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ENDGAMES

PICTURE QUIZ

Disseminated papular lesions in an HIV infected patient

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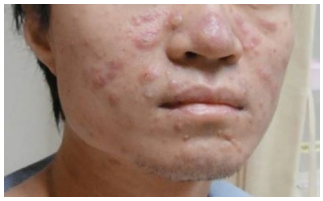
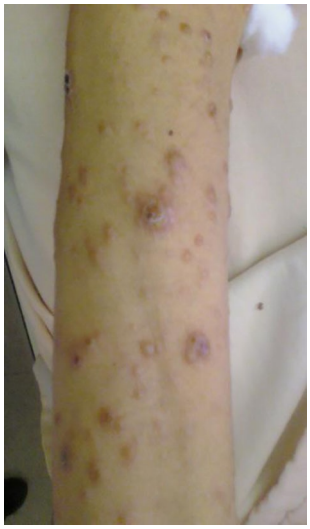
A 31 year old man living in northern Taiwan presented to the emergency department with fever of three days' duration, diffuse skin lesions and nausea for the past two weeks, and weight loss of 9 kg over 10 months. His vital signs were stable except for fever. Physical examination showed hepatosplenomegaly, generalised lymphadenopathy, and diffuse nodular and molluscum contagiosum-like papular lesions mainly on his face (fig 1) and arms (fig 2), some of which were umbilicated.





Blood tests showed pancytopenia and mildly raised liver enzymes (haemoglobin 86 g/L (reference range 130-180), haematocrit 26.2% (40-54%), white blood cells 3.2×10^9/L (4-10), platelets 73×10^9/L (140-450), aspartate transaminase 70 U/L (15-41), and alanine transaminase 35 U/L (14-40). A chest radiograph was unremarkable. He was found to be infected with HIV and his CD4 cell count was 0.7×10^6 cells/L (428-1481). A skin biopsy was obtained and cultured. He was started on highly active antiretroviral therapy (HAART) with efavirenz 600 mg daily and Kivexa (abacavir 600 mg and lamivudine 300 mg) once a day along with antibiotics.

Questions

1. What is the differential diagnosis of the skin lesions?
2. What is the most likely diagnosis?
3. How can we confirm the diagnosis?
4. How is this condition treated?

Answers

1. What is the differential diagnosis of the skin lesions?

Short answer

The differential diagnosis of disseminated papular skin lesions in an HIV positive patient with a low CD4 count includes disseminated viral, bacterial, and fungal infections; neoplastic disorders; and drug reactions.

Long answer

The differential diagnosis of disseminated papular skin lesions in HIV positive patients with a low CD4 count includes disseminated viral infections (for example, molluscum contagiosum, herpes simplex, and varicella zoster), bacterial infections (for example, bacillary angiomatosis, mycobacteria, and syphilis), and fungal infections (for example, penicilliosis,

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histoplasmosis, and blastomycosis). Neoplastic disorders (for example, Kaposi's sarcoma) and drug reactions should also be considered.[1 2] It is important to recognise different underlying disorders and opportunistic infections and to treat them appropriately.[3]

2. What is the most likely diagnosis?

Short answer

On the basis of the systemic symptoms (weight loss, fever, hepatomegaly, and lymphadenopathy) and the geographical location, the most likely diagnosis is disseminated *Penicillium marneffei* infection.

Long answer

On the basis of the systemic symptoms (weight loss, fever, hepatomegaly, and lymphadenopathy) and the geographical location, the most likely diagnosis is disseminated *P marneffei* infection. *P marneffei*, a dimorphic fungus that is endemic in South East Asia, is considered an emerging opportunistic pathogen in people infected with HIV in Taiwan.[4 5] Penicilliosis, invasive infection with *Penicillium* spp, increased dramatically during the 1990s, mainly in patients with advanced AIDS.[1 6] The incidence of penicilliosis varies geographically and was reported as the fourth most prevalent opportunistic infection in northern Thailand (6.8%) in 1994-98.[7] Between 1984 and 2004, 6709 *P marneffei* infections were reported to the Thai Ministry of Public Health.[1] Penicilliosis is regarded as an AIDS defining illness in endemic areas, including Thailand, Myanmar (Burma), Vietnam, Cambodia, Malaysia, northeast India, Hong Kong, Taiwan, and southern China.[1 3 5 6 8-10] Penicilliosis has occasionally been reported in non-endemic areas, such as the United States, Europe, Japan, and Australia, but a travel history to an endemic area could be traced in these patients.[1]

The presence of characteristic molluscum contagiosum-like papular lesions with central umbilication is highly suggestive of disseminated *P marneffei* infection in an HIV infected patient living in or travelling to an endemic area. *P marneffei* infection should be included in the differential diagnosis for patients with such a presentation, especially in endemic areas; immediate diagnosis is needed so that effective management can be instituted and mortality reduced.

Patients with *P marneffei* infection commonly present with fever, hepatosplenomegaly, lymphadenopathy, weight loss, respiratory and gastrointestinal symptoms, anaemia, and abnormal chest radiographs.[3 5 9] However, these conditions are not specific for *P marneffei* infection. Patients with disseminated penicilliosis have low CD4 counts (usually $<50\times10^6$ cells/L), and more than two thirds have characteristic skin manifestations.[3-5 9 11] Identification of the pathognomonic skin lesions may provide a clue for early diagnosis. Penicilliosis occurs mostly in HIV infected patients, whereas few HIV negative patients have invasive *P marneffei* infections. An underlying immunodeficiency should be considered in these patients.[11 12]

3. How can we confirm the diagnosis?

Short answer

Microbiological isolation of *P marneffei* is the gold standard for diagnosis, although serological and molecular rapid diagnostic tools are under investigation.

