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Secondary cutaneous aspergillosis in a child with Behçet's disease: a case-based update

Soumia Nachate[1,2*], Mouad El Mouhtadi[2,3], Yousra Zouine[2,4], Mohamed Amine Haouane[2,5], Mohamed Amine Azami[2,5], Mohamed Oulad Saiad[2,6], Dounia Basraoui[2,4], Hicham Jalal[2,4], Houda Nassih[2,5], Rabiy Elqadiry[2,3], Aicha Bourrahouat[2,3], Imane Ait Sab[2,3] and Awatif El Hakkouni[1,2]

Abstract

Background Invasive aspergillosis (IA) is one of the rarest opportunistic fungal infections and has increased in frequency worldwide in recent years. It is a life-threatening infection associated with high mortality rates. Invasive pulmonary aspergillosis (IPA) is the most severe form of the disease. Extrapulmonary forms can develop as a primary infection or occur as part of a disseminated infection from the lung in severely immunocompromised patients. The major limitation in the management of these infections is the challenge of early diagnosis.

Case presentation Here we report a case of secondary cutaneous aspergillosis that developed from extensive pulmonary aspergillosis in a 3-year-old female who underwent immunosuppressive therapy for a diagnosed Behçet disease (BD). *Aspergillus* hyphae were identified on skin biopsies. Cultures grew *Aspergillus fumigatus*. The diagnosis of cutaneous aspergillosis enabled us to diagnose IPA, although there was no mycopathological proof of lung infection. The patient was successfully treated with voriconazole (8 mg/kg/day) and surgical debridement of the skin lesion.

Conclusions Although cutaneous involvement in aspergillosis is extremely uncommon, it may be the presenting feature in some cases, allowing for an accurate and timely diagnosis of deeply infected sites. Accordingly, when evaluating skin lesions in immunocompromised individuals, especially debilitated children with underlying diseases requiring long-term immunosuppressive agents, cutaneous aspergillosis should be vigilantly considered.

Keywords Behçet disease, Invasive pulmonary aspergillosis, Cutaneous aspergillosis, Immunosuppressants

Background

Recently, the expansion in the number and heterogeneity of immunocompromised patients has been associated with a significant increase in the prevalence of opportunistic fungal infections [1]. *Aspergillus fumigatus* species are ubiquitous airborne opportunistic fungi that produce a broad spectrum of clinical manifestations in humans, ranging from mild allergic symptoms to severe invasive forms. Invasive aspergillosis (IA) is a potentially fatal disease associated with high mortality rates. In the pediatric age group, attributable mortality is estimated at 37.5%. This rate can be as high as 63–72% in non-neutropenic patients [1]. It represents one of the most frequently overlooked diagnoses, and, according to autopsy studies, only one in two invasive fungal infections is diagnosed

*Correspondence:
Soumia Nachate
docteurnachate@gmail.com
[1] Department of Medical Mycology and Parasitology, University Hospital Mohamed-VI, Avenue Ibn Sina, Marrakech 40080, Morocco
[2] Faculty of Medicine and Pharmacy, Cadi Ayyad University, Marrakech 40000, Morocco
[3] Pediatric B Department, University Hospital Mohamed-VI, Avenue Ibn Sina, Marrakech 40080, Morocco
[4] Department of Radiology, University Hospital Mohamed-VI, Avenue Ibn Sina, Marrakech 40080, Morocco
[5] Department of Pathology, Avicenna Military Hospital, Marrakech 40000, Morocco
[6] Departement of Pediatric Surgery, University Hospital Mohamed-VI, Avenue Ibn Sina, Marrakech 40080, Morocco

before death. Moreover, clinicians are challenged by the increasing rates of resistant strains [2]. The respiratory tract is the site of predilection for IA through inhalation of infectious spores. While these are unlikely to germinate in healthy tissues, germination, and hyphal invasion can occur in a variety of situations, including periods of neonatal immune immaturity, drug-induced immunosuppression, antibiotic-induced disturbance of fungal and bacterial flora, massive inoculation of *Aspergillus* spores, local tissue alterations, immune dysregulation caused by hematologic and autoimmune diseases, and miscellaneous debilitating conditions [3].

Cutaneous invasive aspergillosis (CIA) is a rare pathological entity that remains under-characterized. It may be a primary event resulting from direct inoculation of the *Aspergillus* species into the skin injury sites or secondary, either by contiguous extension from adjacent infected structures or by blood-borne dissemination of hyphae, most commonly following a primary pulmonary focus [4]. A recent review of the literature reveals only a few published cases of secondary CIA, most of which are associated with hematologic disorders and organ transplants [5–12]. The association of cutaneous and pulmonary aspergillosis with Behçet's disease (BD) is scarcer and has been previously described in two adult patients—a Japanese male patient, in whom the diagnosis was made at postmortem [13], and a Chinese adult patient in 2019 [14]. To the best of our knowledge, this is the first instance of IPA that occurred during BD in a pediatric patient and resulted in skin invasion.

Case presentation

This 3-year-old female child was diagnosed with BD in November 2020, revealed by a pyoderma gangrenosum, and retained on the basis of a confirmed maternal history of BD, recurrent bipolar aphthosis, and positive HLA-B51. Subsequently, the patient received five months of mycophenolate mofetil (MMF) (1200 mg/m^2/day), then switched to methotrexate (MTX) (5 mg/week).

In August 2021, the child was admitted to the pediatric department, complaining of a dry cough, prolonged fever, and an altered general condition. The mother mentioned a respiratory symptomatology in the previous months, which she self-treated with conventional antibiotics without a favorable response. On physical examination, the child was conscious but impaired. Regarding the patient's vital signs, the body temperature was 36.3 °C, the pulse rate was 132 beats per minute, the blood pressure was 116 mmHg systolic over 60 mmHg diastolic, and the respiratory rate was 35 breaths per minute. The pulmonary examination revealed no detectable abnormalities. A single 2 × 2 cm erythemato-violaceous skin nodule was discovered on the right medial thoracic side during the dermatological examination. The first enhanced chest CT scan showed on the parenchymal window a scattered bilateral nodular consolidation surrounded by ground-glass opacities, realizing the halo sign. Biological findings showed anemia and increased CRP levels (Table 1). All microbiological tests were negative. A pathological examination of the skin nodule biopsy revealed a non-specific, polymorphic inflammatory reaction. Pulmonary tuberculosis (TB) was considered probable and treated accordingly. The immunosuppressants were discontinued.

