Penicilliosis-Associated Hemophagocytic Syndrome in a Human Immunodeficiency Virus-Infected Child: The First Case Report in Children

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Abstract

Infection-associated hemophagocytic syndrome (IAHS) has been found in many systemic infectious conditions with a high mortality rate. Disseminated *Penicillium marneffei* infection is a common opportunistic condition among HIV-infected patients in many regions in Southeast Asia. We report the first case of IAHS caused by penicilliosis in an HIV-infected child who presented with cytopenias and recovered promptly after antifungal and intravenous immunoglobulin therapy.

Key word : Penicilliosis, Hemophagocytic Syndrome, HIV-Infected Child

CHOKEPHAIBULKIT K, VEERAKUL G, VANPRAPAR N, CHAIPRASERT A, TANPHAICHITR V, CHEARSKUL S
J Med Assoc Thai 2001; 84: 426-429

Infections caused by *Penicillium marneffei* are found mostly in the immunocompromised host in Southeast Asia and were quite rare before the spread of human immunodeficiency virus (HIV) infection[1,2]. The clinical picture of penicilliosis in HIV-infected patients has been invariably that of systemic disseminated disease similar to other systemic mycosis such as histoplasmosis or cryptococcosis. More than half of the patients with penicilliosis had haematologic manifestations such as anemia or thrombocytopenia[3] which are partly also due to HIV infection. However, penicilliosis associated hemophagocytotic sydrome is uncommon and has been reported only once in an immu-

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nosuppressed adult[4]. We report here the first case of penicilliosis induced haemophagocytosis in an HIV-infected child.

CASE REPORT

A previously healthy 18 month-old boy presented with fever and diarrhea for 1 day. His illness started with persistent bleeding on his lower lip after a minor trauma. He developed fever and watery diarrhea the next day. His mother also noticed some acne-like papules on his face and trunk. He was the only child in the family. The past history was unremarkable except for frequent upper respiratory tract infections. His mother was from a northern province of Thailand.

On physical examination, he was lethargic and mildly dehydrated with a temperature of 38.7°C, respiratory rate of 50/minute, pulse rate of 160/minute and blood pressure of 110/60 mmHg. There were mild generalized acne-like papular eruptions, 3-5 millimeter in size, on his face and trunk. Some of the lesions were umbilicated. He had oral thrush, hepatosplenomegaly and generalized small lymphadenopathy, diameter of 5-7 millimeters. Initial work-up found anemia and thrombocytopenia. His hemoglobin was 5.3 g/dl, white blood count of 4800/mm^3 (83% polymorphonuclear cell, 17% lymphocyte) and platelet count of 49,000/mm^3. Red blood cell morphology was normal. He also had pulmonary infiltration on the right lower lung field in his chest roentgenogram.

He received a blood transfusion and was put on intravenous ampicillin for 7 days then cefotaxime for another 2 days without any clinical response. His white blood cell count dropped to 2200/mm^3 and his platelet count dropped to 10,000/mm^3. He required 2 more blood transfusions. Other work-ups revealed aspartate aminotransferase of 212 U/L, alanine aminotransferase of 112, LDH of 5668 U/L, total bilirubin of 0.3 mg/dL, serum Epstein-Barr virus antibody (anti-VCA-IgG and Ig M) was negative and anti-human immunodeficiency virus antibody was positive by enzyme linked immunosorbent assay and gel particle agglutination. His blood culture prior to antibiotic therapy showed no growth. A spinal tap revealed normal cerebrospinal fluid with negative india ink preparation and cultures.

Because of the worsening pancytopenia, bone marrow aspiration was peformed. Wright's stained bone marrow revealed hypocellularity and a decreased number of all cell lines but with normal maturation. There was a notable increase in histiocytes with active hemophagocytosis. A large number of intracellular and extracellular basophilic spherical, oval, and elliptical yeasts were found. Some of the yeast cells were budding which helped to exclude histoplasmosis (Fig. 1). The yeast cells were seen on the Wright stained slides of skin lesion scrapings. The cultures of bone marrow as well as skin lesion scrapings confirmed the presence of *P. marneffei*.

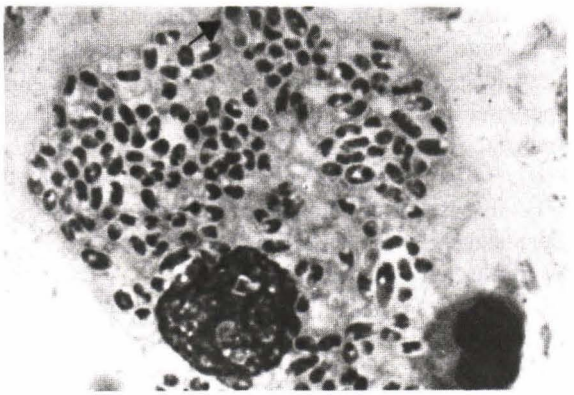

Fig. 1. A large number of yeast cells in a histiocyte. The arrow indicates a yeast cell in the stage of binary fission.

