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Neosartorya udagawae pulmonary infection requiring a surgical treatment in a paediatric haematopoietic progenitor cell recipient

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ABSTRACT

Neosartorya udagawae is a known cause of fungal infection in humans and animals. It is found to be more refractory to antifungal treatment in comparison to other *Aspergillus* species. With this report we present a case of proven invasive infection with *Neosartorya udagawae* in a child with chronic myeloid leukaemia after haematopoietic stem cell transplant. The patient received several lines of antifungal therapy including dual therapy appropriate to the antifungal susceptibility profile with progression of the invasive fungal disease requiring left lung upper lobe lobectomy. The case emphasizes the importance of early biopsy with antifungal susceptibility testing for targeted therapy and demonstrates the potential requirement for surgical management in addition to appropriate antifungal treatment.

1. Introduction

Haematopoietic stem cell transplant (HSCT) recipients are at high risk of invasive fungal disease, which is a common cause of mortality in this category of patients [15]. *Neosartorya udagawae* is an *Aspergillus fumigatus*-related species identified and described for the first time in 1995 [1,2,8]. It has been reported to be more refractory to standard antifungal therapy with a longer median duration of illness than other *Aspergillus* species. *Neosartorya udagawae* isolates exhibit higher minimum inhibitory concentrations with various antifungal agents when compared to *Aspergillus fumigatus* [3,4].

There are very few culture-proven cases of invasive fungal disease associated with *Neosartorya udagawae* in the literature and only a proportion of those included pulmonary involvement [4–6]. Here we report the case of antifungal-refractory *Neosartorya udagawae* – associated invasive pulmonary disease in a child after HSCT for Chronic myeloid leukaemia (CML).

2. Case

A three-year-old boy presented to a hospital with cough, lethargy, pallor, fever, and hepatosplenomegaly. The full blood count showed anaemia and leukocytosis with a white cell count of 156 × 10^9/L and blasts on the blood film. Following investigations, he was diagnosed with central nervous system (CNS) positive CML in the blast crisis phase. He was started on chemotherapy treatment but despite that developed progression of CNS disease and subsequently the second blast crisis. He was treated with systemic and intrathecal chemotherapy consolidated by HSCT from a matched unrelated donor with myeloablative conditioning 11 months from diagnosis.

From admission to the transplant, he was on primary antifungal prophylaxis with itraconazole (2.5 mg/kg twice daily). Therapeutic drug monitoring (TDM) performed on a weekly basis showed good levels (≥0.5 mg/L). When the child was unable to tolerate oral medications, itraconazole was changed to liposomal amphotericin B primary prophylaxis (1 mg/kg three days a week).

The early post-transplant period was complicated by engraftment syndrome requiring treatment with methylprednisolone in a dose of 1

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mg/kg. At 3 weeks post-transplant the child developed a severe acute form of graft-versus-host disease (GvHD) involving skin and gut (overall grade IV), requiring intravenous methylprednisolone in the highest dose of 2 mg/kg, cyclosporine, mycophenolate mofetil, etanercept, extracorporeal photopheresis (ECP), topical immunosuppressants and admission to the Paediatric Intensive Care. After a clinical response, the steroids were weaned down gradually to the lower dose, however, the child remained on steroids long-term. Subsequently, he had further episodes of skin and gastrointestinal GvHD reactivation, necessitating increased immunosuppression. He remained on primary prophylaxis with itraconazole with adequate drug levels.

Four months after the transplant, the child started to complain of persistent cough attributed to different viral infections. At approximately eight months post-transplant (Day 0), a HRCT chest was performed, which showed an 8 mm nodule in the left upper lobe, smaller nodules at the periphery of the right middle lobe and a patchy ground-glass opacity at the left pulmonary apex (Fig. 1a). Serum fungal markers at that time were negative (galactomannan [GMN] 0.110 and beta-D-glucan [BDG] <30.0 pg/mL). The child was treated empirically as an outpatient with oral Posaconazole 200 mg three times a day with adequate TDM levels (>1.0 mg/L). No bronco-alveolar lavage (BAL) was performed at that time.

