Chronic Granulomatous Disease with Disseminated Trichosporonosis : A Case Report

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Abstract : **A case of a two year and three month old Thai boy with a history of recurrent bacterial infections since aged 2 months. A definite absence of superoxide activity in the patient' s granulocytes detected by nitroblue tetrazolium test indicated the diagnosis of chronic granulomatous disease. He suffered from septicemia and systemic fungal infection, resulting in death despite vigorous medical care. The postmortem findings showed extensive granulomatous inflammation in several internal organs. Tissue culture led to diagnosis of disseminated trichosporonosis, an uncommon infection in immunocompromised patients. This is the first case report of disseminated trichosporonosis in a chronic granulomatous disease patient.**

เรื่องย่อ : **Chronic Granulomatous Disease ร่วมกับการแพร่กระจายเชื้อ Trichosporonosis : รายงานผู้ป่วยรายแรกของประเทศไทย**

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รายงานผู้ป่วยเด็กชายอายุ 2 ปี 3 เดือน มีประวัติการติดเชื้อซ้ำซากตั้งแต่อายุ 2 เดือน ได้รับการวินิจฉัยว่าเป็นโรค chronic granulomatous disease โดยการตรวจ Nitroblue tetrazolium พบว่าเม็ดเลือดขาวของผู้ป่วยไม่สามารถสร้างสารจำพวก superoxide ได้ ผู้ป่วยเกิดภาวะติดเชื้อในกระแสเลือดและเสียชีวิตในที่สุด การตรวจศพพบการอักเสบแบบแกรนูโลมาตัสแพร่กระจายในหลายอวัยวะ การเพาะเชื้อจากเนื้อเยื่อได้ผลเป็นเชื้อ *Trichosporon spp.* ซึ่งเป็นการติดเชื้อที่พบได้ไม่บ่อยในกลุ่มผู้ป่วยภูมิคุ้มกันบกพร่อง คณะผู้รายงานได้ทบทวนรายงานของโรคนี้และนำเสนอพร้อมกันด้วย

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INTRODUCTION

Chronic granulomatous disease (CGD) is an extremely rare inherited immunodeficiency disease. Due to a phagocyte function disorder, there is failure to generate superoxide and toxic metabolites to kill ingested microbes. Most patients usually develop signs and symptoms of recurrent pyogenic and fungal infection during the first 2 years of life. The diagnosis is confirmed by an abnormal in vitro superoxide production of neutrophils.[1] *Staphylococcus aureus* is the most common bacterial infection but *Aspergillus fumigatus*, the most common fungal infection in these patients, is a major cause of morbidity and mortality.[2]

Trichosporon spp. can cause infections rarely in either normal or immunodeficient patients. Disseminated trichosporonosis has been reported in immunodeficient patients especially those who have neoplastic diseases, organ transplants, or burn patients.[3,4] We report the first case of disseminated trichosporonosis in a young boy with CGD and review other reports of CGD.

CASE REPORT

A two year and three month old Thai boy had been well until 2 months of age when he presented to Siriraj Hospital with fever, hepatosplenomegaly, pneumonia and diarrhea. At that time, he also had a seizure episode. Lumbar puncture revealed only high protein in the CSF and slightly low sugar. He was treated for presumed tuberculous meningitis and pneumonia. Concurrently, the patient was noted to be anemic with hematocrit of 19%. Bone marrow aspiration performed at that time was compatible with pure red cell aplasia. An ultrasound of the abdomen showed enlarged liver and spleen, containing diffusely hypoechoic nodules. A liver biopsy revealed evidence of acute cholangitis. The patient underwent serological investigation for other causes of hepatosplenomegaly as follows: VDRL, anti-HIV, and CMV titer, all of which were negative. His medical history was unremarkable for being the first born child. No family history of tuberculosis, frequent infections or childhood mortality was noted. He received isoniazid and rifampicin for 12 months. Before discharge, a left groin abscess was noted and cloxacillin was prescribed as home medication. He continued to have chronic cough and intermittent fever upon subsequent follow-up visits.

At age of 9 months, he was readmitted for the treatment of abscesses at the temporal region and anterior chest wall. No history of head injury was elicited. Leukocyte count showed leukocytosis. Liver function tests were normal with the exception of an elevated alkaline phosphatase at 338 U/L. A computerized tomogram revealed hepatomegaly with multiple calcification, multiple lymphadenopathy and a right lower lung nodule. Several special studies were performed. He had normal humoral and cell-mediated immunity. Immunologic studies revealed abnormal nitroblue tetrazolium test (0%) with no response to endotoxin stimulation. A pus culture from the temporal abscess revealed *Klebsiella pneumoniae*. He received intravenous cefotaxime and subsequent augmentin before being discharged. After that time, the patient required several medical visits because of either recurrent respiratory infection or septicemia.

