Aspergillosis in immunocompromised patients with hematological malignancies

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Summary

Aspergillosis, which is saprophytic in nature, is known to cause massive destruction of paranasal sinuses in immunocompromised hosts, but in immunocompetent individuals invasive aspergillosis is rare. Diagnosis is posed from history, physical examination including anterior and posterior rhinoscopy, endoscopy of the nose and paranasal sinuses, radiological findings (CT and/or MRI), fungus cultures and histopathological examination. Non-specific presenting symptoms provide time for infection to extent from sinuses to vital surroundings such as bony, vascular and central nervous system structures, thereby increasing morbidity and mortality. Mass lesions involving the sinuses are initially misdiagnosed as tumors, inflammatory pseudotumors or pituitary adenomas. Therefore, diagnosis should be always confirmed by histopathology. Aspergillus sinusitis is a potentially fatal complication of immunosuppression or of chemotherapy-induced leucopenia. Concerning patients with hematologic malignancies, it seems that its incidence is progressively increased. A combination of early diagnosis and application of specific antifungals provides the perfect management and prognosis in the corresponding patients. In the current special review, we present new data regarding the infection in patients with hematologic malignancies.

Key words: aspergillosis, hematologic malignancy, infection

Introduction

Approximately 100,000 species of fungi have been recognized, but only about 20 are pathogenic to humans. However, fungi are a common cause of infection in clinical practice, ranking closely behind viruses and bacteria. Fungal infections are frequently opportunistic, i.e. they occur in immunocompromised individuals. Diabetic ketoacidosis, lymphoma and leukemia are the immunodeficiency states that are most frequently associated with opportunistic fungal infection. Further predisposing disorders include corticosteroid treatment, radiation therapy, chemotherapy and the acquired immune deficiency syndrome. Aspergillosis (A. fumigatus and A. flavus), Mucormycosis and Candidiasis are the most common forms of opportunistic fungal infections. De Shazo et al. and Hora classified fungal rhinosinusitis into invasive and noninvasive forms, based on histopathology [1,2]. This classification depends on the presence of the fungal agent in the mucous membrane, bone or vessels. Noninvasive infections include fungus ball and allergic fungal rhinosinusitis (AFR) [3-5]. Invasive fungal infections include acute (or fulminant) and chronic (or indolent) fungal rhinosinusitis.
In acute invasive fungal rhinosinusitis, patients are usually immunocompromised and frequently the prognosis is poor [6]. On the contrary, in an immunocompetent host chronic invasive aspergillosis is rare. It is characterized by a prolonged clinical course with slow disease progression across mucosa and bone or other structures such as orbit and brain [7]. Concerning patients with hematologic malignancies, it seems that its incidence is progressively increased as it happens with invasive pulmonary aspergillosis. A combination of early diagnosis and application of specific antifungal provides the perfect management and prognosis in the corresponding patients [8]. In the current special review, we present new data regarding the infection in patients with hematologic malignancies.

**Aspergillosis: diagnosis and treatment in haematological malignancy patients**

Aspergillus species are the leading cause of fungal sinusitis throughout the world. Aspergillosis, which is saprophytic in nature, is known to cause massive destruction of paranasal sinuses in immunocompromised hosts, but in immunocompetent individuals invasive aspergillosis is rare. Clinical suspicion should arise whenever a patient with chronic maxillary sinusitis does not respond to the usual conservative therapy [9]. Diagnosis is posed from history, physical examination including anterior and posterior rhinoscopy, endoscopy of the nose and paranasal sinuses, radiological findings (CT and/or MRI), fungus cultures and histopathological examination. In most cases diagnosis is delayed. Non-specific presenting symptoms are indistinguishable from those of bacterial, viral or allergic sinusitis. This fact provides time for infection to extent from sinuses to vital surroundings such as bony, vascular and central nervous system structures, thereby increasing morbidity and mortality. Often these cases present with headache, retro-orbital pain, diplopia, exophthalmos and blindness. The anatomic location and extent of infection plays an important role to outcome. Cases with isolated sphenoid sinus involvement are very rare, because of the decreased nasal airflow in this area [10]. These lesions are potentially lethal [11]. Likewise, the non-specific findings on CT scan frequently confound the correct diagnosis; mass lesions involving the sinuses are initially misdiagnosed as tumors, inflammatory pseudotumors or pituitary adenomas [12]. Extension to soft tissue and bone lyses on CT scan are suggestive of invasive pathology, but such abnormalities may also be observed in the noninvasive form of fungal sinusitis (fungus ball and AFR). MRI seems to be more sensitive in evaluating orbital or brain extensions. Finally, both diagnostic methods are recommended to estimate bone and soft tissue extensions in such cases. In addition, the clinico-radiological features are not specific to distinguish aspergillosis from other sino-orbital pathologies. Therefore, diagnosis should be always confirmed by histopathology. Acute fulminant, granulomatous and chronic invasive are the three forms of invasive fungal infections. In the granulomatous form of sinusitis, hyphae are contained within a mass of fibro-connective tissue with inflammatory cells. The affected patients are of younger age. Infections slowly invade surrounding structures. Intracranial extension is common by the time of diagnosis (60%). Overall mortality is 20%. The granulomatous form is caused by A. flavus in 90% of cases [13]. In the non-granulomatous chronic invasive form of sinusitis, hyphae invade into the blood vessels and tissues. They are not found within the inflammatory mass. Patients are older than those with the granulomatous form. Infection invades surrounding structures relatively early and all patients exhibit intracranial extension at the time of diagnosis. The mortality rate is 80%. The invasive form is caused by A. fumigatus in almost 100% of the cases. The diagnosis is posed from large and deep biopsy specimens from mucosa, submucosa and bone, which are necessary to establish the presence of hyphae within the tissue. The pathologist’s attention must be focused on this point because hyphae often are present in small numbers within the submucosa or bone.

