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Case Report

Case report: Fever- pneumonia- lymphadenectasis- osteolytic-subcutaneous nodule: Disseminated chromoblastomycosis caused by phialophora☆

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ABSTRACT

Chromoblastomycosis (CBM) is a chronic cutaneous and subcutaneous fungal infection caused by certain dematiaceous fungi (usually *Fonsecaea, Phialophora*, or *Cladophialophora)*. Histologically, CBM is characterized by the presence of medlar bodies. However, the diagnosis is difficult because of the rarity of these pathognomonic presentations and the wide variety of presentations. Treatment of these infections is challenging as it lacks standardization. Herein, we report a case of chromoblastomycosis caused by *Phialophora*, in a 42-year-old immunocompetent male agriculturist from the humid and subtropical region of southern China. He had a 3-month history of pneumonia with intermittent fever, coughing, and expectoration. The infection subsequently spread to the bone and lymph nodes forming deep lesions and eventually resulting in osteolysis and lymphadenectasis. These subcutaneous nodules were observed after 9 months. Antifungal treatment was administered for 20 months leading to clinical improvement before the patient was lost to follow-up. This case is unique because such deep lesions are rare in immunocompetent individuals and because the initial onset was associated with pneumonia.

1. Introduction

Chromoblastomycosis (CBM) is defined as a chronic cutaneous and subcutaneous fungal infection resulting from traumatic penetration of certain dematiaceous fungi (usually *Fonsecaea pedrosoi*, *Phialophora verrucosa*, and *Cladophialophora carrionii*) through the skin [1–4]. In a typical manifestation, the dermal lesions can range from small nodules to large papillary-like eruptions. Cases of CBM have been reported worldwide, but its prevalence is higher in rural populations in countries with a tropical or subtropical climate, such as Madagascar in Africa and Brazil in South America. The lesions are rarely inflammatory and may lead to epidermoid carcinomas. Deep lesions remain very rare, except in immunocompromised patients [1–3]. Diagnostic techniques are based on direct examination, culture, and histopathological examination. Histologically, CBM is characterized by the presence of medlar bodies, also known as sclerotic or muriform cells [5]. However, the diagnosis of CBM is difficult because of the rarity of these pathognomonic presentations and the wide range of presentations. The treatment is challenging as it lacks standardization. Herein, we report a rare case of disseminated CBM caused by *Phialophora* in an immunocompetent male patient, and describe the clinical, radiographical, histopathological, and immunohistochemical features of the infection.

2. Case report

A 42-year-old male agriculturist from the Guangxi Province of China was admitted to the outpatient department in October 2015 with a 3-month history of intermittent fever (with a peak temperature of 40.5 °C), coughing, and expectoration that had developed after he had sprayed pesticides (dimethoate, methamidophos, dichlorvos, paraquat) and handled the treated soil with his bare hands. He had a peculiar personal history, such as killing and eating several bamboo rats and freshwater sashimi, and drinking raw sheep blood. He had not taken any immunosuppressive drugs.

Abbreviations: CARD9, caspase activation and recruitment domains 9 gene; CBM, chromoblastomycosis; HRCT, high-resolution computed tomography; PAS, Periodic acid-Schiff.

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Routine blood examination revealed a leukocyte count of 17.5 × 10^{-9}/L, neutrophil percentage of 58.7%, eosinophil percentage of 12.2%, and hemoglobin level of 71 g/L. Microbiological cultures of blood, bone marrow, and sputum yielded negative results. High-resolution computed tomography (HRCT) of the chest showed exudate disseminated throughout both lung fields, especially in the lower lung (Fig. 1A and B). Based on the characteristic imaging findings and clinical manifestations, a diagnosis of community-acquired pneumonia was confirmed. He received a 6-week antibiotic regimen of levofloxacin, piperacillin sulbactam, meropenem, vancomycin, clindamycin, and linezolid. Post-treatment chest HRCT showed that the lesions were larger than their pretreatment size and the patient's condition had worsened. He was then administered fluconazole intravenously for superinfection at a dose of 400 mg/d. Three weeks later, the patient's temperature had dropped to normal, and the signs and symptoms showed improvement. Thus, only the oral fluconazole 400 mg/d was continued and the patient was discharged. After three weeks, the patient stopped taking the oral fluconazole by himself.

