

Paraneoplastic acute fibrinous and organizing pneumonia from lymphoma completely responding to bendamustine-rituximab

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Abstract

Acute fibrinous and organizing pneumonia (AFOP) is a rare histopathological pattern of lung injury characterized by prominent fibrin deposition in alveolar spaces. It may be idiopathic or associated with medications, connective tissue disease, infection, environmental exposures, transplantation, and malignancy. There is no proven treatment but multiple reports describe response to corticosteroids. We report the case of a 65-year-old male never-smoker with a 15-month history of dry cough, dyspnoea, anorexia, and night sweats only partially responsive to doxycycline and oral prednisolone. Computed tomography chest demonstrated adenopathy on both sides of the diaphragm and patchy consolidation in a peribronchovascular and subpleural distribution with lower zone predominance. Axillary node biopsy revealed low-grade non-Hodgkin's lymphoma. Lung biopsy showed AFOP but no lymphoma. Complete pulmonary and neoplastic responses were achieved with bendamustine-rituximab. We report a compelling instance of paraneoplastic AFOP responding to chemotherapy for lymphoma with very limited use of corticosteroids.

Introduction

Acute fibrinous and organizing pneumonia (AFOP) is a rare histopathological pattern of lung injury first described by Beasley et al. in 2002 as being characterized by prominent intra-alveolar fibrin deposition with associated organizing pneumonia (OP), without hyaline membranes to indicate diffuse alveolar damage [1]. Beasley et al. describe fibrin deposition, often forming fibrin “balls,” affecting 50% (range: 25–90%) of alveolar spaces; other features include a mild-to-moderate lymphoplasmacytic interstitial infiltrate, neutrophils mainly in alveolar walls, and type II pneumocyte hyperplasia. The pattern was not included as a distinct entity in the most recent ATS/ERS statement on the classification of interstitial pneumonias as it was felt to lack sufficient unique features. Nonetheless, AFOP is an increasingly recognized finding with growing evidence for associations with drugs, connective tissue disease, infection,

environmental exposure, transplantation, and malignancy [2,3]. The trajectory of patients with AFOP tends to follow either a fulminant fatal path or a subacute course with recovery; this observation, along with the rare co-existence of AFOP with other distinct pulmonary diseases, supports the consensus that the pattern is best conceptualized as a form of lung injury existing on a spectrum between OP and diffuse alveolar damage [4]. Distinction between AFOP and OP, whether cryptogenic or secondary to a known association, is made histologically on the basis of prominent fibrin involving at least 25% of sampled alveolar spaces; although best considered as related patterns with many shared clinical features, a more fulminant course would favour AFOP as the diagnosis. Most case reports of AFOP describe treatment with long courses of corticosteroids with variable but frequently good responses, with hitherto very limited data to support a therapeutic strategy minimizing the use of these potentially harmful drugs.

Case Report

We report the case of a 65-year-old male never-smoking teacher from rural Australia who was referred by his haematologist for investigation of multifocal pulmonary consolidation in the setting of a recent diagnosis of a low-grade stage IV non-Hodgkin's lymphoma (NHL). He was previously well with a history of gastro-oesophageal reflux disease and nephrolithiasis only.

The patient had a 15-month history of dry cough, dyspnoea, anorexia, and night sweats, which had been managed locally with long courses of doxycycline and prednisolone; this had partially attenuated the anorexia and night sweats but not his respiratory symptoms. Failure to improve eventually prompted a computed tomography (CT) chest, which demonstrated patchy consolidation in peribronchovascular and subpleural distributions with bibasal predominance plus splenomegaly and widespread intra- and extra-thoracic lymphadenopathy (Fig. 1). CT abdomen/pelvis confirmed sub-diaphragmatic lymphadenopathy. Positron emission tomography (PET) found all the lymphadenopathy to have mildly increased 18-fluorodeoxyglucose (FDG) avidity (highest standardized uptake value maximum 5.8 in a cervical node), with the pulmonary consolidation also having mildly increased activity. Ultrasound-guided axillary node biopsy yielded limited material showing an abnormal lymphoid population with a nodular appearance, with follicles positive for CD10 and BCL2 but negative for cyclin D1, consistent with a low-grade B-cell lymphoma; there was insufficient material for flow cytometry.

