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SHORT COMMUNICATION

Severe acute fibrinous and organizing pneumonia (AFOP) causing ventilatory failure: Successful treatment with mycophenolate mofetil and corticosteroids

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Summary

Acute fibrinous and organizing pneumonia (AFOP) has recently been identified as an unusual variant of acute lung injury. We describe a man with rapidly progressive lung disease who had AFOP detected via surgical lung biopsy. The patient acutely decompensated while in the hospital and required mechanical ventilation as well as a prolonged ICU stay. He responded poorly to initial treatment and progressively worsened, but he subsequently responded very well to combined therapy with mycophenolate mofetil and methylprednisolone. The combination of corticosteroids and mycophenolate may provide a safe and effective treatment strategy for severe forms of this newly defined pulmonary syndrome.

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Case description

A 56-year-old Caucasian male with a history of severe chronic obstructive pulmonary disease (COPD) ($FEV_1 = 0.86$; 21%

predicted), nonocclusive coronary artery disease, and gastroesophageal reflux disease was admitted to our hospital for evaluation of six weeks history of progressive, non-productive cough that was associated with dyspnea, chest pressure, and new infiltrates on thoracic imaging. He was employed as a forklift operator and was not aware of any occupational exposures. He was a smoker (30 pack years) but quit smoking 2 weeks prior to presentation due to worsening respiratory symptoms. He had been seen in the hospital 2 weeks earlier for

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anterior chest pressure and dyspnea and concern for acute coronary syndrome. A chest radiograph showed bilateral reticulonodular opacifications with basal predominance (Fig. 1A). A CT scan confirmed bilateral changes of consolidation (Fig. 1B). The patient was given oral azithromycin for presumed community-acquired pneumonia but had progressive worsening of his symptoms and developed high grade fevers with chills and night sweats and re-presented for evaluation.

On admission the patient was alert with body temperature of 98 F (oral), pulse 95/min, respiratory rate 16/min and blood pressure 155/87 mm Hg. He appeared lethargic but had no obvious signs of respiratory discomfort. Cardiac and abdominal exams were normal and there was no peripheral edema. Chest auscultation revealed decreased air entry and prolonged expiration without any wheezes or rhonchi. Faint rales were heard over the mid lung fields bilaterally, with diminished breath sounds at the apices and bases.

Laboratory data revealed a white blood count of 16,900/ μ l, hemoglobin 12 gm/dl, and platelet count of 451,000. Erythrocyte sedimentation rate was mildly elevated at 53 mm/h. Electrolytes, creatinine, liver function tests and urine analysis was normal. A sputum Gram smear showed scant numbers of neutrophils, and sputum culture detected growth of normal respiratory flora. Arterial blood gas at room air revealed pH 7.43, PaO_2 61 mm Hg and a $PaCO_2$ 39 mm Hg.

A repeat CT scan revealed progression of the ill-defined pulmonary opacities (consolidation) located predominantly in the mid and lower lung fields without any evidence of

hilar or mediastinal adenopathy (Fig. 1C). The disease seemed to spare the extreme periphery of the lung but affected the lower lobe in a more proximal, peribronchial location. No microorganisms were detected in BAL specimens. Despite being started on broad spectrum intravenous antibiotics (piperacillin-tazobactam, vancomycin and levofloxacin), fever persisted and dyspnea progressed.

Bronchoscopy performed on hospital day 2 did not reveal any endobronchial lesions or abnormal secretions. Bronchoalveolar lavage (BAL) and trans-bronchial biopsies were performed in the right lower lobe (lateral and posterior basilar segments). The patient developed a respiratory rate of 40 per min after the procedure and was transferred to the ICU for close monitoring. He subsequently required intubation and continued to deteriorate clinically over the next 4 days requiring a high FiO_2 [FiO_2 90%, PEEP 5 cm, H_2O , arterial blood PaO_2 66 mm Hg] to maintain adequate oxyhemoglobin saturation. Daily bedside chest radiographs showed progression of the bilateral infiltrates.

