Chronic Granulomatous Disease in the Adult

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Chronic granulomatous disease is a rare, inherited disease occasionally found in adults. It is characterized by repeated infections of the skin, lymph nodes, and viscera. The underlying cause is a metabolic inability of the leukocyte to destroy certain ingested bacteria and fungi that normally are saprophytes. The diagnosis should be suspected in children and adults who present with repeated episodes of infection without an apparent underlying cause. The diagnosis can be established by the nitroblue tetrazolium test. Treatment is nonspecific and directed towards the underlying bacterial or mycotic infection rather than the genetically related deficiency of the leukocyte.

Chronic granulomatous disease (CGD) is a rare inherited condition, usually manifested in young males and invariably fatal. The disease is characterized by recurrent, severe, bacterial and mycotic infections of the skin, lymph nodes, and viscera that evoke granulomatous responses. The underlying defect is the inability of the leukocyte to destroy certain ingested bacteria and fungi which are usually of low virulence and may be semi-saprophytes that normally do not evoke any response and are readily destroyed. Cellular and humoral immune responses are normal. The following report concerns a 24-year-old male who unknowingly manifested the disease at age 14 and survived numerous infections over the following ten years before succumbing to pneumonia.

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Case Report

A 24-year-old white male was admitted to the hospital in November 1974 for treatment of a persistently high fever of at least ten days duration which was unresponsive to lincomycin therapy. Chest x-rays revealed bilateral pneumonitis. The patient had been well until 1964 when, at the age of 14, he developed an infected sebaceous cyst. This responded to treatment and cleared. In 1967 he had several episodes of bloody diarrhea. Proctosigmoidoscopy and barium enema in December 1968 revealed what was interpreted as ulcerative colitis that was symptomatically relieved with therapy (Figure 1). One year later a perirectal abscess was drained. In October 1970, he again experienced bloody diarrhea, followed several weeks later by pain in the right upper quadrant of his abdomen and right shoulder. A barium enema indicated progression in the changes demonstrated two years before, still interpreted as ulcerative colitis (Figure 2). Serial liver scans revealed the presence of two abscesses which were surgically

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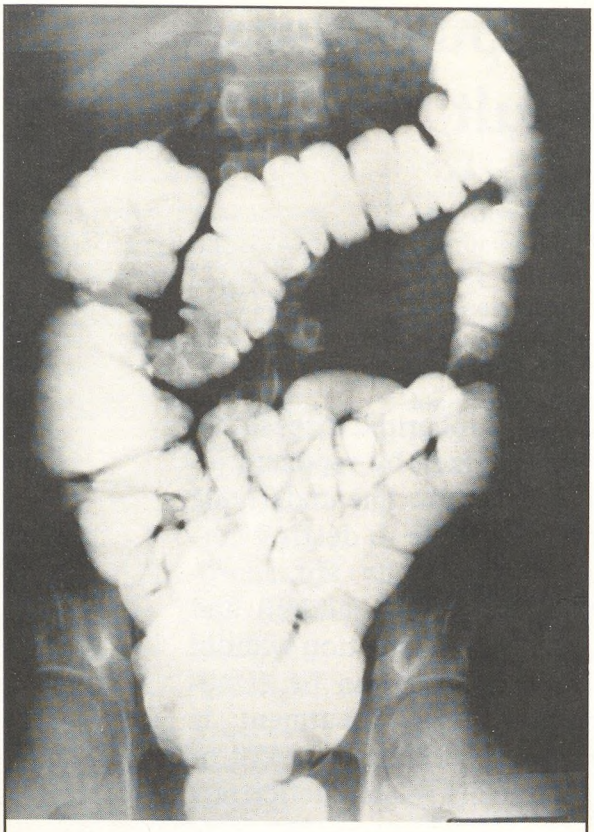

Figure 1. Barium enema showing minimal narrowing of a localized segment of the splenic flexure and of right side of the transverse colon.

