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LUNG IMAGES

Thoracic Hyper-IgG4-Related Disease Mimicking Malignant Pleural Mesothelioma

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Abstract

We report a rare case of a IgG4-related disease presenting with recurrent pleural effusion, pleural thickness and multiple mediastinal lymphadenopathies and no involvement of other extrathoracic organs. A 65-year-old man with a previous asbestos exposure presented with cough and pain discomfort. A large right pleural effusion was detected and evacuated (siero-haematic liquid). With the suspicious of a pleural mesothelioma, a CT-scan before and a ^{18F}-FDG PET/CT-scan later were performed revealing multiple pleural thickenings and multiple mediastinal lymphadenopathies with radiotracer uptake. EBUS-TBNA EBUS-TBNA did not result in a formal pathological diagnosis; thus, multiple pleural biopsy were performed via right thoracoscopy. At pathology the pleura was markedly thickened by a chronic fibroinflammatory process with scattered lymphoid follicles and a large number of mature plasma cells. Immunohistochemistry shows a mixed B (CD20+) and T (CD3+) population of lymphocytes, without light chain restriction and an increased number of IgG4-positive plasma cells. A presumptive diagnosis of IgG4-related disease was formulated. Total body CT-scan excluded other organ involvement. Blood test showed elevated serum IgG4 concentrations (253 mg/dL) and mild elevation of acute-phase reactants (C-reactive protein 10.7 mg/L). Autoimmune profile was negative. A diagnosis of definite IgG4-related disease was made, and treatment with prednisone 50 mg/day was started.

Keywords IgG4-related disease · Pleura · Mesothelioma · Pleural effusion

A 65-year-old man presented to our hospital complaining of cough, a 6-week history of progressive exertional dyspnoea, and right chest discomfort. He was a heavy smoker, while his previous medical history was substantially unremarkable a part from a previous asbestos exposure. There is no history of fever, weight loss, anorexia, hemoptysis, dysphagia or other localizing systemic symptom, and no superficial lymph nodes were noted at the physical examination. Routine laboratory tests were within the range. A chest X-ray showed a right pleural effusion and a CT-scan (Fig. 1a, c, e) confirmed the right pleural effusion among with multiple right pleural thickenings and mediastinal lymphadenopathies. No other abnormalities were observed at the level of pulmonary parenchyma. The pleural effusion (about 1600 cc of siero-haematic liquid) was evacuated. Laboratory analysis showed the effusion to be an exudate and culture and cytology were negative. With the suspicious of a pleural mesothelioma, a ^{18F}-FDG PET/CT-scan (Fig. 1b, d, f) was performed with staging purpose revealing an intense uptake (SUVmax: 7.3) at the level of mediastinal lymph nodes with mild uptake in basal pleural thickness. EBUS-TBNA (Fig. 2a) shows an unspecific chronic inflammatory process, but it did not result in a formal pathological diagnosis. Thus, a thoracoscopic