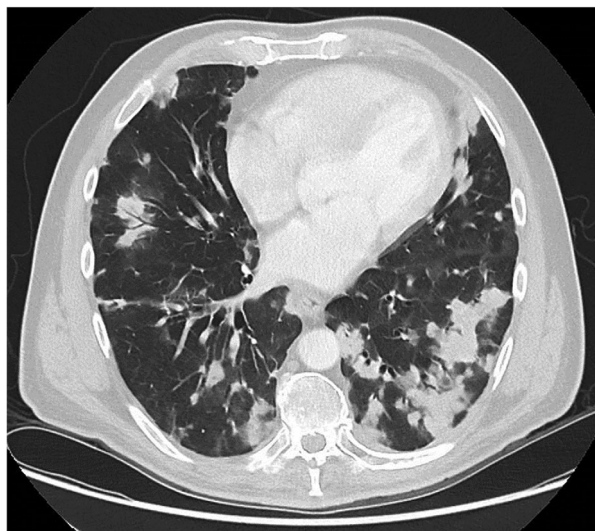


Figure 1. Axial slice of lung window computed tomography (CT) chest depicting a representative example of the peribronchovascular and subpleural pulmonary consolidation.

Diagnosis for the pulmonary consolidation, thought either infective or lymphoma, was sought. Bronchoscopy revealed a lymphocytic lavage (25%) with no monoclonal population on flow cytometry, while transbronchial biopsies yielded only scant crushed lung parenchyma showing a polymorphous lymphoid infiltrate in alveolar septa. Repeat transbronchial biopsies via radial endobronchial ultrasound guide sheath yielded multiple fragments of alveolar parenchyma showing patchy mild fibrous expansion of the interstitium, a focus of interstitial mononuclear cell infiltrate, and no evidence of lymphoma. Microbiological studies from both bronchoscopies were negative. CT-guided core biopsy then revealed prominent intra-alveolar fibrin plugs along with intra-alveolar fibroblastic plugs and a moderate mixed inflammatory cell infiltrate, but again no evidence of lymphoma and or any other process.

Multidisciplinary team discussion concluded there was still diagnostic uncertainty because the OP may simply be co-located with lymphoma. Surgical lung biopsy was performed via video-assisted thoracoscopic surgery three months after initial review, throughout which the patient had remained stable with ongoing dyspnoea and dry cough; wedge biopsies were taken from the left lower lobe, lingula, and left upper lobe without complication. The specimens demonstrated similar features characterized by abundant fibrin within the alveolar spaces and prominent loose fibromyxoid plugs within alveolar spaces, with accompanying type 2 pneumocyte hyperplasia and a mixed inflammatory cell infiltrate (Fig. 2). There was no evidence of lymphoma or any other process.

AFOP was diagnosed. In isolation, the lymphoma would have been considered suitable for observation given its low-grade status. Management options for the AFOP therefore appeared to include either treatment with a prolonged course of corticosteroids via an OP paradigm, or targeted lymphoma therapy on the theoretical basis that the AFOP was a paraneoplastic process; given the potential for corticosteroids to partially but inadequately treat the NHL, consensus was reached to pursue targeted lymphoma therapy. The patient underwent six well-tolerated cycles of bendamustine-rituximab with the only corticosteroid exposure being 20 mg of intravenous dexamethasone given as pre-medication before each cycle. After the first two cycles, he experienced a complete symptomatic response with repeat CT showing near-complete resolution of pulmonary consolidation (Fig. 3). Pulmonary function testing demonstrated resolution of an initial mild restrictive ventilatory defect (forced vital capacity increased from 3.12 L (70% predicted) to 3.78 L (85% predicted)), but diffusing capacity of carbon monoxide (DLCO) remained mildly impaired. Failure of DLCO to normalize was considered most likely due to some residual pulmonary parenchymal and/or vascular effects of the inflammatory process

