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## *Aspergillus flavus* Disseminated Infection in Paediatric Acute Lymphoblastic Leukaemia: A Case Report

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### Abstract

Here we report the case of a disseminated *Aspergillus flavus* infection in an adolescent affected by acute lymphoblastic leukaemia at the beginning of first-line chemotherapy. Association of surgery and combination antifungal therapy (high dose liposomal amphotericin B and caspofungin) allowed infection improvement. 18-FDG PET-MRI was used for response-to therapy monitoring.

Here we report the case of a proven invasive *Aspergillus flavus* infection in an adolescent affected by acute lymphoblastic leukaemia (ALL), with particular attention to clinical presentation, therapy schedule and response-to-therapy monitoring.

### Description

A 17 years old girl followed at Paediatric Oncology-Haematology Clinic of Padova for B-precursor ALL developed a progressive painful swelling of the left forearm. Diagnosis of B-III ALL according to EGIL classification [12] was done in August 2016; central nervous system involvement was excluded. Soon after the diagnosis, the patient was enrolled in AIEOP BFM ALL 2009 international protocol. After the end of the first chemotherapeutic phase Induction A (prednisone 60 mg/m<sup>2</sup>/day for 28 days; vincristine 1.5 mg/m<sup>2</sup> weekly for 4 doses; daunorubicin 30 mg/m<sup>2</sup> weekly for 4 doses; PEG-asparaginase 2500 UI/m<sup>2</sup> for 2 doses every 2 weeks) the patient developed a painful swelling of the left forearm without alteration of overlying skin. According to personal history of a recent accidental trauma and ultrasound findings, the lesion was initially interpreted as a muscular haematoma. When fever appeared, the girl was hospitalized and wide spectrum antibiotic therapy was started (ceftazidime 40 mg/kg/day TID, amikacin 15 mg/kg QD; teicoplanin 10 mg/kg BID the first day, then 10 mg/kg QD), by considering concomitant severe neutropenia and possible haematoma superinfection. For the persistence of fever longer than 72 h, according to our local protocol, antibiotic therapy was shifted to meropenem and antifungal therapy (liposomal amphotericin B 3 mg/kg QD) was started. During hospitalization we observed a worsening of the cutaneous lesions: the first one evolved into a hyperemic painful nodule;

### Introduction

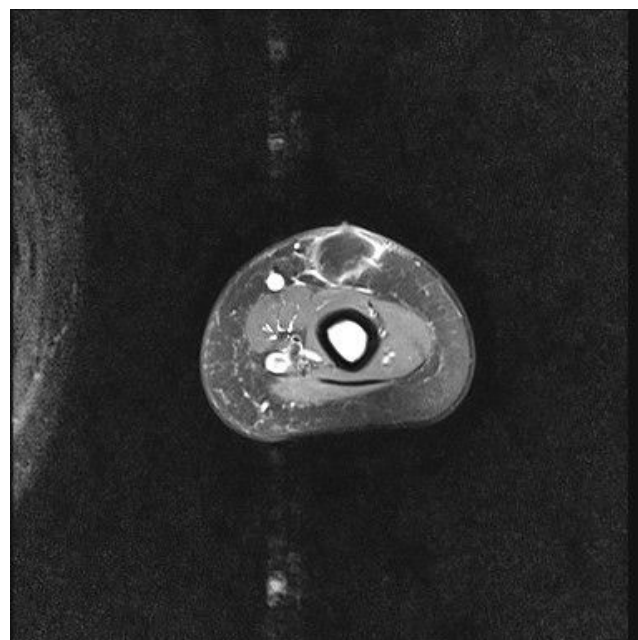
Incidence of invasive fungal infections (IFI) has progressively increased over the past few decades [1]. Invasive aspergillosis (IA) is associated with the highest morbidity and mortality in immunocompromised patients [2,3]. *Aspergillus flavus* is the second leading cause of IA affecting mostly upper airways and skin [4,5]. Invasive cutaneous aspergillosis (ICA) is a rare condition characterized by more or less itching macules, papules, plaques or haemorrhagic bullae, potentially evolving into necrotic ulcers covered by a dark eschar. Primary ICA, deriving from fungus direct inoculation into an injured site, can be distinguished from secondary ICA, usually resulting from systemic dissemination of inhaled hyphae through the blood stream [6-10]. Immunological deficiency in paediatric haemato-oncology patients is due both to the malignancy and chemotherapy regimen, emerging as the main predisposing factors to IFI [11]. Early diagnosis, effective therapy and accurate response-to-therapy monitoring are mandatory in these patients, in order to achieve infection control and reintroduce chemotherapy as soon as possible.

three analogue new lesions appeared on the left leg and left arm, one of which covered by a haemorrhagic bullae (Figure 1).

