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Cutaneous presentation of aleukemic monoblastic leukemia cutis – a case report and review of literature with focus on immunohistochemistry

Aleukemic monoblastic leukemia cutis is a rare cutaneous manifestation of a systemic hematological disorder associated with dermal infiltration of monoblasts preceding bone marrow or peripheral blood involvement. We report a case of a 75-year-old woman who presented with an erythematous maculopapular rash, which was clinically diagnosed as viral exanthema. Microscopy of the skin biopsy showed features of monoblastic leukemia. Her general physical condition rapidly deteriorated and she died 4 weeks later. We present this case to alert dermatologists of innocuous erythematous skin lesions clinically resembling a viral exanthema, which, in rare instances, may be a presenting feature of an aleukemic monoblastic leukemia cutis. This entity poses problems for dermatopathologists even on immunohistochemistry as monoblasts are negative for hemopoietic precursor cell antigens like CD34, Terminal deoxynncleotidy1 transferase (TdT) and CD117.

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Leukemias are well characterized by diffuse involvement of the bone marrow and blood stream by neoplastic white blood cells.[1] In addition, infiltration of the visceral solid organs and skin is also well documented.[1,2] Aleukemic leukemia cutis is a condition where skin involvement by leukemic cells precedes systemic involvement.[2] We report a case of aleukemic monoblastic leukemia cutis, which presented with a clinical picture resembling viral exanthema and briefly discuss the difficulties encountered in interpreting the immunohistochemistry profile.

Case report

A 75-year-old woman presented to this hospital with a history of fever, loss of appetite and a skin rash, which was present for 8 weeks. On examination, the rash appeared as erythematous macules and papules measuring up to 1 cm and was distributed initially over her trunk and later spread to her buttocks and upper thighs (Fig. 1). The dermatological impression was of a viral exanthema. The other clinical differential diagnosis considered was Sweet's syndrome. She had a history of hypothyroidism, chronic obstructive pulmonary disease, non-insulin-dependent diabetes mellitus, ischemic heart disease and peripheral vascular disease. She was a chronic smoker. She was empirically treated with emollients, and a punch biopsy of the skin rash was performed. The rash appeared to improve with the offered treatment. Her blood investigations showed normal electrolytes, and her liver function tests were normal. The only

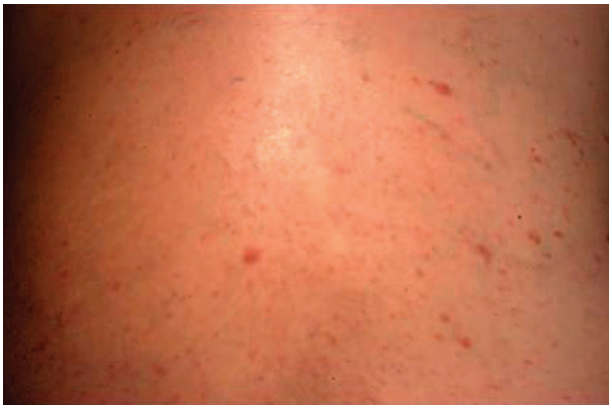

Fig. 1. Erythematous maculopapular rash scattered over the trunk.

abnormality was a rise in monocytes from 1.9×10^9/l to 2.2×10^9/l (normal limit $0.2–0.8 \times 10^9$/l) during her hospital stay. Her total white cell count and the rest of the parameters in the peripheral blood examination were normal, and her chest radiograph showed increased opacities over both lung bases.

