The Turkish Journal of Pediatrics 36: 341-345 1994

INVASIVE PULMONARY ASPERGILLOSIS IN CHRONIC GRANULOMATOUS DISEASE: RESPONSE TO SYSTEMIC PREDNISOLONE TREATMENT AND LOCALLY APPLIE AMPHOTERICIN B*

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SUMMARY: Güler N, Yalçın I, Salman N, Öneş Ü. (Department of Pediatrics, Istanbul University Faculty of Medicine, Istanbul, Turkey). Invasive pulmonary aspergillosis in chronic granulomatous disease: response to systemic prednisolone treatment and locally applied amphotericin B. Turk J Pediatr 1994; 341-345.

A five-year-old boy with deforming and destructive invasion of pulmonary aspergillosis to the thoracic cage was diagnosed as having chronic granulomatous disease. Conventional antifungal therapy failed in this patient. Prednisolone therapy was added and rapidly improved the general condition of patient but deterioration had already been very rapid. The failure of systemic therapy prompted us to give amphotericin B locally to the granulomatous lesions through the bronchocutaneous fistula. This application yielded a good clinical response with closure of fistula. Despite this improvement the patient died from septicemia. We believe that systemic prednisolone treatment is useless in such cases, but local application of amphotericin B into the granulomatous lesions together with systemic therapy during the earlier stages of infection can contribute to a change in prognosis. *Key words: pulmonary aspergillosis, chronic granulomatous disease, local amphotericin B.*

Quantitative and qualitative neutrophil defects are the most frequent risk factor for opportunistic fungal infections[1]. Chronic granulomatous disease (CGD) is a rare inherited disease characterized by a decreased or absent ability of neutrophils and monocytes to kill microorganisms that have undergone phagocytosis. In addition to infectious complication, obstructive lesions resulting from granuloma formation compressing vital structures have been major sources of morbidity and mortality in patients with CGD[2]. This report describes a child with CGD and invasive pulmonary aspergillosis in whom conventional antifungal therapy had failed.

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Case Report

A five-year-old boy was transferred from another hospital to ours with a three-month history of bronchopneumonia resistant to antibiotic therapy and progression of the disease to the chest wall. His past medical history revealed recurrent pustulosis on the skin which had been treated with oral antibiotics in the first year of life. The parents of the child were unrelated and healthy. The first-born child of the family had died of diarrhea at five months of age.

Physical examination revealed a cachetic child (weight 14.5 kg, height 120 cm). The child was pale, weak and febrile. The chest wall was deformed with bulging masses on the anterior right side and on the back. There were inspiratory crackles over both lungs. The liver and spleen were palpated two centimeters and one centimeter below the costal margings, respectively.

Hematologic values on admission included: hematocrit 27%, leukocyte count 15,000/mm^3 with 40% mature neturophils and 8% band forms, and erythrocyte sedimentation rate of 60 mm/h. Bacterial cultures of numerous tracheal aspirates and sputum specimens grew only normal flora, and cultures for mycobacteria were negative. A chest x-ray showed diffuse infiltrates in the right upper and left lower lobes. Upper right ribs were also deformed. Computerized tomography of the lungs demonstrated a solid tumoral mass 10 cm in diameter in the upper lobe of the right lung and destruction of ribs. Pleural space was also involved on the left side. On immunologic investigation, polymorphonuclear leukocytes revealed an inability to reduce nitroblue tetrazolium dye, and the bacterial killing index suggested defective killing of test organism (S.aureus). CGD was diagnosed based on these clinical and laboratory findings. Biopsy of the granulomatous lesion on the right posterior chest wall revealed Aspergillus sp in granuloma tissue.

Antifungal therapy with a combination of amphotericin B and 5-fluorocytosine was effective initially. Both lung infiltrates and abscesses healed within three months of this treatment, but deformity of the ribs did not change. One month after therapy was stopped, the same lesions in the lungs became active again. Over the ensuing month, administration of the drugs was continued, with no response observed this time. Prednisolone at a dose of 2 mg/kg/day was added to this treatment. Within two weeks a dramatic clinical improvement occurred. Granulomatous lesions penetrating the chest wall became smaller and pus formation stopped, but the radiologic picture of the lungs did not change markedly. The initial prednisolone dosage was continued for three weeks and then tapered during the following two weeks. At the end of this period, the child's general condition deteriorated and the lesions on the chest wall progressively showed paraspinal infiltration with the destruction of the vertebral

bodies between T1 and T11. Paraplegia had developed with the compression of the medulla spinalis (Figs. 1, 2). Excessive formation of pus and loculations in abscesses had been demonstrated, and a bronchocutaneous fistula was diagnosed with instillation of methylene blue. Although no organism was identified by routine microbiologic invastigation, antibiotics were initiated empirically.

