



# Disseminated Mucormycosis Due to *Saksenaea vasiformis* Complex in an Immunocompetent Adult with Sustained Response to Posaconazole Treatment

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**Abstract** *Saksenaea vasiformis* complex is an emerging cause of mucormycosis. We report a case of an immunocompetent patient presenting with a non-resolving lung mass who developed multiple skin nodules. Skin biopsy yielded *Saksenaea vasiformis* complex. This showcases an uncommon occurrence of disseminated *Saksenaea* infection without cutaneous inoculation that improved with posaconazole.

**Keywords** Mucormycosis · Posaconazole · Immunocompetent

## Introduction

Mucormycosis is an uncommon invasive mold infection usually associated with immunosuppression. *Saksenaea vasiformis* complex is an emerging cause of mucormycosis that usually affects immunocompetent hosts [1]. Most cases in the literature are associated with localized disease and involve spread from a cutaneous portal of entry or from rhinocerebral invasion [2]. Cases of disseminated disease are rare; where they have been described, they are invariably fatal [3]. We describe a case of disseminated mucormycosis due to *S. vasiformis* complex in an immunocompetent individual with no apparent cutaneous portal of entry, who improved with posaconazole and remained alive at 1-year follow-up.

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## Case Description

A 69-year-old Singaporean Chinese male presented to our institution with a 6-week history of fevers, malaise, loss of appetite and new development of necrotic skin lesions. The skin lesions initially developed over the lower back and subsequently spread to the upper back, chest, neck and forehead. They started out as flat plaques that gradually became raised nodules with central necrotic ulcerations (Fig. 1a). Six months prior, he had been investigated for a non-resolving left hilar lung mass (Fig. 1b) and had undergone multiple bronchoscopic evaluations (trans-bronchial needle aspiration and bronchoalveolar lavage) for which microbiological sampling was persistently negative and cytology showed no evidence of malignancy. A positron emission tomography (PET) scan was performed 1 month prior, which demonstrated the previously known left hilar lung mass as well as interval development of a fluorodeoxyglucose (FDG)-avid soft tissue mass encasing the mediastinal structures, together with a right retroperitoneal soft tissue lesion that was mildly FDG-avid and posterior to the right psoas muscle (Fig. 1c).

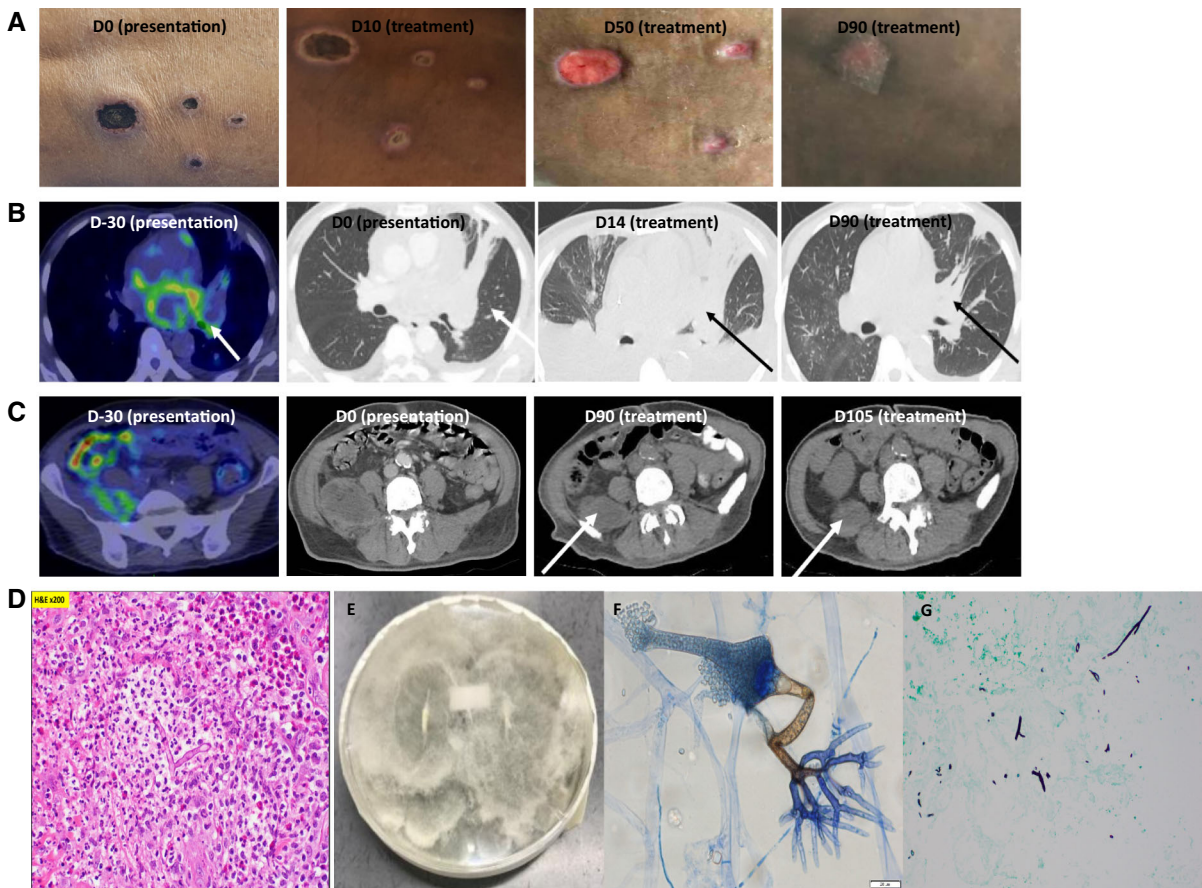
The patient's past medical history included hypertension, hyperlipidemia, ischemic heart disease and long-standing eczema. He was on routine dermatology outpatient review and had been receiving topical steroids but no systemic therapies or biologics. He had retired 2 years prior and used to work as a purchaser of antiques. While he had an extensive travel history in the past (including Argentina, Mexico, Spain, Italy, Indonesia), his last overseas travel was 1 year prior to his presentation, during which he had travelled to Northern India for leisure and had visited Kashmir, Agra and Delhi. He did not have prolonged contact with soil as part of his job or hobbies. There was no prior history of traumatic inoculations or cutaneous or intramuscular injections.

