Chronic granulomatous disease with cranial fungal osteomyelitis and epidural abscess

Case report

IAN F. POLLACK, M.D., DACHLING PANG, M.D., F.R.C.S.(C), AND KENNETH E. SCHUIT, M.D., PH.D.

Departments of Neurosurgery and Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

A patient is described with osteomyelitis of the cranium and epidural abscess due to Aspergillus fumigatus as the presenting manifestations of chronic granulomatous disease. The diagnosis was suggested by the unusual nature of the organism isolated and confirmed by appropriate laboratory studies. The details of diagnostic assessment and therapeutic management are discussed, and the central nervous system manifestations of chronic granulomatous disease are reviewed.

KEY WORDS - epidural abscess - abscess, fungal - chronic granulomatous disease - osteomyelitis - skull - Aspergillus fumigatus

Chronic granulomatous disease (CGD) is an inherited disorder of leukocyte function characterized by impaired killing of intracellular organisms. Death generally occurs in early childhood but, with aggressive surgical and medical therapy, prolonged survival has been achieved. The patient described here represents the first documented case of CGD with central nervous system (CNS) infection as the initial manifestation. The diagnosis of an immunodeficiency syndrome was suggested by the unusual nature of the infection. The present report reviews the spectrum of CNS features encountered during the course of this disease as well as the diagnostic evaluation and therapeutic approach for patients with this disorder.

Case Report

This 4-year-old boy was admitted to Children's Hospital of Pittsburgh (CHP) with a draining right parietal scalp wound. The child had an unremarkable medical history with normal growth and development. Three weeks prior to admission, he had been struck on the head with a plastic toy, without an obvious break in the skin. Several days later, progressive right parietal swelling and erythema developed. Three days before admission, creamy reddish purulent material drained spontaneously. The wound was incised and drained by the patient's pediatrician and cultures grew Aspergillus fumigatus as the sole organism. The patient was referred to CHP for further management.

Examination. The patient was an afebrile healthy-appearing child in no distress. A 3 × 4-cm area of soft tissue swelling was noted in the right parietal region from which purulent drainage could be expressed. The remainder of the patient's general and neurological examination was entirely normal.

Laboratory studies disclosed a hypochromic microcytic anemia and a mild leukocytosis. Skull x-ray films demonstrated a lytic lesion with irregular borders high in the right parietal region. A computerized tomography (CT) scan showed a large enhancing soft-tissue mass in the right parietal region eroding through both the inner and outer skull tables and extending into the epidural space (Fig. 1 left and center). In addition, several small punctate enhancing areas with surrounding edema were noted in the left frontal lobe, left centrum semiovale, and right temporal lobe (Fig. 1 right). A 3 × 3-cm rounded retrocardiac area of density was noted on the admission chest x-ray film (Fig. 2). The chronicity of the radiographic findings and the trivial nature of the blow to the head suggested that the epidural abscess and osteomyelitis were unrelated to the antecedent trauma.
Fungal osteomyelitis of the skull

**Fig. 1.** Contrast-enhanced coronal computerized tomography scans. *Left:* Scan through the anterior parietal region showing erosion of the right parietal bone with extension of the lesion into the subgaleal and epidural spaces. The area of inflammation extended to the superior sagittal sinus, but no evidence of invasion was demonstrated at the time of surgery. *Center:* Bone algorithms of the same cut shown left demonstrating the irregular border of the osteomyelitic cranium. *Right:* A slightly more rostral section demonstrating an enhancing lesion in the left centrum semiovale.

(Operation. Because the multiple parenchymal lesions within the brain and the retrocardiac mass both suggested systemic fungal dissemination, two doses of amphotericin B were administered prior to surgery. The patient underwent extensive curettage of the osteomyelitic skull defect and excision of epidural granulation tissue with placement of an epidural drain.

Pathological Examination. Microscopic examination of the tissue revealed acute granulomatous inflammation of the scalp, skull, and epidural space with heavy infiltration of neutrophils, eosinophils, histiocytes, plasma cells, and multinucleated giant cells (Fig. 3A). Grocott silver stain demonstrated many branching hyphae (Fig. 3B). The tissue grew pure cultures of *Aspergillus fumigatus.*

Postoperative Course. Following surgery, 5-fluorocytosine was added to the antibiotic regimen for its possible synergistic effect. In view of the unusual nature of the infection, the child’s immune function was tested. Leukocyte studies disclosed a defect in nitroblue tetrazolium (NBT) reduction, indicative of an abnormality of intracellular oxidation typical of CGD. Chemotaxis and phagocytosis were normal, and myeloperoxidase activity was elevated. Tests of humoral and cell-mediated immunity were normal. An exhaustive search for other sites of infection was negative.

