CASE REPORT

Penicillium marneffei presenting as an immune reconstitution inflammatory syndrome (IRIS) in a patient with advanced HIV

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SUMMARY

A 62-year-old British man with advanced HIV was established on antiretroviral therapy and treatment for disseminated *Mycobacterium avium* complex and *Cytomegalovirus* infections. One month later he re-presented with epigastric pain, an epigastric mass and skin lesions. Abdominal imaging revealed large volume lymphadenopathy, which was not present on previous imaging. Blood cultures yielded *Penicillium marneffei*, a dimorphic fungus endemic to South-east Asia. The patient had spent several years travelling in Thailand prior to the diagnosis of HIV. Penicilliosis is a common AIDS-defining illness in endemic areas, but remains rare in Europe. In this case, it presented in the context of a rapidly decreasing viral load as an immune reconstitution inflammatory syndrome. The challenges of management in the context of multiple comorbidities and polypharmacy are discussed.

BACKGROUND

This is a rare presentation of *Penicillium marneffei* in a non-endemic area. The case illustrates the multiple pathologies that can co-exist in severely immunocompromised patients, the importance of an accurate travel history and the pathogenesis of immune reconstitution inflammatory syndrome (IRIS). Polypharmacy leading to complex drug interactions is common in HIV-positive patients, but this case led to difficulty in ongoing patient management and the need for a change in antiretroviral therapy (ART).

CASE PRESENTATION

A 62-year-old heterosexual British man presented with shortness of breath, productive cough, weight loss, lethargy, fever and dysphagia. He had been diagnosed with HIV-1 infection 1 month previously while on holiday in Thailand. On examination he was cachectic with follicular skin lesions. There was no palpable lymphadenopathy, his chest was clear and his abdomen was soft and non-tender with no organomegaly. Investigations revealed pancytopenia, a CD4 count of 16 cells/mm^3 and an HIV viral load of 263 000 copies/ml. A CT scan showed only a slightly enlarged spleen. He was started on valganciclovir for cytomegalovirus (CMV) infection (CMV PCR >88 000 copies/ml), ethambutol, azithromycin, rifabutin and moxifloxacin for *Mycobacterium avium* complex (MAC) infection (blood cultures and sputum were positive), and fluconazole for oesophageal candidiasis. His chest radiograph was clear and a bronchial alveolar lavage specimen was positive for CMV and a rhinovirus by PCR. He was started on with ART (Truvada and Efavirenz) 2 weeks into the 6-week admission. He was also started on co-trimoxazole for *Pneumocystis jirovecii* pneumonia prophylaxis. After a good clinical response to therapy, he was discharged with planned follow-up in his local genitourinary clinic 2 weeks later.

Eight weeks after discharge, he was readmitted with a 4-week history of epigastric pain, weight loss and fever. Examination revealed a large, tender epigastric mass and multiple nodular skin lesions, predominantly on the trunk, but also affecting the arms. He remained on the treatment outlined above except that the course of valganciclovir had been completed.

INVESTIGATIONS

His CD4 count on readmission was 29 cells/mm^3 with an HIV viral load of 47.3 copies/ml. A table of CD4 and viral load results is shown below (table 1).

Extensive para-aortic, mesenteric and inguinal lymphadenopathy was demonstrated by a CT scan of the abdomen; the largest node measuring 2.4 cm in short axis diameter. The liver was enlarged and

Table 1 Patient's CD4 and viral load results

Time from initial admission (days)	0	22	27	35	60	87	108
CD4 count (cells/mm^3)	16	9	–	17	21	27	29
Viral load (copies/ml)	263000	–	998	424	46	45	47.3
	Admitted	ART started on day 13			Discharged day 44. These bloods were done in the community		Blood on re-admission

ART, antiretroviral therapy.

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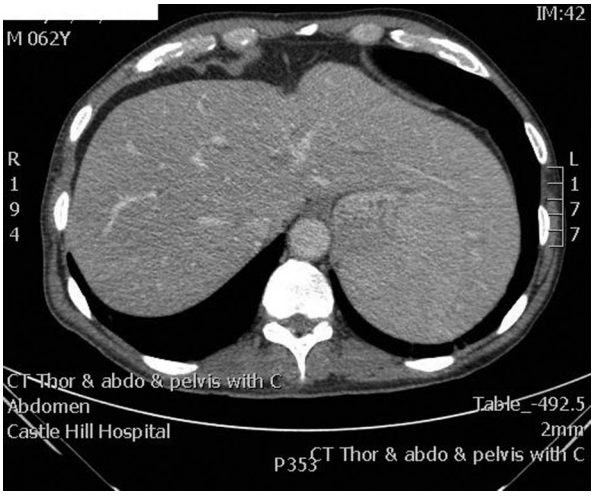

Figure 1 Hepatosplenomegaly on CT scan.

surrounded the spleen, which measured 17 cm. There was no significant mediastinal or hilar lymphadenopathy; see figures 1–3 for CT and ultrasound images.

