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The Community Oncologist: Case Report

Plasmacytoid Dendritic Cell Leukemia: A Rapidly Evolving Disease Presenting with Skin Lesions Sensitive to Radiotherapy plus Hyperthermia

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ABSTRACT

Plasmacytoid dendritic cell leukemia (pDCL) is a rapidly evolving disease, which frequently presents with skin lesions, particularly nodules and plaques with a typical reddish-brown or brown color. Treatment of pDCL is based on multiagent chemotherapy followed by allogeneic hematopoietic stem cell transplant, but skin lesions may be refractory to therapy. Here, we report on a 61-year-old patient affected by pDCL who first presented with multiple cutaneous nodules and plaques on the trunk. Lesions showed an excellent response to radiotherapy plus hyperthermia. Although this treatment did not avoid the systemic evolution of disease, it resolved skin lesions and prevented their relapse, thus representing a therapeutic option to be used in combination with chemotherapy regimens. The case presentation is followed by a general discussion with an emphasis on the diagnosis and treatment of this rare malignancy. *The Oncologist* 2009;14:1205–1208

CASE PRESENTATION

A 61-year-old white man was referred with a diagnosis of acute monocytic leukemia cutis manifesting with a 3-month history of skin nodules. The patient presented with reddish-brown or brown multiple skin nodules and plaques up to 5 cm in diameter on the trunk and neck. Brown macules were also present on the upper trunk. Lesions were moderately itchy and painful. He had no systemic symptoms. Physical examination revealed axillary lymphadenopathies. Routine blood tests and a peripheral blood smear were negative. The bone marrow aspirate showed low-level involvement (20%) by medium/large-sized agranular blast cells present-

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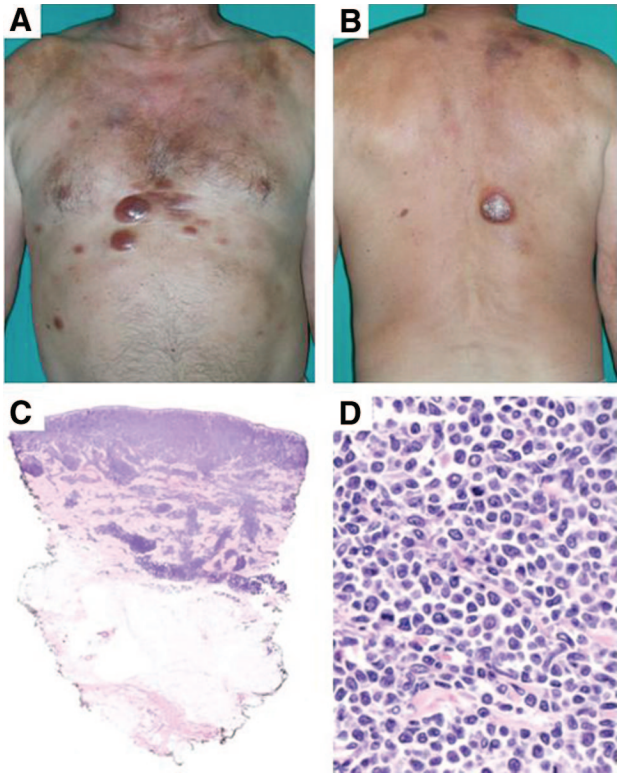

Figure 1. Clinical appearance and histological features of pDCL skin lesions at diagnosis. **(A, B):** Red-brownish nodules and plaques on the trunk. **(C):** Dense infiltration of the dermis with both diffuse and nodular patterns, extending into the s.c. fat and with a subepidermal Grenz zone (hematoxylin and eosin; original magnification, 4×). **(D):** Monomorphous infiltrate composed of atypical medium-to-large-sized cells with irregular nuclei (hematoxylin and eosin; original magnification, 400×).

