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Lichtheimia Infection in a Lymphoma Patient: Case Report and a Brief Review of the Available Diagnostic Tools

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Abstract We describe the case of a patient with a T-lymphoblastic lymphoma whose disseminated mucormycosis was diagnosed with delay, and we address the diagnostic and therapeutic decision-making process and review the diagnostic workup of patients with potential IFD. The diagnosis was delayed despite a suggestive radiological presentation of the patient's pulmonary lesion. The uncommon risk profile (T-lymphoblastic lymphoma, short neutropenic phases) wrongly led to a low level of suspicion. The diagnosis was also hampered by the lack of indirect markers for infections caused by *Mucorales*, the low sensitivity of both fungal culture and panfungal PCR, and the limited availability of species-specific PCR. A high level of suspicion of IFD is needed, and aggressive diagnostic procedures should be promptly initiated even in apparently low-risk patients with uncommon presentations. The extent of the analytical workup should be decided on a case-by-case base. Diagnostic tests such as the galactomannan and β-D-glucan test and/or PCR on biological material followed by sequencing should be chosen according to their availability and after evaluation of their specificity and sensitivity. In high-risk patients, preemptive therapy with a broad-spectrum mould-active antifungal agent should be started before definitive diagnostic findings become available.

Keywords Diagnosis · Emerging risk groups · Molecular biology · Mucormycosis · *Mucorales*

Introduction

The epidemiology of invasive fungal infections is changing over time. During the 1990s, *Candida* species were the most common agents of invasive

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fungal infections [1] and in most settings they still are [2]. Infections caused by moulds of the genus *Aspergillus*, on the other hand, are becoming increasingly common, in particular among patients with haematological malignancies [3, 4]; probably also as a consequence of the prolonged prophylactic and therapeutic use of broad-spectrum antifungals such as voriconazole, itraconazole and caspofungin, mucormycoses are emerging as often fatal diseases in immunocompromised patients [5].

Overall, the diagnosis of fungal disease (IFD) can be challenging, even after the introduction of tools such as high-resolution chest computed tomography (CT) and immunological [Galactomannan (GM) and β-D-Glucan (BDG) assays] or molecular biology (PCR) techniques [6] that contribute to a comparatively reliable diagnosis in the absence of culture data. IFD has often been, and may still be, identified unambiguously only by autopsy [7]. Although *antemortem* diagnosis of IFD has improved [8], a proportion of IFD still remains undetected. Unfortunately, the marked reduction in autopsies over time [8] hinders a reliable estimate of its real prevalence in high-risk patients.

Concomitantly with the changing spectrum of pathogens, the range of patients at risk of IFD is also expanding. In addition to the commonly identified at-risk groups such as patients with haematological malignancies (mainly acute myeloid leukaemia and recipients of allogeneic HSCT) and solid organ transplant recipients, patients treated with corticosteroids for exacerbated COPD or with multiple myeloma are increasingly at risk for IFD [9–11].

Guidelines for the diagnosis of fungal infections in high-risk patients have been published [12–14], but the emergence of new at-risk groups as well as the differential availability of diagnostic tools in individual institutions leave a number of open questions that are reflected by variations in the diagnostic procedures used in different centres. Maertens et al. [15, 16] recommend that the diagnostic procedure and the therapeutic approach be chosen on the basis of the perceived risk, thus emphasising the importance of clinical judgement in the diagnostic and therapeutic approach.

Here, we describe an unexpected case of mucormycosis in a patient with T-lymphoblastic lymphoma. Using this real-life case as an example, we address general and site-specific issues linked to the diagnostic and therapeutic decision-making process in at-risk patients and review the diagnostic workup of patients with potential IFD, outlining the pros and cons of the most common diagnostic and therapeutic options in the daily routine of the fight against invasive mycoses.

