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Myositis due to *Cryptococcus neoformans* in a Diabetic Patient

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We report a rare case of cryptococcal myositis with dissemination to lung in a 66-year-old diabetic woman who had no apparent risk factors for cryptococcal disease. She visited the hospital with a continuous pain in the right thigh and fever despite of treatment with antibiotics. She developed a localized lung infiltration. *Crytococcus neoformans* was isolated from the abscess of the right thigh and confirmed by molecular identification with DNA sequence analysis. Biopsy of the involved lung showed numerous budding yeasts consistent with *Cryptococococcus* species. The patient was successfully treated with surgical drainage and systemic antifungal agents. **(Korean J Clin Microbiol 2009;12:141-143)**

Key Words: *Cryptococcus neoformans*, Myositis, Diabetes mellitus, Sequence analysis

INTRODUCTION

Cryptococci are opportunistic yeasts that typically infect immunocompromised hosts, and infections are most often caused by *Cryptococcus neoformans*. The most commonly involved site of cryptococcosis is the central nervous system. Cryptococci may also involve the skin, lungs, eyes, bones and joints[1]. Myositis is usually caused by Gram-positive bacteria, such as *Staphylococcus aureus* and *Streptococcus* species. *C. neoformans* infections rarely presented with infectious myositis and usually occurred in the setting of disseminated cryptococcal disease among immunocompromised patients[2,3].

We report a case of cryptococcal myositis with pulmonary dissemination caused by *C. neoformans* with no risk factors for cryptococcal infection, except diabetes mellitus (DM).

CASE REPORT

A 66-year-old woman was transferred from a local clinic to our hospital because of persistent fever and pain in her right thigh despite of treatment with empirical systemic antibiotic agents for 2 weeks. She had been diagnosed with type 2 DM a year ago, and was taking oral hypoglycemic agents. She has no history of trauma to the leg. On physical examination, the temperature was 38.7°C (101.6°F), blood pressure 130/90 mmHg, pulse 82 beats per minute, and respiration 24 breaths per minute. Auscultation of the lung revealed inspiratory fine crackles in the left lung field. Her right thigh was tender, swollen, red, and warm. The remainder of the physical examination was normal.

The initial laboratory examination obtained the following values: white blood cell count, 23.45×10^9/L; hemoglobin, 10.7 g/L; hematocrit, 30%; and platelet count, 441×10^9/L. The serum glucose was 10.2 mmol/L. The erythrocyte sedimentation rate and C-reactive protein were elevated at 53 mm/h and 185 mg/L, respectively. The serological tests for HIV infection were negative. The chest radiograph showed multifocal patchy opacities confined to the left lung. There was no evidence of deep venous thrombosis on a duplex ultrasound study of the lower extremities. To further evaluate the swollen right thigh, computed tomography (CT) of the lower extremites was performed and revealed a low-density fluid collection within the vastus muscle of right thigh (Fig. 1). Aspiration of the lesion yielded yellow and mucoid fluid proceeded for the microbiological culture. Ciprofloxacin and amikacin were administered empirically for treatment of a possible bacterial pneumonia and pyomyositis. However, fever persisted despite the initial use of broad-spectrum antibiotic agents for 3 days, the patient underwent an emergent surgical drainage of her right thigh. The multiple patch lesions on the left lung persisted despite the continued antimicrobial therapy. CT of the chest showed multifocal peripheral consolidation in the left lung. A percutaneous transthoracic needle biopsy of the peripheral lung lesions was performed. Histologic examination of lung biopsy specimens showed that variable-sized yeast cells were seen on light microscopy and occasional narrow-based single budding yeasts consistent with *Cryptococcus* species were observed within giant cell granulomas on the Gomori methenamine silver stain

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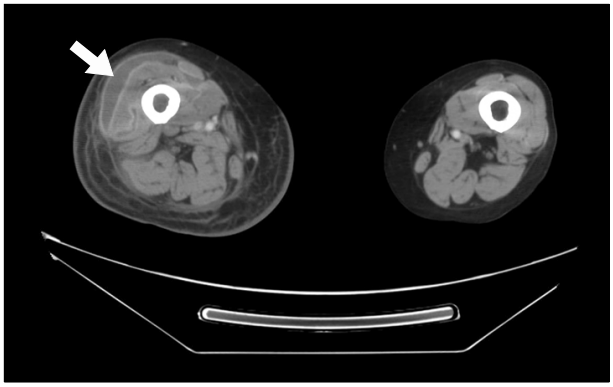

Fig. 1. Enhanced CT of the patient's lower extremity reveals swelling of the right gluteus medius muscle and fluid collection (arrow) between the fascia lata and vastus muscle. There is no evidence of bone involvement.

