



CASE BASED DISCUSSIONS

What lies beneath: poking a hole in the diagnosis

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A man aged 77 years was referred to the emergency department (ED) of our hospital by his primary physician for evaluation of dyspnoea and hypoxaemia. On presentation to the ED, he reported 2 months of progressively worsening dyspnoea and non-productive cough. He also endorsed weight loss and fatigue. He had been prescribed a recent course of clarithromycin after an episode of fever, but this did not ameliorate either the dyspnoea or the cough. On the day he was referred to the ED, his primary physician found him to be hypoxemic, which is what prompted the referral.

The patient's medical history was significant for hypertension and coronary artery disease with myocardial infarction and coronary stenting 4 years prior to admission. His usual home medications included aspirin, carvedilol, losartan, rosuvastatin, sertraline and zolpidem. He was a former smoker who quit 25 years earlier after accumulating 40 pack-years. He had no occupational or environmental exposures.

On admission, his hypoxaemia was confirmed with an oxygen saturation by pulse oximetry on room air of 76%. The patient was visibly dyspnoeic and had diffuse bilateral crackles on auscultation. His jugular venous pulse was normal. There was no clubbing or oedema. Routine laboratory evaluation was remarkable for a brain natriuretic peptide level of 557 pg/mL (normal <100 pg/mL). There was no blood eosinophilia. Testing of a nasopharyngeal swab specimen for the most common respiratory viral pathogens and *Bordetella pertussis* by PCR was negative. Frontal chest radiograph (CXR) obtained in the ED demonstrated extensive bilateral airspace opacification (figure 1A), which was new compared with a CXR taken 18 months earlier. There were no pleural effusions. Intravenous furosemide was administered for a presumptive diagnosis of

cardiogenic pulmonary oedema. However, the patient's symptoms and oxygenation failed to improve. Transthoracic echocardiography showed focal left ventricular wall motion abnormalities. However, systolic function and myocardial relaxation were normal. Based on this clinical course, CT of the chest was ordered and respiratory consultation requested.

ANNA ROZENSHEIN (AR), CONSULTANT THORACIC RADIOLOGIST

CT of the chest without intravenous contrast obtained 2 days after the initial CXR demonstrated diffuse ground glass and semi-solid opacities predominating in the periphery and in the upper lung zones. In addition, there were scattered centrilobular cysts without clearly definable walls, presumably due to emphysema in a former smoker (figure 1B). The differential diagnosis of this pattern in an immunocompetent host includes non-specific interstitial pneumonia, organising pneumonia (OP), chronic eosinophilic pneumonia (CEP) as well as drug-induced interstitial lung disease. In an appropriate clinical setting, community-acquired viral pneumonia, pulmonary haemorrhage and a variety of pneumoconioses could also produce this appearance. In an immunocompromised host, pneumocystis, cytomegalovirus and other opportunistic pneumonias should be higher on the list of potential diagnoses, although peripheral and upper lung zone predominance would be atypical. Mildly enlarged mediastinal lymph nodes demonstrated at CT were thought to be reactive to the parenchymal disease. Comparison with a CT of the abdomen performed 16 months previously proved that the disease was new, at least in the lower lobes (not shown).

OLEG EPELBAUM (OE), RESPIRATORY CONSULTANT

We evaluated the patient after the chest CT was already available for review. The patient's primary clinical team initially assumed him to be presenting with cardiogenic pulmonary oedema. Misattribution of diffuse parenchymal lung disease to a cardiac aetiology is a well-described occurrence, especially in patients with cardiovascular disease or its risk factors. However, certain features of his illness favoured primary lung disease. The patient reported prominent constitutional symptoms. On physical examination, there were neither elevated cardiac filling pressures nor volume overload. No pleural effusions were demonstrated at CXR. Scepticism appropriately crept in after intravenous diuretics proved ineffective. Chest CT findings unusual for

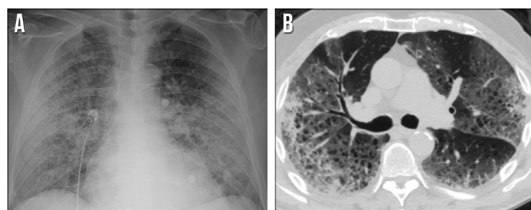


Figure 1 (A) Portable chest radiograph obtained at presentation shows diffuse bilateral airspace opacities. (B) Axial chest CT at the level of the upper lobes in lung window shows a mixture of solid and semi-solid opacity superimposed on emphysema.