A repeat HRCT chest done in two months, showed a worsening of the thoracic findings with extensive ground-glass, more conspicuous subpleural micronodularity, and a persistent solitary nodular opacification in the left upper lobe measured 8 × 6 mm. The patient was started on outpatient treatment with caspofungin in addition to posaconazole and underwent a BAL. There were no positive findings on BAL (negative fungal culture, GMN and 18s PCR). He received dual therapy (caspofungin and oral posaconazole) for 6 weeks. Oral posaconazole dose was adjusted on a weekly basis with target therapeutic level of >1.0 mg/L but at that point, levels were often subtherapeutic, likely in the context of chronic gut GvHD). During this time, he remained on immunosuppressive treatment for chronic GvHD.

The subsequent chest HRCT scans performed while on treatment with posaconazole and caspofungin (Fig. 1b), showed a continuous worsening with the increased size of the lesion to 15 × 13 mm. At this point, the GMN remained negative (0.1), but the BDG was elevated (368 pg/mL).

In view of the continuous deterioration despite antifungal therapy (Fig. 1c), a lung biopsy was performed in 8 months. The fungal culture grew *Neosartorya udagawae*. The colonial and microscopic morphological appearance of the isolate was consistent with a poorly sporing member of the *Aspergillus fumigatus* species complex (*Aspergilllus* section *Fumigati*). The colony was predominantly white, floccose, and radially-folded with areas of central blue-grey coloration due to limited conidium formation. Microscopic tease mounts revealed scanty *Aspergillus* vesicles covered over the upper 50% of their surface with a single layer of phialides producing small (2–3 μm) smooth, spherical conidia in chains. Definitive identification of the organism was achieved by MALDI-ToF mass spectrometric analysis as described previously [20], which produced mass spectral profiles that matched those for *Neosartorya udagawae* with robust scores (MSI database, scores of 26.32 and 39.9 with independent isolates). Antifungal susceptibility testing by CLSI broth microdilution revealed low minimum inhibitory concentrations (MICs) with amphotericin B, caspofungin and anidulafungin and elevated MICs indicative of resistance with most azoles (isavuconazole MIC = 8, itraconazole MIC >16, voriconazole MIC = 8, except for posaconazole = 1mg/L). The patient was started on liposomal amphotericin B (3 mg/kg) after the biopsy. Anidulafungin (1.5 mg/kg) was added on in 6 weeks' time following MICs results, and subsequently changed to caspofungin (50 mg/m2) once susceptibility was confirmed.

After two weeks of the dual therapy and in 10 months from Day 0, the child developed signs of respiratory distress and pleuritic pain. A repeated HRCT showed further enlargement of the lesion (Fig. 1d), despite this targeted treatment and no significant changes on his levels of immunosuppressive therapy. Another HRCT chest performed in 11 months (counting from Day 0) showed a further significant increase of the consolidation in the left upper lobe to 40 × 55 × 34 mm.

A second lung biopsy showed fungal hyphae within foci of necrosis.

