CASE REPORT

Leukaemia cutis after starting bendamustine: cause or coincidence?

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Accepted 2 September 2015

SUMMARY

A 55-year-old man with a history of chronic lymphocytic leukaemia presented with diffuse skin lesions that began 1 week after starting a new chemotherapy regimen with bendamustine and rituximab. The lesions appeared as erythematous papules that were neither itchy nor tender, and did not blanch with pressure. Initially, they began on his scalp and flanks and, over the next few days, spread diffusely throughout his body, becoming darker in colour. Skin biopsy showed atypical clonal B-cell proliferation in a perivascular, periadnexal and dermal band-like distribution, which was further characterised by immunohistochemical evaluation. These findings were suggestive of leukaemia cutis and consistent with the patient's chronic lymphocytic leukaemia, which was previously confirmed by bone marrow biopsy. The bendamustine was stopped and the patient's chemotherapy regimen was switched to fludarabine, cyclophosphamide and rituximab. Shortly thereafter, the leukaemia cutis regressed significantly.

BACKGROUND

Leukaemia cutis is an uncommon skin manifestation of various forms of leukaemia, and occurs when neoplastic leucocytes infiltrate the dermis, resulting in clinically visible skin lesions.¹ It usually portends a poor prognosis, as 90% of patients with this condition tend to have additional sites of extramedullary involvement.² While only a few case reports have previously reported leukaemia cutis occurring following chemotherapy, none, to the best of our knowledge, have reported it in relation to bendamustine. We report a rare case of a 55-year-old man with atypical chronic lymphocytic leukaemia who developed leukaemia cutis after starting bendamustine chemotherapy.

CASE PRESENTATION

A 55-year-old man with atypical chronic lymphocytic leukaemia, diagnosed in 2001 in Nigeria, presented with diffuse skin lesions that started a week after his first cycle of bendamustine and rituximab chemotherapy.

The patient began therapy for his chronic lymphocytic leukaemia on arrival to the USA in 2008, with one cycle of cyclophosphamide, vincristine and prednisone. Bone marrow biopsy and peripheral blood smear at the time revealed extensive infiltration with lymphocytes, positive for CD5, CD20 and CD23, and negative for CD38, t(11,14) and cyclin D1. In 2009, the patient completed four cycles of fludarabine, cyclophosphamide and rituximab (FCR), with clinical improvement. He was lost

to follow-up for 2 years and presented again in 2013, with radiographic evidence of disease progression. At that time, he was started on his first cycle of bendamustine-rituximab. The regimen significantly reduced tumour burden. The patient's complete blood count on the day prior to starting the cycle of bendamustine-rituximab revealed a white cell count of 191 000/ μ L; haemoglobin of 9.1 g/dL and platelet count of 35 000/ μ L. After the first cycle, complete blood count revealed reduction in all cell lines as follows: white cell count of 89 600/ μ L; haemoglobin of 7.9 g/dL and platelet count of 17 000/ μ L.

A week after starting this new chemotherapy regimen, the patient developed diffuse skin lesions and presented to the hospital. The lesions appeared as erythematous papules that were non-tender and non-pruritic, and did not blanch with pressure. Initially, they began on his scalp and flanks and, over the next few days, spread diffusely throughout his body, becoming darker in colour. There were no associated constitutional symptoms such as fevers, chills, night sweats or weight loss, and no arthralgia.

Physical examination revealed erythematous and violaceous indurated nodules and papules concentrated on the back, scalp, face, chest, abdomen, bilateral arms and bilateral legs (figures 1 and 2). The distal arms and legs were spared. A large, non-tender lymph node was palpated in the left axilla. The remainder of the examination was unremarkable.

INVESTIGATIONS

A complete blood count and comprehensive metabolic panel revealed a white cell count of 87 900/mm³, haemoglobin of 8.4 g/dL, platelet count of 36 000/mm³ and creatinine level of 1.32 mg/dL. Liver function tests were unremarkable. A CT of the chest, abdomen and pelvis, performed a week prior, had revealed diffuse lymph node enlargement, including periportal, mesenteric, portacaval, periaortic, pericaval, bilateral common iliac, external iliac, obturator and inguinal lymph nodes, consistent with worsening chronic lymphocytic leukaemia. An ultrasound of the left axilla revealed a 4.6×3.7×3.8 cm heterogeneous, hypoechoic mass with no internal vascular flow, suggestive of an enlarged lymph node.

