CASE REPORT

Cutaneous herald: leukaemia cutis as presenting manifestation of relapse in acute promyelocytic leukaemia

Prasanth Balasubramanian, Ram V Nampoothiri, Deepak Goni, Pankaj Malhotra

Department of Internal Medicine, Post Graduate Institute of Medical Education and Research, Chandigarh, India

Correspondence to
Dr Pankaj Malhotra,
hematpgi@gmail.com

Accepted 6 February 2018

SUMMARY

Leukaemia cutis or cutaneous infiltration of neoplastic myeloid or lymphoid cells is usually seen in the acute myelomonocytic and acute monocytic variants of acute myeloid leukaemia. Here, we report a case of acute promyelocytic leukaemia who achieved remission, presenting with skin lesions, the biopsy of which revealed leukaemia cutis, heralding the relapse of the disease. After establishing the diagnosis with bone marrow analysis, the patient was started on daunorubicin chemotherapy along with arsenic trioxide and all-trans retinoic acid. Afterwards, the skin lesions resolved, and the patient is planned for consolidation with bone marrow transplantation.

BACKGROUND

Leukaemia cutis (LC) is due to cutaneous infiltration of lymphoid or myeloid leucocytes that are neoplastic in origin.¹ LC may be present in 10%–15% cases of acute myeloid leukaemia (AML) at various stages of the disease.² However, dermatological involvement in acute promyelocytic leukaemia (APML) is quite uncommon, and LC as a presenting manifestation of relapse in APML is very rare.³ Here we present a case of APML in remission that presented with skin lesions as the first sign of relapse.

CASE PRESENTATION

This 30-year-old woman was initially referred to the adult haematology clinic of our centre with

Figure 2 Infiltration of large atypical cells arranged in sheets throughout the biopsy tissue with small lymphocytes, basophils and eosinophils scattered in-between them: (A) H&E, (B) magnification view.

a history of easy fatigability and menorrhagia of 1-month duration with abnormal cells in her peripheral smear. The patient's laboratory tests revealed pancytopenia (haemoglobin 4.8 g/dL, total leucocyte count $3.9 \times 10^9/L$ and platelet count of $33 \times 10^9/L$), and the peripheral smear showed 98% abnormal promyelocytes. Bone marrow aspiration showed an excess of abnormal promyelocytes with reverse transcriptase PCR (RT-PCR) positive for Promyelocytic Leukemia/Retinoic Acid Receptor Alpha (PML-RAR α) fusion gene product. A diagnosis of APML—intermediate risk—was made. The patient was treated with induction chemotherapy comprising injection arsenic trioxide (ATO) 0.15 mg/kg/day and oral all-trans retinoic acid (ATRA) 45 mg/m²/day in two divided doses, as per standard National Comprehensive Cancer Network (NCCN) guidelines. Bone marrow done at the end of 4 weeks induction showed no excess of blasts or

Figure 1 Multiple dark bluish-red maculopapular lesions (arrow) over the anterior part of chest (A) and the dorsal aspect of the right forearm (B) and the resolution of the lesions after the treatment (C and D).

Figure 3 Immunohistochemistry showing strong positivity for MPO and weak positivity for CD68, CD45 and Ki67 indicating myeloid lineage.

To cite: Balasubramanian P, Nampoothiri RV, Goni D, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2017-222906

Table 1 Relevant investigations of the patient at initial presentation and current admission (relapse) along with reference values

	Initial presentation	Current presentation (relapse)	Reference values
Haemoglobin (g/dL)	4.8	8.6	12–18
Total leucocyte count ($\times 10^9$ cells/L)	3.9	1.2	4–11
Platelet count ($\times 10^9$ cells/L)	33	161	150–400
Peripheral smear	98% abnormal promyelocytes	Normal study	
Bone marrow examination	48% abnormal promyelocytes	45% abnormal promyelocytes	
Bone marrow RT-PCR for PML-RAR α fusion transcript	Positive	Positive (68%)	Negative

RT-PCR, reverse transcriptase PCR.

abnormal promyelocytes, and RT-PCR for PML-RAR α transcript was negative. The patient was started on ATO+ATRA consolidation x three cycles followed by maintenance chemotherapy. Her 2-monthly RT-PCR for PML-RAR α was negative throughout the consolidation and initial maintenance. During her eighth month of maintenance therapy, she presented to our clinic with fatigue and skin rash. On examination, she was pale with a well-defined reddish-brown palpable maculopapular rash on her upper chest and right forearm (figure 1A,B). There was no hepatosplenomegaly on abdominal examination.

