Not Another Rodent Ulcer

A 45-year-old Chinese sewage pipe repairman with a longstanding history of untreated human immunodeficiency virus (HIV) infection presented with a 3-month history of multiple ulcers with red papules on his face. The lesions did not improve with oral co-amoxiclav. He reported high-grade fever and weight loss of 8 kg over the preceding 3 months. He had stayed for 2 weeks in Chiang Rai, Thailand 5 months prior to his presentation. Clinical examination revealed two irregular, deep, large ulcers on his forehead and left cheek with multiple erythematous papules on his face (Figures 1 and 2). He also had widespread cervical and axillary lymphadenopathy. Skin biopsies taken from the edge of the forehead ulcer are as shown (Figures 3A and 3B).

What is your diagnosis?

A. Syphilitic chancre
B. Ecthyma gangrenosum
C. Disseminated talaromycosis
D. Pyoderma gangrenosum
E. Squamous cell carcinoma

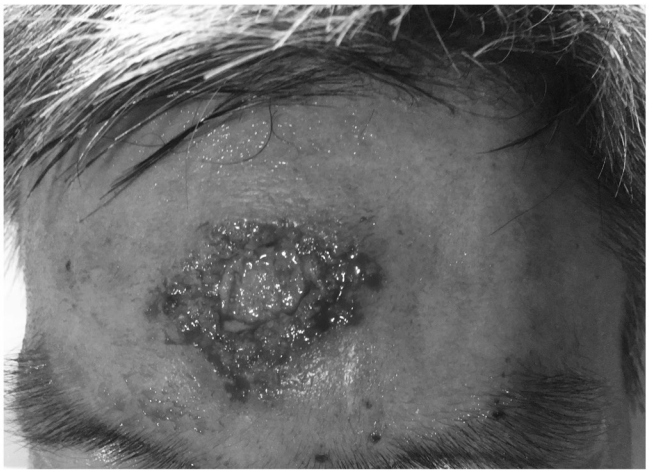

Fig. 1. Clinical photograph showing a central forehead ulcer with irregular undermined edge and granulation tissue at base of ulcer. Crusted erythematous papules are seen along the left eyebrow.

Findings and Diagnosis

The clinical photographs show two large ulcers with haemoserous crusting and multiple erythematous papules on the face. The patient reported that the ulcers initially begun as small erythematous papules, which enlarged and ulcerated subsequently. There were also ulcers noted on the soft palate and pharynx, as well as multiple excoriated papules on the patient's limbs.

Investigations revealed leucopenia [2.2 x 10^9/L; normal 4-11 x 10^9/L], lymphopenia [0.25 x 10^9/L;

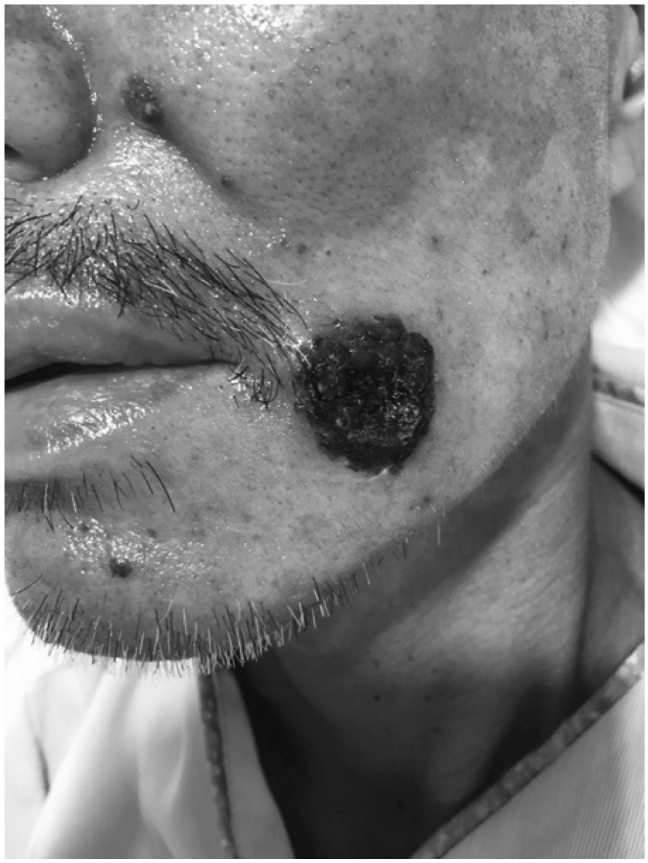

Fig. 2. Erythematous papules with central umbilication on the left nasolabial fold and chin are seen within the vicinity of a large left cheek ulcer topped with a haemoserous crust