Unfortunately, the patient was lost to follow-up for 2 months before presenting with a more altered general condition and worsening respiratory symptoms, requiring rehospitalization. At that time, the child weighed 7.500 kg (−3 SD) and was 86 cm (−3 SD). Brachial (BC) and cranial (CC) circumferences were 9.5 cm and 43 cm, respectively, and the BC/CC ratio was 0.22, indicating severe undernutrition. The clinical examination indicated a temperature of 39°C, a rapid pulse, and respiratory distress. The absence of breath sounds and dullness to percussion was evident over the right hemithorax. The thoracic skin lesion had markedly increased in size. The control-enhanced chest CT in the mediastinal and parenchymal windows showed parenchymal consolidation predominantly on the right lung with reduced lung volume, a slight ipsilateral shift of the mediastinum, and

Table 1 The patient's laboratory data

Parameter (units)	November 2020	August 2021	October 2021	December 2021	March 2022	May 2022
Haemoglobin (g/dL)	7.6	7.9	6.2	10.6	11.6	11.5
white blood cell count (10^3/mm^3)	11.06	10.51	15.75	16.33	12.63	14.31
ANC (10^3/mm^3)	3.02	5	7.41	7.69	7.07	6.35
Lymphocyte (10^3/mm^3)	7.02	4.25	5.86	7.86	4.19	6.39
Platelet (10^3/mm^3)	380	467	409	528	511	551
C-reactive protein (mg/L)	70.98	119	151.23	90	37.01	-
Galactomannan antigenemia [a]	-	-	-	1.2 (+)	0.4 (−)	0.1 (−)

[a] The results are presented as an optical density (OD) index. According to the manufacturer's instructions, sera with an index ≥ 0.5 are considered to be positive

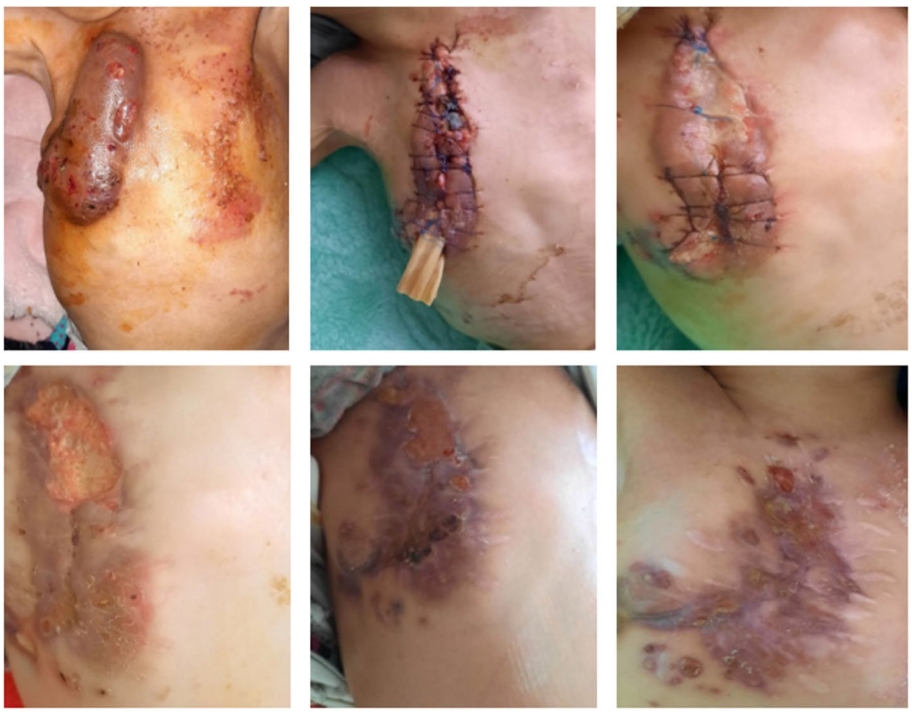

Fig. 1 The time course of the skin lesion after surgical debridement and while receiving voriconazole shows marked improvement and practically complete healing

a right pleural effusion. It also revealed lytic bone lesions with cortical thickening and periosteal reaction on the anterior and posterior costal arches. Dermatologically, the lesion was 7 × 4 cm in diameter and was fistulized with serous discharge, with the appearance of multiple blisters on the surrounding chest skin (Figs. 1 and 2). All blood cultures and respiratory specimens were negative, as were all other bacteriological tests. The hemogram and CRP values are detailed in Table 1.

Surgical debridement with drainage and a biopsy of the cutaneous lesion was performed by the pediatric surgery team (Fig. 1). Histopathology of deep biopsied specimens and microscopic examination of the drained content revealed large, septate, and irregular hyphae with acute-angle branching consistent with *Aspergillus* (Figs. 3A, B, and 4). *A. fumigatus* was grown in culture after 2 days of incubation on Sabouraud's dextrose agar medium with chloramphenicol (SC) at 37 °C (Fig. 3C and D). The *Aspergillus* galactomannan antigenemia (immunoenzymatic sandwich microplate assay, Platelia™ Aspergillus Ag, Bio-Rad, France) was positive in two separate sera (Table 1).

