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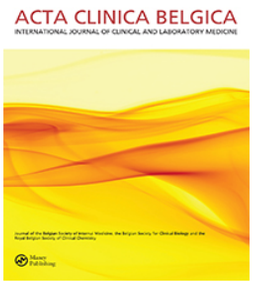

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CASE REPORT

IgG4-related pleural disease in a patient with a history of unknown origin acute pancreatitis: a case report and review of the literature

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ABSTRACT

Immunoglobulin G4-related disease is a rare autoimmune systemic disease with the capability of involving every organ. The disease is microscopically defined by a diffuse tissular inflammation with an infiltration of IgG4 positive plasma cells in the affected organs. IgG4 disease has an increasing incidence in the last few years with a growing interest in its pathophysiology still misunderstood to date. Despite the growing recognition of this pathology, the literature still does not allow to propose a simple diagnostic algorithm. In this article, we present a case of a 56-year-old man with a history of unknown etiology acute pancreatitis and a unilateral pleural effusion.

KEYWORDS

IgG4; pleural disease; pancreatitis; auto-immunity; pleuritis

Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a recently discovered, rare systemic disease which is characterized by mass-forming sclerosing lesions, elevated serum IgG4 and tissue infiltration by IgG4-positive plasma cells [1]. It was first described in Japan as an autoimmune pancreatitis with elevated serum levels of IgG4. Two years later the term IgG4-RD was proposed after discovering that patients who presented an autoimmune pancreatitis also had extra-pancreatic involvement [2]. The occurrence of chronic organ fibrosis and inflammation may be present in nearly every organ without any specific clinical features. Acute pancreatitis is recognized to be the most frequent manifestation. Other often-affected organs are the bile duct, liver, salivary gland, aorta, kidney, lacrimal gland, lymph nodes and lung [1,3]. The lung involvement in IgG4-RD can be various and includes lung parenchyma, airways, pleura and mediastinum. The disease can affect one or multiple organs in a simultaneous or metachronous way [4]. Here, we report a case of an IgG4-related pleural disease presenting as a unilateral right-sided pleural effusion with a recent history of acute pancreatitis.

Case report

A 56-year-old man was admitted to the emergency department complaining of abdominal pain located in the upper right quadrant associated with a dyspnea NYHA grade II. The pain was present since the last 15 days. There was no fever, no chest pain, no weight loss, no diarrhea or other gastrointestinal symptoms. In his recent medical history, we retain a diagnosis of an acute pancreatitis without any etiology found. Furthermore, he had a medical history of diabetes mellitus type II and Peyronie's disease. He had no familial history of pancreatic disease or any autoimmune disease. He had a smoking history of 64 pack-years. He consumed one alcoholic drink per week. At admission, the clinical examination of the abdomen revealed a sensible spot in the right upper quadrant without any sign of peritonitis. Pulmonary examination showed a right pleural syndrome. There was no lymphadenopathy detected. The remainder of the clinical examination was normal. Laboratory analysis revealed the following values: C-reactive protein 57.7 mg/L, gamma glutamyl transferase 140 U/L, alanine aminotransferase 42 U/L, aspartate aminotransferase 37 U/L, conjugated bilirubin 0.40 mg/dL, lipase 19 U/L, amylase 69 U/L. Analysis of procalcitonine was negative. The other biochemical analyses were in the range of the normal values. An abdominal ultrasound showed signs of *a* chronic steatosis. Computed tomography (CT) of the abdomen revealed a right pleural effusion. No abnormalities were objectivated in the abdomen: pancreas, kidneys, liver and bile duct were all normal. Further examination with a chest CT (Figure 1) confirmed the presence of unilateral right-sided pleural effusion without any abnormality observed in regard of the pulmonary parenchyma. There was no pleural thickening and pancreatic-pleura fistula was excluded. Effusion analysis obtained after thoracentesis showed an exudate with lactate dehydrogenase 489 U/L, proteins 49,900 mg/L, 45% lymphocytes, 11% neutrophils, 9% eosinophils and 34% monocytes. Glucose in the pleural fluid was 212 mg/dL. Serum autoantibodies includes: anti-neutrophil cytoplasmic antibody, anti-cyclic citrullinated peptide antibody were all negative. Antinuclear antibody (ANA) screening was positive with a titration of 1/320. Further characterization was negative. Rheumatoid factor