The postoperative course was complicated by pneumonia in the right upper lobe (no organism was isolated), bilateral otitis media (treated with trimethoprim and sulfamethoxazole), and a *Staphylococcus aureus* paronychial infection (treated with nafcillin). The patient’s *Aspergillus* infection was well managed on the antifungal regimen described, and follow-up CT scan and chest x-ray films showed complete resolution of all abnormalities after 4 weeks of treatment. Antibiotic therapy was administered for 6 weeks. No recurrence of infection was noted during 3 months of outpatient follow-up monitoring. Leukocyte function testing of
FIG. 3. Photomicrographs of paraffin-embedded sections of excised granulation tissue. A: A microabscess is seen within the epidural space demonstrating acute and chronic inflammation with numerous multinucleated giant cells (arrows) and fungal hyphae (open arrows). PAS, × 90. B: An adjacent microabscess showing numerous branching septate hyphae. Grocott, × 90.

the patient’s family members demonstrated asymptomatic CGD in a 2-year-old brother and a carrier state in the mother.

Discussion

Chronic granulomatous disease, a disorder of leukocyte bactericidal activity, was first described in 1957 by Berendes, et al. Inheritance is predominantly X-linked, although female patients with CGD have been described. Death generally occurs before 7 years of age, but a small subgroup of patients with an apparently milder form of the disease have survived past 25 years.

Pathophysiology

Disorders of leukocyte function can be subdivided into defects of: 1) chemotaxis and locomotion; 2) adherence and phagocytosis; and 3) intracellular killing. Dysfunction in any of these processes may predispose the patient to recurrent infection.

In CGD, the primary abnormality is in bacterial killing. The basic pathophysiological process is a defect in the conversion of oxygen to superoxide or hydrogen peroxide secondary to a dysfunction of oxidative metabolism. This defect can be assessed by the NBT test, in which colorless NBT is reduced to a blue precipitate by the oxidase activity of normal leukocytes which have been exogenously activated. When combined with leukocytes from patients with CGD, the NBT fails to change color (negative NBT test). Another indirect test of bactericidal function makes use of the fact that granulocytes produce chemiluminescence during bacterial killing. In patients with CGD no chemiluminescence is observed.

Chédiak-Higashi disease and myeloperoxidase deficiency are also characterized by abnormalities in intracellular killing. The former disease, thought to involve a dysfunction of lysosomal activity as well as chemotaxis, is easily distinguished from CGD by the finding of large intracytoplasmic inclusions within phagocytic cells on light and electron microscopy. Patients with myeloperoxidase deficiency typically have a normal host defense against bacteria, but they are at increased risk from *Candida albicans*. Assessment of myeloperoxidase activity confirms the diagnosis in affected individuals.

Patients with CGD typically present in early childhood with severe recurrent infections caused by catalase-positive organisms, specifically, *Staphylococcus aureus*, most Gram-negative organisms, and many fungi. The hydrogen peroxide normally produced by these organisms is broken down by their catalase enzyme system; because the phagocytes are unable independently to generate the hydrogen peroxide needed for...
bacterial killing, the intracellular bacteria remain viable and may lead to severe prolonged infections. Catalase-negative organisms, on the other hand, maintain a high enough hydrogen peroxide concentration within the enclosed phagocytic vesicles to support the bactericidal action of the normally functioning myeloperoxidase system, and are therefore handled without difficulty in patients with CGD. The delayed presentation in our patient may have been due to an increase in myeloperoxidase activity, resulting in a compensatory improvement in bacterial killing.

Clinical Features

In CGD patients, the common sites of infection are those that receive constant exposure to catalase-positive organisms such as the skin, the reticuloendothelial system, and the gastrointestinal tract. In contrast, the nervous system is an uncommon site of infection, and by the time a patient manifests CNS involvement, the diagnosis is normally well established by the occurrence of multiple prior infections in more typical sites. Nevertheless, the development of CNS disease in these individuals can be devastating and is often the cause of death. The nervous system may be infected via two routes: 1) hematogenous dissemination from a primary source elsewhere in the body, and 2) contiguous spread from adjacent sites of infection. In the present case, the trivial nature of the initial injury and the finding of multiple parenchymal lesions within the brain along with an associated chest mass suggested that the mechanism of spread was hematogenous dissemination from a primary asymptomatic lung infection.