The diagnosis of IPA with secondary cutaneous involvement was made. The patient was treated with voriconazole (8 mg/kg/day) for 3 months, up to a cumulative dose of 720 mg. Significant clinico-biological and radiological improvements were noted, with the disappearance of cough and infectious symptoms; weight regain (from 7.5 kg in October 2021 to 8.9 kg in December 2021; 11 kg in March 2022); healing of skin lesions; recovery of anemia; decreased CRP levels; and progressive resolution of lung parenchymal damage as noticed on the 3-month interval CT scan (Fig. 5). The *Aspergillus* galactomannan antigen was negative on the last serological test in May 2022. Screening for an associated primary immune deficiency was negative (view timeline, Fig. 6).

Discussion

Aspergillosis and Behçet disease

BD is a multisystem inflammatory chronic disease of unclear origin that causes immune dysregulation and vasculitis involving vessels of all sizes. The prevalence of pediatric BD is not well documented. It is reported that 4–26% of patients with BD have a pediatric onset, with a mean age of appearance ranging from 4.9 to 12.3 years and a delay in diagnosis of about 3 years [15]. The recommendations for the management of BD in pediatrics are often derived from guidelines used for adult patients. This requires the use of anti-inflammatory agents and immunosuppressants, with the primary objectives being symptom control, suppression of the ongoing inflammation, counteracting the immune response, and prevention of organ damage [16].

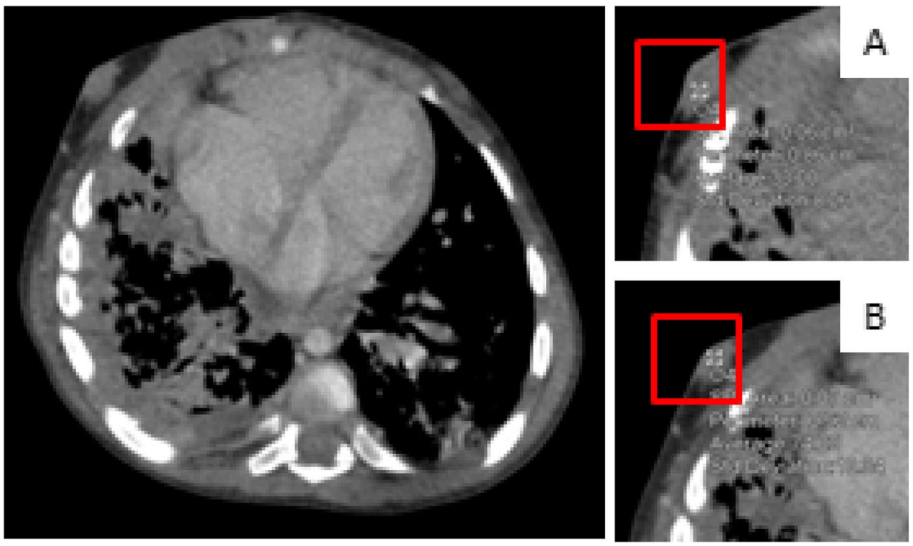

Fig. 2 Subcutaneous nodular lesion. **A** Mediastinal window without contrast injection showing a dense subcutaneous nodule of the anterior chest wall. **B** Enhancement of the subcutaneous nodule after contrast injection

In the last few decades, there has been an increase in the incidence of invasive fungal infections, attributed primarily to the widespread use of immunosuppressive therapies, which has broadened the patient population at risk. In 157 patients with vasculitis, 4.5% developed IPA within 2–13 weeks of immunosuppressive therapy [17]. In our patient, the first chest CT scan that revealed scattered consolidation with a halo sign was performed 4 weeks after the initiation of mycophenolate mofetil. The use of immunosuppressive medicines such as MMF and MTX may induce profound immune suppression with compromised cellular immunity, resulting in the development of opportunistic infections.

A number of studies have suggested a relationship between the pathogenesis of BD and bacterial and/or viral infections and/or a disturbed gut microbiome composition [18–24].

The direct association of BD with fungal infections remains unclear. In a case of invasive pulmonary aspergillosis with secondary skin involvement in an adult with BD, the authors suggested that *Aspergillus* infection triggered BD [14].

Recently, polymorphism in genes encoding innate immunity components, such as Toll-like receptors (TLR) 2, TLR 4, and TLR 9, has been found to increase susceptibility to pulmonary aspergillosis [25]. The polymorphism in TLR 9 genes was also found to be associated with susceptibility to BD in a Japanese population [26]. Considering this literature, the association between BD and pulmonary aspergillosis, which is unusually reported, may reflect the likelihood of a common immunological mechanism involved in the pathogenesis of BD and also promote the occurrence of fungal infections in these patients.

Cutaneous invasive aspergillosis

Disseminated aspergillosis is defined as the involvement of two or more non-contiguous sites. It occurs in 10.5 to 38% of pediatric patients with IA as a result of hematogenous spread, most commonly from a pulmonary portal of entry. In the case of IPA, *Aspergillus* may also be locally invasive and extend from the lung to the pleura and to the chest wall, resulting in costal lysis and ultimately to the skin [27]. Secondary cutaneous invasive aspergillosis (SCIA) is a rare disease, accounting for less than 5% of all disseminated aspergillosis [28]. In a 5-year French multicenter study, 0.7% of 1410 adult patients had SCIA [29]. While this prevalence was reported to be 8% in children (9/111), this suggests that pediatric patients are more likely to be affected than adults [30].

There are no typical clinical features of IA skin lesions, which generally occur at previous wound sites, including intravenous catheter and adhesive tape sites [5]. Findlay et al. [3] described five non-exhaustive secondary aspergillosis patterns: multiple persistent maculo-papules with a tendency to suppurate, vegetate, or necrotize; erythematous eruptions and toxicodermas; confluent granulomata with papules and nodules; a solitary necrotizing dermal plaque; and subcutaneous granuloma or abscess. SCIA is often characterized by multiple scattered lesions. The presence of a single lesion, which is the usual presentation of PCIA, is rarely described in SCIA, making it more difficult to diagnose disseminated forms when the first site observed is the skin [29].

