

A case of *Mycobacterium avium-intracellulare* pulmonary disease and Crohn's disease

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Abstract

We report a case of pulmonary *Mycobacterium avium-intracellulare* (MAI) in a previously fit 48-year-old man who subsequently developed Crohn's disease. We discuss the potential predisposing factors for pulmonary MAI; the diagnostic uncertainties in this particular case; the relationship between pulmonary MAI and Crohn's disease; and the difficulties in management that are highlighted by this case.

Keywords

Mycobacterium avium-intracellulare, *Mycobacterium paratuberculosis* = *Mycobacterium avium* subspecies; anti-tuberculous therapy; Crohn's disease.

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Case report

A 48-year-old man presented with a two-month history of general malaise, a cough productive of mucopurulent sputum, weight loss of 1 stone (6.3 kg) and non-specific generalised aches.

Two years previously he had undergone a left thoracotomy and pleurectomy for a recurrent left-sided pneumothorax. He had never smoked and his work involved extensive travel. On examination he was tall and of slender build. Respiratory examination was unremarkable. He had normal spirometry and CXR showed consolidation at the right apex with possible cavitation. A Heaf test was grade 3 positive. Sputum specimens were Ziehl-Neelsen stain positive. An HIV test was negative.

He was treated with standard antituberculous therapy, but culture of his sputum became *Mycobacterium avium-intracellulare* (MAI)-resistant to all first line antituberculous therapy. Courses of rifabutin, clarithromycin 1g day⁻¹, and ethambutol 1200 mg day⁻¹ were started. The patient discontinued treatment after four days as he considered the side-effects to be worse than his symptoms.

Six months later he was unwell again with cough productive of purulent sputum and a weight loss of 6.5 kg. His CXR showed consolidation in his right upper lobe with marked volume loss in both right and left upper zones. He was admitted for initiation of rifinah 600 mg day⁻¹, clarithromycin 500 mg day⁻¹, and ethambutol 1200 mg day⁻¹. A CT scan was performed to exclude an abscess. It showed bullae in the left upper lobe.

Disease progress

Three to four months after restarting the antimycobacterial therapy he developed persistent and severe watery diarrhoea, including nocturnal diarrhoea with abdominal pain and a reduced appetite. Stool specimens showed no pathogens and *Clostridium difficile* toxin was negative. His symptoms persisted and he was investigated further with a colonoscopy that showed mild mucosal oedema. Biopsies showed a patchy but extensive

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lymphoplasmacytic chronic inflammatory infiltrate occupying the full thickness of the lamina propria, small epithelioid granulomas, and submucosal chronic inflammation. The infiltrate and architectural distortion suggested inflammatory bowel disease, and the presence of occasional granulomas suggested Crohn's disease. A small fragment of acid-fast material, possibly representing an acid-fast bacillus, was seen on caecal biopsy (Fig. 1(a)), raising the possibility of a mycobacterial enterocolitis or systemic MAI. Further investigations were therefore carried out. An abdominal CT scan showed thickened oedematous mucosa. A radio-labelled white cell scan showed involvement of the terminal ileum and a large part of the gastrointestinal tract. At laparoscopy the abdomen looked normal macroscopically with no lymphadenopathy and a small bowel biopsy was performed to try to determine the diagnosis. These also showed epithelioid granulomas and patchy chronic inflammation. Overall, the most likely diagnosis was MAI affecting the right upper lobe cavity, with no evidence of immunosuppression (a second HIV test was negative), and coexistent Crohn's disease.

Subsequent treatment and progress

His diarrhoea responded to a reducing course of prednisolone. Antimycobacterial therapy was continued for one year. However, his cough returned two weeks after stopping treatment, which was then restarted, and he was electively admitted for surgical resection four months later. Unfortunately, at the time of admission, he had an incidental left upper lobe pneumonia that responded to intravenous cefuroxime and metronidazole. One sputum culture subsequently grew MAI. Antimycobacterial treatment, with isoniazid omitted due to the side-effects, was continued for a further year before elective admission for right upper lobectomy.

Macroscopically, within the lobectomy specimen a large necrotic cavitating lesion measuring $8 \times 6 \times 6$ cm was present. Microscopy showed a necrotising cavitating granulomatous inflammation with easily visible acid-fast bacilli on Ziehl-Neelsen stain, confirming mycobacterial infection (Fig. 1(b)).

