Disseminated fusariosis in leukemia patient

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ABSTRACT:

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Disseminated fusariosis is an infection caused by *Fusarium* spp. that primarily affects patients with hematologic malignancies and hematopoietic stem cell transplant recipients.[1] The infection typically involves pulmonary system and can lead to metastatic skin lesions. The portal of entry is the airway through inhalation of aerosols of fusarial conidia or direct skin penetration.[2] We reported the refractory acute lymphocytic leukemia patient with disseminated fusariosis who presented with fever and characteristic skin lesions. He also had invasive pulmonary and muscle infection which can be identified by imagin.

Key words: Disseminated fusariosis, leukemia

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บทคัดย่อ:

วริษฐา ไมตรีสถิต*, วศิน วาสิกะสิน, ชุติกา ศรีสุทธิยากร* รายงานผู้ป่วยที่มีการแพร่กระจายของฟิวซาเรียม ในผู้ป่วยที่มีภาวะมะเร็งเม็ดเลือดขาวเอแอลแอล วารสารโรคผิวหนัง 2561; 34: 292-298.**

**แผนกผิวหนัง*

***แผนกโรคติดเชื้อ กองอายุรกรรม โรงพยาบาลพระมงกุฎเกล้า*

การแพร่กระจายของฟิวซาเรียมในร่างกาย (Disseminated fusariosis) เกิดจากการติดเชื้อราในกลุ่ม *Fusarium* spp.มักเกิดในกลุ่มผู้ป่วยที่มีภาวะภูมิคุ้มกันของร่างกายต่ำโดยเฉพาะในกลุ่มผู้ป่วยที่เป็นมะเร็งเม็ดเลือดและกลุ่มผู้ที่ได้รับการปลูกถ่ายเซลล์ต้นกำเนิดของเม็ดเลือดและองค์ประกอบของเลือดโดยติดเชื้อได้จากระบบทางเดินหายใจเอาสปอร์ของเชื้อฟิวซาเรียมหรือจากทางผิวหนังที่มีบาดแผลนำมาก่อนซึ่งสามารถเป็นทางเข้าของเชื้อได้

รายงานฉบับนี้เป็นการนำเสนอผู้ป่วยอายุ 22 ปี มีโรคประจำตัวคือมะเร็งเม็ดเลือดขาวชนิดลิมโฟไซติกได้รับการวินิจฉัยว่ามีการติดเชื้อราฟิวซาเรียมในร่างกาย มาด้วยอาการไข้ ผื่นทั่วร่างกาย รวมถึงมีการติดเชื้อราที่ปอด และที่กล้ามเนื้อโดยวินิจฉัยได้จากการทำเอกซเรย์คอมพิวเตอร์ซีทีสแกนบริเวณปอดและอัลตราซาวด์ที่บริเวณขาทั้งสองข้าง

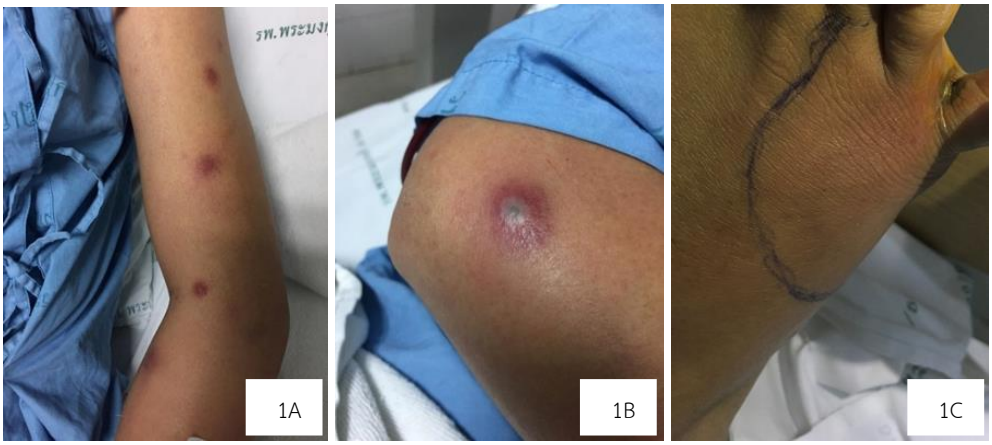
คำสำคัญ: การแพร่กระจายของฟิวซาเรียม, มะเร็งเม็ดเลือดขาว