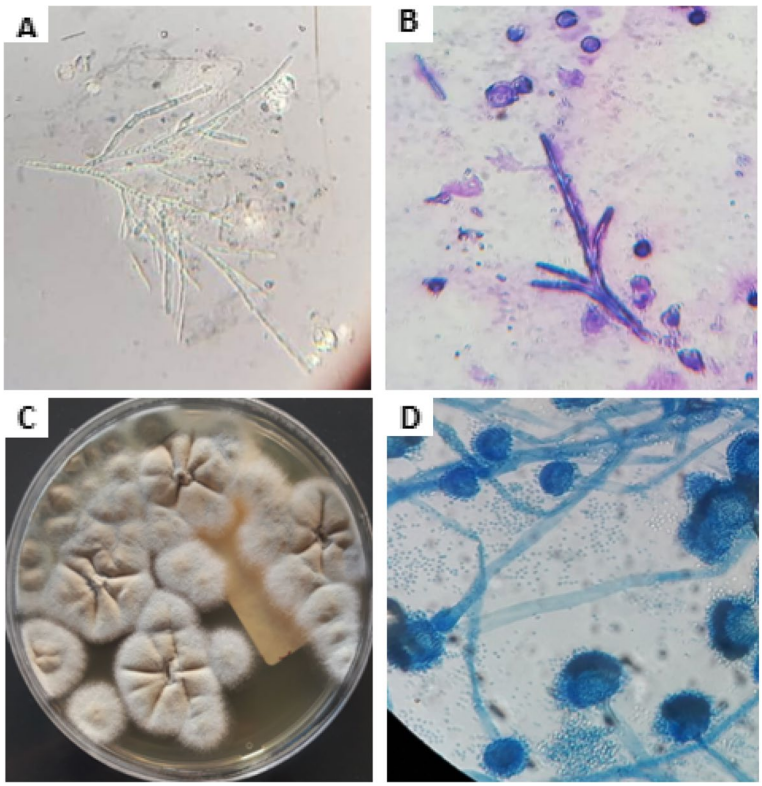

Fig. 3 Direct examination of the subcutaneous collection content, both unstained (A.4: magnification × 400) and after Giemsa staining (B.4: magnification × 1000), shows large, septated, irregular fungal hyphae with acute angle branching. (C.4): On SC, pure, wrinkled, whitish-green-colored colonies developed after 2 days of incubation at 37 °C. (D.4): Lactophenol blue-cotton mount showing conidiophores and uniseriate conidial heads with phialides borne directly on a pyriform vesicle identified as *A. fumigatus*

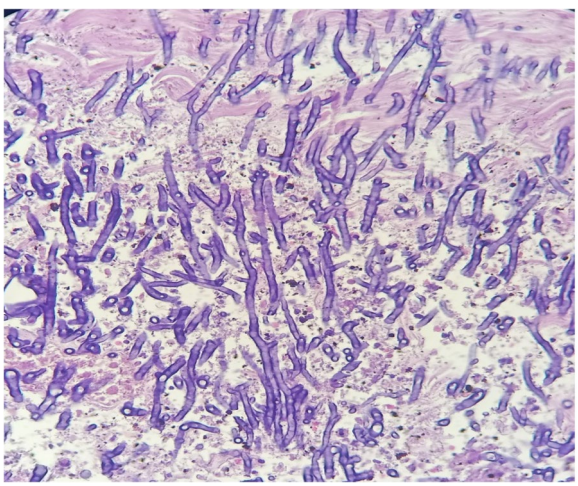

Fig. 4 Histological examination of the debrided pathological tissue with the periodic acid–Schiff technique found septated, dichotomously branched mycelium consistent with *Aspergillus* species

Our patient had no apparent signs of cutaneous injury prior to the appearance of the subcutaneous lesion, which had a pseudotumor morphologic pattern, was pus-filled, and was larger in size (7 cm). According to the grouping of Findlay et al., this aspect matches the last pattern. Cawley et al. [31] similarly reported a subcutaneous *Aspergillus* abscess in a child following *A. fumigatus* spread from an underlying costal periostitis with a probable primary pulmonary focus. We also believe that contiguous diffusion to the skin was most likely to have occurred in our patient, given the extent of pulmonary involvement, pleural dissemination, costal lysis, and the solitary skin lesion.

Our patient initially received conventional antibiotics and was then treated with anti-TB drugs for a presumptive diagnosis of pulmonary tuberculosis given the prolonged fever, altered general state, respiratory symptomatology, the endemic status of tuberculosis in Morocco, and scattered nodular consolidation with a halo sign also encountered in miliary TB but with no significant improvement. The diagnosis of IPA was made at the stage of skin involvement. Cutaneous manifestations can be a helpful feature for early diagnosis