Histology of the skin punch biopsy (Fig. 2) showed a monomorphic dermal infiltrate of hemopoietic cells with angulated nuclei and extremely convoluted nuclear membranes. The infiltrate involved the dermis and extended into the subcutaneous tissue. The hemopoietic cells were arranged in an interstitial pattern between collagen bundles. Mitotic figures were easily identified. No mature myeloid cells were evident. Immunohistochemistry (Fig. 3) was performed and these cells expressed CD45 (1:10; DAKO, Cambridgeshire, UK), CD43 (1:10; Novocastra, Newcastle upon Tync, UK), CD4 (1:400; Novocastra), CD68 (KP1) (1:700; DAKO), CD68 (PGM1) (1:50; DAKO), human leukocyte antigen-DR (1:100; DAKO) and lysozyme (1:3000; DAKO). A proportion of the cells also expressed CD163. Ki-67 (1:50; Novocastra) expression was seen in 60% of the tumor cells. The cells were negative for CD2 (1:50; Novocastra), CD3 (1:50; Novocastra), CD5 (1:50; Novocastra), CD7 (1:50; Novocastra), CD8 (1:50; Novocastra), CD30 (1:50; Dako), CD56 (1:100; Novocastra), CD57 (1:40; Becton & Dickinson, Oxford, UK), perforin (1:20; Novocastra), granzyme B (1:20; Novocastra), CD20 (1:250; DAKO), CD79a (1:20; DAKO), Pax-5 (1:400; Santa Cruz, CA, USA), CD138 (1:100; Serotec, Oxford, UK), CD34 (1:100; Dako), TdT (1:50; Novocastra), CD117 (1:400: Dako), myeloperoxidase (1:2000; Dako), S100 (1:1000; Novocastra) and mast cell tryptase (1:3000; Dako). The morphology and immunohistochemical features indicated dermal infiltration by acute leukemia of monocytic lineage also termed monoblastic sarcoma.

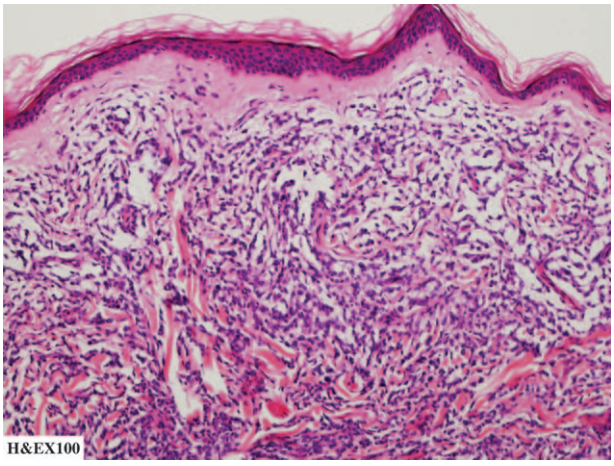

Fig. 2. Hematoxylin and eosin (H&E)-stained microphotograph showing dermal involvement by monoblasts in an interstitial pattern between collagen bundles (×100).

Four weeks after her initial presentation, she presented in the emergency department with sudden onset of breathlessness, reduced appetite and blurred vision. She had no history of cough or chest pain. The initial clinical impression was of acute exacerbation of chronic obstructive pulmonary disease following a chest infection. Her blood investigations showed deranged electrolytes with altered liver function tests and a rise in the total white cell count of 14.9×10^9/l (normal $4–11 \times 10^9$/l). There was evidence of lymphocytosis (5.3×10^9/l, normal $1–4 \times 109$/l) and monocytosis (6.3×10^9/l, normal $0.2–0.8 \times 109$/l). Following the histology of the skin biopsy, she was referred for hematological opinion, and a complete hematological work-up including a bone marrow biopsy was planned. Her general physical condition deteriorated rapidly and she developed metabolic acidosis and died 3 days later. Her death was attributed to respiratory failure secondary to a lower respiratory tract infection.