The trans-bronchial biopsies revealed a non-specific pattern of inflammation and no evidence of infection or malignancy. A surgical lung biopsy was subsequently obtained from the left lower lobe and left upper lobe to obtain a definitive diagnosis. The pathology findings showed patchy involvement of lung parenchyma by fibrin deposits in the form of "fibrin balls" in alveolar ducts and alveoli (Fig. 2A and B). In addition mild interstitial widening with mild inflammatory infiltrate (including mononuclear cells and neutrophils) was noted. Classical organizing pneumonia with intra-alveolar fibroblastic plugs "Masson bodies" was also present as a less

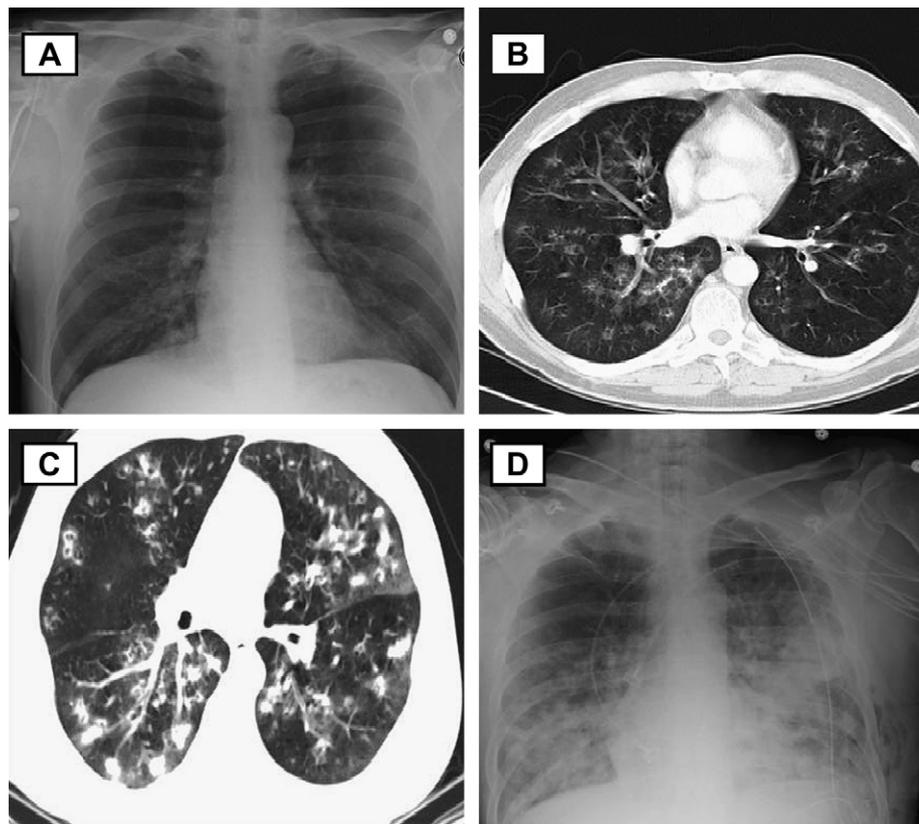


Figure 1 Initial chest radiograph showing subtle infiltrate (A); initial chest CT scan showing bilateral reticulonodular infiltrate (B); CT scan showing progression of bilateral infiltrates (C); chest radiograph showing bilateral infiltrates with consolidation (D).