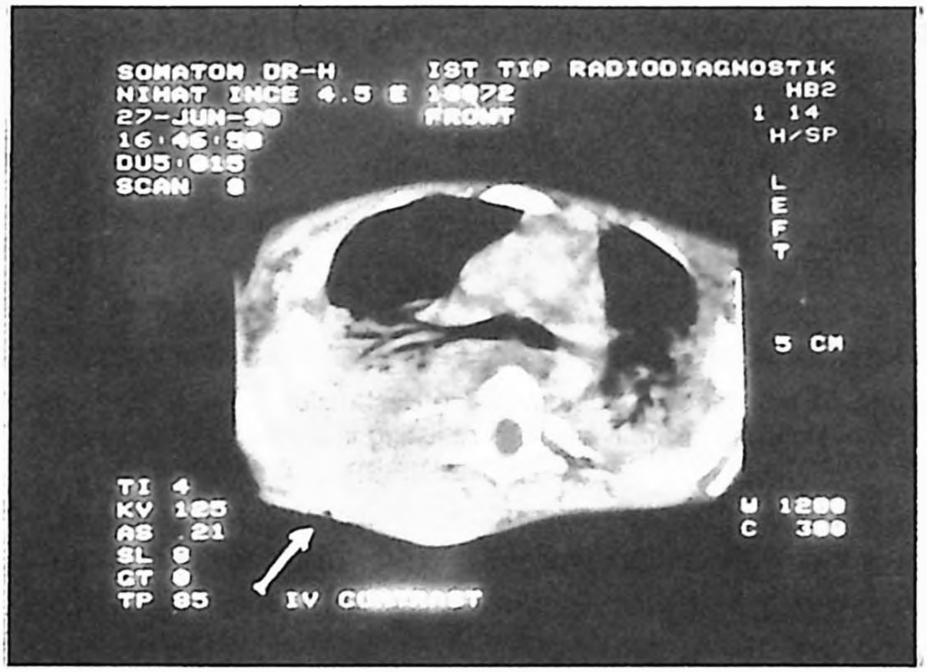

Fig. 1: Computed tomography of patient showing the invasion of granulomatous lesions to the lungs, ribs and vertebrae. The external opening of the bronchocutaneous fistula is shown with an arrow.

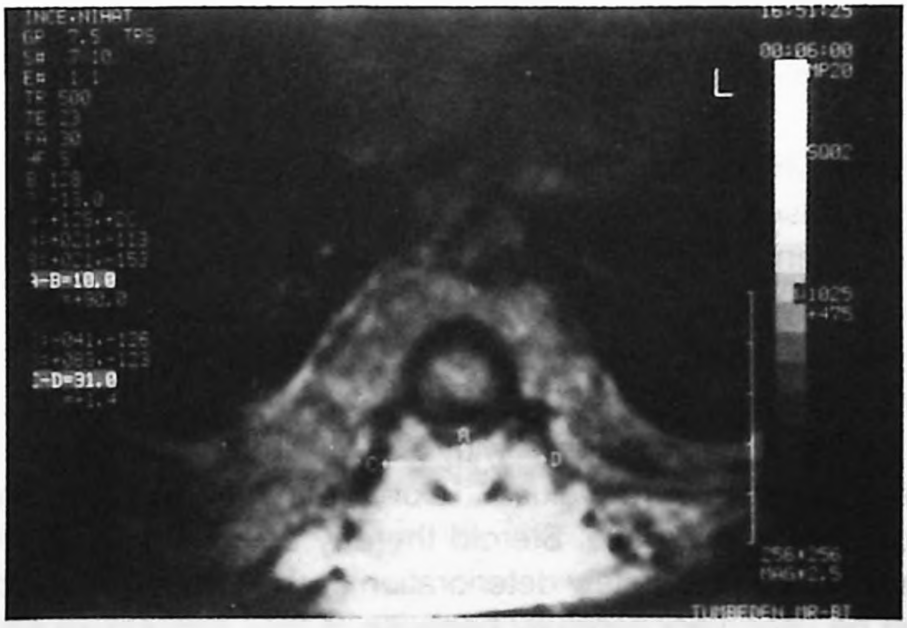

Fig. 2a: Magnetic resonance imaging of the spine demonstrating paraspinous mass.

