

Case Report

Primary cryptococcosis of paranasal sinus in immunocompetent patient: two case reports and review of literature

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Abstract: Chronic invasive granulomatous fungal sinusitis (CIGFS) caused by cryptococcus is extremely rare, especially in immunocompetent patients. We report two cases of CIGFS caused by cryptococcus in immunocompetent patients. Case 1 was infected in the left ethmoid sinus with orbital invaded later. Case 2 was infected in the left maxillary sinus and sphenoid sinus with Intracranial invaded later. The two cases all underwent two surgical operations, and postoperative pathology showed granulomatous inflammation. The third postoperative pathology confirmed cryptococcal infection by PAS and AB-PAS stain. Case 1 was underwent orbital exenteration debridement and appropriate antifungal therapy after surgery, and was followed up for 18 months without recurrence. Case 2 had no chance of surgery at last and went to a higher level hospital for continue therapy and then losted follow-up. Early recognition of cryptococcal sinusitis and appropriate surgery with administration of appropriate antifungal therapy has a great impact on the good prognosis.

Keywords: Cryptococcal sinusitis, chronic invasive fungal sinusitis

Introduction

Cryptococcosis is an invasive mycosis which associated with significant morbidity and mortality. Cryptococcus is an encapsulated haploid yeast that causing diseases in both immunocompetent and immunosuppressed individuals. Its pathogenicity depends on the polysaccharide capsule [1]. Cryptococcus has a global distribution, mainly distributed in bird droppings, especially the pigeon droppings. The most common site is lung and the central nervous system, but virtually all organs can be affected [2]. The susceptible patients are immunocompromised individuals that include: HIV, hematologic malignancies and solid-organ transplant recipients. However, chronic invasive granulomatous fungal sinusitis (CIGFS) occur in immunocompetent individuals is extremely rare.

Here we report two cases of CIGFS caused by cryptococcus in immunocompetent patients, along with a review of the relevant English-language literature (**Table 1**). Both patients denied to keep birds (especially pigeons) or had a history of drug abuse.

Case report

Case 1

A 48-year-old male presented with nasal obstruction and headache to the department of otolaryngology. He denied postnasal drainage, diplopia, hyposmia, epistaxis, facial numbness and any impairment in his visual acuity. Computed tomographic (CT) scan of the paranasal sinuses showed an isodense soft tissue mass of the left ethmoid sinus with extension to the orbit. The patient was then underwent endo-

Table 1. Clinical data of five sinusitis cases caused by cryptococcus in the English-language literature

Author/Publish year	Age/Sex	Immune status	Extent
Kohlmeier (1955)	34/M	Competent	Right maxillary and ethmoid sinus with orbital extension
Choi (1988)	31/M	Compromised (HIV)	Diffuse sinus and intracranial
Prendiville (2000)	48/F	Competent	Sphenoid sinus
Present case (2016)	48/M	Competent	Left ethmoid sinus with orbital extension
Present case (2016)	37/M	Competent	Left maxillary and sphenoid sinus with intracranial invasion

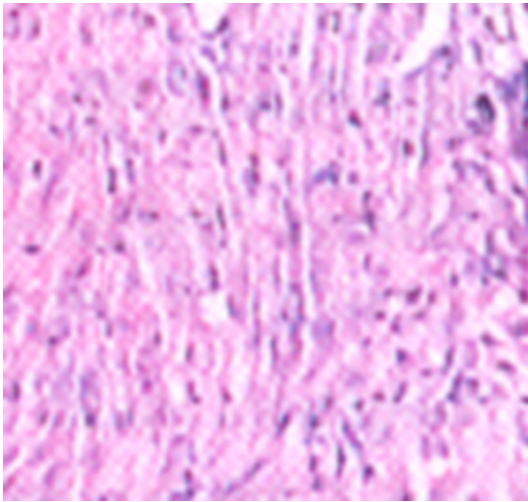


Figure 1. After the first surgery, the Histopathological result showed granulomatous inflammation (HE $\times 100$).



Figure 2. Axial MRI of paranasal sinuses showed the left ethmoid sinus component of the mass with extension to the orbit had heterogeneous hyperintensity on T2WI (arrow).

scopic sinus surgery. The Histopathological result was granulomatous inflammation (**Figure 1**). The patient had no treatment after discharged. 5 months later, the patient presented with swelling of the left eye. Magnetic resonance imaging (MRI) of the paranasal sinuses showed the left ethmoid sinus component of the mass with extension to the orbit had heterogeneous hyperintensity on T2-weighted images (T2WI) (**Figure 2**). The patient was underwent endoscopic sinus surgery again. Both the frozen section and postoperative pathology revealed granulomatous inflammation (**Figure 3**). The patient underwent no treatment after discharged again.