Discussion

Aleukemic monoblastic leukemia cutis is a rare condition characterized by leukemic cells involving skin before presenting in the peripheral blood or bone marrow. It is unknown whether this neoplastic clone originates in the bone marrow with early seeding to extramedullary sites or whether it originates in the dermal hematolymphoid tissue with hematogenous spread to bone marrow and peripheral blood.[2] The past literature includes a few case reports of aleukemic monoblastic leukemia cutis,[3–6] and there was only one case report that was clinically diagnosed as a benign exanthema, as seen in our case.[7]

Tumor masses consisting of immature myeloid cells at extramedullary sites are termed myeloid sarcoma. Myeloid sarcomas may develop *de novo*, concurrent or subsequent to a myeloproliferative/myelodysplastic disorder or myeloid neoplasms. In a large series of 92 adult patients with myeloid sarcoma, 27% patients presented *de novo*.[8] Skin is the most common site of

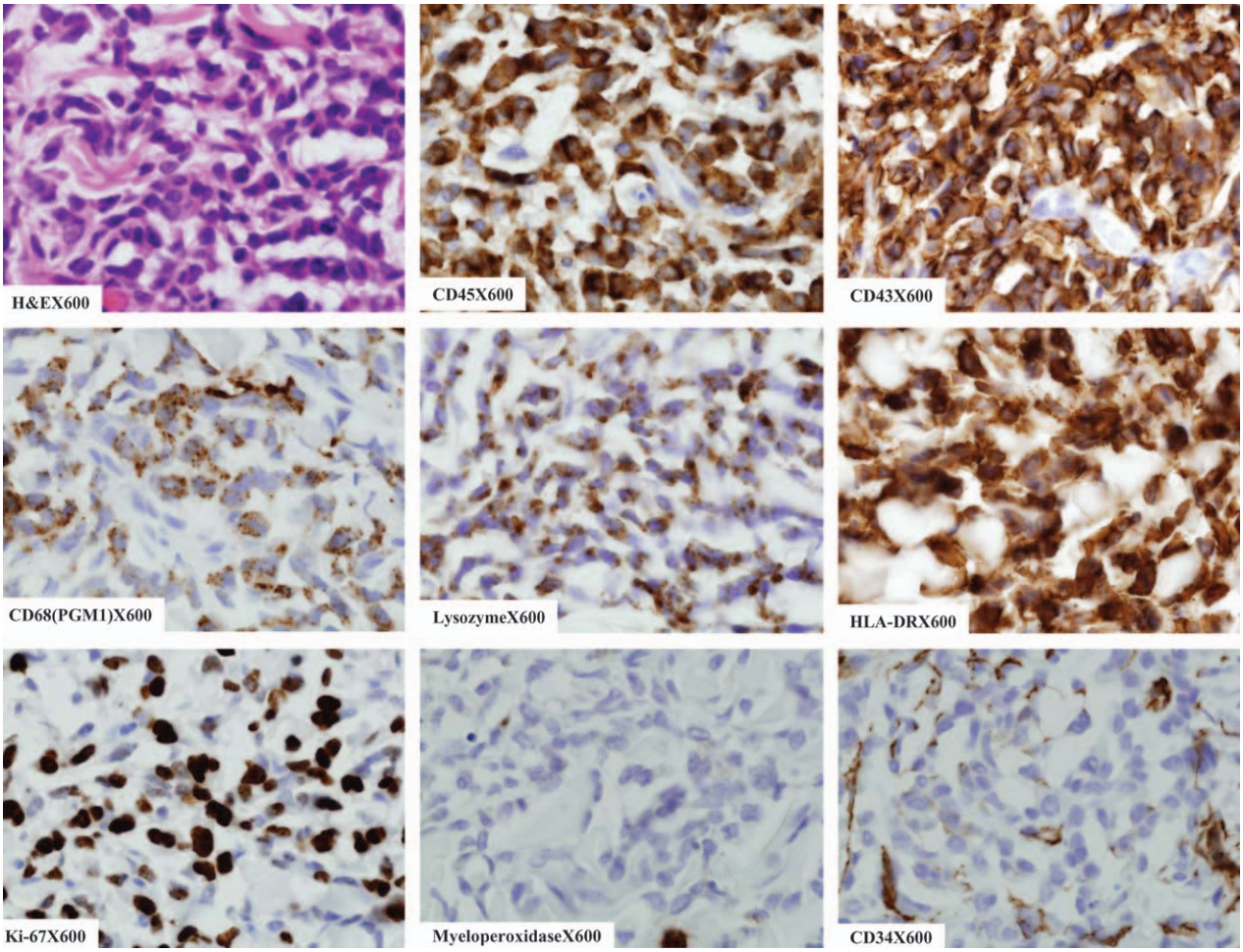

Fig. 3. Immunohistochemistry showing positivity of tumor cells for CD45, CD43, CD 68, lysozyme, human leukocyte antigen (HLA)-DR and Ki-67 and negativity for myeloperoxidase and CD34 (×600). H&E, hematoxylin and eosin.

involvement of myeloid sarcoma and is involved in >25% cases.[8] More than 20% of myeloid sarcomas are of monoblastic type and are referred to as monoblastic sarcomas, where the blastic cells have phenotype of cells seen in acute monoblastic leukemia (M5).[1] Monoblastic sarcoma has a higher tendency to involve skin and skin happens to be the presenting site in 50% of cases.[8] Myeloid sarcoma can be mistaken for lymphoblastic lymphoma, Burkitt lymphoma, diffuse large B-cell lymphoma or a non-hemopoietic tumor. A histological clue to the diagnosis of leukemia cutis is the interstitial pattern of hemopoietic cells between collagen bundles. About 40% of the *de novo* myeloid sarcomas are said to be wrongly diagnosed.[8]

Clinically, the diagnosis of aleukemic leukemia cutis is extremely difficult, and generally, most patients present with asymptomatic papulonodules, with clinical manifestations ranging from a single nodule to erythroderma.[7] In our case, the lesions present were discrete erythematous macules and papules, and the clinical diagnosis was that of a viral exanthema. A study by Su et al.