Primary Cutaneous Cryptococcosis due to *Cryptococcus neoformans* in a Woman with Non-Hodgkin's Lymphoma

Sir,

Cryptococcus neoformans is a ubiquitous encapsulated yeast common in the environment; it is found throughout the world in soil, trees, pigeon excreta and dust. It is an agent of opportunistic infections, usually in immunodeficient subjects, affecting the lungs, central nervous system and skin, and less frequently the eyes, abdominal organs, bones and joints. Cutaneous cryptococcosis is more often secondary than primary. Herein we report a case of primary cutaneous cryptococcosis, manifesting as a solitary lesion, in a 46-year-old woman with non-Hodgkin's lymphoma.

CASE REPORT

A 46-year-old woman was referred to our hospital with a non-painful, nodular lesion at the nape of the neck. The nodule, about 2 cm in diameter and crowned with a scab, had developed 30 days earlier (Fig. 1). The patient had non-Hodgkin's lymphoma. When the scab was removed, the lesion had an ulcerated appearance. A biopsy specimen was obtained for histological examination and culture. Haematoxylin–eosin staining revealed an abundant infiltrate consisting of histiocytes and giant cells in the dermis and subcutaneous tissue. The cytoplasm of the giant cells contained roundish fungal elements and occasional hypha. The roundish elements were 4–12 μm in diameter, single or clustered, and surrounded by a pale halo. The infiltrate contained almost no lymphocytes. The spores were more evident with specific staining (Grocott) and stained with Alcian blue. Culture on Sabouraud agar revealed colonies of *C. neoformans*. Colony identification was performed using the commercial identification system ATB 32 C (BioMèrieux) (1). A blood test for *C. neoformans* antigen (CALAS; Meridian Diagnostic Inc., Cincinnati, OH), based on detection of a polysaccharide of the *C. neoformans* capsule in serum, was negative (2). Chest X-ray and computed tomodensitometry of the chest, abdomen and retroperitoneal area, as well as eye fundus, and neurological examination to reveal lung, eye, abdominal, nervous system, bone and joint localizations, were negative. The patient refused lumbar puncture to test cerebral spinal fluid. Fractures of left ribs XI and XII, osteolysis of the left iliac crest and 4th lumbar vertebra and mediastinal lymph node adenomegaly, all related to lymphoma, were found. An HIV test was negative. The lesion was surgically excised and the patient was treated with 200 mg/day i.v. fluconazole for 31 days, achieving clinical and mycological recovery. Follow-up at 12 months was negative: there were no signs of relapse of the neck lesion or any new lesions in other parts of the body.

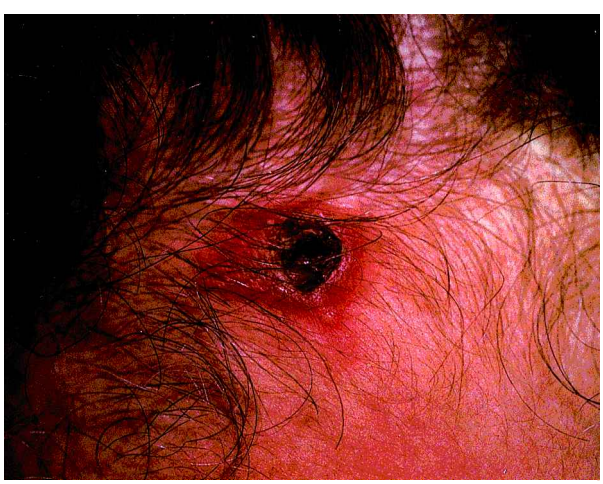

Fig. 1. Nodular lesion bearing scab, located on the nape of the neck.

The patient had an 11-year history of non-Hodgkin's centrofollicular lymphoma, in stage IV A at the time of observation, and was undergoing cytostatic chemotherapy with i.v. vincristine (2 mg/day), novantrone (15 mg/day), cyclophosphamide (700 mg/day) and methylprednisolone (16 mg/day). Routine blood chemistry was normal except for reduced red blood cell count (3.42×10^6), haemoglobin (10.2 g/dl), haematocrit (30.2%) and white blood cell count (3.1×10^3). Lymphocyte count was as follows: CD3/CD19 lymphocytes 2% (normal 6.4–22.6%); CD3/CD4 lymphocytes 22% (normal 28.5–60.5%); and CD3/CD8 lymphocytes 56% (normal 11.1–38.3%). Humoral immunity was deficient, with low plasma levels of immunoglobulins: IgG 446 g/l (normal 700–1,600 mg/dl); IgM < 17 g/l (normal 40–230 mg/dl); and IgA 31 g/l (normal 70–400 mg/dl). Follow-up at 12 months was negative: there was no sign of either relapse of the neck lesion or any new lesions in other parts of the body.