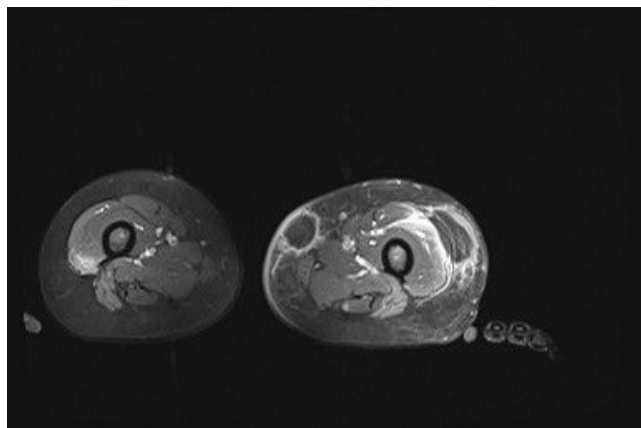


**Figure 1:** *Aspergillus flavus* subcutaneous lesions of the left arm

Inflammation indexes were only mildly elevated (maximum C-reactive protein value: 35 mg/L). Initial Galactomannan (GM) and 1-3,β-D-Glucan (BG) serum dosages were negative. Ultrasound evaluation and local Magnetic Resonance Imaging (MRI) showed subcutaneous colliquating abscesses (Figure 2). Surgical drainage was performed and abundant purulent material collected: *Aspergillus flavus* was isolated. According to previous experience at our Centre in fungal infection diagnosing and monitoring, a 18-fluorodeoxyglucose Positron Emission Tomography-MRI (18-FDG PET-MRI) was performed. This exam allows to study anatomically and functionally the whole body, detecting disseminated lesions and minimizing radiation exposure [13]. Mild to high metabolic uptake (Standardized Uptake Value–SUV 2.4–4.8) was shown at the following sites: right leg (2 muscular lesions); left leg (2 subcutaneous lesions); right dorsal muscles (1 lesion); left arm (2 subcutaneous lesions); left underarm (1 lymphatic lesion); kidneys (2 parenchymal lesions); right upper pulmonary lobe (1 lesion). No central nervous system (CNS) involvement was detected. Eyes evaluation and echocardiography excluded respectively ocular and cardiac involvement.



**Figure 2 (A):** MRI at diagnosis: left arm



**Figure 2 (B):** MRI at diagnosis: left limb

Combination antifungal therapy with high dose liposomal amphotericin B (7.5 mg/kg QD) and caspofungin (70 mg QD the first day, then 50 mg QD) was started. We opted for this intensive pharmacological schedule by considering the extension of fungal infection and the necessity to control it promptly and reintroduce chemotherapy as soon as possible. Surgical curettage of subcutaneous abscesses was performed three times a week by paediatric surgeons. We observed fever resolution after 3 days of combination therapy and slow improvement of subcutaneous lesions.

GM was persistently negative, while BG increased progressively (maximum value >523 pg/ml). After 21 days of combination therapy we repeated 18-FDG PET-MRI, that showed a partial improvement of the fungal lesions. This finding allowed us to start a maintenance chemotherapy with oral methotrexate and 6-mercaptopurine waiting for a complete resolution of the infection.

## Discussion

Invasive aspergillosis has been emerging as an increasingly important cause of morbidity and mortality in immunocompromised children. *Aspergillus fumigatus* is the most frequent pathogen, followed by *Aspergillus flavus* and *Aspergillus terreus* [14,15]. IA usually develops soon after prolonged and severe neutropenia and commonly affects lungs, less often paranasal sinuses, central nervous system (CNS), skin and soft tissues. Disseminated form accounts for about 30% of cases [7,16]. Clinical presentation may be aspecific (i.e. prolonged fever in severe neutropenia not responding to wide spectrum antibiotic therapy) or as expression of organ damage (i.e. cough, pleural pain, and haemoptysis in lung infection or focal neurological deficits or seizures in CNS localization).