CMV PCR was $<2\times10^3$copies/ml. The following tests were all negative: serum cryptococcal antigen, hepatitis A, B and C, *Toxoplasma*, *Strongyloides* and schistosomiasis serology, histoplasmosis antibody and Epstein-Barr virus (EBV) PCR. Repeated mycobacterial blood cultures did not yield any growth. The diagnosis was made when a blood culture grew *P marneffei* (figures 4 and 5). Subsequent tissue samples (skin biopsy of a nodular lesion and lymph node biopsy by laparoscopy) also cultured *P marneffei*. Lymph node histology did not show any evidence of lymphoma.

DIFFERENTIAL DIAGNOSIS

The combination of hepatosplenomegaly and lymphadenopathy in a patient with advanced HIV disease leads to a wide differential diagnosis. Malignancy, particularly lymphoma and Kaposi's sarcoma (KS), were considered. The incidence of lymphoma in HIV-positive individuals is significantly higher than in the general population due to a combination of factors including the transforming properties of the retrovirus, cytokine dysregulation and opportunistic infection with lymphotropic viruses such as EBV and human herpes virus (HHV)-8.[1] In this case, it

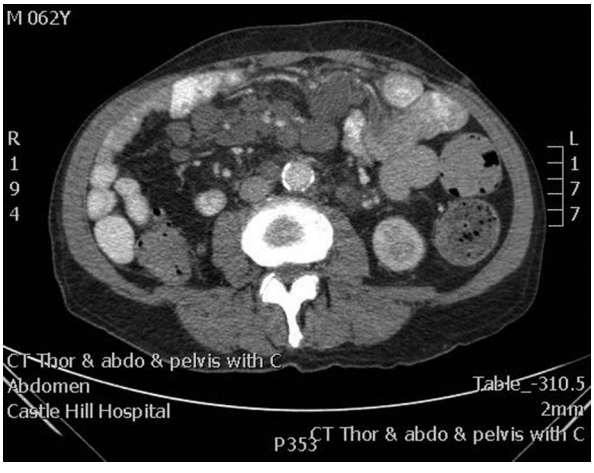

Figure 2 Lymphadenopathy on CT scan.

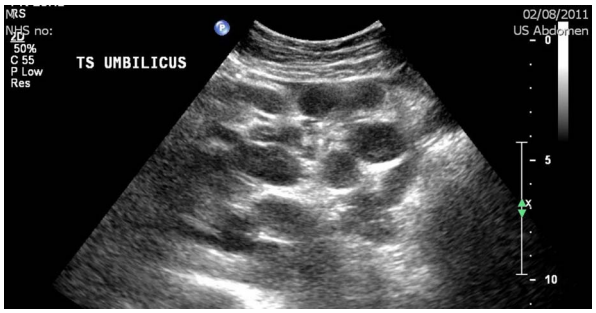

Figure 3 Multiple hypoechoic lesions on ultrasound scan representing large-volume para-aortic lymphadenopathy.

was felt that a lymph node biopsy was essential to exclude a concomitant diagnosis of lymphoma even after blood cultures revealed the diagnosis of *P marneffei*.

KS, a tumour associated with HHV-8, can present in severely immunocompromised patients with cutaneous or systemic involvement. KS can also present as an IRIS.[2] This is important in the context of our patient who had recently started ART, which had resulted in a marked decline in viral load; IRIS is more common in such patients, particularly when the baseline CD4 count is very low, as in our patient. A wide variety of opportunistic infections have been described during IRIS; see discussion below.

Repeat mycobacterial cultures, which were negative, were performed in case his presentation represented either new mycobacterial disease (eg, due to *Mycobacterium tuberculosis*) or non-compliance with medication, the development of resistance or a paradoxical mycobacterial reaction. Interestingly, acid-fast bacilli were visible on staining in the lymph node biopsy specimen, but did not grow.