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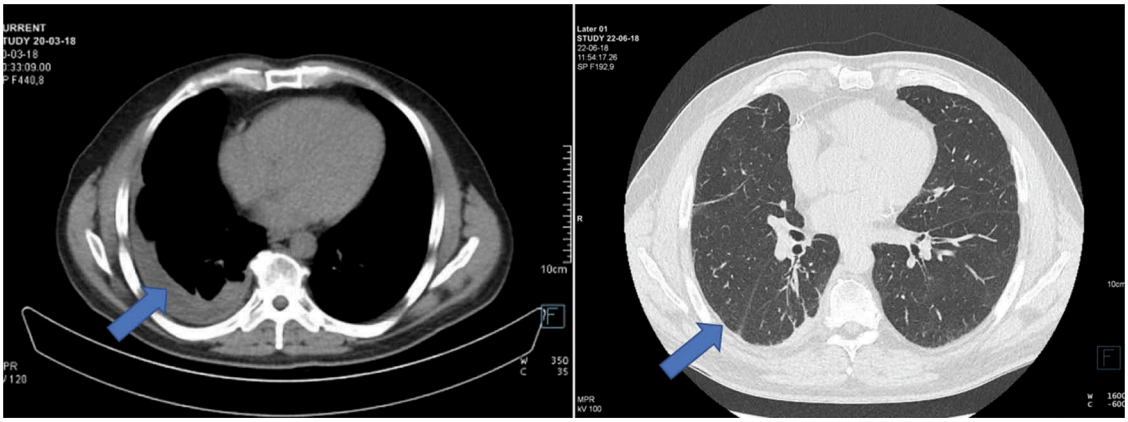

Figure 1. Images of chest CT. On left side: unilateral right-sided pleural effusion. On right side: CT after 4 months of follow-up: residual pleural effusion after glucocorticoid therapy.

(RF) was negative. Quantiferon testing and human immunodeficiency virus serology were negative. The level of brain natriuretic peptide and thyroid function was normal. Serum protein electrophoresis revealed multiple abnormal bands with an oligoclonal profile on immunoglobulin (Ig)-G on immunofixation. Dosage of the serum Igs identified an elevated IgG of 17.24 g/L (normal value <14.5 g/L) with an elevation in IgG4 subclass of 3.982 g/L (<1.25 g/L). A systematic exclusion of an underlying malignancy with a fluorodeoxyglucose positron emission tomography (FDG-PET) was performed and showed an increased uptake in the right-sided pleural effusion (Figure 2). There was no other abnormal uptake. The patient was referred for a pleuroscopy that identified a diffuse inflammation of the visceral and parietal pleura with fibrin deposits (Figure 3). Pleura biopsies showed a lymphoplasmacytic infiltration with storiform fibrosis. There were no signs of malignancy. Immunohisto chemical analysis with anti-CD38 showed the presence of plasma cells and with semi-quantitative immunostaining analysis, a plasma cell ratio of IgG4+/IgG cells above 50% measured (Figure 4). In view of the clinical presentation with a unilateral pleural effusion and an acute pancreatitis of unknown origin, the presence of an elevated serum IgG4 concentration, the presence of a lymphoplasmacytic infiltration with storiform fibrosis and an elevated IgG4 concentration in the pleura, the diagnosis of an IgG4-related pleural disease was made. The patient was treated with methylprednisolone 32 mg during 4 weeks, and here after gradually tapered over time. After 8 weeks, there was a significant reduction of the pleural effusion on thoracic imaging with high resolution computed tomography (HRCT) of the thorax (Figure 1) and a normalization of patient biochemical inflammation. Re-evaluation of pancreas was made by MRI and dismissed the diagnosis of pancreatic cancer. Glucoco rticoid therapy was gradually reduced over a time of 3 months until complete stop. No recurrence was observed after 6 months of follow-up.

Discussion

IgG4-RD is a rare systemic inflammatory disease and is mostly seen in male patients older than 50 years. The disease can involve various organs from which pancreatitis is the most common manifestation. Other known affected organ sites are the bile duct, liver, salivary gland, aorta, kidney, lacrimal gland, lymph nodes and lung [1,5]. The clinical presentation can be vague and nonspecific or related to the involved