Case report

A 22 year-old Thai man presented with high grade fever and an ulcer on right foot for 1 day. He had an underlying disease of refractory acute lymphocytic leukemia (ALL) with CNS involvement and a had status of post chemotherapy 14thday. Two days after fever, he developed multiple tender red bumps on his trunk and extremities. Physical examinations revealed body temperature (BT) 38.5°c, blood pressure (BP) 110/60 mmHg, pulse rate (PR) 110/min, respiratory rate (RR) 20/min. Cutaneous examinations showed an ulcer with necrotic crust, surrounded with mild tender and erythema on fourth and fifth interdigital spaces on right foot. There were also multiple erythematous to purpuric indurated nodules with ill-defined borders on scalp, face, trunk and extremities. Some lesions had central necrosis which resembled target-like lesion (Figures 1a,1b,1c). No mucosal involvement was found. Other examinations were unremarkable. Septic work up was obtained and showed marked leukopenia (WBC=100/mm3, ANC=0). Renal function and liver function tests were normal.

The skin biopsy was done from an indurated nodule on right forearm and revealed epidermis and sweat glands necrosis with sparse perivascular infiltration with lymphocytes and extravasated red blood cells. There were vascular thrombosis with red blood cell stagnation. Numerous large septate hyphae were

found in vascular lumens and also in vascular walls and dermis (Figure 2a,2b,2c). The Periodic acid-Schiff (PAS) and Gomori Methenamine-Silver (GMS) stains highlighted numerous large septate hyphae. Tissue culture and hemoculture confirmed the disseminated fungal infection which showed positive for *Fusarium* spp.



Figures 1A, 1B, 1C The pictures reveal multiple ill-defined border erythematous to purpuric indurated nodules with ill-defined borders on trunk and extremities. Some lesions have central necrosis which resemble target-like lesion.

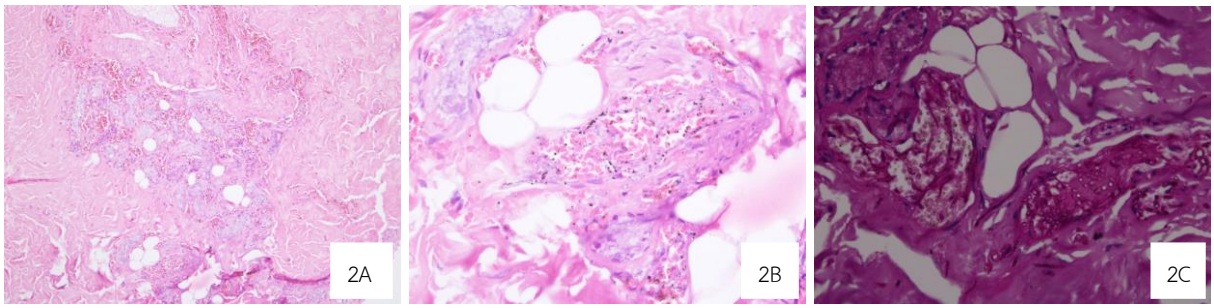


Figure 2A, 2B, 2C The skin biopsy from right forearm shows sweat glands necrosis with stagnation of red blood cells and thrombosis in vascular lumens. (Figure 2A, Hematoxylin & eosin stain, x 200) There are numerous septate hyphae in vascular lumens. (Figure 2B, H&E stain, x400) The PAS stain highlights numerous septate hyphae in vascular lumens and walls. (Figure 2C, x400)

Further investigations was processed and revealed an abnormal opacified lesion in right middle lobe (RML) from chest x-ray. Computerized tomography (CT) scan of the

chest wall also showed similar features of round-shape consolidations and appearance of halo sign involving the anterior segment of right upper lobe (RUL) and the medial segment of right middle lobe (RML) which was suggestive for fungal infection (Figure 3). Unfortunately, the patient denied undergoing a bronchoscope for definite tissue diagnosis.