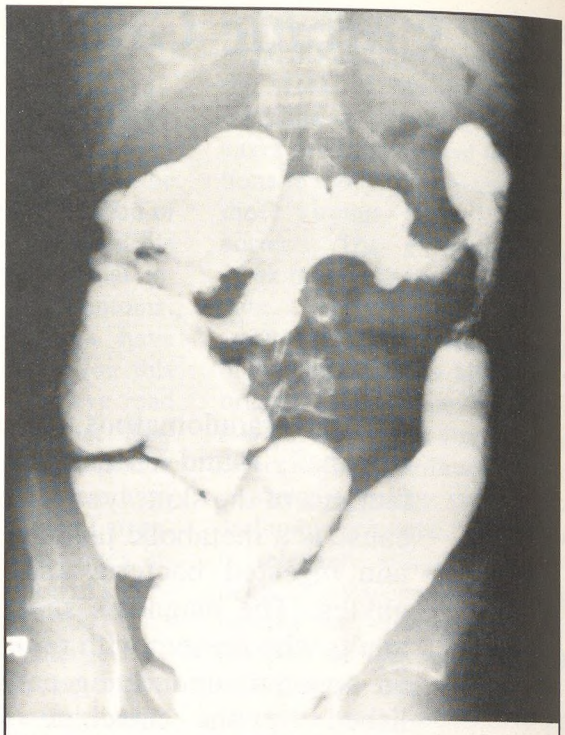

Figure 2. Twenty months following Figure 1. Note extensive changes of colitis in the splenic flexure and transverse colon. The skip areas and asymmetrical involvement of the wall of the bowel are characteristic of granulomatous colitis.

drained (Figure 3). A few days later he developed dyspnea and cyanosis, necessitating drainage of a large right purulent pleural effusion. All these findings were presumably complications of "ulcerative colitis."

Over the next three months he had several more episodes of bloody diarrhea and pain in the right upper quadrant of his abdomen and chest. These ultimately responded to further surgical drainage of liver abscesses and rib resection with open drainage of an empyema. One month later he had a grand mal seizure followed by severe headaches. A serial brain scan showed multiple abscesses which were treated surgically as well as with intensive antibiotic therapy (Figure 4). During this hospital admission, a physician saw his chart on the desk and mentioned that he had treated his brother for chronic granulomatous disease four years earlier. A nitroblue tetrazolium test (NBT) was found to be positive and, for the first time, the diagnosis of chronic granulomatous disease was established.

Over the next three years the patient was maintained on a multivalent gram-negative Staphylococci-Candida whole cell vaccine, gamma globulin, and transfer factor. He had several hospitalizations for pneumonia and severe cellulitis which responded to intensive, intravenous antibiotic therapy. He was actively working as a cement mason. However, in mid 1974 he became despondent over an unrequited love affair and discontinued his regular visits for transfer factor and vaccine. Eventually, he developed pneumonia that necessitated a readmission.

X-ray and laboratory studies revealed extensive bilateral pneumonitis and leukocytosis with a pronounced shift to the left. For the following three weeks, x-ray studies of his chest varied with the pneumonia, sometimes partially clearing and sometimes worsening. Arterial blood gases re-

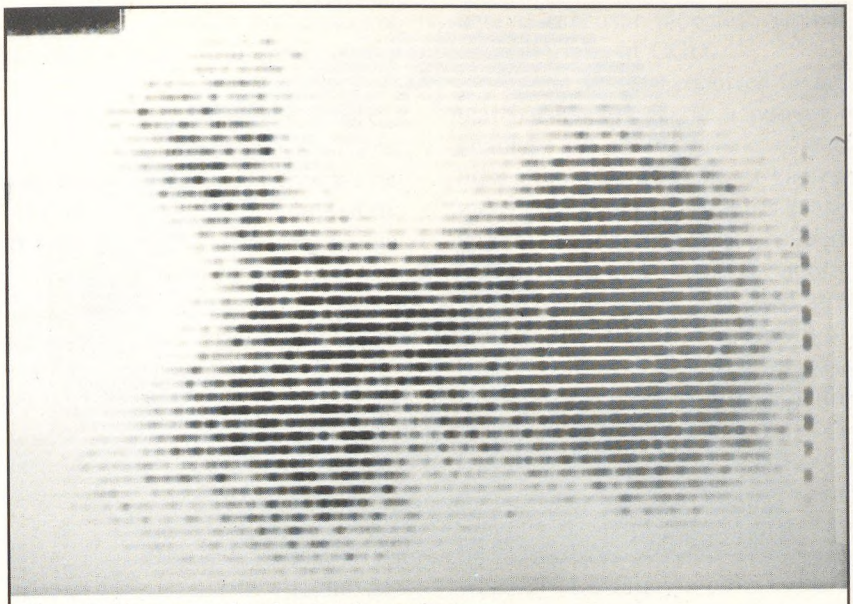

Figure 3. Liver scan showing two large abscesses.

vealed marked desaturation necessitating tracheostomy. Blood cultures were negative. Tracheostomy cultures grew mostly aspergillus with fewer colonies of Candida and an occasional Staphylococcus aureus. He was usually febrile but this, too, fluctuated widely. In spite of intensive antibiotic therapy, tracheostomy, and respiratory assistance, he developed progressive respiratory failure, marked leukopenia, and thrombocytopenia, and died.