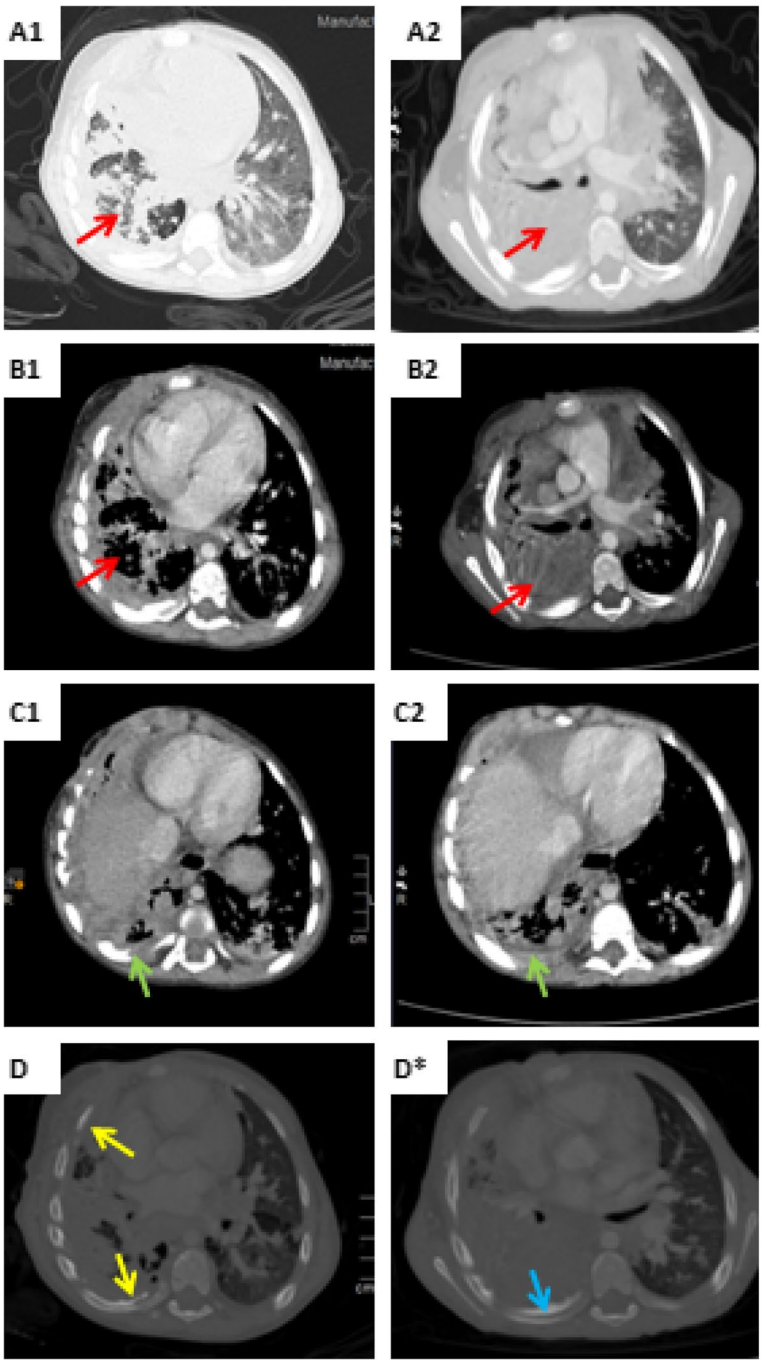

Fig. 5 Chest CT scans three months apart. (A1, A2), (B1, B2), and (C1, C2): enhanced chest CT scans at a 3-month interval in the parenchymal (**A**) and mediastinal (**B**, **C**) windows, showing a reduction in parenchymal consolidation (red arrows) with a decrease in the right lung volume. The disappearance of the small right pleural effusion was also noticed (green arrow). **D**, **D*** Chest CT scan in bone reconstruction showing bone lesions of the anterior and posterior costal arches: lytic bone lesions with cortical thickening (**D**, yellow arrow), periosteal reaction (**D***, blue arrow)

and treatment of disseminated forms, especially when the skin is the first site of dissemination. Once detected, they should prompt the physician to perform a skin biopsy for histological and mycological examination in order to establish a proper diagnosis. It is then essential to determine whether the infection is primary or the

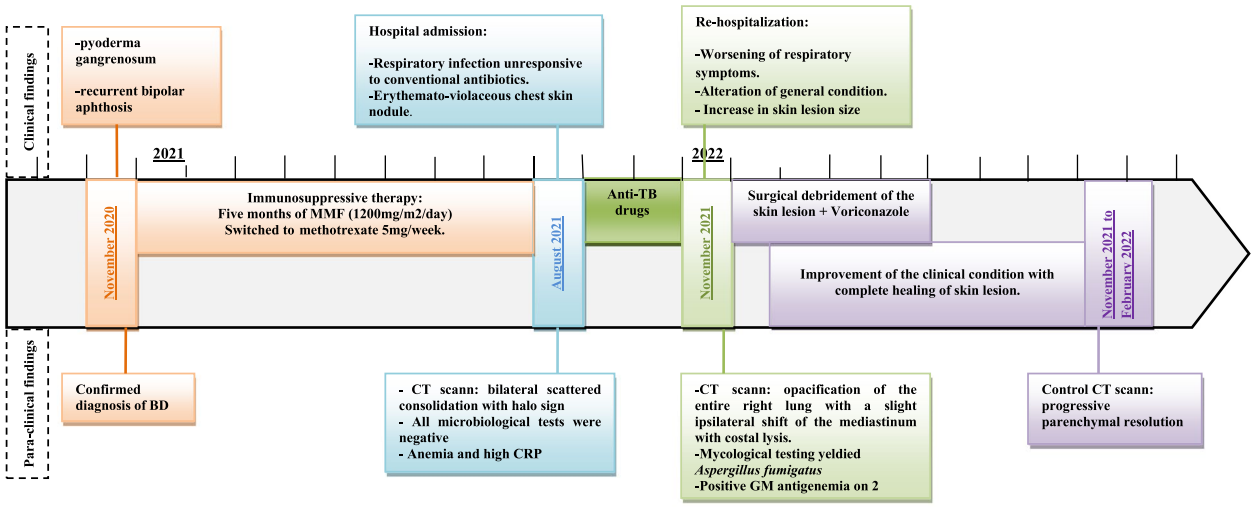

Fig. 6 Case report timeline, made in accordance with CARE guidelines

result of secondary spread from a primary focus such as the lungs, thus improving the outcome [29, 32].

Challenging diagnosis of IPA

Pulmonary involvement is the most common form of IA in immunocompromised patients. As in adults, the main causative agent is *A. fumigatus*, responsible for 53% of pediatric cases [30]. Early diagnosis of IPA remains a real challenge [2].

One of the early radiologic findings during IPA is the "CT halo sign," which refers to a zone of ground-glass attenuation surrounding usually hemmoragic pulmonary nodules but less commonly nonhemmoragic ones. This radiologic finding is nonspecific but highly suggestive of angioinvasive fungal infections, most commonly IPA [33]. A broad range of conditions can also be associated with the halo sign, including malignant diseases (hemorrhagic metastases of angiosarcoma or choriocarcinomas, lymphomas, acute leukemia, Kaposi's sarcoma), bacterial infections (tuberculosis and actinomycosis), viral infections (cytomegalovirus, herpes simplex virus, or varicella-zoster virus), Wegener granulomatosis, and transbronchial biopsy [33, 34].