Correct answer: C

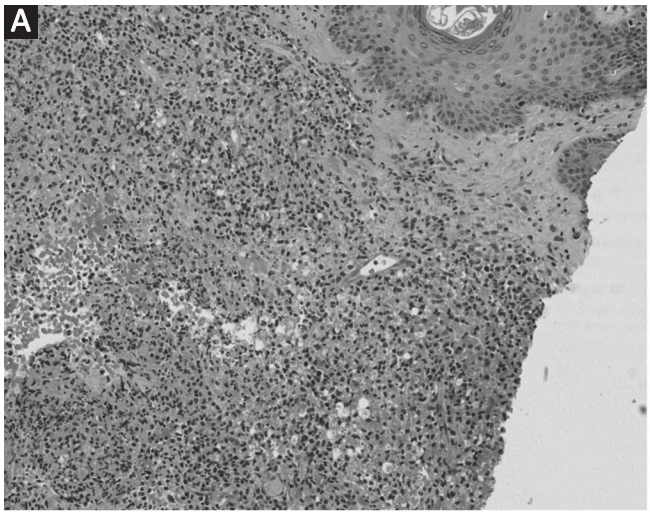

Fig. 3A. Hematoxylin and eosin stain of an incisional biopsy from the edge of the forehead ulcer (Original magnification x100).

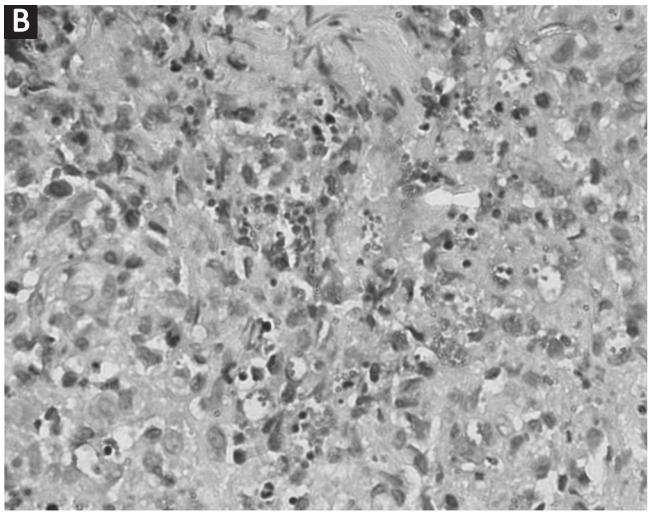

Fig. 3B. The same specimen stained with Periodic acid-Schiff stain (Original magnification x 400).

normal 0.9-3.3 x 10^9/L], CD4 count <20cells/μL, and a HIV viral load of 693,600 copies/ml suggestive of advanced HIV. The rapid plasma reagin (RPR) was non-reactive and syphilis line immunoassay (LIA) IgG was 12 RU/mL (negative). Computed tomographic (CT) imaging showed soft tissue thickening in the posterior nasal space and bilateral cervical, supraclavicular, axillary and intra-abdominal lymphadenopathy. There were scattered centrilobular nodules present in both lungs.

Histopathologic examination of the edge of the forehead ulcer revealed a dense dermal infiltrate of foamy histiocytes and multinucleated giant cells containing ovoid organisms, which stained positive on Grocott's methenamine silver (GMS) and periodic-acid Schiff (PAS). The overlying epidermis showed compact hyperkeratosis with no atypia. Gram stain did not show any bacteria. Blood cultures and biopsies of the forehead ulcer, posterior nasal space and cervical lymph nodes grew talaromyces marneffei, supporting a diagnosis of disseminated talaromycosis infection. Herpes simplex virus PCR swab and tissue mycobacterial culture from the ulcer were negative. Blood sample for cytomegalovirus PCR also returned negative.

He was commenced on abacavir 600mg/lamivudine 300mg once daily and dolutegravir 50mg once daily for HIV and initiated on intravenous amphotericin 5mg/kg/day for disseminated talaromycosis. Amphotericin was switched to intravenous voriconazole 4mg/kg every 12-hourly due to acute kidney injury. His cutaneous lesions resolved after a total of 29 days of systemic antifungals. Seven months later, he was admitted for abdominal pain, ascites and pleural effusion. Interval CT thorax, abdomen and pelvis confirmed persistence of lymphadenopathy. Cytological examination of peritoneal fluid and pleural aspirate as well as bone marrow biopsy confirmed diagnosis of plasmablastic lymphoma. Bone marrow and peritoneal fluid cultures were negative. He was switched to oral itraconazole 200mg twice daily after resolution of cutaneous lesions to prevent a relapse of talaromycosis. However, due to non-compliance to his HIV medications and clinic visits, his CD4 count remained low and he eventually demised from his lymphoma.

