CLINICAL IMMUNOLOGY AND ALLERGY

UDC 616-022.12:615.37-07-08

Atypical presentation of IgG4-related disease

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For citation: Artemev I. A. Atypical presentation of IgG4-related disease. *Vestnik of Saint Petersburg University. Medicine*, 2019, vol. 14, issue 4, pp. 347–349. https://doi.org/10.21638/spbu11.2019.423

IgG4-related disease is a clinical entity which is characterized by tumefaction and fibrosis of affected organs, elevated serum IgG4 level, and tissue infiltration by IgG4-positive plasma cells. Most often, it affects the pancreas, main salivary and lacrimal glands, retroperitoneum. In this article an atypical manifestation of IgG4-related disease. The first manifestation of the disease was erroneously diagnosed as cutaneous systemic sclerosis. Pancreatic manifestation of the disease occurs during the second and the third relapse of the disease 11 and 13 years later correspondingly and were combined in the latter case with the coffee ground emesis, hepatic artheriitis, thrombosis of splenic artery and vein and diffuse peritonitis. Thus, the manifestation of IgG4-related disease may imitate some other clinical conditions, and therefore physicians must be aware of such a rare but multifaceted disorder in daily clinical practice.

Keywords: IgG4-related disease, systemic sclerosis, Raynaud's phenomenon, retroperitoneal fibrosis.

IgG4-related disease (IgG4-RD) is a clinical entity which has been described by Japanese rheumatologists in 2001 [1]. The disease is characterized by tumefaction and fibrosis of affected organs, elevated serum IgG4 level, and tissue infiltration by IgG4-positive plasma cells [2]. Most often, IgG4-RD affects the pancreas, main salivary and lacrimal glands, retroperitoneum, but the arteries, thyroid gland, liver and prostate are usually not affected. The aetiology and pathogenesis of IgG4-RD remains largely unknown. IgG4 is a heterogeneous antibody, which could be directly pathogenic, and also could be a casual marker of the abnormal inflammatory response or fulfill a protective role. IgG4 possess exclusive structural and functional characteristics suggesting anti-inflammatory and tolerance-inducing effects. Farm workers, beekeepers and individuals undergoing allergen immunotherapy dysplay high serum levels of allergen-specific IgG4, which demonstrates

immunosuppressive functions, preventing the individual from anaphylactic reactions. In some autoimmune diseases, such as pemphigus vulgaris and MuSK-myasthenia gravis, IgG4 autoantibodies are pathogenic [3]. In other words, IgG4 alone can execute pathogenic effects and structural damage, but may on the contrary function as a protective antibody dampening the more harmful effects of IgG1 when directed against the same epitopes. Here, we report a case of atypical manifestation of IgG4-related disease.

A 40-years old man was admitted to our Rheumatology department (2018) with mild dyspnea and possible diagnosis of scleroderma. Previously, around 13 years before (2006), the patient noticed Raynaud's phenomenon in his digit, after weight loss of 6 kg in previous 3 months. Two weeks after that, he suffered from fever, arthralgia, proximal muscles' weakness and ischaemic pain in fingers with the development of digital ulceration of three fingers. After physical examination at the hospital, a diffuse cutaneous systemic sclerosis was diagnosed (but capillaroscopy was not performed). The patient was treated with nitroglycerin, alprostadil, pentoxifylline, plasmapheresis, pulse intravenous therapy with methylprednisolone, and cyclophosphamide. Despite this therapy, gangrene of the two fingers developed during treatment. Due to the ineffectiveness of the therapy, endoscopic sympathectomy was performed with a beneficial clinical effect. Penicillaminum and medium doses of prednisolone were recommended for long term use.