On the fatal admission, he appeared acutely ill, with a temperature of 39.2°C. The pulse rate was 190 BPM. There was bilateral cervical lymphadenopathy with hepatosplenomegaly. No other pertinent findings were noted. The white blood cell count showed leukocytosis with a left shift. The central venous pressure was low indicating a septic shock. *Chromobacterium violaceum* was cultured from peripheral blood; amikacin and imipenem were begun according to antibacterial sensitivity testing. The patient progressively developed purpura fulminans on the 7th day of admission. His PT and PTT was prolonged with increasing number of D-dimer. *Candida spp.* were cultured from blood, urine, stool and bronchial suction. Amphotericin B was added to treatment. Unfortunately, the purpura fulminans was progressed and both upper and lower GI bleeding developed. The patient became increasingly dyspneic with progressive, diffuse alveolar infiltrates and required mechanical ventilation with high FiO2. He could not be weaned from the respirator, and death ensued after 26 days of hospitalization despite vigorous antimicrobial therapy and resuscitation efforts.

Postmortem pathologic examination

The autopsy was performed 1 day after death and revealed a hyposthenic boy of 9,150 grams of body weight with mild anemia. Bilaterally superficial lymphadenopathy was present. Both pleural cavities contained no excess fluid. The right and left lungs weighed 300 and 230 grams, respectively. Cut surface showed multiple abscesses of 2 cm in maximal diameter (Figure 1). Microscopic finding showed numerous small and large granulomas with numerous giant cells, most of which are of foreign body type. Some granulomas contained small septate hyphae, pseudohyphae and yeast form of fungi proved by tissue culture to be *Trichospora spp* (Figure 2). All lymph nodes taken from paratracheal, hilar, peripancreatic, mesenteric and para-aortic regions also showed multiple granulomas with the organism. The liver weighed 950 grams and markedly enlarged containing multiple caseating nodules (Figure 3). Light microscopy demonstrated numerous small granulomas containing the organism (Figure 4). The spleen was enlarged, weighing 140 grams. Gross and microscopic findings were similar as in the liver. The intestine showed discreted granulomas in both serosa and submucosa (Figure 5). The culture from the lung lesion yielded no growth of AFB and other bacteria. The pathological findings as described above supported the clinical diagnosis of chronic granulomatous disease.

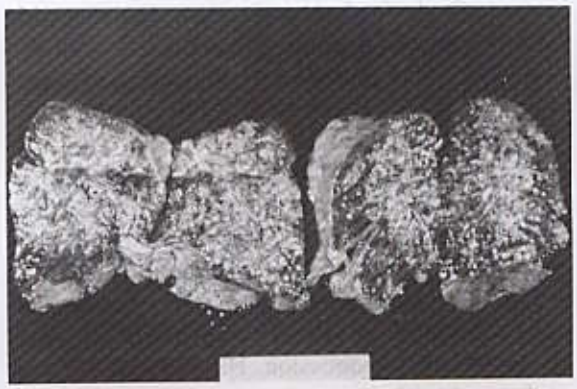

Figure 1. Both lungs revealed marked congestion and innumerable coalescent caseating nodules.

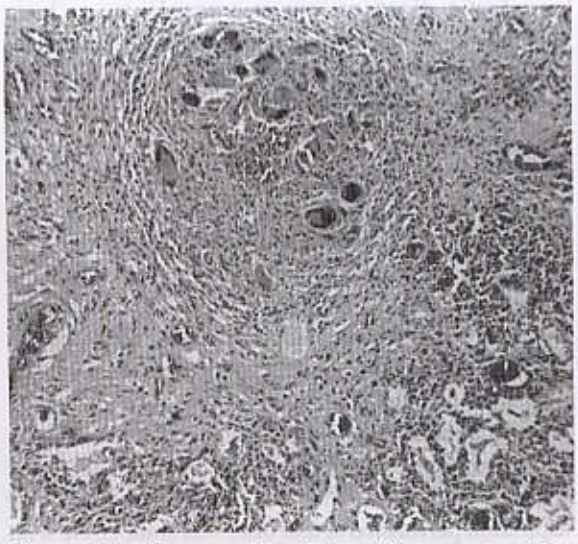

Figure 2A. Microscopic picture from a caseating granuloma in the lung to illustrate central caseation and multimucleated giant cells. (H&Ex10)

