**Photo quiz: disseminated violaceous skin lesions post allogeneneic stem cell transplant**

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**Case presentation**

A 58 year-old man was admitted for management of *Pseudomonas aeruginosa* infection of his tunnelled central venous catheter. Eleven months previously, he received an allogeneic bone marrow transplant for acute myelogenous leukemia secondary to a mutation in the runt-related transcription factor 1 (RUNX1), a protein that helps control hematopoiesis. In preparation for transplantation, he underwent a reduced-intensity regimen of therapy with fludarabune, melphalan and alemtuzumab for disease eradication, immunosuppression and donor stem cell engraftment.

Induction chemotherapy comprised fludarabine, cytarabine, filgrastim and idarubicin, and was complicated by *Saprochaete capitata* fungemia. Stem cell transplant complications included suspected invasive fungal pulmonary infection (which responded to isavuconazole), chest sepsis attributed to *Raoultella ornithinolytica*, and CMV reactivation with virological failure of foscarnet (secondary to UL54 mutation) necessitating salvage therapy with maribavir. The patient had concurrent chronic skin and mucosal graft versus host disease requiring ongoing prolonged immunosuppression including steroids, cyclosporine, rituximab, imatinib, abatacept, and topical immune suppression (steroids and tacrolimus).

Following the identification of *P aeruginosa* bacteraemia, the tunnelled catheter was removed and the patient was treated with piperacillin-tazobactam via a peripheral cannula. One day prior to admission for this antimicrobial therapy, he developed disseminated violaceous skin lesions involving his trunk, limbs face and hard palate (sparing his palms and soles) [FIGURE, panels A and B]. Over 100 lesions were present. The lesions were mostly nodular in morphology, although some had an umbilicated appearance (PANEL A) and some others were crusting over (PANEL B). The lesions were not pruritic or painful, and the patient remained afebrile and haemodynamically stable throughout. A punch biopsy was taken, and histopathologic analysis identified multinucleated giant cells with intranuclear inclusions, nuclear molding and margination of chromatin. [FIGURE, panel C].

What is your diagnosis?

A picture containing photo, old, face, made

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**Figure legend**

Images taken on 4th day of rash. Disseminated violaceous skin lesions (panels A and B), present all over the body and also involving the hard palate (B, black arrow) but sparing palms and soles. Punch biopsy of skin lesion (Panel C, haematoyxlin and eosin stain, 40 x magnification) showing a multinucleated giant cell (white arrow) with intranuclear inclusions, nuclear molding and margination of chromatin.

**Photo Quiz Answer: Disseminated varicella zoster virus**

The patient was prescribed oral valaciclovir when the lesions first appeared, and after seven days of treatment most of lesions resolved. PCR of swabs from the lesions was positive for varicella-zoster virus (VZV) DNA. Stains and culture for bacteria, fungi and acid-fast bacilli were negative. The patient confirmed that he had clinical chickenpox as a child.

The initial differential diagnosis was wide, given the patient’s prolonged immunosuppression and concomitant cutaneous graft versus host disease (GvHD). Ecthyma gangrenosum secondary to systemic *Pseudomonas* infection was considered, but this typically presents with far fewer lesions, which increase in size and ulcerate (1). Disseminated fungal infection was also considered, especially following previous fungal complications. Atypical VZV infection was considered more likely, based on the number and distribution of the lesions as well as the presence of crusting around some of the lesions. The color of the lesions was attributed to intralesional hemorrhage in the setting of profound thrombocytopenia (platelet count 35 x 109/L). VZV infection commonly spares the palms and soles and involves the oral cavity, particularly the hard palate (2). Histopathological examination of a biopsy sample may identify the pathognomonic “three M’s” (Multinucleation, nuclear Molding and Margination of chromatin) of herpetic infection, as seen in our patient (3). However, these findings are seen in infections due to herpes simplex viruses I and II as well as VZV, and therefore PCR (or specific immunohistochemical staining) is required for a species-level diagnosis. Commercial multiplex PCR assays (e.g. the Quidel Solana platform) can test for all three viruses at once.

Long-term acyclovir reduces the incidence of VZV infection in the year following allogeneic stem cell transplantation (4). However, the incidence of VZV infection rises once acyclovir is discontinued (5). In case series conducted before the era of prolonged acyclovir prophylaxis, the incidence of VZV infection post-transplant ranged from 16.6—41%, depending on the intensity and duration of follow-up (6, 7). Although the majority of cases occur within one year, the timing of onset varied substantially within cohorts; one case series reported a median interval between transplantation and infection of 227 days but a range from 45 days to 3.7 years (6). Around one in five cases of post-transplant VZV are disseminated (6, 7), and a prior history of chickenpox does not appear to affect the odds of developing localised zoster compared with generalised varicella (7). GvHD has been identified as an independent risk factor for VZV infection (5, 7).

Our patient was not prescribed acyclovir prophylaxis as he was receiving full-dose foscarnet for CMV reactivation; foscarnet retains activity against herpesviruses 1—3 as well as CMV. However, when foscarnet-resistant CMV was identified, the patient was switched to maribavir through a compassionate early access scheme. Maribavir targets the UL97 protein of CMV, and therefore prophylaxis against other herpesviruses (with acyclovir or valacyclovir) should continue during therapy with maribavir, until successful immune reconstitution.

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