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I'VE GOT YOU UNDER MY SKIN – THE MOULDS OF MAN

There are thought to be over 1.5 million species of fungi. Of these, most live on decaying vegetation, in partnership with algae (lichens) or tree roots (mycorrhizas) or are parasites of plants or insects. Only a few tens of species cause us any direct harm but *Mycologist* is featuring a series of articles about the main species that do cause irritating, and in some cases life-threatening human infections. In this issue *Penicillium marneffei* is discussed.

Penicillium marneffei: penicilliosis and the red peril in the east

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Anyone who followed the developing epidemic of Severe Acute Respiratory Syndrome (SARS) in the media would be in little doubt as to the threat posed by new and unexpected diseases. Whilst the general public is probably more familiar with the various 'exotic' viruses that have emerged in the past thirty years, medical mycology also has its own share of important emergent pathogens. In a regional context the most important of these is *Penicillium marneffei* Segratin *et. al.* – the causative agent of penicilliosis. This has become a very important complication in AIDS patients in large parts of the Far East, particularly in Thailand, Southern China and Hong Kong. Unlike more familiar fungal pathogens, such as *Candida albicans* and *Aspergillus fumigatus*, *P. marneffei* has only a short history – indeed it was first described as recently as the mid-1950s.

Until the late 1980s only a handful of cases were described in the literature – however this all changed with the arrival of the AIDS pandemic in the Far East. Within a very few years the incidence of *P. marneffei* infections had rapidly climbed, particularly in northern Thailand, until this fungal disease had assumed a regional importance that rivalled more well known killers of AIDS patients, such as tuberculosis. Without treatment (about which more is said below), infection with *P. marneffei* within this patient group was, and is, invariably fatal. Fortunately, in Thailand at least, great strides have been taken in controlling the spread of AIDS and as a result the national incidence of *P. marneffei* infection is now falling. However, significant numbers of cases have been recorded in Vietnam, Burma, Taiwan, Singapore, Malaysia, India and Hong Kong, and given that some of these countries have been rather less successful at controlling AIDS the number of *P. marneffei* infections is only likely to grow further. The situation in southern China (particularly along the Thai/Burma/Laos borders) is particularly worrying. Whilst the Chinese government has been loathe to publish accurate figures on its own AIDS epidemic it seems likely that there are large numbers of *P. marneffei* susceptible patients in this area who will go on to develop the disease.

What of the causative agent itself? *P. marneffei* is the only member of its genus which is regarded as a genuine human pathogen – indeed in the UK it is classified as a category three pathogen which requires that it should be handled in dedicated contained laboratory facilities. The fungus is also unique in its genus in being dimorphic – that is it exists as a mycelial phase at environmental temperature, but it undergoes a temperature induced transformation at 37°C to give rise to yeast like organisms (although the latter are more properly described as fission arthroconidia). When grown in the mycelial phase the organism produced a highly distinctive dark red pigment, which recent studies have shown is probably some type of melanin. The mycelial form has rarely been isolated from soil – somewhat bizarrely it has proved rather easier to isolate the organism from bamboo rats, which are relatively common inhabitants of much of the endemic area. Accordingly for some time it was thought that the rats were the environmental reservoir

of the disease – in fact it seems likely that they are actually merely fellow sufferers. Widespread forest clearance in areas such as northern Thailand has probably done much to increase exposure of people to environmental sources of the fungus.

It is believed that the infectious process involves the inhalation of tiny conidia produced by the mycelia; the former pass into the alveolar spaces within the lungs where the transformation process occurs. In healthy individuals it is assumed that infection is stopped in the lungs by the action of immune cells. However in those with immune dysfunction there is rapid spread by yeasts from the lungs to many of the most important organs of the body, such as the liver and spleen. Symptoms of disease at this stage are fairly non-specific and include fever cough and weight loss. Indeed, the dissemination process is so extensive that one of the most obvious external signs of *P. marneffei* infection in AIDS patients is the development of extensive skin lesions, each of which may contain large numbers of replicating yeast cells. One of the easiest ways to make a definitive diagnosis of the disease involves taking a smear from such lesions and examining it microscopically to identify the small budding yeast cells. Diagnosis may also now be made by the detection of antibodies produced against various fungal proteins or by the direct detection of fungal proteins either in sera or in urine.

Infection is also possible via inoculation injury – indeed the scientist who originally described the organism (a Dr Segretain) managed to infect himself accidentally by puncturing his own skin (an observation that has been inadvertently duplicated in several laboratories since). Fortunately for Dr Segretain the Health and Safety Executive was not in existence at the time and as a consequence he was able to bring his investigations to a successful conclusion without being the subject of a major investigation.

Although the area of endemicity is restricted to the Far East it is not unknown for cases to be diagnosed in Europe and the US. However, without exception, such patients represent imported cases, and have been found exclusively in those suffering from some dysfunction of the immune system (as a result of AIDS or cancer). Interestingly a few cases have occurred in which the period between exposure (i.e. travel to the Far East) and the development of penicilliosis is an extended one (of several years). This may suggest that in some individuals the disease can lay dormant or repressed until a subsequent episode of immune dysfunction enables it to reactivate. This is not, on the face of it, dissimilar to the reactivation seen in TB, and is worthy of further study.

Given that penicilliosis is capable of rapid and ultimately fatal dissemination it is a relief to know that reasonably effective drug therapy exists. Patients who are initially diagnosed with the disease will almost invariably be treated with Amphotericin B, the most commonly used antifungal drug for treating systemic fungal diseases. However, Amphotericin B is often poorly tolerated and patients are typically shifted on to treatment with itraconazole, which has proved itself successful at preventing relapse. The latter is a common feature of penicilliosis infection in AIDS patients and as a result maintenance therapy must be life long which imposes a significant burden on health care budgets particularly in developing countries.

Because it is a relative newcomer we know considerably less about the basic biology of *P. marneffei* than we do about other fungal pathogens such as *A. fumigatus*. Its ability to grow at 37°C must play a major role in its infectivity and this is an area that is being studied intensively. The production of pigment (melanin) may also play some part in allowing the organism to cause disease. Future work in such areas may enable us to identify new targets for therapeutic intervention, which is needed to both improve treatment and to bring its cost down. Finally although *P. marneffei* is probably the most important endemic fungal disease to emerge in the last few decades we cannot be sure that there are not similar fungal organisms 'out there'. The ever-increasing percentage of immunocompromised individuals within the general population makes it very likely that other 'new' fungi will pose significant health threats in the future.

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