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Headaches and hemiparesis in an immunocompetent inmate

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Title: Headaches and Hemiparesis in an Immunocompetent Inmate.

Running Title: Headaches and Hemiparesis in an Inmate.

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Clinical history

This is a case of a 22 year-old African American male inmate with no significant past medical history who regularly cleaned moldy bathrooms and showers during his incarceration. The patient presented with progressive development of left-sided weakness, dizziness, headaches, and vomiting over a two month period. A MRI performed at admission revealed a large enhancing lesion located in the right frontotemporal region with involvement of the right basal ganglia and thalamus, as well as extension into the corpus callosum and contralateral cerebrum (Figure 1A and 1B). The mass showed no diffusion restriction and also demonstrated heterogeneous enhancement on T1 post-contrast study. These features were very suggestive of a high grade glioma and a stereotactic biopsy was subsequently performed. Intraoperative interpretation of the biopsy revealed "granulomatous inflammation with fungal elements" and this finding prompted immediate treatment with Amphotericin B and Voriconazole as well as culture of the biopsy material. The remainder of the biopsy was processed for routine hematoxylin and eosin (H&E) sections and special stains. Additional imaging studies including a chest X-ray revealed a lesion in the right upper lobe of the lung, and bronchoalveolar lavage was remarkable for herpes viral cytopathic effect although viral cultures remained negative. The remainder of his laboratory studies yielded a positive urine culture (*Klebsiella pneumonia),* while subsequent blood and CSF cultures as well as HIV serologies were negative. The patient continued to deteriorate postoperatively, and follow-up head imaging studies showed ventricular extension of the lesion with increased mass effect and midline shift. The resultant hydrocephalus required ventriculostomy

placement and emergent intubation after which the patient developed a cerebellar infarct. The patient died shortly after and a complete autopsy was performed.

Pathology:

Tissue sections obtained prior to death showed fungal encephalitis with exuberant granulomatous inflammation and branching, pigmented fungal hyphae (Figure 2A and 2B). Gomori methenamine silver (GMS) stain highlighted thick-walled septate hyphae and conidia (Figure 3); however, fungal cultures on biopsy material were negative.

At autopsy, a 3cm nodule was noted in the right upper lobe of the lung which was microscopically composed of caseating granulomatous inflammation with associated pigmented septate fungi. Additionally, the brain (weight: 1300 grams) was grossly edematous, and there was a mycotic aneurysm of the basilar artery with surrounding clotted hemorrhage covering the ventral brainstem and cerebellum. Coronal sections revealed bilateral intraparenchymal softening of the frontotemporal white matter, hemorrhage within the 3rd and 4th ventricles, a cerebellar infarction, and a large necrohemorrhagic mass (Figure 4) with associated softening and discoloration in the right frontal hemisphere. Microscopically, these findings were associated with meningoencephalitis with fungal vascular invasion (Figure 5) into the basilar artery leading to subsequent hemorrhage.

A portion of the above mentioned necrohemorrhagic frontal lobe mass was positive for dematiaceous mold on culture. Additional studies, including polymerase chain reaction (PCR) and sequencing techniques, further classified the mold as *Bipolaris* species.

Diagnosis

Cerebral phaeohyphomycosis due to *Bipolaris* sp.

Discussion

Phaeohyphomycosis is caused by a group of fungal organisms that have in common the presence of melanin within their cell wall. These organisms can cause severe infections in immunocompromised patients as well as seemingly healthy individuals. The fungi are ubiquitous in nature and can be found in soil and decaying vegetation. Infection predominantly develops following inhalation or traumatic implantation of conidia resulting in abscess formation in the skin, lungs, and other organ systems[1]. Cerebral phaeohyphomycosis is the most lethal form of infection and can occur in healthy and immunocompromised hosts[1]. In fact, the largest study of cerebral phaeohyphomycosis consisting of a review of 101 cases showed that about half of the affected patients were immunocompetent[1].

Overall, cerebral phaeohyphomycosis is rare and likely occurs via hematogenous spread or direct extension through the nasal sinuses[1-4]. Primary infections of the CNS may be clinically silent; however, CNS infections secondary to dissemination from another site is often fatal[1].