One year after the second operation, the patient presented with pained proptosis of the left eye. On physical examination, his visual acuity was normal. Laboratory investigations demonstrated a white blood cell count of $15.02 \times 10^9/L$, absolute neutrophil count of $12.31 \times 10^9/L$, lymphocytes count of $1.91 \times 10^9/L$, hemoglobin count of 145 g/L, platelets

count of $283 \times 10^9/L$. Hepatitis B virus surface antigen (HBsAg) +, hepatitis B e antibody (HBeAb) +, hepatitis B core antibody (HBcAb) +, Human Immunodeficiency Virus antibody (HIV-Ab) -. Computed tomographic (CT) scan of the paranasal sinuses showed an isodense soft tissue mass of the left ethmoid sinus with extension to the orbit and had a unclear boundary with the eyeball (**Figure 4**). The patient underwent orbital exenteration and debridement adjacent to the orbital bone. After surgery, the patient was commenced on 3 months course of 400 mg orally fluconazole treatment. Periodic acid Schiff stain and alcian blue were conducted in the pathological specimens which revealed cryptococcus infection (**Figure 5**). The patient was followed up for 18 months without recurrence (**Figure 6**).

Case 2

A 37-year-old male presented with two months history of left-side facial paralysis to the department of otolaryngology. MRI of the paranasal

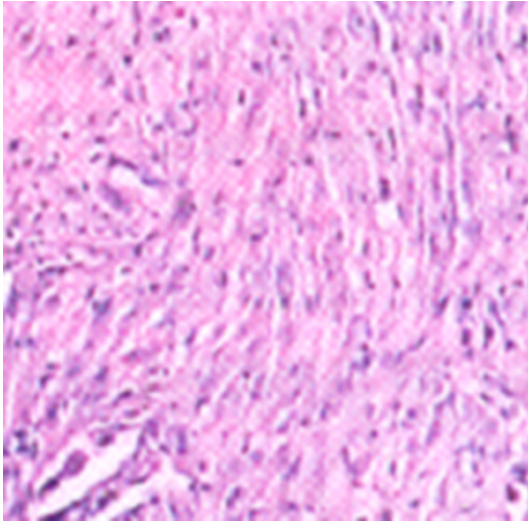


Figure 3. After the second surgery, the postoperative pathology revealed granulomatous inflammation (HE × 100).

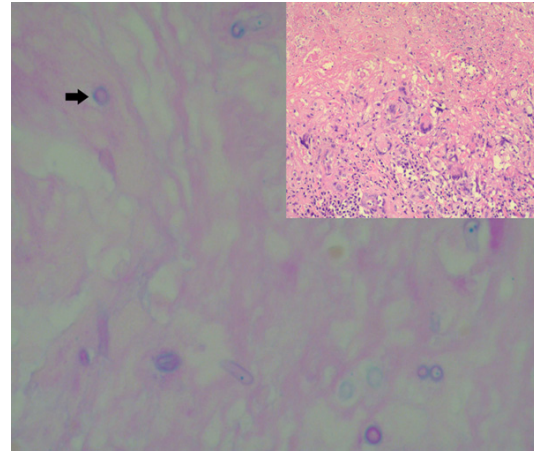


Figure 5. After the third surgery, Periodic acid Schiff stain and alcian blue showed numerous round-to-oval, non-encapsulated and budding yeast-like cells (× 400) (arrow). Inset: multinuclear giant cell with surrounding granulomatous inflammation (× 200).



Figure 4. Axial CT scan of the paranasal sinuses showed an isodense soft tissue mass of the left ethmoid sinus with extension to the orbit and had an unclear boundary with the eyeball (arrow).

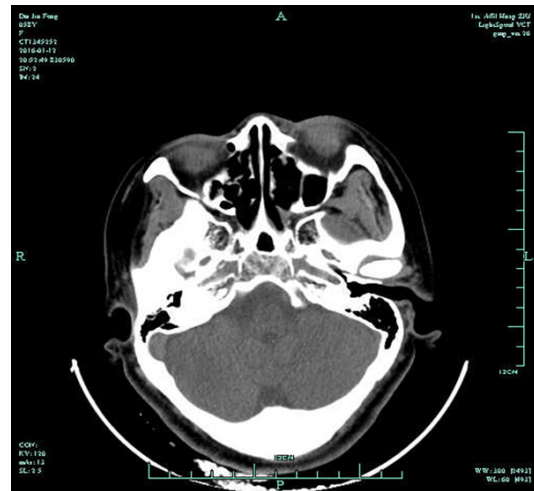


Figure 6. Axial CT scan of the paranasal sinuses showed that the patient was followed up for 18 months without recurrence.