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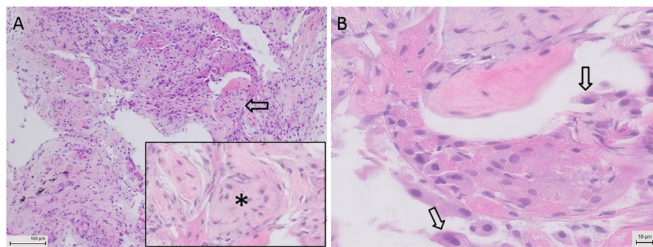


Figure 2 (A) Low-power view of a representative section of lung obtained via transbronchial biopsy with an arrow identifying the characteristic lesion of organising pneumonia: an alveolus occupied by a fibromyxoid connective tissue plug with fibroblasts embedded within the immature collagenous matrix. Inset (lower right) contains a magnified image of such a lesion (asterisk), also known as a Masson body, from another section (H&E, original magnification $\times 100$). (B) High-power view highlights foamy macrophages (arrows) lining the alveolar spaces (H&E, original magnification $\times 400$).

cardiogenic pulmonary oedema in our mind further raised suspicion for a diffuse parenchymal lung disease, most prominently OP. It is worth noting that clarithromycin has been associated with CEP in isolated reports.^{1 2} However, CEP was rendered clinically unlikely by the lack of peripheral eosinophilia, which is a near-universal finding in this condition, including the two cases involving clarithromycin. In light of his smoking history, we also considered pneumonic-type lung adenocarcinoma (ie, well-differentiated adenocarcinoma with lepidic growth pattern), which can present insidiously and mimic benign lung disease. Consequently, we proceeded to flexible bronchoscopy with bronchoalveolar lavage and biopsies of the right upper and lower lobes.

YEVGENIY LINNIK (YL), CONSULTANT PATHOLOGIST AND SOUMYA MIKKILINENI (SM), PATHOLOGY TRAINEE

We reviewed bronchoalveolar lavage fluid submitted for differential cell count and cytology; neither sample contained eosinophils. Biopsy specimens from the upper and lower lobes showed nodular fibroblastic and myofibroblastic proliferations arranged in whorls and embedded within a pale myxoid matrix filling the airspaces. This lesion, known as a Masson body, is marked by an arrow in [figure 2A](#) and magnified in the inset. Background lung parenchyma was relatively intact with a mild interstitial mononuclear infiltrate and occasional foamy macrophages ([figure 2B](#)). There was no tissue infiltration by eosinophils. There was no malignancy. While the observed histomorphology is non-specific and therefore cannot be used in isolation for definitive pathological classification, given the clinical and radiological findings this pattern is consistent with organising pneumonia in its proliferative or early mature phase.

NK: the patient was started on intravenous methylprednisolone at a dose of 40 mg every 6 hours. Cultures of bronchoalveolar lavage fluid for bacterial, viral, fungal and mycobacterial organisms eventually returned negative.

OE: like the pathologist, the clinician should interpret the finding of OP as simply a non-specific response by the lung to an insult. In the majority of cases, the trigger is not identified and therefore cryptogenic OP (COP) is the operative term. Among the most clearly established aetiological associations are medications, autoimmune disorders, infections, haematological malignancies, stem cell transplantation and radiation therapy. The spectrum of OP's clinical presentation runs the gamut from absence of symptoms to catastrophic respiratory failure fulfilling

criteria for the acute respiratory distress syndrome (ARDS). Correspondingly, the chest CT appearance can range from a solitary pulmonary nodule to diffuse bilateral consolidations reminiscent of ARDS. Some authorities have suggested that a confident diagnosis of OP requires surgical lung biopsy, although sufficient diagnostic material using conventional bronchoscopic biopsies. Of note to the clinician, although the histopathology of OP is characterised by collagen deposition by fibroblasts and myofibroblasts, the collagen that is laid down is not type I but rather type III, which is degradable and explains the usual reversibility of OP in contrast to fibrotic lung diseases. Spontaneous resolution is known to occur, but symptomatic cases are typically treated. It is customary to extend the treatment for as long as 6 months to minimise the likelihood of relapse. Glucocorticoids are the first-line agents, and resolution without sequela is the norm. Rarely, OP follows a rapidly fibrosing course and causes progressive, irreversible lung damage, sometimes with a fatal outcome.

NK: 4 days into therapy with intravenous glucocorticoids, the patient had a repeat CXR due to an episode of oxygen desaturation. This film showed free air under the right hemidiaphragm, best appreciated on the left lateral decubitus projection ([figure 3](#)). Emergency exploratory laparotomy revealed a small descending colon perforation. A partial left hemicolectomy was performed. Histopathological examination of the resection specimen demonstrated diverticulitis and a focus of adenocarcinoma. The immunohistochemical staining pattern was most consistent with a primary gastrointestinal origin. Subsequent extent of disease evaluation, which included subtotal colectomy, established stage IIIC poorly differentiated adenocarcinoma of the cecum.