Primary cutaneous aspergillosis has been reported more frequently in children than in adults, in association with direct skin lacerations [16,17]. Our patient developed a disseminated *Aspergillus flavus* infection with multiple subcutaneous, muscular and parenchymal lesions. IA is an unexpected finding in paediatric ALL at the beginning of the first line therapy, as we observed in our patient: no antifungal prophylaxis is usually

recommended in paediatric ALL [18-20]. Even if patient's personal history was positive for a traumatic event, disseminated IA was more likely the consequence of fungal vascular migration from an initial pulmonary site than direct inoculation of *Aspergillus flavus* into the skin, also considering that no cutaneous laceration was detected or referred.

IA prognosis mainly depends on early diagnosis, appropriate treatment and restoration of host defences [21]. Timely infection control is mandatory in haemato-oncology paediatric patients, considering that a prolonged interruption of chemotherapy may affect dramatically the oncological prognosis. On the other hand IA diagnosis, therapy and monitoring are still challenging. Isolation of fungal pathogen is necessary for the definition of proven IA, but is rare and usually needs surgical approaches [22].

Galactomannan (GM), a polysaccharide cell-wall component of all *Aspergillus spp*, is the most accurate marker for IA screening in adults, but has shown a wide range of true-positive and true-negative results in paediatric studies (sensitivity 0.76; specificity 0.86) [23]. In our patient serum GM was repeatedly negative, even in presence of a proven *Aspergillus flavus* infection. 1-3, Beta-D-Glucan (BG) is a cell wall component of many fungal pathogens such as *Aspergillus spp*, *Candida spp*, *Fusarium*, *Trichosporum* or *Saccharomyces*, and *Pneumocystis jiroveci*, whereas lacks in *Cryptococcus neoformans* and *Mucorales*. Its serum testing has been proving to be useful in adult patients, but data are too limited in children to recommend [24]. In our patient basal serum BG was negative and increased progressively during therapy to the maximum detectable level (>523 pg/ml). In our opinion BG should be considered as an indicator of the presence or absence of fungal infection more than an indirect estimator of disease extension. The increasing serum levels in our patient might be due to moulds destruction rather than to IA progression.

As regards radiological investigation, CT and MRI have a high accuracy in the early diagnosis of IA, but may result inadequate in evaluating disseminated disease and monitoring of residual infection. Furthermore cumulative radiation exposure due to CT scan has to be considered, especially in paediatric population [25,26]. 18-FDG PET-MRI has been recently proposed as a combined functional-anatomical methodical to better distinguish active fungal lesions from residual scars [13]. In our patient 18-FDG PET-MRI allowed to study the whole body, detected additional lesions and monitored their evolution in terms of activity and anatomical definition.

No standardized therapy are available, both for the variability of local epidemiology and paucity of clinical trials [27]. ECIL-5 guidelines recommended monotherapy administration in IA (voriconazole 2 x 6 mg/kg the first day, then 2 x 4 mg/kg - evidence grade AI - or liposomal amphotericin B 3 mg/kg - evidence grade BI) [18]. Anyway clinical experience seems to indicate combination therapy as an efficacious treatment of IA in haemato-oncology paediatric patients, in order to accelerate the infection control and reduce chemotherapy delay. Association of caspofungin and voriconazole or caspofungin and liposomal amphotericin B has been previously described [9,28-30]. Combination therapy with high dose liposomal amphotericin B



(5-7.5 mg/kg) and caspofungin (70 mg the first day, then 50 mg/day) was well tolerated in our patient. No renal or liver impairment was detected. Moderate hypokalemia appeared and was easily corrected with intravenous potassium chloride infusion. Surgical curettage of necrotic lesions had a leading role in the improvement of subcutaneous localizations.

In conclusion, IA is a challenging complication of chemotherapy-induced immunosuppression in paediatric haemato-oncology patients. It requires a multidisciplinary approach in order to obtain promptly the most appropriate diagnosis. Aggressive therapy is mandatory to control the infection and allows the clinician to reduce chemotherapy suspension. 18-FDG PET-MRI may be useful for a more accurate diagnosis and response-to-therapy monitoring.

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