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The rare case report of interstitial lung disease with normal serum level of IgG4 developed six years after treatment of autoimmune pancreatitis

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Dear Editor,

We read with great interest the paper published in the journal by Zhang and colleagues entitled "Solely lung-involved IgG4-related disease: a case report and review of the literature". Authors analyzed the clinical data of one case of IgG4-related lung disease (IgG4-RD) and done the review of literature. IgG4-RD represents systemic sclerosing disease characterized by IgG4-positive plasma cell, T-lymphocyte infiltration of different organs and elevated serum IgG4 level in the majority of patients (1). Studies published over the past few years documented relationship between high level of IgG4 in serum and characteristic lesions of dense lymphoplasmacytic infiltrates containing IgG4-positive plasma cells in various organs including the biliary ducts (sclerosing cholangitis), salivary gland (sclerosing sialadenitis), lacrimal gland (sclerosing dacryoadenitis), liver (IgG4-hepatopathy), kidney (inflammatory pseudotumour), aorta (inflammatory aneurysm), lymph nodes and lungs (2). The igG4-related disease could be localized in two or more different organs simultaneously or metachronously.

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Thoracic manifestations of IgG4-related disease could be present as different parenchymal lesions (nodules or masses, interstitial lung disease), airway lesions (tracheobronchial stenosis), pleural lesions (nodules or effusion) or mediastinal lesions (lymphadenopathy or fibrosing mediastinitis) (3).

In addition to report o Zhang and colleagues published in this journal, we report the case of the patient with IgG4-RD and normal IgG4 serum level proven by the histopathological re-evaluation of pancreatic tissue obtained from surgical procedure six years before.

A 74-year-old man presented with six months history of a dry cough and dyspnea. His past medical history included Whipple operation six years ago, because of icterus with elevated total bilirubin serum level of 582 μmoll/L and the direct bilirubin level of 324 μmoll/l. Intraoperatively pseudotumor of the pancreas was found. The pathohistological finding revealed diffuse autoimmune pancreatitis. No further diagnostic procedures were done due to the patient's poor health general condition. Because of the previous operation, he had a diagnosis of secondary insulin dependent diabetes mellitus. In the moment of admission to the hospital, he was asthenic, painful with decreased breath sound and bilateral inspiratory crackles in the lower lobes. Chest X-ray and chest computed tomography (CT) scan revealed bilateral consolidations in the both lower lobes (Figure 1 and 2). Laboratory test found elevated sedimentation rate

