A patient with widespread firm nontender nodules

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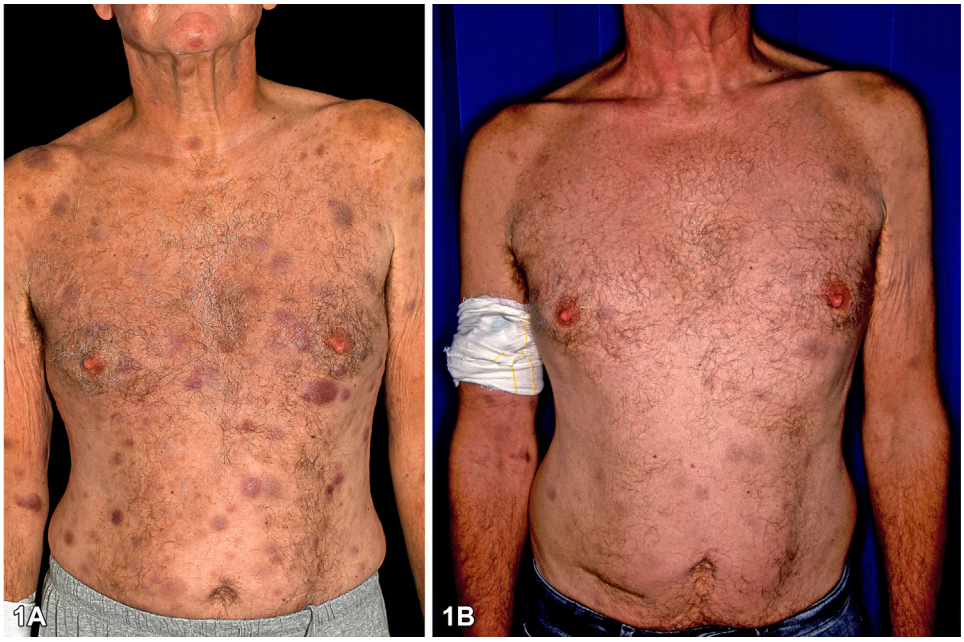

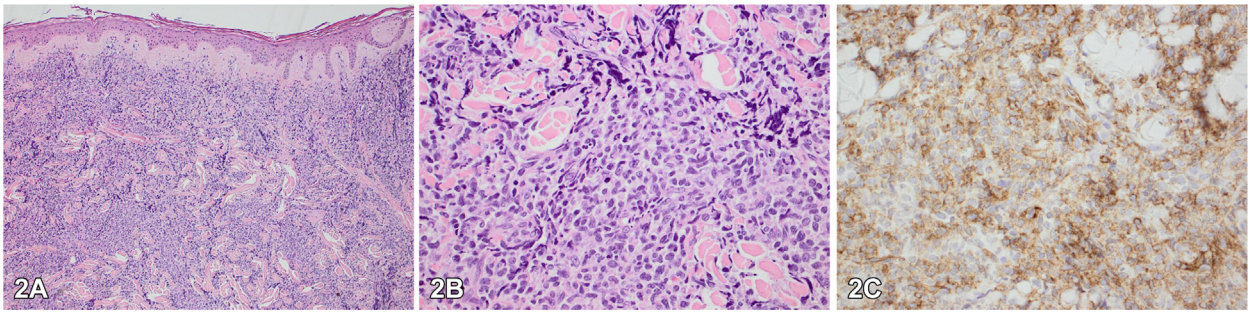

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HISTORY

A 63-year-old man with a history of chronic myelomonocytic leukemia (CMML) presented with a 2 month history of widespread nonpainful skin lesions. Otherwise he felt well and reported no systemic symptoms. On examination, there were nontender violaceous, firm nodules on his face, torso, arms, and legs; some lesions appeared 'bruise-like' (Fig 1, *A* and *B*). An urgent diagnostic skin biopsy showed a dermis widely infiltrated by monomorphic blasts (Fig 2, *A* and *B*). Immunohistochemistry revealed the lesional cells strongly expressed CD4, CD43, CD45, CD56, CD123 (Fig 2, *C*), and BCL2. Treatment with a novel therapy, Tagraxofusp, over 3 months led to a significant improvement with resolution of the cutaneous lesions.

Question 1: What is the most likely underlying diagnosis?

A. Blastic plasmacytoid dendritic cell neoplasm (BPDCN)

B. Leukemia cutis secondary to CMML

C. Sarcoidosis

D. Cutaneous T-cell lymphoma (CTCL)

E. Kaposi sarcoma

Answers:

A. Blastic plasmacytoid dendritic cell neoplasm (BPDCN) — Correct. BPDCN is a rare hematological malignancy caused by a clonal proliferation of precursors of plasmacytoid dendritic cells. It often presents with brown or purple nodular cutaneous lesions (although bruise-like patches also occur) which can be numerous or solitary. The histopathology and immunohistochemistry described in the history are typical of BPDCN.[1]

B. Leukemia cutis secondary to CMML — Incorrect. Leukemia cutis is unlikely to be the underlying diagnosis due to the positivity for CD4, CD56, and CD123, as well as negativity for myeloperoxidase.