ing, on flow cytometric analysis, the following immunophenotype: $CD4^+$, $CD56^+$, $CD123^+$, $HLA\text{-}DR^+$, MPO^-, $cCD3^-$, $cyCD79a^-$, and $CD11c^-$. Clonal rearrangement of T-cell receptor was excluded. A cytogenetic analysis was normal. Based on the reported data, the earlier diagnosis was changed to plasmacytoid dendritic cell leukemia (pDCL) and the patient was deemed suitable for allogeneic hematopoietic stem cell transplant (HSCT); hydroxyurea was initiated while waiting for a human leukocyte antigen (HLA)-matched donor. Two months later, as a result of a significant increase in the number and size of the cutaneous nodules (Fig. 1A, 1B), a new skin biopsy was performed, and histological examination revealed the presence of a monomorphous infiltrate with both a diffuse and nodular pattern composed of atypical medium-to-large-sized cells with irregular nuclei, fine chromatin, and evident nucleoli consistent with a blast-like morphology. Many mitotic figures were visible (Fig. 1C, 1D). Immunohistochemistry confirmed the hematodermic nature of the tumor, with the majority of cells being $CD4^+$, $CD56^+$, $TCL\text{-}1^+$, $CD3^-$,

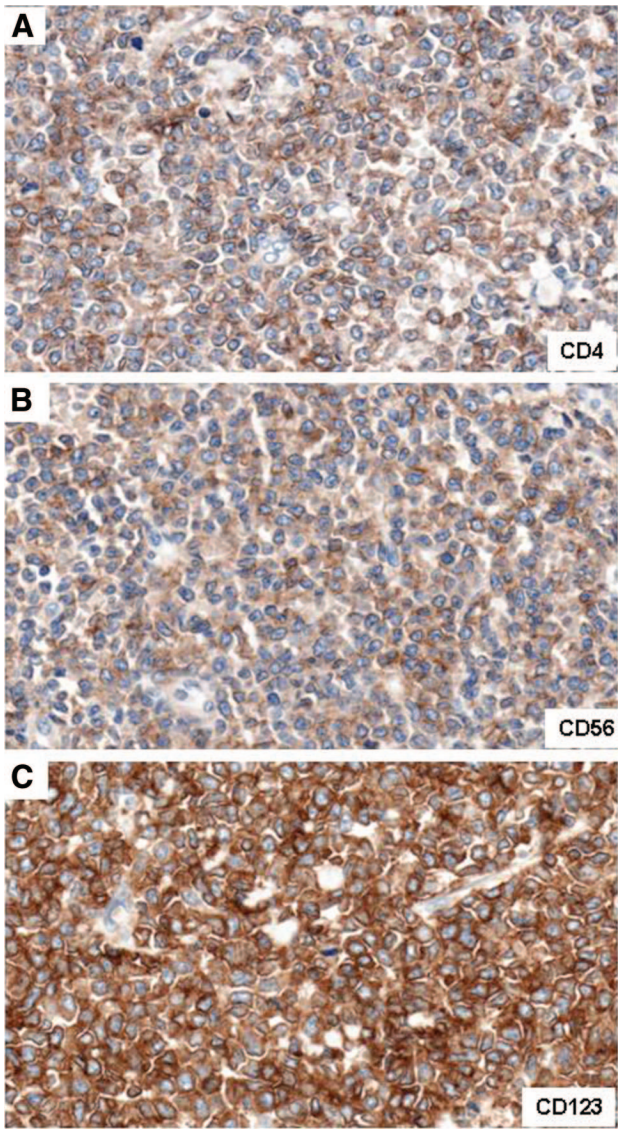

Figure 2. Neoplastic cells showing strong reactivity for CD4, CD56, and CD123 (original magnification, 400×).

$CD123^+$, $CD20^-$, and MPO^- (Fig. 2A–2C). At that time, a physical examination revealed axillary and inguinal lymphadenopathies and hepatomegaly. A hemochromocytometric analysis was still normal. To contain the cutaneous progression of disease, which was causing pain and severe discomfort, radiotherapy (RT) was performed with a total of 36 Gy administered in 18 fractionated doses, five fractions per week, using electrons with an energy of 6 MeV. RT was delivered in combination with superficial hyperthermia (HT), one fraction per week, using a 915-MHz microwave source (BSD 500; BSD Medical Corporation, Salt Lake City, Utah). The treatment achieved a remarkable and stable regression of the skin nodules as confirmed by a biopsy obtained from an irradiated nodule (Fig. 3A–3D). Shortly after the completion of RT, because of the onset of

