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Simultaneous diagnosis of allergic bronchopulmonary aspergillosis and *Mycobacterium avium* complex lung disease

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SUMMARY

Allergic bronchopulmonary aspergillosis (ABPA) and *Mycobacterium avium* complex lung disease (MAC-LD) often coexist because bronchiectasis, caused by ABPA or MAC, might be an important predisposing factor for both conditions. Here, we describe a man with asthma symptoms who had centrilobular small nodules and mucoid impaction on chest CT. We diagnosed the patient with simultaneous ABPA and MAC-LD on the basis of bronchoscopy findings. Itraconazole monotherapy led to substantial clinical improvement, avoiding the adverse effects of systemic corticosteroids. Sputum culture conversion of MAC was achieved after switching from itraconazole monotherapy to combination therapy comprising clarithromycin, rifampicin and ethambutol. ABPA recurred but was controlled by reinitiation of itraconazole. Overall, corticosteroid management was avoided for 38 months. Itraconazole monotherapy may be selected as initial treatment for ABPA with chronic infection, including MAC.

BACKGROUND

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic disease characterised by eosinophilic inflammation that results in mucoid impaction, central bronchiectasis and pulmonary infiltrates.[1] Because ABPA is caused by a hypersensitivity reaction to *Aspergillus fumigatus*, the standard therapy consists of systemic corticosteroids. *Mycobacterium avium* complex lung disease (MAC-LD) has been reported as a result of long-term systemic corticosteroid use in patients with ABPA.[2 3] The prevalence of MAC-LD is increasing worldwide;[4–6] it is difficult to cure, especially in immunocompromised hosts.[7] If possible, corticosteroid therapy should be avoided for ABPA with MAC-LD.

Here, we describe a patient who was simultaneously diagnosed with both ABPA and MAC-LD before initial treatment. We chose itraconazole monotherapy as initial treatment for ABPA, and we avoided corticosteroid management for 38 months. Itraconazole monotherapy may be a useful alternative for ABPA with MAC-LD.

CASE PRESENTATION

A man in his 70s developed severe coughing and wheezing. He had been diagnosed with bronchial asthma in his 40s and received inhaled corticosteroid treatment (fluticasone propionate, 200 µg/day) for 20 years by a local physician. However, asthma control was inadequate; three oral corticosteroid bursts (betamethasone 2 mg/day for 3 days) were required each year. A chest X-ray showed an infiltrative shadow in the left lower field (figure 1A), and he was referred to our hospital.

Laboratory data showed an eosinophil count of 1100/µL, C-reactive protein concentration of 0.21 mg/dL and serum total immunoglobulin E (IgE) concentration of 20 301 IU/mL. The patient exhibited specific IgE and serum precipitation antibodies to *Aspergillus*. His forced vital capacity (FVC) was 3.16 L (95.4% of predicted), forced expiratory volume in 1 s (FEV_1) was 2.10 L (86.0% of predicted) and FEV_1/FVC ratio was 66.45%. High-resolution CT of the chest revealed mucoid impaction and centrilobular small nodules (figures 1B and 2A).

INVESTIGATIONS

Bronchoscopy showed mucous plugs in the left upper lobe bronchus (figure 1C). Sputum and bronchial washing cultures revealed *A. fumigatus*. Histology revealed filamentous fungi and Charcot–Leyden crystals with an eosinophilic reaction in lung tissue obtained by transbronchial lung biopsy (figure 1D). The patient's condition fulfilled the International Society for Human and Animal Mycology (ISHAM) criteria. Although no mycobacteria and/or granulomas were histologically detected, *M. avium* was isolated by bronchial washing mycobacterial culture; clarithromycin susceptibility was confirmed (minimum inhibitory concentration, 0.5 µg/mL). On the basis of bronchoscopy findings, we diagnosed the patient with simultaneous ABPA and MAC-LD.

TREATMENT

Although systemic corticosteroids are preferred for stabilisation of ABPA symptoms, immunosuppression is an inevitable adverse effect of corticosteroids. MAC-LD is a refractory and progressive infectious disease, especially in immunocompromised hosts.[8–10] Itraconazole monotherapy (400 mg/day) was selected as initial treatment to avoid immunosuppression with systemic corticosteroids. The patient's inhaler treatment was stepped up to fluticasone propionate plus formoterol fumarate (600 and 20 µg/day) for asthma symptoms.

OUTCOME AND FOLLOW-UP

After 4 months of itraconazole treatment, the patient's total IgE concentration decreased by 6287 IU/mL (69.1% reduction from

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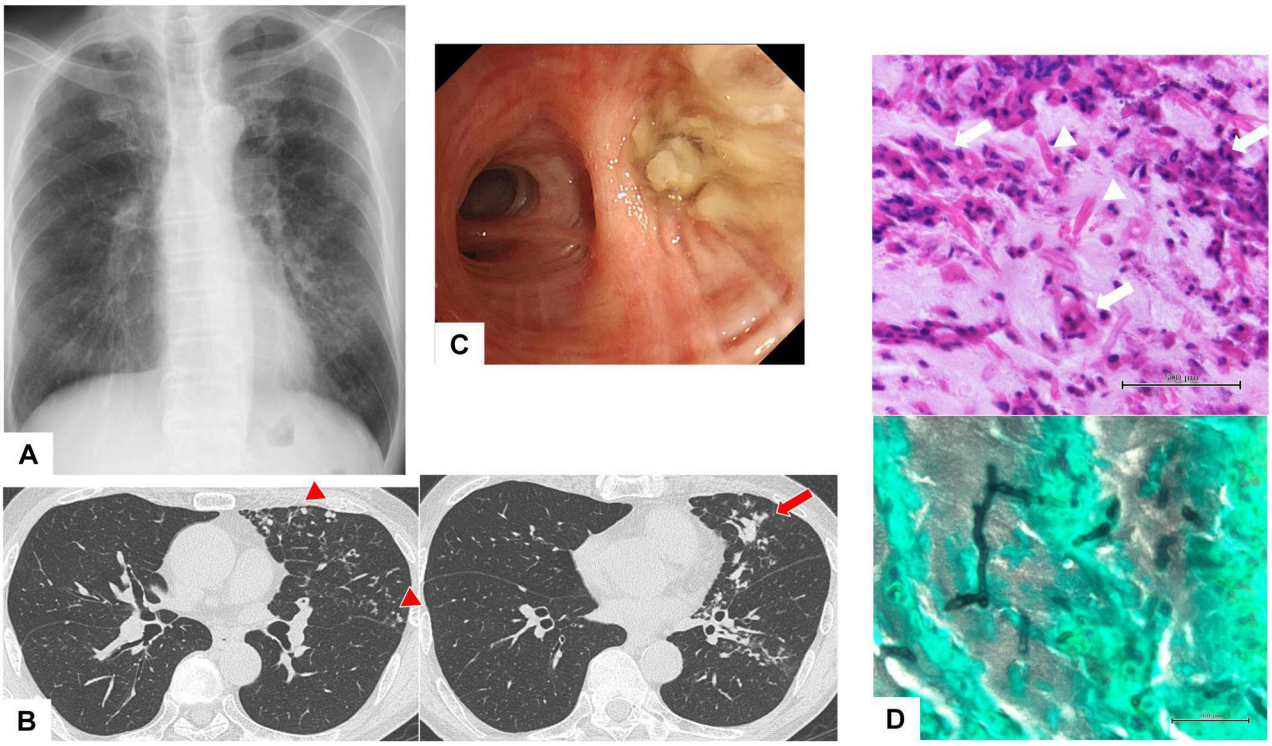

Figure 1 Chest imaging and bronchoscopic and histological findings at the time of diagnosis. (A) Chest radiograph showing infiltration in the left lower fields. (B) Chest CT revealing central bronchiectasis with mucous plugs (arrow) and a small nodular shadow (arrowhead) in the left upper lobe. (C) Bronchoscopy findings showing mucous plugs filling the left upper lobe bronchus. (D) Eosinophilic infiltration (arrow) (H&E, 400×), Charcot–Leyden crystals (arrowhead) and fungal hyphae are present (Grocott methenamine silver, 400×).

baseline) (figure 3). Although the patient's asthma symptoms were controlled, his cough gradually worsened; *M. avium* was repeatedly identified by sputum culture (figure 3). Chest CT showed that the mucoid impaction had improved, but centrilobular small nodules remained (figure 2B). We suspected that the cough was caused by MAC-LD; therefore, we switched the antifungal therapy to combination antimicrobial therapy comprising clarithromycin (800 mg/day), rifampicin (450 mg/day) and ethambutol (750 mg/day) for the management of MAC-LD. We observed clinical improvement in the cough and negative culture conversion of MAC; both results were achieved without systemic corticosteroids (figure 3). Seven months after termination of itraconazole, the ABPA relapsed with asthmatic symptoms, and the IgE concentration was elevated again (figures 2C and 3). Itraconazole was reinitiated; rifampicin for MAC-LD was discontinued because of the potential for a severe drug interaction between itraconazole and rifampicin. Considering the presence of elevated liver enzymes, we reduced the itraconazole dosage to 200 mg/day to reduce the risk of a drug interaction between itraconazole and clarithromycin. The ABPA recurred 12 months after sputum culture conversion of MAC; therefore, we terminated the anti-MAC therapy (total duration, 18 months) and restored the itraconazole dosage to 400 mg/day (figures 2D and 3). The patient's asthma symptoms immediately improved, and he did not exhibit ABPA or MAC-LD relapse for 14 months after the termination of clarithromycin and ethambutol (figures 2E and 3).

DISCUSSION

On the basis of bronchoscopy findings, we diagnosed the patient with simultaneous ABPA and MAC-LD. The prevalence of MAC is increasing worldwide, and immunosuppression is a risk associated with MAC infection.[11 12] Coinfection by nontuberculous mycobacteria (NTM) is a major complication in patients with ABPA. Ishiguro *et al*[3] examined cases of NTM in patients with ABPA; they found that NTM was diagnosed at an average of 6.4 years after the administration of systemic steroids for ABPA, suggesting that the administration of systemic corticosteroids is a risk factor for NTM exacerbation and lower respiratory tract infections. Kunst *et al*[12] described four patients with ABPA among 30 patients with concurrent NTM and bronchiectasis. These reports suggest that bronchiectasis caused by ABPA or NTM might be an important predisposing factor; clinicians should carefully evaluate this dual presentation.[13]

Regarding the characteristic CT findings, bronchiolitis with bronchiectasis is typical feature of MAC-LD; ABPA also displays bronchiolitis with bronchiectasis-associated mucous plugs. In the present case, the mucoid impaction disappeared with antifungal treatment, but the centrilobular small nodules remained. Although we suspected that this bronchiolitis was caused by MAC-LD, it did not improve after anti-MAC treatment (figure 2). Because both ABPA and MAC-LD mainly occur in the bronchus and MAC-LD is a refractory infection, it is difficult to distinguish the two diseases based on CT findings in cases of dual presentation.

Although we initially considered corticosteroid±antifungal agent±anti MAC agent therapy in this case, we chose itraconazole monotherapy as initial therapy. To the best of our knowledge, there is minimal discussion regarding the treatment of patients with this dual presentation because the diseases are rarely diagnosed simultaneously. In most cases of dual presentation, treatment for the predisposing disease is prioritised. Although at least several months of systemic corticosteroid administration is the preferred approach for ABPA treatment,

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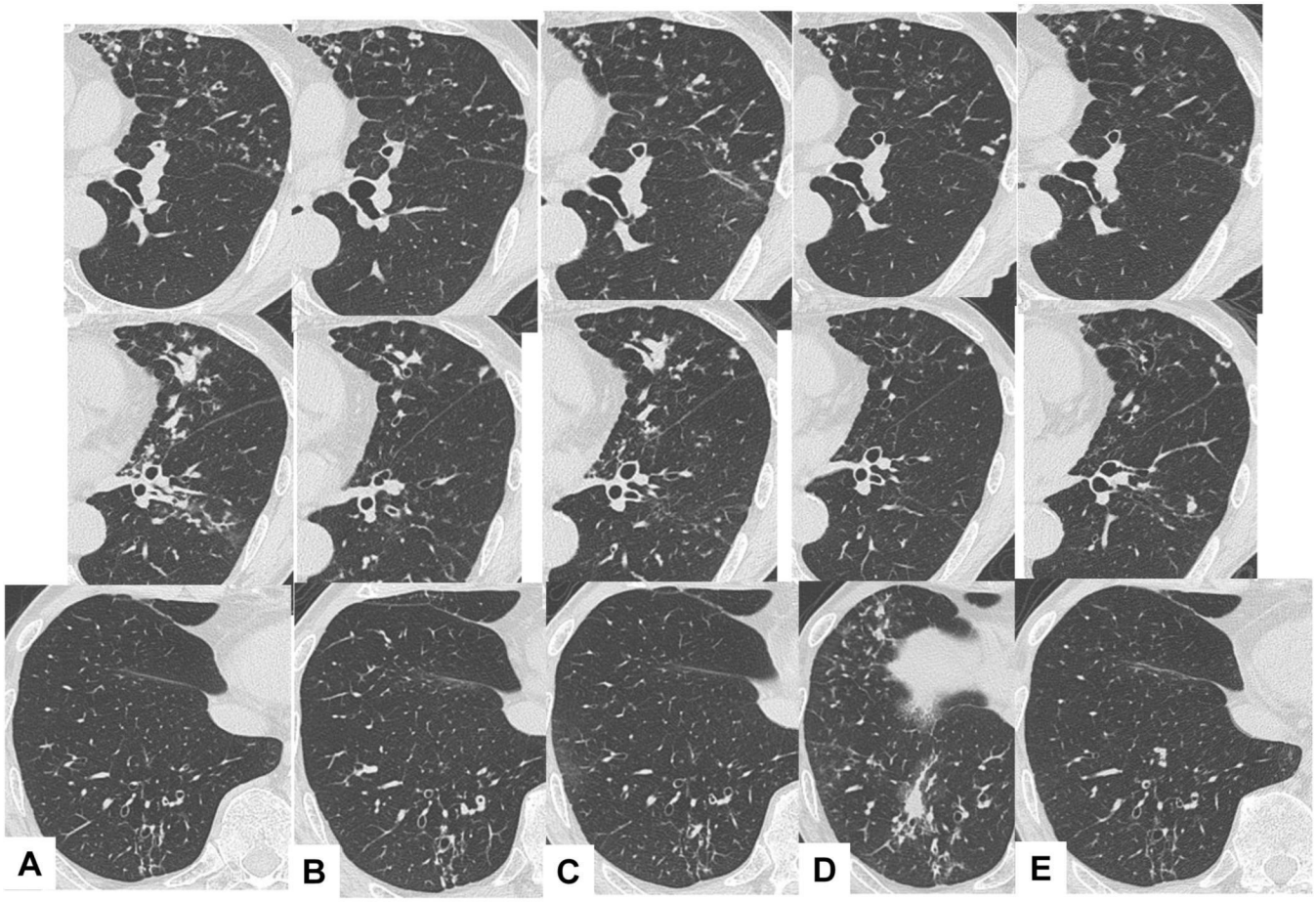

Figure 2 CT revealing transition of ABPA and MAC-LD. (A) Chest CT at admission before the initiation of itraconazole (0 months). Chest CT revealed central bronchiectasis with mucous plugs and a small nodular shadow in the left upper lobe. (B) Chest CT before the initiation of clarithromycin, rifampicin and ethambutol (5 months). Chest CT revealed disappearance of the mucous plugs and no change in small nodular shadows in the left upper lobe. (C) Chest CT before the reinitiation of itraconazole (12 months). Chest CT revealed recurrence of the mucous plugs and no change in small nodular shadows in the left upper lobe. (D) Chest CT at termination of antimicrobial therapy for MAC-LD (24 months). Chest CT revealed the appearance of mucous plugs in the right lower lobe and no change in small nodular shadows in the left upper lobe. (E) Chest CT at 14 months after the termination of antimicrobial therapy for MAC-LD (38 months). Chest CT revealed disappearance of the mucous plugs in the right lower lobe and no change in small nodular shadows in the left upper lobe. ABPA, allergic bronchopulmonary aspergillosis; MAC-LD, *Mycobacterium avium* complex lung disease.

Agarwal *et al*[14] reported that itraconazole monotherapy might be an alternative therapy for ABPA, with fewer adverse effects of immunosuppression.

We chose a watchful waiting approach for MAC-LD because we presumed that the patient's asthmatic symptoms were caused by ABPA, rather than MAC-LD. An official guideline from The American Thoracic Society, European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and Infectious Diseases Society of America recommends antimicrobial therapy for MAC-LD with positive acid-fast bacilli sputum smears and/or cavitary lung disease.[15] We suspected a nodular bronchiectasis type of MAC-LD without positive sputum smear and cavitary findings; antimicrobial therapy was not immediately necessary if we avoided the use of corticosteroids. We also suspected that the MAC was commensal. Although the ABPA was controlled, MAC was repeatedly isolated and centrilobular small nodules remained visible on CT. We switched the antifungal therapy to antimicrobial therapy for MAC-LD and achieved sputum culture conversion of MAC. Accordingly, the ABPA and MAC-LD were controlled without systemic corticosteroids for 38 months. Despite some reports of successful corticosteroid and anti-MAC treatment for ABPA with MAC-LD,[13 16 17] the long-term prognosis in such cases is unclear. The negative sputum culture conversion rate with standard chemotherapy for MAC-LD with systemic corticosteroids is reportedly 33%,[7] and the rate for all types of MAC-LD is 71.8% to 92.3%.[18–20] Although relapse and reinfection rates for MAC-LD with any type of immunosuppression are unclear, the rates for all types of MAC-LD remain high (33%–74%).[18 21] Mussaffi *et al*[22] reported that ABPA during systemic corticosteroid therapy is a risk factor for NTM deterioration in patients with cystic fibrosis. To minimise the risk of refractory MAC-LD progression, we chose itraconazole monotherapy rather than systemic corticosteroids.

There is a need to consider possible drug interactions between itraconazole and rifampicin. Rifampicin is a powerful CYP3A4 inducer that accelerates the hepatic metabolism of itraconazole and prednisolone; concurrent administration can substantially reduce the serum concentration of itraconazole.[23 24] We chose to avoid concomitant administration of itraconazole and rifampicin. Rifabutin is a major alternative to rifampicin because it has fewer reported drug interactions. Moon *et al* reported that