Four months later, the patient developed hyperpyrexia accompanied by severe coughing and expectoration after he had sprayed pesticides. Symptomatic subcutaneous nodules developed on the right forehead, left shoulder, and bilateral anterior tibia (Fig. 2). A physical examination revealed the body temperature to be 41 °C. Several lymph nodes were palpable in the left neck. Chest HRCT revealed aggravation of the lung lesions, enlargement and calcification of the mediastinal lymph nodes, and dissemination of exudate throughout the left lower lobe (Fig. 1C and D). Hepatomegaly was visible in the brightness mode. Bronchoscopy revealed mucosal congestion. A routine blood examination revealed a leukocyte count of 24.8 × 10^{-9}/L, neutrophil percentage of 70.7%, eosinophil percentage of 12.3%, and hemoglobin level of 73.4 g/L. The CD + T cell concentration was 1491 cells/L, and the CD4+-to-CD8+T cell ratio was 2.38. The C-reactive protein level was 105.5 mg/L, and the erythrocyte sedimentation rate was 92 mm/h. The galactomannan antigen level was 0.552. He tested negative for plasma beta-D-glucan, antistreptolysin O, antinuclear antibody, and rheumatoid factor. Microbiological cultures of blood, sputum, and bronchoalveolar lavage fluid and HIV testing of blood samples yielded negative results. These tests were repeated several times to ensure the reliability of the results. X-ray imaging revealed moth-eaten bone destruction and periosteal proliferation in the left tibia (Fig. 3). Emission computed tomography showed significantly increased uptake in the skull, left clavicle, limbs, and joints (Fig. 4). A biopsy was performed for nodules in the left shoulder and lymph nodes in the left neck. Histopathological analyses of the biopsied specimens revealed that most of the tissue was destroyed. Hyperkeratotic epidermal hyperplasia and many micro-abscesses were observed, accompanied by fibrinoid necrosis in the walls of the small blood vessels, with scattered eosinophils and individual

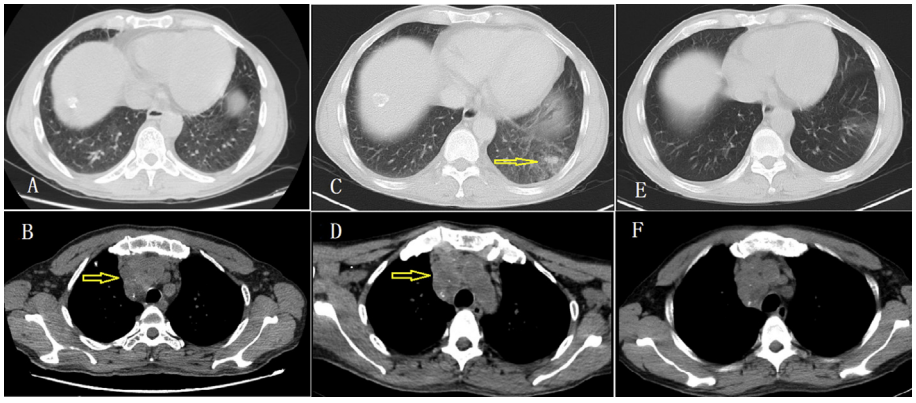

Fig. 1. Chest high-resolution computed tomography revealing exudate disseminated throughout both lung fields, especially in the lower lung (Fig. 1A and B). Lung lesions with multiple enlarged and calcified mediastinal lymph nodes, and disseminated exudate throughout the left lower lobe (Fig. 1C and D). Post-treatment chest HRCT showed that the lesions were completely resorbed after antifungal treatment. (Fig. 1E and F).