TREATMENT

Intravenous liposomal amphotericin-B 1 mg/kg/day was started for 21 days followed by oral itraconazole 200 mg twice daily. National guidelines recommend treatment with amphotericin-B induction therapy for 2 weeks followed by itraconazole 200 mg twice daily orally for 10 weeks and then a maintenance dose of itraconazole 200 mg once daily.[3]

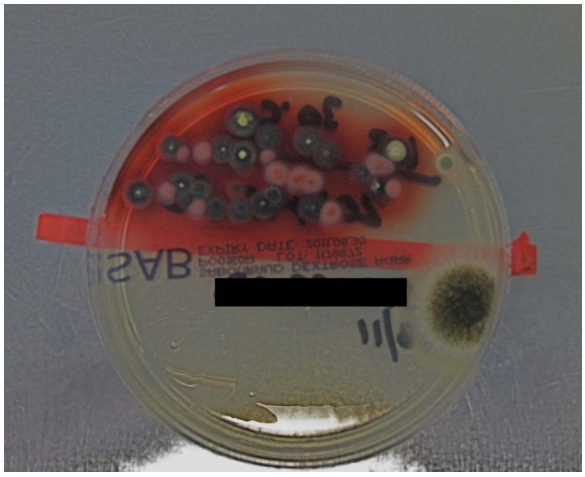

Figure 4 Culture plate demonstrating bright red diffusing pigment of *Penicillium marneffei* at 25°C (the black spots are contaminants).

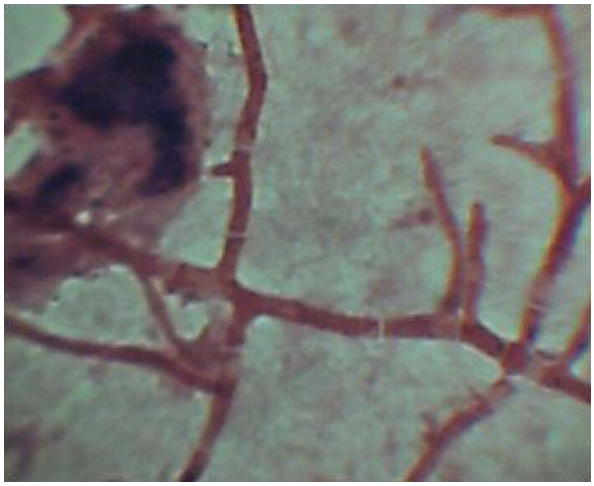

Figure 5 Gram stain of culture showing branching and spur formation of hyphae.

There has been debate about the duration of maintenance itraconazole; national guidance is that this can be discontinued once individuals are established on ART with a sustained CD4 count >100cells/μl.[3] HIV-positive individuals who have a CD4 count <100 cells/μl who are travelling to endemic areas should receive prophylaxis against *P marneffei* with itraconazole 200 mg once daily.[3] Patients diagnosed with penicilliosis prior to ART should commence ART once a clinical response to treatment of penicilliosis has occurred.[3]

Interest in the use of voriconazole as a therapeutic agent for treatment of penicilliosis is developing. Voriconazole is a triazole antifungal agent with a broad spectrum of activity against moulds, yeasts and fungi. In vitro activity of voriconazole against *P marneffei* is superior to that of amphotericin-B and comparable with itraconazole in terms of MIC.[4] In vivo data is limited to case series; a Thai case study of eleven patients with HIV and disseminated *P marneffei* infection administered short-course intravenous voriconazole followed by oral treatment to two patients and oral therapy alone to nine patients.[5] None of the patients received concomitant ART. In two cases, therapy had to be discontinued early due to abnormal liver and renal function. Eight of the nine patients had a favourable response, with five having a complete response. The paper concluded that voriconazole may be more convenient than the standard regime as it could potentially be offered orally throughout the therapy. An additional advantage of voriconazole is its improved and more reliable absorption compared with itraconazole.

OUTCOME AND FOLLOW-UP

The patient made rapid clinical response to therapy; at 1 month into treatment he was gaining weight and the abdominal lymph nodes and hepatosplenomegaly were less prominent—resolution of hepatomegaly and lymphadenopathy was confirmed radiologically by ultrasound. His CD4 count began to rise and reached 53 cells/mm^3 at first follow-up with a viral load of <34 copies/ml.

Unfortunately, his itrazonazole levels remained repeatedly undetectable despite several dose increases. There are complex drug interactions between itraconazole, ART and rifabutin, which are discussed further below. After 2 months it was decided that while the patient remained on the current antiretroviral regime, it was unlikely that a therapeutic itraconazole level would be achievable; his ART was changed to Truvada and Raltegravir. At the time of writing this report, his itraconazole levels have remained low, although higher than when taking Efavirenz.