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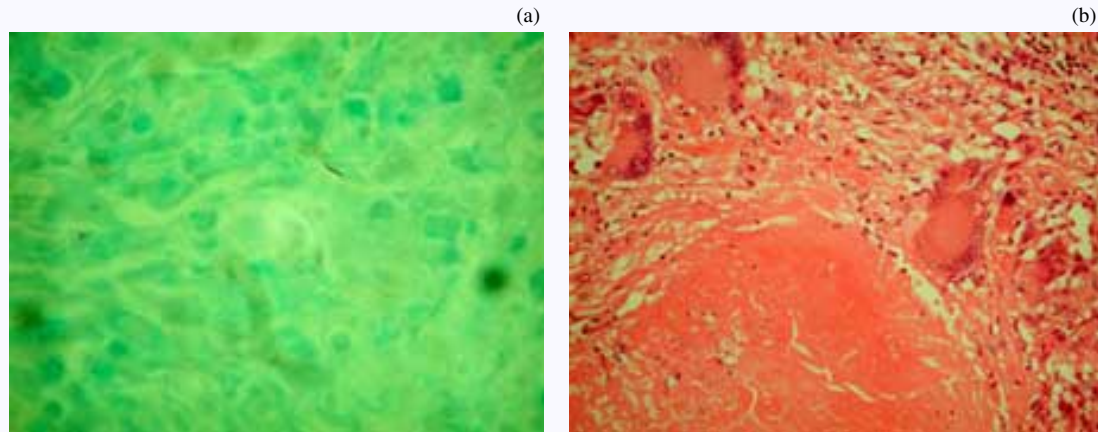


Fig. 1. Caseating granulomatous inflammation. There is a rounded area of necrosis (lower half of picture) surrounded by inflammatory cells and several Langhan's type multinucleate giant cells.

Following the right upper lobectomy he developed vomiting and anorexia, eventually requiring parenteral feeding. He is now well, 15 months after the lobectomy. He occasionally coughs up sputum, which is AFB negative. His Crohn's disease is controlled on prednisolone, 2.5 mg on alternate days.

Discussion

This case highlights several issues relating to MAI pulmonary disease: the presentation in a non-immunocompromised man, the development of Crohn's disease, and whether this is related to the MAI infection, and the problems of treatment.

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Predisposing factors for pulmonary MAI

MAI is a ubiquitous opportunistic pathogen known to cause disease in either cell-mediated immunodeficiency states or in the presence of underlying lung disease including COPD, previous tuberculosis, bronchiectasis, pneumoconiosis, thoracic anomalies and Marfan Syndrome^[1]. However, there may be predispositions not yet recognized, as studies looking retrospectively at MAI pulmonary disease in the community have shown that the majority of cases are in middle-aged to elderly non-smoking women with no history of lung disease or immunodeficiency^[2,3]. Our patient had a past history of recurrent pneumothorax and bullae at the left apex on CT scan of his chest. Notably, he was of markedly slender build. These features may point towards an underlying connective tissue defect without a specific diagnosis such as Marfan Syndrome^[1]. In a review of MAI pulmonary disease cases, up to 70% had one or both of scoliosis and pectus excavatum; it has been postulated that these features may represent phenotypic markers of hereditary connective tissue disorders that result in an abnormality of lung structure or mucociliary function, thereby increasing host susceptibility to this opportunistic pathogen^[1]. Pulmonary MAI can cause a variety of lung pathologies but is associated with cavitation when underlying lung disease is present, as in our case^[1].

The relationship between pulmonary MAI infection and Crohn's disease

The diagnostic possibilities in this case increased when the patient developed diarrhoea. When Crohn's disease was confirmed with the involvement of both the upper and lower small bowel, this raised questions about the potential association of pulmonary MAI with Crohn's disease. The gastrointestinal tract has been suggested as the portal of entry for disseminated MAI in one immunocompetent patient^[4]. However, this is unlikely to be the case in our patient in view of the sequence of clinical presentation. Although the precise portal of entry remains uncertain, pulmonary MAI, like other mycobacterial infections, is believed to be transmitted by inhalation, such as aerosolised infected particles during showering^[1].

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The relationship between MAI infection and Crohn's disease is not fully understood and the development of Crohn's disease is believed to result from both environmental and genetic factors. Crohn's disease was originally termed hyperplastic tuberculosis in the early 1900s, recognising the similarity in histopathology with gastrointestinal tuberculosis, excepting the caseous necrosis and acid-fast bacilli. There is increasing evidence to suggest an association between *M. avium* subspecies *paratuberculosis* and Crohn's disease. This organism is endemic in the food chain and water supply of the western world and is not killed by standard food processing, cooking and water treatments. Thus, the epidemiology of MAI would make it a suitably placed environmental factor in the development of Crohn's disease in a susceptible individual. Furthermore, it causes inflammatory bowel disease in cattle (Bovine Johne's Disease) and has been reported to produce a disease indistinguishable from Crohn's disease on clinical and radiological grounds in an immunocompromised and immunocompetent patient^[5,6]. In the immunocompromised patient, histology showed that the granulomas contained numerous acid-fast bacilli, identified on culture as MAI^[5].