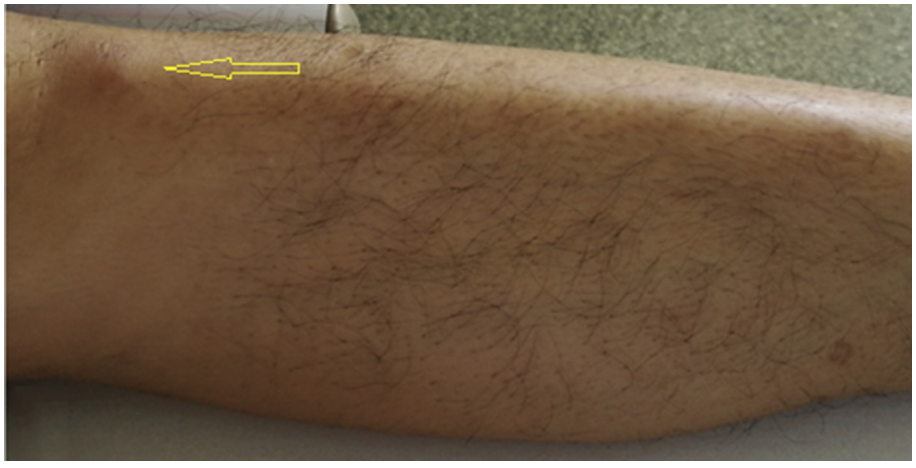

Fig. 2. An asymptomatic subcutaneous nodule on the left bilateral anterior tibia.

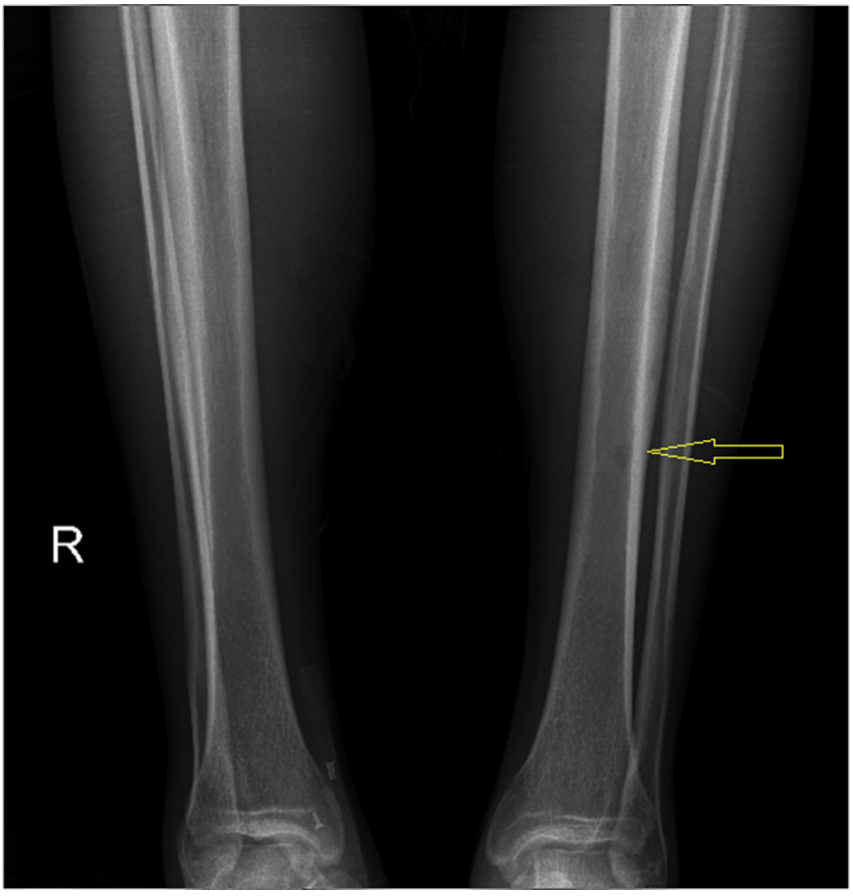

Fig. 3. X-ray imaging showing moth-eaten bone destruction and periosteal proliferation in the left tibia.

multinucleated macrophages (Fig. 5). Pathological examination of lung tissue showed macrophage aggregation in the focal alveolar space. Periodic acid-Schiff (PAS) and acid-fast staining of lung tissue, lymph nodes, and the subcutaneous nodules yielded negative results. *Phialophora* was isolated 2 weeks later from the lung, subcutaneous nodule, and lymph node cultures in Sabouraud dextrose agar at 25 °C and 37 °C. The isolated fungi formed black colonies, which were ash-gray in the middle and greenish-black at the back (Fig. 6). Finally, based on the clinical presentation, histopathology, and fungal culture results, disseminated CBM caused by *Phialophora i*nvolving the lungs, lymph nodes, bone, and subcutaneous tissue was diagnosed. The patient received intravenous liposomal amphotericin B (1 mg/kg per day) combined with oral itraconazole (200 mg twice daily) for 2 weeks. He showed significant improvement. In addition, post-treatment chest HRCT showed that the lesions were completely resorbed after antifungal treatment. (Fig. 1E and F). Subsequently, he was referred to a local hospital for antifungal treatment with intravenous liposomal amphotericin B (1 mg/kg per day) combined with oral itraconazole (200 mg twice daily) for 6 weeks. After that, he received oral fluconazole 400 mg/d only for 12 weeks. No relapse was observed during the 18-month follow-up during which he was treated only with oral fluconazole 400 mg/d.