DISCUSSION

P marneffei is a dimorphic fungus endemic to south-east Asia, existing in mould form at 25°C and yeast form at 37°C. It causes a variety of clinical syndromes varying from cutaneous lesions to hepatosplenomegaly, fever and lymphadenopathy.[6] Disseminated *P marneffei* infection is a common opportunistic infection in HIV-infected patients in endemic areas (the third commonest after tuberculosis (TB) and cryptococcosis in Thailand[7]), and an increasing number of imported cases in HIV-positive individuals have been reported in Europe.[8] What makes this case unusual is that penicilliosis only revealed itself after initiation of ART, raising the possibility of it being part of an IRIS.

IRIS is clinical manifestation of the pathological immune response that can occur during 'immune reconstitution'; the immune system recovery that occurs following initiation of ART when the HIV viral load declines and the CD4 count starts to rise. It can lead to 'unmasking' of previously undiagnosed infections, as in this case or 'paradoxical' worsening of existing infections. The relationship between the clinical presentation and the timing of immune reconstitution and the presence of an inflammatory picture not consistent with the usual course of the illness helps distinguish it from simple development of a new infection.[9] In this case, the basis for classifying the presentation of *P marneffei* as part of an IRIS is: the lack of clinical evidence for active *P marneffei* infection before ART was started, which we know had already been acquired since the patient did not travel back to an endemic area between admissions; no growth from initial blood cultures; rapid reduction in HIV viral load and subsequent 'unmasking' of the disease.

IRIS is classically described in association with *M tuberculosis*, but has also been described with many other bacterial, fungal and viral pathogens, as well as autoimmune conditions.[9] A thorough screen for opportunistic infection is therefore important in severely immunocompromised patients prior to ART commencement. The presence of disseminated infection, low CD4 count (<50 cells/μl) and early initiation of ART are all risk factors for IRIS development.[9]

P. marneffei presenting in the context of an IRIS has only been reported rarely—there has been one reported case in Europe[10] and four cases worldwide.[11] In three of the cases, presentation was dermatological, with development of papules or nodules after the start of ART.[10–12] Interestingly, in two of these cases the patient had skin lesions prior to the start of ART which were thought to be consistent with molluscum; the skin lesions associated with *P marneffei* can closely resemble those of molluscum or cryptococcal skin lesions. In our patient's case, the skin nodules, which developed after ART, were distinct from the (subsequently histologically proven) molluscum and follicular lesions present at initial assessment. In the other two cases, lymphadenopathy and/or hepatosplenomegaly were the presenting signs.[13 14]

We have experienced difficulty in attaining therapeutic itraconazole levels. Itraconazole is a substrate of CYP3A4, but can also inhibit metabolism of many CYP3A4 substrates; it thus increases the plasma concentration of many protease inhibitors. Non-nucleoside reverse transcriptase inhibitors (eg, Efavirenz) promote metabolism of itraconazole and significantly reduce its concentration.[6] This interaction has led to persistently undetectable itraconazole levels and a change in ART regimen in other cases.[10] In addition, our patient was taking Rifabutin for MAC

treatment; Rifabutin reduces itraconazole concentration, but conversely itraconazole increases plasma concentration of Rifabutin.[15] This interaction might explain why the patient's itraconazole levels have remained low despite a change in ART. We have explored the possibility of using voriconazole in place of itraconazole for our patient, but this also poses significant challenges in terms of interaction with Rifabutin; voriconazole is metabolised by and inhibits CYP2C19, CYP2C9 and CYP3A4 and Rifabutin induces CYP3A isoenzymes, resulting in an overall decrease in voriconazole levels. However, voriconazole inhibits Rifabutin metabolism and increasing the voriconazole dose will increase Rifabutin levels and potentially lead to increased risk of adverse effects.[16]

Learning points

- A detailed travel history is important in the immunocompromised.
- Multiple pathologies are often present in severely immunocompromised patients.
- Immune reconstitution can lead to 'unmasking' of a variety of different organisms and processes, including *Penicillium marneffei*.
- Consider *P marneffei* prophylaxis for HIV positive individuals with a CD4 count of <100 cells/μl who are planning to travel to *P marneffei* endemic areas.
- Polypharmacy poses many challenges; therapeutic drug monitoring is often necessary.

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Competing interests None.

Patient consent Obtained.

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