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Case Report

Pulmonary vascular malformation complicating cryptococcal pneumonia in an immunocompetent patient

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Abstract: An immunocompetent 50-year-old male presented with slight cough and occasional lung congestion. The radiologic findings included diffuse, bilateral reticular and one nodular opacity at the upper lobe of right lung without clear margin. A wedge resection of the lesion showed disordered distribution of the medium-sized vessels and arterioles, several arterioles densely gathered including a few occlusive arterioles, or medium veins dilated with irregular and elongated cavity, indicating the existence of vascular malformation. Interestingly, near to the malformed vessels, a large area of necrosis with granulomatous inflammation was found. Of note, numerous intracytoplasmic organisms with a nucleus, a wall and a thick capsule, were free in the alveoli or located within the macrophages and polykaryocytes, suggesting cryptococci infection. This is to our best knowledge the first case showing concurrent vascular malformation and local pulmonary cryptococcosis, and vascular malformation was likely an important pathological predisposing factor for local pulmonary cryptococcosis infection.

Keywords: Pulmonary cryptococci, vascular malformation

Introduction

Cryptococcus is an encapsulated yeast that causes granuloma-pneumonia in both immunocompetent and immunosuppressed individuals [1, 2]. The organism usually enters via the respiratory tract and causes a group of illnesses ranging from asymptomatic infection to severe disease. Chang et al compared the clinical and radiographic characteristics of pulmonary cryptococcosis in immunocompetent and immunocompromised patients, and found that pulmonary cryptococcosis usually follows a benign clinical course in immunocompetent patients, often presenting a more localized, self-limiting lesion. On the contrary, immunocompromised patients often undergo an evolution to cavitary lesions with a more aggressive disease nature [3].

Primary pulmonary cryptococcosis in immunocompetent hosts were found mainly aged <50 years without preexisting lung disease [4]. While more and more cases were identified, small number of patients were reported to have primary pulmonary cryptococcosis associated with local preexisting pulmonary lesions. Guy et al highlighted one interesting case presenting cryptococcal lung inflammation with underlying asbestosis [5]. Another patient with sarcoidosis was found to have limited pulmonary cryptococcal infection following exposure to pigeon excreta [6], then the concept of the pathogenesis of cryptococcus depends on the interplay between the immune status of the host and the virulence of the infecting organisms was proposed [6]. Here, we present one case of a 50-year-old man without prior medical history who had vascular malformation, showing higher alveolar-arterial oxygen difference ($P_{(A-a)}O_2$), while companied by localized cryptococcal pneumonia. This case exemplifies the relatively lower capacity of local ventilation/perfusion mismatch in

resisting the fungal infection because of vascular malformation of the lung.

Case report

A 50-year-old Chinese man complained of right chest pain and slight cough for one month, and a progressive worsening of chest congestion occasionally. Such symptoms became severe after activities in nights. He had no fever, headache, dyspnea, hoarseness or night sweats, hemoptysis or weight loss. He had no history of allergies, never smoked or used illicit drugs. He had no significant medical history and did not own any pets. This study was performed in accordance with the ethical guidelines of the Tongji University Graduate School of Medicine.

Initial examination included a chest X-ray, which showed increase of bilateral lung markings. Of note, there was a mass in the upper lobe of right lung, with a feature of patch and cloudy-like high density without clear margin, suspicious for a malignant lesion. A non-contrast CT of the head did not show any lesion.

Basic laboratory studies revealed white-blood-cell count of $3.9*10^9$ cells/L, with a differential of 5.2 neutrophils, 6.2 lymphocytes, and 0.1 eosinophils. Arterial blood gas analysis revealed higher PaO_2 of 156.0 mmHg (range: 80-100 mmHg), and slightly higher $PaCO_2$ of 46.0 mmHg (normal range: 35-45 mmHg). In addition, both alveolar-arterial oxygen difference ($P_{(A-a)}O_2$) and standard bicarbonate radical (HCO_3^-) were higher, showing 73 mmHg (<8 mmHg) and 25.1 mmol/L (21.3-24.8 mmol/L) respectively.