Necropsy revealed severe distortion of the pulmonary architecture with congestion of capillary blood vessels and intrabronchial and intra-alveolar areas of recent hemorrhage. There were multiple foci of chronic granulomata, many of which contained fungi with peripherally-lined hyphae, as well as numerous microabscesses also filled with hyphae. Culture of lung tissue grew Aspergillus and albicans. Other areas of the lungs showed chronic interstitial fibrosis, presumably the end result of many bouts of pneumonitis. The liver was not enlarged but did show areas of interstitial scarring and fibrosis. The colon appeared normal.

Discussion

Chronic granulomatous disease is a disease of paradoxes.[1] Its victims are competent to handle virulent organisms, such as beta hemolytic streptococci, meningococci, and pneumococci, but succumb to less virulent organisms like staphylococci or enterobacteriaceae and opportunists such as candida and aspergilli. Cellular and humoral responses are normal. Immunoglobulins are normal or slightly elevated, the result of repeated infections.

The underlying defect lies within the leukocyte which can engulf bacteria and fungi but cannot destroy some of them.[2] During phagocytosis, the normal leukocyte increases its oxygen consumption, hydrogen peroxide production, and hexose monophosphate pathway activity several times, leading to the ultimate destruction of the organisms.[3] In chronic granulomatous disease, these activities are not enhanced and the normal metabolic oxidation of phagocytosis is lacking, apparently due to an enzyme deficiency yet to be determined. In spite of this deficiency Quie[4] showed that catalase-negative organisms, which are frequently highly pathogenic, are destroyed within the leukocyte due to bacterial production of peroxide. In short, the bacteria destroys itself even though leukocytic phagocytosis is absent. On the other hand, catalase-positive organisms, often of low virulence and frequently normal opportunists within the body, are not destroyed and

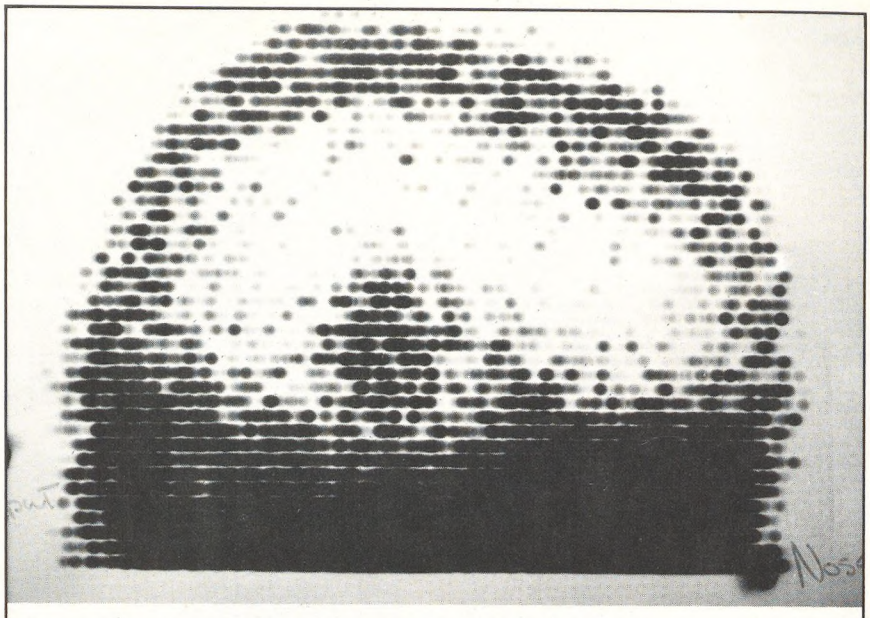

Figure 4. Brain scan showing a large temporoparietal abscess.

plague the patient clinically. Specifically, catalase detoxifies bacterial peroxide. Therefore, in the absence of normal leukocyte response and bacterial peroxide, these organisms remain viable, engulfed within the white cell, impervious to antibodies and antibiotics. Eventually, they are disseminated throughout the body by migrating neutrophils and produce granulomata.