First relapse was documented after 1 year of treatment with prednisolone (2007). The patient was admitted to the hospital again with dyspnea, fever, arthritis of knees, elbows and wrists. The complete blood count (CBC) was normal, C-reactive protein (CRP) 23.5 mg/L (N = 0.00 — 5.00 mg/L), erythrocyte sedimentation rate (ESR) 47 mm/h (2.00 — 15.00 mm/h). Pulmonary ground glass opacity with no infiltrative changes was observed on multislice computed tomography (CT). The patient was treated with 13 cyclophosphamide pulse therapy due to the next 3 years and the complete remission was achieved. Since 2009, the patient did not receive any drugs.

The next relapse occurred 10 years after (2016), and the disease manifested with fever, epigastric pain, nausea and vomiting. Patient was taken to a surgical hospital with pancreatitis. Laboratory investigations: moderate acute phase response (CRP 56.8 mg/L), normal liver function tests and mild elevated pancreatic enzymes. Abdominal computed tomography and ultrasound imaging revealed destructive pancreatitis, multiple cysts in the pancreatic tail and the fibrotic changes in the retroperitoneal fat. Conservative treatment was performed with good response.

The third relapse appeared in 2018. Similarly, as 2 years before, the patient suffered from fever, severe diffuse abdominal pain, coffee ground emesis and dizziness and was admitted to our hospital. A source of gastrointestinal bleeding was not found on the oesophagogastroduodenoscopy. On contrast abdominal CT physicians found enlargement of the pancreatic tail with cysts formation, thrombosis of splenic artery and vein, zone of necrosis of the spleen, hepatic hypoperfusion due to the presence of hepatic vasculitis, lymphadenopathy, fibrosis of retroperitoneal fat and diffuse peritonitis. Patient was transferred to the operating room, pancreatic resection and sanitation of the abdominal cavity was performed. However high levels of inflammation markers are persisted after 1 week therapy and the patient was consulted by a rheumatologist.

Taken into account clinical and laboratory data, rheumatologist suspected IgG4-RD. Sicca syndrome (positive Schirmer's test and non-stimulated sialometry), dyspnea and cough dominated the clinical picture, but any swelling or enlargement of salivary and

lacrimal glands was not observed. Thoracic CT scans showed frosted-glass image and fibrotic bands in the lower lobes of both lungs, probably, as a result of an underlying condition. Patient was transferred to the Rheumatology department. The laboratory findings included: negative immunological assays (for: ANA, anti-dsDNA, ANCA, RF, ACPAs), elevated level of acute phase markers (CRP 35.2 mg/L, ESR 51 mm/h), IgG4 543 mg/L (N =10.00 — 135.00 mg/L), IgG4/IgG ratio 0.47, thyroid stimulating hormone (TSH) 25.142 mIU/L (0.350 — 4.940 mg/L). No scleroderma pattern was discovered on nailfold capillaroscopy. Histology tests showed lymphoplasmacytic infiltration, storiform fibrosis and obliterative phlebitis of the pancreas. Immunohistochemistry stain demonstrated infiltration with lymphoplasmacytic and IgG4-positive cells (IgG4/IgG ratio > 40 %). Also, we investigated antithyroid autoantibodies: against thyroid peroxidase — 1961.0 IU/mL (N = 0.0–5.6 IU/mL), and towards TSH receptor — 3.69 IU/L (0.0–1.75 IU/L). Revealed changes are typical for autoimmune thyroiditis (Hashimoto's and Riedel's thyroiditis are most common types in IgG4-RD patients). Thus, patient fulfilled classification criteria for IgG4-RD.

We started treatment with a combination of glucocorticoids at high doses and azathioprine (2 mg/kg) as the steroid-sparing therapy according to the recommendations on the management and treatment of IgG4-RD [4]. Some days after that we noted normalization of blood parameters such as CRP. Patient is in remission to the moment of this paper writing. He reports improvement in dyspnea and has no complaints for any system dysfunction. Thus, the manifestation of IgG4-related disease may imitate some other clinical conditions, and therefore physicians must be aware of such a rare but multifaceted disorder in daily clinical practice.

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Received: February 12, 2020
Accepted: May 25, 2020

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