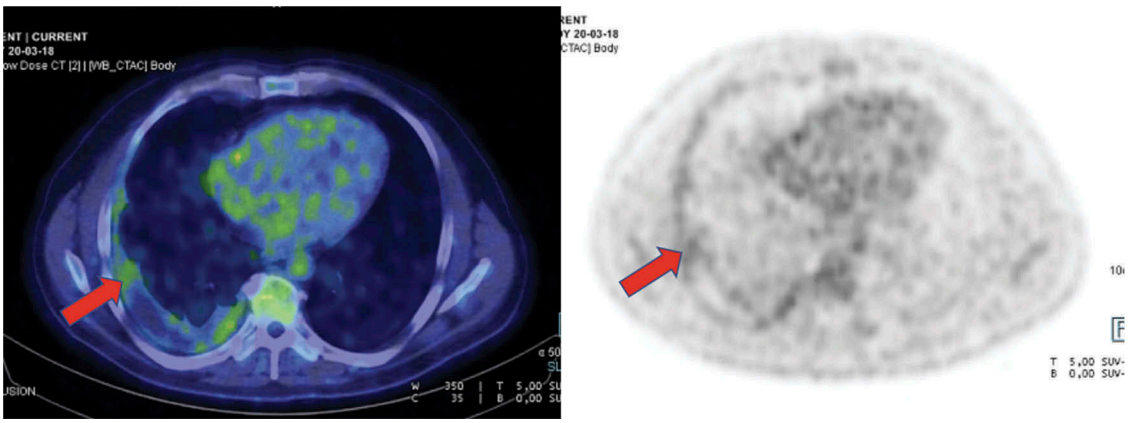

Figure 2. FDG-PET shows an increased uptake in the right-sided pleural effusion.

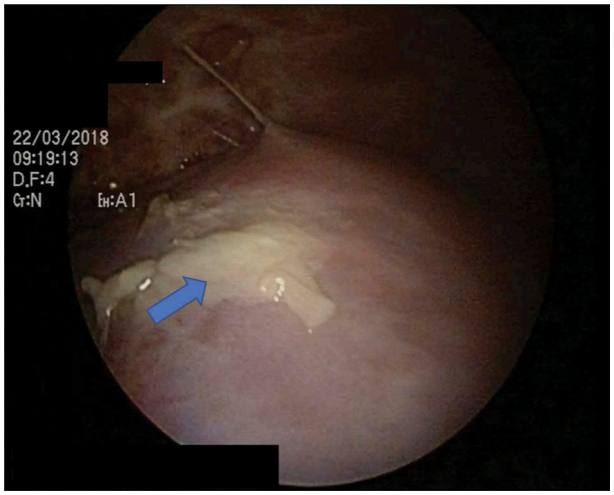

Figure 3. Image from pleuroscopy demonstrates a diffuse inflammation of the visceral and parietal pleura with fibrin deposits.

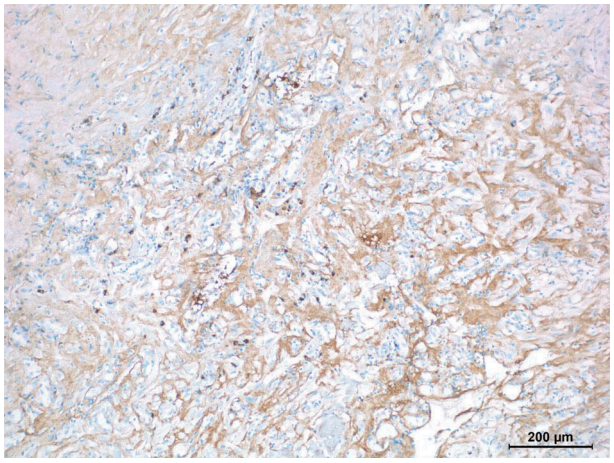

Figure 4. Immunohistochemical analysis identifies a plasma cell ratio of IgG4+/IgG cells above 50%.

