

Case Report

# *Blastomyces* species and orbital apex syndrome: Unsuspected co-infection



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## Abstract

*Blastomyces* species are thermally dimorphic fungi existing as yeast in tissue. We report an initially immunocompetent patient with orbital apex syndrome (OAS) whose presentation suggested giant cell arteritis. Subsequently, metastatic carcinoma was entertained as a cause of OAS until bronchoscopy yielded *Blastomyces* species. The patient rapidly succumbed with multiorgan failure despite Amphotericin B administration. At post-mortem, *Blastomyces* co-infection with fungal hyphae in keeping with *Aspergillus* species was found in cavernous sinus and in infarcted optic nerve. To the best of our knowledge, co-infection with these two organisms in this clinical setting has not been reported.

**Keywords:** *Blastomyces*, Blastomycosis, *Aspergillus*, Orbital apex syndrome, Cavernous sinus thrombosis, Co-infection

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## Introduction

*Blastomyces dermatitidis* is a thermally dimorphic fungus found world-wide, including in Saudi Arabia, Lebanon, Africa and India.<sup>1</sup> Most infections, however, occur in Canada and the United States, hence the term North American blastomycosis. Lung is almost invariably the organism's entry site and although the infection may appear localized, it is, with few exceptions, systemic. Ocular involvement is rare: a 2007 literature review documents just 40 cases.<sup>2</sup> To the best of our knowledge, there have been no reports of *Blastomyces* with fungal co-infection consistent with *Aspergillus* in the ocular region. We detail such a case.

## Case report

A 71-year-old woman with hypertension, hypothyroidism and previous breast carcinoma (2004), presented in mid-

summer 2016, to a Northwestern Ontario hospital. She had severe headache with scalp and periorbital tenderness accompanied by epiphora, weight loss and fatigue. ESR and CRP were elevated. Temporal arteritis was diagnosed and oral prednisone (50 mg daily) begun. Subsequent temporal artery biopsy in Winnipeg, Manitoba was non-diagnostic, showing only sparse macrophages and lymphocytes in the arterial wall.

Two weeks later, she noted double vision, decreased vision OD, and right ptosis. August 30th CT scan showed no acute intracranial abnormality. Prednisone improved her headache although not her visual symptoms and was continued.

By mid-September, neuro-ophthalmology examination documented decreased visual acuity (counting fingers at 2 feet) with eccentric fixation, almost complete ptosis, an afferent pupillary defect and limited extraocular motility especially abduction, all on the right. Both fundi were normal.

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The left eye was unremarkable. Differential diagnosis included giant cell arteritis (GCA) resulting in posterior ischemic optic neuropathy and right III and VI cranial nerve palsies, and alternatively, a right cavernous sinus and orbital canal disease process.

Brain and orbital MRIs revealed a contrast-enhancing lesion in right orbital apex extending into right cavernous sinus and bulging into sphenoid sinus. Chest and abdomen MRIs showed multiple lung and splenic nodules. Malignancy (metastases from the patient's breast carcinoma, a new primary lung carcinoma or lymphoma) was favored but an atypical infection could not be excluded.

In early October, the patient had right optic nerve head pallor and was hospitalized. The orbital apex was radiated based on the strong suspicion of metastatic disease. Bronchoscopy yielded *Blastomyces* species, the fungus identified initially on cytology (Fig. 1 inset) and subsequently on culture. Prednisone and radiotherapy were stopped and Amphotericin B administered.

Despite treatment, the patient developed rapidly decreasing respiratory function, a bleeding gastric ulcer and pancreatitis. November 6th MRI demonstrated an inflammatory mass suspected to be blastomycosis at the right anterior clinoid process extending into cavernous sinus with either vasospasm or invasion of the right internal carotid artery. Additionally there was a large right middle and anterior cerebral artery distribution acute infarct, also involving the basal ganglia, and acute infarction involving the left frontal and parietal lobes in a left anterior cerebral artery distribution. Acute infarction involved the right optic nerve and right aspect of the optic chiasm. The patient died that day due to multiorgan failure. An autopsy was performed.

## Pathology

Lungs were diffusely consolidated and thyroid, kidneys and spleen were partially necrotic. On microscopy, these organs all had varying degrees of inflammation and massive numbers of *Blastomyces* yeast. However, in the lung, occasional small foci comprised of septate fungal hyphae and intense acute inflammation were also observed. The hyphae had acute angle branching and were morphologically consistent with *Aspergillus* species. Tongue ulcers were positive for *Herpes simplex* virus but no herpetic changes were identified in any other organ including the eye. The autopsy was negative for malignancy.