The majority of patients (87%) with cerebral phaeohyphomycosis present with clinical features characteristic of a brain abscess; similarly, patients can also present with signs and symptoms consistent with meningitis, encephalitis and myelitis[1,3,4]. A single case is reported in the literature in which the initial presentation of cerebral phaeohyphomycosis caused by Bipolaris sp. featured a ring-enhancing lesion mimicking a brain tumor[5]. The

current case would represent only the second known instance of Bipolaris cerebral infection presenting with clinical and radioimaging features highly suspicious for an infiltrative high grade glioma[5]. Differentiation between abscess vs. glioma on clinical evaluation can be challenging, since both are space occupying lesions that can result in headaches, seizures, and hemiparesis due to mass effect. MRI can be helpful in the differential diagnosis as gliomas typically do not show diffusion restriction, whereas an abscess often has foci of restriction on diffusion-weighted images. Additionally, abscesses tend to present as single or multiple lesions that demonstrate thick peripheral enhancement with a central non-enhancing area in post contrast T1 weighted images. Our patient's imaging (Figure 1B) showed no diffusion restriction and heterogeneous enhancement on T1 post-contrast study, features more suggestive of a high grade glioma.

In addition to microbiologic assessment (culture and/or molecular workup), the definitive diagnosis of phaeohyphomycosis is made by identifying brown-black branching fungal elements on H&E stain. GMS or periodic acid-Schiff (PAS) stains highlight fungal elements and may be useful in cases that have few organisms present. Furthermore, several of the dematiaceous fungi are known to be scanty pigment producers. In instances where little or no pigment is seen on H&E stain, a Masson-Fontana stain can be helpful in highlighting minimal amounts of melanin. Finally, formalin-fixed paraffin-embedded tissue can be used by reference laboratories to identify fungi by PCR and DNA sequencing assays.

Additional distinctive features can be seen on microscopic evaluation depending on the immune status of the patient. For example, immunocompetent patients often show evidence of a robust immune response on histopathologic examination including

meningoencephalitis with vasculitis and granulomatous inflammation[6]. Conversely, patients with disseminated infection and/or compromised immune function are unable to manifest an effective granulomatous response and typically demonstrate evidence of more severe infection including tissue necrosis and fungal vascular invasion with thrombosis and infarction[6]. Our patient was an immunocompetent host who had granulomatous lesions identified on biopsy; however, as his clinical status declined the patient developed vascular invasion of the basilar artery, a feature more frequently encountered in immunocompromised hosts.

Treatment consists of thorough surgical resection and antifungal therapy. The most accepted therapeutic regimen includes Amphotericin B combined with Voriconazole or Itraconazole for at least six months[7-9]. Despite aggressive treatment with high dose anti-fungal medications, the mortality rate for these intra-cranial infections remains high. Early diagnosis with complete surgical resection can improve patient outcome, decreasing the mortality rate to 62% as compared to 83% with only partial resection[1].

In summary, we report this case to boost awareness of the potential for CNS phaeohyphomycosis infection to present as a clinical and radioimaging mimic of high grade glioma. Our patient, a previously healthy adult, is one of less than a dozen cases of cerebral phaeohyphomycosis due to Bipolaris documented in the literature, and is only the second patient to present with imaging features very suggestive of high grade infiltrative glioma[1,2,6,10,11]. It is thought that dematiaceous fungi cause CNS infections because of enhanced neurotropism; this is a feature that Bipolaris lacks and is likely the reason why there are so few documented cases of cerebral phaeohyphomycosis caused by this genus[3]. However, the recent increase in reports of Bipolaris CNS infection may be

the result of improved detection methods or a change in virulence patterns. If, in fact, the increase is due to a change in virulence patterns this may indicate a need for development of more effective methods for rapid detection. The current patient may have had increased risk of exposure (aerosol or possible dermal abrasion) due to his bathroom cleaning duty while he was incarcerated; however, this is only speculation based on a single incident. In general, increased awareness of this broadened spectrum of presentation for CNS Bipolaris infection, timely diagnosis, and complete surgical resection with aggressive antifungal therapy will hopefully improve clinical outcome.