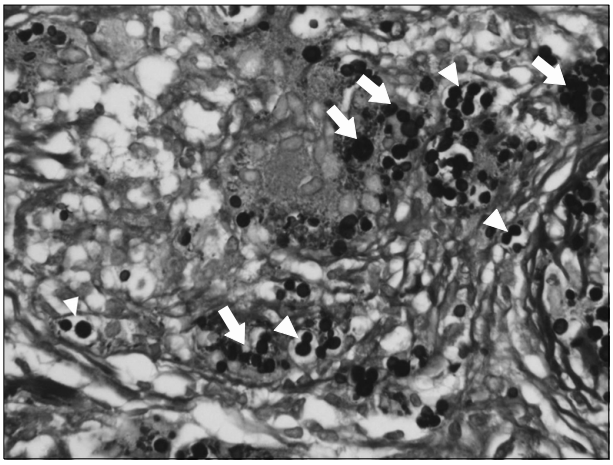

Fig. 2. Lung biopsy specimen shows variable sized, small round fungal spores with surrounding clear halo (arrow head). Most spores are found within giant cells in granulomas (arrow) (Gomori methenamine silver (GMS) stain, original magnification ×400).

(Fig. 2). The microorganism was grown on the culture of surgically drained pus and identified as *Cryptococcus neoformans*. Biochemical reaction tested by Vitek-2 system (BioMeriux Vitek Inc., Durham, NC) using YST card revealed *C. neoformans* with a probability of 93%. Chromosomal DNA was isolated with i-genomic BYF DNA Extaction Mini Kit (iNtRON Biotechnology Inc., Sungnam, Korea) according to the manufacturer's manual. To confirm the DNA sequence of the isolate, 18S rRNA was amplified with 18SF and 18SR primer set and 5.8S rRNA-28S rRNA with internal transcribed spacer 3 (ITS3) and ITS4 primer set[4]. The sequences of primers are as follows: 18SF, ATT GGA GGG CAA GTC TGG TG; 18SR, CCG ATC CCT AGT CGG CAT AG; ITS3, GCA TCG ATG AAG AAC GCA GC; ITS4, TCC TCC GCT TAT TGA TAT GC. The isolate was identified as *C. neoformans* with a probability of 96% with 18S and 95% with ITS primer set. A lumbar puncture was done. The cerebrospinal fluid (CSF) contained no cells, glucose of 91 mg/dL and protein of 41.0 mg/dL. India ink stain, cryptococcal antigen and fungal culture of the CSF were negative.

After completing a 35-day course of treatment with intravenous amphotericin B at 1 mg/kg/day, the patient was discharged from the hospital on oral fluconazole 400 mg/day. Repeat CT performed 3 months later showed resolution of the muscle abscess and lung lesion. One year after discharge, the patient remained free of infection while taking oral fluconazole.

DISCUSSION

C. neoformans is the most frequent *Cryptococcus* species found as a human pathogen. However, human cryptococcal infection occurs mostly in immunocompromised patients, such as those with AIDS, lymphoreticular malignancy, immunosuppression after corticosteroid therapy or organ transplantation or, infrequently, liver cirrhosis[5,6].

Initially the diagnosis of cryptococcosis was not suspected in this case, because the patient was not immunocompromised. Skin and soft tissue involvement of cryptococcal infection is rare[7] and only a handful of cases of cryptococcal myositis have been reported[2,8,9]. A case of cryptococcal infection that involve the skeletal muscle has been described in a patient with diabetes mellitus, but he also had another risk factor for cryptococcosis[10,11]. In domestic case, one case was reported about cryptococcal tenosynovitis with multiple lung nodules in the patient with Wegener's granulomatosis[12]. However, this is the first case that *C. neoformans* involved to the muscle.

Cryptococcal soft-tissue infection serves as a marker of disseminated cryptococcosis[13]. In our case, cryptococcal myositis developed in a patient with DM, and disseminated pulmonary infiltration was proven pathologically. We assumed the primary infection began in the right thigh and the organism spread to the left lung via blood stream.

Cryptococcus species is not easy to identify only by biochemical tests requiring molecular biology techniques for the accurate identification. The authors analyzed the DNA sequences of 18S rRNA and ITS genes. These genes are commonly used for the molecular identification of the yeasts.