INVESTIGATIONS

During this admission, complete blood counts revealed anaemia (haemoglobin 8.6 g/dL, Mean corpuscular volume (MCV) 77 fL, Mean corpuscular hemoglobin (MCH) 25.2 pg, Mean corpuscular hemoglobin concentration (MCHC) 320 g/L) with leucopenia (total leucocyte count 1.2×10^9 /L) and normal platelet counts (161×10^9 /L/ μ L). Peripheral smear did not show any abnormal promyelocytes or blasts. Biopsy of the skin lesion revealed large atypical cell infiltrating the epidermis and dermis with immunohistochemistry showing positivity for myeloid markers, Myeloperoxidase (MPO), CD45 and CD68 (weak), thus confirming the diagnosis of LC (figures 2 and 3). Bone marrow biopsy showed 45% abnormal promyelocytes, and quantitative RT-PCR for PML-RAR α transcript was 68%, further confirming the relapse of APML (table 1).

TREATMENT

A reinduction therapy consisting of daunorubicin 90 mg/m² for 3 days along with ATO injections 0.15 mg/kg/day and oral ATRA 45 mg/m²/day in two divided doses was given. The above regimen was chosen since there was no prior exposure to anthracycline-based chemotherapy. The induction phase was complicated by febrile neutropenia which was attributed to pneumonia and thrombophlebitis which resolved with parenteral antibiotics.

OUTCOME AND FOLLOW-UP

With the anthracycline-based reinduction, her skin lesions disappeared completely in 2 weeks (figure 1C,D), and haematological remission was achieved in 4 weeks. Bone marrow done at the end of 4-week reinduction showed no excess of blasts or abnormal promyelocytes, and quantitative RT-PCR for PML-RAR α transcript was negative. She is now planned for consolidation with autologous bone marrow transplant.

DISCUSSION

LC is known to occur in around 15% of patients who are diagnosed with AML and is less commonly seen in patients with chronic myeloproliferative disease, lymphoproliferative diseases and myelodysplastic syndromes.² Among AML, the frequency of skin involvement is up to 50% in acute myelomonocytic and

acute monocytic variants.⁴ Patients with LC may have solitary or multiple skin lesions, usually seen on legs and arms, but can also involve the chest, face and scalp. It may appear as violaceous, reddish-brown or haemorrhagic papules. Only one-third of the cases have concomitant involvement of the skin and bone marrow. Occasionally (around 10% of LC cases), skin lesions may appear even prior to the onset of the systemic disease, known as 'leukaemic leukaemia cutis'.¹ Biopsy of the cutaneous lesion reveals infiltration of the leukaemic cells in the dermis and the subcutis with a predominant perivascular and periadnexal pattern.⁵

LC is an uncommon manifestation of APML. Baer *et al*⁶ studied LC in 18 patients with AML from 1969 to 1986. One of them had APML in remission who presented with a large lesion on the back that turned out to be LC on biopsy and was subsequently treated with local electron-beam irradiation. Following this, Giralt *et al* reported three cases of APML that were in remission following treatment with ATRA and manifested LC as a sign of

Patient's perspective

My doctors told me initially that my blood cancer was possibly curable and I underwent the chemotherapy advised to me. When I started getting these rashes on my skin, I never thought they would be related to my malignancy or it might be because of a relapse. But after taking a biopsy from the lesion, doctors told me it's a relapse of the blood cancer and has affected my skin, which is rare. Although chemotherapy this time was more intense, I could almost feel the disappearance of the lesions. I am glad that they have disappeared and the malignancy has gone back to remission again. Now I am preparing for my stem cell transplantation and hopeful that cancer will never return.

