A Rash in an Elderly Woman

An 82-year-old Chinese woman presented with a 1-week history of an increasingly pruritic rash over the face, neck, upper chest and arms. She was first seen by a haematologist 3 months prior for acute monocytic leukaemia (AML-M5) which had developed on a background of probable chronic myelomonocytic leukaemia (CMML). As she had multiple comorbidities including previous stroke with limited ambulatory function, she was considered a poor candidate for intensive chemotherapy and was treated palliatively with supportive blood transfusions when needed. Her medications included omeprazole, lactulose, senna, paracetamol, calcium, vitamin D, risedronate, and a recent course of co-trimoxazole for an upper respiratory tract infection (commenced 7 days prior to presentation). She received her most recent blood transfusion one month prior to onset of the rash.

Examination revealed multiple purpuric papules and plaques distributed on the cheeks (Fig. 1), neck, upper chest (Fig. 2) and upper limbs. The patient was afebrile and non-toxic. Skin biopsies were obtained from a representative forearm lesion.

What is your diagnosis?

A. Drug eruption

B. Acne rosacea

C. Leukaemia cutis (cutaneous leukaemic infiltrates)

D. Acute febrile neutrophilic dermatosis (Sweet syndrome)

E. Cutaneous vasculitis

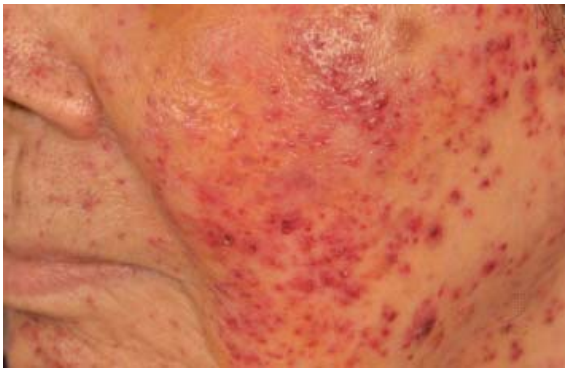

Fig. 1. Purpuric papules and plaques on the face.

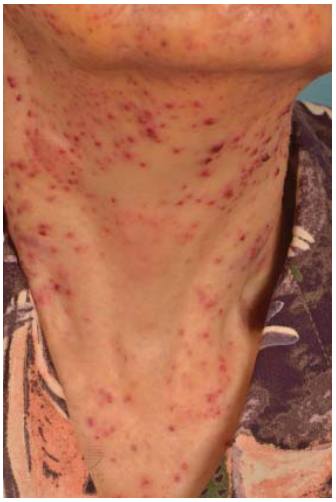

Fig. 2. Purpuric papules and plaques on the neck and upper chest.

Discussion

Histopathological examination revealed superficial and deep perivascular and patchy upper dermal interstitial infiltrate of lymphocytes which formed tight cuffs around upper dermal vessels, accompanied by prominent red cell extravasation within the dermis. Blast cells with large, rounded to hyposegmented nuclei with dispersed chromatin, and variable amounts of cytoplasm were scattered within the infiltrate (Fig. 3). These stained strongly positive for myeloperoxidase and CD117, were patchily positive for CD34 and CD68, and negative for CD3 and CD20. This confirmed the diagnosis of leukaemia cutis (LC). Direct immunofluorescence was negative. Her full blood count showed marked thrombocytopenia (8×10^9/L), anaemia (haemoglobin 8 g/dL) and mild leukocytosis (total white cell count 13.3×10^9/L) with increased blasts (16%).

The dual burdens of severe pruritus and cosmetic distress warranted intervention. After discussion with the patient and her family, a course of palliative chemotherapy with etoposide was given. Itch and number of skin lesions were significantly reduced, along with decrease in the number of blasts in peripheral blood. Her symptoms were well-palliated up to 2 months after chemotherapy when she was last seen for her skin lesions. She finally succumbed to the disease after another 6 months.

LC refers to cutaneous infiltration by neoplastic leukaemic cells resulting in clinically evident skin lesions, and is a rare condition that can occur across various forms of leukaemia.[1]

Answer: C

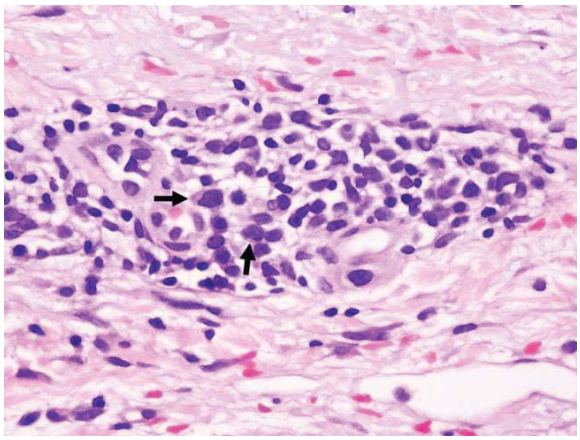

Fig. 3. Within the perivascular infiltrate are blast cells with large rounded to hyposegmented nuclei, dispersed chromatin, and variable amounts of cytoplasm (block arrows). Typical lymphocytes are scattered within the infiltrate (H&E stain, x 400).