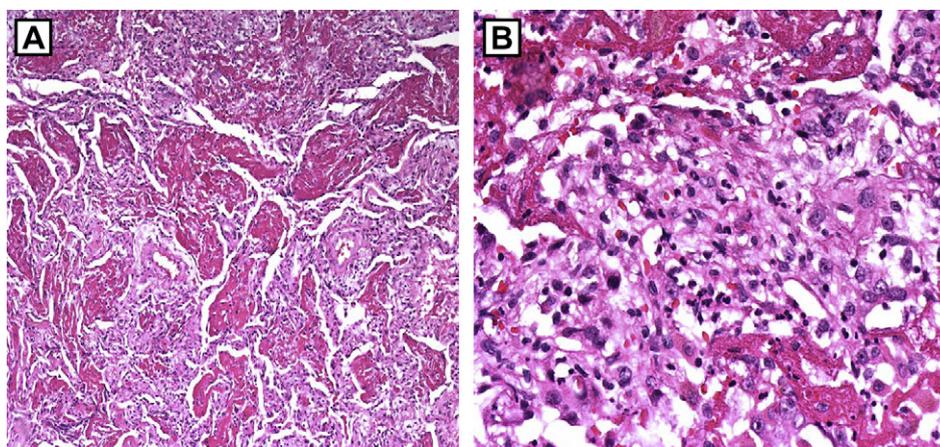


Figure 2 A: 100× photomicrograph showing fibrin deposits in the form of “fibrin balls” in alveolar ducts and alveoli. B: 400× photomicrograph showing mild interstitial widening with mild inflammatory infiltrate including mononuclear cells and neutrophils.

dominant feature. No hyaline membranes were seen, and special stains for fungal and mycobacterial organisms were negative. Findings were consistent with the reported description of acute fibrinous and organizing pneumonia (AFOP). The pathology specimens were sent for verification to the Armed Forces Institute of Pathology, Washington DC [where the first 17 cases were reported], and the diagnosis of AFOP was confirmed.

After establishing the diagnosis of AFOP, antibiotics were discontinued and the patient was started on both intravenous methylprednisone at 1 mg/kg as well as mycophenolate mofetil (MMF) 500 mg PO twice daily via his feeding tube. The PaO_2/FiO_2 ratio gradually improved over the first few days of therapy with a decrease in ventilator requirements (FiO_2 40% with PEEP 5 cm H_2O ; arterial blood gas with PaO_2 69 mm Hg, PCO_2 56 mm Hg, pH 7.45). Subsequently however, the patient could not be weaned off the ventilator and chest radiograph (Fig. 1D) did not show resolution or significant improvement in the bilateral infiltrates. The MMF dose was increased to 1 g twice daily one week later. The patient gradually improved, and the clinical response was accompanied by resolution of radiographic infiltrates over the subsequent 5 days as he was weaned from mechanical ventilation on hospital day number 20. He was discharged on a tapering schedule of prednisone while continuing mycophenolate as mycophenolate sodium (myfortic) at 360 mg twice daily. After 12 months of follow-up, the patient had regained 26 lbs and had greatly improved exercise capacity.

Comment

In 2002 Beasley et al.¹ described a new histological pattern of diffuse infiltrative lung disease that was termed acute fibrinous and organizing pneumonia (AFOP). Tissue histopathology revealed intra-alveolar fibrin in the form of fibrin “balls” and organizing pneumonia with a patchy distribution. This pattern is differentiated from diffuse alveolar damage (DAD) by the absence of hyaline membranes while the lack of eosinophils distinguishes it from eosinophilic pneumonia (EP).² The fibrin deposition that is characteristic of AFOP is typically patchy, with an average of 50% airspace involvement, as opposed to the more diffuse changes

typically present with DAD. In AFOP alveolar walls adjacent to areas of fibrin deposition demonstrate a variety of changes that can include acute or chronic inflammatory cell infiltration, interstitial widening, and type II pneumocyte hyperplasia. However, areas of lung tissue without fibrin deposits typically show only minimal histological changes.¹ Because of its patchy distribution, the diagnosis of the AFOP is difficult to make on bronchoscopic biopsy specimens. A confident diagnosis of AFOP is unlikely to be made without performing a surgical lung biopsy.¹

The onset of dyspnea and non-productive cough of less than 2 months duration were observed in all 17 patients described by Beasley et al.¹ and our patient had similar symptoms of six weeks duration prior to presentation. Beasley et al.¹ described two distinct patterns of disease progression and outcomes: fulminant illness with rapid progression to death and a sub-acute course with recovery.¹ All 5 of the patients who required mechanical ventilation died. Our patient had fulminant illness requiring mechanical ventilation but responded to immunosuppressive therapy. Additionally, our patient’s HRCT scan demonstrated bilateral patchy lower lobe infiltrates that are consistent with what has been observed in previous reports of this entity.^{1,2}

AFOP has been linked to infection, connective tissues disorders, and occupational and drug exposures. It also occurs as an idiopathic entity, and our patient did not appear to have an associated exposure or disorder other than cigarette smoking.