The classic form of the disease is inherited as an x-linked recessive trait[5,6] in male offspring of female carriers. Mothers, grandmothers, and approximately half the sisters of victims have been identified as carriers.[7] In a second form, the defect is transmitted as an autosomal recessive trait which, to date, has been found and manifested only in females.[8] These patients present a clinical picture similar to but less severe than that of chronic granulomatous disease. Other forms of the disease, usually more benign, are coming to light due to intensive investigation of bactericidal deficiencies of the leukocyte.

The clinical features of chronic granulomatous disease are varied. Recurrent infections, with low-grade pathogens, are its hallmark.[9] Recurrent severe skin lesions that are slow to heal and that progress to suppuration and granulomata are common. Lymphadenitis, in any area of the body, affects the patient sometime during the course of the disease. Hepatosplenomegaly, including hepatic granuloma and abscesses, pericarditis, granulomatous septic osteomyelitis, and brain abscesses, frequently occur. However, repeated episodes of pneumonia with organisms of low virulence are the telltale feature that eventually leads to diagnosis of this disease. Classically, the pneumonia responds slowly to treatment and often leads to empyema. Chronic granulomatous disease can be a fulminating, rapidly fatal disease in newborns or young infants. More often it is chronic and unrecognized, as in this case, lasting for years and defying treatment until eventually terminating in a fatal pneumonia.

The diagnosis of chronic granulomatous disease can be established by the nitroblue tetrazolium test (NBT).[10] During phagocytosis, normal leukocytes reduce NBT, producing a dark blue precipitate. The leukocytes of CGD totally lack this capability, making this histochemical test specific for CGD. An intermediate level of reduction occurs in carriers and in people afflicted with related but less virulent forms of bactericidal deficiencies. More elaborate, functional, and metabolic studies of the neutrophil will confirm its inability to destroy catalase-positive organisms. Other labora-

tory tests are nonspecific. Cellular and humoral immune responses are normal. Immunoglobulins are normal or elevated, the latter due to repeated infections. Blood cultures are usually negative.

X-rays of the chest vary, depending upon the stage and activity of the pneumonia. There may be extensive infiltrates, hilar adenopathy, and patchy or coalescent pneumonia that is slow to change and slow to heal. During remission, there may be complete clearing or the scars of repeated pneumonia with focal areas of emphysema, nonspecific infiltrates, and areas of chronic, unremitting pneumonia may persist. The x-ray picture is not characteristic and reflects only the type of infection besetting the patient at that time. However, CGD should be added to the lengthening gamut of diseases that produce recurrent pneumonia. Often these people are found in pulmonary clinics, being followed and treated for years without any specific diagnosis. Repeated skin and pulmonary infections by low-grade pathogens are the warning that should alert the physician to this diagnosis. The NBT test confirms it.

This case illustrates most of the salient features of chronic granulomatous disease. Somewhat uncommon is the fact that the disease did not manifest itself until the patient was 14 years of age and that he survived to his mid 20s. The relationship of ulcerative colitis and CGD has never been reported and is speculative. Proctoscopy and barium enema seemed to establish the diagnosis of ulcerative colitis. In fact, the liver abscesses and empyema were initially thought to be complications of colitis. Steroid therapy did control the diarrhea. However, the two barium enemas performed on this patient several years prior to his death revealed findings more characteristic of granulomatous than of ulcerative colitis. The lack of distal large bowel involvement, the noncircumferential involvement of the wall of the colon, and the apparent skip areas are more consistent with granulomatous colitis. Furthermore, at autopsy the bowel appeared normal, a finding that does not contradict this diagnosis.[11] Ament and Ochs[12] found that four of nine patients with CGD had gastrointestinal symptoms; three of these developed perianal fistulas and two had friable rectal mucosa. All nine had normal barium enemas; two had nonspecific mucosal changes on the small bowel x-ray, and all revealed, on the rectal and jejunal mucosal biopsies, pigmented histiocytes characteristic of CGD.

This is the first reported instance of an abnormal barium enema in a patient with CGD. The changes are characteristic of granulomatous colitis, although ulcerative or bacterial colitis are remote possibilities. It seems reasonable to postulate that the colitis was not coincidental but related to CGD, and may be merely another manifestation of leukocyte deficiency and granulomatous response. Cave et al have shown that transmissible agents will produce Crohn disease.[13] It is intriguing to speculate that the colitis found in this case resulted from such an agent. Presumably, normal leukocytes would have destroyed this agent; the leukocytes of CGD permitted its viability and dissemination. Furthermore, the repeated pulmonary infections were similar manifestations of the aftermath of leukocyte deficiency, the common denominator of all the medical tragedies that befell this person.

