Mycetoma formation in *Trichophyton rubrum* infection

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**SUMMARY**

An adult male patient with a chronic *Trichophyton rubrum* infection of the feet, toe nails and groin, for 15 years, developed on the dorsum of the right foot a tumour with draining sinuses. Histological examination of tissue from the growth revealed granulomatous inflammation with abscesses containing granules characteristic of mycetoma. *T. rubrum* was cultured from skin scrapings and toe nails. The concurrent complete clearing of the superficial lesions and the mycetoma during treatment with griseofulvin, as well as the disappearance of complement fixing antibodies against *T. rubrum* antigen, indicate that this hitherto unreported complication of a dermatophyte infection may be related and may not be coincidental to the infection.

We report a patient who had had persistent *Trichophyton rubrum* infection of the skin of the feet, groin, and the nails of the toes for over 15 years and who subsequently developed a mycetoma on the dorsum of one foot. We consider this event a hitherto unreported complication of a dermatophyte infection of the skin.

Mycetomas are usually considered to be reactive inflammatory nodules of the skin and subcutaneous tissue with sinus tracts exuding material, usually containing granules made up of colonies of actinomycetes or true fungi. The subcutaneous inflammatory disease involving the skin of our patient fulfils the clinical and histological criteria of mycetoma, although no granules or organisms were found on direct microscopic examination of exudate from the sinus tracts. For a discussion of organisms causing mycetoma, the reader is referred to the paper by Macotela-Ruiz presented at the recent International Symposium on Mycoses (Macotela-Ruiz, 1970) and to the monograph by Mahgoub & Murray (1973).

**MATERIALS AND METHODS**

*Smears*

Exudate was taken from sinus tracts and smeared on clean dry slides for routine direct microscopic examination in 10% potassium hydroxide solution and after staining with Gram’s and Wright’s stains.

*Cultures*

Exudate from sinus tracts was inoculated on Sabouraud’s and Littman’s oxgall agar, and incubated at
20°C. Cultures for fungi were not made from the surgical specimens. Discharge from sinus tracts was collected for aerobic and anaerobic bacterial culture.

**Histopathology**
All biopsy specimens were prepared routinely, using 10% buffered formalin fixative solution. The specimens were embedded in paraffin blocks and the sections were stained with haematoxylin and eosin. The sections were also studied using special staining techniques, including periodic acid-Schiff (PAS), PAS with diastase digestion, Gram, and Gomori methenamine-silver nitrate stains (Luna, 1968).

**Serology**
Test antigens used were a saline extract of mycelia and cell wall polysaccharides of *T. rubrum*. The patient’s serum was analysed for the presence of circulating antibodies by charcoal agglutination, complement fixation, and immunodiffusion techniques (Grappel, Blank & Bishop, 1971).

**CASE REPORT**

The patient was a 52-year-old Caucasoid male, who complained of a slowly enlarging non-tender growth which appeared on the dorsum of the right foot during the summer of 1963. The surface of the tumour intermittently became eroded and exuded purulent material from the resulting sinus tracts.

The past medical history was noteworthy, for he had had for 15 years non-seasonal asthma of sufficient severity to require oral corticosteroid (prednisone 20 mg daily in divided doses) for control of symptoms for the last 6 years. He was known to be allergic to penicillin.

**First hospital admission**
He was admitted on 31 August 1964 to a surgical service. On physical examination, a soft non-tender mobile tumour measuring 3 x 4 cm with several small draining sinuses was found on the dorsum of the right foot overlying the distal second to fourth metatarsals. A culture of the exudate from the sinus tracts for bacteria grew a mixed flora (*Staphylococcus albus*, coliforms, haemolytic streptococci). Routine studies, including urinalysis, complete blood count, and serum cholesterol were within normal limits. Radiological examination of the chest showed evidence of emphysema. X-ray examination of the right foot showed a soft tissue tumour overlying the second to fourth metatarso-phalangeal joint spaces but no evidence of bony abnormality; there was medial wall calcification of the anterior and posterior tibial arteries and their respective branches within the foot.

The mass was dissected free, down to the level of the deep fascia, and the skin flaps closed over the deject. The operative site healed satisfactorily. The gross specimen consisted of greyish-pink tissue measuring 3.5 x 6.5 cm. Microscopic examination of sections from the specimen was reported by the surgical pathologist to show 'nodular collections of lipid laden macrophages surrounded by an inflammatory infiltrate in the dermis'. These findings were interpreted as 'consistent with xanthoma with secondary infection'.