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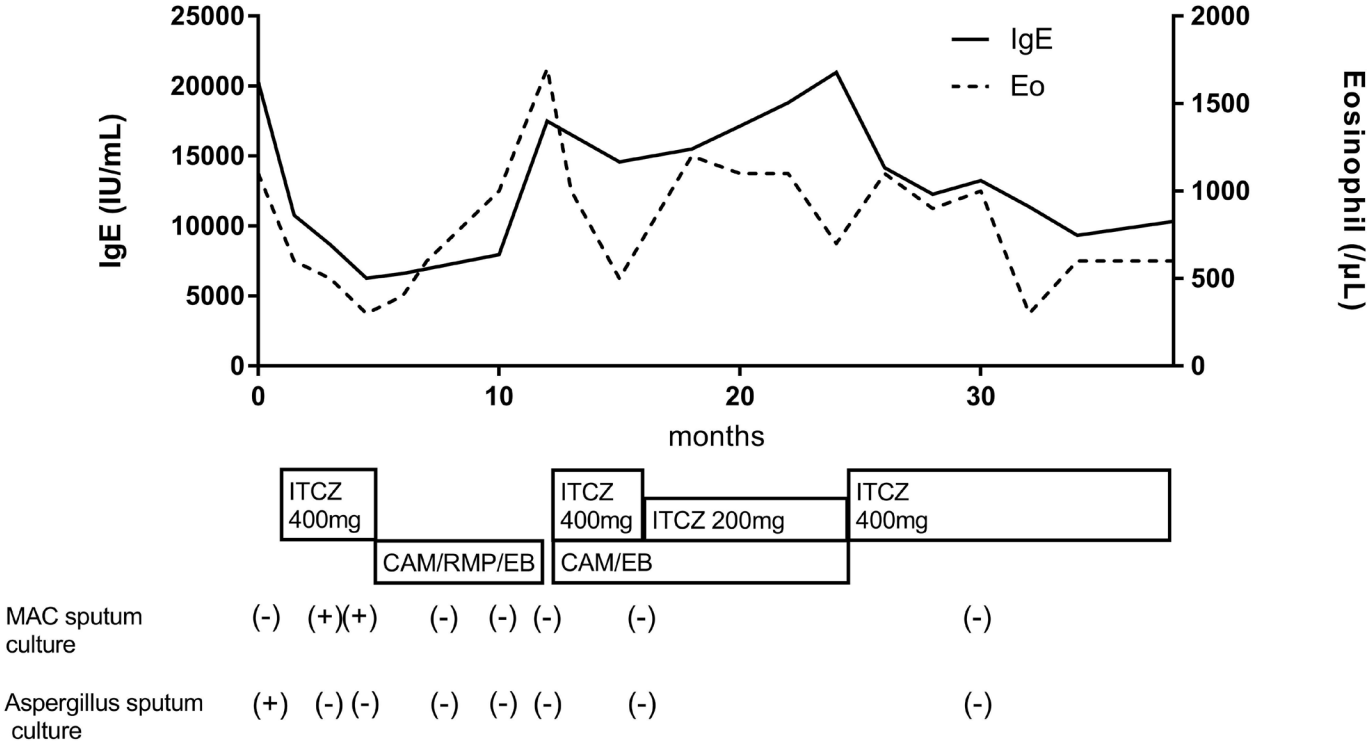

Figure 3 The patient's clinical course. CAM, clarithromycin; EB, ethambutol; IgE, immunoglobulin E; ITCZ, itraconazole; MAC, *Mycobacterium avium* complex; RMP, rifampicin.

one-third of patients receiving itraconazole and a low dosage of rifabutin reached a therapeutic concentration of serum itraconazole.[25] Rifampicin also increases prednisolone clearance by 45%, and at least a twofold increase in prednisolone dosage is required for concurrent administration of rifampicin and prednisolone.[26] Recently, Miwa *et al* reported that the clarithromycin/ethambutol regimen is not inferior to the standard clarithromycin/rifampicin/ethambutol regimen;[27 28] the clarithromycin/ethambutol regimen might be reasonable for cases with itraconazole-containing regimens, rather than rifampicin-containing regimens. There is also a need to consider possible drug interactions between itraconazole and clarithromycin. Both itraconazole and clarithromycin are CYP3A inhibitors that can reduce each other's hepatic metabolism. Auclair *et al* reported that although itraconazole increased the serum clarithromycin concentration, these two agents can be coadministered safely.[29] Importantly, we managed elevated liver enzymes by reducing the administration of itraconazole.

In conclusion, we have presented a case of dual presentation of ABPA and MAC-LD. To the best of our knowledge, this is the first report of itraconazole monotherapy for dual presentation of ABPA and MAC-LD.[13 16 17] Itraconazole monotherapy may be selected as initial therapy for ABPA with chronic infection, including MAC.

Patient's perspective

For a long time, I had cough and sputum. I thought they were due to asthma, and all I could do was take inhaled corticosteroids. I am delighted that I am feeling much better after treatment of allergic bronchopulmonary aspergillosis (ABPA) and *Mycobacterium avium* complex. I think appropriate evaluation of refractory asthma and initial treatment for ABPA were important for me.

Learning points

- Although coinfection with *Mycobacterium avium* complex lung disease (MAC-LD) is a major complication in patients with allergic bronchopulmonary aspergillosis (ABPA), the simultaneous diagnosis of this dual presentation is rare.
- Many clinicians hesitate to use corticosteroids for patients with simultaneous ABPA and MAC-LD.
- Itraconazole monotherapy may be selected as initial therapy for ABPA with MAC-LD.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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