The patient was hospitalized and underwent a wedge resection of lung for the lesion. Then the specimen was submitted for routine histopathological examination. Upon gross examination, there was a circumscribed grey-white region without clear margin, which was nearly 1.5 cm×1.5 cm with moderately fine texture. Under the microscopy, the disordered distribution of vessels and arteries could be found (**Figure 1A**). The range of lesion was relatively wide and nearly up to pleura. Some arterioles densely gathered including a few occlusive arterioles (**Figure 1B**). In other areas, medium veins with uneven blood vessel wall dilated (**Figure 1C**, Masson stain), showing irregular and elongated cavity (**Figure 1D**). Under the pleura, several small vessels without smooth muscle clustered together (**Figure 1E**). Immunochemistry staining of CD34 showed aforementioned disorders of vessels clearly (**Figure 1F**), indicating the existence of vascular malformation. Interestingly, near the malformed vessels, a large area of necrosis (**Figure 2A**) surrounded by multi-nucleated cells could be observed, showing chronic granulomatous inflammation (**Figure 2B**). Of note, numerous transparent and encapsulated yeast forms with refractivity were also found indistinctly. They were free in the alveoli or located within the macrophages and polykaryocytes, associated with an inflammatory infiltrate in the interalveolar spaces or pulmonary interstitial, predominantly composed of lymphocytes. Periodic acid-Schiff (PAS) (**Figure 2C**) and Grocott's methenamine silver stain (GMS) (**Figure 2D**) showed yeasts with numerous intracytoplasmic organisms, a nucleus, a wall and a thick capsule, consistent with cryptococcosis.

He was treated with fluconazole (400 mg, 6 mg/kg) per day orally for two months. Then he was reported to get a marked improvement in his symptoms and general conditions.

Discussion

Cryptococcus is an encapsulated, haploid yeast that causes disease in both immunocompetent and immunosuppressed individuals. Up to one third of infected immunocompetent patients do not manifest symptoms and the remaining patients present with a variety of symptoms, including fever, cough, dyspnea, and chest pain.

Among the immunocompetent patients, some had preexisting diseases such as asbestos and tuberculosis. But only a few clinical reports [1-3] have linked preexisting disease and pulmonary fungi. However, the vascular malformation followed by pulmonary cryptococcal infection has not been reported. In the present study, we showed one case presenting slight cough and occasional chest congestion, was showed to have a relatively wide region of vascular malformation, while near to this area, the granulomatous inflammation induced by cryptococcal infection did exist.

The local pulmonary vascular malformation leads to structure and hemodynamic changes

