgG4-RD in childhood, and the concurrent IBD in our case is much more exceptional. Awareness of the disease by pediatric gastroenterologists is important to prevent disease progression and its complications because IgG4-RD may be associated with fibrosis and irreversible tissue damage in affected organs when untreated.

Informed Consent: A written informed consent of the patient is obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - B.Ş.A., D.E.; Design - B.Ş.A.; Supervision - E.T., D.E.; Data Collection and/or Processing - R.E., Ç.A.Ç.; Literature Review - E.T., B.Ş.A.; Writing - B.Ş.A.; Critical Review - D.E.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Hastanın bilgilendirilmiş, yazılı onamı alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir - B.Ş.A., D.E.; Tasarım - B.Ş.A.; Denetleme - E.T., D.E.; Veri Toplanması ve/veya İşlemesi - R.E., Ç.A.Ç.; Literatür Taraması - E.T., B.Ş.A.; Yazıyı Yazan - B.Ş.A.; Eleştirel İnceleme - D.E.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Mali Destek: Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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