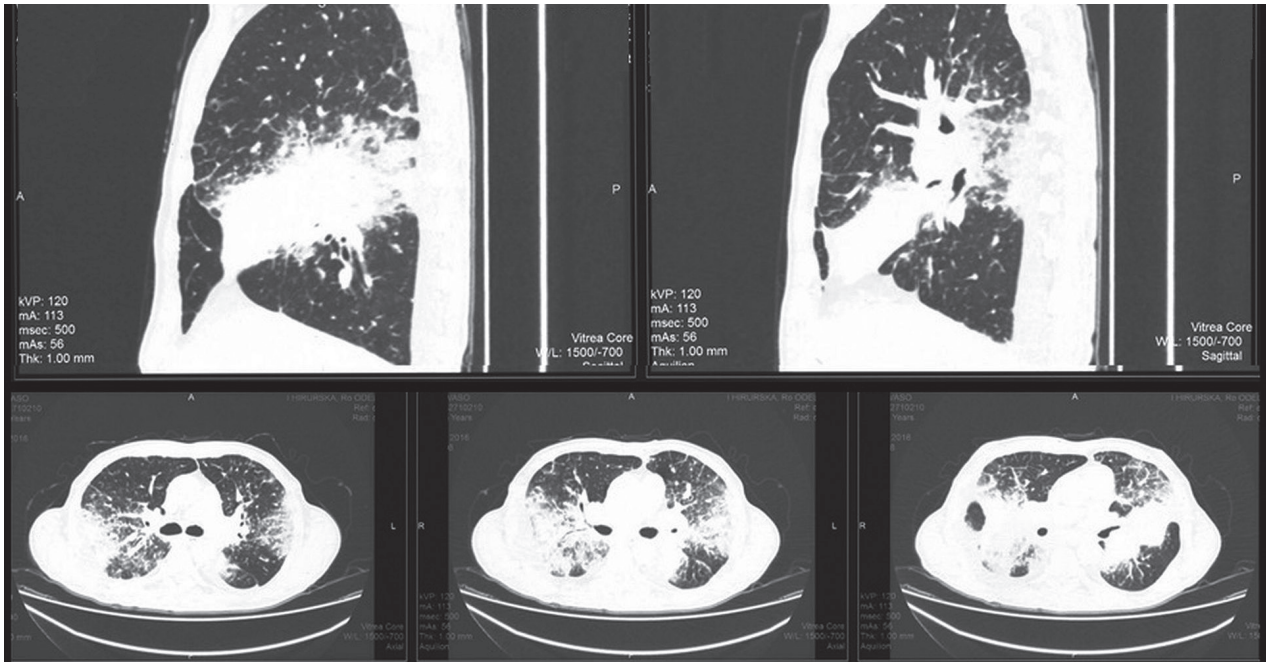

Fig. 1. Chest X-ray revealed bilateral consolidations in the both lower lobes

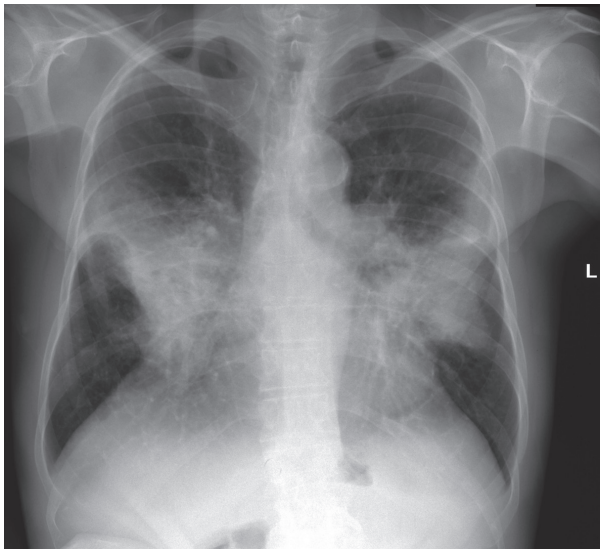

Fig. 2. Chest computed tomography scan revealed bilateral consolidations in the both lower lobes

(105/hour), and C-reactive protein (CRP) value 14.6 mg/dl, normocytic anemia with hemoglobin level 76.6 g/dl, elevated value of urea (13.3 mmol/l) and creatinine in serum (111 mmol/l), while proteinuria was borderline (500 mg/24h). Blood gas analysis was slightly decreased with pO_2 9.3 kPa and pCO_2 4.5 kPa. The pulmonary functional test demonstrated a restrictive pattern with mildly reduced (55%) diffusing capacity or transfer factor of the lung for carbon monoxide (DLCO). The immunological test showed increased antinuclear antibody level 1:320, and increased Rheum factor (RF) 1:121.4 (normal range up to 14). Serum immunoglobulins levels including IgG4 were normal. Fiberoptic bronchoscopy was done with a trans-bronchial biopsy from the right lung. Microscopically evaluation of bronchial mucosa revealed diffuse and dense lymphoplasmacytic infiltration. Pathological re-examination of pancreatic tissue samples obtained during Whipple operation six years before was done. Microscopically, lymphocytic and plasma cells infiltration (Figure 3a; Figure 3b) dominated in storiform fibrous tissue (Figure 3c). The scattered eosinophils were present in the fibrous tissue. The lymphocytic infiltrate was predominantly composed of T cells, with a few B cells. Plasmocytic origin of inflammatory cells was confirmed by marker CD38 (Figure 3d) and CD 138 (Figure 3e). Immunohistochemically, IgG4 plasma cells predominance was confirmed on three high power fields (HPF) x40. An average number of IgG4 plasma cells was more than 50 (n=53) (Figure 3f), while IgG expression was found in less than 10 (n=9)

