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A CASE OF LATE PRESENTING CHRONIC GRANULOMATOUS DISEASE*

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An eleven-year-old boy with a history of severe lung infection which had been resistant to antibiotic therapy for a period of six months demonstrated a functional leukocyte defect similar to that found in children with chronic granulomatous disease (CGD). X – ray findings suggested a hilar mass, and granulomatous lesions developed on the thorax wall. The documentation of this case suggests that there may be a late presenting form of CGD.
Key words: chronic granulomatous disease, late onset.

Chronic granulomatous disease (CGD) is a syndrome of recurrent bacterial or fungal infections associated with defective microbicidal capacity of the phagocytic cells and an abnormal oxidative metabolic response during phagocytosis. It occurs both in males and females, and usually during the first two years of life[1-4]. This report describes an unusually late presenting case of CGD and summarizes the related literature.

Case Report

An eleven-year-old boy, whose parents were first degree relatives, was admitted to our hospital with complaints of failure-to thrive, a cough, fever, and sweating which had developed about six months prior to his admission. The child had been examined by various physicians in several hospitals. He was diagnosed as having pneumonia and was treated with various antibiotics. In spite of all the antibiotic and anti-tuberculous drug regimens used, there was no clinical or radiological response, thus the patient was referred to our hospital for further evaluation and treatment.

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Physical examination revealed an underweight child (below third percentile) in respiratory distress. His subcutaneous tissue was wasted away and pallor was prominent. He had hyperthermia and clubbing of the fingers. There was cervical and axillary microlymphadenopathy. His liver and spleen were not palpable. On auscultation the lung fields showed fine crepitant rales on both bases. There was some intercostal retraction, with a respiratory rate varying from 25 to 30/min. The rest of the physical examination was unremarkable.

Urinalysis was normal; blood and sputum cultures yielded no bacterial growth. The delayed hypersensitivity skin test with PPD (5 and 250 TU) was negative. Remarkable laboratory findings were a high blood cell count with segmented neutrophil preponderance, and an elevated erythrocyte sedimentation rate.

Chest X-ray demonstrated parahilar and paracardiac diffuse, nonhomogenous interstitial infiltrates bilaterally which were considered to be nonspecific broncho-pneumonic infiltration.

Upon repeated chest X-ray, the infiltrates became homogenous and dense, similar to the characteristic X-ray findings of atelectasis. The chest X-ray findings also suggested a hilar mass. Computer tomography of the lungs and bronchoscopy revealed no further diagnostic evidence.

Since there was no clinical or radiological response to the treatment, a thoracotomy was performed which revealed pneumonia and a lung abscess. Almost simultaneously, two subcutaneous abscesses each 4 x 5 cm in diameter appeared on the thorax wall along the two sides of the sternum. After surgical drainage, a culture of the aspirate yielded *S. aureus.*

The diagnosis of CGD was considered because of the clinical features of the case and because the patient failed to respond to routine antibiotic therapy. Tests for humoral and cell-mediated immunity and for qualitative defects of phagocytes were performed (Table I). The nitroblue tetrazolium test (Slide test) was negative and bacterial killing index (for *S. aureus*) showed defective killing. Serum immunoglobin levels were high. Other tests were normal.

TABLE I: Immunological Evaluation of the Case

A – Test of humoral immunity

1) Serum concentrations of immunoglobulins
   Ig G: 2410 mg/dl (N: 700 – 1650 mg/dl)
   Ig M: 448 mg/dl (N: 50 – 260 mg/dl)
   Ig A: 558 mg/dl (N: 29 – 270 mg/dl)
2) Isohemagglutinins:
   1): 128 (Anti – A)
3) Anti – Streptolysin – 0 titer (ASO):
   200 Todd Units

B – Tests for cell – mediated immunity

1) E – rosette forming cells: 54 %
2) Delayed hypersensitivity skin tests: PHA – Positive
   PPD – Negative

C – Tests for qualitative defects of phagocytes

1) Nitroblue Tetrazolium Test (NBT): 0 %
2) Stimulated Nitroblue Tetrazolium Test with *E. Coli* endotoxin: 0 %
3) Bacterial Killing Index: 0.21 (Defective killing)
4) Rebuck Skin Window Test: Positive response

Discussion

CGD is a rare disease most often inherited as an X-linked trait but 20-40 percent of patients have been found to have an autosomal recessive pattern of inheritance[3]. Recognition and phagocytosis of bacteria occur normally in phagocytic cells, but the ingested microbes are not killed. Defects in oxydative metabolism and production of reactive oxygen radicals during phagocytosis are the essential defects in CGD. NADH and NADPH oxydases are present in phagocytic cells, but increased activity is not stimulated during phagocytosis[1,4,5].

Nearly all males with CGD and X-linked genetics have absent or grossly abnormal cytochrome b which is required for electron transport and reduction of oxygen to superoxide[6-9].

Several clinical pictures suggest CGD. Any patient with recurrent lymphadenitis should be suspected of having the disease. In addition, a patient with bacterial hepatic abscesses, osteomyelitis at multiple sites in the small bones of the hands and feet, and a family history of recurrent infections demands an investigation of the immunologic status[2]. Granulomata, characterized by phagocytes and giant cells sometimes loaded with pigmented lipid material, can develop in virtually any organ system. The mechanism of granuloma formation in CGD is unknown. It has been postulated that because of the defective respiratory burst in phagocytes, there is persistent inflammation. In our case, microlymphadenopathy, several episodes of pneumonia, subcutaneous and lung abscesses with *S. aureus* were the main features. Our patient's age was unusual for CGD, but similar cases have been reported[10,11].

The diagnosis of CGD is made by the NBT test. In the most common forms of the disease, NBT reduction is not observed in any of the cells[12]. The results of our case were also negative. One of the major criteria for classifying CGD is the cytochrome b spectrum[13,14]. But we could not determine it. The bacterial killing index for staphylococci is also defective in cases of CGD. Other laboratory

findings include anemia, neutrophil leukocytosis, an elevated erythrocyte sedimentation rate, raised immunoglobulin levels, normal antibody responses and tests for cell-mediated immunity.

The laboratory results of our case correlated with all the above-mentioned findings such as an absence of NBT reduction, a defective bacterial killing index for *S. aureas,* anemia, neutrophil leukocytosis, an elevated erythrocyte sedimentation rate, raised immunoglobin levels, normal tests for cell-mediated immunity, and extremely abnormal chest X-rays.

Since bone marrow transplantation is the only known cure for CGD, vigorous supportive care is important. Cultures must be obtained as soon as infection is suspected, since unusual organisms are commonly the source of infection. Recent studies suggest that gamma interferon can be used as an adjunct to antimicrobial therapy during acute infections in CGD[15].

Treatment which requires the administration of effective concentrations of bactericidal antibiotics may be continued for as long as two to four months because most antibiotics do not penetrate the neutrophils and, therefore, phagocytized bacteria are protected from their action. Rifampicin penetrates living cells, but unfortunately staphylococci rapidly become resistant to this drug, thus, its clinical usage in CGD may be less successful than in vitro tests suggest[16]. We used several antibiotics including rifampicin, but no successful results could be obtained.

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