Right eye and orbital tissues without lacrimal gland were received in consultation along with right cavernous sinus, sphenoid sinus and brain. On gross examination, orbital soft tissues and right globe were essentially unremarkable both externally and on sectioning. Right optic nerve appeared reddish and soft with discolored meninges except immediately adjacent to the globe. (Fig. 2A and B) On microscopy, orbital apex tissue showed hyphae consistent with *Aspergillus* species infiltrating amongst adipocytes with nearby necrosis and non-granulomatous inflammation. No *Blastomyces* organisms were identified in orbital tissues but small numbers were present in the choroid with essentially no associated inflammation. No hyphae were observed in the globe, optic nerve head, lamina cribrosa or immediate post laminar nerve. However, the remaining optic nerve which was infarcted showed intense meningeal invasion by hyphae sur-

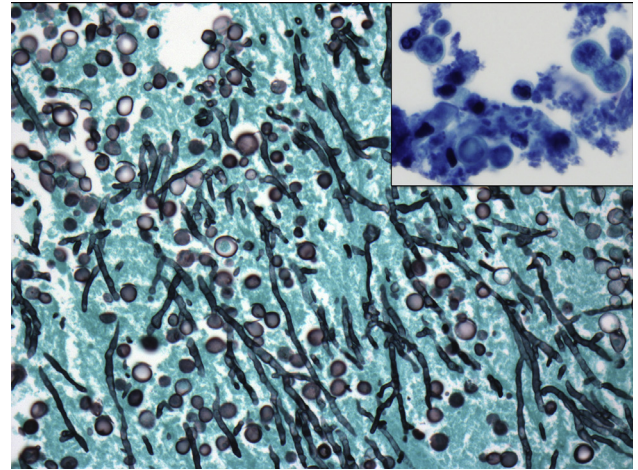


Fig. 1. Inset: Bronchoscopy specimen containing yeasts with double contour walls and single broad based budding consistent with *Blastomyces* species. Papanicolaou stain,  $\times 600$ . Large photo: Septate fungal hyphae with acute angle branching consistent with *Aspergillus* species and *Blastomyces* yeast together in the cavernous sinus. Methenamine silver,  $\times 400$ .

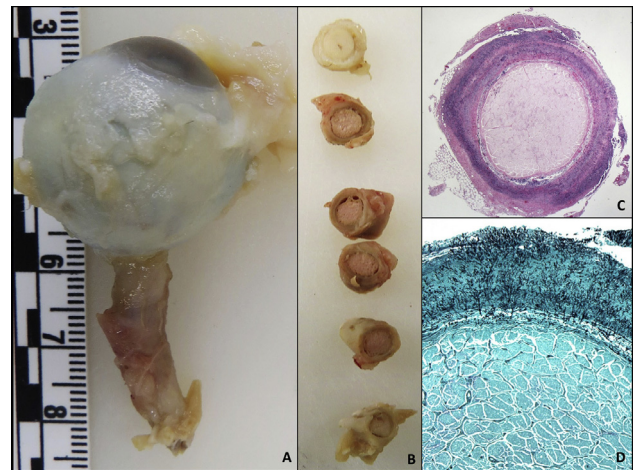
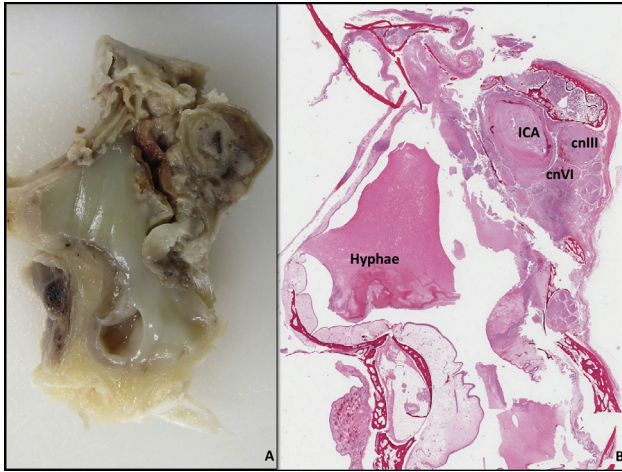


