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Healing of Severe Perineal and Cutaneous Crohn's Disease With Hyperbaric Oxygen

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Recurrent perineal Crohn's disease can be an extremely debilitating complication that may be difficult to treat. We report a patient with progressively worsening perineal and biopsy-proven cutaneous Crohn's disease that had been refractory to surgery and medical treatment (sulfasalazine, steroids, 6-mercaptopurine, metronidazole, antibiotics). As the lesions were reminiscent of problem wounds occurring in other situations, hyperbaric oxygen treatment was instituted while the patient was continued on metronidazole. Response was dramatic with almost immediate relief of symptoms and regression within 2.5 mo of wounds that had previously defied therapy for 8 yr. Clinical remission has not been sustained as four subsequent courses of hyperbaric oxygen have been given over a period of 11 mo. However, the patient has been essentially asymptomatic since her initial course and the extent of her cutaneous disease has been minimal compared with that before hyperbaric oxygen. Hyperbaric oxygen treatment is costly and should not be routinely used in every patient with perineal Crohn's disease. However, this case report may herald an advance in the understanding of the pathogenesis of this complication and ultimately, its therapy.

Perineal Crohn's disease remains an extremely difficult condition to treat from a medical or surgical standpoint. Patients frequently become physically and socially disabled from the chronic recurrent nature of the perineal manifestations of their disease. Management is often frustrating for both the patient and physician. Current treatment modalities include a variety of surgical procedures such as incision and drainage, fistulotomy and diverting ileostomy, or colostomy with and without proctocolectomy (1,2). The medical treatment of Crohn's disease typically involves the use of sulfasalazine and immunosuppressive agents with occasional success from broad spectrum antibiotics (3,4). However, most of the conventional therapies (steroids, sulfasalazine, broad spectrum antibiotics) have not been effective in perineal Crohn's disease (1,2,4–6), while azathioprine or 6-mercaptopurine may be helpful in some patients (7–9). Total parenteral nutrition may also be beneficial in a few patients with perineal and fistulous disease, but relapse is common (1,3,5,6,10–13). Several reports suggest that high-dose metronidazole may benefit perineal Crohn's disease (14–16). However, controlled studies are lacking, patients often have been given other agents, and a high incidence of side effects, as well as disease exacerbation with dose reduction, have limited the usefulness of this drug (3,5,14–17). We report the dramatic response of severe perineal and cutaneous Crohn's disease to hyperbaric oxygen in a patient who had previously failed multiple medical and surgical treatment modalities.

Case Report

This 48-yr-old black woman initially presented in 1972 with weight loss and bloody diarrhea. A diagnosis of ulcerative colitis was made based on proctoscopic and radiographic findings. She improved on sulfasalazine, but had two exacerbations requiring steroids over the next 2 yr. In 1974, tissue obtained at laparotomy for a pelvic mass demonstrated granulomatous salpingitis. Stains for acid-fast bacilli and fungi were negative. Review of prior proctoscopic biopsies also showed granulomas and a diagnosis of Crohn's disease was made. A rectal stricture requiring repeated dilatations and recurrent perirectal abscesses necessitated a diverting colostomy in 1977. Her symptoms temporarily improved, but by 1979 extensive perineal disease had developed with extension into pelvic, gluteal, and abdominal wall intertriginous areas. Barium

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enema through the colostomy showed only descending colon involvement with stricture and multiple fistula. She was treated with metronidazole (250–500 mg t.i.d.) and various oral and parenteral antibiotics for prolonged periods without significant improvement. Beneficial effects of corticosteroids were negated by side effects (obesity, diabetic ketoacidosis) and doses of sulfasalazine >1 g/day could not be tolerated because of nausea and vomiting.