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Figures

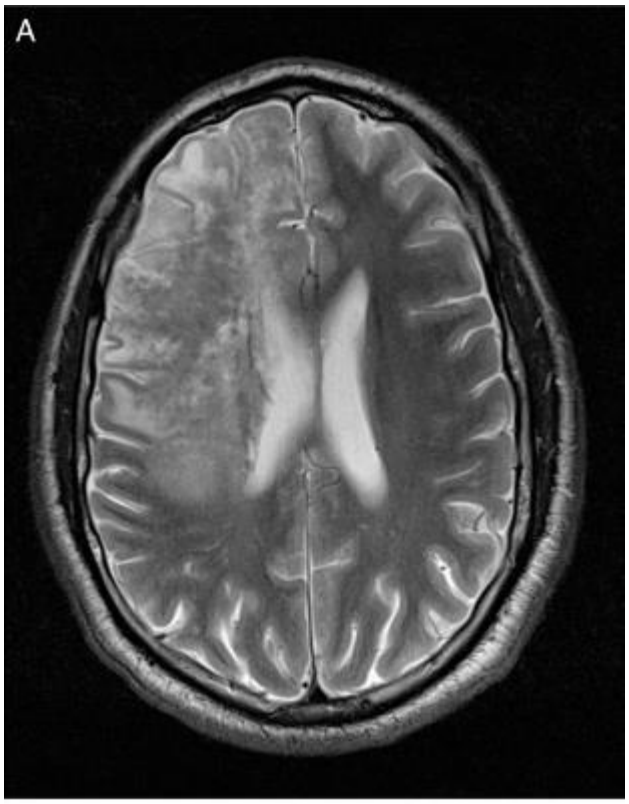

Figure 1A. MRI, T2 weighted axial image. Heterogeneous T2 hyperintense lesion in the right frontotemporal region involving mostly white matter with partial extension into gray matter. Note the mass effect on the right lateral ventricle.

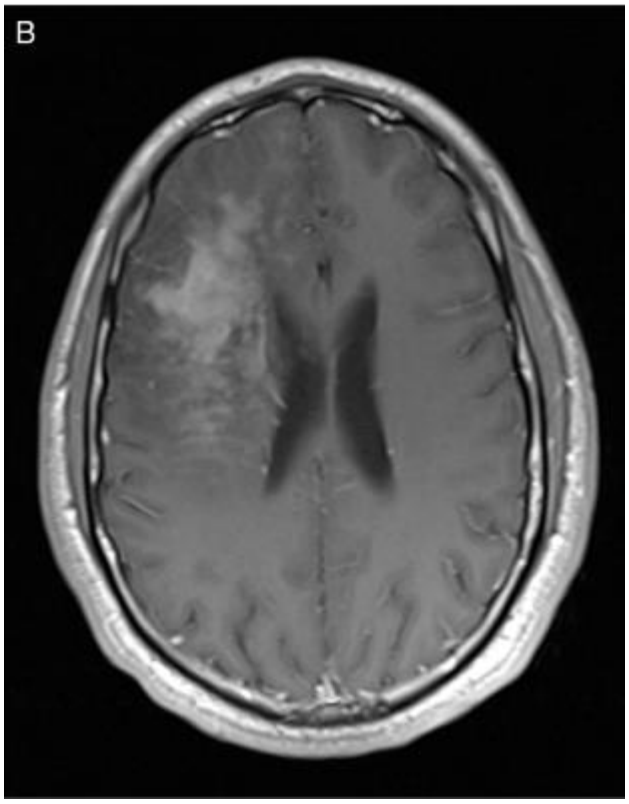

Figure 1B. MRI, post-contrast axial T1 weighted image. The central portion of the lesion has heterogeneous enhancement, suggestive of an infiltrative high grade glioma.

