Cutaneous North American blastomycosis: Report of a case from central Canada

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North American blastomycosis is a capricious and often dangerous deep fungus infection, which may be expressed clinically as a cutaneous granulomatous infection or a chronic systemic infection.1,4 Though still endemic in the Mississippi and Ohio River valleys, no cases have been reported in Canada since 1963. This rarity has prompted us to present the details of a case of primary cutaneous North American blastomycosis which was referred to the Royal Victoria Hospital, Montreal, in 1968. Amphotericin B lotion (Fungizone, Squibb) was first used in an unsuccessful attempt to control the evolution of the lesion, which later responded favourably to treatment with intravenous amphotericin B.

Mr. G.M., aged 43, worked as a bookkeeper for a mining company in Northwestern Ontario, near the Manitoba border. In January 1968 he noticed a small group of papules and pustules appearing gradually on the vertex of his scalp, but otherwise he seemed to be in good health. When the lesions persisted and hair loss was observed, topical and systemic antibiotics were prescribed but had no effect. Within a period of three months the alopecic dermatitis reached a diameter of 3 cm., exuded serum and bled easily, and the patient again consulted the doctor. Routine hematology, blood chemistry, and pulmonary and renal functions were found to be within normal limits, and intradermal skin tests with histoplasmin, blastomycin and coccidiomycin (dilutions of 1/1000 and 1/100) gave negative results. A chest radiograph indicated a questionable pneumonitis in the right lower lobe, but films repeated three weeks later did not demonstrate this.

In September 1968 the patient was referred to the Royal Victoria Hospital, Montreal, where he was admitted. The skin lesion was a heavily crusted 3 to 4 cm. plaque on the vertex of the scalp at the hair margin of a male-pattern alopecia (Fig. 1). At its centre the lesion appeared to be deeply ulcerated and the borders were purulent and infiltrated. Physical examination confirmed the negative findings already reported. Regional nodes were not enlarged; skin tests with histoplasmin, blastomycin and coccidiomycin were negative. The clinical features suggested a cutaneous granuloma caused by Blastomyces dermatitidis, other deep fungi or bacteria, a sarcoidal or metallic granuloma, or a lymphomatous process.

Sections of a biopsy from the margin of the lesion, stained with hematoxylin and eosin, were consistent histologically with cutaneous North American blastomycosis,5 showing a chronic inflammatory reaction characterized by verrucose hyperplasia of the epidermis, with intradermal and dermal microabscesses. Amid a dense dermal infiltrate were several pale double-contoured organisms 8 to 18 μ in diameter with coarsely granulated cytoplasm (Fig. 2). The periodic acid-Schiff stain greatly improved the visualization of these purple-staining organisms.

Crusts were examined in chloral lactophenol, and several yeast-like cells 14 to 18 μ in diameter with highly refractile cell walls and single broad-based buds were observed. A culture of crust from the lesion at 37° C. on blood agar gradually
over several weeks developed a single-budding yeast-like organism of the B. dermatitidis type (Fig. 3). (Blastomyces brasiliensis is similar in appearance at this temperature but produces multiple buds. ) At 25°C on Sabouraud's slants, crust fragments yielded a white-to-buff filamentous mould-like growth consistent with B. dermatitidis. (Cryptococcus neoformans remains yeast-like at room temperature.) Mice injected with a saline homogenate of fresh crusts, and sacrificed eight weeks later, were found to be infected with B. dermatitidis.

Before he could be given intravenous treatment with amphotericin B, the patient was compelled to return to his home for personal reasons. While there he applied amphotericin B lotion twice daily to the affected site. On readmission at the end of four months the lesion centre had become a flat white scar, but its extension beyond the anterior margin and a new occipital lesion established that the disease had progressed clinically (Fig. 4). This was confirmed when B. dermatitidis was recultured from scrapings of the cutaneous lesions. As the patient's general clinical status and laboratory investigation had not changed, a series of intravenous infusions with amphotericin B solution was initiated.

His tolerance of the drug was tested by a six-hour intravenous infusion of 25 mg. of amphotericin B in 5% glucose solution. Mild rigrors and pyrexia occurred briefly at its termination, but this characteristic response to the drug was not considered a deterrent to therapy. At first, therapeutic infusions of 50 mg. were given on alternate days, but after six doses the dose was raised to 75-100 mg. for 13 doses. A total accumulated dose of 1.5 g. was given. Nausea, rigors and post-infusion pyrexia (40°C) were encountered regularly but were controlled with acetylsalicylic acid and phenobarbital.