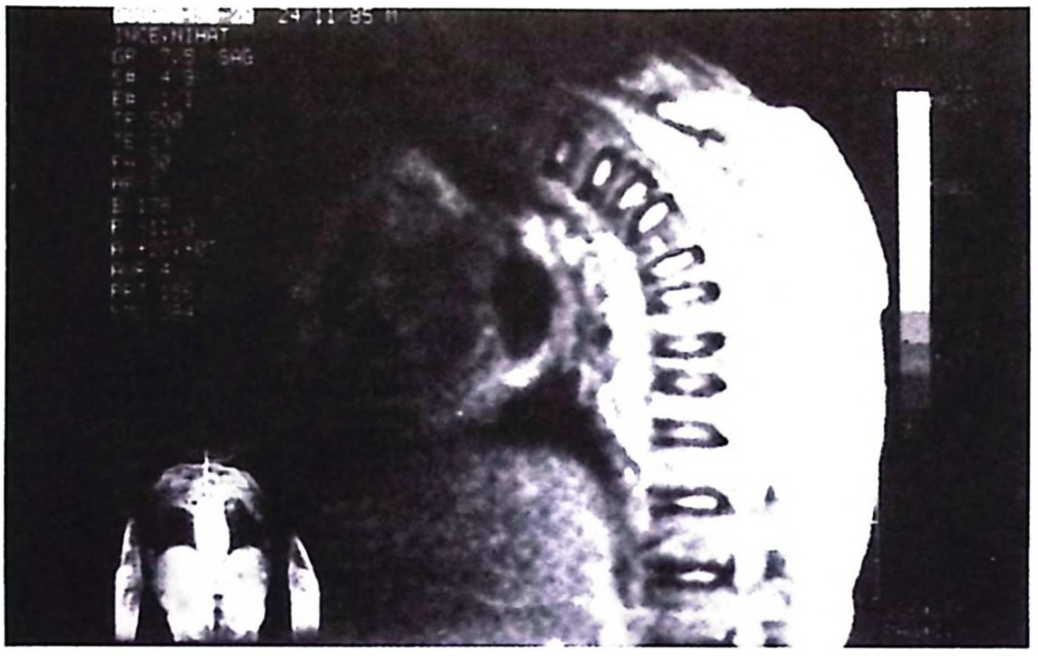

Fig. 2b: Magnetic resonance imaging showing destruction of the thoracic vertebrae and paravertebral infiltrative lesions resulting in epidural compression.

The failure of systemic therapy prompted us to give an antifungal drug locally. After sterilizing the skin, a catheter was advanced into the abscess cavity and amphotericin B was administered slowly at a dose of 15 mg/day. This procedure was repeated every day for two weeks. With this therapy, a cough was provoked in the first days, due to a bronchocutaneous fistula. After several days, this symptom disappeared and the patient began to improve with closure of the fistula. The size of the thorax wall decreased and pus formation gradually diminished. Despite this improvement, the clinical picture of septicemia developed and the patient died.

Discussion

Although opportunistic aspergillus infection is seen relatively frequently in immunocompromised patients and almost always arises from the respiratory route with involvement of the lungs, invasion to the chest wall is extremely rare[1,3-5].

This case presented with bronchopneumonia rapidly progressing to the chest wall.Conventional antifungal therapy failed in this patient. Corticosteroids have been used successfully in patients with CGD to treat obstructive lesions when antimicrobial therapy is of no value[6,7]. Our experience in corticosteroid usage was not promising in this case. Steroid therapy acted rapidly in improving the patient's status, but unfortunately deterioration had also been very rapid. Steroids in CGD must be used very carefully because of their supressive effects on host defenses[8].

Transbronchial hyphal invasion of pulmonary arterioles usually results in ischemic necrosis of the lung. This histopathologic picture of vascular invasion may explain clinical features such as cavitation and fistulae[9].

Progressive deterioration despite systemic treatment, absence of other focuses in other parts of the body and abundant purulant discharge through the bronchocutaneus fistula prompted us to give amphotericin B locally to the granulomatous lesion. There have been several reports describing the use of intracavitary therapy to treat pulmonary aspergilloma with rapid improvement[10]. Rapid effectiveness of amphotericin B is probably due to its irritative and sclerosing properties. We also observed sclerosis and closure of the fistula. Local application of amphotericin B had a palliative effect on symptoms but did not affect the outcome of the patient, probably because it was initiated at the terminal stage of the disease. We believe that early administration of local therapy along with systemic amphotericin B may affect the prognosis of such patients.

REFERENCES

1. Cohen MS, Isturiz RE, Malech HL, et al. Fungal infection in chronic granulomatous disease. The importance of the phagocyte in defense against fungi. Am J Med 1981; 71: 59-66.
2. Curnutte JT: Classification of chronic granulomatous disease. Hematol Oncol Clin North Am 1988; 2: 241-252.
3. Caligiuri P, MacMahon H, Courtney J, Weiss L. Opportunistic pulmonary aspergillosis with chest wall invasion. Arch Intern Med 1983; 143: 2323-2324.
4. Wolfson JJ, Kane WJ, Laxdal SD, et al. Bone findings in chronic granulomatous disease of childhood. J Bone and Joint Surg 1969; 51A: 1573.
5. Schoumacher RA, Tiller RE, Berkow RL. Invasive pulmonary aspergillosis in an infant: an unusual presentation of chronic granulomatous disease. Pediatr Infect Dis J 1987; 6: 215-217.
6. Chin TW, Stiehm ER, Falloon J, Gallin JI. Corticosteroids in treatment of obstructive lesions of chronic granulomatous disease. J Pediatr 1987; 111: 349-352.
7. Collman RJ, Dickerman JD. Corticosteroids in the management of cystitis secondary to chronic granulomatous disease. Pediatrics 1990; 85: 219-221.
8. Quie PG, Belani KK. Corticosteroids for chronic granulomatous disease. J Pediatr 1987; 111: 393-394.
9. Albelda SM, Gefter WB, Epstein DM, Miller WT. Bronchopleural fistula complicating invasive pulmonary aspergillosis. Am Rev Respir Dis 1982; 126: 163-165.
10. Shapiro MJ, Albelda SM, Mayock RL, McLean GK. Severe hemoptysis associated with pulmonary aspergilloma. Percutaneous intracavitary treatment. Chest 1988; 94: 1225-1231.