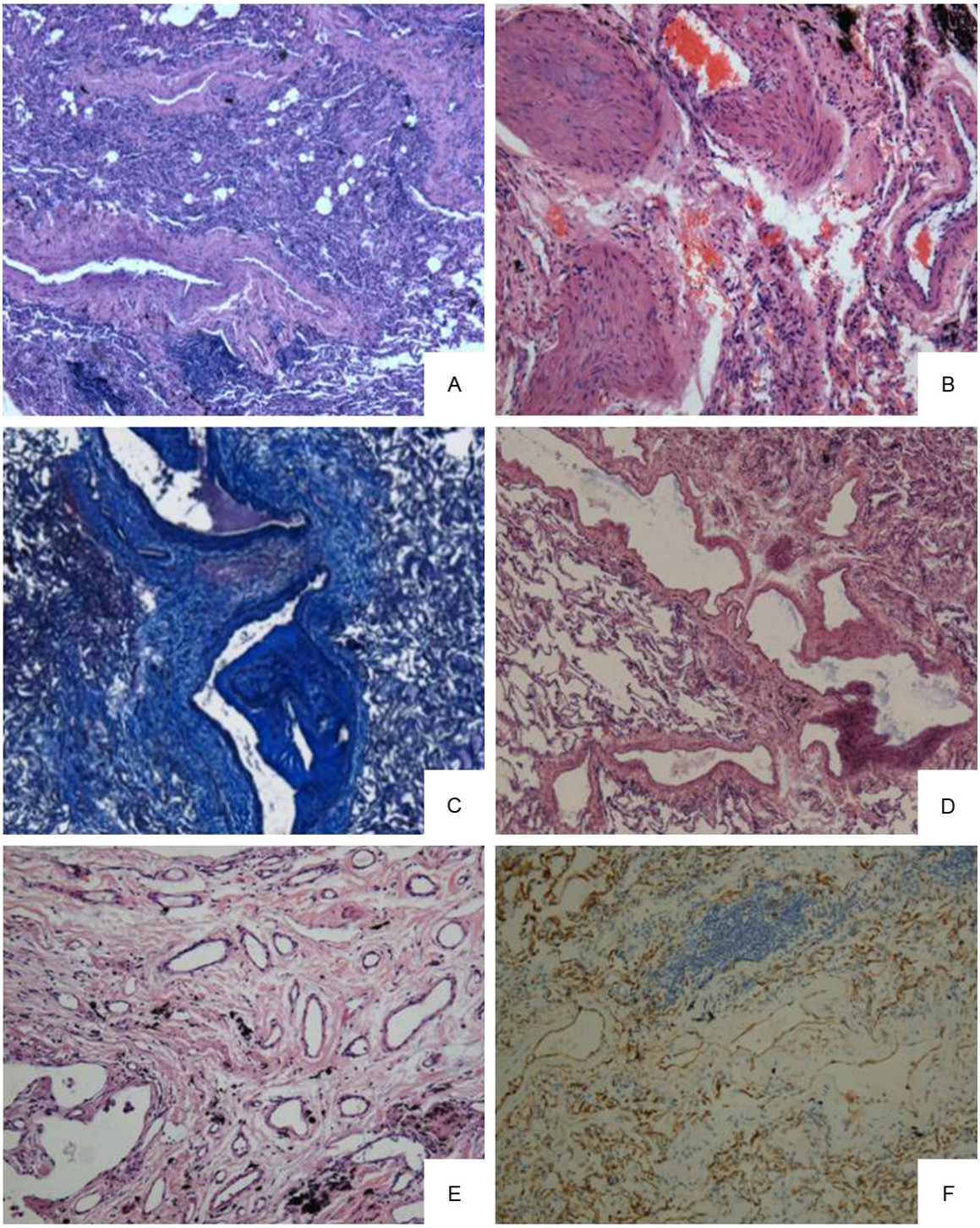

Figure 1. Histology of vascular malformation under microscopy. The lesion exhibited wide area of disarranged vessels (A, Hematoxylin and Eosin stain, ×100 fold). Some arterioles including a few occlusive arterioles gathered (B, Hematoxylin and Eosin stain, ×40 fold). In other area, medium veins showing uneven wall (C, Masson stain, ×40 fold) dilated with irregular and elongated cavity (D, Hematoxylin and Eosin stain, ×40 fold). Under the pleura, several small vessels without smooth muscle focally clustered together (E, Hematoxylin and Eosin stain, ×100 fold), which showing CD34 positivity (F, Immunohistochemistry stain, ×100 fold).

of the lung, so the blood supply to this area may be partially compromised or blood gas exchange and the capacity of excretion of foreign body would be interfered, which converse-

