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

Bilge Şahin Akkelle¹, Engin Tutar¹, Rabia Ergelen², Çiğdem A. Çelikel¹, Deniz Ertem¹
¹Department of Pediatric Gastroenterology, Hepatology and Nutrition, Marmara University Faculty of Medicine, İstanbul, Turkey
²Department of Radiology, Marmara University Faculty of Medicine, İstanbul, Turkey
³Department of Pathology, Marmara University Faculty of Medicine, İstanbul, Turkey

Corresponding Author/Sorumlu Yazar:
Deniz Ertem
E-mail/E-posta: denizertem@marmara.edu.tr

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

©Copyright 2020 by Turkish Pediatric Association - Available online at www.turkpediatriarsivi.com
DOI: 10.14744/TurkPediatriArs.2019.83435
OPEN ACCESS
This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction
Autoimmune pancreatitis (AIP) is an unusual form of 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

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 belirgin. Birçok organ da sistem tutulumunun görülebildiği hastalıktan pankreas tutulumu otoimmun pankreatit olarak tanımlanmıştır. Hastalıkta serum immünglobulin G4 düzeyi genellikle yüksektir. Enflamatotuar bağışıklık hastalığı birlikte görülen hastaların pankreatit ve eş zamanlı sklerozan kolanjit tablosu ise başvuran yedi yaşındaki olgunumuzda dikkate değer nedenlerdeki gelişen kanlı dışkılama nedeniyle endoskopik olarak incelenmiştir. Renkli holdingin ve enflamatotuar bağışıklık hastalığı süreçte saptanmıştır. Ayrıca lağrima alçımsız tutulumu saptanan hasta immünglobulin G4 ilişkili sistemik hastalık tıbbis alması ve steroid tedaviye girdiği arından hastanın semptom ve bulgularında dramatik iyileşme sağlanmıştır. Immünglobulin G4 ilişkili sistemik hastalıkta farkındalık, erken tanıda ve hastalık ilişkili organ hastalara önlenmesinde önemlidir.

Anahtar sözcüklər: Immünglobulin 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.
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. 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...
Immunoglobulin G4-related disease is a chronic, fibro-inflammatory 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. Peribiliary 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.C.; 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 İşlenmesi - R.E., Ç.A.C.; Literatür Taraması - E.T., B.Ş.A.; Yazılı Yazan - B.Ş.A.; Eleştirel İnceleme - D.E.

**Çıkar Çatışması:** Yazarlar çıkartma hakkında görüşmelerde bulunmamışlardır.

**Mali Destek:** Yazarlar bu çalışma için mali destek almamışlardır.

**References**
1. Scheers I, Palermo JJ, Freedman S, et al. Autoimmune Pancreatitis in Children: Characteristic Features, Diagnosis, and Management. Am J Gastroenterol 2017; 112: 1604–11.
2. Umehara H, Okazaki K, Masaki Y, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol 2012; 22: 1–14.
3. Vlachou PA, Khalili K, Jang HJ, Fischer S, Hirschfield GM, Kim TK. IgG4-related sclerosing disease: autoimmune pancreatitis and extrapancreatic manifestations. Radiographics 2011; 31: 1379–402.
4. Shimosegawa T, Chari ST, Frulloni L, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011; 40: 352–8.
5. Ghazale A, Chari ST, Smyrk TC, et al. Value of serum IgG4 in the diagnosis of autoimmune pancreatitis and in distinguishing it from pancreatic cancer. Am J Gastroenterol 2007; 102: 1646–53.
6. Zen Y, Nakanuma Y. Pathogenesis of IgG4-related disease. Curr Opin Rheumatol 2011; 23: 114–8.
7. Umehara H, Okazaki K, Nakamura T, et al. Current approach to the diagnosis of IgG4-related disease - Combination of comprehensive diagnostic and organ-specific criteria. Mod Rheumatol 2017; 27: 381–91.
8. Ravi K, Chari ST, Vege SS, Sandborn WJ, Smyrk TC, Lofthus EV Jr. Inflammatory bowel disease in the setting of autoimmune pancreatitis. Inflamm Bowel Dis 2009; 15: 1326–30.
9. Ghazale A, Chari ST, Zhang L, et al. Immunoglobulin G4-associated cholangitis: clinical profile and response to therapy. Gastroenterology 2008; 134: 706–15.
10. Kamisawa T, Shimosegawa T, Okazaki K, et al. Standard steroid treatment for autoimmune pancreatitis. Gut 2009; 58: 1504–7.