A biogram was performed twice weekly but at no time indicated that hepatic, renal or hematopoietic function was sufficiently abnormal to warrant discontinuation of therapy. The hemoglobin fell from 16.8 to 11.8 mg. per 100 ml. during the treatment. A neutrophilic leukocytosis reached a peak of 34,000 during febrile attacks and fell to 15,000 between infusions. Eosinophilia and thrombocytopenia were not observed. The serum creatinine rose from a baseline value of 1.1 mg. per 100 ml. to 3.0 mg. per 100 ml. at the end of therapy, the BUN rose from 16 mg. to 46 mg. per 100 ml., and the serum potassium rose from 3.9 to 5.2 mEq. per l. in the treatment period. These values returned to pre-treatment levels two weeks after therapy was concluded.

The clinical response to systemic therapy was dramatic. In the first week of treatment the lesions became more inflamed, tender and exudative. Wet saline dressings were used to prevent the formation of crusts. Thereafter the involution was progressive. After three weeks (0.5 g. amphotericin B administered) the lesions were flattened and dry, and active foci were few. After six weeks (1.5 g.) the lesion sites were blanched alopeciae scars with minimal residual desquamation (Fig. 5). Post-treatment lesion biopsy sections revealed epidermal atrophy, mild edema, and perivascular lymphocytic infiltration in the midcutis, but no fungal elements.

An examination of the patient 18 months after completion of therapy showed no residue of the severe mycotic infection.

Discussion

B. dermatitidis has been isolated from the soil and from wild and domestic animals, particularly dogs, it causes sporadic disease in man around the world. The disease is most frequently encountered in the Mississippi and Ohio River Valleys and the North Carolina coastal plain at an elevation of 100 to 400 feet above sea-level, where the soil is light and sandy and the annual rainfall is 40 to 80 inches. Our patient lives on the northern rim of this central endemic area, in a region which is approximately 700 feet above sea-level.

Primary lesions of North American blastomycosis occur most frequently on exposed surfaces of the legs, where papulopustules become serpiginous gummatous granulomas which rarely induce systemic blastomycosis. Though chronic, the primary skin infection apparently induces little immunologic response in the host, since the complement fixation titre and blastomycin skin tests are usually negative throughout the course of the disease. In contrast, systemic North American blastomycosis usually begins as a pulmonary infection with cough, followed by weight loss and night sweats. Hematogenous dissemination of the organism may give rise to visceral and osseous lesions; it may also cause deep nodular skin lesions which later discharge pus and scar over or become indolent ulcers. A highly positive blastomycin skin test is usually seen in systemic disease and is a good prognostic sign, but a weak skin test and a high-titre complement fixation with yeast-phase B. dermatitidis indicate a poor prognosis.

Though the source of our patient's infection was never traced, from the outset he was considered to be suffering from the primary
cutaneous form of North American blastomycosis. The lesions were superficial, never nodular, and were located on an exposed surface. Although a suspicious pneumonitis was observed on one early chest film, it proved transient and was not associated with constitutional symptoms; the skin test was negative.

Amphotericin B was the drug of choice because the physicians were familiar with its use, and because it had been reported as being superior to iodides, X-5079C, and hamycin for the treatment of North American blastomycosis. Reports to date indicate that X-5079C induces remissions in many cases but is associated with higher relapse rates. Hamycin (an amphotericin B analogue) is effective orally, is non-toxic, and has given promising but variable clinical results. Stilbamidine and 2-hydroxystilbamidine are preferred by some authors who claim these drugs are equally as efficacious as amphotericin B and have fewer side effects; however, they too require similar prolonged intravenous administration to ensure freedom from relapse.

The toxicity associated with intravenous amphotericin B therapy is dose-related, and includes headache, chills, fever, vomiting and phlebitis; more serious side effects are anemia, hypokalemia and azotemia with possible irreversible renal damage. After the intravenous infusion of 1 mg. per kg. body weight over six hours, a peak blood level of the drug is reached within one hour, which drops to half this level in 24 hours. Since total dosages of more than 1 g. have given the lowest incidence of relapses, a dose of 1.5 g. was set as the therapeutic goal for our patient, to be administered within six weeks. This permitted the alternate daily dose to be adjusted in order to avoid nephropathy, though it is recognized that equally satisfactory results might have been achieved with lower daily doses over a longer period, as suggested by Drutz et al.

An opportunity to employ topical amphotericin B lotion as a temporizing measure arose during the second six months of the infection, but no benefit appeared to be derived from this therapy as the lesion continued to spread and new lesions developed. However, since the patient was not available for observation during this period it is not possible to draw firm conclusions concerning the efficacy of this form of treatment.

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References