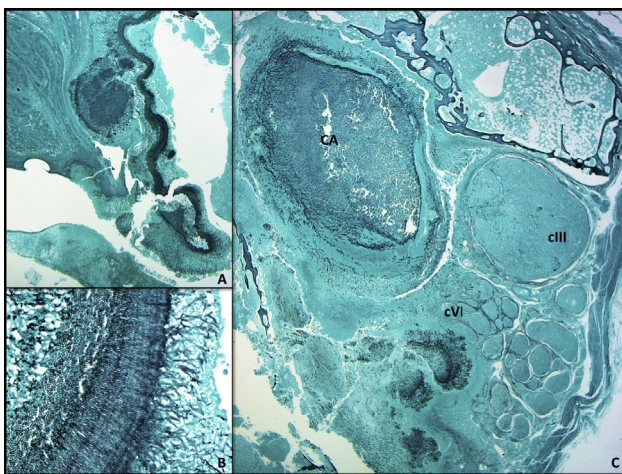
Fig. 2. A: Right globe and discolored optic nerve; B: Cross sections of optic nerve. Note the superior most section from adjacent to the globe is relatively well preserved while the remainder is infarcted with reddish tan meninges; C: Cross section of optic nerve with fungal hyphae in keeping with *Aspergillus* diffusely infiltrating meninges. Hematoxylin and eosin,  $\times 12.5$ ; D: Fungal hyphae invading optic nerve meninges. Methenamine silver,  $\times 40$ .

rounded by acute and chronic non-granulomatous inflammation. (Fig. 2C and D) In necrotic optic nerve adjacent to the chiasm, both *Blastomyces* organisms and hyphae in keeping with *Aspergillus* species were visible.

Green mucous and tan membranes which proved histologically to be hyphal palisades in keeping with *Aspergillus* species filled the sphenoid sinus (Figs. 3A, B and 4A, B) Hyphae were unaccompanied by inflammation in one area but part of a necrotic inflammatory mass where the bony wall between the sphenoid and cavernous sinuses was largely destroyed. Cavernous sinus contained much necrotic debris, inflammation and fibrosis. Both *Blastomyces* organisms and hyphae were evident (Fig. 1 large photo), including in necrotic cranial nerves III, IV and VI, with hyphae predominating. (Figs. 3 and



**Fig. 3.** A: Right cavernous sinus and sphenoid sinus, filled with green mucous and rust membranes consisting of palisading fungal hyphae. A and B: There is much necrosis in the cavernous sinus, involving especially cranial nerves III and VI. The internal carotid arterial wall (ICA) is thickened and the vessel occluded. B, Hematoxylin and eosin, low power Aperio scan.



**Fig. 4.** A: Palisading fungal hyphae in sphenoid sinus mucous, Methenamine silver,  $\times 12.5$ ; B: Close up of *Aspergillus*-like fungi seen in A. Methenamine silver,  $\times 200$ ; C: Cavernous sinus with fungal hyphae infiltrating and destroying cranial nerves III and VI (cnIII and cnVI) as well as infiltrating and occluding the internal carotid artery. *Blastomyces* organisms were present in the cavernous sinus and within cranial nerves but not involving the internal carotid artery (ICA). Methenamine silver,  $\times 12.5$ .

4) The carotid artery was occluded with hyphae diffusely infiltrating arterial wall. (Fig. 3A, B and 4C)

Brain infarction was in keeping with November 6th MRI findings. Fungal abscesses containing both organisms, mixed granulomatous and purulent inflammation, meningitis and ventriculitis were seen. Multiple foci of arteritis with angioinvasive hyphae consistent with *Aspergillus* species were present as well.

## Discussion

In nature, *Blastomyces dermatitidis* exists as mycelia. At 37 °C, *Blastomyces* species quickly convert to yeast, typically

8–12 microns in size with double contoured walls and single broad-based budding. This transformation increases virulence with production of factors such as blastomyces adhesion 1 that facilitate attachment to host tissues and weaken host immune response.<sup>3</sup> The presence of hyphae in a patient with blastomycosis indicates co-infection, an unusual finding even in hyperendemic areas.

Characterization of septate fungal hyphae with acute angle branching on morphological findings alone is not possible.<sup>4</sup> Culture is the gold standard but unfortunately only *Blastomyces* organisms were isolated from our patient's samples. Immunostains for fungal typing on histologic sections of formalin-fixed paraffin-embedded tissue can be unreliable due to antigenic overlap. This has also been a problem for the *Aspergillus* galactomannan enzyme immunoassay where cross reactivity with *Blastomyces dermatitidis* and other fungi has been documented.<sup>5</sup> Molecular techniques of classification performed on formalin-fixed paraffin-embedded material can have similar issues. Thus, we cannot state with certainty that our second fungus is *Aspergillus*; however, we believe that *Aspergillus* is the most likely pathogen based on the opinions of experts in fungal morphology with whom we consulted, the ubiquitous nature of *Aspergillus*, and the multiple reported instances of *Aspergillus* sinus involvement and subsequent orbital infection.