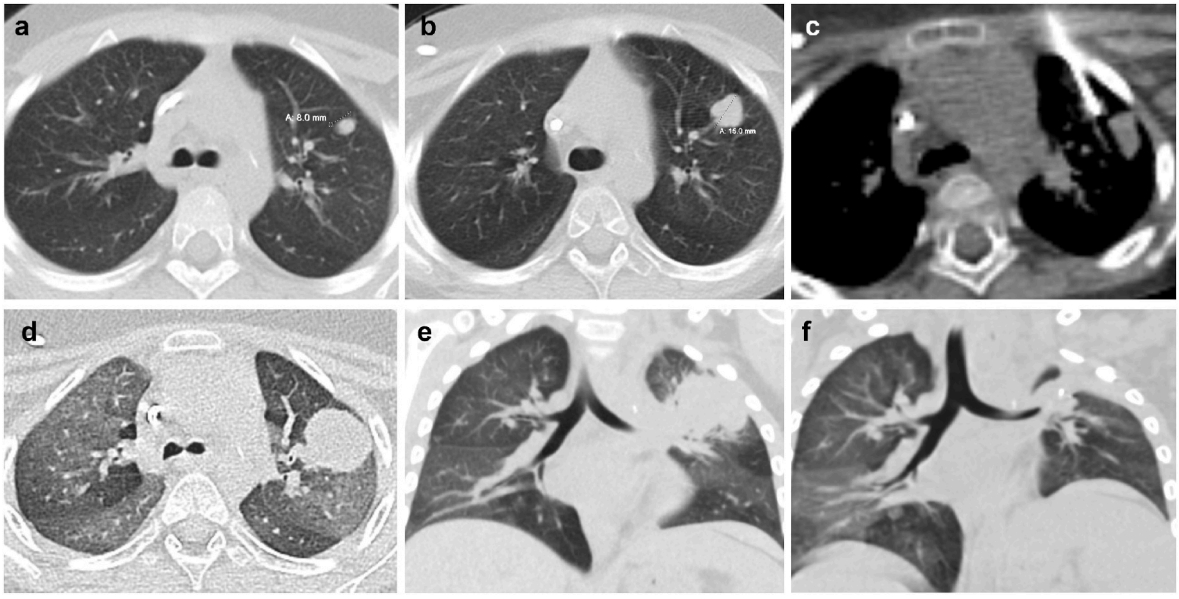

Fig. 1. HRCT chest findings at different stages of the treatment.
(a) The initial HRCT chest showing a solitary solid nodule in the left upper lobe measures 8mm. (b) The subsequent chest HRCT scan performed in 7 months from the initial finding of the lung nodule demonstrating a continuous worsening with the increased size of the lesion to 15 × 13 mm. There are a few background ground glass patches in the lungs. (c) The biopsy of the nodule complicated by post-biopsy haemorrhage. (d) The solid solitary nodule continues to enlarge, reaching 2.7 cm, with marked mosaicism of the background lung parenchyma. (e) The repeat HRCT chest performed in 4 weeks after the second biopsy while on triple antifungal therapy. The nodule has become much more mass-like, with irregular lobulated margins, and has enlarged to 4 cm, contacting the hilum centrally and the pleural surface laterally. The mosaicism in the background lungs is again seen – suggestive of bronchiolitis obliterans. (f) Post-lobectomy for the left upper lobe lesion. The background lung mosaicism remains.

Fungal culture grew *Neosartorya udagawae* again which was confirmed by positive 18S PCR results. The antifungal susceptibility profile remained unchanged. In view of these results, oral Posaconazole in a high dose of 200 mg four times a day was added to antifungal treatment with the specific aim of achieving serum drug concentrations above 3.0 mg/L. This target was difficult to achieve despite dose increases. At 12 months (after 4 weeks of triple therapy), a repeat HRCT demonstrated further progression of the left upper lobe mass which encroached into the superior mediastinum (Fig. 1e). Serum BDG concentrations remained extremely elevated (persistently >500 pg/mL) throughout both dual and triple antifungal therapy. In view of this continue deterioration and apparent clinical failure of the antifungal treatment, a surgical resection of fungal disease was agreed.

The child underwent a left upper lobe lobectomy without major complications. The surgical approach was via muscle sparing left posterolateral thoracotomy. Intraoperatively, there were adhesions between chest wall and the anterior surface of the left upper lobe (Fig. 1e). In addition, multiple lymph nodes were noted at the hilum, along the fissure and at the aortopulmonary area. After releasing the adhesions around the left upper lobe, the left upper lobectomy was done in standard fashion.

