Fig. 1 *Candida duobushaemulonii* after 48 h incubation on CHROMagar Candida medium.

Asia and the Americas.^{5–7} Surveillance for *C. auris* in Panama in 2016–2017 identified 17 of 36 submitted isolates as *C. duobushaemulonii*.² Ten of these isolates were blood-stream isolates and half were from a single institution. A study from the US Centers for Disease Control (CDC) described 50 clinical *C. duobushaemulonii* isolates from Panama, Guatemala, US and Venezuela.⁸ Whole-genome sequencing demonstrated a cluster of clonally related isolates within a hospital in Panama which had reported a suspected outbreak.⁸

Like *C. auris*, phenotypic identification systems can misidentify *C. duobushaemulonii* as closely related species such as *C. haemulonii*.² In recent years, updates to MALDI-TOF MS databases and VITEK2 Yeast ID systems have improved the ability to differentiate *C. auris* and closely related species and was able to accurately differentiate *C. duobushaemulonii* from *C. auris* in our case.³ However, even updated phenotypic identification systems such as Vitek2 Yeast ID can misidentify *C. auris* as *C. haemulonii* or *C. duobushaemulonii*.⁹ MALDI-TOF MS systems with updated databases are able to accurately identify isolates to species level.³

Antifungal susceptibility for *C. duobushaemulonii* has demonstrated elevated MICs to fluconazole and amphotericin. Like *C. auris*, there are no clinical breakpoints for *C. duobushaemulonii*.^{2,3} MICs to the echinocandins remain low and they are suggested as first line therapy for cases of invasive *C. duobushaemulonii*.

In summary, patients may carry more than one resistant *Candida* species. We describe a case with *C. duobushaemulonii* bloodstream infection and *C. auris* colonisation, in a patient who had been hospitalised in Vietnam where there have not been any previous documented cases. *Candida duobushaemulonii* demonstrates elevated MICs to multiple antifungals and ongoing surveillance is required should it emerge as another cause of potentially transmissible multidrug resistant infection.

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Daratumumab-induced pancytopenia: collateral damage from the silver bullet

Sir,

A 78-year-old man with relapsed, refractory IgG kappa plasma cell myeloma was commenced on daratumumab

Fig. 1 (A) Bone marrow aspirate and (B) trephine biopsy demonstrating profound hypocellularity, with particularly reduced granulopoiesis.

monotherapy in September 2019, having previously progressed through cyclophosphamide, bortezomib and dexamethasone (CyBORd); bortezomib, thalidomide and dexamethasone (VTD); and lastly, lenalidomide monotherapy. The latter was ceased after 7 months on the basis of both biochemical and radiological evidence of disease progression, with an 11 g/L increase in his IgG serum paraprotein and appearance of innumerable new lytic bone lesions. Daratumumab was commenced 3 days after cessation of lenalidomide at an initial dose of 16 mg/kg intravenously weekly. Upon commencement of therapy, a full blood count (FBC) demonstrated evidence of moderate marrow suppression, with a haemoglobin of 105 g/L, platelet count of $126 \times 10^9/L$ and neutrophil count of $0.6 \times 10^9/L$. This was thought attributable to combination of plasma cell infiltration and myelosuppression from the recently ceased lenalidomide, although a bone marrow examination was not performed at this time.

Within 2.5 months of the initiation of daratumumab, a marked deterioration in all three FBC lineages occurred, with the haemoglobin falling to 73 g/L, platelet count $95 \times 10^9/L$ and neutrophil count $0.1 \times 10^9/L$. The patient received a total of three red cell transfusions on two separate occasions during this period. Cotrimoxazole antimicrobial prophylaxis was withheld. However the pancytopenia continued to progress, with a further FBC 2 weeks later demonstrating a haemoglobin of 65 g/L, platelet count of $53 \times 10^9/L$, and neutrophil count of $0.05 \times 10^9/L$. A reticulocyte count was inappropriately reduced at $15 \times 10^9/L$. Blood film examination revealed tear-drop poikilocytosis and no circulating plasma cells. Bone marrow aspirate and trephine biopsy (Fig. 1) demonstrated profound hypocellularity with a predominance of erythroid precursors and virtual absence of granulopoiesis. No increase in blast cells was seen. Marrow plasma cells remained suppressed at <5% of total cellularity based on CD138 immunohistochemistry, which along with the reduction in IgG paraprotein to 1.9 g/L from a peak of 20 g/L, was consistent with daratumumab efficacy in inducing myeloma remission. Scattered small, monolobated megakaryocytes were encountered, however there was otherwise no evidence of granulocytic dysplasia. A diagnosis of marrow hypoplasia with agranulocytosis presumably induced by daratumumab was established. Daratumumab was accordingly ceased following the brief and ultimately unsuccessful employment of cyclosporin as empirical treatment for aplastic anaemia. Granulocyte colony stimulating factor (G-CSF) was also introduced at a dose of 300 µg subcutaneously thrice weekly. Nine weeks later, evidence of apparently spontaneous