**Second hospital admission**
The growth recurred and he was re-admitted on 7 September 1965 and was seen in dermatological consultation. He stated that for 15 years he had had dryness and scaling on the plantar surfaces of the feet, thickening of the toe nails, and a recurrent, pruritic rash in the groins. About 8 months after the excision of the growth on his right foot, several small ‘lumps’ appeared parallel to the scar of the excision site and slowly enlarged. Small erosions appeared on the surface of the nodules and discharged
Mycetoma and Trichophyton rubrum

'bits of yellowish-white' material (Fig. 1a). The corticosteroid dosage had been continued (prednisone 20 mg/day in divided doses) since the first admission.

**Physical examination.** There was an erythematous scaling eruption with sharply defined borders located on the proximal medial aspects of the thighs, the pubic area, and the buttocks. The toe nails were discoloured and subungual keratotic debris was found beneath the nail plates. The soles showed diffuse scaling with slight erythema. There was a linear scar involving the skin overlying the distal portions of the metatarsals of the right foot. Proximal to the scar and surrounding it, the skin was dusky and oedematous, and felt infiltrated on palpation. Removal of crusts from several inflammatory areas revealed draining sinuses. The femoral and inguinal lymph nodes were significantly enlarged.

![Figure 1.](image)

(a) Recurrent tumour showing dusky coloured infiltrated growth with multiple crusted and draining sinuses surrounding scar of original excision; note onychomycosis. (b) Mycetoma has cleared after 13 months of treatment with griseofulvin. Scarring post-inflammatory vascular changes and regression of nail infection. (c) Appearance of foot 5 years after treatment showing scarring at original site and recurrence of nail infection.

**RESULTS**

**Direct examination and cultures**
Septate hyphae were found on direct microscopic examination of scrapings from the skin of the groin, buttocks, plantar surfaces of the feet, and from beneath the toe nails. *T. rubrum* was grown from each of these locations. Gram-stained smears of the exudate from the sinus tracts showed epithelial cells, polymorphonuclear leukocytes, and a number of multinucleated giant cells, but no granules were found. No pathogenic organisms were grown on culture of the exudate from the tumour on either Sabouraud's or Littman's oxgall media, nor were pathogenic bacteria grown on bacterial cultures.

**Histopathology.** The original sections of the tumour surgically excised from the right foot during the first period of hospitalization were re-studied. The haematoxylin and eosin stained sections showed multiple nodular cellular infiltrates composed of histiocytes with foamy, granular cytoplasm, macrophages, fibrocytes, plasma cells and lymphocytes. The centre of many of the nodules consisted of an abscess composed mainly of polymorphonuclear leukocytes; many of these abscesses contained one
Figure 2. (a) Abscess formation in nodular cellular infiltrate in dermis showing granules (PAS, ×50).

Figure 2. (b) Higher magnification showing granule formation in centre of abscess (PAS, ×175).
or more granules. The centre of the granules appeared amorphous or granular while their periphery consisted of elongate, club-like structures (Fig. 2). The stroma within and about the nodules was oedematous and showed fibrosis and proliferation of capillaries. The centre of the granules was PAS reactive, and the club-like structures stained yellow with the counterstain in sections treated with PAS after digestion with diastase and counterstained with picric acid. There was a linear arrangement of PAS reactive material within this central amorphous and granular material, which resembled fungal filaments, but these were not distinct and could have represented an artifact. The central and peripheral areas of many of the granules were reactive with the Gram stain and resembled filaments. Some of the areas within the granules stained with the Gomori methenamine–silver technique but no organisms could be recognized. The histological sections were reviewed by consultants who concluded that there was a mycetoma in the histological sense of the definition, that the visible ‘grains’ were formed by a fuchsinophilic substance, and that no fungal or actinomycotic, bacterial elements were detectable in the material (Ajello, 1969; Destombes, 1969).

Two additional 4 mm punch biopsy specimens were obtained during the second hospital admission, but these did not include the deep dermis and subcutaneous tissue. The sections showed only granulomatous inflammation. No abscesses or grains were seen in these specimens.

**Serological investigations.** Samples of blood were drawn on 9 September 1965, 14 November 1968, and 23 February 1971. The serum was analysed for the presence of circulating antibodies by charcoal agglutination, complement fixation, and immunodiffusion. The saline extract of mycelia and poly-
saccharides of *T. rubrum* were used as antigens. Significant serological reactivity, however, was obtained only with the saline extract of mycelia. The results of these investigations are presented in Table 1.