The fungal culture again confirmed the growth of *Neosartorya udagawae*. At 14.5 months (six weeks after lobectomy) a repeat HRCT chest showed post-surgical changes with no evidence of active fungal disease following resection. The triple antifungal treatment was de-escalated 2 weeks after surgery to dual therapy with caspofungin and liposomal amphotericin. Posaconazole was stopped in view of the difficulty achieving adequate serum concentrations. Within a month post-surgery, the treatment was reduced to monotherapy with caspofungin. The repeat HRCT chest in 16 months demonstrated no evidence of fungal disease recurrence (Fig. 1f) and normalization of serum BDG concentrations (<30 pg/mL). At 3 years the child had completely recovered from the fungal infection episode without recurrence. He remained on extended secondary prophylaxis with posaconazole whilst on immunosuppression and to ensure that serial follow-up HRCT scans remained normal without any evidence of residual fungal disease but was subsequently weaned off both antifungal treatment and immunosuppression. Overall, he received 33 months of antifungal treatment.

3. Discussion

We are reporting a clinical case of *Neosartorya udagawae* disease in a paediatric patient with a haematological malignancy following HSCT requiring pulmonary lobectomy. There are very few cases of *Neosartorya udagawae* infection reported in the literature to our knowledge [4–8]. *Neosartorya udagawae* is a relatively rare species in the genus *Aspergillus*, which is associated with infections that are often chronic in nature and refractory to antifungal therapy with a propensity to spread across anatomic planes [4]. All those features were observed in our case.

The outcome of invasive fungal disease associated with *Aspergillus* species varies depending on the host factors and the biology of the fungi. The patient in our case was considered high risk. Additionally, to chemotherapy, allogenic HSCT and a period of prolonged neutropenia, he required intensive combined immunosuppressive therapy and a prolonged course of systemic corticosteroids for advanced stage GvHD.

Despite early biopsy with timely identification of the pathogen and antifungal therapy tailored according to the antifungal susceptibility profile, the disease required surgical treatment for debulking. The current case demonstrated the challenges of refractory *Neosartorya udagawae* associated invasive fungal disease management in severely immunocompromised patient with a contribution of both host and fungi factors.

The biopsy procedure is a standard of care for the definitive diagnosis of invasive fungal disease and for identification of the causative organism and establishment of antifungal susceptibility. The combination of microscopy, fungal culture and PCR on biopsy tissues significantly increases the diagnostic yield [12,13]. In view of the growing diversity of organisms causing IFD alongside increasing prevalence of species resistant to antifungal agents, the importance of microbiological confirmation and susceptibility testing is increasing [16–18]. As immunocompromised patients are at high risk of acquiring IFD that is refractory to standard first line therapy as well as rapid progression and development of severe complications of IFD; an ineffective or delayed treatment can result in fatal consequences [19].

Whereas most patients can be treated for IFD with systemic antifungal therapy only, there are cases when adjunctive surgical debulking is important. It should be considered when disease is refractory to antifungal treatment or when a fungal mass causes life-threatening symptoms [14]. Lung resection in pulmonary invasive fungal disease in hematologic patients should be carefully considered in view of mortality risk especially in the patients on immunosuppression. It is an approach that can be implemented for debulking in the cases of progressive IFD that is refractory to antifungal agents [9–11]. The current case showed an example of combined targeted antifungal and surgical treatment with a good outcome.

Conflict of interest

Authors do not have any conflicts of interests to declare.

Ethical statement

According to most journal policies, we were granted consent by the parents of the patient for publishing the case report and relevant imaging.

As a case report is not considered research, no ethics committee approval was required.

CRediT authorship contribution statement

Olga S. Tatarinova: Writing – original draft, Resources. **Caroline L. Furness:** Supervision, Writing – review & editing. **Andrew M. Borman:** Conceptualization, Investigation, Methodology, Writing – review & editing, Supervision, Writing – original draft. **Joy Barber:** Visualization, Writing – review & editing. **Nagarajan Muthialu:** Investigation, Writing – original draft, Writing – review & editing. **Laura Ferreras-Antolin:** Conceptualization, Supervision, Writing – review & editing.

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