neutrophil count recovery was seen on a repeat FBC, however moderate anaemia and thrombocytopenia persisted. Despite this, the patient made an informed decision to pursue a palliative course of management and has since died.

Daratumumab is an anti-CD38 monoclonal antibody approved by the United States Federal Drug Administration (FDA) as monotherapy for patients refractory to both a proteasome inhibitor and immunomodulatory therapy.¹ Phase I and II trial data^{2,3} reported an incidence of therapy-associated cytopenias of 12–33%, with the incidence of neutropenia of grade 3 or higher severity ranging from 5% to 12%. Of patients in the phase II SIRIUS trial,² 38% received red cell transfusions and 8% required G-CSF. The mechanism responsible for daratumumab-induced myelosuppression is unclear, but the target CD38 is known to be present on myeloid stem cells where it acts to regulate neutrophil chemotaxis.⁴

Severe neutropenia secondary to daratumumab monotherapy has previously been described in the post-marketing literature in a 73-year-old Japanese woman.⁵ Of note, both this patient and ours had a moderate neutropenia of 0.5 – $1.0 \times 10^9/L$ at baseline, whereas the aforementioned clinical trials expressly excluded any participant with an initial neutrophil count of $<1.0 \times 10^9/L$, a relatively common scenario in heavily pre-treated myeloma patients. Therefore, our case highlights the real-life risk of severe haematotoxicity associated with daratumumab when it is instigated in neutropenic patients outside the controlled setting of a clinical trial.

However, both the Japanese case and ours send a similarly reassuring message with regard to the potential for reversibility of neutropenia. Complete neutrophil count recovery was observed within 2 months in both cases, following the cessation of daratumumab and administration of G-CSF therapy. Suggestion this phenomenon may be reversible provides an argument for at least the initial employment of appropriate supportive therapy in the event of neutropenia occurring whilst on daratumumab. Furthermore, it might be prudent to employ adjunctive routine G-CSF prophylaxis in those patients commencing daratumumab with neutrophil count $<1.0 \times 10^9/L$ who are also deemed at high risk of severe prolonged neutropenia.⁶

Further investigation is required to better understand the natural history and identify potential risk factors for this rarely reported event ascribed to a novel therapy which for many Australasian patients remains their last resort.

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Tumour-stage mycosis fungoides initially misdiagnosed as Langerhans cell histiocytosis

Sir,

Mycosis fungoides, initially presenting in tumour stage, is rare. Langerhans cells can be associated with cutaneous T-cell lymphomas, and when numerous may form the nodular clusters that can mimic Langerhans cell histiocytosis and mask an underlying cutaneous lymphoma. Here we report such a case.

A 54-year-old diabetic man with a history of adenoid cystic carcinoma in the right maxillary sinus 5 years previously, treated with surgery and concurrent chemoradiotherapy at that time, received regular follow-up for right maxillary osteoradionecrosis. He presented to the Plastic Surgery Department with a progressively enlarging mass of the right little finger for 6 months. The mass measured 4.5×4×4 cm and the overlying skin was ulcerated with multiple non-healing wounds (Fig. 1A). On the adjacent palmar skin, there was erythema with some tiny vesicles and scales, reminiscent of dyshidrotic eczema (Fig. 1A). He denied loss of sensation and range of movement was normal. No evidence of bony involvement was seen on the right hand radiograph. Laboratory data including biochemistry and complete blood counts were normal. The patient underwent an excision of the mass. Pathologically, the overlying skin of the mass revealed focal ulceration (Fig. 1B). The mass was composed predominantly of lymphocytes and histiocytoid cells (Fig. 1C). The lymphocytes showed mild atypia; the histiocytoid cells, forming multiple nodules, possessed ovoid to spindle-shaped nuclei with grooving and moderate to abundant amount of cytoplasm, infiltrating the dermis and subcutis (Fig. 1C, inset). Focal spotty necrosis and increased

