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Recurrent Pleural Effusion: Not Tuberculosis and Not a Malignancy Either

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Abstract

A 47-year-old male with signs of metabolic syndrome, tobacco exposure of 3 pack years and a medical history of pancreatitis and myocardial infarction presented with unilateral pleural fluid which evolved to recurrent sometimes bilateral pleural fluid. Despite rigorous diagnostic efforts a clear diagnosis could not be established. Eventually on an abdominal ultrasound pancreatic abnormality was detected leading to a suspected diagnosis of autoimmune pancreatitis and giving way to a diagnosis of pleurisy due to Immunoglobulin G4 Related Disease (IgG4 RD) based on the 2019 ACR/EULAR classification criteria for IgG4 RD. Treatment with corticosteroids followed by rituximab resulted in sustained resolution of the pleural fluid and patient improvement.

Keywords

Pleural Effusion, Pancreatitis, IgG4 Related Disease, Tuberculosis

1. Introduction

A patient presenting with a fairly common medical condition of pleural fluid [1] evolved to a case with recurrent massive pleural exudate [2], without a cause being identified. It was only after a sausage-shaped pancreas [3] [4] was detected at abdominal ultrasound that it became clear there was a connection between the recurrent pleural effusion [5] and the pancreatitis with flares [6] patient had been

suffering for a decade. This unusual cause of pleural effusion [7] prompted us to write this case report, with written permission obtained from the patient.

2. Case Presentation

Our case regards a 47-year-old male trucker who was referred to the pulmonologist in December 2023 because of dyspnea, coughing and the first episode of left-sided pleural fluid (**Figure 1**). To alleviate his dyspnea and for diagnostic evaluation, left-sided pleural drainage was performed with evacuation of dark brown (chocolate colored) pleural fluid.

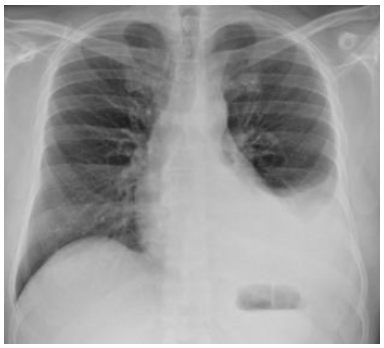

Figure 1. Chest X-ray with left-sided pleural effusion on 19 December 2023.

Patient is a former smoker with a smoking history of 3 pack years who had quit smoking some 3 years ago. He is known with type 2 diabetes mellitus and arterial hypertension, hypertriglyceridemia and has been suffering from non-alcoholic/non-gallstone pancreatitis since 2014. In 2021, he endured a Non-ST Elevation Myocardial Infarction (NSTEMI), which was treated with stenting of the left anterior descending artery. Post-stenting echocardiography showed preserved left ventricular function with no evidence of valvular abnormalities or pulmonary hypertension. His daily medication dose consisted of metformin, pioglitazone, bisoprolol, gemfibrozil, atorvastatin, isosorbide dinitrate sub lingual and aspirin. Examination of the pleural fluid resulted in an exudate (LD 485 IU/L, total protein 56.2 g/L, albumin 31.6 g/L and glucose 7.7 mmol/L) based on Light criteria [2] with no evidence of infection or malignancy [7]. Likewise, no tuberculosis, echinococci or amoebae were found in the pleural fluid. His glucose, calcium, potassium, sodium, creatinine, blood urea nitrogen, ALAT, ASAT, LDH, hemoglobin, white blood cells, red blood cells and platelets were normal, except for an elevated number of 23% eosinophils in his white blood cell differentiation. The HIV test was negative, and ANF and c-ANCA were also negative. As pleural fluid kept recurring with bilateral presence sometimes, patient often visited the pulmonologist because of dyspnea. Frequently pleural drainage was performed, sometimes with evacuation of massive amounts of pleural fluid, a pleural infection or pulmonary malignancy never being diagnosed. Cardiac evaluation remained unremarkable; repeat echocardiography demonstrated no interval change compared with prior

studies. Repeated abdominal ultrasound done because of abdominal pain was also normal. A CT scan of the chest done in January 2024 showed a massive collection of left-sided pleural fluid with atelectasis of most of the left lung, with no other lung abnormalities detected. Abdominal ultrasound of February 2024 revealed a sausage-shaped pancreas with poor echo reflection, starkly in contrast to the many abdominal ultrasound evaluations patient has had from 2015 on **Figure 2**. This sausage-shaped pancreas was suggestive of autoimmune pancreatitis and brings to mind the thought of IgG4 Related Disease (IgG4 RD) [3] [4].

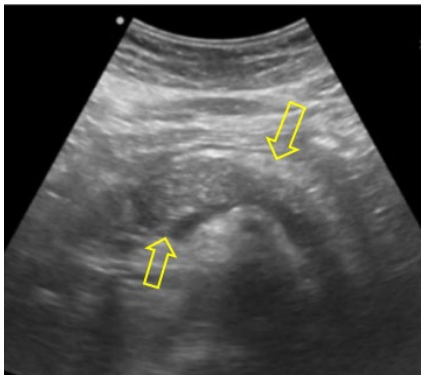

Figure 2. Yellow arrows pointing to the sausage-shaped pancreas.

At the end of February 2024, left sided thoracotomy was performed to obtain material for a histologic diagnosis. At the same time, pleurectomy was done to achieve surgical pleurodesis. Histological examination of the resected thickened pleura showed the presence of fibrous connective tissue in a storiform pattern with chronic inflammation consisting of abundant lymphocytes, numerous plasma cells (>50 per high power field) and eosinophils. Also, extravasation of erythrocytes, suggestive of arteritis was seen, but no signs of pleural malignancy. The overall morphological pattern in the resected pleura was suggestive of IgG4 RD [8]-[10] (**Figure 3**).