On admission, he was persistently febrile, though hemodynamically stable. Skin biopsy of a representative nodule on the left chest was performed, and fungal stains demonstrated non-septate hyphae, on a background of dermal necrosis and dermal abscess formation (Fig. 1d). Culture of the skin biopsy grew a white fluffy mold on Sabouraud dextrose agar on D4 (4th day) (Fig. 1e). As sporulation was delayed, targeted internal transcribed spacer (ITS) sequencing was done

[4] which yielded result consistent with *S. vasiformis* complex. The mold showed flask-shaped sporangium with columellae and rhizoids typical of *S. vasiformis* complex after prolonged incubation (30 days) on tap water agar at room temperature (20–25 °C) (Fig. 1f).

In view of the suspicion of disseminated fungal infection, the patient was started on liposomal amphotericin B at D3 of hospitalization and additionally received a week of micafungin concurrently from D5–D12. A repeat CT scan was performed, which demonstrated interval development of a left renal phlegmon, a new-onset left-sided pleural effusion in conjunction with the previously noted left hilar mass (Fig. 1b) and mediastinal soft tissue thickening, as well as persistence of the right retroperitoneal soft tissue density (Fig. 1c). CT-guided sampling of the right retroperitoneal mass yielded corynebacterium on cultures, which was thought to reflect contamination; histopathology showed cell detritus. The patient declined incision/excision biopsy of the mass. Sampling of the left pleural effusion yielded a lymphocytic-predominant transudate by Light's criteria, with cytology being negative for malignancy as well as fungal elements. At D15 of hospitalization, he subsequently deteriorated with type 1 respiratory failure and had to be supported with noninvasive ventilation in the high-dependency unit for 2 days. Given worsening renal function and clinical deterioration, he was switched to posaconazole on D15 and IV liposomal amphotericin B was stopped on D18 after an overlap of 3 days. His condition stabilized, and he was discharged on D40, with posaconazole. In the same admission, he was evaluated for possible systemic immunocompromise or concomitant autoimmune disorder. Screening for human immunodeficiency virus (HIV) was negative; an autoimmune screen including anti-nuclear antibody, anti-PR3, anti-MPO and anti-dsDNA was also negative; serum immunoglobulin analysis revealed normal levels of IgA and IgM but high levels of IgE (2123 IU/ml; normal reference ranges 18–100 IU/ml) and IgG (25.44 g/l; normal reference ranges 5.49–17.11 g/l). IgG subclasses showed elevated IgG4 levels (2.71 g/l; normal reference ranges 0.04–1.57 g/l).