In IPA, the halo sign reflects the initial phase of angioinvasion by hyphae. It is considered early but ephemeral evidence of IPA even before serologic tests become positive, and it warrants the initiation of systemic antifungal therapy [33]. Through the presented case, we strongly recommend giving greater weight to the halo sign, especially in such a setting of immunocompromised status, considering its precocious appearance at a stage where the antifungals could be fully effective. However, in many cases, a final diagnosis requires a histopathological examination [34].

In a previous review of 39 cases of IA from a Canadian pediatric hospital, mortality was close to 100% (15/16) in patients with a respiratory localization due to delayed diagnosis. Even with invasive pulmonary procedures such as bronchoscopy, the presence of hyphae, which is necessary to establish the diagnosis, can be overlooked [32]. In the same series, positive lung biopsy results were found in only 5 out of 12 patients with radiological involvement, including two at autopsy. This may reflect the increased difficulty of making a pre-mortem diagnosis at a respiratory site, particularly in children [32]. Among 93 severe pediatric pneumonias confirmed on postmortem lung specimens from 119 Bangladeshi children, *Aspergillus* was implicated in 3% of all these pneumonias and 10% of the necrotizing ones [35].

The diagnosis of IA has considerably benefited from the consensus definitions of the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG) for invasive fungal infections (IFIs). These were classified according to the level of certainty for the disease as proven, probable, and possible IFIs, based on three elements: host factors, clinical features, and mycological evidence. The classification criteria were last updated in 2016 by 10 expert groups [36].

According to the most recent EORTC/MSG definitions [36], our patient fulfilled the criteria for probable IPA, which requires the presence of at least one host factor, one clinical feature, and one mycological evidence, which in our case were, respectively, prolonged use of immunosuppressants during the past 90 days, pulmonary

involvement (initial halo sign and pulmonary consolidation), and a positive serum galactomannan antigen > 1. The proven cutaneous aspergillosis on histological biopsies and mycological results in our patient supported the diagnosis of IPA. Nowadays, the category of proven IFIs, which is defined by histological evidence of tissue invasion on biopsy specimens or needle aspiration of tissue content, can apply to any patient, regardless of age or immunocompromised status [36, 37]. In addition, remission of clinical symptoms and progressive resolution of radiological signs on voriconazole, despite the absence of myco-pathological evidence of pulmonary infection, affirmed the diagnostic hypothesis.

Relevance of Galactomannan antigenemia

In recent years, galactomannan (GM) antigenemia has been incorporated into the EORTC/MSG diagnostic criteria for IA. The GM is a major polysaccharide component of the cell wall of *Aspergillus* spp., released during tissue invasion. The detection of circulating GM antigen is commonly performed by the double sandwich enzyme-linked immunosorbent assay method (Platelia^{TM} Aspergillus antigen, Bio-Rad), which allows the detection and quantification of GM antigenemia and also the follow-up of its kinetics [37–39]. The sensitivity and specificity of the GM antigen test are variable depending on the patient population and the specified cutoff level, reaching 84% and 88%, respectively, in children. However, the use of certain antibiotics such as piperacillin-tazobactam, infusion of electrolytes, and the presence of other fungi such as *Fusarium* spp., *Histoplasma capsulatum*, and *Penicillium* spp. may cause false positive results, which have to be cautiously interpreted [27, 40]. This assay complements the existing modalities for the early diagnosis of IA. The expression of GM antigen may even precede clinical, microbiological, or radiological signs of the disease [41]. A positive GM test in at-risk patients with consistent clinical and radiographic findings should be considered highly indicative of IA. In our case, the positivity of the GM antigenemia enabled us, besides the positivity of the cutaneous mycological examinations and the pulmonary imaging evidence, to affirm the diagnosis of disseminated IA. The GM antigen has also been shown to correlate with clinical diagnosis and outcome, i.e., responsiveness to antifungal treatment and survival [38, 39].

Management of IA

A variety of antifungals are effective against *Aspergillus* species, notably polyenes such as amphotericin B, triazoles such as voriconazole, and echinocandins. Three expert groups, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the European Conference on Infection in Leukaemia (ECIL), and the Infectious Diseases Society of America (IDSA), recommend the use of voriconazole as the preferred first-line agent to treat IA in pediatric patients older than 2 years [42]. The European Medicines Agency has approved the use of an intravenous dose of 7 mg/kg of voriconazole in this category of patients. This medicine acts as a fungicide by inhibiting the buildup of ergosterol, which is a key component of the fungal cell membrane. This is effectively destroyed, and the fungus is prevented from spreading. In an immunocompromised host, successful management of the disease is not always achieved. A favorable outcome is conditioned by an early diagnosis, prompt and intensive antifungal therapy, resolution of neutropenia, and management of the immunodeficiency state. The surgical debridement is performed on an individual basis, utilizing a multidisciplinary approach [32]. In our case, a combination of surgical excision and treatment with voriconazole provided a successful outcome.

Conclusions

The prognosis of IA is directly determined by early diagnosis and appropriate management. Only close collaboration and communication among clinicians, radiologists, pathologists, and mycologists can ensure a higher quality of medical service and thus mitigate the prognosis of this devastating fungal infection. This clinical case underlines the importance of considering cutaneous aspergillosis in the context of immunocompromised patients presenting with a skin lesion evolving into necrosis and refractory to broad antibiotic coverage and standard local care. Particular attention must be paid to this type of lesion, which can represent only the tip of the iceberg and be the mode of the revelation of a deep organ invasion.

