Unusual association of diseases/symptoms

An opportune finding in suspected liver metastases

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Summary

Opportunistic mycobacterial infections are rare in immunocompetent patients. The authors describe a case of disseminated *Mycobacterium avium* complex disease in a previously healthy patient presenting with hepatosplenomegaly and non-specific symptoms which initially led to a diagnosis of metastatic carcinoma. After correct treatment she made a full recovery, with resolution of symptoms and the radiological findings.

BACKGROUND

This is an important case as it demonstrates a presentation of disease that has not been published before in the literature. Pulmonary disease caused by *Mycobacterium avium* complex (MAC) has been described in middle-aged immunocompetent males and females, but disseminated MAC disease apparently affecting only the liver and spleen in a patient without any underlying immune deficiency has not yet been reported.

In addition to being a rare presentation of disease, this case is also of interest as it highlights the clinical usefulness of liver biopsy in patients who are in reasonable health. Following appropriate antimycobacterial treatment, the patient made an excellent recovery. However, she may have been subject to inappropriate treatment (eg, chemotherapy for presumed malignancy) or may have elected palliative treatment only, had an accurate diagnosis not been made.

CASE PRESENTATION

A 50-year-old woman presented with marked weight loss – over 14 kg in less than 3 months, anaemia and elevated liver function tests. Initial investigations arranged by her general practitioner included a normal upper gastrointestinal endoscopy and an abdominal ultrasound scan which revealed significant hepatosplenomegaly, and suggested multiple liver lesions.

There was no significant medical history, and she was a life-long non-smoker. Of Mauritian origin, she had lived in France for many years before moving to the UK, but had no other recent travel history. She had worked as a cleaner in both France and the UK.

On examination, she was cachectic, but had no stigmata of chronic liver disease. Marked hepatosplenomegaly was evident, however, there was no ascites, peripheral oedema or lymphadenopathy.

INVESTIGATIONS

Initial laboratory tests revealed normal renal function, thyroid function and coagulation profile, but a haemoglobin of 9.7 g/dl (normal range 11.5–15.5 g/dl) with mean corpuscular volume of 67 fl. The C reactive protein (CRP) was raised

at 38 mg/l (normal <6 mg/l), the erythrocyte sedimentation rate (ESR) was 45 mm/h (normal range 1–10 mm/h) and her liver function tests were abnormal with a γ -glutamyl transferase of 368 IU/l (normal range 5–56 IU/l) and alkaline phosphatase (ALP) of 518 IU/l (normal range: 30–115 IU/l). Alanine transaminase was 45 U/l (normal range 5–40 U/l) and aspartate transaminase was 37 IU/l (normal range 5–45 IU/l). α 1-Antitrypsin levels, serum caeruloplasmin, autoantibodies (including antineutrophil cytoplasmic antibodies, antimitochondrial antibodies, anti-double-stranded DNA antibodies), α -feto-protein, tumour markers (CEA, Ca125, Ca 19-9) and folate and B12 were normal. Her ferritin was 37 ng/ml. She was negative for HIV, hepatitis B and C. Her corrected calcium level was within normal limits. A tuberculin skin test (Mantoux 1/1000) was negative. She has previously undergone testing for haemaglobinopathies, which were negative.

In view of the absence of lower gastrointestinal symptoms, her significant weight loss and the result of the abdominal ultrasound, further radiological imaging was undertaken. CT scan of the chest, abdomen and pelvis revealed an enlarged, diffusely abnormal liver, with areas of low attenuation seen in all segments. There were multiple space occupying lesions within the spleen (figure 1). No lymphadenopathy was evident. The lungs were normal. The appearances on CT were thought to be those of a highly vascular infiltrative tumour, likely metastatic disease, but there was no suggestion as to the site of the primary lesion.

CT guided liver biopsy was performed: the portal tracts contained numerous granulomata with caseous necrosis, and although the lobules contained occasional granulomata, the liver cell plates were of normal thickness. The bile ducts were normal. No organisms were seen on Ziehl-Nielsen or fungal staining, but PCR analysis showed that MAC organisms were present. PCR was negative for *Mycobacterium tuberculosis*.

TREATMENT

Due to the presence of caseating granulomata on liver biopsy, she was initially treated for *Mycobacterium tuberculosis* using the standard regime of once daily rifampicin

Figure 1 CT abdomen demonstrating marked hepatosplenomegaly with multiple areas of low attenuation.

(450 mg), isoniazid (300 mg) for the first 6 months, supplemented in the first 2 months by ethambutol 1200 mg daily and pyrazinamide 1.5 g once daily. She then developed a pruritic rash, so the pyrazinamide was discontinued. The regime was then altered to ethambutol 800 mg and rifampicin 600 mg once daily, to continue for 2 years once the PCR confirmed a diagnosis of MAC.

OUTCOME AND FOLLOW-UP

At 4-month follow-up, the patient was in good health and gained 10 kg in weight since treatment began. Her blood tests also showed improvement, with a haemoglobin of 11.4 g/dl, a CRP of 9 mg/l, ESR of 10 mm/h and ALP of 320 IU/l. An interval abdominal ultrasound was performed, showing resolution of the hepatosplenomegaly, with normal liver texture.

DISCUSSION

Disease caused by MAC can manifest as pulmonary disease, lymphadenitis, disseminated disease, skin soft tissue and bone infection. The most common presentations are pulmonary MAC in immunocompetent individuals, lymphadenitis in children and in immunocompromised individuals as disseminated MAC. Disseminated disease usually is associated with severe underlying deficiencies such as advanced AIDS and other immune system abnormalities – mainly impaired cellular immunity – and

lymphoma; however, the number of incidences where there appears to be no predisposing condition is growing. There is a lack of accepted strict case definition for disseminated opportunistic mycobacterial disease, and it is not defined by the British or American Thoracic Societies. Disseminated and miliary are terms used interchangeably in relation to tuberculosis (TB), and with the advent of AIDS and increase of MAC infection, the term disseminated has appeared to replace miliary in the published literature. Lai *et al*,¹ adapted a definition originally developed for miliary TB, that is isolation of opportunistic mycobacteria from bone marrow or blood, from a liver biopsy specimen or from specimens from two or more non-contiguous sites such as the respiratory tract, ascites, pleural effusion, pericardial effusion, joint fluid or cerebrospinal fluid.

Before the late 1970s, reports of disseminated disease were rare and mortality high. Over half of the reported cases had known underlying immunological disease or were immunosuppressed as a result of disease or drug administration, for example, renal or cardiac transplantation patients and those receiving long-term chronic corticosteroids.² MAC infection was more likely to be seen in children with leukocytosis or leukemoid reaction. However, Lincoln and Gilbert³ reviewed 12 cases, all fatal, of disseminated opportunist mycobacterium in children in 1972 and found that most of the children were infected

with MAC, were below the age of 3 years and had no apparent underlying disease.

There are only a small number of case reports in recent years of disseminated disease affecting immunocompetent adults. The largest case series is from Taiwan, where eight non-HIV infected patients were identified between 1997 and 2004¹; however, three of these patients had underlying haematological conditions which would have caused the patients to be immunosuppressed. Only one patient had MAC affecting the liver. In this study only 20% of patients presented with weight loss, and more than 80% had abnormal levels of haemoglobin, CRP and ALP levels.

A case report from Korea described a 26-year-old immunocompetent pregnant woman who presented with fever and general malaise and was found to have MAC isolated from the sputum and placenta.⁴ However, it was concluded that disseminated infection in this case might be related to pregnancy, as there are alterations of the immune status in pregnant women which lead to impaired cell-mediated immunity. Cytomegalovirus, TB and disseminated aspergillosis have all been reported as opportunistic infections in pregnant women.

Other presentations of disseminated disease in immunocompetent patients in the literature include spinal infection,⁵ septicaemia and osteomyelitis,⁶ paravertebral abscesses and osteomyelitis⁷ and multiple osteomyelitis and pulmonary disease.⁸

Pulmonary disease caused by MAC in non-immunosuppressed subjects typically occurs in middle-aged to older Caucasian men with underlying lung disease, in particular chronic obstructive pulmonary disease, previous TB, bronchiectasis, silicosis and lung cancer. In recent years, it has been not infrequently noted in women without associated lung disease, there have been many cases of MAC disease diagnosed, although extrapulmonary complications are rare.⁹ Lung disease secondary to aerosolised MAC from hot tubs has been described as a new form of MAC disease known as 'hot tub lung', which is believed by some to be a hypersensitivity pneumonitis reaction.¹⁰ Clearly, MAC pulmonary disease can affect patients with no detectable systemic immune dysfunction or previous lung disease.