The most common pattern of CNS involvement is meningitis associated with generalized sepsis. In a review by Johnston and Newman in 1977, “septicemia or meningitis” was documented in 29 of 168 patients with CGD. Chronic fungal ventriculitis and meningitis have been described and typically require prolonged courses of intravenous and intrathecal antibiotics. In spite of adequate medical treatment, however, hydrocephalus with multiloculated ventricles may result and present a difficult shunting problem. Powers recently reported a case in which endoscopic fenestration of the cyst walls with the argon laser was successful in simplifying the shunting procedure.

In contrast to meningitis, localized infections within the CNS are uncommon. Vertebral body osteomyelitis has been known to spread from a contiguous pneumatic lesion. Fungus, specifically *Aspergillus*, was isolated in five of six such cases. Only one case of actual cord compression from an epidural abscess can be found in the literature.

A case of bacterial cranial osteomyelitis associated with CGD in a 20-month-old child was reported by McCallum, et al. This infection was successfully treated by debridement of necrotic tissue and antibiotic therapy. *Staphylococcus epidermidis* and *Serratia marcescens* were cultured from the wound. The underlying bone was markedly thinned although no communication with the epidural space was noted. No bone was removed and the epidural space was not explored. To our knowledge, cranial epidural abscess has not previously been described in patients with CGD.

Our patient also had CT evidence of intraparenchymal brain lesions which were presumably areas of focal cerebritis from hematogenous fungal dissemination. Biopsy confirmation was not obtained because these lesions were asymptomatic and because they promptly resolved, as shown on subsequent CT scans, while the patient was receiving antifungal therapy. Only one case of brain abscess associated with CGD has been previously reported.

Diagnostic Evaluation

Systemic *Aspergillus* infection is rarely seen in immunocompetent individuals, whereas it is common in patients with CGD. A review of 245 patients with CGD showed evidence of severe and recurrent *Aspergillus* infection in 41. The isolation of an unusual organism such as *Aspergillus*, particularly from a CNS infection, mandates a thorough search for an underlying immunodeficiency disorder. This should include a differential white blood cell count to identify quantitative neutrophil deficiencies, serum immunoglobulin tests and total hemolytic complement assay to evaluate the humoral immune system, and delayed hypersensitivity skin tests and T cell enumeration to assess cell-mediated immunity. If no abnormality is identified on preliminary testing, a more detailed evaluation of leukocyte function should be pursued, the elements of which have been well described in a recent review by Quie. In the present case, assessment of leukocyte chemotaxis, phagocytosis, and intracellular killing was crucial in identifying the underlying pathological process. The finding of an abnormal NBT test confirmed the diagnosis of CGD in our patient.

Management

Early diagnosis and aggressive intervention is the key to the successful management of infections in patients with CGD. In general, patients with localized soft tissue and bone infections respond better to treatment than do those who present with pulmonary or disseminated disease. Localized infections should be treated by open debridement and drainage. Antibiotic therapy should be started prior to the surgical procedure and continued for prolonged periods following surgery. Fungal infections, a particularly difficult problem, are best managed with intravenous amphotericin B, which may be combined with antibiotic agents with a synergistic effect such as 5-fluorocytosine or rifampin. In patients with severe infections not responding well to antibiotics, some success has been obtained with granulocyte transfusions although no controlled trial of this treatment has been reported. Recurrent fever after an initial favorable response to treatment is a common occurrence in immunodeficient patients and should raise the possibility of a superinfection with a new organism or
the emergence of resistant strains of the original organism. In our patient, the several episodes of recurrent fever were due to unrelated infections by other organisms, a phenomenon also characteristic of CGD. In all cases of recurrent fever, fresh cultures should be obtained and appropriate therapy implemented.

References


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Address reprint requests to: Ian F. Pollack, M.D., Department of Neurosurgery, 9402 Presbyterian-University Hospital, Desoto at O’Hara Streets, Pittsburgh, Pennsylvania 15213.