3. Discussion

CBM is a chronic fungal dermatosis that mainly affects the lower limbs. Although traumatic inoculation from thorns or wood splinters is a likely source of infection [5,6], the infection process and route of dispersal have been insufficiently elucidated, particularly in disseminated cases [1,5]. The first manifestation is a papule that progressively evolves into a keratotic or squamous verrucous nodule, which may look like a tumor nodule or a psoriasiform or atrophic plaque. Lesions are usually neither painful nor prurient [1–5]. However, the present case had an acute onset with hyperpyrexia and pneumonia, and the first lesion site was the lung, not the cutaneous and subcutaneous tissue. Subsequent dissemination resulted in the formation of deep lesions in the bone and lymph nodes. This indicates that other than transcutaneous wounds, the respiratory tract may also be a likely route of the onset and spread of CBM.

Phialophora is commonly found in the environment but causes infection only infrequently due to its low pathogenicity. The disease is usually insidious, and the lesions increase slowly [5]. Deep lesions in CBM remain very rare, except in immunocompromised patients [1,5,7]. However, in the case described herein, deep lesions were found in the lymph nodes and bone, and subcutaneous nodules were observed after 7 months in an immunocompetent patient, which is very rare.

The patient in this case had a unique life and occupational history. In particular, his dietary habit was quite unique, with an elevated risk of infection from various pathogens. Thus, infections from parasites and *Talaromyces marneffei* were suspected. But traumatic inoculation from thorns or wood splinters is a major source of infection for CBM [5,6]. Furthermore, the episodes related to when the patient began to suffer from cough and fever all occurred after spraying pesticides with his bare hands. There was a clear back-and-forth relationship between his work and the