Learning points

- ▶ Even though leukaemia cutis is a common manifestation of acute myelomonocytic and monocytic variants of acute myeloid leukaemia, it can rarely present in acute promyelocytic leukaemia as well.
- ▶ Skin lesions with underlying systemic symptoms should not be neglected, and biopsy of skin lesions must be done wherever possible along with workup for possible relapse with a bone marrow biopsy.
- ▶ Leukaemia cutis as a sign of acute promyelocytic leukaemia relapse must be treated with salvage chemotherapy with anthracycline and arsenic trioxide-based chemotherapy regimen followed by haematopoietic stem cell transplantation.

relapse.⁷ Less than 25 cases of LC have been reported to date in patients with APML, and interestingly, all of them were relapses following ATRA therapy. APML presenting de novo as LC has been reported by Markowski *et al* in a patient who presented with an erythematous pruritic lesion in the left lower limb that was initially treated as contact dermatitis due to poison ivy.⁸

The reason for the appearance of LC following ATRA therapy is still unclear. Proposed hypotheses include upregulation of the transcription of genes related to integrins and leucocyte adhesion receptors after treatment with ATRA, as a part of the 'retinoic acid syndrome'.^{9–10} This increased gene transcription promotes endothelial adhesion, tissue migration and organ infiltration by the leukaemic cells in APML.

Available evidence suggests managing LC, like any other extra-medullary relapse in APML, with reinduction chemotherapy which includes ATO and anthracycline (daunorubicin)-containing regimens, followed by haematopoietic stem cell transplantation once the patient is in remission.¹¹

Contributors PB: preparation of manuscript. RVN: literature review and preparation of manuscript. DG: managing the index case. PM: concept, design and managing the index case.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Cho-Vega JH, Medeiros LJ, Prieto VG, *et al* *Am J Clin Pathol* 2008;129:130–42.
- 2 Agis H, Weltermann A, Fonatsch C, *et al*. A comparative study on demographic, hematological, and cytogenetic findings and prognosis in acute myeloid leukemia with and without leukemia cutis. *Ann Hematol* 2002;81:90–5.
- 3 Straus DJ, Mertelsmann R, Koziner B, *et al*. The acute monocytic leukemias: multidisciplinary studies in 45 patients. *Medicine* 1980;59:409–25.
- 4 Kaddu S, Zenahlik P, Beham-Schmid C, *et al*. Specific cutaneous infiltrates in patients with myelogenous leukemia: a clinicopathologic study of 26 patients with assessment of diagnostic criteria. *J Am Acad Dermatol* 1999;40:966–78.
- 5 Paydas S, Zorludemir S. Leukaemia cutis and leukaemic vasculitis. *Br J Dermatol* 2000;143:773–9.
- 6 Baer MR, Barcos M, Farrell H, *et al*. Acute myelogenous leukemia with leukemia cutis. Eighteen cases seen between 1969 and 1986. *Cancer* 1989;63:2192–200.
- 7 Giral S, O'Brien S, Weeks E, *et al*. Leukemia Cutis in Acute Promyelocytic Leukemia: Report of Three Cases After Treatment with All-Trans Retinoic Acid. *Leuk Lymphoma* 1994;14:453–6.
- 8 Markowski TR, Martin DB, Kao GF, *et al*. Leukemia cutis: a presenting sign in acute promyelocytic leukemia. *Arch Dermatol* 2007;143:1209.
- 9 Hickstein DD, Hickey MJ, Collins SJ. Transcriptional regulation of the leukocyte adherence protein beta subunit during human myeloid cell differentiation. *J Biol Chem* 1988;263:13863–7.
- 10 Frankel SR. The 'retinoic acid syndrome' in acute promyelocytic leukemia. *Ann Intern Med* 1992;117:292–6.
- 11 Wang HX, Duan LN, Ji SQ, *et al*. Arsenic trioxide-responsive leukemia cutis in a patient with acute promyelocytic leukemia after ATRA treatment. *Leuk Lymphoma* 2006;47:1438–40.

Copyright 2018 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit

<http://group.bmj.com/group/rights-licensing/permissions>.

BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow