Unusual association of diseases/symptoms

Mycobacterium avium infection improved by microbial substitution of fungal infection

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Summary

We reported a case of *Mycobacterium avium* infection in which disease activity appeared to have been suppressed after fungal infection. After the increase in β -D-glucan, her symptoms of fever and chest pain disappeared. We think this phenomenon may be microbial substitution and mild fungal infection may improve the activity due to *M avium*.

BACKGROUND

We did not identify the insidious fungal infection, which was detected only by the increase in β -D-glucan, but it may suppress *Mycobacterium avium* or *Pseudomonas aeruginosa* infection.

CASE PRESENTATION

A 68-year-old woman with bloody sputum presented at our hospital on 3 February 2006. She had a past history of pulmonary *M avium* infection and had been treated with clarithromycin (CAM), streptomycin (SM), rifampicin (RFP) and ethambutol (EB) for 15 years. She had not taken these treatments after January 2005. There was no history of allergy, previous major illness or risk factors for immunodeficiency. She did not have a smoking history. The white cell count was 21 700 per mm³ with 87% neutrophils, 8% lymphocytes and 5% monocytes. Serum C reactive protein (CRP) showed an elevation to 17.33 mg/dl. The aspartate aminotransferase and alanine aminotransferase values increased to 242 and 263 IU/l, respectively. Renal function and serum fasting glucose level were normal. Sputum culture showed *M avium*. Plain chest radiograph demonstrated bilateral giant bullae and destruction in the left lung with pleural effusion. Due to fever of 38°C and complaint of right chest pain, she was admitted to our hospital. Chest CT showed bilateral giant bullae. The left lung bulla was surrounded by a thick wall (figure 1A). The right bulla had a thin wall. Sputum smear did not demonstrate any pathogens. After treatment with ceftazidime 2 g/day for 12 days, her temperature normalised and her complaints improved. The treatment was changed to azithromycin (AZM) 500 mg every other day from March 2006 in the outpatient patient clinic. AZM was continued for 8 months and changed to erythromycin after 26 October 2006. During this period, the white cell count changed from 8 200 to 13 100 per cubic millimetre mm³ with neutrophils of 80–90% and she frequently complained of high-grade fever over 38°C, which was relieved by administration of an antipyretic twice a day. Although sputum sometimes contained *P aeruginosa*, *M avium* was not detected. After August 2007, chest CT demonstrated a thickening of bilateral bulla wall (figure 1B). Although the serum β -D-glucan (Fungitec G test MK;

SRL, Tokyo, Japan) slightly increased (5.6–7.0 pg/ml), the white cell count decreased to fewer than 10 000 per mm³ (figure 2) and CRP decreased to less than 10 mg/dl. At this time, she did not complain of fever or chest pain and her body temperature was normal. After 2009, she was not admitted to hospital, despite three to five admissions per year before 2009. In November 2009, CRP was 6.4 mg/dl and the white cell count was 9300 per mm³ with 84% neutrophils, 10% lymphocytes and 2% eosinophils. The serum β -D-glucan was 10.6 pg/ml. Serum aspergillus antigen and antibody were not detected at any point throughout the clinical course. Chest CT demonstrated left upper cavity irregular sponge-like mass (figure 1C).

DIFFERENTIAL DIAGNOSIS

When the left lung bulla wall became thicker, we suspected that the lesion resulted from fungal infection, especially aspergillus.

OUTCOME AND FOLLOW-UP

We should further investigate the progression of fungal infection or regression of *M avium* infection.

DISCUSSION

M avium complex (MAC) is commonly isolated from water, house dust and soil.¹ Data on the treatment of pulmonary MAC in HIV-seronegative patients is limited by the paucity of randomised controlled trials (RCTs). Older, non-comparative studies in which patients were treated with combinations of conventional anti-tuberculous agents reported highly variable outcomes. Patients in these studies did not necessarily have uniform definitions of disease, radiographic response or cure. In most cases, conversion of sputum cultures to negative was the primary outcome.¹ Sputum conversion rates using standard antituberculous agents, primarily in populations with classic MAC pulmonary disease, ranged from 38–91% across studies published between 1967 and 1988.^{2–4} A more recent RCT compared 2 years of INH, RFP and EB to 2 years of RFP plus EB in 75 patients from the UK and Scandinavia.^{5 6} David Griffith and colleagues studied both CAM-based and AZM-based

Figure 1 (A) Chest CT showed bilateral giant bullae. The left lung bulla was surrounded by a thick wall. (B) Chest CT demonstrated thickening of the left bulla wall. (C) Chest CT demonstrated left upper cavity irregular sponge-like mass.

Figure 2 The change in serum β -D-glucan and C reactive protein showed an inverse relation.

intermittent regimens for treatment of pulmonary MAC disease. Fifty-nine per cent of patients who took daily AZM-based treatment attained treatment success—defined as 12 consecutive months of negative sputum cultures while

the patient was on treatment. Fifty-five per cent of patients who took AZM three times weekly along with daily companion drugs and 65% of patients who took all drugs three times weekly met criteria for treatment success. There were

no significant differences in the rates of treatment success among these three groups. Furthermore, drug toxicity was significantly less with intermittent administration of AZM.⁷

Although this patient had been treated with CAM, SM, RFP and EB for 15 years, her disease condition did not improve. AZM three times weekly slightly improved the control of *M avium* infection. However, she continued to show bloody sputum and high-grade fever and was admitted to our hospital three to five times a year. Furthermore, *P aeruginosa* was sometimes detected in the sputum. When the left lung bulla wall became thicker, we suspected that the lesion resulted from fungal infection, especially aspergillus. Although aspergillus antigen was negative throughout the clinical course, the value of β -D-glucan slightly increased in inverse proportion to the inflammatory findings of white blood cell count or CRP. With these findings, her complaints of persistent fever and chest pain improved and she has not required hospital admission since then.

β -D-Glucan is a polyglucose compound consisting of a chain of glucopyranosyl rings, united primarily by β -1,3-polyglucoside linkages, and is known as one of the major and common constituents of fungal cell walls of fungi in general.^{8–10} The assay of β -D-glucan is a promising means for diagnosing fungal diseases.¹¹ False-positive β -D-glucan reactions are known to occur in patients with renal failure who are undergoing haemodialysis with cellulose membranes, patients treated with intravenous immunoglobulins, and specimens or patients exposed to gauze or other materials that contain glucans. Albumin, coagulation factors and plasma protein fraction manufactured by certain vendors for intravenous injection also have been shown to contain high levels of β -D-glucan. High concentrations of bilirubin and triglyceride have been reported to be inhibitory and would cause false-negative results, while haemolysis would also cause false-negative results.¹² Our patient had not had recent surgery and had not been exposed to any gauze or other materials that contain glucans, and bilirubin, triglyceride and haemoglobin showed fairly stable normal values after 2007. A study based on autopsy cases reported the positive predictive value of the β -D-glucan test when used in a population where prevalence of fungal infection was 11.8%, and was only 47% even if a cut-off of 30 pg/ml was used.¹³ As β -D-glucan testing in the study was performed within 2 weeks before death, the disease condition was more severe than in our case. Although the increase of β -D-glucan was only 10–20 pg/ml in this case, the values gradually increased accompanied with left lung mass. Despite no detection of fungus, we suspected fungal infection, which was not demonstrated by aspergillus antigen or antibody but by β -D-glucan, may have suppressed the MAC activity, which is microbial substitution. We did not identify the insidious fungal infection, which was detected only by the increase in β -D-glucan, but it may suppress *M avium* or *P aeruginosa* infection.

We should further investigate the progression of fungal infection or regression of *M avium* infection.

Learning points

- ▶ Fungal infection may have suppressed the MAC activity.
- ▶ In this case we should consider fungal infection with MAC or microbial substitution of fungal infection.
- ▶ The insidious fungal infection was detected by the increase in β -D glucan.

Competing interests None.

Patient consent Obtained.

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