Concerning disease management, it is difficult to define the optimal treatment for invasive sinus aspergillosis. Aggressive surgical resection aimed at complete extirpation of infecting organisms is the cornerstone of effective therapy. Partial resections through the intranasal route, staged or subtotal resections, repeated debridement and drainage, approaches frequently advocated in the past, result in unacceptably high failure and mortality rates. Refined surgical techniques over the past decade have allowed more radical approaches [14]. A subset of patients with invasive sinus aspergillosis, can be cured with radical surgical resection. Frequently, due to the anatomic localization, radical resection is technically difficult to achieve. Furthermore, complete resection intra-operatively cannot always be confirmed. These along with the high relapse rates make antifungal treatment a very valuable adjunctive therapy. The literature is too limited to compare the benefits of antifungal agents. The greatest experience is with amphotericin B. Newer agents such as liposomal preparations of amphotericin B and intraconazole are effective in some cases, but treatment failure has also been
reported. Combinations of amphotericin B with either fluconazole or itraconazole are controversial. Following an initial course of amphotericin B, chronic antifungal therapy might be considered. Itraconazole with its potent in vitro activity against aspergillus, oral administration, and low toxicity profile has made this strategy feasible. Of particular note, chronic itraconazole therapy results in stable disease in patients with incomplete surgical resection of intracranial infection [15]. Controlled trials are lacking and they are principally not feasible, due to the rareness of the disease. Therefore the duration of treatment is totally empirically guided by clinical and radiological evaluation. Chronic administration of antifungal agents is nephrotoxic and hepatotoxic, therefore a tight monitoring should be done. Follow up includes nasal endoscopy and radiological examination with CT scan or MRI or both [16]. A study group analyzed five cases of invasive fungal sinusitis and proposed a combined pharmacological and surgical approach with post-operative local therapy based on a new ethmoidal drainage system which seems to support radical antifungal sinus treatment [17]. Similarly, significant metanlyses of systematic clinical studies have shown that antifungal prophylaxis was correlated to a lower rate of invasive aspergilosis in patients with haematological malignancies. Despite the progress in developing therapeutic regimens in these patients, invasive aspergilosis is a major life-threatening condition and there is an increasing need for implementation and improvement of novel, effective antifungal stewardship programs [18]. Concerning the screening for the diagnosis of invasive aspergillosis (IA) in neutropenic patients with haematological malignancies, a study group showed that the detection of (1,3)-β-d-glucan (BDG) in serum is a reliable marker, especially in combination with galactomannan (GM) levels [19]. Similarly, another study based on molecular analysis by implementing polymerase chain reaction (PCR) with a multifungal DNA-microarray (Chip) showed that BDG and GM biomarkers combination in blood and bronchoalveolar lavage (BAL) samples as a diagnostic algorithm is an advantageous approach [20].

Conclusions

Invasive sinus aspergillosis in apparently immunocompetent hosts - especially in patients with haematological malignancy - is frequently not initially recognized and is associated with significant morbidity and mortality. It is hoped that increased awareness of this disease will result in more timely diagnosis, earlier therapeutic intervention and improved outcome. Aggressive surgical resection, aimed at complete extirpation of infecting organisms, is the cornerstone of successful therapy. Antifungal agents serve an adjunctive role to surgery. A regular follow up should be done after initial therapy.

Conflict of interests

The authors declare no conflict of interests.

References