Discussion

Disseminated talaromycosis is an Acquired Immune Deficiency Syndrome (AIDS) defining illness which presents with multiple acneiform or umbilicated facial papules in an immunocompromised patient with a CD4 count lower than 100 cells/μL.[1] Other uncommon cutaneous presentations include facial ulcers, orogenital ulcers, panniculitis and Sweet Syndrome. Non-cutaneous manifestations may include fever, weight loss, lymphadenopathy, hepatosplenomegaly and arthritis.[1]

Talaromycosis marneffei, previously known as penicilliosis marneffei, is transmitted through the inhalation of the infectious conidia from a soil reservoir and should be considered in an immunosuppressed patient who presents with fever, weight loss and

multiple facial lesions after returning from an endemic region such as Thailand, Vietnam, and China.[2]

A diffuse dermal infiltrate comprising of foamy histiocytes or multiple granulomata containing unicellular round-ovoid organisms highlighted by GMS or PAS stains[2,3] as our patient's case depicts, is consistent with cutaneous talaromycosis. The extracellular elongated cells with centrally located transverse septa highlighted by GMS stain is useful in distinguishing T. marneffei from histoplasma capsulatum infection.[3] Blastomycosis, cryptococcosis and molluscum contagiosum are other differential diagnosis to consider for facial erythematous papules with central umbilication. Tissue or blood fungal culture with speciation of the fungal organism confirms the diagnosis.[2,3]

The key differential diagnoses to consider for non-healing facial ulcers in an immunocompromised host include ecthyma gangrenosum, atypical mycobacterial, syphilitic cutaneous gumma, cytomegalovirus, herpes simplex infections, atypical pyoderma gangrenosum and squamous cell carcinoma.

Ecthyma gangrenosum typically presents with a necrotic ulcer on the buttocks and lower extremities. The commonest aetiology is due to pseudomonas aeruginosa, however other angio-invasive organisms such as escherichia coli and mucor have been implicated.[4] The absence of necrotizing haemorrhagic vasculitis[4] or bacteria on Gram stain make ecthyma gangrenosum an improbable differential diagnosis.

Extragenital syphilitic chancre and cutaneous gumma would be unlikely in view of the negative syphilis line immunoassay and RPR titre. The typical histological findings of superficial and deep dermal infiltrate of plasma cells and endothelial swelling as seen in syphilis were not present in our biopsy.

Pyoderma gangrenosum in patients with HIV more commonly involves the perineum. Moreover, our patient's facial ulcer biopsy lacked the dense neutrophilic dermal infiltrate as would be anticipated in pyoderma gangrenosum.

Squamous cell carcinoma can present as cutaneous ulcers on sun-exposed areas such as the face. However, the lack of dysplastic keratinocytes with invasion into the dermis layer seen on histopathological examination makes it an incorrect diagnosis in this case.

Expeditious treatment with broad-spectrum antifungal agents such as intravenous amphotericin is imperative if disseminated talaromycosis is suspected. Treatment with amphotericin B has been shown to confer a survival benefit compared to intravenous itraconazole for disseminated talaromycosis. Mortality as high as 75% has been reported if treatment is delayed.[5]

Patients with disseminated talaromycosis as an AIDS-defining illness should also be commenced on antiretroviral therapy and secondary prophylaxis with oral itraconazole or voriconazole until the CD4 count is sustained at more than 100cells/μL.[2]

This case illustrates the diagnostic dilemma faced by clinicians treating HIV-positive patients with non-healing cutaneous ulcers and highlights the importance of a detailed physical examination and an accurate patient travel history.

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Xiaotian Wu, [1]*MBBS*, Ling Yee Kuan, [2]*MBBS,MRCP(UK)*, Jiun Yit Pan, [2]*MBBS,FRCP(UK)*

[1]Department of General Medicine, Tan Tock Seng Hospital, Singapore
[2]National Skin Centre, Singapore

Address for Correspondence: Xiaotian Wu, Department of General Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433
Email: xiaotian.wu@mohh.com.sg