Unlike TB, MAC is not transmitted from person to person. It is present in dust, soil, fresh and salt water and has been isolated in milk, animals, birds and foodstuffs. It is likely that infection is acquired from environmental exposure. Natural waters are believed to be reservoir for most human infections caused by MAC and it has been isolated from drinking water as a result of resistance to disinfectants used in water treatment centres.¹¹ A 1994 study of disseminated disease in AIDS patients demonstrated that some cases were probably acquired from hospital tap water.¹² As it is so ubiquitous in the environment MAC is inhaled and ingested by most individuals, but very rarely causes disease in immunocompetent patients. It has been shown that MAC has been recovered from residential bathrooms of patients with pulmonary MAC.¹³ It can be acquired by direct contact with damaged skin, and so we postulate that our patient's job as a cleaner may have predisposed her to infection.

The symptoms of disseminated MAC are non-specific and can include persistent fever, fatigue, severe weight

loss and diarrhoea.² Some patients complain of abdominal pain, other local pain and cough. Clinical examination findings include fever, lymphadenopathy, hepatomegaly and splenomegaly. The most common laboratory findings are those of anaemia and an elevated ALP.

The diagnosis of disseminated MAC infection depends on maintaining a high index of suspicion and is made by combining clinical symptoms and signs with isolation of MAC from blood, bone marrow or other normally sterile tissue or body fluids.¹⁴ Most patients are anergic, so tuberculin tests are not helpful. A single blood culture has a sensitivity of approximately 90%.

The combination of rifampicin (450–600 mg daily) and ethambutol (15 mg/kg) for 2 years are recommended for treatment but the success of treatment relies on the patient's underlying immune system. A recent study in patients not known to be HIV positive showed no differences in outcome between groups treated for 2 years with clarithromycin or ciprofloxacin in addition to rifampicin and ethambutol for pulmonary disease caused by MAC. The regimen including clarithromycin was associated with a higher all-cause death rate.¹⁵ Treatment response can be determined by settling of fever, reduction in inflammatory markers and absence of MAC growth on blood cultures. Disseminated disease is associated with an increased mortality in patients with AIDS with one study reporting 13% of patients alive at 12 months.¹⁶ In contrast, in the Taiwan case series 87.5% of patients with disseminated MAC survived after appropriate therapy.³

To our knowledge, there has been no previous description of MAC presenting with isolated hepatosplenomegaly in an immunocompetent patient without any clinical symptoms or signs suggestive of underlying infection and with no identifiable risk factors. Miliary mycobacterium TB, as the most common form of liver and spleen TB, would have been considered a more likely diagnosis. However, given her negative Mantoux test, which is unusual in a middle-aged female from Mauritius who would have almost certainly been exposed to TB, it is possible that she may have some form of immune compromise that we do not have the means to detect with the current investigations available.

In conclusion, it is important to consider that MAC infection can cause hepatosplenomegaly in patients without underlying immune system dysfunction. Because the

Learning points

- ▶ Disseminated/multifocal MAC disease may occur in immunocompetent individuals.
- ▶ Hepatosplenomegaly may be the only clinical sign.
- ▶ CT findings are often non-specific and further investigation is mandatory.
- ▶ In patients with suspected liver metastases, where there is no suggestion as to the site of the primary lesion and the patient is in reasonable health, a liver biopsy is an important diagnostic tool.
- ▶ Treatment should be with rifampicin and ethambutol for 2 years, adding isoniazid or ciprofloxacin if response is not satisfactory.

clinical and radiological features may be non-specific, a high index of suspicion is important; treatment can then be instituted early and successfully.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Hurley JJ, Turner J, Campbell IA, Dolwani S. An opportune finding in suspected liver metastases. *BMJ Case Reports* 2011;10.1136/bcr.05.2010.3013, date of publication

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