mitotic figures were found (~13/10 HPF). Immunohistochemically, CD3 highlighted small T cells with mild atypia, and CD20-positive cells were patchy in distribution. The ovoid/spindle cells were positive for S100 (Fig. 1D), CD1a (Fig. 1E), Langerin (Fig. 1F), and BRAF V600E (Fig. 1G). The Ki-67 proliferative index was 40–50% in the highest area. Based on these features, the case was initially reported as Langerhans cell histiocytosis with atypical features.

Subsequent to the above diagnosis, the patient came to the Department of Dermatology, where multiple erythematous patch, plaque and nodular skin lesions over the trunk and four extremities were found. He also noted the dyshidrotic dermatitis-like lesions for 10 years. With a tentative clinical diagnosis of mycosis fungoides, multiple biopsies were performed on skin lesions of the extremities. Histopathologically, the right palmar skin showed dyshidrotic dermatitis with epidermotropism by atypical lymphocytes (Fig. 1H). The nodule of left lateral foot also showed dense infiltration of atypical lymphocytes with scanty to moderate amount of cytoplasm and cerebriform nuclei infiltrating the dermis and subcutis (Fig. 1I). Some eosinophils were seen. Immunohistochemically, these cells were CD3⁺ (Fig. 1J), CD7⁺, CD25⁺ (Fig. 1J inset), and dominantly positive for CD4 compared to CD8. They were however negative for CD20 and BRAF V600E. These features were consistent with mycosis fungoides in tumour phase.

In context of the skin biopsy findings, the morphology of right little finger mass was reviewed. Atypical lymphoid cells with mild nuclear irregularities were identified, which infiltrated the dermis and subcutis associated with many Langerhans cells, histiocytes and eosinophils. The atypical lymphocytes were CD3⁺, CD20⁺, CD5⁺, CD4⁺, focally CD25⁺, and focally CD30⁺. CD7 and CD8 were negative. *In situ* hybridisation for Epstein–Barr virus encoded RNA (EBER) was negative and the Ki-67 proliferative index was high (~50%). The background Langerhans cells, positive for BRAF V600E by immunostaining (Fig. 1G), were negative for BRAF V600E mutations assessed by PCR-based methods as well as negative for cyclin D1 immunohistochemically. Instead, analysis of *TRB* and *TRG* rearrangements showed a monoclonal pattern (Fig. 2A), similar to that in the right posterior thigh skin lesion (Fig. 2B). The case was finally reported as mycosis fungoides (tumour stage) with atypical Langerhans cell hyperplasia. A computed-tomography (CT) scan of the chest revealed bilateral lung nodules. Lung needle biopsy showed metastatic adenoid cystic carcinoma, and bone marrow aspiration and biopsy were negative; neither biopsy showed Langerhans cell histiocytosis or lymphoma. The patient was stage T3N0M0, IIB according to the American Joint Committee on Cancer (AJCC) 8th edition staging system for primary cutaneous lymphoma. He subsequently received radiotherapy 3000 cGy in 10 fractions to the right 3rd finger and left lateral sole skin, and 3900 cGy in 13 fractions to the right 5th finger. The tumours resolved gradually. He also underwent psoralen and ultraviolet A (PUVA) therapy for plaque lesions on right upper arm and left flank area at the dermatology clinic. In the recent follow-up, a new skin plaque was seen on the left heel.

Mycosis fungoides (MF), an indolent cutaneous T-cell lymphoma of skin resident memory T cells (TRM), is confined predominantly to the skin as patches and plaques.¹ The aetiology and pathogenesis of MF is multifactorial and