OE: the perforation was a twist of fate that uncovered latent colorectal cancer in this patient. While haematological malignancy has been implicated in cases of OP in multiple series the connection between solid neoplasms and OP is less conclusive. The best described phenomenon is the incidental discovery of focal OP in association with lung cancer in resection specimens. This case represents a striking constellation of features: clinically overt OP in the setting of previously undetected extrapulmonary malignancy without lung involvement or prior oncological therapy. To date, the most comprehensive assessment of the clinical characteristics of OP in the oncological population is a 2002 study of 43 Memorial Sloan-Kettering Cancer Center (MSKCC) patients.³ The majority of these patients (63%) had solid organ tumours, and of these 27 patients, only 10 had pure small-cell or non-small cell lung cancer. The majority of solid tumour sites were thus extrapulmonary. Three of the 27 patients (11%) had single gastrointestinal primaries. The current patient is different because all of the patients in the MSKCC study carried a known diagnosis of malignancy and all had previously received oncological treatment. His presentation raises the question of whether COP should be considered a possible lung signal of occult malignancy and, if so, how many cases of so-called 'cryptogenic' OP have actually been harbingers of cancer.

NK: we hypothesised that the patient's glucocorticoid therapy was a contributing factor to his colonic perforation. Continued administration of systemic steroids was also undesirable from the perspective of wound healing. His treatment regimen was changed to azithromycin 500 mg twice daily.

OE: the immunomodulatory properties of macrolide antibiotics made their first big splash on the respiratory medicine scene with a 1998 study from Japan showing that erythromycin decreases mortality in diffuse panbronchiolitis.⁴ Since then,



Figure 3 Left lateral decubitus radiograph revealing free intraperitoneal air between the liver and the diaphragm.

erythromycin's more contemporary relatives clarithromycin and azithromycin have entered the therapeutic armamentarium for other non-infectious lung diseases such as bronchiolitis obliterans syndrome non-cystic fibrosis bronchiectasis and chronic obstructive pulmonary disease.

Based on studies of bronchoalveolar lavage fluid, it has been postulated that the immunobiology of OP primarily involves the Th-1 T-lymphocyte response with consequent activation of alveolar macrophages.⁵ Nuclear factor- κ B (NF- κ B) is a transcription factor that promotes Th-1 differentiation of T-lymphocytes while tumour necrosis factor- α (TNF- α) is an important pro-inflammatory cytokine released by the stimulated macrophages as a result. To close the loop, TNF- α can in turn upregulate NF- κ B activity. The putative central role of these and other Th-1 mediators in the molecular pathogenesis of OP is concordant with the effectiveness of glucocorticoids in this condition.

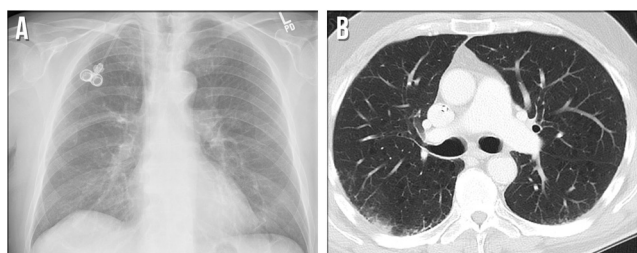


Figure 4 Posteroanterior chest radiograph (A) and axial chest CT (B) image from approximately the same level as in figure 1B obtained following completion of therapy both demonstrate marked improvement.

Macrolides have likewise been shown to inhibit activation of NF- κ B and downregulate the production of TNF- α by alveolar macrophages, the latter specifically in OP.⁵

This lends mechanistic plausibility to the favourable response of OP to macrolides, namely clarithromycin, observed in the clinical experience. Ironically, this patient completed a 10-day course of clarithromycin prior to his presentation to hospital, but that did not prevent progression of his lung disease, which had perhaps become too advanced by that time.

NK: after conversion to azithromycin during the index hospitalisation, he continued to demonstrate both clinical and radiological improvement of his OP. This macrolide regimen was administered during his complicated postoperative course. He was ultimately discharged and underwent adjuvant chemotherapy as an outpatient. Two months into the treatment of his OP, azithromycin was replaced by prednisone at a dose of 30 mg daily, which was tapered over the ensuing 4 months for a total course of 6 months. At treatment end, he exhibited normal spirometry and lung volumes and markedly improved chest imaging (figure 4A and B).

OE: this is a thought-provoking case about the relationship between OP and solid malignancy. The heretofore reported associations can be characterised broadly as either bystander OP in lung cancer resection specimens or OP in previously diagnosed and treated solid tumours of all types. This case of OP in a patient with latent malignancy opens the door to consideration of such a possibility in other cases of apparent 'COP,' which may or may not actually be 'cryptogenic'.

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