C. Sarcoidosis — Incorrect. No granulomas were seen on histology. An infiltrate composed of blasts would also not be consistent with sarcoidosis.

D. Cutaneous T-cell lymphoma (CTCL) — Incorrect. CTCL can show a wide variety of morphological and immunohistochemical features, but most cases would show positivity for some of the classic T-cell markers - CD2, CD3, CD5 and CD7 - although individual CTCLs can drop one or more of these markers. CD123 would be an unusual marker to be positive in CTCL.

E. Kaposi sarcoma — Incorrect. It would be unusual to develop Kaposi sarcoma in the absence of HIV infection or strong immunosuppression. Histochemical CMML had not required any active treatment. The histology did not show an atypical spindle cell proliferation.

Question 2: Which of the following statements regarding the presentation and diagnosis of this condition is correct?

A. It can present with or without bone marrow involvement and leukemic dissemination

B. Extracutaneous disease including lymphadenopathy, splenomegaly, and hepatomegaly is rare

C. The infiltrate typically extends from the dermis into the epidermis

D. The malignant clone in this condition arises directly from the clone in CMML

E. Dual positivity for CD4 and CD56 on immunohistochemistry allows the diagnosis to be made

Answers:

A. It can present with or without bone marrow involvement and leukemic dissemination — Correct. In this case, the patient presented with only cutaneous symptoms and there was no evidence of BPDCN in the bone marrow biopsy. However, bone marrow involvement can occur and patients can present with an acute leukemia.[1]

B. Extracutaneous disease including lymphadenopathy, splenomegaly, and hepatomegaly is rare — Incorrect. Lymphadenopathy, splenomegaly, and hepatomegaly are common sites of extracutaneous disease in BPDCN. They have been reported to occur in 56%, 44%, and 42%, respectively.[2]

C. The infiltrate typically extends from the dermis into the epidermis — Incorrect. A typical histological feature in BPDCN is the 'grenz zone'. This is an area of sparing in the papillary dermis. The infiltrate does not extend into the epidermis.

D. The malignant clone in this condition arises directly from the clone in CMML — Incorrect. BPDCN is a separate malignancy to CMML-1. However, genomic analysis suggests that these 2 conditions arise from a shared founding clone. Concurrent myeloid malignancies are present in

more than 20% of cases of BPDCN, and CMML is particularly common.[3]

E. Dual positivity for CD4 and CD56 on immunohistochemistry allows the diagnosis to be made — Incorrect. Diagnosis requires positivity for CD4, CD56 and markers specific to plasmacytoid dendritic cells. These include CD123, CD303, and TCL1. The absence of positivity for lineage-specific markers for B cells and myelomonocytic cells is also required.[1]

Question 3: Which of the following statements regarding the management and prognosis of this condition is correct?

A. It has a good prognosis

B. Younger age at presentation is a prognostic marker of poor outcome

C. Traditional myeloablative chemotherapy has yielded excellent responses

D. Hematopoietic stem cell transplantation (HSCT) is required to enable long-term remissions

E. Relapse is unlikely following remission

Answers:

A. It has a good prognosis — Incorrect. BPDCN has an extremely poor prognosis due to rapid disease progression with a median survival of 12-14 months.

B. Younger age at presentation is a prognostic marker of poor outcome — Incorrect. Age under 40 years and cutaneous symptoms only confer a favorable prognosis.

C. Traditional myeloablative chemotherapy has yielded excellent responses — Incorrect. Although an initial response may be seen, chemotherapy has limited benefit. Acute myeloid leukemia and acute lymphoblastic leukemia regimens, as well as regimens used in non-Hodgkin lymphoma have been used.[1]

D. Hematopoietic stem cell transplantation (HSCT) is required to enable long-term remissions — Correct. The aim of induction chemotherapy is to achieve remission and to act as a bridge to a HSCT. Overall 3-year survival of 41% following HSCT has been reported.[4] Tagraxofusp, a novel therapy recently approved in the treatment of BPDCN, has shown promising clinical responses. It is a cytotoxin consisting of recombinant human interleukin 3 (or CD123 receptor) fused to a truncated diphtheria toxin which targets CD123. Tagraxofusp is given by intravenous infusion at a dose of 7 to 12 micrograms per kilogram of body weight on day 1 to 5 of each 21 day cycle. As with traditional chemotherapy, it is given as a bridge to HSCT.[5] Unfortunately, despite an initial response to Tagraxofusp, our patient suffered a relapse prior to undergoing HSCT.

E. Relapse is unlikely following remission — Incorrect. The disease regularly relapses contributing to its poor prognosis.[2]

We thank the patient for consent to publication of their case details and images.

Abbreviations used:

BCL-2: B-cell lymphoma 2
BPDCN: blastic plasmacytoid dendritic cell neoplasm
CMML: chronic myelomonocytic leukemia
H&E: hematoxylin and eosin
HSCT: hematopoietic stem cell transplantation
TCL1: T-cell leukemia/lymphoma protein 1

Conflicts of interest

None disclosed.

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