Case Report: A Patient with T-Lymphoblastic Lymphoma

A 46-year-old female patient hospitalized at the Berne University Hospital with a mediastinal mass was diagnosed with T-lymphoblastic lymphoma. Pre-induction with corticosteroids reduced the tumour mass drastically, and the first two cycles of a modified hyper CVAD regimen (cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and high-dose cytarabine) induced only a few days of neutropenia and were well tolerated. No antifungal prophylaxis was given.

Before the third cycle of chemotherapy, a staging PET CT showed a 4-cm ring-shaped lesion with central ground glass attenuation in the right lower lobe of the lung. The patient was afebrile and mildly pancytopenic. GM determination and cultures from bronchoalveolar lavage (BAL) fluid were negative, as was the serum GM test.

Two weeks after the start of the third cycle of chemotherapy, the patient became febrile and complained of bilateral flank pain and left homonymous hemianopia. The CRP level was 340 mg/L, and the renal function was normal. CT-guided percutaneous lung biopsy of the solitary lesion in the right lower lobe revealed fragments of angioinvasive fungal hyphae and widespread necrosis. Cultures yielded no growth, and the serum GM test was negative (for a discussion, see [17]). DNA was extracted from the biopsy according to an established protocol [18]. A panfungal real-time PCR amplifying the ITS1 region of the rRNA [19] and a semi-nested PCR targeting the mitochondrial DNA of *A. fumigatus* [20] gave negative results. Biopsy of the largely necrotic right kidney showed necrotic tissue and angioinvasive hyphae compatible with mucormycosis. An MRI scan identified a large haemorrhagic lesion in the right occipital pole. GM was not detected in the cerebrospinal fluid, and a panfungal PCR carried out according to the methods described above was negative.

Empiric treatment for presumed disseminated mucormycosis was initiated with liposomal amphotericin

B (L-AmB) at the dosage recommended by the ECIL guidelines [21, 22].

After 24 days of L-AmB treatment, the pulmonary lesion was resected and cultures grew *Lichtheimia corymbifera*. Species identity was confirmed by sequencing of the amplified ITS1 region of rRNA in a reference laboratory in Spain [23]. The results of the antifungal susceptibility testing (*E* test) showed MICs for amphothericin B of 0.75 mg/L, for itraconazole of 8.0 mg/L, for voriconazole of 32 mg/L, and for posaconazole of 0.75 mg/L.

The same mould was later detected by a panfungal PCR [19] performed on the resected right kidney in the Berne laboratories. Many dichotomously branching hyphae were seen in the necrotic cerebral lesion, but cultures were negative at the time of resection after 71 days of L-AmB treatment. When the polyene was stopped 79 days after treatment start, the patient was given posaconazole (400 mg bid) for 6 months. Eighteen months after the end of antifungal treatment, she was still free of any mould infection.

In summary, diagnosis of this patient's disseminated mucormycosis was delayed despite the suggestive radiological presentation ('reverse halo sign') of her pulmonary lesion [24]. The long turn-around time for the *Mucorales*-specific PCR (4 weeks), as a consequence of the need to involve an external laboratory, the limited availability of *Mucorales*-specific PCRs in our laboratory, as well as the uncommon risk profile (T-lymphoblastic lymphoma, short neutropenic phases) of this patient led to a low level of suspicion (see also [25, 26]). The lack of indirect markers for infections caused by *Mucorales* and the low sensitivity of fungal culture contributed to the challenges of this diagnosis. The favourable outcome of this case of disseminated mucormycosis affecting the lung, both kidneys, and the brain may be a consequence of the relatively low virulence of *Lichtheimia corymbifera* and its sensitivity to the empiric treatment, the rapid recovery from neutropenia, the aggressive surgery, and the high-dose antifungal therapy used.

Discussion

The epidemiology of IFD has changed substantially in recent years, and rare fungal pathogens are continuously emerging [27]. IFD-related mortality is high and prognosis is poor, unless IFD is diagnosed early and treated promptly. This case exemplifies the need to critically appraise the risk profile of apparently low-risk patients such as those receiving high-intensity treatment for lymphoid neoplasia. In addition, it is crucial to optimize the diagnostic tools available in a clinical centre, by carefully reviewing the methods used in the diagnostic laboratory and the skills and knowledge of the people involved in the diagnostic workup.

