Imported mycoses: some diagnostic problems

W. ST C. SYMMERS
M.D.

Charing Cross Hospital and Medical School, The Reynolds Building, St Dunstan's Road,
London W6 8RP

Summary

Infections by actinomycetes or by true fungi may cause diagnostic difficulties in countries where they are not familiar. Illustrative cases from a series of 353 instances are given together with rare indigenous examples of the same infections. Early, accurate diagnosis is essential for rational and effective treatment.

Introduction

The first, and in many cases the greatest, problem in the correct clinical management of mycoses is their recognition. In general, delay in the diagnosis of mycoses results primarily from failure to consider that a fungal or actinomycetous infection may be the cause of a patient's symptoms. In this respect the problem is a commonplace one, not confined to mycoses: its solution lies in greater knowledge and greater awareness of diagnostic possibilities. Among the 353 cases of 'imported mycoses' in the accompanying table, the possibility of a mycosis was among the initial diagnostic considerations in just under 15%.

Mycoses in north-western Europe

In north-western Europe (the area covered by Belgium, Denmark, France, the German Federal Republic, the Irish Republic, Luxemburg, The Netherlands, Norway, Sweden, and the United Kingdom), the indigenous mycoses (excluding superficial mycoses of the skin, ocular mycoses and otomycoses) that are liable to cause serious and progressive disease, or that are potentially disabling or potentially life-threatening, include the following: actinomycosis; adiaspiromycosis; aspergillosis; basidiobolomycosis; candidiasis; chromomycosis (cutaneous and subcutaneous; cerebral and meningocerebral; other visceral infections); cryptococcosis; geotrichosis; mycetoma (caused by *Acremonium* spp., *Aspergillus nidulans* and *Petriellidium boydii*); nocardiosis (caused by *Nocardia asteroides*); penicilliosis; petriellidiosis (pulmonary, see also mycetoma, above); phycomycosis (caused by *Absidia* spp., *Rhizopus* spp. and probably other genera); sporotrichosis.

It should also be remembered that species of

Trichophyton and possibly of other fungi that cause dermatophytosis may invade the subcutaneous tissues and eventually give rise to distant lesions as a result of spread by the lymphatics or in the blood stream.

In any case of the infections listed above, and particularly in any case of those infections that occur less frequently in Europe than in other parts of the world, the possibility that infection took place while the patient was resident or travelling outside Europe ought to be considered. None of the infections is confined to Europe. In contrast, some important mycoses do not occur naturally in north-western Europe.

Mycoses not indigenous in north-western Europe

Blastomycosis (caused by *Blastomyces dermatitidis*); coccidioidomycosis; histoplasmosis, including African histoplasmosis; lobomycosis; mycetomas (except those caused by the fungi named in the list of indigenous mycoses of north-western Europe above); paracoccidioidomycosis; rhinoentomophthoromycosis; rhinosporidiosis.

However, instances of all these diseases have been seen in patients in north-western Europe whose infection originated while they were in parts of the world where the condition is indigenous. Further, in exceptional circumstances, blastomycosis, coccidioidomycosis, histoplasmosis and lobomycosis have been acquired in north-western Europe (Table 1) either through inadvertent exposure to infective forms of the causative organism in laboratories or as a result of contact with imported goods contaminated with the fungus (or, in the case of lobomycosis, in consequence of a needle prick while excising a biopsy specimen from an infected dolphin).

Diagnostic awareness

Although in comparison with the situation 10-20 years ago there is now much more awareness among clinicians and in laboratories of the occurrence of mycoses, their recognition is still frequently delayed. This is a world-wide shortcoming; even in North America, where we in Europe expect familiarity with mycoses to be general, the diagnosis of those infections that are endemic in parts of the continent is

very liable to be as much delayed, or almost so, through failure to consider the possibility of a mycosis. A basic knowledge of some of the exotic mycoses including histoplasmosis, and less often of coccidioidomycosis, is quite usual among young British doctors. Yet the same doctors, and their seniors, tend to be at best only vaguely and insufficiently informed about such infrequent indigenous

mycoses as nocardiosis, the phycosmycoses and sporotrichosis.

Geographical considerations

The importance of enquiring about a patient's geographical history and relating it to the presenting clinical problem cannot be stressed too strongly. Failure to do this may result in ignoring the possibility of an exotic fungal disease; this may lead to the patient's death.

Illustrative cases

Only a brief sketch of some causes of delayed recognition of 'imported' mycoses can be included here. The cases are from the series summarized in Table 1.