[9] showed that specific skin lesions preceded peripheral blood involvement in 7% of cases. Immunohistochemical markers play a pivotal role in diagnosing cutaneous hematolymphoid infiltrates. In our case, the negativity of all B-cell markers and most of the T-cell markers excludes the possibility of a lymphoma. The lack of specificity of CD43 must be recognized when this marker is incorporated in immunophenotyping panels. Nevertheless, in the review by Segal et al.[10] of 17 cases of 'CD43-only' phenotype in patients with lack of expression of CD20 and CD45RO, eight cases were extramedullary leukemic infiltrate of which five were of myeloid type, two monocytic and one mixed lineage, and the remaining comprised four T-cell lymphomas, three B-cell lymphomas and two plasmacytomas.[10] The positivity of CD4 immunostaining initially raised the possibility of a cutaneous hematodermic tumor,[11] but a subsequent panel showed negativity for CD56 and positivity for CD68 supporting monoblastic origin. As in most monoblastic tumors involving skin,[8] myeloperoxidase was negative in our case; therefore, the diagnosis is based on morphology and supported by

additional stains. Among the 20 monoblastic sarcomas published in a recent series,[8] only two cases expressed CD34, two expressed TdT, five expressed myeloperoxidase and seven expressed CD117. However, all cases were uniformly positive for CD68 (KP1) and CD68 (PGM1). These results are similar to our case. The majority of these cases show systemic progression to involve the bone marrow and peripheral blood, and aggressive chemotherapy is the main treatment modality. There was an obvious rise in the monocytic count in our case, but evidence of bone marrow involvement could not be confirmed, given the rapid deterioration of the patient's general condition and sudden death.

In this correspondence, we would like to raise awareness among dermatologists of the possibility of a benign looking skin rash as the first sign of aleukemic monoblastic leukemia cutis, which can be diagnosed only on a skin biopsy given the lack of evidence of systemic spread at the time of presentation. For correct identification and subtyping of myeloid sarcoma, immunohistochemical stains like CD34, myeloperoxidase, CD117 and CD68 (PGM1) are extremely helpful. Typically, monoblastic sarcomas are negative for CD34, myeloperoxidase and CD117 and uniformly positive for CD68 (PGM1).[8]

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