Medical Mycology Case Reports 11 (2016) 36–39

Contents lists available at ScienceDirect

Medical Mycology Case Reports

journal homepage: www.elsevier.com/locate/mmcr

Isavuconazole as salvage therapy for mucormycosis

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ARTICLE INFO

Article history:
Received 30 December 2015
Received in revised form
2 March 2016
Accepted 7 March 2016
Available online 8 March 2016

Keywords:
Mucormycosis
Isavuconazole

ABSTRACT

Mucormycosis carries a high mortality rate with few therapeutic options available. We describe a man with pulmonary/splenic mucormycosis complicating hypoplastic myelodysplastic syndrome on a background of chronic kidney disease, who achieved a complete response with salvage isavuconazole therapy following intolerance of consecutive courses of liposomal amphotericin and posaconazole therapy.

1. Introduction

Mucormycosis, an infection caused by fungi of the order Mucorales, typically presents as an aggressive angio-invasive disease in immunosuppressed hosts. Patients with hematological malignancies and recipients of hematopoietic stem cell transplants are at highest risk for pulmonary mucormycosis with reported mortality rates of up to 76% [1].

Early diagnosis and aggressive management with surgical debridement and antifungal treatment are critical for optimal outcomes [2]. Previously, the only two systemic antifungals available with reliable activity against Mucorales were amphotericin B and posaconazole. Isavuconazole, a new extended-spectrum triazole with activity against yeasts, molds and dimorphic fungi, has recently been approved for treatment of invasive aspergillosis and mucormycosis [3]. We report a case of successful salvage treatment of pulmonary/splenic mucormycosis with isavuconazole, in a hematology patient intolerant of primary therapy with liposomal amphotericin B and posaconazole.

2. Case

A 59 year old male gardener was transferred from another hospital with left lower lobe pneumonia unresponsive to nine days of intravenous broad-spectrum antibiotics. This was on a background of a recent diagnosis of hypoplastic myelodysplastic syndrome (MDS). His hypoplastic MDS had been treated, 38 days earlier, with antithymocyte globulin (ATG) and five days of pulsed intravenous methylprednisolone (1 mg/kg/day). At presentation, he was taking cyclosporine 200 mg orally twice daily and a tapering dose of prednisolone, 5 mg daily. His neutrophil count was 1.1 cells/mm^3 at presentation, however in the six weeks prior, had been < 1.0 cells/mm^3. Antifungal prophylaxis with posaconazole oral solution, 200 mg three times daily (TDS), had been commenced at the onset of ATG and methylprednisolone treatment. This was increased to 200 mg four times daily (QID), following a sub-therapeutic serum concentration of 0.3 μg/ml, seven days after commencement.

His past medical history was significant for chronic kidney disease due to primary focal and segmental hyalinosis and sclerosis, presenting as nephrotic syndrome in 2012, resulting in chronic proteinuria and a baseline creatinine clearance 91 ml/min.

At presentation to our institution, chest computed tomography (CT) (Fig. 1A) revealed a cavitating left lower lobe lesion with contiguous splenic involvement, suspicious for invasive fungal disease (IFD). Sinus imaging was clear. Empirical treatment was commenced with liposomal amphotericin B (L-AmB) 5 mg/kg and piperacillin-tazobactam 4.5 mg QID. Histopathology on a CT guided biopsy, obtained on day 2 of admission, demonstrated broad

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http://dx.doi.org/10.1016/j.mmcr.2016.03.002