Our treatment decision was based on the recommended management for *C. neoformans*[14]. Although fluconazole has been used as the initial therapy in selected patients, such patients require aggressive antifungal chemotherapy. Our patient was given amphotericin B for 5 weeks, followed by oral fluconazole for 1 years. She responded to this therapy adequately, resulting in resolution of the myositis and clearance of the lung lesions.

Since cryptococcal infection is treatable, prompt recognition of the disease is important. As the fungal organisms rarely cause myositis; the diagnosis is difficult, and the mortality is increasing. Although unusual, *Cryptococcus* should be considered in the differential diagnosis of myositis, particularly in refractory cases with antibiotics.

REFERENCES

1. Chayakulkeeree M and Perfect JR. Cryptococcosis. Infect Dis Clin North Am 2006;20:507-44.
2. Sharma M, Khatib R, Jones BA, Fakih MG. *Cryptococcus Neoformans* myositis without dissemination. Scand J Infect Dis 2002; 34:858-9.
3. Crum-Cianflone NF. Bacterial, fungal, parasitic, and viral myositis. Clin Microbiol Rev 2008;21:473-94.
4. Millar BC, Xu J, Earle JA, Evans J, Moore JE. Comparison of four rDNA primer sets (18S, 28S, ITS1, ITS2) for the molecular identification of yeasts and filamentous fungi of medical importance. Br J Biomed Sci 2007;64:84-9.
5. Khawcharoenporn T, Apisarnthanarak A, Mundy LM. Non-neoformans cryptococcal infections: a systematic review. Infection 2007;35:51-8.
6. Kontoyiannis DP, Peitsch WK, Reddy BT, Whimbey EE, Han XY, Bodey GP, et al. Cryptococcosis in patients with cancer. Clin Infect Dis 2001;32:E145-50.
7. Baer S, Baddley JW, Gnann JW, Pappas PG. Cryptococcal disease presenting as necrotizing cellulitis in transplant recipients. Transpl Infect Dis 2009;11:353-8.
8. O'Neill KM, Ormsby AH, Prayson RA. Cryptococcal myositis: a case report and review of the literature. Pathology 1998;30:316-7.
9. Flagg SD, Chang YJ, Masuell CP, Natarajan S, Hermann G, Mendelson MH. Myositis resulting from disseminated cryptococcosis in a patient with hepatitis C cirrhosis. Clin Infect Dis 2001; 32:1104-7.
10. Chakrabarti A, Chatterjee SS, Shivaprakash MR. Overview of opportunistic fungal infections in India. Nippon Ishinkin Gakkai Zasshi 2008;49:165-72.
11. Gupta RK, Khan ZU, Nampoory MR, Mikhail MM, Johny KV. Cutaneous cryptococcosis in a diabetic renal transplant recipient. J Med Microbiol 2004;53:445-9.
12. Chung SM, Lee EY, Lee CK, Eom DW, Yoo B, Moon HB. A case of cryptococcal tenosynovitis in a patient with Wegener's granulomatosis. J Korean Rheum Assoc 2004;11:66-71.
13. Gave AA, Torres R, Kaplan L. Cryptococcal myositis and vasculitis: an unusual necrotizing soft tissue infection. Surg Infect (Larchmt) 2004;5:309-13.
14. Saag MS, Graybill RJ, Larsen RA, Pappas PG, Perfect JR, Powderly WG, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. Clin Infect Dis 2000;30:710-8.

=국문초록=

당뇨 환자에서 *Cryptococcus neoformans*에 의해 발생한 근염

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허상택[1,3], 배인규[1,3], 박진용[1], 김선주[2,3]

저자들은 뚜렷한 감염 위험인자가 없는 66세 여자 당뇨 환자에서 cryptococcus 근염을 경험하였기에 보고한다. 환자는 지속되는 우측 장딴지 동통과 발열로 내원하였는데 항생제 치료에 효과가 없었고, 오히려 국소적인 폐 침윤이 발생하였다. 우측 장딴지의 화농에서 배양한 진균은 생화학적 방법과 DNA 염기서열분석에서 *Cryptococcus neoformans*로 동정되었고, 폐 조직 생검에서도 cryptococcus를 시사하는 다수의 효모가 관찰되었다. 환자는 수술적으로 배농을 시행하고 항진균제를 투여한 후 회복되었다. **[대한임상미생물학회지 2009;12:141-143]**

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