sinuses showed a hypointense soft tissue mass in the left maxillary sinus, a isointensity soft tissue mass in the nasopharynx and a hypointense soft tissue mass in the left sphenoid sinus on T1-weighted images (T1WI) (Figure 7). Chest CT was normal. The patient was underwent endoscopic sinus surgery. Histopathology revealed granulomatous inflammation, inclined to tuberculosis. However, we did not find any etiological agent. Diagnosis treatment of tuberculosis was underwent 6 months (isoniazid 0.3 g per day orally, rifampicin 0.45

g per day orally, pyrazinamide 1.5 g per day orally in 4 divided doses). The symptoms of the patient did not aggravate. The patient presented with swelling on the left-side face after anti-tuberculosis therapy for next six months. MRI of the paranasal sinuses showed a soft tissue mass in the left sphenoid sinus and debridement of the left sphenoid sinus was done. Periodic acid Schiff stain and alcian blue were conducted in the pathological specimens, but did not find etiological agent again. The patient underwent no treatment after discharged. Eight months after the second surgery, the patient

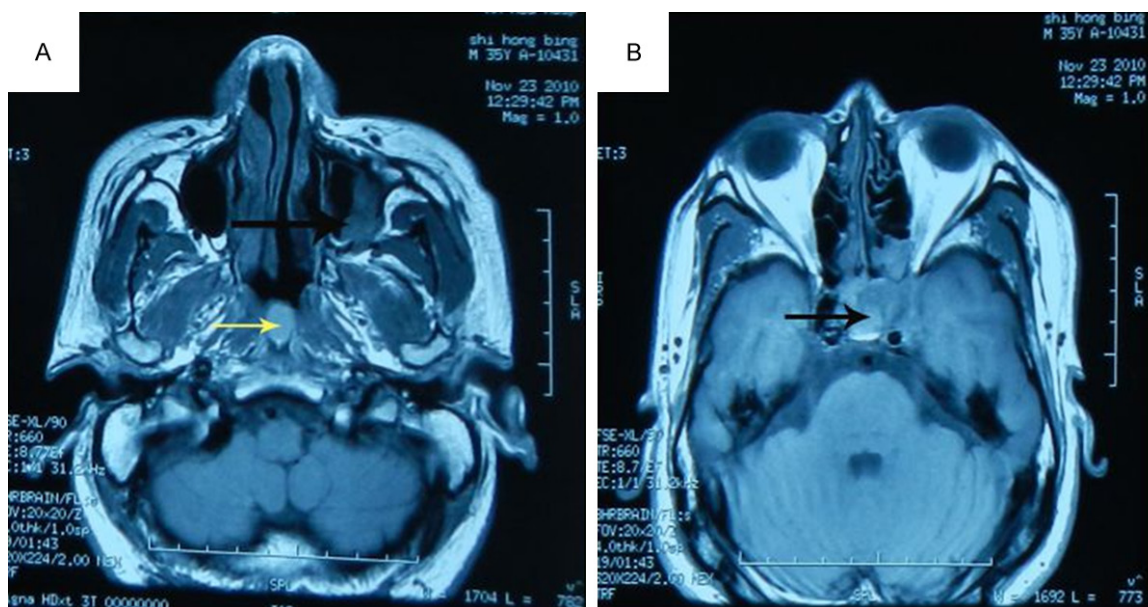


Figure 7. MRI of paranasal sinuses showed a hypointense soft tissue mass in the left maxillary sinus, an isointensity soft tissue mass in the nasopharynx and a hypointense soft tissue mass in the left sphenoid sinus on T1WI (arrow).



Figure 8. Axial T1 postcontrast image showed masses of the left maxillary sinus and sphenoid sinus with intracranial invaded (arrow).



Figure 9. Axial T1 postcontrast image showed the intracranial lesions obviously reduced compared with before (arrow).

presented with dizziness. MRI of the paranasal sinuses showed masses of the left maxillary sinus and sphenoid sinus with intracranial invaded (**Figure 8**).

On physical examination, his visual acuity was normal. Laboratory investigations demonstrated a white blood cell count of $9.04 \times 10^9/L$, absolute neutrophil count of $4.43 \times 10^9/L$, lymphocytes $2.38 \times 10^9/L$, eosinophilic granulocyte $1.52 \times 10^9/L$, hemoglobin 151 g/L, pla-

telets $231 \times 10^9/L$, erythrocyte sedimentation rate (ESR): 21 mm/h. HBsAg(+), HBeAb(+), HBcAb(+), HIV-Ab(-). Surgical debridement of the left maxillary sinus was performed. Periodic acid Schiff stain and alcian blue were conducted in the pathological specimens which revealed cryptococcus infection. As the lesions destroyed the extensive skull base and invaded intracalvarium, there was no opportunity of surgery. A lumbar puncture was performed, the opening pressure was more than 300 mm H₂O.

