Successful Treatment of *Scedosporium* Pneumonia With Voriconazole During AML Therapy and Bone Marrow Transplantation

To the Editor: *Scedosporium apiospermum* is a rare but aggressive cause of infection in the immunocompromised host. This organism is difficult to distinguish from *Aspergillus* species except by culture. It may be helpful to others to record our experience in managing *S. apiospermum* pneumonia in an immunocompromised host. The patient, a girl, was successfully treated with surgery and a new triazole antifungal, voriconazole. She subsequently received additional myelosuppressive therapy and a matched unrelated bone marrow transplant without recurrence of the fungal infection.

Our patient was a 14-year-old Caucasian female with a 2-week history of increased bruising, lethargy, decreased appetite, dizziness, and gum bleeding. She lived on a farm and raised horses, cattle, cats, and dogs. On admission she was febrile and had extensive bruising over all four extremities, multiple small firm mobile cervical nodes, and a spleen palpable 2 cm below the costal margin. Laboratory studies revealed a white blood cell count of 45,200/mm^3 with blasts, Hb 8.6 g/dl, and platelets 16,000/mm^3. Chest radiograph demonstrated bilateral basilar infiltrates and a left pleural effusion. A bone marrow aspirate and biopsy confirmed acute myelogenous leukemia, M5a subtype. Cerebrospinal fluid was negative for leukemia cells at diagnosis.

After a stormy induction course punctuated by septic episodes, a chest CT scan was performed that demonstrated a 4-cm nodule in the left base consistent with fungal disease. Gram stain of a needle biopsy showed many hyphal elements suggestive of *Aspergillus* species but culture results confirmed *S. apiospermum*/*Pseudallescheria boydii*. Itraconazole 200 mg i.v. three times daily was started. A left lower lobe lobectomy was performed to remove the largest fungal nodule. Miconazole 600 mg i.v. every 8 hours and 5-flucytosine (5-FC) were started pending sensitivity testing. Amphotericin B that had been initiated empirically was discontinued. Follow-up chest radiograph showed residual left-sided airspace disease. Ophthalmologic examination, urine and blood cultures were negative.

Sensitivity testing on the *S. apiospermum* showed minimal inhibitory concentrations for amphotericin B >16 mcg/ml, miconazole 0.5 mcg/ml, and itraconazole 4 mcg/ml.

Voriconazole was obtained for compassionate use from Pfizer, Inc. (New York, NY) and the patient was started at 270 mg IV twice a day. All other antifungals were discontinued. High dose cytarabine and asparaginase chemotherapy were started for the consolidation phase of chemotherapy. The patient was discharged on voriconazole 200 mg orally twice a day. A chest CT, scan 3 weeks after starting voriconazole showed improvement in the pleural thickening and parenchymal lung disease. Chemotherapy was completed in 3 months with a plan to continue oral voriconazole for an additional 6 months.

Her course thereafter was complex. The AML recurred and was treated aggressively including bone marrow transplantation using busulfan, cyclophosphamide, and etoposide as the preparative regimen. She relapsed a second time and died. All the while, voriconazole was continued and objective signs of the fungal infection (CT scans) showed continued improvement.

S. apiospermum is a dematiaceous mold found in soil and barns. Transmission is usually by inhalation or skin contact. In immunocompromised patients, the organism is usually cultured from blood or lungs but autopsy studies often confirm disseminated disease [1,2]. Our patient lived on a cattle and horse farm and this was the probable source of infection.

Most *Scedosporium* species are resistant to even high dose amphotericin B [3]. The MIC on this patient was >16 mcg/ml. Successful treatment using the azole antifungals including miconazole [1], ketoconazole [4], itraconazole [5,6], and more recently voriconazole [7] have been reported. The literature review by Strickland et al. reported a 96% mortality rate in cancer patients. Only those with localized disease treated with azole antifungals survived [1].

Voriconazole is a new triazole antifungal agent that has been shown to have in vitro activity comparable to itraconazole against *S. apiospermum* [8]. Voriconazole has 96% bioavailability when given orally which may contribute to its efficacy while the absorption of itraconazole is more erratic [9]. In patients with cancer and poor mucosal integrity, the intravenous route may be preferable.