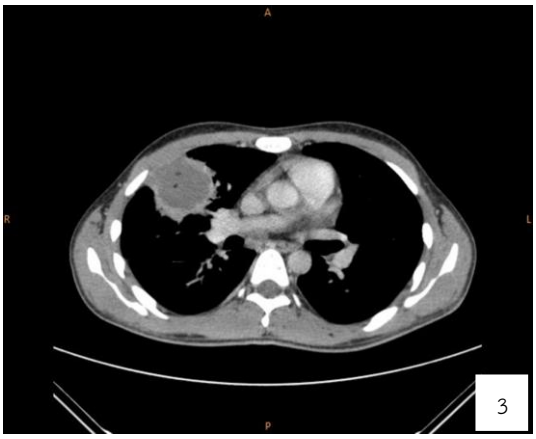


Figure 3 Computerized tomography (CT) scan of the chest wall shows round-shape consolidations involving the anterior segment of RUL and the medial segment of RML, with surrounding ground-glass attenuation (halo sign).

Finally, he had a final diagnosis as disseminated fusariosis. The antifungal treatment with a loading dose of intravenous voriconazole 6 mg/day every 12 hours was initiated, followed by 4 mg/day every 12 hours. During the treatment, the patient suffered from severe calves pain. Soft tissue ultrasound on both calves was obtained and the results were suspicious of intramuscular fungal infection which showed multiple intramuscular nodules with the appearance of halo sign on both calves (Figure 4).

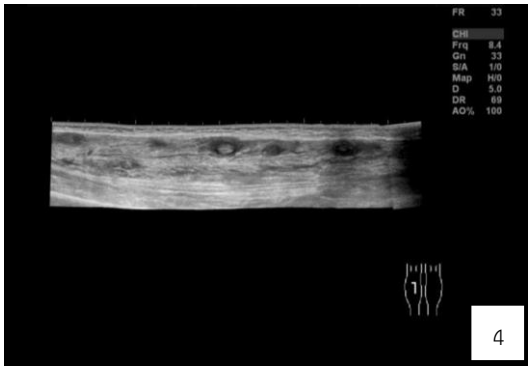


Figure 4 Soft tissue ultrasound shows multiple intramuscular nodules with halo signs on both calves.

Due to his underlying condition which was refractory to treat. The patient and his family decided to receive supportive treatment at local hospital in their living area.

Discussion

Fusarium is a genus of widely distributed saprophytic molds. More than 50 species are capable of causing diseases in plants, animals, and humans.[3,4] *Fusarium* species can cause broad spectrum of infections in human, involving superficial infections (keratitis, onychomycosis), locally invasive infections (sinusitis, arthritis, thrombophlebitis, endophthalmitis) and disseminated infections which depend on the

immunological status of the host and the portal of entry of the infection.[4]

According to host immunity, innate immunity plays a major role to prevent mold infections.[4] Macrophages and neutrophils can damage hyphae directly. T cell also has a role in the defense mechanism against *Fusarium* species infection which demonstrate the occurrence of disseminated fusariosis in non-neutropenic hematopoietic stem cell transplant (HSCT) recipients.[4]

The main portal of entry is the airway through inhalation of fusarial conidia aerosols, followed by the site of skin breakdown.[4] The *fusarium* species are widespread in normal environment. There were reported of discovering *fusarium* species from outdoor air samples, hospital water system and also hospital air environment.[5]

The clinical manifestations in immunocompetent hosts usually present with keratitis and onychomycosis. In immunocompromised hosts, locally invasive infection and disseminated infection are the common presentations.[4]

The typical manifestations in disseminated infections are fever, followed by disseminated and characteristic skin lesions.