Intractable perineal disease with pelvic sepsis culminated in a proctosigmoidectomy with gracilis flap in 1982. Recurrence of fistulous disease within 4 mo of surgery was treated with total parenteral nutrition for 1 mo to no avail. Biopsy specimens from nonhealing wounds and incision sites showed noncaseating granulomas that were negative for fungi and acid-fast bacilli. In 1983, she received 6-mercaptopurine (100 mg/day) and high-dose steroids (60 mg/day) for 2 mo, but 4 mo after discontinuing these medications her perineal and cutaneous disease again worsened. Within 2 mo of restarting 6-mercaptopurine (125 mg/day), she was admitted for incision and drainage of perirectal and perianal abscesses. Over the next 11 mo, her course was typified by multiple admissions for incision and drainage of sinus tracts, fistula, and pelvic abscesses. Beginning July 1985, 6-mercaptopurine (100 mg/day) was taken for 8 mo, but was discontinued when the patient was hospitalized for a severe flare-up of her perineal disease. Throughout this time, the patient had been on continuous metronidazole therapy (500 mg t.i.d.), which was also stopped in mid-1986. From July 1986 through December 1987 she was treated for severe, debilitating, painful exacerbations every 1–2 mo with oral and parenteral antibiotics as well as frequent local wound care by physical therapy two or three times per week. The painful nature of her lesions suggested secondary infection as the perineal manifestations of Crohn's disease are relatively painless. Multiple cultures during 1980–1987 of wounds, fistula, and sinus tracts recovered a variety of organisms (*Proteus mirabilis*, diphtheroids, enterococci, staphylococci) but specific anaerobic cultures were not done. In January 1988, she experienced her worse flare-up to date with severe dermal necrosis particularly in the intertriginous areas of her abdominal wall and perineum (Figures 1*A* and 1*B*). Intensive daily local care was extremely painful and this time parenteral antibiotics as well as metronidazole were unsuccessful and the patient was referred for a trial of hyperbaric oxygen therapy.

Methods

Daily hyperbaric oxygen treatments and wound care were provided on an outpatient basis. Wound care was similar to that used before hyperbaric oxygen and consisted of irrigation with saline and wet-to-dry daily dressings with fine mesh gauze soaked with 2% boric acid. Six days a week, the patient was accompanied by a medical attendant inside a large, multipatient hyperbaric chamber inside which the air pressure was increased to 2.4 atmospheres absolute, equivalent to 20.5 psi greater than ground level pressure. This pressure is equal to water pressure at 45 ft of sea water. Once at 2.4 atmospheres absolute, a plastic helmet was fitted and humidified 100% oxygen was allowed to flow through the helmet at 35 L/min with exhaust outside the chamber. Sampling of oxygen inside the head tent during each treatment ensured 100% inspired oxygen. Arterial blood gas measurements under these conditions have demonstrated arterial oxygen partial pressures of 1100–1300 mmHg. After saturation of hemoglobin, additional oxygen is delivered in physical solution in blood. Transcutaneous oxygen tension measured in skin next to the wound has confirmed skin Po_2 elevation to 800–1200 mmHg adjacent to wounds. Each day's hyperbaric oxygen treatment lasted 2 h, using a schedule of three 30-min oxygen breathing periods interrupted by 10-min periods with the hood open, allowing the patient to breathe chamber air. No topical application of oxygen was used.