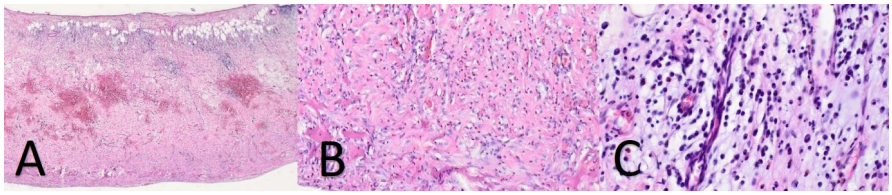

Figure 3. Panel A: dense lymphoplasmacytic cell infiltration and fibrosis at scanning magnification (H&E; ×20); Panel B: abundant lymphoplasmacytic cells, eosinophils and storiform fibrosis at medium magnification (H&E; ×200); Panel C: numerous plasma cells are shown, more than 50 per high power field (H&E; ×400).

The diagnosis of pleural IgG4 RD could not be histologically confirmed due to unavailability of specific Immunohistochemical (IHC) staining. Measurement of IgG4 level in serum and pleural fluid was also unavailable. Tuberculous pleuritis

was excluded by the TB GeneXpert test. Despite lack of biochemical and histologic confirmation, but based on the recurrent idiopathic pleural effusion, a sausage-shaped pancreas suggestive of autoimmune pancreatitis and the histological findings of the pleura, IgG4 RD was considered to be the disease state of patient and we decided to treat him with steroids from April 2024 on. To achieve long-term remission and a steroid sparring effect, prednisone was gradually replaced by rituximab in July 2024, which is to be prescribed for at least 2 years [11] [12]. Currently patient is doing well and his chest X-ray has normalized as can be seen in **Figure 4**.

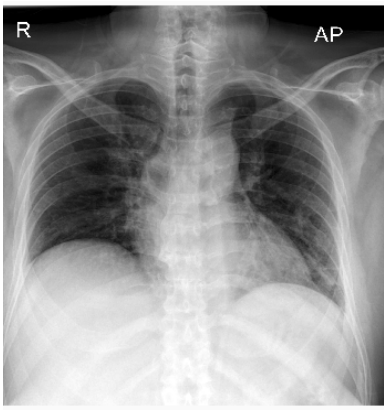

Figure 4. Normal chest X-ray after treatment with rituximab on 19 August 2025.

3. Discussion

IgG4 RD is a systemic fibroinflammatory disease with the clinical symptoms depending on the organs involved. It has the potential to involve any organ like the pancreas, resulting in an autoimmune pancreatitis [8] or pleural involvement manifesting as pleural nodules, pleural thickening or pleural effusion [9]. IgG4 RD is histologically characterized by lymphoplasmacytic infiltration rich in IgG4-positive plasma cells, storiform fibrosis, obliterative phlebitis and elevated or not IgG4 serum levels [13] [14]. Diagnosis of IgG4 RD is based on the Comprehensive Diagnostic (CD) criteria consisting of: organ involvement, >10 IgG4+ plasma cells per high power field with IgG4+/IgG+ plasma cells > 40% in diseased tissue samples and serum IgG4 levels > 135 mg/dl. In immunohistochemistry examination elevated IgG4+ plasma cells of >50 per field [15] are seen.

Our patient, a former smoker with signs of the metabolic syndrome [16] and a medical history of NSTEMI and pancreatitis a decade ago, was seen because of massive sometimes bilateral idiopathic pleural effusion. Our patient met the following criteria of IgG4 RD: involvement of the pleura witnessed by pleural thickening, the histologic findings of dense lymphoplasmacytic cell infiltration, storiform fibrosis, arteritis and more than 50 plasma cells per high power field in the resected pleural specimen. Thus, with the exclusion of malignancy, active cardiac disease, liver and kidney disease and based on the clinical presentation, pancreas morphology and pleural histology, a diagnosis of IgG4 RD was made based on the

2019 ACR/EULAR classification criteria [17] and accordingly treated with good clinical response.

Although our treatment strategy resulted in normalization of the chest x-ray and the patient feeling well there are shortcomings in the workup of our case. As such we were not able to measure IgG4 levels in serum and pleural fluid and we also were not able to perform IgG and IgG4 immune histochemical staining of the pleural specimen. Another limitation is that we cannot determine if the resolution of the left sided pleural effusion is due to either the surgical pleurodesis or the effect of rituximab or a combination of both interventions. Discontinuation of rituximab could lead to disease relapse [18] with recurrence of pleural effusion, so resurgence of pleural effusion on the right side while being absent on the left side after discontinuation of rituximab is indicative of the surgical pleurodesis being an effective treatment.

4. Conclusion

The clue to a diagnosis in this case of recurrent pleural fluid was the sausage-shaped pancreas, emphasizing multi-disciplinary collaboration. Although the diagnostic evidence for IgG4 RD was incomplete, the treatment results merit our idea that we have correctly addressed this medical case. Hence, this case highlights the diagnostic limitations physicians run into in limited settings, but still have to try to reach a correct diagnosis.

Author Contributions

A. J. D.: data curation, reviewing, R. B.: data curation, reviewing, D. S.: data curation, reviewing, P. V.: data curation, reviewing, M. C.: data curation, resources, reviewing, I. T.: data curation, resources, reviewing, F. A. G.: conceptualization, data curation, original draft preparation, resources, supervision.

Conflicts of Interest

We have no conflict of interest to report, nor have we received any funding for the preparation of this case report.

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