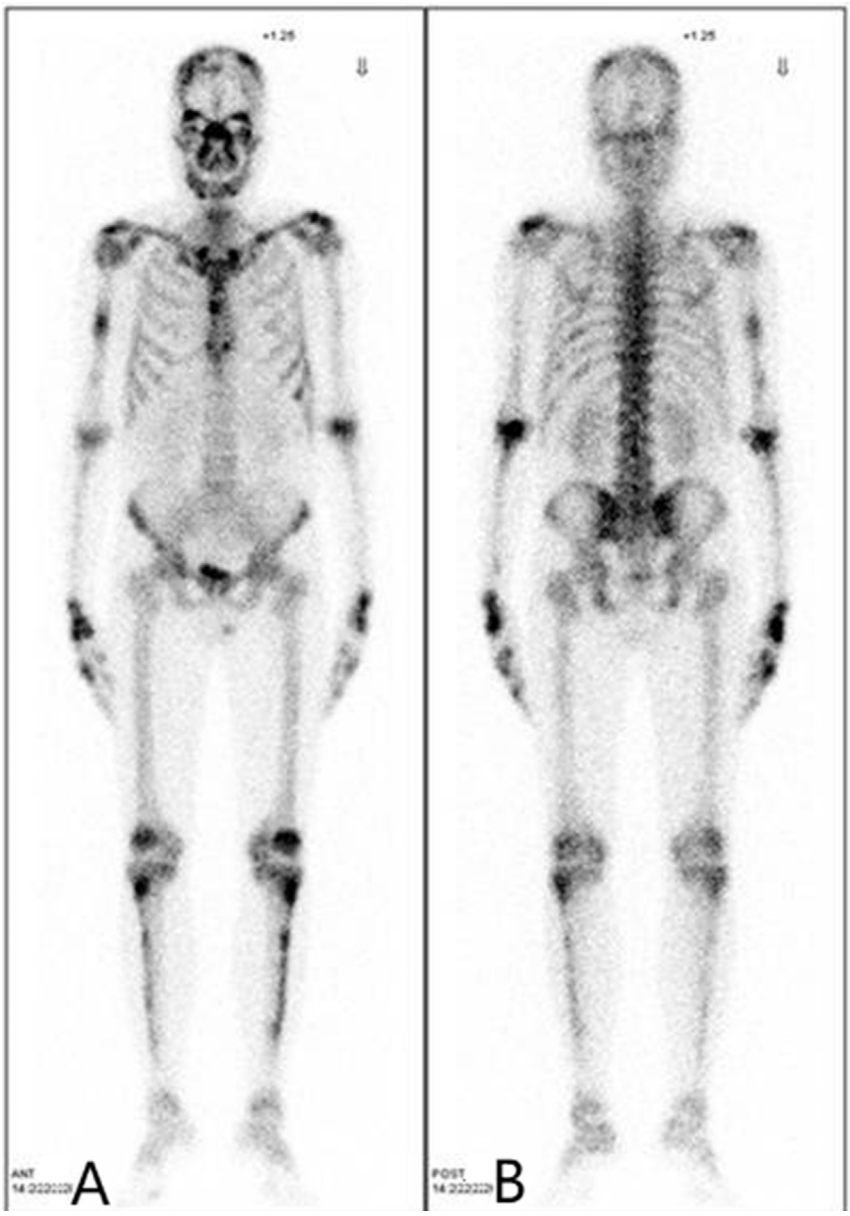

Fig. 4. Emission computed tomography showing significantly increased uptake in the skull, left clavicle, limbs, and joints.

disease. Thus, repeated exposure to spores from the environment, leading to traumatic inoculation from thorns or splinters in the soil, was the most likely source of infection for this disseminated mycoses case. But our patient did not have HIV or any other underlying diseases. He and his family lived on the farm in the same environment, but only he was infected with *Phialophora*. The reasons for this are not yet clear.

Recently, several studies have shown that anti−IFN−γ autoantibodies may play an important role in opportunistic pathogenic infections, autoimmune disease, and adult-onset immunodeficiency in patients with severe immune system defects [8−10]. Studies have reported mutations of the caspase activation and recruitment domains 9 gene (*CARD9*) in patients presenting with disseminated infections caused by *Exophiala* spp [11]. These mutations lead to loss of function of CARD9 and alter the fungicidal capacities of monocytes, macrophages, and microglial cells. Hence, investigation of primary immunodeficiency diseases, especially CARD9 deficiency, would be interesting in patients presenting with disseminated infections. Although we did not examine the patient for anti−IFN−γ autoantibodies and *CARD9* mutations, these might have been the cause of the deep disseminated infections.

The unique onset, varied clinical presentations of CBM, and insidious and delayed cutaneous dissemination in this patient made the diagnosis difficult. A pathological biopsy and especially mycological culture should therefore be performed in patients presenting with chronic tumor-like lesions in countries where this infection is endemic. However, if chronic cutaneous and subcutaneous nodules are absent, the possibility of deep tissue involvement associated with the dissemination type need to be considered carefully, and a pathological biopsy and especially mycological culture from multiple sites should be obtained.

Treatment of infections caused by dematiaceous fungi is challenging as it lacks standardization. The treatment usually involves surgical excision that may be coupled with antifungal treatment. The best therapeutic option for cutaneous CBM seems to be a combination of surgical treatment and antifungal treatment (azole

