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Case Report

Invasive filamentous fungus infection with secondary cerebral vasculitis in a patient with no obvious immune suppression

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SUMMARY

Invasive mold infections represent an emerging and important diagnostic challenge, especially in immunocompetent patients when microscopy and cultures of the biological fluids remain negative. A central nervous system localization is not common and the clinical presentation is aspecific.

1. Introduction

Invasive mold disease (IMD) represents an emerging and important diagnostic challenge, especially in patients with no obvious immune suppression. Up to 75% of IMD cases are diagnosed post-mortem.[1] A central nervous system (CNS) localization of the infection is not common and the clinical presentation is aspecific. Most of the patients with host factors that predispose to IMD are not candidates for invasive procedures for the sampling of tissues adequate for culture and histopathology, due to the risk of bleeding. Moreover both radiological and microscopic examinations are insensitive for a definite diagnosis of IMD.

2. Case presentation

In August 2012, a 60-year-old woman was referred to our department for fever resistant to 5 days of amoxicillin. Her past medical history was significant for an episode of atrial fibrillation suppressed with propafenone. On day 0, her Glasgow Coma Scale (GCS) score was 15; an objective examination was unrevealing. Urine and blood cultures were negative for bacteria and mycobacteria. Chest radiography, abdominal ultrasound, and an echocardiogram did not reveal focal infections. Results of HIV testing were negative. Serological assays ruled out common etiologies of classic fever of unknown origin (FUO). On day 5, thorax–abdomen computed tomography (CT) excluded malignancies and abscesses. On day 7, stupor without motor deficits developed abruptly; results of magnetic resonance imaging (MRI) of the brain were negative. The patient was started empirically on meropenem 1 g three times daily and acyclovir 750 mg three times daily awaiting the microbiology results. Cultures, serology, and PCR of the cerebrospinal fluid (CSF) did not detect bacteria, neurotropic viruses, mycobacteria, or fungi. On day 10, primary cerebral vasculitis was suspected and steroids were begun (methylprednisolone 1 g daily). Fever persisted on day 13 and a whole-body indium-111 granulocyte scintigraphy (^{111}In-GS) was performed; the patient died before the response. Autopsy revealed a pulmonary, renal, and left parietal–occipital CNS invasive mold infection associated with leukocytoclastic vasculitis (Figure 1a, b). Later on ^{111}In-GS demonstrated a weak focal uptake in the same cerebral lobes (Figure 1c).

3. Discussion

IMD is a rare cause of FUO in the immunocompetent host. We emphasize that our patient did not present any of the comorbid conditions recently reviewed.[2–5] This group of ‘unsuspected’

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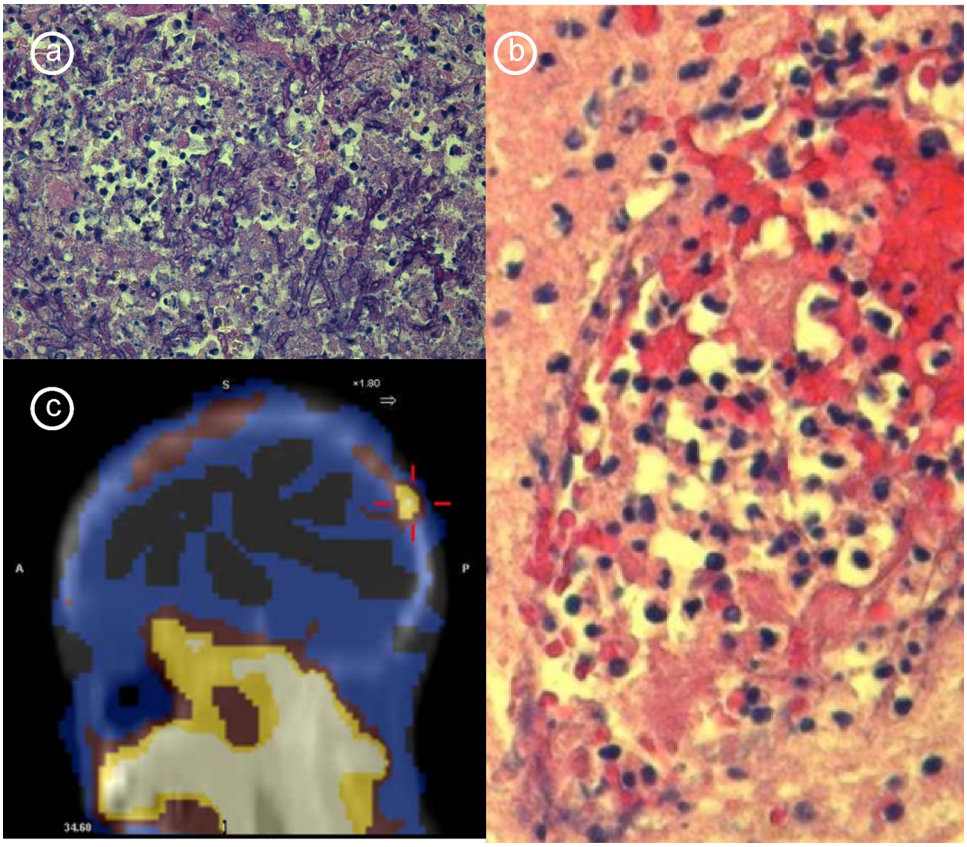

Figure 1. (a) Pas staining of the lung tissue showing septated hyaline hyphae with dichotomous acute angle branching (strongly suspected to be *Aspergillus spp* hyphae). (b) Hematoxylin and eosin staining of the brain showing florid mononuclear inflammation of a small meningeal artery, suggesting CNS vasculitis. (c) ^{111}In-GS showing an aspecific weak focal uptake in the left parietal–occipital lobes.

patients is accumulating and may easily be missed. Culture combined with evidence of tissue invasion on histology, or culture of adequate tissue specimens, provides the most certain evidence of IMD. This is why diagnostic strategies are directed at obtaining a biopsy of any suspicious lesion. In this case, the aspecific focal uptake shown with ^{111}In-GS could have encouraged a stereotactic brain biopsy. Moreover, thrombocytopenia, which usually limits invasive procedures in hematologic patients, was not present in our patient.

Using the available data (cultures and PCR for fungus were not performed at autopsy), the most appropriate diagnosis was an invasive *Aspergillus spp* infection, since only hyphae with the same diameter and 45 degree-branching were detected in tissues; non-Aspergillus hyaline fungal pathogens regularly show variations in diameter and both 45- and 90 degree-branching. The distinction from zygomycetes (broad non-septate hyphae that exhibit right-angle branching) is essential for the initiation of pre-emptive antifungal therapy; in fact Murcorales are not susceptible to voriconazole.

Conflict of interest: There is no conflict of interest for this manuscript.

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