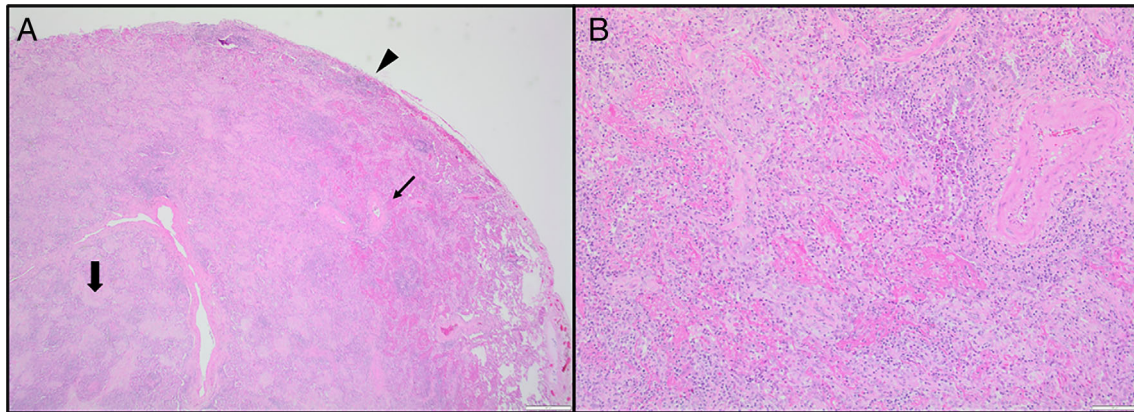


Figure 2. (A) Low-power image of section of lung tissue with standard haematoxylin and eosin stain demonstrating pleural surface (arrowhead), prominent fibrin in alveolar spaces (thin arrow), and fibromyxoid plugs (thick arrow) and (B) higher power image of section of lung tissue with standard haematoxylin and eosin stain demonstrating fibrin in alveolar spaces.

which may not be evident on CT imaging. End-of-treatment PET demonstrated no abnormal FDG-avidity, consistent with a complete oncological response, and low-dose CT images from this scan showed total resolution of all pulmonary consolidation. The patient remains well now nine months after completion of his bendamustine-rituximab therapy.

Discussion

We conclude that bendamustine-rituximab was responsible for the resolution of AFOP despite the dexamethasone

contained in the regimen as a pre-medication because the patient had already received far greater and longer courses of corticosteroid from his local medical officer over the preceding 15 months, yet had nonetheless experienced progression of his pulmonary disease.

This rare case is notable for many reasons. It highlights the breadth of AFOP, here presenting indolently. It exemplifies the diagnostic challenges with this rare histopathological pattern which can co-exist with other entities [5]. It provides compelling evidence that AFOP can arise as a paraneoplastic process, here due to lymphoma. Finally, it suggests that targeted therapy for the underlying disease process may lead to excellent results despite limited use of corticosteroids.

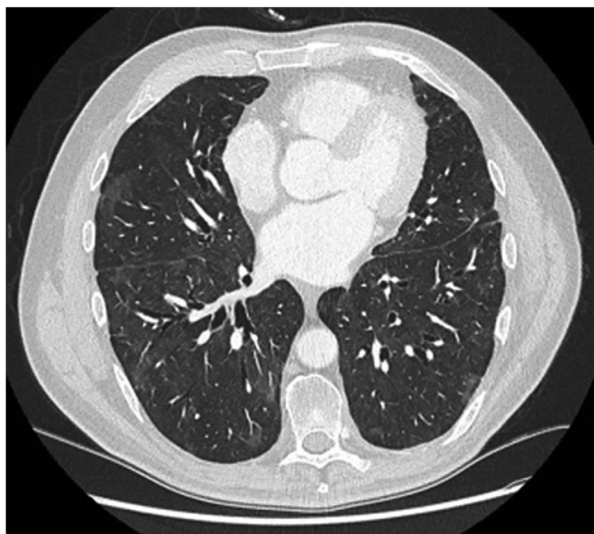


Figure 3. Axial slice of lung window computed tomography (CT) chest at the same level as Figure 1 after two cycles of bendamustine-rituximab depicting near-complete resolution of the pulmonary consolidation, with only minor ground-glass opacity remaining.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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