Clinical signs and symptoms related to IFD are unspecific and need to be followed up by appropriate diagnostic procedures [14] as part of an integrated care pathway [28]. In most cases, however, we believe that empirical therapy should be started early even if findings are negative. Other authors (e.g., [29]) have come to the conclusion that empiric and preemptive treatments are equally effective in the presence of positive diagnostic findings.

CT scan findings have a high positive predictive value for IFD when promptly carried out on patients with febrile neutropenia at risk for fungal infections, and almost always they precede results of other diagnostic tests. They usually differ, however, across risk groups [7, 30]. The halo sign on chest CT is associated with an early, haemorrhagic stage of invasive aspergillosis (IA) and provides evidence of an angioinvasive infection. In a neutropenic patient, any pulmonary nodules in the upper lobes should prompt suspicion for fungal disease. Radiologic findings at repeat imaging in patients with early diagnosis of IA evolve from micronodules to partly solid or ground glass nodules, pleural effusion and consolidations to macronodules with no halo sign, cavities and nodules with air crescent signs [31]. The reversed halo sign ("atoll sign") may be indicative of pulmonary mucormycosis, particularly in neutropenic patients, but has been described for infections due to many different pathogens in other settings [24, 32].

Histological and/or cultural evidence from tissue biopsies or resection material are still the gold standard for a diagnosis of proven IFD [14]. Direct microscopy of biopsies originating from relevant material and histopathology should all be used in the mycological diagnostic workup, taking into account the limitation of each method in selected patient collectives [33–35].

Serology (GM test, β-D-glucan test) as well as cultures from relevant tissues should also be an

integral part of the diagnostic workup. The utility of the GM test for the detection of IA has been repeatedly demonstrated (e.g., [36]). A recent report has shown that a combined GM/BDG test detected all 7 biopsy-proven *Aspergillus* infections, but not a *Fusarium* fungaemia [37]. The benefit of the BDG test alone, however, is limited [38] and repeated measurements are recommended.

PCR followed by sequencing can be an extremely powerful and specific diagnostic tool when applied to appropriate clinical samples such as BAL or biopsies. PCR sensitivity and specificity also depend on the targeted sequences: the target of a panfungal PCR can be too long for formalin-fixed biopsies and primers might interact with human DNA, thus reducing sensitivity in contrast to nested PCRs targeting *Mucorales*-specific sequences [39]. Despite the inherent methodological difficulties (reviewed in [17]), standardization of PCR-based diagnosis of invasive fungal infections is advancing [40]. PCR assays are significantly more sensitive than culture, but results need to be put in context: detection of fungal DNA from BAL or paraffin-embedded tissue without radiological or histopathological signs of fungal infection does not necessarily mean IFD. The accidental presence of colonizers or contaminants must always be considered.

The need for invasive diagnostics is somewhat controversial. Various studies [41, 42], however, have shown that CT-guided percutaneous lung biopsy provides good diagnostic material and thus contributes to better therapeutic decisions and to improve the outcome. Some authors [41, 43–45] reported only minor adverse events related to invasive procedures (which may lead to fatal pulmonary haemorrhage and infection). To support safe patient handling practices, however, CT-driven biopsies should be taken only from patients in stabilized clinical conditions.

Conclusions

As exemplified in the presented case, it is imperative to maintain a high level of suspicion of IFD even in apparently low-risk patients with uncommon presentations. Aggressive diagnostic procedures should be promptly initiated. Diagnostic tests such as the GM, BDG test and/or PCR on biological material collected by bronchoscopy or more invasive procedures (CT-guided biopsies) should be chosen according to their availability, after careful evaluation of their specificity and sensitivity and after evaluation of the patient's status. In any case, empirical therapy with a broad-spectrum mould-active antifungal agent should be started in high-risk patients before definitive diagnostic findings become available, possibly already during the analytical workup.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflicts of interest to declare.

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