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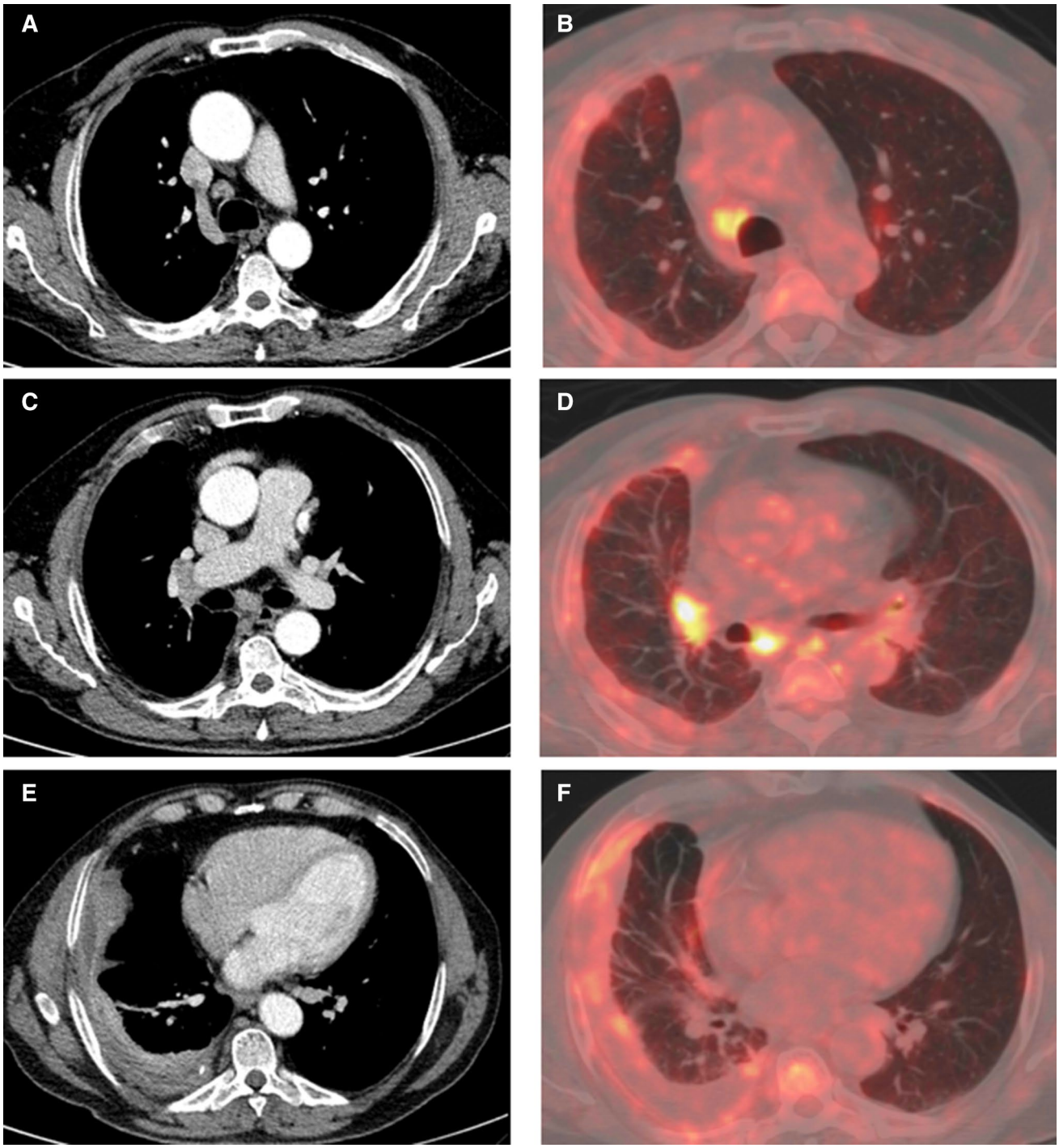

Fig. 1 Radiological (**a**, **c**, **e**) and radio-metabolic (**b**, **d**, **f**) evaluation show pleural and lymph nodal abnormalities

approach was indicated this revealing multiple pleural thickenings with a remarkable macroscopic structural alteration of the parietal pleura among with diffuse pleuro-parenchymal adhesions (Fig. 2a). The scenario was highly indicative for malignant pleura mesothelioma. Full-thickness "large" (4 cm in diameter) pleural biopsies were taken from the extensive parietal thickening at multiple sites (Fig. 2b).

At pathology, the parietal pleura was markedly thickened by a chronic fibroinflammatory process with scattered lymphoid follicles and a large number of mature plasma cells (2C). Storiform pattern fibrosis was also identified. Immunohistochemistry shows a mixed B (CD20+) and T (CD3+) population of lymphocytes (2D-E), without light chain restriction and an increased number of IgG4-positive