Abbreviations

IA	Invasive aspergillosis
IPA	Invasive pulmonary aspergillosis
BD	Behçet disease
A.	*Aspergillus*
CIA	Cutaneous invasive aspergillosis
MMF	Mycophenolate mofetil
MTX	Methotrexate
TB	Tuberculosis
BC	Brachial circumference
CC	Cranial circumference
SC	Sabouraud chloramphenicol
TLR	Toll-like receptors
SCIA	Secondary cutaneous invasive aspergillosis
EORTC/MSG	European Organization for Research and Treatment of Cancer and the Mycoses Study Group
IFIs	Invasive fungal infections
GM	Galactomannan
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ECIL	European Conference on Infection in Leukaemia
IDSA	Infectious Diseases Society of America

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Authors' contributions
SN conducted the literature review, drafted the manuscript, and guided the mycological diagnostic procedures. MEM, HN, RE, AB, and IAS wrote part of the case report and managed the patient. YZ, DB, and HJ interpreted the imaging data and provided CT images and descriptions. MOS was the pediatric surgeon in charge of the patient. MH and MAA RH performed the histological examination of the surgical material. AEH guided the mycological diagnostic procedures and critically revised the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials
Available upon request.

Declarations

Ethics approval and consent to participate
Written informed consent to participate was obtained from the parent. This publication fulfills the ethical requirements of the Declaration of Helsinki.

Consent for publication
Written consent for publication was obtained from the parent.

Competing interests
The authors declare that they have no competing interests.

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References

1. Enoch DA, Yang H, Aliyu SH, Micallef C. The changing epidemiology of invasive fungal infections. Methods Mol Biol. 2017;1508:17–65. https://doi.org/10.1007/978-1-4939-6515-1_2.
2. von Lilienfeld-Toal M, Wagener J, Einsele H, Cornely OA, Kurzai O. Invasive fungal infection—new treatments to meet new challenges. Dtsch Arztebl Int. 2019;116:271–8. https://doi.org/10.3238/arztebl.2019.0271.
3. Findlay GH, Roux HF, Simson IW. Skin manifestations in disseminated aspergillosis. Br J Dermatol. 1971;85(suppl. 7):94–7.
4. van Burik JA, Colven R, Spach DH. Cutaneous aspergillosis. J Clin Microbiol. 1998;36(11):3115–21. https://doi.org/10.1128/JCM.36.11.3115-3121.1998.
5. Fonda-Pascual P, Fernández-González P, Moreno-Arrones OM, Miguel-Gómez L. Pustular secondary cutaneous Aspergillosis in an immunosuppressed patient. Actas Dermosifiliogr (Engl Ed). 2018;109(3):287–90. https://doi.org/10.1016/j.ad.2017.07.004.
6. Kim CW, Seo JS, Kim MK, Jun EJ, Choi JC, Choi BW. Secondary cutaneous aspergillosis disseminated from the lungs of a patient with asthma on 1 month steroid treatment. Diagn Microbiol Infect Dis. 2010;66(1):104–7. https://doi.org/10.1016/j.diagmicrobio.2009.05.01.
7. Galimberti R, Kowalczuk A, Hidalgo Parra I, Gonzalez Ramos M, Flores V. Cutaneous aspergillosis: a report of six cases. Br J Dermatol. 1998;139(3):522–6. https://doi.org/10.1046/j.1365-2133.1998.02424.x.
8. Nenoff P, Kliem C, Mittag M, Horn LC, Niederwieser D, Haustein UF. Secondary cutaneous aspergillosis due to Aspergillus flavus in an acute myeloid leukaemia patient following stem cell transplantation. Eur J Dermatol. 2002;12(1):93–8 PMID: 11809609.
9. Ozcan D, Güleç AT, Haberal M. Multiple subcutaneous nodules leading to the diagnosis of pulmonary aspergillosis in a renal transplant recipient. Clin Transpl. 2008;22(1):120–3. https://doi.org/10.1111/j.1399-0012.2007.00740.x.
10. Schimmelpfennig C, Naumann R, Zuberbier T, Ordemann R, Baurmann H, Beyer J, et al. Skin involvement as the first manifestation of systemic aspergillosis in patients after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2001;27(7):753–5. https://doi.org/10.1038/sj.bmt.1702835.
11. Helm TN, Mazanec D. Disseminated aspergillosis presenting as a skin abscess. Cleve Clin J Med. 1990;57(1):92–4. https://doi.org/10.3949/ccjm.57.1.92.
12. Vedder JS, Schorr WF. Primary disseminated pulmonary aspergillosis with metastatic skin nodules: successful treatment with inhalation nystatin therapy. JAMA. 1969;209(8):1191–5. https://doi.org/10.1001/jama.1969.03160210023006.
13. Handa T, Nakatsue T, Baba M, Takada T, Nakata K, Ishii H. Clinical features of three cases with pulmonary alveolar proteinosis secondary to myelodysplastic syndrome developed during the course of Behçet's disease. Respir Investig. 2014;52(1):75–9. https://doi.org/10.1016/j.resinv.2013.05.005.
14. Sun F, Cao H, Wang F, Cao G. Behçet's disease with invasive pulmonary aspergillosis and Aspergillus auriculatus infection: a case report. Medicine (Baltimore). 2020;99(6):e18938. https://doi.org/10.1097/MD.0000000000018938.
15. Yildiz M, Haslak F, Adrovic A, Sahin S, Koker O, Barut K, et al. Pediatric Behçet's disease. Front Med (Lausanne). 2021;8:627192. https://doi.org/10.3389/fmed.2021.627192.
16. Costagliola G, Cappelli S, Consolini R. Behçet's disease in children: diagnostic and management challenges. Ther Clin Risk Manag. 2020;16:495–507Published 2020 Jun 11. https://doi.org/10.2147/TCRM.S232660.
17. Su T, Li HC, Chen M, Gao L, Zhou FD, Wang RG, et al. Invasive pulmonary aspergillosis in patients with antineutrophil cytoplasmic antibody associated vasculitis. J Clin Rheumatol. 2009;15(8):380–2. https://doi.org/10.1097/RHU.0b013e31819e67b1.
18. Sciascia S, Arbrile M, Trunfio M, Calcagno A, Radin M, Roccatello D, et al. The role of bacteria and viruses in Behçet syndrome: should we move towards new paradigms? Autoimmun Rev. 2022:103237. https://doi.org/10.1016/j.autrev.2022.103237.
19. Tong B, Liu X, Xiao J, Su G. Immunopathogenesis of Behcet's disease. Front Immunol. 2019;10:665. https://doi.org/10.3389/fimmu.2019.00665.
20. Ye Z, Zhang N, Wu C, Zhang X, Wang Q, Huang X, et al. A metagenomic study of the gut microbiome in Behcet's disease. Microbiome. 2018;6(1):135. https://doi.org/10.1186/s40168-018-0520-6.
21. Keseroglu HO, Gönül M. Infectious agents in etiopathogenesis of Behçet's disease. In: Gonul M, Kartal SP, editors. Behcet's diseaseIntechOpen; 2017. https://doi.org/10.5772/intechopen.68776.
22. Galeone M, Colucci R, D'Erme AM, Moretti S, Lotti T. Potential infectious etiology of Behçet's disease. Pathol Res Int. 2012;2012:595380. https://doi.org/10.1155/2012/595380.
23. Mumcu G, Inanc N, Yavuz S, Direskeneli H. The role of infectious agents in the pathogenesis, clinical manifestations and treatment strategies in Behçet's disease. Clin Exp Rheumatol. 2007;25(4 Suppl 45):S27–33.
24. Kaneko F, Tojo M, Sato M, Isogai E. The role of infectious agents in the pathogenesis of Behçet's disease. In: Zouboulis CC, editor. Adamantiades-Behçet's disease. Advances in experimental medicine and biology, vol 528. Boston: Springer; 2004. https://doi.org/10.1007/0-306-48382-3_35.
25. Carvalho A, Pasqualotto AC, Pitzurra L, Romani L, Denning DW, Rodrigues F. Polymorphisms in toll-like receptor genes and susceptibility to pulmonary aspergillosis. J Infect Dis. 2008;197(4):618–21. https://doi.org/10.1086/526500.
26. Sakamoto N, Sekine H, Kobayashi H, Sato Y, Ohira H. Association of the toll-like receptor 9 gene polymorphisms with Behcet's disease in a Japanese population. Fukushima J Med Sci. 2012;58(2):127–35. https://doi.org/10.5387/fms.58.127.
27. Wattier RL, Ramirez-Avila L. Pediatric invasive Aspergillosis. J Fungi (Basel). 2016;2(2):19Published 2016 Jun 13. https://doi.org/10.3390/jof2020019.
28. Chakrabarti A, Chatterjee SS, Das A, Shivaprakash MR. Invasive aspergillosis in developing countries. Med Mycol. 2011;49(Suppl 1):S35–47. https://doi.org/10.3109/13693786.2010.505206.
29. Bernardeschi C, Foulet F, Ingen-Housz-Oro S, Ortonne N, Sitbon K, Quereux G, et al. Cutaneous invasive aspergillosis: retrospective multicenter study of the French invasive-aspergillosis registry and literature review. Medicine. 2015;94(26):e1018. https://doi.org/10.1097/MD.0000000000001018.
30. Burgos A, Zaoutis TE, Dvorak CC, Hoffman JA, Knapp KM, Nania JJ, et al. Pediatric invasive aspergillosis: a multicenter retrospective analysis of 139 contemporary cases. Pediatrics. 2008;121(5):e1286–94. https://doi.org/10.1542/peds.2007-2117.