Long answer

P marneffei is a pathogenic dimorphic fungus, and microbiological isolation of the organism is the gold standard for diagnosis. The morphology of the colony and microscopic findings are characteristic, and temperature dependent mould to yeast conversion is required for definite diagnosis.[1 13] Blood and tissue culture specimens typically yield a flat, velvety, wrinkled, granular mould colony with a characteristic red diffusible pigment on Sabouraud's dextrose agar after seven days' incubation at 25°C (fig 3); this mould converts to a yeast-like form at 37°C. Microscopic examination of the fungus in the mould form showed septate hyaline hyphae and fruiting structures with spherical conidia in chains (fig 4). Several rapid serological and molecular rapid diagnostic tools that have high sensitivity and specificity have been reported.[1 14 15] However, because these newer diagnostic tools are not widely available, the time consuming process of culture and identification of the organism remains the mainstay for the diagnosis of penicilliosis.[16] Therefore, vigilance and familiarity with distinctive skin presentations can contribute to timely diagnosis and treatment of *P marneffei* infection.

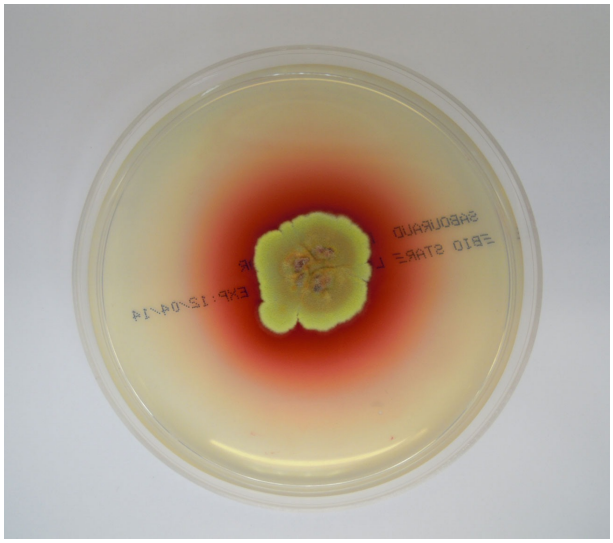

Fig 3 Sabouraud's dextrose agar showing a flat, velvety, wrinkled, granular mould colony with a characteristic red diffusible pigment

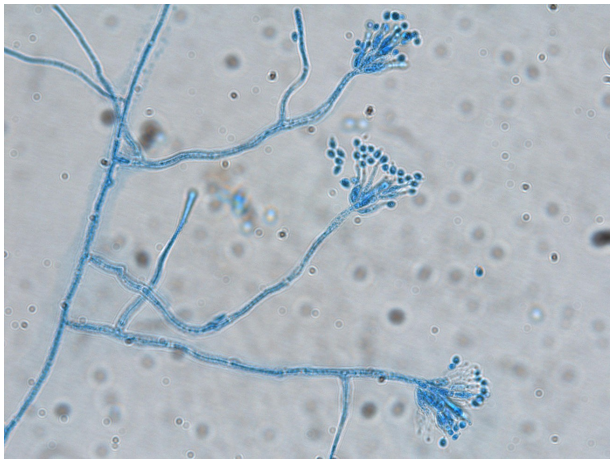

Fig 4 Microscopy showing septate hyaline hyphae and fruiting structures with spherical conidia in chains, indicative a diagnosis of *Penicillium marneffei*

4. How is this condition treated?

Short answer

Intravenous amphotericin B followed by oral itraconazole is the preferred regimen for the treatment of disseminated penicilliosis.

Long answer

Timely treatment with an antifungal agent is the key therapeutic intervention, and initial induction therapy followed by long term maintenance therapy is suggested. Because most patients who present with *P marneffei* infection have advanced immunosuppression at the time of diagnosis, concurrent initiation of HAART is recommended.[16] *P marneffei* is susceptible in vitro to several antifungal agents, including amphotericin B, itraconazole, ketoconazole, miconazole, 5-flucytosine and micafungin.[17] The recommended induction therapy for disseminated penicilliosis is intravenous amphotericin B (0.6 mg/kg/day for two weeks) followed by oral itraconazole (200 mg twice daily for 10 weeks).[18 19] After induction therapy, long term suppressive therapy is recommended because of the high risk of relapse. Thus, maintenance therapy with oral itraconazole (200 mg once daily) is suggested if the CD4 count is less than 100×10^6 cells/L.[16]

Patient outcome

The patient's symptoms and skin lesions improved and his fever subsided five days after fluconazole was started. Two days later, *P marneffei* was finally identified but his treatment was not changed because of the clinical improvement. He was discharged with oral fluconazole as maintenance therapy. However, 42 days after discharge, he was re-admitted with fever and shock. The skin lesions were aggravated with crust and pus formation (fig 5). Superimposed salmonella sepsis was diagnosed and he died six days later.

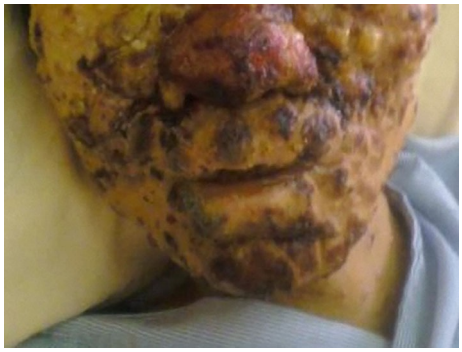

Fig 5 Aggravated skin lesions with crust and pus formation

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Patient consent obtained.

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