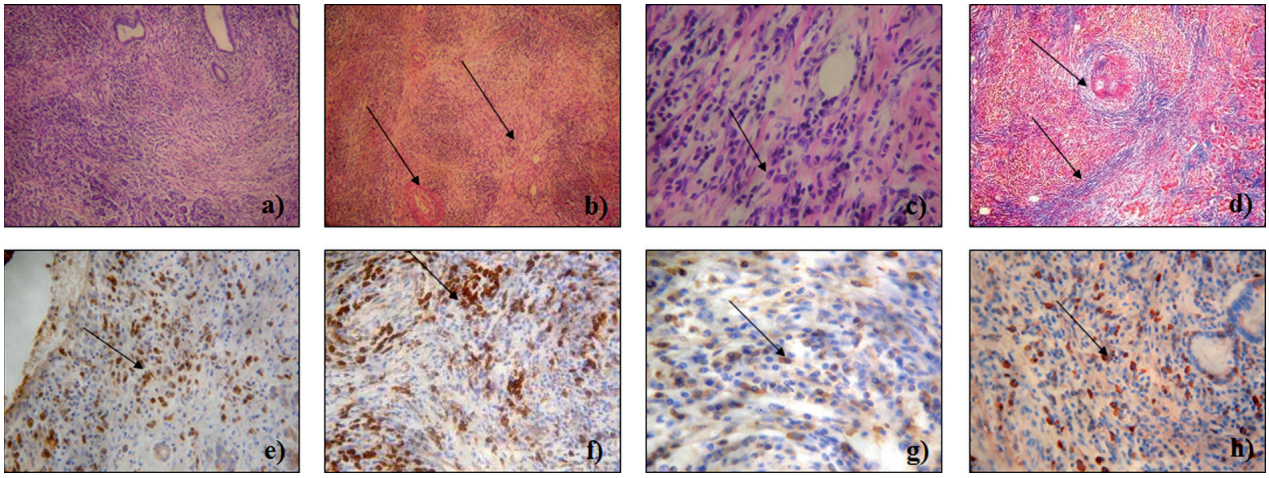

Fig. 3. a) Diffuse lymphocytic and plasma cells infiltration in the rest of pancreatic tissue was established, H&Ex10; b) Predominant storiform fibrous tissue and obliterative phlebitis were also noted in pancreatic tissue (H&Ex10; arrows); c) Plasmocytes were predominant inflammatory cells, H&Ex40; arrow; d) Histochemicaly by Masson-trichrome staining storiform pattern of fibrous tissue and obliterative phlebitis were evidented, H&Ex40; arrows; e) Plasmocytic origin of predominant od inflammataory cells was confirmed immunohistochemicaly, by CD38x20, arrow; f) And also by CD138x20; arrow; g) Immunohistochemicaly, a few IgG plasma cells were detected, IgGx40; arrow; h) On the same tissue samples IgG4 plasma cells were predominant, IgG4x40; arrow. According to all these findings IgG4 related diseases was established

plasma cells (Figure 3g and Figure 3h). Morphological changes and IgG4/IgG ratio, with sufficient clinical data, were highly suggestive of the diagnosis of IgG4-RD. Based on these findings, a final diagnosis of metachronous IgG4-RD with pancreas and lung involvement was made. Video-assisted thoracoscopic surgery (VATS) or open lung biopsy was not considered because of patient's poor general condition and highly suggestive diagnosis of IgG4-RD on re-examined pancreatic samples after immunohistological staining. Treatment started with oral prednisolone (30 mg/day). The two months after initiating a treatment, the patient showed improvement of clinical condition. Chest X-ray, as well as pulmonary function test, demonstrated significant condition improvement.