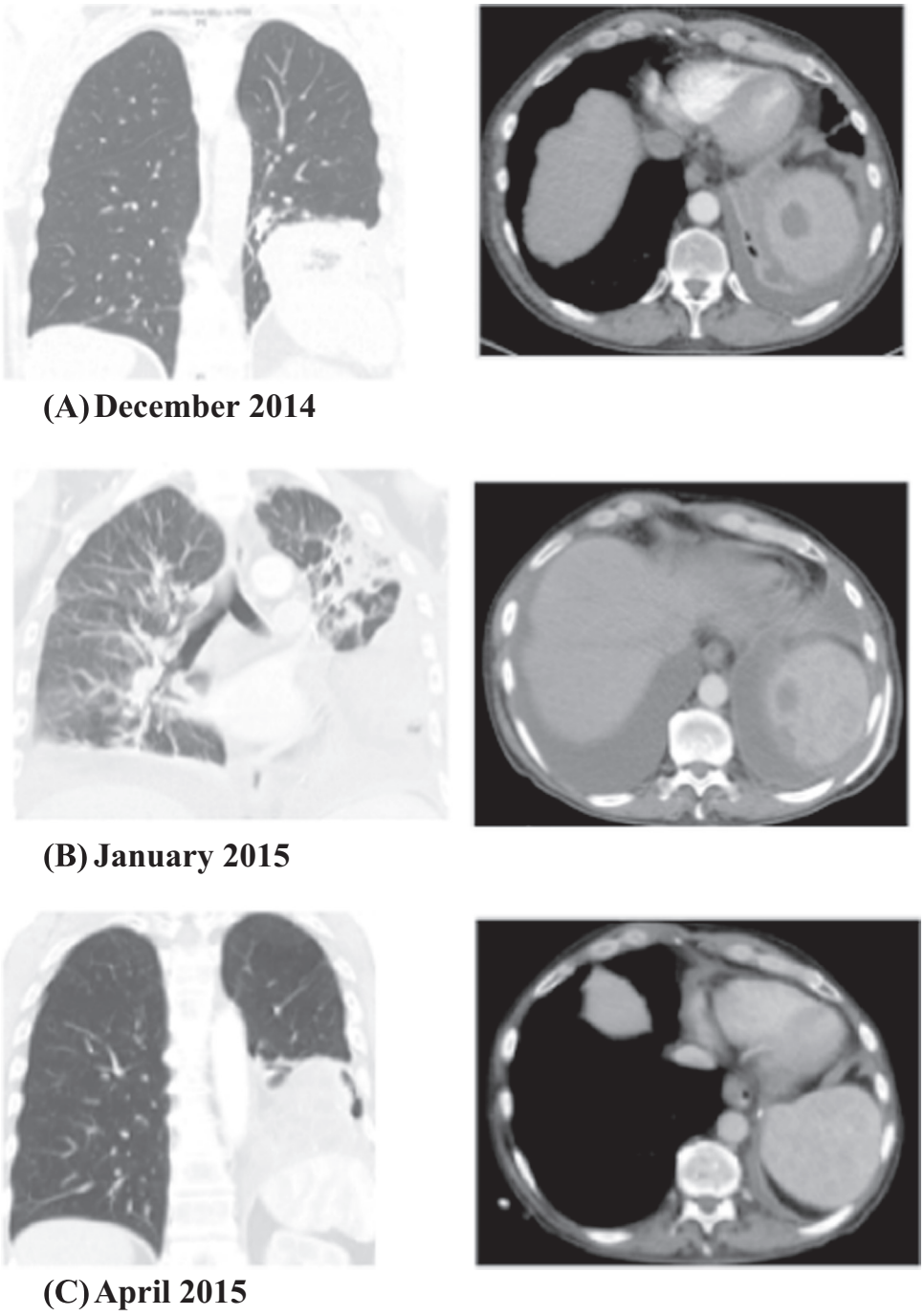

Fig. 1. (A) CT chest at diagnosis demonstrating right lower lobe lesion with "reverse halo sign" and contiguous splenic involvement. (B) CT Chest following clinical deterioration post lobectomy demonstrating bilateral pleural effusions and peri-bronchial consolidation with a second splenic lesion. (C) CT Chest 11 weeks post isavuconazole therapy demonstrating resolution of the splenic lesions. Abbreviations: CT = computed tomography.

ribbon-like hyphae within necrotic tissue (Fig. 2), consistent with mucormycosis. On day 4 of admission he underwent a left lower lobectomy, with latissimus dorsi muscle flap transposition. Culture and pan-fungal PCR were negative, on both CT-guided biopsy and resected lung tissue.

The patient deteriorated clinically 15 days post lobectomy (Day 19 of L-AmB therapy) with hypoxia, delirium, renal failure and raised inflammatory markers. Repeat chest CT demonstrated bilateral pleural effusions with significant peri-bronchial consolidation in the remaining left lung and evidence of a new subcapsular splenic lesion concerning for disease progression (Fig. 1B). A right-sided pleurocentesis revealed a transudate and was culture negative. The patient was re-commenced on pipercillin-tazobactam and underwent diuresis. Posaconazole oral solution, 300 mg TDS, was added to L-AmB 5 mg/kg and increased to 300 mg QID following a sub-therapeutic level of 0.38 μg/ml, six days after commencement.

The patient achieved clinical stability on day 21, but was intolerant of high-dose posaconazole with severe nausea unresponsive to multiple anti-emetics, requiring a dose reduction to 200 mg TDS. Worsening renal function, with a reduction in creatinine clearance to 30 ml/min, after 46 days of L-AmB and despite ceasing cyclosporine and other nephrotoxic medications, prompted consideration of isavuconazole.