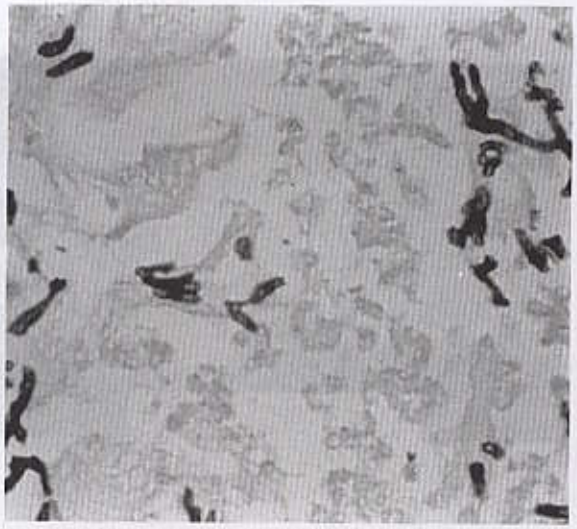

Figure 2B. High power of (A) showed pleomorphic septate hyphae and yeast cells in granuloma.-(GMSx400)

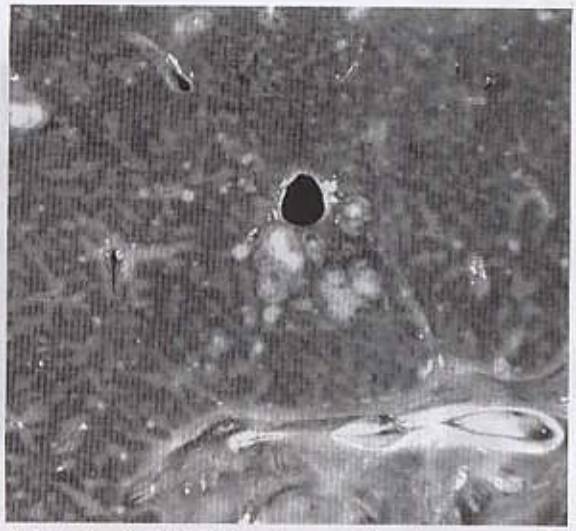

Figure 3. Sectioned surface of the liver revealed multiple small caseating nodules.

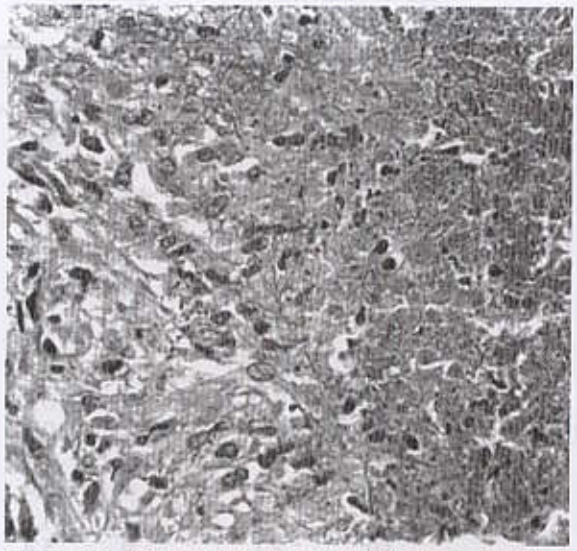

Figure 4. Microscopic picture of the liver showing caseating granuloma surrounded by epitheloid cells. (H&Ex400)

DISCUSSION

Chronic granulomatous disease (CGD) is a rare inherited immunodeficiency disorder characterized by recurrent, often life-threatening bacterial and fungal infections and granulomas in multiple organs.[1,5,6] Neutrophils, monocytes and macrophages from patients with CGD have normal phagocytic activity but lack the ability to convert moleecular oxygen into high-energy metabolites (H_2O_2) that contributes to microbial death.[7,8] Persistence of viable intracellular organisms excites the granulomatous response.[9]

Briefly, the process of phagocytosis can be dissected into (a) adhesion of particles to the leukocyte membrane (b) particle ingestion and creation of the phagocytic vacuole (c) rupture of lysosomal granules with a release of granular enzymes into the phagocytic vacuole (d) a burst of oxidative metabolic activity manifests by increase oxygen consumption and hydrogen peroxide production.[7] Phagocytes from patients with CGD have defect in the last step.