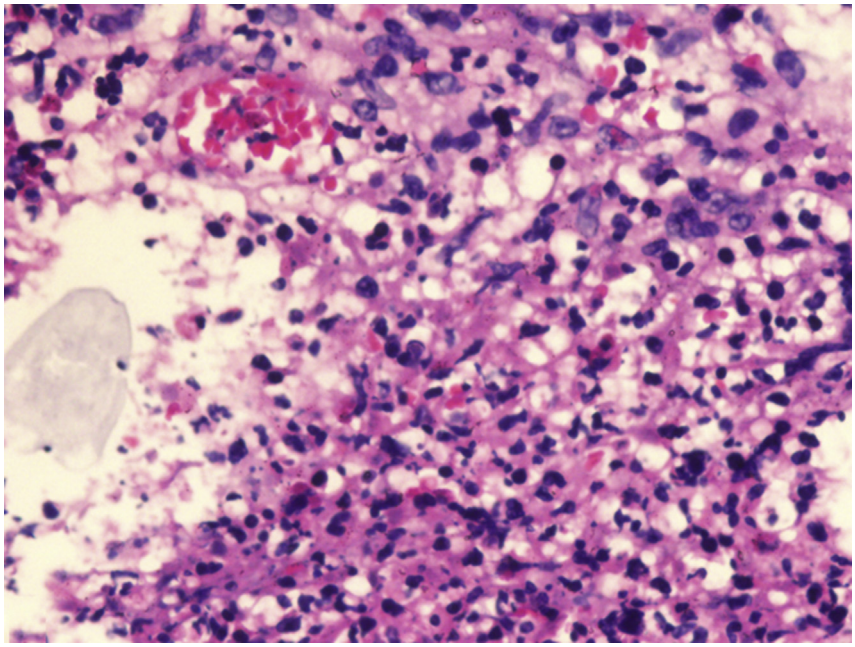

Fig. 5. Histopathological analysis of lymph nodes in the left neck shows that most of the structure is destroyed. Hyperkeratotic epidermal hyperplasia and many micro-abscesses are observed, accompanied by fibrinoid necrosis in the walls of the small blood vessels, with scattered eosinophils and individual multinucleated macrophages.

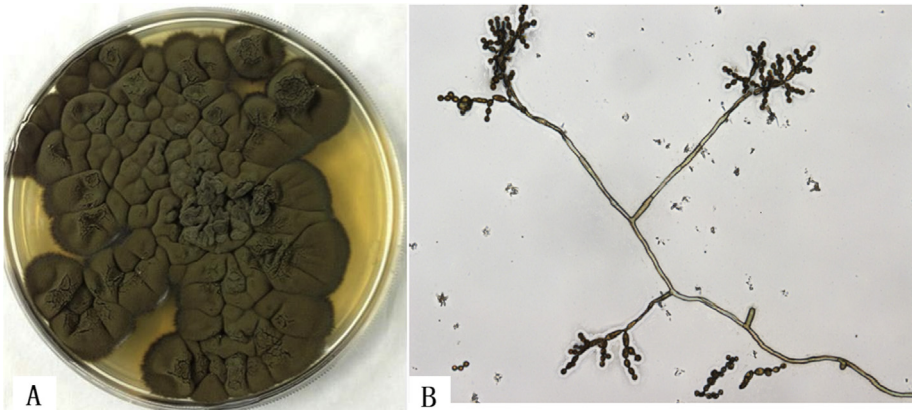

Fig. 6. *Phialophora verrucosa* was isolated 2 weeks later from the lung, subcutaneous nodule, and lymph node cultures in Sabouraud dextrose agar at 25 °C and 37 °C. The isolated fungi produced black colonies, which were ash gray in the middle and greenish black at the back (6A). Direct microscopic examination revealed the presence of flask-shaped phialide, cup-shaped collarette, and hyphae that produced elliptical microconidia (6B).

antifungal agent and/or terbinafine) [5,12,13]. When surgical excision is complete and in patients with only a single lesion, the antifungal treatment is not necessary [14]. However, cutaneous CBM is difficult to eradicate when it is disseminated. The global cure rate is approximately 30% [5]. Antifungal agents are moderately active in countries with access to such treatments and relapses are frequent [5]. The medical treatment must be administered at the very least for several months to reduce the risk of relapse, but there is no consensus on the treatment duration.

Disseminated CBM is associated with a poor prognosis. Early diagnosis and treatment are essential when deep tissues are involved. Survival also depends on the control of any immunodeficiency. Our patient presented with involvement of the lung, bone, lymph nodes, and subcutaneous nodules, and was treated with medication only. Antifungal treatment administered for 20 months resulted in clinical improvement before the patient was lost to follow-up. Despite a variety of treatment modalities, which include long courses of antifungal agents, surgical excision, and destructive physical therapies, the disease remains one of the most difficult-to-treat deep mycotic infections.

Ethical statement

This study was approved by the ethics committee associated with the Faculty of Medicine at The First Affiliated Hospital of Guangxi Medical University. The patient received an explanation regarding the study's objectives in his own language, and he provided written informed consent for the treatment and our subsequent data analysis. Copies of the written consent forms are available for review by the Editor of this journal.

Conflicts of publication

All authors of the manuscript have read and agreed to the conditions of submission.

Conflicts of interest

None.

Authors' contributions

Conceived and designed the experiments: YQ, JZ, and YT. Analyzed the data: YQ, JD, and YT. Contributed analysis software: XZ. Wrote the paper: YQ, YT and JZ. All authors have read and approved the final manuscript.

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