organs. In some cases, there are abnormalities in imaging or in laboratory findings without any clinical features [6]. Currently, there are no established diagnostic criteria for IgG4-RD. Diagnosis is based on an elevated serum IgG4 value and the presence of marked IgG4-positive plasma cell infiltration in the affected organ tissue [7,8]. General laboratory findings can show an inflammatory syndrome in the majority of the patients accompanied by abnormalities in the involved organs. In our case, two organs are affected: pancreas and pleura. There was no sign of other concomitant IgG4-related conditions based on clinical, biological analysis and imaging studies. Hypergammaglobulinemia is frequently found with a mean serum IgG level of approximately 2.6 g/L [2]. The serum IgG4 level is usually elevated above 1.4 g/L [8]. A positive ANA titration or positive RF can be seen in less than 30% of the patients with mostly a low/moderate titration as it was seen in our patient with ANA titration of 1/320 [2]. The diagnostic cornerstone of the disease is a histopathological analysis of specimens from the affected organ. There are four key morphologic features: dense lymphoplasmacytic infiltrates; storiform fibrosis; obliterative phlebitis and eosinophilic infiltration. One of the strongest characteristics of IgG4-RD is tissue infiltration by IgG4 positive plasma cells. The plasma cells are the main cell type in the inflammatory infiltrates, followed by lymphocytes and histiocytes. Eosinophils can also be present [2,5,6]. The total number of IgG4 positive plasma cells per high-power field can be measured by semi-quantitative immunostaining analysis and measurement of the IgG4/IgG positive cell ratio may also be useful. It is considered to be abnormal when the ratio is above 30%. The characteristic fibrosis recognized in IgG4-RD is generally present in the pancreas whereas it is less frequent in the lungs. The obliterative phlebitis is due to an intimal and mural inflammation of the pulmonary arteries and veins [9,10]. In our case we have two organs involved in a metachronous way, a serum IgG4 value of 3.98 g/L and marked IgG4-positive plasma cell infiltration in pleura biopsies with plasma cell ratio of IgG4+/IgG cells above 50%. Intra-thoracic IgG4-related disease can be present in the lung parenchyma (nodules, masses or interstitial lung disease), in the pleural cavity (pleural nodules or effusion), in the mediastinum (lymphadenopathy, fibrosing mediastinitis) and in the airways (tracheobronchial stenosis) [5,6]. The incidence of lung involvement in IgG4-RD is not known precisely. However in one cross-sectional study of 114 patients the lung involvement was 14% [7], another retrospective study, in which imaging studies of 90 patients were reviewed, showed that lung involvement was around 54% [6]. Imaging studies are useful for detecting affected areas since IgG4-RD can be present in nearly every organ. Conventional HRCT of the suspected areas based on clinical examination and laboratory findings can provide interesting information regarding the organ involvement. Another sensitive tool for detecting lesions related to IgG4-RD is positron emission tomography (PET) with fluorodeoxyglucose (FDG) knowing that the levels of FDG uptake are related to the activity of the lesions. However, there are no data regarding the FDG uptake in IgG4 pleural disease. In one case report, the diagnosis was based on positive biopsy while FDG-PET showed no pleural abnormal FDG uptake. The authors suggested that low pleural metabolic activity could be associated with a good prognosis [3,11]. In this case, FDG-PET showed only an increased uptake in the right-sided pleural effusion. FDG-PET and pancreas MRI ruled out the diagnosis of pancreatic cancer. IgG4-RD with intra-thoracic involvement usually responds favorably to corticosteroid therapy whether the main lesion is in the lung, the airway, the pleura or the mediastinum. There is no clear consensus about the dose or the duration of corticosteroid therapy but recent therapeutic

guidelines recommend the use of glucocorticoids as the first line treatment, more specific the use of prednisolone (0.6 mg/kg/d) for 4 weeks as induction therapy. Higher doses could be used in patients with severe complications and lower doses in elderly patients. The doses should be tapered gradually during a 3–6 months period. A maintenance dose of 2.5–5 mg a day could be maintained or a switch to 'steroid-sparing' agents could be made [2,5,8]. Azathioprine is the immunosuppressive agent that is used in nearly 90% of the reported cases and since the level of evidence for the use of immunosuppressive agents is the same as for the use of glucocorticoids in IgG4-RD there is no consensus in which agent is preferred. Other immunosuppressive agents that could be used are mycophenolate mofetil, methotrexate, tacrolimus and cyclophosphamide. In case of a refractory or severe disease the biological therapies have an increased interest, but since there is often a lack of license, their use is limited [2]. Nowadays, there are few data available concerning the prognosis and clinical outcome of an IgG4-RD. In general, a multi-organ disease is more frequent than a single organ disease but metachronous evolution of the disease is well known. The evolution of the disease is very various ranging from temporary spontaneous involvement to indolent and progressive disease leading in the most severe presentations to death [2]. Of note, several authors have reported the potential association between IgG4-RD and malignancies ranging from 11% to 22% of patients [12,13]. Huggett et al. report in their study that most of the malignancies presented were pancreaticobiliary cancers [13]. However, more specific data are needed to clarify the association between IgG4-RD and malignancy.

Conclusion

IgG4-related disease is a rare autoimmune disease with a various and unspecific clinical presentation and the capability of involving nearly any organ. The organ involvement can occur in a simultaneous or metachronous way. The pleural disease related to IgG4-RD is an unusual and underdiagnosed pleural lymphocyte exudate. In our case, we present a rapid improvement with corticosteroids that were administered in high doses at the initiation of the treatment. However, since the evolution of the disease is variable, and refractory cases are not uncommon, a systematic follow-up is needed and the possibility to develop a malignancy should always be kept in mind.

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