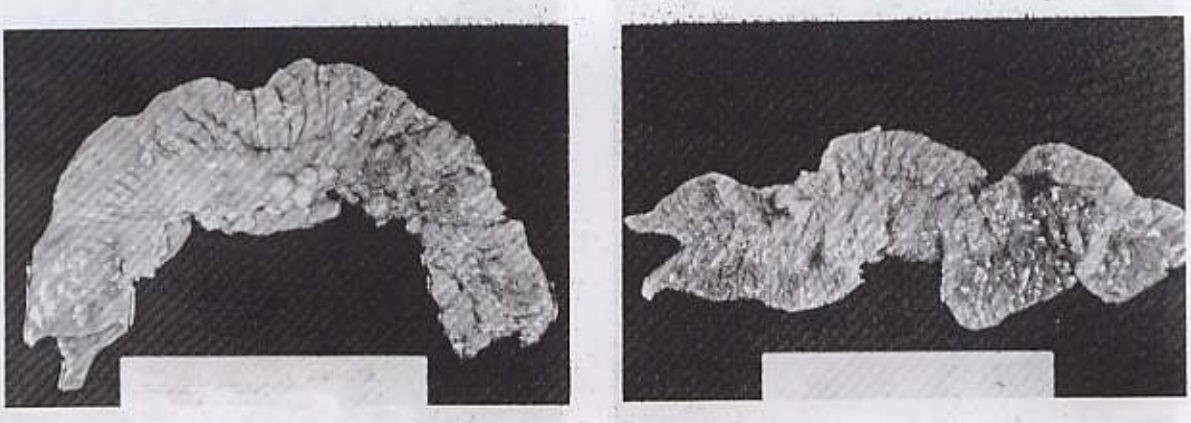

Figure 5A,B. The small intestine revealed multiple nodules at both serosa and submucosa.

Table 1. Localization and frequency of 478 infections and 167 severe infections* in 39 patients with CGD.

Localization	All documented infections		Severe infections	
	No.	%	No.	%
Lung infections (pneumonia, bronchitis, pleuritis, lung tuberculosis, lung abscess)	110	23.0	50	29.9
Gastrointestinal tract infections	88	18.4	43	25.7
Enteritis	25	5.2	3	1.8
Colitis	6	1.3	1	0.6
Intra-abdominal abscesses	26	5.4	25	14.9
Perianalabscess	20	4.2	9	5.4
Other	11	2.3	5	3.0
Lymphadenitis and lymph node abscesses	87	18.2	33	19.8
Skin abscess and dermatitis	86	18.0	18	10.8
Ear, nose and throat infections (otitis, tonsilitis, tonsilar abscess, stomatitis, sinusitis, parotitis, rhinitis)	58	12.1	1	0.6
Urinary tract infection (ureteral granuloma, nephritis)	17	3.6	4	2.4
Osteomyelitis	14	2.9	7	4.2
Septicemia	10	2.1	9	5.4
Pericarditis	4	0.8	1	0.6
Conjunctivitis	3	0.6		
Meningitis	1	0.2	1	0.6
Total	478	100	167	100

*Severe infections defined as infections requiring hospitalization and intravenous antimicrobial treatment, surgical intervention, or both.

The mode of inheritance is predominant X-linked inheritance (60%). Approximately 40% of patients have autosomal recessive inheritance.[1,6,10] A male to female ratio is about of 7:1.[7] The diagnosis is usually made before the age of 10 years.[1] Only one reported case is diagnosed at the age of 23 years.[10] The age of their first manifestation is usually within the first year of life. The most frequent types of infection that resulted in first manifestation of the CGD are lymphadenitis in 44% of the patients. Lung tuberculosis rarely occurs at first infection. A summary of the localization of 478 infections from a total of 39 patients with CGD registered in immunologic laboratories at the children' s hospital in Munich and Gottingen between 1971 and 1993 is shown in table 1.[1]

Patients with CGD usually suffer from frequent and serious bacterial and fungal infections. Richard, et al, summarized their largest series of CGD in 1971 indicating that there were 45 deaths from total 88 patients with 38 deaths occurring before the age of 12 years. One female patient lived to 34 years of age.[7] Bacterial infection is the common cause of fatal infection and *A. fumigatus* is the leading cause of fungal infections.[11] Few reports of other fungi are documented.[12,13,14] Long term prophylaxis with trimethoprim-sulfomethoxazole has been shown to reduce the number of bacterial infections. One prospective randomized trial showed that prophylactic γ -IFN further decrease the frequency of the infection. Oral itraconazole had been shown to reduce fungal infections in patients with CGD.[1] But the definite therapy is still hematopoietic stem-cell transplantation.[15]

In Thailand, there have been only 2 reported cases of CGD[16,17] and no case of CGD with disseminated trichosporonosis. Our patients demonstrated recurrent pneumonia, lymphadenitis, multiple skin, lung and liver abscesses. The diagnosis was made both at autopsy and necropsy by histologic and fungal examination. Disseminated trichosporonosis is an uncommon but increasingly reported infections in immunocompromised patients. It often presents as fungemia, cutaneous lesions and pulmonary infiltrations, This systemic mycosis is often refractory to conventional antifungal therapy and is frequently fatal. Antifungal susceptibility testing of the *T. beigelii* showed that the organism is inhibited but not killed by amphotericin B.[3,4]

In conclusion, we reported the CGD with disseminated trichosporonosis to remind the clinician who deals with cases with frequent, repeated unexplained infection.

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