(A) Diagnostic delay through failure to consider the possibility of mycosis

Case 1. *Madurella mycetomatis* mycetoma of the tibia. A boy whose home was in India was struck over the tibial tuberosity by a cricket ball while at school in England. The unexpectedly severe pain that this caused led to X-ray examination which showed a large osteolytic lesion with some new bone formation. The radiological diagnosis was 'probable osteosarcoma'. Radiotherapy and amputation were advised. The child's guardians refused permission for such treatment. The lesion enlarged and showed signs of extension into the skin, with imminent ulceration. Biopsy was then undertaken and showed colonies of *M. mycetomatis* in a chronic inflammatory mass. There was no neoplasm. For the first time a careful history was taken: this disclosed that the child had accidentally run an acacia thorn into the leg at the site of the eventual mycetoma. The remains of the thorn were found in tissue removed during further conservative surgical treatment. Recovery followed.

Case 2. *Nocardia brasiliensis* mycetoma of the shoulder region. A Mexican student in London was treated over many months for 'chronic furunculosis' of the skin of the back of one shoulder. There was little effect from a wide range of antibacterial antibiotics and fresh lesions continued to appear over an increasingly wide area. Eventually, the patient consulted a fellow countryman who was on a post-graduate course in England: the latter made an immediate diagnosis of *N. brasiliensis* infection on clinical grounds; this was soon confirmed both histologically and by isolation of the organism. Treatment with a sulphone resulted in cure.

Case 3. *N. brasiliensis* mycetoma of foot. An English student gave a history of transfixion of one foot by a thorn, which pierced it from the sole to the dorsum in the region of the head of the metatarsal bones of the fourth and fifth toes. The thorn was

TABLE 1. Three hundred and fifty-three cases of non-indigenous and rarely indigenous mycoses seen personally in Britain from 1946 to 1977 (figures in parentheses indicate the number of cases with firm evidence or good circumstantial evidence that infection was acquired in Britain or elsewhere in north-western Europe)

Mycosis	Number of cases
Basidiobolomycosis	5 (2*)
Blastomycosis ('North American') caused by <i>Blastomyces dermatitidis</i>	32 (2†)
Blastomycosis, South American; see papacoccidioidomycosis.	
Chromomycosis	63 (21)
cutaneous	31 (6*)
subcutaneous (phaeosporotrichosis) caused or presumptively caused by <i>Phialophora gourgerotii</i>	18 (6*)
central nervous system, caused or presumptively caused by <i>Cladosporium trichoides</i> in most cases	11 (7*)
other visceral infections (heart and/or lungs)	3 (2*)
Coccidioidomycosis	41 (27–22‡; 5†)
Histoplasmosis, caused by <i>Histoplasma capsulatum</i>	101 (3–1‡; 2†)
Histoplasmosis, African, caused by <i>H. duboisii</i>	14 (0)
Lobomycosis (occupational contact with naturally infected dolphin that had been captured in European waters)	1
Mycetoma:	71 (2)
actinomycetous:	24 (0)
<i>A. maduræ</i>	6 (0)
<i>Actinomyces pelletieri</i>	3 (0)
<i>Nocardia brasiliensis</i>	10 (0)
<i>Streptomyces somaliensis</i>	5 (0)
fungal:	47 (2)
<i>Acremonium falciforme</i>	2 (0)
<i>Aspergillus</i> spp.	2 (0)
<i>Leptosphaeria senegalensis</i>	4 (0)
<i>Madurella grisea</i>	3 (0)
<i>M. mycetomatis</i>	19 (0)
<i>Microsporium ferrugineum</i>	4 (0)
<i>Petriellidium boydii</i>	5 (2*)
<i>Phialophora jeanselmei</i>	7 (0)
<i>Zopfia rosatii</i>	1 (0)
Paracoccidioidomycosis	9 (0)
Penicilliosis presumptively caused by <i>Penicillium marneffei</i>	1 (0)
Rhinoentomophthoromycosis	2 (0)
Rhinosporidiosis	13 (0)

* Naturally occurring indigenous infections.

† Infections presumptively mediated by fomites.

‡ Laboratory infections.

immediately withdrawn intact. Some months later a 'boil' appeared at the site of the former puncture on the dorsum of the foot. By this time the student had returned to England from the region of Central America in which he had been working on an archaeological site at the time of the injury. The 'boil' persisted in spite of treatment with anti-bacterial drugs. After some months colonies of *N. brasiliensis* were recognized in the discharge. The infection subsided permanently on treatment with dapsone.