Results

The patient began hyperbaric oxygen on January 11, 1988, and continued on metronidazole (500 mg t.i.d.). She received a total of 67 hyperbaric oxygen treatments by March 31, 1988, and during this time her lesions essentially healed completely (Figures 2*A* and 2*B*) except for one area near her buttocks. The only side effect experienced was blurred vision, and this resolved. In the latter part of April, a small area opened below her coccyx that failed to respond to conservative local therapy and hyperbaric oxygen was reinstituted for 20 more treatments from May 16 to June 10, 1988. The previous wound in the gluteal fold healed completely and the area near the coccyx had almost completely healed. In August, after beginning active exercise, a 2-cm area opened in her gluteal fold. It did not heal with extensive local care and enlarged to a 14-cm-long wound. Transcutaneous oxygen measurement (Radiometer TCM2; Radiometer, Copenhagen, Denmark) while breathing room air confirmed hypoxia of the skin next to the wound with an oxygen tension of 18 mmHg and a chest control of 66 mmHg. Wound site oxygen tension increased to 636 mmHg at 2.4 atmospheres absolute while breathing 100% oxygen. After demonstrating this therapeutic elevation of tissue oxygenation with hyperbaric oxygen, she underwent 18 more treatments between August 30 and September 20, 1988, resulting in resolution of her skin lesions except for a 1–2 mm^2 area in her gluteal fold that had not fully reepithelialized. Since mid-October 1988 this residual lesion has been retreated on two occasions with 22 and 23 hyperbaric treatments when it has enlarged to ~1 cm in diameter. The longest interval between treatments has been only 2.5 mo, but the patient has been essentially asymptomatic and the extent of her cutaneous disease has been minimal compared with her condition before hyperbaric oxygen.

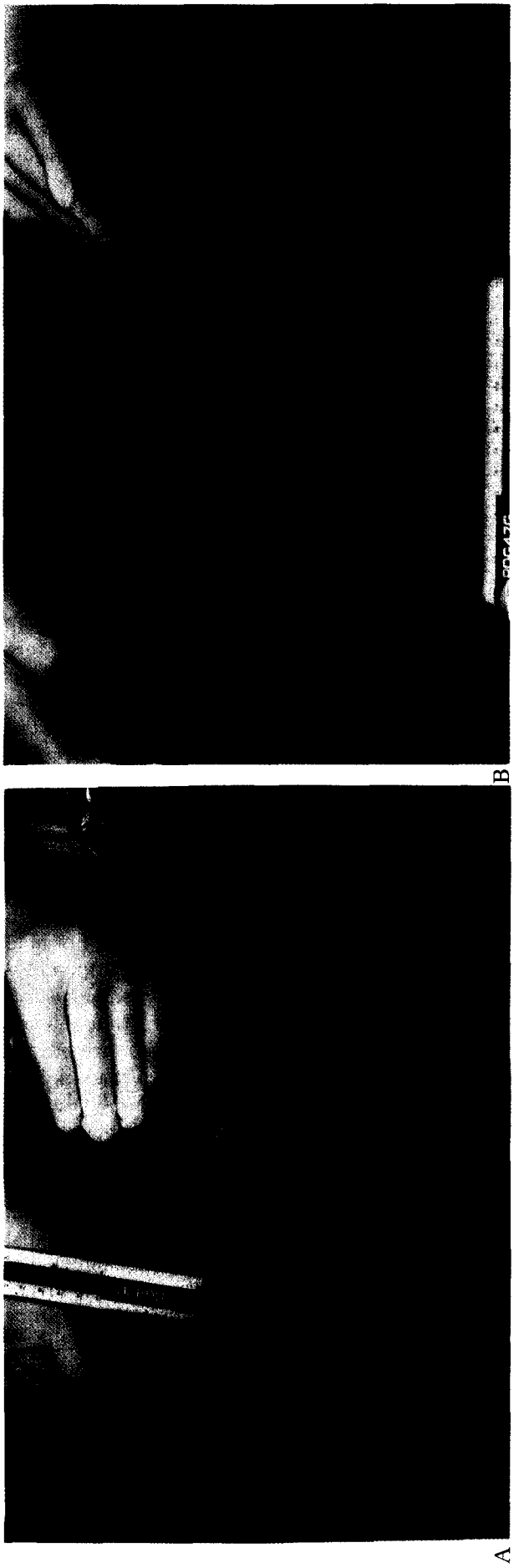

Figure 1. January 12, 1988. *A.* Intertriginous and abdominal wound cutaneous Crohn's disease. *B.* Perineal Crohn's disease with Foley catheter in place.