IgG4-related disease (IgG4-RD) is characterized by hyper-IgG4-gammaglobulinemia and massive infiltration of IgG4-positive plasma cells in various organs. Serum IgG4 concentration >135 mg/dl is cut-off value for the diagnosis of IgG4-RD. The serum IgG4 concentration is elevated in the most of the IgG4-RD patients (70-90%), but serum concentrations of this immunoglobulin are normal in up to 40% of patients with biopsy-proven IgG4-RD, as was shown in presented case (4). It is well known that an elevated value of serum IgG4 (>140 mg/dl) is also found in 5% of the normal population (5). IgG4 represents the smallest subclass of IgG and accounts for only 3-6% of total IgG in a normal serum (6). Autoimmune immunological mechanisms are involved in the pathogenesis of IgG4-RD, but the exact role of IgG4 is still unclear (7).

Two largest multicentric registries, Spanish from 2015 (8) and Japanese from 2012 (9) tried to explain the role of IgG4-RD in multiple organs. The first one involved 55 IgG4-RD patients using the current IgG4-RD diagnostic criteria. Authors showed a middle-aged male predominance (8). The disease tended to affect multiple organs as retroperitoneum (15), orbital pseudotumor (12), pancreas and salivary glands (9) as the most common places. The favorable disease outcome was noticed in the patients on corticosteroid, immunosuppressive or biologics therapy. The second registry was established in Japan in 2012, according to data of 132 patients with IgG-RD (9). More than half patients (n=64) had the so-called Mikulicz's disease with symmetrical swelling of at least two sets of lacrimal, parotid or submandibular glands. Pancreas involvement was found in 15% patients, kidney in 16% and lungs in 5% all patients (9).

The most patients with IgG4-RD show multiple organ involvements at diagnosis, with both high total serum IgG4 concentration and serum IgG4/

IgG ratios. Recently some patients with IgG4-RD were found to have lymphoma (10) and other cancers (11). The first cases of interstitial lung disease (ILD) associated with IgG4-RD were reported in 2004 and 2006, both in patients with autoimmune pancreatitis (AIP) (12,13). Cases of isolated IgG4-related ILD were described in 2008, 2012 and 2013, as proved pathologically after VATS biopsies (2, 3, 14). The first and the second one were suspected to nonspecific interstitial pneumonitis (NSIP), while the last was suspected to usual interstitial pneumonia (UIP) (2, 3, 14). Diagnostic criteria for IgG4-RD should be based on morphological and immunohistochemical findings, serum IgG4-concentration and radiological feature. In our presented case, crucial step to determine the cause of autoimmune pancreatitis was pathological finding on biopsy specimens.

IgG4-RD most frequently involved salivary glands, lungs, and pancreas (15). Pathohistological, according to consensus statement, there are three major features associated with IgG4-RD: dense lymphocytes and plasma cells infiltrate, a storiform pattern of fibrosis and obliterate phlebitis (15, 16). In the majority of cases, clinical and serological findings are typical for IgG4-RD. However, in some cases if there are a lack of these criteria, like in the present one, histopathological findings would confirm the disease. Beside of a morphology, the histopathological diagnosis relies considerably on the number of IgG4 cells as well as on IgG4 to IgG+ plasma cells, detected immunohistochemically (16). We used recommended counting on three HPF (x40) and calculation of the average number of IgG4+ plasma cells within these fields (53/3HPF). In 2012, Masaki et al. established that IgG4+/IgG+ plasma cell ratio over 50% is highly specific and sensitive for diagnosis IgG4-RD (9). These authors found that in storiform fibrous tissue IgG4 plasma cells were diminished suggesting that a ratio >40% is a better histopathologic cut-off value (9). In addition, Deshpande et al. suggested that the number of IgG4 besides on fibrosis depends on a sort of involved tissue (16). Finally, in our patient's case, according to morphology and immunohistochemistry, the pathohistological diagnosis was highly suggestive on IgG4-RD.

We suggest that changes of lung parenchyma suspect to ILD should be proved pathologically and immunologically, in order to avoid misdiagnosis of other diseases such as malignancies. The diagnosis of IgG4-RD requires collaboration between the pathologist and clinicians, especially in patients where serum level of IgG4 is within referent values. Normal serum level of IgG4 is not mandatory for the diagnosis of IgG4-RD. The very important question for further studies is how long oral prednisolone should be applied due to patient's secondary conditions, such as diabetes mellitus, and what should be expected after discontinuation of treatment.

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