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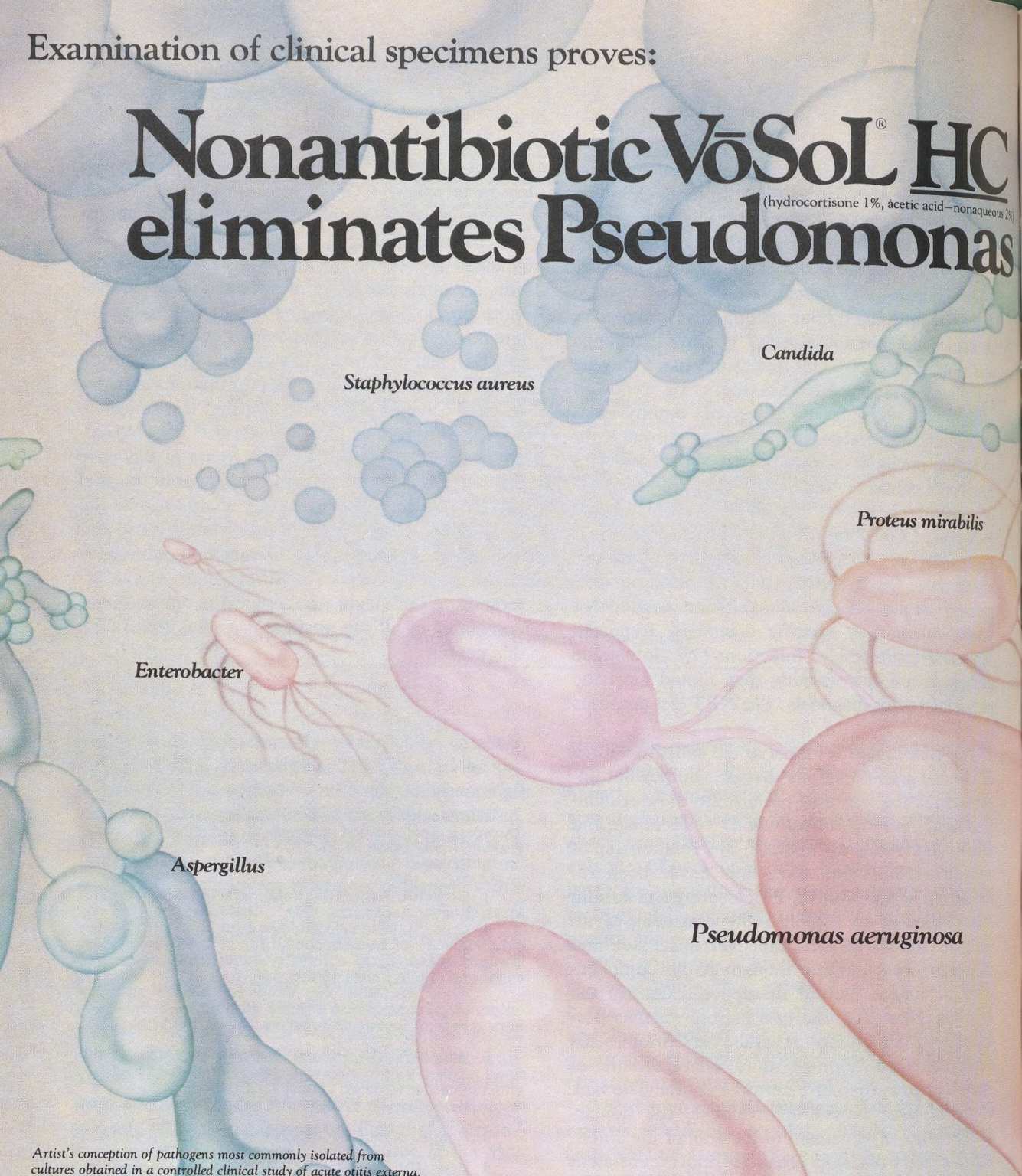

Artist's conception of pathogens most commonly isolated from cultures obtained in a controlled clinical study of acute otitis externa. Size and spatial relationships of organisms have no clinical significance and are not intended to reflect the incidence or virulence of any one organism relative to the others.

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