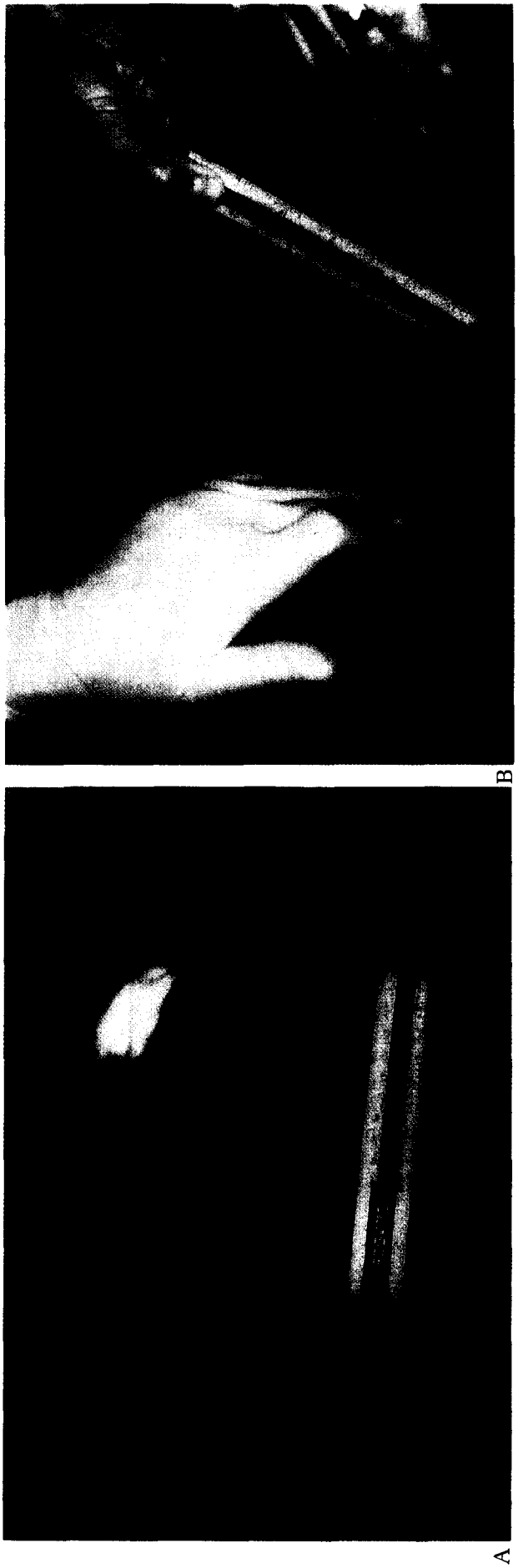

Figure 2. March 7, 1988. *A.* Healed intertriginous and abdominal wounds. *B.* Healed perineum.

Discussion

The cutaneous manifestations of Crohn's disease can be some of the most debilitating complications experienced by patients. Our patient manifested not only perineal ulcerations, but lesions (ulcerations in abdominal skinfolds) compatible with metastatic Crohn's disease (18–20). Treatment involves therapy of the primary disease process affecting the bowel, including both medical and surgical measures (1–3,5,6), as well as local therapy to the perineal lesions (1,2,5). The use of immunosuppressive agents (7–9) and metronidazole (14–16) in difficult cases has shown promise, but not all patients have a favorable response. Our patient had received multiple trials of various agents including conventional medications (sulfasalazine, steroids), 6-mercaptopurine, and metronidazole with only temporary benefit at best. Total parenteral nutrition and surgery also had little effect on her perineal disease. Since this patient's cutaneous and perineal lesions reminded one of the authors (C.B.) of the problem wounds encountered in some other diseases in which hyperbaric oxygen is efficacious, we decided to try hyperbaric oxygen.