Skin lesions consist of multiple erythematous papules or nodules, occasionally painful with central necrosis giving the appearance of an ecthyma gangrenosum-like lestion.[6,7] Bullae lesions are is rarely developed, while target lesions may present in approximately 10% of patients.[4] Skin lesions spread dominantly on the extremities, and evolve rapidly, usually in a few days.[4]

The portal of entry in disseminated infection are usually a periungual cellulitis, onychomycosis or intertrigo as in our case.[7]

Nucci M, *et al* reported pulmonary involvement in approximately 50% of hematological malignancy patients.[6] The findings are similar to pulmonary aspergillosis which has radiologic report as lung infarction, cavities and characteristic nodules with or without halo sign.[7] Other presentations including interstitial infiltrates, ground-glass infiltrates, and pleural effusions are mentioned.[4,7] The clinical presentations are non-specific with dry cough, pleuritic chest pain and shortness of breath.[4]

Muscle involvement has been reported but is a rare manifestation. All cases were reported in leukemic patients post chemotherapy. The patients developed fever, disseminated skin lesions and complained about muscle tenderness.[8,9] One case also had acute paronychia of left big toe before developed other symptoms. *Fusarium* spp. were identified mainly by skin biopsy.[8,9] Muscle biopsy was done in one case, while another case received a Magnetic Resonance Imaging (MRI) scan of both

calves which showed numerous small ring-enhancing lesions throughout the calf muscles.[9]

The risk factors for develop disseminated disease are prolonged (> 14 days) and profound neutropenia (< 100/mm3) and/or severe T-cell immunodeficiency (post-transplantation) or history of receiving high dose of corticosteroids.[6]

The prognosis depends on patient's immune status. The significantly poor prognostic factors are persistent neutropenia (> 14 days) and therapy with corticosteroid.[6] The actuarial survival rate from the series of hematologic malignanciy patients were 0% and 4% in patients with both risk factors and patients with only persistent neutropenia, respectively. [6]

The diagnosis of fusariosis requires positive growth of *Fusarium* spp. from the patient's hemoculture or cultures of samples obtained from sterile sites of the patients with clinical signs of infection.[6] Tissue biopsy from suspected sites presents hyaline and septate filaments with right angle, similar to *Aspergillus* species.[4] Positive blood culture for *Fusarium* species is always found compared to *Aspergillus* species. The unique appearance is the banana-shaped macroconidia produced from culture plate.[4]

Drug of choice for the treatment of disseminated fusariosis is either voriconazole or liposomal amphotericin B. Treatment outcome is quite poor and is largely dependent on the recovery of the immune status of the host.[7]

Colony-stimulating factors (CSF) have some benefits in neutropenic patients.[4,10] The prevention such as placing patient in a room with HEPA filters, avoiding contact with reservoirs is more advantageous.[4]

In our patient, he had prolong and profound neutropenia as a risk factor for disseminated fusariosis. He also developed characteristic presentation of fever, cutaneous lesions with indurated erythematous nodules and followed by pulmonary and muscle involvements. The definite diagnosis was made form skin biopsy and hemoculture. We suppose the portal of entry in our patient may be from the erosion at toe webs. Although, we cannot collect the tissue specimen from pulmonary and calf muscles, the chest X-ray and soft tissue ultrasound from calves can support the existence of fungal infection. The prognosis in our patient was poor. Apart from his prolong and profounded neutropenia, he still developed muscle involvement during the treatment with voriconazole.

In conclusion, we report disseminated fusariosis in a leukemia patient, presenting with fever, skin lesions, pulmonary and calf muscles involvements. Since disseminated fusariosis has a very poor prognosis with a high mortality rate, it should be detected and treated as early as possible. Prevention of the infection is therefore essential.

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