However, there is no conclusive evidence to fulfil the Henle-Koch postulates for causality; namely, that the organism is always found with the disease, that the organism is not found with any other disease, and that cultured organisms isolated from a diseased individual will reproduce the disease in a susceptible animal. There is also no conclusive demonstration of a cellular immune response consistent with the characteristic pathology in Crohn's disease of a delayed-type hypersensitivity reaction. The most supportive evidence comes from a combination of cultural and molecular biology techniques. In particular DNA isolation^[7] and combining IS900, a species-specific insertion of *M. paratuberculosis* with the polymerase chain reaction, has shown the presence of *M. paratuberculosis* in 65% of Crohn's disease patients, 4.3% of ulcerative colitis patients and 12.5% of controls. These data show there is a significant predominance in Crohn's disease (chi-squared result = 0.0001) suggesting that *M. paratuberculosis* plays an important aetiological role above the common background environmental exposure^[8].

Finally, studies looking at standard antituberculous therapy as alternative treatment to steroids in Crohn's disease have not shown clinical benefit^[9] whilst others looking

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at therapy used for atypical mycobacteria have shown clinical improvement in active disease in the medium term^[10] and in acute disease in the short term^[11]. One case report of presumed Crohn's disease developing five years after proven MAI lymphadenitis responded to antimycobacterial therapy. However, there was no comment on the bowel histology before therapy^[12]. There is a need for larger and placebo-controlled treatment studies to clarify the optimum combination and course of treatment. In our case the pulmonary infection was controlled when the diarrhoea started, arguing against MAI being the cause of the diarrhoea.

Management and follow-up of pulmonary MAI

This case also highlights some of the common problems of managing pulmonary MAI. There is usually a delay in diagnosis because of the non-specific prominent constitutional features and an insidious course of coughing, fever, weight loss and sputum production together with a high false negative sputum culture rate (except in cavitatory disease)^[2]. There is evidence that delayed diagnosis or treatment reduces success rates and therefore prognosis^[1,2]. This may be due to the establishment of permanent lung damage such as bronchiectasis, and indeed those with less advanced disease have a favourable response to treatment^[3].

MAI organisms are resistant to many of the standard antituberculous drugs such as isoniazid and pyrazinamide. Overall, studies suggest the highest sputum conversion rates are achieved with multi-drug treatments comprising a combination of clarithromycin, rifabutin and ethambutol^[13]. However, this combination frequently requires dose adjustments due to direct drug toxicity sometimes enhanced by drug interactions, the most significant of these being the interaction between clarithromycin, a cytochrome p450 enzyme inhibitor, in precipitating rifabutin toxicity and uveitis. Patients sometimes report that the adverse drug effects are worse than their symptoms (as in this case). Prolonged treatment is usually required to achieve long-term sputum conversion and avoid long-term lung damage, further reducing compliance. Monotherapy leads to macrolide resistance so cannot be used safely to enhance compliance. Analogous to the treatment of TB,

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directly observed (intermittent) therapy can reduce non-compliance and improve overall conversion rates^[13]. Finally, monitoring response to treatment is problematic as there is difficulty in gauging the patient's clinical improvement and sputum cultures have a high false negative rate^[2].

Surgery remains an important therapy adjunct and is indicated if medical treatment has failed, in clarithromycin-resistant MAI, in massive haemoptysis, and in those with limited disease where early surgical intervention has been consistently shown to be successful with a low mortality rate, as in our case^[14]. Future management may involve immunomodulatory therapy, as it is postulated that in those patients with no currently recognized predisposing factor there may be an acquired host immune defect^[15].

Summary

In summary, we have reported an unusual case of pulmonary MAI in an immunocompetent man, who we postulate may have an underlying connective tissue defect leading to bullae formation. The man subsequently developed Crohn's disease and this created significant diagnostic difficulties because of the possible causative role of MAI in his bowel symptoms. Although there is a growing body of evidence to support MAI as a causative factor in Crohn's disease, Crohn's disease should continue to be regarded as a disorder of multi-factorial aetiology. This case also highlights management problems and the failure to control his pulmonary infection without resection.

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