**Treatment and clinical course.** The prednisone dosage was continued (20 mg/day) throughout the period of treatment because of the severity of the asthma. The patient was given 1 g of griseofulvin by mouth each day after the evening meal. Within 2 weeks clinical signs of infection on the buttocks and groin had disappeared completely. After 4 weeks of treatment, the scaling on the soles had diminished approximately 85%, while the tumefaction of the dorsum of the foot had regressed approximately 50%. The infection of the toe nails remained unchanged. By 12 weeks, the scaling on the soles had cleared completely, but there had been no further improvement in the inflammatory area on the dorsum of the foot. The dosage of griseofulvin was increased to 2 g by mouth after the evening meal. After 8 weeks of treatment with this dose, the tumefaction diminished by approximately 75–85%; by 12 weeks, the tumefaction had regressed completely, except for scarring and a post-inflammatory vascular reaction observed on change of temperature or on placing the foot in the dependent position. Treatment with griseofulvin was continued at a dosage of 1 g/day for an additional 8 months, then stopped (Fig. 1b). Throughout the course of treatment, the infection of the toe nails slowly improved but did not resolve completely. He has been seen at regular intervals since treatment was discontinued and there has been no recurrence of the mycetoma, although the nail infection has relapsed (Fig. 1c).

**Table 1. Serological tests**

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<tr>
<th>Date of test</th>
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<tr>
<td></td>
<td>Immunodiffusion</td>
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<tr>
<td>September 1965</td>
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<tr>
<td>November 1968</td>
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<td>February 1971</td>
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* Titre 1:16 (0.05 ml serum); † two precipitin bands; ‡ one faint precipitin band (serum concentrated x 5).

**DISCUSSION**

The diversity of agents, ranging from actinomycetes to moulds, which are capable of producing the same clinical picture, is one of the peculiarities of mycetoma. Rarely, the cutaneous lesions caused by a staphylococcal infection (botryomycosis) may superficially resemble mycetoma clinically and histologically, but Gram-stained sections show the club-like projections of the granules to be made of masses of staphylococci (Waisman, 1962).

In experimentally produced mycetomas in animals, it has been shown that the development of maduromycotic and actinomycotic grains is a function of time. In the dynamic formation of grains, hyphae are abundant in young grains but sparse or absent in old ones. This observation in part accounts for the difficulty in making a diagnosis of the pathogen from histological preparations of tissue specimens (Avram, 1967). Until recently, identification of the causative organism in mycetomatous infections depended on histological and cultural methods. The diagnosis is sometimes difficult
because histological identification of the organism is imprecise and because of laboratory contaminants of cultures from exudates. A demonstration of precipitating and complement-fixing antibodies in sera of patients with mycetomas has been useful in diagnosis or in the confirmation of diagnoses of mycetomas due to several species of fungi and actinomycetes (Murray & Mahgoub, 1967; Avram & Nicolau, 1969).

Serological studies in our laboratory have shown that, in an analysis of sera from patients with T. rubrum infections, 48/150 (32%) reacted with mycelial extracts of T. rubrum by charcoal agglutination tests with titres up to 1:64; whereas 3/50 (6%) of sera from non-infected adults reacted by this method of analysis, with titres below 1:16.

Sera from infected patients also contained precipitins (24/133; 18%) and complement-fixing antibodies (20/62; 32%), which are probably more significant since they were not found in any sera from non-infected individuals (Grappel et al., 1972).

In our patient, complement-fixing antibodies were detected only in sera taken while the mycetoma was present. The absence of complement-fixing antibodies following resolution of the inflammatory process, and the disappearance of precipitating antibodies with clearing of the T. rubrum infection on the skin, even though the nail infection persisted, may be further evidence for relationship between the T. rubrum infection and the events observed. We have observed a similar precipitin, agglutination, and complement-fixing antibody decrease to a saline extract of T. sulfureum in a child with tinea capitis and kerion formation caused by T. sulfureum following griseofulvin-induced resolution of the infection (Grappel et al., 1972).

T. rubrum infection of skin and nails is common, but the concurrent appearance of the mycetoma syndrome is hitherto unreported. A reasonable explanation for this unusual event may be found in the patient's long term treatment with corticosteroids. Although the dosage would not be considered sufficient to produce immunosuppression, it may have compromised the host's immuno-competency.

The question as to whether T. rubrum caused the mycetoma cannot be definitely answered since the organism was not demonstrated in or cultured from the mycetoma. Other micro-organisms known to cause mycetoma, Nocardia brasiliensis excepted (Latapi, 1960), have not usually been shown to be sensitive to griseofulvin. Therefore, regression of the mycetoma with griseofulvin treatment and the serological changes suggest a causal relationship between T. rubrum and the mycetoma.

Addendum
After the acceptance of our manuscript, Baylet et al. (1973) reported four scalp mycetomas characterized by the association of a subcutaneous lesion with white granules and isolation of Microsporum ferrugineum on culture.

ACKNOWLEDGMENTS
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REFERENCES
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