31. Cawley ep. Aspergillosis and the Aspergilli: report of a unique case of the disease. Arch Intern Med (Chic). 1947;80(4):423–34. https://doi.org/10.1001/archinte.1947.00220160002001.
32. Walmsley S, Devi S, King S, Schneider R, Richardson S, Ford-Jones L. Invasive Aspergillus infections in a pediatric hospital: a ten-year review. Pediatr Infect Dis J. 1993;12(8):673–82. https://doi.org/10.1097/00006454-199308000-00009.
33. Pinto PS, The CT. Halo sign. Radiology. 2004;230(1):109–10. https://doi.org/10.1148/radiol.2301020649.
34. Marchiori E, Hochhegger B, Zanetti G. The halo sign. J Bras Pneumol. 2017;43(1):4. https://doi.org/10.1590/S1806-37562016000000354.
35. Tomashefski JF Jr, Butler T, Islam M. Histopathology and etiology of childhood pneumonia: an autopsy study of 93 patients in Bangladesh. Pathology. 1989;21(2):71–8. https://doi.org/10.3109/00313028909059538.
36. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71(6):1367–76. https://doi.org/10.1093/cid/ciz1008.
37. Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis. 2002;34(1):7–14. https://doi.org/10.1086/323335.
38. Mercier T, Guldentops E, Lagrou K, Maertens J. Galactomannan, a surrogate marker for outcome in invasive Aspergillosis: finally coming of age. Front Microbiol. 2018;9:661. https://doi.org/10.3389/fmicb.2018.00661.
39. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. Lancet Infect Dis. 2005;5(10):609–22. https://doi.org/10.1016/S1473-3099(05)70238-3.
40. Nucci M, Carlesse F, Cappellano P, Varon AG, Seber A, Garnica M, et al. Earlier diagnosis of invasive fusariosis with Aspergillus serum galactomannan testing. PLoS One. 2014;9(1):e87784. https://doi.org/10.1371/journal.pone.0087784.
41. Hayden R, Pounds S, Knapp K, et al. Galactomannan antigenemia in pediatric oncology patients with invasive aspergillosis. Pediatr Infect Dis J. 2008;27(9):815–9. https://doi.org/10.1097/INF.0b013e31817197ab.
42. Apsemidou A, Petridis N, Vyzantiadis TA, Tragiannidis A. Invasive Aspergillosis in children: update on current guidelines. Mediterranean J Hematol Infect Dis. 2018;10(1):e2018048. https://doi.org/10.4084/MJHID.2018.

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