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Melanotic Neuroectodermal Tumour of Infancy Arising in Skull

Key words: melanoma; p PNET; cancer in infancy

To the Editor: Melanotic neuroectodermal tumour of infancy (MNTI) was first described by Krompecher in 1918. It is described as a rare lesion that occurs in children up to 1 year of age. About 93% of these lesions develop in the head and neck region, commonly involving maxilla (68.8%), skull (10.8%), and brain (4.3%) [1,2]. The most common extracranial sites are the genital organs [3]. MNTI has also been reported in the mediastinum, thigh, foot, shoulder, and the ovary. Though mostly benign, it has a high potential to display locally aggressive and invasive behaviour. The recurrence rate following surgical excision is 10–15% [4]. About 2–6% of these tumours have been reported to be malignant.

Our experience with a 6-month-old boy is instructive. He developed a rapidly enlarging swelling in his left parieto-occipital region which in 9 weeks had become a 4×2 cm hard, non-tender swelling behind his left ear. It had a regular border and surface, and was firmly adherent to the underlying bone. The overlying skin was normal. Routine haematologic, biochemical, and imaging studies were non-contributory so that an excision biopsy was performed. The swelling had to be chiselled off the bone. The gross appearance was that of a grey/black elliptical tumour mass measuring $4 \times 2 \times 2$ cm with a fragment of bone at one pole of the specimen. Histology showed a tumour with a biphasic histopathologic profile (Fig. 1).

Urinary catecholamines and serum alpha feto protein levels were checked after the surgery and were found to be within normal limits. Post-operative CT and MRI scans documented a large intracranial but extracerebral component of this lesion that indented the posterior temporal area (Fig. 2). He was referred to the National Neurosurgical Unit in Dublin where during a radical excision of the tumour it was found to extend up to the dura but not across it. The dura was not opened during surgery. The defect was covered by a rotational flap and the child remains very well with no signs of recurrence 2 years later.

Since the first description in 1918 there have been over 240 cases of MNTI reported in the world literature with very few occurring in the skull [4]. The most widely accepted theory regarding histogenesis is that it belongs to a group of neuroectodermal tumours arising from cells of neural crest origin.

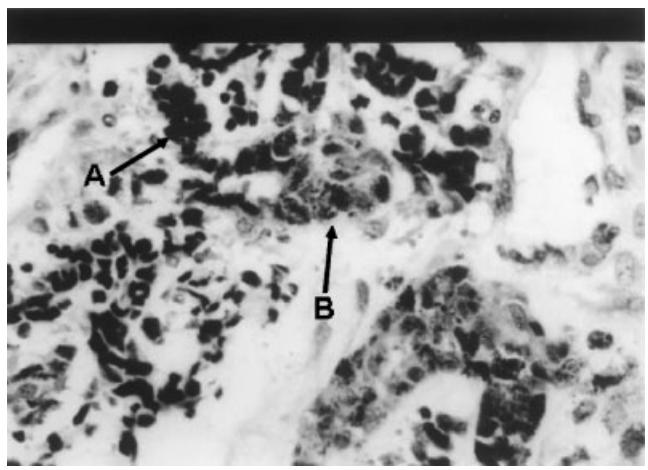

Fig. 1. Biphasic tumour composed of small blue cells (**A**) and large cuboidal epithelioid cells containing pigment (**B**) embedded in a fibrous stroma (H & E staining).

This has been supported by embryologic, ultrastructural, and biochemical evidence [5]. Raised levels of catecholamines, alphafeto protein, and neuron specific enolase (NSE), characteristic of other tumours of neural crest origin are also seen in these tumours [4,6].

MNTI shows a biphasic histopathologic profile, consisting of a population of epithelioid melanin-containing cells and neuroblastic cells within a prominent stroma [7]. The melanin-containing cells can be arranged in alveolar, pseudoalveolar, or gland like structures.

Unquestionably, the mainstay of treatment for MNTI is surgery. When the skull is the primary site, a planned single curative operation can be carried out by a team of

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