A skin punch biopsy of several skin lesions was obtained from the right thigh. Histopathology revealed atypical clonal B-cell proliferation in a perivascular, periadnexal and dermal band-like distribution. Clonality was defined by a clonal IgH gene rearrangement by PCR. The skin biopsy

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To cite: Mawri S, Nabi S, Jallad B, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-209025

Figure 1 Skin lesions, day 2 after onset. Erythematous nodules and papules on the skin (photograph taken by the patient prior to hospitalisation).

Figure 2 Skin lesions regressing after chemotherapy was switched to fludarabine, cyclophosphamide and rituximab regimen. Day 18 after onset.

revealed dense infiltrates of purely B cells with clonality as defined above, thus we do not suspect the tissue lesions were simply reactive in nature but, rather, believe they were neoplastic. Further immunohistochemical evaluation revealed positive reactivity for CD20, CD3 and BCL-2, and negative reactivity for CD5, CD23, cyclin D1, BCL-6 and CD10 (figures 3–8). These findings were consistent with leukaemia cutis and compatible with the diagnosis of atypical lymphocytic leukaemia, which was previously confirmed by bone marrow biopsy.

The patient's prior bone marrow biopsy had revealed co-expression of CD5 and CD23, which were only dimly expressed; however, these were not detected on the cutaneous infiltrates. Several reasons may explain this aberration. First, the skin biopsy was assessed with histology and immunohistochemistry only. Flow cytometry, a more sensitive technique that can detect dimly expressed receptors, was not performed due to scant tissue sample. Second, given the duration of time between bone marrow and skin biopsies, it is possible that phenotypic variation, as a result of genotypic evolution over the life time of the cancer cell line, may have taken place. Third, phenotypic evolution in cancer cells postchemotherapy has been described previously and may have occurred. These three possible explanations may account for the noted aberration.

To determine clonality, IgH gene rearrangement testing was carried out on the skin biopsy. The cell population was found to be monoclonal. However, at our institution, we do not routinely perform IgH gene rearrangements on bone marrow biopsies but, rather, we assess for clonality by flow cytometry. However, since flow cytometry is not usually performed on skin specimens due to the minute nature of the biopsies, in these instances, PCR methodology with IgH gene rearrangement is performed at our institution, because it can be performed on formalin fixed tissues and can be carried out on relatively scant specimens.

TREATMENT

The bendamustine was stopped and the patient's chemotherapy regimen was switched to FCR. Shortly thereafter, the leukaemia cutis regressed significantly.

OUTCOME AND FOLLOW-UP

The patient completed two cycles of FCR. He did not reach remission. He was lost to follow-up after the two cycles and later died due to infectious complications before being re-staged.

Figure 3 Skin biopsy. Low-power examination ($\times 10$) of H&E stains showing perivascular and periadnexal lymphocytic infiltrates in the dermis.

Figure 4 Skin biopsy. High-power examination (x20) showing similar findings in more detail.

Figure 6 Immunohistochemical staining. Tumour cells positive for CD20.

DISCUSSION

Leukaemia cutis is a term used to describe infiltration of leukaemic white cell counts or their precursors into the skin, resulting in clinically apparent skin lesions. This condition can manifest in various leukaemia types, including chronic lymphocytic leukaemia, acute lymphoblastic leukaemia, acute myelogenous leukaemia and chronic myelogenous leukaemia. Leukaemia cutis is relatively rare, affecting only about 3% of patients diagnosed with leukaemia. Interestingly, it can manifest as the initial clinical presentation of leukaemia in about 7% of these cases, prior to any evidence of malignant leucocytes in the blood.³ This is dubbed aleukaemic leukaemia cutis. Hence, accurate diagnosis in such cases can have tremendous prognostic significance. Furthermore, leukaemia cutis can be a manifestation of a relapse of previously treated systemic leukaemia. A diagnosis of leukaemia cutis in the setting of acute leukaemia generally portends a poor prognosis and strongly correlates with additional sites of extramedullary involvement. Treating this condition can be a challenge, as it might be resistant to chemotherapy.⁴