On outpatient follow-up, the skin lesions regressed with antifungal treatment, with resolution after 11 weeks of treatment with posaconazole (Fig. 1a). Interval follow-up imaging with CT and chest radiographs 3 months from initial presentation showed



**Fig. 1** **a** Cutaneous lesions and treatment progression. **b** Lung mass and treatment progression, on PET-CT and CT-thorax. **c** Retroperitoneal mass and treatment progression, on PET-CT and CT-abdomen/pelvis. **d** Histopathology of representative skin biopsy from left chest wall (hematoxylin–eosin stain). **e** Gross morphology on potato dextrose agar showing whitish-

fluffy mold. **f** Microscopic examination of the mold showing flask-shaped sporangium with columellae and rhizoids after 30-day incubation on tap water agar at room temperature. **g** Fungal hyphae seen on biopsy of retroperitoneal mass (Gomori's methenamine silver nitrate stain)

interval regression of the left hilar lung lesion, (Fig. 1b) as well as the left renal phlegmon; the right retroperitoneal lesion, though persistent, was slightly smaller. Subsequently, he was re-admitted 3 months after initial presentation for hypercalcemia, with a serum calcium of 3.54 mmol/l. Serum ACE-I level was 38 U/l (normal reference ranges 8–53), and a bone scan performed was negative for malignancy. A repeat biopsy of the right retroperitoneal mass was sought in view of the relatively slower regression. Histological examination demonstrated fragments of fungal hyphae, of variable thickness, on a background of necrotizing granulomatous inflammation (Fig. 1g). IgG and IgG4 immunostains revealed ~ 10 IgG4<sup>+</sup> plasma cells at the edge of a granuloma and an

IgG4<sup>+</sup>:IgG<sup>+</sup> ratio of ~ 20%, which did not support a diagnosis of concomitant IgG4-related disease. Fungal cultures did not yield positive growth, perhaps because the patient had had a prolonged course of posaconazole treatment by this juncture. Hypercalcemia improved with a trial of oral prednisolone (initially 20 mg OD, then tailed down and stopped after 2 weeks). He was discharged again after an inpatient stay of 35 days.

Almost 4 months from initial presentation, the patient re-presented with new-onset abdominal pain. CT scan showed an incidental finding of pneumoperitoneum; incidentally the admission chest radiograph did not show recurrence of the left hilar lung mass and the retroperitoneal mass was smaller compared to

previous imaging studies. Conservative management was instituted as per patient's wishes, and posaconazole was stopped after 107 days of treatment. Surprisingly, the patient recovered with conservative management and was discharged after an inpatient stay of 45 days. He remains well on outpatient follow-up 1 year from initial presentation, with no recurrence of disease.

## Discussion

*Saksenaea vasiformis* complex is an emerging cause of mucormycosis. It is commonly found in soil and has a predisposition for warm climates [5]. The majority of infections have been reported in immunocompetent individuals and are usually associated with some form of cutaneous inoculation or trauma or invasive rhinosinusitis [1, 2, 6]. There are less than 50 cases reported in the literature since discovery [2, 5]. The organism's failure to sporulate in routine mycological media could lead to under-reporting [1, 6]. Rare Mucoralean species such as *Saksenaea* should be considered when a non-sporulating mucormycete is isolated from an infected lesion.

There were several unique features of this case. Firstly, disseminated *S. vasiformis* complex infection is uncommon. The majority of cases involved localized infection [2], with dissemination only identified in five cases [3, 7–10]. Secondly, in this case, no cutaneous portal of entry was identified; we hypothesize that the route of infection was inhalational, given the initial presentation with a lung mass. This contrasted with most localized cases [2, 11–13], in which infection occurred after inoculation or trauma. Among the small number of disseminated cases, in the majority the primary site of infection was attributed to aggressive skin and soft tissue infection; [7–10], only in one other case was the primary infection attributed to inhalation of a heavy airborne inoculum, given the patient's hobbies of orchid farming and opal mining which may have predisposed him to soil exposure [3]. No such unusual exposures were identified in our patient. Thirdly, in this case, apart from ~ 2 weeks of IV liposomal amphotericin B, posaconazole alone was used for the bulk of the patient's treatment, with good response. Conversely, in case series, liposomal amphotericin B has been most commonly used in the management of *S. vasiformis* complex infections,

together with aggressive debridement of localized lesions [2, 10–12]. The majority of disseminated cases were also treated with a polyene [2, 7, 8, 10]; only in one other case was a switch to posaconazole performed halfway through treatment [9]. In a murine model, posaconazole appeared to be more efficacious in prolonging survival and reducing the fungal load compared to a polyene [14]. Finally, the patient's condition improved with anti-fungal treatment. This was in contrast to the other cases of disseminated disease reported in the literature, in which only 1 patient survived [9]. Coincidentally, in this case, treatment was also switched to posaconazole [9]. Unfortunately, the effect of posaconazole in vitro could not be studied in this case, given difficulties experienced with the organism's slow sporulation. Molecular techniques enabled earlier identification of *S. vasiformis* complex, given the organism's slow sporulation; this demonstrates the potential for molecular techniques in achieving earlier diagnosis of this rare pathogen [2].

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## Compliance with Ethical Standards

**Conflict of interest** The authors report no conflict of interest.

**Informed Consent** Written informed consent for publication was obtained from the patient.

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