DISCUSSION

Diagnosis of cutaneous infection due to *C. neoformans* was made on the basis of histological examination, which revealed single and clustered, roundish spores, surrounded by a pale halo, in the dermis and subcutaneous tissue, and on the basis of isolation of C. neoformans in a skin biopsy culture. The infection was classified as primary, as no evidence of infection of other organs or systems could be found.

Primary skin cryptococcosis is typical of patients with immune deficiency, generally those with HIV infection or AIDS (3), and is observed less frequently in transplant (4) or lymphoma patients (5) or individuals with iatrogenic immunosuppression due to long-standing steroid therapy (6, 7). Cases of primary skin infection in immunocompetent hosts have only occasionally been reported (8–11). In most of these cases, medical history revealed a traumatic event that may have enabled direct inoculation of the yeast (3, 6, 8, 12). Clinical manifestations have been varied, including ulcerated lesions (13), papules (14), plaques and granulomas (9), nodules, sometimes with sporotrichoid spread (15), umbilicated lesions resembling molluscum contagiosum (16), crusted ulcerations (17), cellulitis (18, 19) and bullous erysipelas (6). Lesions have almost always been multiple rather than isolated, and have been reported on the face and neck and less often on the thumbs, arms or fingers. Clinically, lesions need to be distinguished from those caused by tuberculosis mycobacteria and agents of deep mycosis, such as phaeohyphomycetes.

Our patient, who did not recall any trauma at the site where the lesion developed, was treated with fluconazole. Although there is no well-established protocol for the treatment of exclusively cutaneous forms of cryptococcosis, fluconazole is the most successful therapy. The duration of therapy and the dosage vary between reports (6, 9). Itraconazole has less often been used (6). Topical imidazoles have been used even less frequently. Only one patient, who was immunocompetent, is reported to have recovered without any antifungal therapy (9).

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Crude Coal Tar Treatment Every Day Versus Every Other Day for Plaque Psoriasis

Sir,

Coal tar has been used in the topical treatment of psoriasis for more than a century and is assumed to have keratolytic, anti-pruritic, anti-mitotic and anti-inflammatory effects (1–3). Tar has, mostly due to its smell and staining properties, to some extent been replaced by other local treatments.

Coal tar is a complex mixture of thousands of compounds produced by condensation during the carbonization of coal (1, 4); however, the active substances in coal tar have never been identified (1, 4). It is well known that exposure to UV irradiation in the days following tar treatment can result in sunburn, indicating that the effect of tar in the skin persists for > 24 h.

In Denmark, crude coal tar (CCT) is still used daily for the treatment of plaque psoriasis. The procedure is very time-consuming and is limited by the number of nurses and bathrooms available. To evaluate the procedure and perhaps observe an extended effect of the tar in the skin, we investigated the effect of treatment with CCT every other day as compared with every day.

MATERIAL AND METHODS

The trial was conducted as a prospective, investigator-blinded, right/left randomized comparison of CCT treatment every day versus every other day. The study was approved by the Ethics Committee of Copenhagen.

A total of 15 adults (six males, nine females; mean age 54 years; range 23–90 years) volunteered for the study and gave their informed consent. Patients were recruited among those referred to the Department. All patients suffered from chronic plaque psoriasis and none of them received any other treatment for their skin disease during the study. Exclusion criteria were allergy to coal tar and pregnancy. All patients were > 18 years old.

Treatment with CCT every weekday was randomly assigned to one side of the body by drawing lots. On the opposite side of the body CCT was applied every other weekday. The application of CCT was followed by 20 min in a bathtub (37°C). The patients used tar cream 5% during weekends.

The psoriasis was assessed by a second doctor who was unaware of the treatment. Psoriasis severity was assessed with respect to erythema, infiltration and desquamation by means of a modified Psoriasis Area and Severity Index (PASI) (5). The severity of the psoriatic lesions was recorded on a five-point scale (0 = absent, 1 = slight, 2 = moderate, 3 = severe and 4 = very severe). Patients were assessed before treatment and once a week during the treatment period. The maximum treatment period was 4 weeks.

The efficacy was evaluated by comparing PASI score at the end of treatment to PASI score at baseline using the Wilcoxon matched-pairs signed-rank test. PASI scores at baseline and 1, 2, 3 and 4 weeks after the start of treatment were compared using the non-parametric Friedman two-way analysis of variance. $p < 0.05$ was regarded as statistically significant.

RESULTS

Patients participated in the study until their psoriasis was markedly improved or cleared or they withdrew from the study. On average, patients participated for 3.3 weeks (range 1–4 weeks).