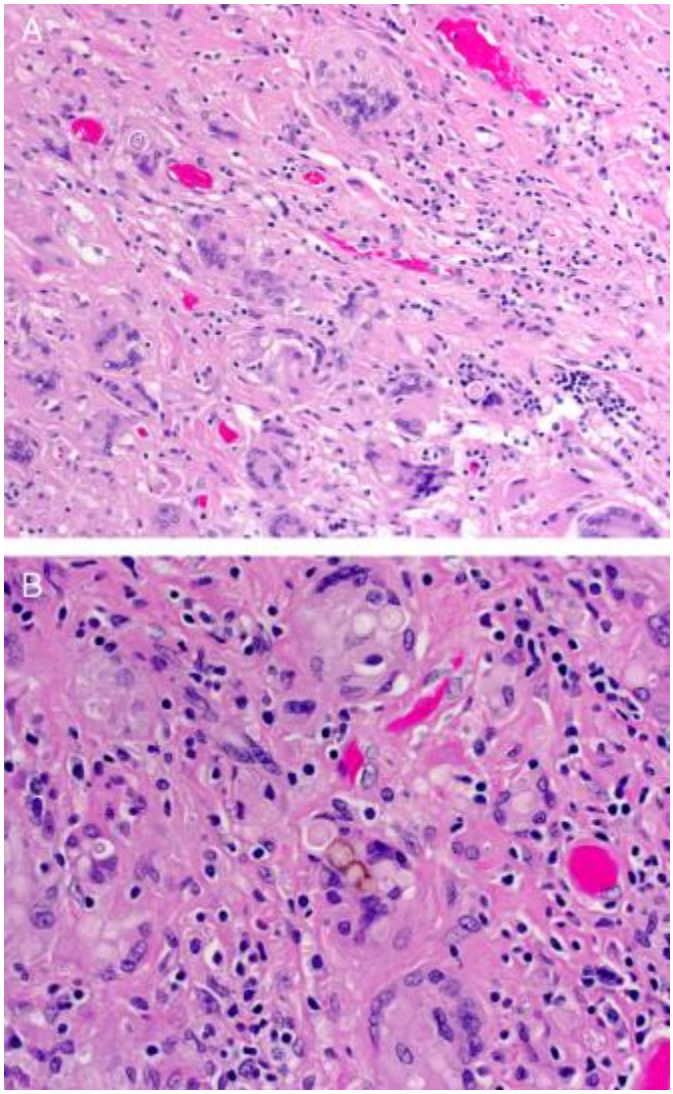

Figure 2A. Hematoxylin and eosin (H&E) stain, 20Xmag. Brain parenchyma with numerous granulomas, giant cells and chronic inflammation.

Figure 2B. Hematoxylin and eosin (H&E) stain, 40Xmag. Brain parenchyma showing granulomas with giant cells engulfing numerous round, rigid walled hyphal elements. Central granuloma contains two pigmented fungal elements.

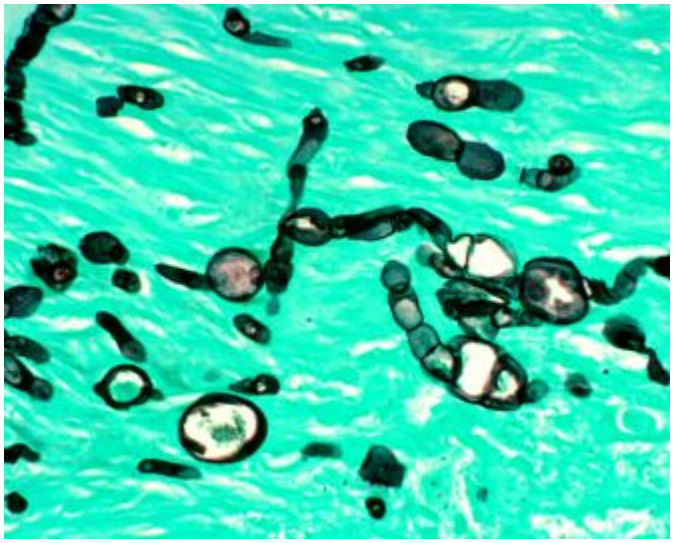

Figure 3. Gomori methenamine silver (GMS) stain. 60X mag. The Silver stain decorates branched hyphal elements.

Figure 4. Coronal section of right frontal lobe showing a necrohemorrhagic lesion with softening and discoloration of white matter with focal extension to cortex.

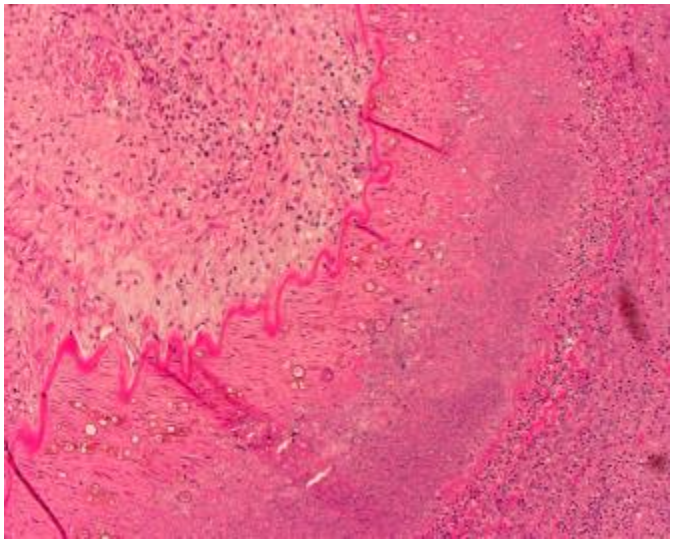

Figure 5. Hematoxylin and eosin (H&E) stain. X10 mag. Cross section of a portion of the basilar artery wall filled with numerous pigmented hyphae.