Case 4. *N. brasiliensis* mycetoma of the forearm. A Venezuelan, resident in London, developed a series of ulcerating nodules in the subcutaneous tissue of one forearm. His case was demonstrated at a clinical meeting as a classic example of the ascending lymphangitic type of sporotrichosis, although *Sporothrix* had not been isolated. It was a young Mexican doctor in the audience who made the correct clinical diagnosis of *N. brasiliensis* mycetoma: he had been taught in his own country that sporotrichosis is only one of several infections that may present with this picture. His diagnosis was confirmed. The condition responded to treatment with dapsone.

Case 5. Verrucose chromomycosis of the arm. An Englishman who had recently retired to Germany after many years' residence in Jamaica sought treatment for a chronic verrucose eruption that extended from the dorsum of one hand to above the elbow. A clinical and histological diagnosis of chronic verrucose tuberculosis was made and intensive treatment with a range of anti-tuberculosis drugs, supplemented by excision of the larger of the lesions, was undertaken. It was not until one year later that a review of the histological specimens in another country disclosed the presence in every lesion examined of typical pigmented fungal cells of *Phialophora* sp.

Case 6. Psoriasiform chromomycosis of the elbow. A lesion, variously regarded as pustular psoriasis, lichen, traumatic keratosis and dermatitis artefacta, proved after many months of study in various hospitals to be chromomycotic. The fungal cells had been overlooked in biopsy specimens. The patient had never been outside the British Isles. His occupation was agricultural.

Case 7. Subcutaneous chromomycosis (phaeosporotrichosis) (Symmers, 1971b). A large 'cold abscess' in the upper part of a thigh was assumed to be tuberculous. It was repeatedly aspirated but it regularly re-formed. Anti-tuberculosis drugs had no effect. The patient was a Pakistani immigrant in Britain. He moved to Germany, where biopsy of the wall of the abscess showed pigmented fungal elements. *P. gougerotii* was isolated.

Case 8. Sporotrichosis of the face. An Iranian girl

at school in Europe was looked after by a succession of doctors over a period of 9 months during which extensive ulceration of the skin of one cheek developed; the accompanying cervical and submental lymphadenitis became complicated by sinus formation. Although no *Leishmania* could be shown in the lesions she was repeatedly treated for leishmaniasis. Eventually the possibility of a fungal infection was suggested and *Sporothrix schenckii* was isolated. Treatment with iodide led to healing. Gross scarring was left.

Case 9. Generalized coccidioidomycosis. An Italian man, living in Britain, developed what was regarded as a classic gummatous ulcer in the skin over the sternum. Medical students were summoned to see what was demonstrated to them as that contemporary rarity, clinical evidence of tertiary syphilis. When serological tests for syphilis proved to be negative a biopsy was undertaken and showed *Coccidioides immitis*; the fungus was isolated in culture (and a number of members of the laboratory staff acquired the infection). The patient's condition had deteriorated seriously during the weeks between the initial diagnosis of syphilis and the eventual diagnosis of coccidioidomycosis; he died in spite of intensive treatment with amphotericin and flucytosine. He had worked as an agricultural labourer in California, U.S.A.

Case 10. Coccidioidal pneumonia complicating Hodgkin's disease (Symmers, 1967 - Case 1). A medical student from California died in Britain of pneumonia that did not respond to antibacterial antibiotics. The post-mortem showed the pneumonia to be coccidioidal. Review of the clinical case notes showed that although the patient's statement that he had once had 'valley fever' had been recorded, apparently no steps had been taken to discover what 'valley fever' was. Had it been realized that 'valley fever' was the vernacular term for the illness accompanying the initial infection by *Coccidioides*, acquired in the San Joaquin Valley, in California, it might have been realized that the patient's pneumonia could be a manifestation of the fungal infection, reactivated by the coincident development of Hodgkin's disease and the immunosuppressive effects of the treatment that was given for the latter.

Case 11. Bilateral apical cavitating pulmonary histoplasmosis complicated by *Histoplasma* meningitis. Haemoptysis led to the radiological demonstration of cavities in both lungs of a European businessman who had spent many years in Kentucky and Ohio, U.S.A. He was treated with anti-tuberculosis drugs, in spite of failure to demonstrate mycobacteria in his sputum; the treatment was ineffectual and he died. Histoplasmosis was found at post-mortem to have been the cause of the pulmonary disease; the

infection had spread to the meninges in the terminal stages of the illness.

Case 12. Oral ulceration and Addison's disease due to histoplasmosis (Symmers, 1972). A Dutchman who had spent many years as a public works contractor in south-eastern Asia developed Addison's disease during his retirement in Europe. He also had extensive ulceration of the tongue, lips and throat. Hormone therapy and anti-tuberculosis drugs had little effect. Post-mortem showed destruction of both adrenals by caseous tissue that contained great numbers of *H. capsulatum*. The oral ulcers were also a manifestation of histoplasmosis. There had been no biopsy or other laboratory examination of these lesions at any time during his illness.