The gross appearance of leukaemia cutis may vary. It can present as firm papules, diffuse eczema, annular erythema, purpura, petechiae or blisters that are usually asymptomatic.^{5,6} Although leukaemia cutis may be suspected from the patient's history and the cutaneous appearance, a skin biopsy is necessary to confirm the diagnosis. It classically reveals a diffuse

infiltration of malignant leucocytes in the dermis. Different patterns can be observed on histology, depending on the primary leukaemia. Additional immunohistochemistry may reveal the specific cell type involved. It is sometimes very difficult to diagnose leukaemia cutis. Managing leukaemia cutis consists of treating the underlying malignancy. Generally, agents such as rituximab, cyclophosphamide and cladribine have been shown to be effective.^{7,8}

It is very unusual for leukaemia cutis to develop as a response to chemotherapy, which is used for the treatment of leukaemia.⁹ A review of the literature reveals only a few case reports documenting this phenomenon, with cyclophosphamide as the presumed culprit. One report describes a middle-aged woman who developed leukaemia cutis after completing her fourth cycle of cyclophosphamide and doxorubicin for treatment of infiltrating ductal carcinoma of the breast.¹⁰ Another report describes an elderly woman who developed leukaemia cutis after completing her third cycle of cyclophosphamide, hydroxydaunorubicin, vincristine and prednisone for treatment of blasticplasmacytoid dendritic cell neoplasm.¹¹ Other reports describe various skin manifestations, other than leukaemia cutis, following initiation of bendamustine.^{12–14} However, skin biopsy findings in such cases show simple inflammation rather than leukaemic infiltration. A case of leukaemia cutis in association with activation of varicella-zoster virus has also been described.¹⁵

Figure 5 Immunohistochemical staining. Tumour cells positive for BCL-2.

Figure 7 Immunohistochemical staining. Tumour cells negative for CD5.

Figure 8 Immunohistochemical staining. Tumour cells negative for CD3.

Studies have demonstrated that alteration in leukaemic cell receptors can occur over time as a response to chemotherapy or as part of the natural evolution of the neoplastic cells. These receptor changes may lead to chemotherapy resistance as well as progression of disease in leukaemic patients.^{16 17} While different receptors were noted on histopathochemistry testing for cutaneous versus bone marrow biopsy lymphocytes in our patient, this may have been due to phenotypic alteration of the receptors over time or lack of detection of dimly expressed receptors with use of immunohistochemistry testing instead of flow cytometry. Our leukaemic patient did not have any skin lesions before starting bendamustine. The observation that leukaemia cutis developed immediately after starting bendamustine and regressed

rapidly with cessation of this chemotherapeutic agent strongly suggests that the leukaemia cutis was related to and likely triggered by bendamustine.

To the best of our knowledge, there are no prior reported cases of leukaemia cutis developing following initiation of bendamustine. This case illustrates the necessity of maintaining a high level of vigilance for the detection of leukaemia cutis in patients presenting with characteristic diffuse skin lesions, in the setting of history of leukaemia. It also highlights the importance of keeping this diagnosis high in the differential of leukaemic patients presenting with diffuse non-pruritic skin involvement following treatment with bendamustine or other chemotherapeutic agents.

Contributors SM and SN worked together on a thorough literature review as well as on writing this case report. JW and BJ were the mentors on this project and assisted in finalising the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Patient's perspective

I never thought that something as simple as 'skin bumps' could turn out to be spreading cancer.

Learning points

- ▶ Cutaneous involvement of leukaemic cells is a rare event, involving 3% of patients with leukaemia, and is termed leukaemia cutis.
- ▶ In about 7% of cases of leukaemia cutis, skin lesions can be the initial clinical presentation of the leukaemia itself, prior to any evidence of malignant leucocytes in the blood. Such a presentation is called aleukaemic leukaemia cutis.
- ▶ Case reports of leukaemia cutis after starting certain chemotherapeutic agents have been reported. As early diagnosis and prompt management can significantly affect outcomes, a low index of suspicion should be kept in patients with leukaemia presenting with diffuse skin lesions while undergoing chemotherapy.
- ▶ Diagnosis of leukaemia cutis requires skin punch biopsy for histopathology and immunohistochemical staining to identify the leukaemic cells in the skin.

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