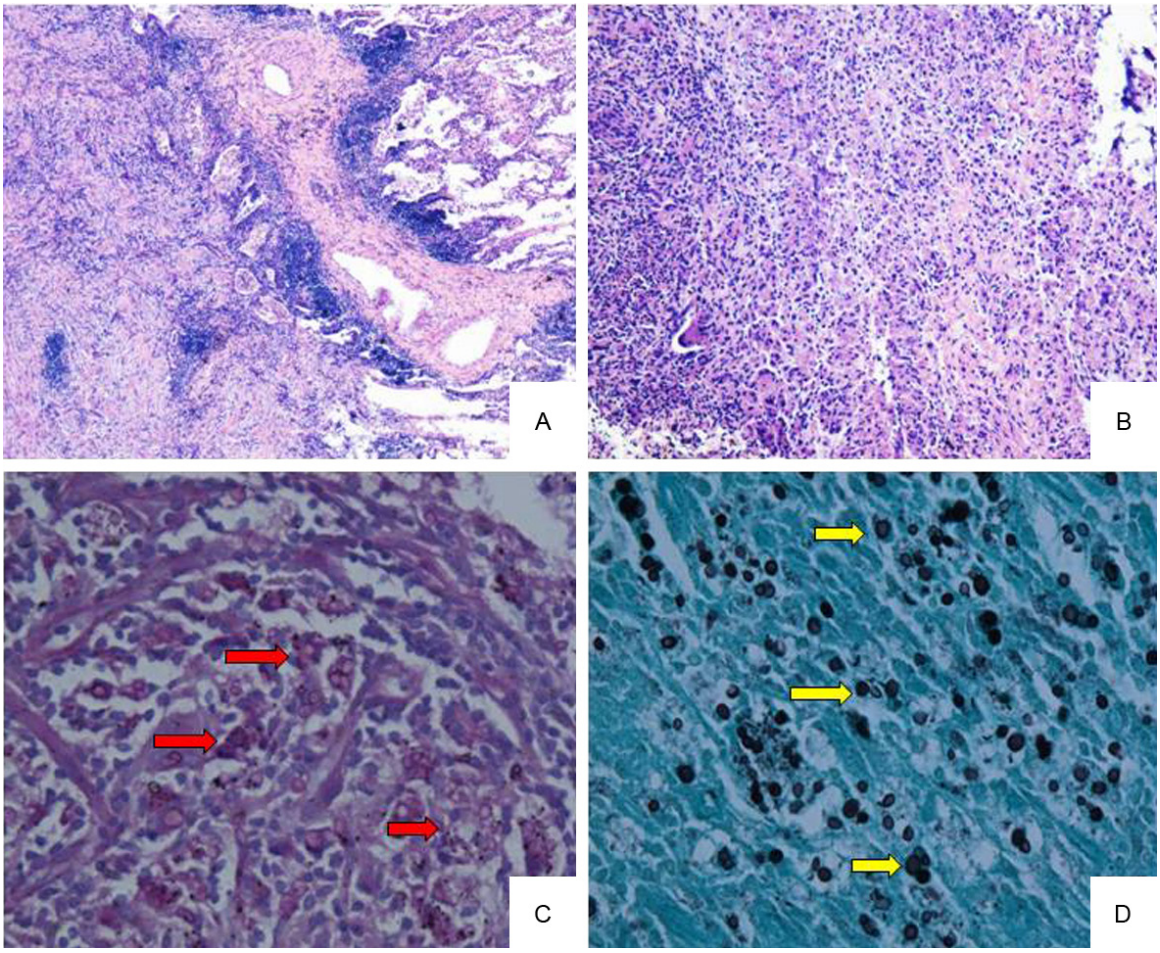

Figure 2. Granulomatous inflammation and cryptococcosis infection near the malformed vessels. (A) Low magnification showed granulomatous inflammation besides the malformed vessels. (B) The large area of necrosis surrounded by multi-nucleated cells, showing chronic granulomatous inflammation. Of note, numerous transparent and encapsulated yeast forms with refractivity and thick capsule were free in the alveoli or located within the macrophages and polykaryocytes. (A and B, hematoxylin and eosin stain, ×40 fold). These organisms were positive for Periodic Acid-Schiff stain (PAS, ×400 fold) (C, arrow) and Grocott's methenamine silver stain (GMS, ×400 fold) (D, arrow), consistent with cryptococcosis.

ly make it more susceptible to inflammation or infectious disease. On the other hand, pulmonary vascular malformation increases the risk for secondary infection, including fungi. In other words, the local vascular malformation might be the predisposing factor for local pulmonary cryptococcosis infection.

In addition, the micro-environmental interaction between local immune status of lung and virulence of cryptococcus is another factor for keeping the persistent existence of cryptococcus in lung. Individuals with defects in T cell-mediated immunity are highly susceptible to infection with cryptococcus. Huffnagle et al verified T cell-deficient athymic (nude) and SCID mice were unable to clear away the infection from their lungs and their pulmonary resistance could be reconstituted in infected SCID mice by the adoptive transfer of anti-cryptococcal immune T cells [7]. So it is likely that the local T cell deficiency in the areas of vascular malformation of lung would be the indirect factor for contribution to cryptococcus infection. Moreover, complement activation plays an important role in protection against infection with cryptococcus. Mershon et al have revealed that both complement component C3-(C3)- and factor B-deficient mice had increased fungal burdens in comparison to wild-type mice through histopathology observation, which undoubtedly prevented efficient gas exchange of

lung [8]. Our patient showed both higher $P_{(A-a)}O_2$ and HCO_3^- than normal level, which might be related with insufficient gas exchange of lung, resulting in the hypoxemia induced by ventilation/perfusion (V/Q) mismatch.

Once cryptococcus colonizes in the lung, infected cells are attacked by macrophages, T cells and NK cells. Age-associated immune dysfunctions are the consequence of declines in both the generation of new naive T and B lymphocytes and the functional competence of memory populations. Our case was a 50 years old patient whose immune system might be in an immunosenescence status. Previous studies have demonstrated an enhanced susceptibility of aged mice to cryptococcus infection [9]. Impairment of a variety of alveolar macrophage functions in association with aging has been described, including the decreased nitric oxide production and cytokine production [10].

In conclusion, we report an interesting case of concurrent vascular malformation and local pulmonary cryptococcosis. His concurrent pulmonary vascular malformation was likely to be an important pathophysiological precursor to his susceptibility to cryptococcus infection.

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Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

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