

CASE REPORT

# Invasive Aspergillosis as the Presenting Manifestation of Small-Cell Carcinoma

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## ABSTRACT

Invasive aspergillosis usually occurs in immunocompromised patients, particularly in patients with hematological malignancies because of severe and prolonged neutropenia and/or cytotoxic therapy. Treatment requires antifungal chemotherapy, with lipid-formulations of Amphotericin B or with azoles together with wide surgical excision of the fungal lesion. We report a case of invasive sino-orbital aspergillosis due to *Aspergillus fumigatus* in a patient with uncontrolled diabetes mellitus and small cell carcinoma. We support the notion that dual immunosuppression due to both diabetes and small cell carcinoma with liver metastases was responsible for the invasive form of aspergillosis in this patient.

## INTRODUCTION

Invasive aspergillosis is a disease caused by filamentous fungi *Aspergillus spp.*, which usually causes infection in immunocompromised patients. The most common pathogenic species is *Aspergillus fumigatus*, while *Aspergillus flavus*, *Aspergillus terreus* and *Aspergillus niger* are less commonly encountered.<sup>1,2</sup> The majority of patients with invasive aspergillosis have an underlying hematological disease and/or are in a state of immunosuppression, such as when receiving corticosteroid and/or cytotoxic therapy, usually after bone marrow or solid organ transplantation, with prolonged and profound neutropenia (<100 cells/ $\mu$ l).<sup>3-6</sup>

## CASE REPORT

A 72-year-old female patient presented to the hospital with ptosis of the right eye. Her illness had begun one month earlier with eye pain and ptosis of the right eye that subsequently deteriorated to complete ptosis and loss of visual acuity and color perception within the last one month.

Her past medical history was otherwise unremarkable, except for smoking. Laboratory test values were as follows: white blood cell count 5.970/mm<sup>3</sup>, hematocrit 34.9%, platelet count 122x10<sup>3</sup>/ $\mu$ L, glucose 156 mg/dL, urea 50 mg/dL, creatinine 1.41 mg/dL, aspartate aminotransferase 18 IU/L, alanine aminotransferase 13 IU/L, alkaline phos-

### ABBREVIATIONS

CD = cluster of differentiation  
CK = cytokeratin  
CNS = central nervous system  
MRI = magnetic resonance imaging  
TTF = thyroid transcription factor

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phatase 104 IU/L, creatine phosphokinase 14 IU/L, albumin 2.4 g/dL, globulins 1.83 g/dL. Computed tomography showed a soft tissue lesion in the right lateral sphenoid sinus extending to the right orbital apex. A cranial magnetic resonance imaging (MRI) examination with gadolinium revealed a local inhomogeneous mass involving the ethmoid and the sphenoid sinuses, which extended to the right orbital apex (Figure 1). Brain MRI did not show any pathological lesions. Laboratory analysis showed a glycated (glycosylated) hemoglobin A1c of 8.4%, thus classifying the patient as a diabetic according to the recent American Diabetes Association recommendations.<sup>7</sup> The otorhinolaryngologist who examined the patient saw a dark greyish tissue that extended through the nostrils and obtained a specimen for biopsy and culture. As the culture grew *Aspergillus fumigatus* and the histopathology of the specimen revealed hyphae, liposomal amphotericin B was administered to the patient.

After consultation with an infectious-disease specialist, excision of the mass was scheduled. The surgeon removed tissue from the sphenoid and ethmoid sinuses and nasal turbinate and left an irrigating catheter in place. On histopathology, multiple hyphae were seen and culture grew *Aspergillus fumigatus*. The patient received liposomal amphotericin B for two weeks after surgery. Because of fever that occurred in the post-operative period and which did not resolve despite extended-spectrum antimicrobial therapy and liposomal amphotericin B, the patient underwent brain, thoracic and abdominal computed tomography scanning, which showed the presence of multiple liver

lesions, suggestive of metastases. A liver biopsy was performed and the histopathology together with immunostaining of the specimen revealed small tissue carcinoma, with cytokeratin (CK) 7 (+), CK8/18 (+), cluster of differentiation (CD) 56 (+), synaptophysin (+), homeobox protein CDX-2 (-), hepatocyte (-), glypican-3 (-), and thyroid transcription factor-1 (TTF-1) (-), which is small cell carcinoma of unknown origin. Unfortunately, two weeks after the operation, the patient succumbed to septic shock caused by *Acinetobacter baumannii*.

## DISCUSSION

The frequency and relative importance of invasive aspergillosis is possibly related to increased numbers of immunocompromised patients, owing to improved survival from the acquired immunodeficiency syndrome, malignancies and more intensive cytotoxic therapy, more transplantation (with immunosuppression) for organ dysfunction, more aggressive immunosuppressive regimens for patients with autoimmune diseases and better therapy and prophylaxis for candida infections.<sup>8-12</sup>

Invasive aspergillosis is a devastating infection that usually affects patients with severe and/or prolonged neutropenia or neutrophil and/or macrophage dysfunction, cytotoxic chemotherapy, long-term corticosteroid therapy, bone marrow or organ transplantation, and congenital or acquired immunodeficiency. An aggressive diagnostic approach in patients at risk and prompt institution of antifungal therapy may be essential for patient survival.<sup>13,14</sup>

The lungs are the most common site of primary invasive disease, although sinus disease approaches it in frequency in some centers.<sup>15</sup> Central nervous system (CNS) is the most common secondary site of invasive disease. Nevertheless, it is particularly worrisome that in about one-third of patients the neurological symptoms may be the first sign of invasive aspergillosis and that in the majority of the patients, CNS aspergillosis may be clinically asymptomatic until severe damage of the CNS has occurred. The progressive nature of this disease and the fact that it is relatively refractory to therapy are, in part, due to the organism's rapid growth and to its tendency to invade blood vessels.

The major concern with *Aspergillus* sinonasal infections is its progression to the eye and/or the CNS.<sup>16</sup> In the present case, the patient had invasive sinus-orbital aspergillosis and at first, we presumed that she was susceptible to invasive aspergillosis due to her indolent diabetes mellitus. Diabetes mellitus patients may be susceptible to fungal infections, such as aspergillosis. Uncontrolled and prolonged diabetes mellitus may alter the normal immunologic response to infections, as these patients have decreased phagocytic and polymorphonuclear capacity.<sup>17,18</sup> However, it was proved that the patient also had a small cell carcinoma, which had already given multiple liver metastases. Therefore, the patient's susceptibility to infection with *Aspergil-*



FIGURE 1. Cranial MRI depicting a mass posterior to the right orbital cavity which invades sphenoid sinus. MRI = magnetic resonance imaging.

*lus fumigatus* was attributed both to the underlying carcinoma and her uncontrolled diabetes mellitus.

Invasive aspergillosis has been described among patients with solid tumors, but usually after chemotherapy or after prolonged treatment with corticosteroids.<sup>19</sup> It has been suggested that invasive aspergillosis may be related to advanced stages of solid tumors as well.<sup>20,21</sup> Our patient proved to have disseminated cancer, too, at the time of presentation of invasive aspergillosis. It is noteworthy that there have been no reports of co-existence of invasive aspergillosis and non-disseminated solid tumors, prior to chemotherapy or corticosteroid administration.

Until today, less than one hundred apparently healthy individuals have been described with invasive aspergillosis. Whether patients with invasive aspergillosis should or not be screened for underlying malignancies remains a matter that needs further investigation.

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