Recently, phylogenetic analysis of *Blastomyces* has resulted in recognition of a second cryptic species, *B. gilchristii*,<sup>6</sup> named after the first physician to recognize blastomycosis in North America. Most infections from the hyperendemic area that encompasses Northwestern Ontario, Wisconsin and Minnesota are due to *B. gilchristii* rather than *B. dermatitidis*.<sup>6,7</sup> The two organisms seem to be associated with differing clinical pictures that have similar mortality rates: *B. gilchristii* with pulmonary and constitutional symptoms and *B. dermatitidis* with disseminated disease, especially in older people, smokers and immunocompromised individuals.<sup>6–9</sup> Current DNA assays to identify *Blastomyces* in culture do not distinguish between the two species and typing is not possible in formalin-fixed paraffin-embedded tissue. Thus we were unable to determine whether our patient had *B. dermatitidis* or *B. gilchristii*.

Co-infection with *Aspergillus* and *Blastomyces* is rare. Two such instances have been reported, both in patients with solid organ transplants, but neither of those cases is documented as having ocular/orbital involvement.<sup>10,11</sup> Our patient was not initially immunocompromised, except by virtue of her age, but steroid administration for presumed GCA could have had a negative effect. Blastomycosis presenting like GCA would be unusual<sup>12</sup> but orbital infection by *Aspergillus* is well known to clinically mimic temporal arteritis with headache, scalp tenderness, jaw claudication and blurred vision.<sup>13–15</sup>

Orbital apex syndrome (OAS), i.e., involvement of the optic nerve as well as some or all of the cranial nerves III, IV, VI and ophthalmic division of V within the cavernous sinus/superior orbital fissure, as occurred in our patient, has a broad differential diagnosis. Malignancy is frequently a consideration clinically, and rarely, OAS is due to GCA,<sup>16</sup> both etiologies having been considered for our patient. The presence of one potential cause, however, does not exclude the possibility of another; for example, OAS secondary to fungus has been documented in patients with GCA.<sup>17</sup> Given the

associated morbidity/mortality, invasive fungal infection is very important in the extensive differential for OAS in both immunocompromised and immunocompetent individuals and must be excluded in a timely manner.<sup>18</sup>

Organisms commonly implicated are *Aspergillus* and Zygomycetes (*Mucor*), the latter especially in diabetics. OAS has not been associated with blastomycosis. We found both *Blastomyces* and fungal hyphae in the cavernous sinus but only hyphae in the sphenoid sinus, orbital apex and ringing the meninges of the infarcted optic nerve. From these findings, it is likely that the presumed *Aspergillus* played a greater role in the development of OAS, the organism having gained access to the cavernous sinus from the sphenoid sinus. Clinically and on CT scans, sinus involvement by invasive fungal infections may not be readily appreciated.<sup>18</sup> This was the situation with our patient where changes were first documented on MRI with contrast rather than in the original CT studies.

Ocular blastomycosis most frequently involves lesions of eyelid/canthal skin but endophthalmitis/panophthalmitis can occur, with or without clinically apparent preceding lung disease.<sup>19</sup> Orbital cellulitis has also been reported.<sup>20</sup> There is one reported case of *Blastomyces* found in the substance of the optic nerve,<sup>2</sup> the patient presenting with superior visual field impairment that ultimately deteriorated to no light perception following a course of steroids. The extensive optic nerve sheath involvement that we attribute to *Aspergillus* species has been documented only rarely.<sup>21</sup> Infection of eye structures with either of these fungi is no doubt underreported.

Knowing the real sequence of events in our patient is impossible. The extent of fungus in her sphenoid sinus suggests she had pre-existing *Aspergillus* colonization that at some point became invasive and acute. We suspect she initially may have had subclinical blastomycosis, thus weakening her immune system, leaving her vulnerable to *Aspergillus* species transformation. What is certain is that both fungi resulted in her demise which would have been incorrectly attributed to *Blastomyces* alone had post-mortem studies not provided further tissue sampling. Difficulty in diagnosing invasive fungal infections is common as in our patient, and contributes significantly to morbidity and mortality.<sup>18</sup> A high index of suspicion and multiple/repeat biopsies may be necessary to establish an accurate diagnosis.

### Conflict of interest

The authors declared that there is no conflict of interest.

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