The dramatic resolution of the lesions in this patient suggests that hyperbaric oxygen was a significant factor in the healing process. How hyperbaric oxygen worked in this case is not known, but the perineal and cutaneous manifestations of Crohn's disease may be similar to the problem wounds seen in diabetes, trauma, or irradiation. Wounds are termed problems because they fail to heal after adequate surgery and antibiotic management. Regardless of the etiology, a common denominator of problem wounds is tissue hypoxia, an inevitable result of tissue injury (21,22). This may be a hitherto unrecognized factor in the pathogenesis of the perineal and other cutaneous manifestations of Crohn's disease. Injury is a stimulus to repair by eliciting a response comprising inflammation, fibroblast proliferation, angiogenesis, tissue synthesis, and epithelization; but also imposes vulnerability to infection. Hemorrhage, which occurs in wounds, activates a number of events that attract neutrophils and lymphocytes. Injury also disrupts vessels leading to poor perfusion and wounds become energy sinks contributing to tissue hypoxia, local acidosis, and lactate accumulation, thus producing an environment favorable for invasion and proliferation of microorganisms (21), which may have been a factor in our case. Such tissue hypoxia decreases leukocyte killing of *Staphyloccus aureus* and *Escherichia coli* and may extend to other aerobic as well as anaerobic bacteria (21).

Under hyperbaric conditions, hypoxia in partially ischemic and infected wounds or in irradiated tissue can often be corrected by high-dose oxygen inhalation (22) and elevation of wound oxygen tension significantly increases the capacity of leukocytes to kill many pathogenic bacteria (21). Throughout our patient's course, a variety of aerobic bacteria were cultured from different sites and hyperbaric oxygen conceivably could have had some direct antibacterial effects that helped her wounds to heal. In addition, anaerobic microorganisms that lack superoxide dismutase or catalase are killed by ambient oxygen in the wound and their ability to produce toxins is impaired (21). Although anaerobic bacteria were not specifically searched for in our case, it is likely that such organisms were present (23). Hyperbaric oxygen would be expected to exert a beneficial effect on such bacteria by correcting the hypoxic environment present in such lesions as seen in our patient. Furthermore, there is some evidence that hyperoxia is additive to the effects of antibiotics (21). It is possible that hyperbaric oxygen could have enhanced the antimicrobial action of the metronidazole that our patient was receiving. Finally, correction of problem wound hypoxia increases fibroblast replication and production of collagen to support capillary proliferation (22), thus contributing to the wound healing in our patient.

Hyperbaric oxygen treatment is not without potential complications that include middle ear barotrauma, sinus squeezes, ocular effects, claustrophobia, pulmonary oxygen toxicity, and central nervous system oxygen toxicity (2). Most of these side effects are minor or self-limited, but some patients undergoing prolonged periods of daily hyperbaric oxygen treatment develop myopia, as did our patient. This effect is probably due to metabolic changes in the lens and is reversible. There is no good evidence to suggest hyperbaric oxygen damage to other ocular structures within limits of current treatment schedules. Pulmonary and central nervous system oxygen toxicity are often cited as major concerns, but in reality are rare or do not occur (24). Perhaps the most significant drawback to hyperbaric oxygen treatment may be cost. Our patient's bill for hyperbaric oxygen treatments is in excess of $40,000. However, this amount needs to be placed into perspective in relation to the cost of treatment incurred over the 8 yr before hyperbaric oxygen. Although we are unable to retrieve an exact figure, we have estimated the expense over the preceding 8 yr to be between $80,000 and $100,000 with no sign of resolution of her disease process at the time hyperbaric oxygen was instituted. Considering her prior miserable existence and the fact that her perineal and cutaneous wounds had never healed at any time in the past 8 yr, the cost seems justified.

What the long-term results may be are unknown and we certainly do not advocate the routine use of hyperbaric oxygen in the treatment of all perineal Crohn's disease. Perhaps such therapy may be useful in resolving perineal sepsis before surgery in some patients. More exciting is the possible role of hyperbaric oxygen as an adjunct to the other medical regimens (sulfasalazine, steroids, immunosuppressive agents, metronidazole, antibiotics) in patients with refractory perineal disease. The role of tissue hypoxia in Crohn's disease deserves further study, particularly in regards to treatment.

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