Examination of the cerebrospinal fluid CSF revealed glucose 2.35 mmol/L, proteins 2.05 g/L, mononuclear cell 157×10^6 /L, multinuclear cell 34×10^6 /L, white cell 239×10^6 /L. The initial treatment was consisted of liposomal amphotericin B at a dose of 1.0 mg/kg per day, 5-flucytosine 6 g/kg per day orally in 4 divided doses and fluconazole 400 mg per day. After 10 weeks, the symptoms slowly improved. For weekly therapeutic lumbar puncture was needed, a total of 6 lumbar punctures was performed. The opening pressure remained 300 mm H₂O. After 8 weeks, MRI of the paranasal sinuses showed the intracranial lesions obviously reduced compared with before (**Figure 9**). The opening pressure was 280 mm H₂O. The patient went to a higher level hospital for continue therapy on week 10.

Discussion

Cryptococcus has a global distribution, mainly distributed in bird droppings, especially the pigeon droppings. Cryptococcosis is more common in immunocompromised patients, including those with impaired cell-mediated immunity, such as HIV, hematologic malignancies, solid-organ transplant recipients, and most commonly associated with sarcoidosis, followed by tuberculosis, steroid therapy and diabetes mellitus [3]. Symptomatic disease does occur in immunocompetent hosts, as evidenced by the recent case descriptions [4, 5]. Cryptococcus often infects the lungs and nervous system, however, the two cases are primary infected in sinuses that classified as chronic invasive granulomatous fungal sinusitis based on the histopathology. There is a granulomatous response with fibrosis, granulomatous inflammation involving the mucosa with fungal hyphae seen within giant cells of granulomas, a typical feature of chronic invasive granulomatous fungal sinusitis [6]. Aspergillus is a common fungi of CIGFS, but chronic invasive granulomatous fungal sinusitis caused by cryptococcus is extremely rare. There are only 5 cases of cryptococcosis affecting the sinus in the English-language literature (**Table 1**).

The diagnosis of cryptococcus infection depends on pathological examination or pathogen detection. Histopathology specimens and cerebrospinal fluid (CSF) can be examined with various stains, including India ink, and more specific stains for the capsular polysaccharide, such as PAS and AB stain. Histopathologi-

cal analysis of the two present cases showed granulomatous inflammation in HE stain, and numerous round-to-oval, non-encapsulated and budding yeast-like cells in AB-PAS stain.

However, cryptococcal sinusitis may be misdiagnosis and missed diagnosis, especially in immunocompetent patient. CIGFS may mimic aggressive neoplastic lesions radiologically, for mass like hyper attenuating soft tissue with bony destruction on CT scan, on MRI, the soft tissue changes were hypointense on T1WI [10, 11]. Histopathology and haematoxylin and eosin-stained (HE) showed granulomatous inflammation, cryptococcus spores were colorless or slightly pale blue or pink in HE stain which easily confused with other granulomatous inflammation, such as tuberculosis and sarcoidosis. Even with special stains, such as Gomori methenamine silver and PAS stain, identify a specific fungal pathogen from tissues is very difficult. Hence, multiple biopsies needed to be taken from various sinuses, as fungal invasion is patchy and the biopsy needed to be repeated if the initial biopsy is negative [12].

Treatment of cryptococcal infection caused by invasive fungal sinusitis is in accordance with the general invasive fungal sinusitis, including radical debridement of necrotic tissues and systemic antifungal antibiotics. Radical debridement of infectious lesions, including orbital exenteration, may be considered in extreme cases, despite the concern over potential surgical complications [13, 14]. Eyeball involvement in case 1, we take orbital exenteration debridement. Unfortunately, as the extensive invasion of skull base and intracranial lesions in case 2, the patient lost the chance of operation.

However, drug treatment of cryptococcal infection remains a problem. The treatment of cryptococcosis depends on the immune status of the host and the clinical manifestations. If immunocompetent CIFS patients after surgery without CNS and fungemia involvement, and infection occurs at a single site, fluconazole treatment (400 mg per day orally for 3 months) should be considered, although guideline recommend 6-12 months. The current guidelines recommend amphotericin B and flucytosine based combination treatment with as induction therapy for non-HIV-infected, nontransplant hosts cryptococcosis followed by consolidation and maintenance therapy with fluconazole [15].

In conclusion, cryptococcal sinusitis is extremely uncommon in immunocompetent patients. It should be highly vigilant no matter in immunocompromised patient or not, as the lesion may be malignant like in radiologic examination and pathology may be show granulomatous inflammation. Special fungal stains and fungal culture should be performed to confirm the diagnosis. Early recognition of cryptococcal sinusitis and appropriate surgery with administration of appropriate antifungal therapy has a great impact on the good prognosis.

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Disclosure of conflict of interest

None.

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