The patient responded very well to amphotericin B therapy and 1 mg/kg single dose of intravenous immunoglobulin (IVIG). The hematologic picture returned to normal within 2 weeks of treatment and the skin lesions disappeared. He was able to go home with ketoconazole for life-long maintenance therapy after 6 weeks of amphotericin B. He was well at the last visit 3 months after hospitalization, then lost from our follow-up.

DISCUSSION

Infection associated hemophagocytotic syndrome (IAHS) is the result of secondary lymphohistiocytic proliferation with hemophagocytosis due to strong immunologic activation following severe systemic infections including viral, bacterial, mycobacterial, fungal and parasite[5-8]. It is probably a form of immunoregulation defect or dysfunction of cellular cytotoxicity[9]. HIV infection causes T cell

dysfunction and might be a predisposing condition to IAHS. The clinical findings of hemophagocytic syndrome include prolonged fever, hepatosplenomegaly, peripheral cytopenias (≥ 2 cell lines), and increased histiocyte and phagocytic activity in bone marrow.

Penicilliosis may occur in any stage of HIV disease in children but tends to occur in the later stages[3]. The frequent presence of acne-like or molluscum-like skin lesions, found in two thirds of the patients, is a distinct clinical feature of disseminated penicilliosis[1-3]. Many organs are usually involved such as the lung, liver, spleen, lymph node, bone, meninges and gastrointestinal tract. Hematologic findings of penicilliosis including anemia, leukocytosis, leukopenia and thrombocytopenia were not uncommon. Yet, persistent pancytopenia has been rare[1-3].

Diagnosis of penicilliosis requires demonstration of the organism which can be done easily by a skin lesion scrapings smear, bone marrow smear, lymph node touch preparation or peripheral blood smear[1-3]. *P. marneffei* can be isolated without difficulty. High index of suspicion and attempts to look for the organism is important for early diagnosis and treatment that is crucial for survival[2,3]. Amphotericin B has been found to be the drug of choice *in vivo* although it was not always effective for *P. marneffei* in the *in vitro* study[2,3,10]. In contrast, *in vitro* study of triazole drugs seemed to correlate well with *in vivo* response. Among its group, itraconazole is the most effective drug followed by ketoconazole and fluconazole [10]. As many as one third to one half of penicilliosis in HIV infected patients who initially responded to treatment will relapse within 6 months regardless of treatment regimens[1,10]. Life long maintenance therapy has been recommended. This report has expanded the spectrum of etiologies of IAHS. This condition should be considered in HIV-infected patients from Southeast Asia who present with cytopenias.

(Received for publication on January 10, 2000)

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กลุ่มอาการฮีโมฟาโกซัยติคที่สัมพันธ์กับโรคเพนิซิลลิโอสิสในผู้ป่วยเด็กที่ติดเชื้อเอ็ชไอวี : รายงานผู้ป่วยเด็กรายแรก

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การติดเชื้อหลายชนิดสามารถกระตุ้นให้เกิดกลุ่มอาการฮีโมฟาโกซัยติคได้ ซึ่งมีอัตราการตายสูง โรคเพนิซิลลิโอสิสแบบแพร่กระจายเป็นโรคติดเชื้อฉกฉวยโอกาสที่พบได้บ่อยในผู้ป่วยที่ติดเชื้อเอ็ชไอวีในภูมิภาคเอเชียตะวันออกเฉียงใต้ รายงานนี้เป็นรายงานผู้ป่วยกลุ่มอาการฮีโมฟาโกซัยติครายแรกในเด็กที่ติดเชื้อเอ็ชไอวี ซึ่งสัมพันธ์กับโรคเพนิซิลลิโอสิส ผู้ป่วยมีอาการเม็ดเลือดหลายชนิดต่ำ และตอบสนองดีต่อรักษาด้วยยาฆ่าเชื้อรา

คำสำคัญ : เพนิซิลลิโอสิส, กลุ่มอาการฮีโมฟาโกซัยติค, ผู้ป่วยเด็กที่ติดเชื้อเอ็ชไอวี

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จดหมายเหตุทางแพทย์ ฯ 2544; 84: 426–429

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