Case 13. African histoplasmosis. A surgeon's arm was amputated because his colleagues failed to see *H. duboisii* in the foreign-body giant cells in the biopsy of an osteolytic lesion in one radius. The giant cells were interpreted as sarcomatous.

Case 14. Paracoccidioidomycosis of the face. A Portuguese man, working in a London hospital as a porter, developed a chronic ulcer of the skin of one cheek. The clinical likeness of the lesion to that in Case 8 (above) led to a diagnosis of sporotrichosis. When treatment with iodide had no effect on the condition the possibility of carcinoma was considered. Biopsy showed no evidence of a tumour. It was a further 7 months before the sections were reviewed and the presence in them of typical forms of *Paracoccidioides brasiliensis* demonstrated. Meantime, the ulcer had almost doubled its extent. Ugly scarring accompanied the eventual cure. The patient had worked in Brazil some years earlier.

(B) Double infections

Case 15. Rhinosporidiosis of the nasal septum with accompanying leprosy (Symmers, 1966 b – Case 34). The pathologist's excitement at seeing his first case of rhinosporidiosis caused him to examine the biopsy specimen inadequately. The presence of *Mycobacterium leprae* in the tissue was not demonstrated until a chance review of the sections some years later.

Case 16. *Entamoeba histolytica* infection of a coccidioidal cavity in a lung. A physician acquired coccidioidomycosis while studying in California. The disease failed to subside spontaneously and a cavity formed and, following inadequate response to amphotericin, was excised. Three years later a recurrent cavity was also excised. The sections showed the presence of both *E. histolytica* and *C. immitis* in the wall of the cavity. The patient had subclinical amoebic colitis. There has been no recurrence of either infection following appropriate treatment. Another case of coexistent pulmonary coccidioidomycosis and pulmonary amoebiasis has

been mentioned elsewhere (Symmers, 1973a, Figs 7 and 8).

(C) Misidentification of fungi

Case 17. Blastomycosis of bone (Sissons, 1979). A solitary skeletal focus of infection by *Blastomyces dermatitidis* was discovered in consequence of the pathological fracture that its presence had caused. Initially, the nature of the lesion was overlooked because only haematoxylin-eosin (HE) preparations of the biopsy specimen were examined. At this time the clinical investigation was oriented toward finding a primary carcinoma as the bone lesion was presumed to be a metastatic deposit. No tumour was found. The sections were reviewed: many budding yeast-like fungal cells were shown by special staining procedures; more careful study made it clear that the organisms were visible in the HE preparations but had been overlooked. Because of their size the organisms were first taken for cryptococci. Later, because the patient had come from South Africa, they were interpreted as African histoplasmas (*H. duboisii* which, in fact, is not known to occur in southern Africa). Finally, they were recognized to be *B. dermatitidis*; this was confirmed by specific immunofluorescent staining. Meantime, the lesion had healed with no treatment other than straightforward orthopaedic measures. There has been no further evident infection.

Conclusion

The infections exemplified above, even if their recognition was belated, were all eventually identified as being caused by known specific organisms. During the same period when these cases were seen there was also a very small number of cases of unidentified but probably fungal infection. The appearances of the fungus (or presumed fungus) could not be identified as belonging to any known genus. Two were examples of a peculiar infection (the so-called 'Wewak disease') which to date has been observed only in patients returning from Papua New Guinea. The lesions are verrucose or superficially ulcerated nodules and areas of induration in the skin of a limb. The histological sections show histiocytosis of the dermis and great numbers of organisms in a mucoid matrix that seems to be a product of their growth (Fig. 1) (unpublished personal observations). The disease appears to be confined to the skin.

Other infections of unidentified nature include a form of widespread verrucose granulomatosis of the skin caused by a morphologically peculiar myceliate fungus and contracted in central or southern Africa (unpublished personal observations). Such cases indicate that the limits of knowledge of the variety of organisms that may cause mycoses or related infections in man have not yet been reached.

FIG 1. Histological sections of the lesions of 'Wewak' disease showing histiocytosis of the dermis and great numbers of organisms in a mucoid matrix which seems to be a product of their growth.

Algal infections seem now to be considered most conveniently along with the mycoses (Baker *et al.*, 1971). Infection by an alga (probably *Prototheca* sp.) has been seen in an American visiting London. The organisms were first mistaken for spherules of *Coccidioides immitis* (Symmers, 1973a, Fig. 6).

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- References prefixed with an asterisk relate to cases in Table 1.
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