Beasley et al.¹ and Damas et al.² have treated AFOP with various agents including steroids, antibiotics, and cyclophosphamide with varying clinical responses. Our patient appeared to have a fulminant form of illness with inability to wean the patient off the ventilator. Because a combination of cyclophosphamide and prednisone had been reported as a successful treatment regimen,² we considered mycophenolate, an immunosuppressive agent approved for the prevention of transplant rejection, as a second agent in combination with corticosteroid therapy. Mycophenolate has been used to treat lupus nephritis that is refractory to cyclophosphamide as well as patients who cannot tolerate cytotoxic therapy with cyclophosphamide. Mycophenolate has also been used in scleroderma-associated ILD^{3,4} in addition to

steroids⁴ and has been found to be safe, well tolerated and effective in preserving lung function in connective tissue disease-related ILD.⁵ The dose of MMF used in these studies ranged from 1 to 2 gm/day with a duration of 12–24 months, and treatment with MMF was associated with a good safety profile.^{3–6} We obtained a good clinical response with oral MMF at a dose of 1 gm twice daily combined with IV methylprednisolone at 1 mg/kg.

The patient remains on these medications as an outpatient and we plan on gradually tapering these over a year or two. The optimal duration of therapy is not known for AFOP, previous studies have treated anywhere from 12 to 24 months.² Despite the higher cost of mycophenolate mofetil, as compared with intravenous cyclophosphamide, there are additional costs associated with cyclophosphamide infusion, including reimbursement for the infusion unit and the cost for antiemetic agents, mesna, and leuprolide. Thus, the actual cost of cyclophosphamide therapy may surpass that of mycophenolate mofetil.⁶ The good clinical response observed in our patient suggests that the addition of mycophenolate to corticosteroids might be a useful treatment for patients with AFOP.

Conflicts of interest

No conflicts of interest or relation to industry for any of the authors.

References

1. Beasley MB, Franks TJ, Galvin JR, Gochuico B, Travis WD. Acute fibrinous and organizing pneumonia: a histological pattern of lung injury and possible variant of diffuse alveolar damage. *Arch Pathol Lab Med* 2002 Sep; **126**(9):1064–70.
2. Damas C, Morais A, Moura CS, Marques A. Acute fibrinous and organizing pneumonia. *Rev Port Pneumol* 2006 Sep–Oct; **12**(5): 615–20.
3. Zamora AC, Wolters PJ, Collard HR, Connolly MK, Elicker BM, Webb WR, King Jr TE, Golden JA. Use of mycophenolate mofetil to treat scleroderma-associated interstitial lung disease. *Respir Med* 2008 Jan; **102**(1):150–5.
4. Vanthuyne M, Blockmans D, Westhovens R, Roufosse F, Cogan E, Coche E, Nzeuseu Toukap A, Depresseux G, Houssiau FAA pilot study of mycophenolate mofetil combined to intravenous methylprednisolone pulses and oral low-dose glucocorticoids in severe early systemic sclerosis. *Clin Exp Rheumatol* 2007 Mar–Apr; **25**(2): 287–92.
5. Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, Meehan RT, Brown KK. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. *Chest* 2006 Jul; **130**(1):30–6.
6. Ginzler EM, Dooley MA, Aranow C, Kim MY, Buyon J, Merrill JT, Petri M, Gilkeson GS, Wallace DJ, Weisman MH, Appel GB. Mycophenolate mofetil or intravenous cyclophosphamide for lupus nephritis. *N Engl J Med* 2005 Nov 24; **353**(21):2219–28.