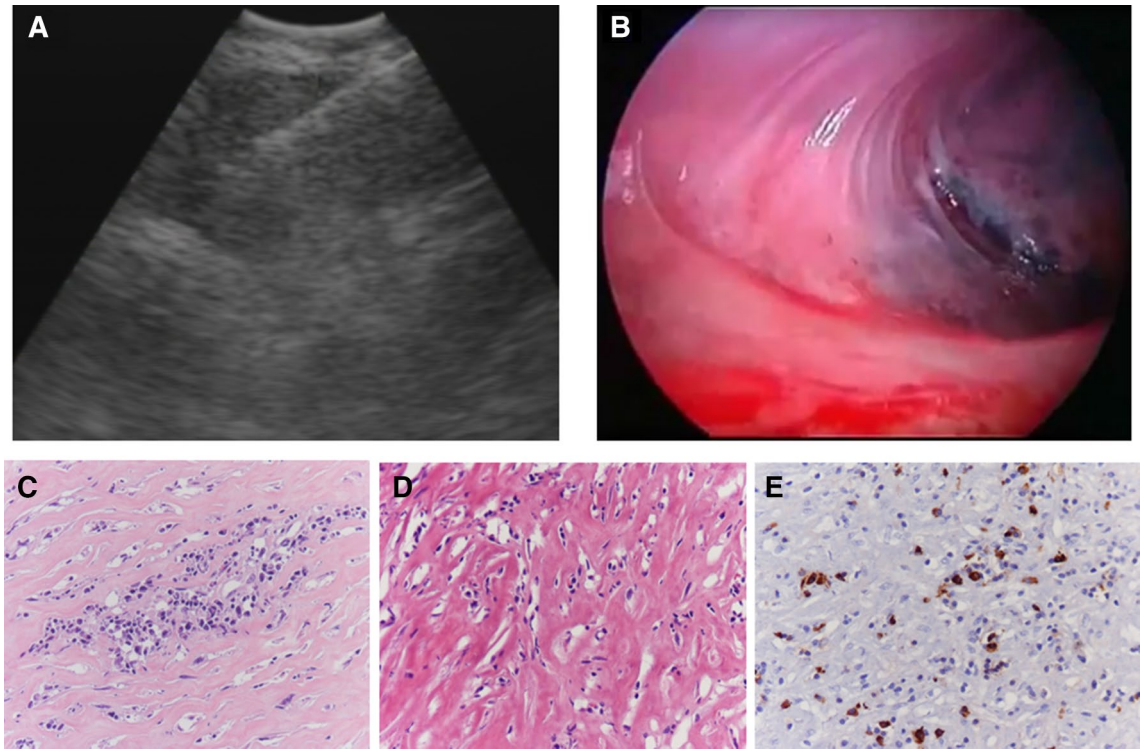

Fig. 2 US-guided endoscopic fine needle aspiration (**a**) was inconclusive for formulating a diagnosis; thus a pleural biopsy was performed via thoracoscopy (**b**) achieving surgical tissue for a definitive diagnosis (**c**–**e**)

plasma cells (with a mean of 70 IgG4-positive plasma cells per high-power field, with a ratio of IgG4-positive to IgG-positive plasma cells > 30%). Blood test showed elevated serum IgG4 concentrations (253 mg/dL) and mild elevation of acute-phase reactants (C-reactive protein 10.7 mg/L). Autoimmune profile including PR3- and MPO anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor, anti-citrullinated protein antibody and antinuclear antibody were negative. Total body CT-scan and ^{18F}-FDG PET/CT-scan excluded other organ involvement. A diagnosis of definite IgG4-related disease was made according to the 2011 comprehensive diagnostic criteria [1], and treatment with prednisone 50 mg/day was started.

Immunoglobulin G4-related disease (IgG4-RD) is an increasingly recognized fibro-inflammatory disorder originally described usually involving multiple organs either synchronously or asynchronously [2].

The thoracic manifestations of IgG4-RD are numerous and can mimic several common and better known conditions [3], including pleural mesothelioma as in the present case. In a recent review of the literature exploring the frequency and nature of thoracic involvement in a prospective cohort of IgG4-related disease patients [4], over 40% of patients had clinic-radiological and/or histological evidence of thoracic involvement, predominantly mediastinal lymphadenopathy but the majority of them were associated with multi-system disease outside the chest. Unlikely to that, the pleural localization is almost uncommon [5] with only six cases of IgG4-related pleuritis described in a recent review [6].

Diagnosis of IgG4-RD is challenging, given the heterogeneity of clinical symptoms and laboratory and pathology results. High serum IgG4 concentrations are neither sufficiently sensitive nor specific for diagnosis. Furthermore, tissue infiltration by IgG4-positive plasma cells alone could not suffice for diagnosing IgG4-RD, because these plasma cells can be present in other inflammatory and neoplastic disorders. Tissue biopsy showing a dense lymphoplasmacytic infiltrate, a storiform pattern of fibrosis, and obliterative phlebitis is considered the gold standard for diagnosis in most settings. However, pathological examination could be challenging, especially in absence of other clinical manifestation or organs involvement, and clinicopathological correlation is always needed to confirm the diagnosis [7].

Since the IgG4-related thoracic disease showing high standardized uptake values on FDG-PET [8], physicians should take in mind this rare entity in the differential diagnosis of pleuritis of unknown origin, as in the present case where the asbestos exposure and radio-metabolic results suggested the presence of a malignant pleural disease. In such cases, establishing the correct diagnosis is critical firstly

because a corticosteroid treatment is not generally administered before excluding a neoplasm and secondly because the majority of patients with IgG4-RD usually respond in the initial phase to corticosteroid treatment [4].

Compliance with Ethical Standards

Conflict of interest None.

Ethical Approval The manuscript was written in compliance with ethical standards.

Informed Consent A written informed consent has been obtained before publication.

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