It has been described to occur mostly in acute myeloid leukaemia (AML), but also occurs in the accelerated phase of chronic myeloid leukaemia (CML), myelodysplastic syndrome (MDS), and more rarely, in acute lymphocytic leukaemia (ALL). Its appearance often signals underlying disease progression, or transformation to acute leukaemia in the setting of MDS. There are also rare cases of 'aleukaemic leukaemia cutis' described in which cutaneous infiltrations preceded peripheral blood or bone marrow involvement.[2]

Cutaneous manifestations of LC are non-specific and variable, ranging from papules and plaques, purpura, exfoliative erythroderma and urticaria, to non-specific exanthema, and may manifest in several different forms over the course of the disease.[1] The most common manifestation is with single or multiple erythematous papules and nodules, most commonly involving the lower limbs, upper limbs, trunk and face, with a predilection for sites of previous or active inflammation.[1]

The diagnosis of LC can be challenging, as LC can be both clinically and histologically confused with other skin conditions. In particular, Sweet syndrome (acute febrile neutrophilic dermatosis) must be excluded. Sweet syndrome is a reactive skin condition occasionally associated with AML, in which intense infiltration of the dermis with neutrophils results in oedematous tender cutaneous papules and nodules associated with fever. Drug eruptions and reactive vasculitis are also not uncommon in patients on treatment for malignancy. Careful clinical examination and skin biopsy are essential for excluding these differential diagnoses, of which the management and prognosis are vastly different from LC.

Skin biopsy in LC typically shows an interstitial infiltrate of leukaemic cells in the dermis and/or subcutis, exhibiting perivascular and/or periadnexal arrangements, with the presence of immature malignant cells which characteristically appear large, with smooth chromatin, increased mitotic activity, and a high nuclear to cytoplasmic ratio.[3] Further immunohistochemical studies can help confirm diagnosis and aid cell lineage profiling.

The diagnosis of leukaemia cutis is important for several reasons. It can occasionally precede and aid in the early diagnosis of systemic leukaemia (as in aleukaemic leukaemia cutis) and is often an indicator of disease progression in established MDS or leukaemia. LC also prognosticates poor outcome as CMML patients with LC have reduced survival time compared to those without LC.[4] Occasionally, if LC is symptomatic, it can warrant more aggressive treatment in patients on supportive treatment, as seen in this case.

Treatment of LC predominantly involves management of the underlying malignancy. Chemotherapy regimen choice and dosing should follow standard age-, cytogenetic- and molecular-based risk profiling.[1] Additional consideration should be given for haematopoietic cell transplantation or total skin electron beam therapy after chemotherapy for persistent LC if marrow negative.[1] Local treatment in the form of electron beam therapy or radiation therapy for palliation of pain or puritus may be helpful in patients who are not candidates for chemotherapy. This patient was treated with chemotherapy aimed at symptomatic relief of LC.

In summary, we present a rare case of LC with florid clinical signs requiring cooperative management between dermatologist and haematologist for best patient care. Diagnosis of LC is crucial as it significantly influences patient management.

REFERENCES

1. Bakst RL, Tallman MS, Douer D, Yahalom J. How I treat extramedullary acute myeloid leukemia. Blood 2011;118:3785-93.
2. Husak R, Blume-Peytaki U, Orfanos CE. Aleukemic leukemia cutis in an adolescent boy. N Engl J Med 1999;340:893-4.
3. Cronin DM, George TI, Sundram UN. An updated approach to the diagnosis of myeloid leukemia cutis. Am J Clin Pathol 2009;132:101-10.
4. Mathew RA, Bennett JM, Liu JJ, Komrokji RS, Lancet JE, Naghashpour M, et al. Cutaneous manifestations in CMML: Indication of disease acceleration or transformation to AML and review of the literature. Leuk Res 2012;36:72-80.

Yee Kiat Heng, [1]*MBBS*, *MRCP (UK)*, *M Med (Int Med)*, Beatrice SS Huang, [2], Lian King Lee, [3]*MB ChB*, *MRCP*, *FRCPath*, Joyce SS Lee, [1]*MBBS*, *MRCP (UK)*, *M Med (Int Med)*, See Ket Ng, [1]*MBBS*, *M Med (Int Med)*

[1]Department of Dermatology, National Skin Centre, Singapore
[2]Faculty of Medicine, University of New South Wales, Sydney, Australia
[3]Department of Haematology, Tan Tock Seng Hospital, Singapore

Address for Correspondence: Dr Yee Kiat Heng, Department of Dermatology, National Skin Centre, 1 Mandalay Road, Singapore 308205.
Email: ykheng@nsc.gov.sg