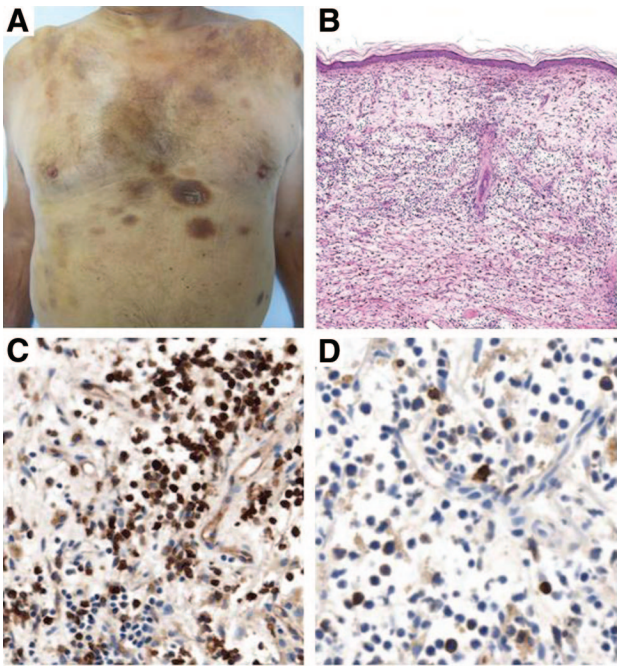

Figure 3. Clinical appearance and histological features of pDCL skin lesions following treatment. **(A):** Regression of skin lesions after radiotherapy plus hyperthermia. **(B):** Histology of an irradiated nodule showing a sparse infiltrate in the superficial dermis with numerous siderophages and edema (hematoxylin and eosin; original magnification, 100×). **(C, D):** Marked reduction in CD123 and CD56 cell numbers (original magnification, 300× and 400×).

severe asthenia, new tests were conducted. A hemochromocytometric analysis showed anemia and a low platelet count. A bone marrow aspirate and peripheral blood smear revealed 90% and 40% blast cells, respectively. A cytogenetic analysis showed a complex karyotype in 17 of 35 metaphase cells (48 XY, inv(7)(p13q34), +20, +21). Bone marrow biopsy revealed evidence of a significant infiltrate (50%) composed of $CD2^+$, $CD4^+$, $CD56^+$, and $TCL\text{-}1^+$ cells. Based on the evidence of disease progression, in the absence of an HLA-matched donor, the patient received cyclophosphamide, doxorubicin, vincristine, and prednisone (the CHOP regimen). After six cycles, no lymphadenopathies or hepatomegaly were documented on either physical examination or computed tomography. No new skin nodules were observed. Both morphological and flow cytometric analyses of the bone marrow aspirate and bone marrow biopsy were consistent with complete remission. Three months later, the patient was admitted to the emergency room with a severe headache, right eye visual impairment, dysphagia, vomiting, dizziness, and hypokinesia of the lower extremities. Cerebral magnetic resonance imaging was negative. Lumbar puncture presented evidence of an elevated opening pressure. Morphological and flow cytometric analyses of cerebrospinal fluid revealed the presence of several elements with the features of plasmacytoid dendritic blast cells. At that time, even the bone marrow and peripheral blood analyses showed evidence of relapsed disease, with 18% and 13% blasts, respectively. Physical examination revealed hepatomegaly in the absence of lymphadenopathies. On the skin, only brown macule remnants of previous lesions were present, but no new nodules or plaques. A high-dose methotrexate and cytarabine-containing regimen, comprising repeated intrathecal administration of the same agents, allowed the achievement of only transient neurological and hematological improvements. Four months later, the patient died from disease progression while in palliative care. His overall survival time was 12 months.

Diagnosis and Clinical Presentation

pDCL is a recently described entity characterized by the abnormal expansion of $CD4^+CD56^+$ cells expressing CD123, TL1-A, and HLA-DR and lacking conventional myeloid and lymphoid T- and B-cell antigens [1]. These elements, which also identify $CD4^+CD56^+$ hematodermic neoplasm (HDN) [2], have been indicated as the malignant counterpart of plasmacytoid dendritic cells [3]. Given the common origin and the nearly inevitable progression of $CD4^+CD56^+$ HDNs to overt leukemia, the alternative term $CD4^+CD56^+$ leukemia/lymphoma of dendritic cell precursor origin was recently suggested to describe both entities [4]. Other authors had previously proposed naming this malignancy $CD4^+CD56^+$ HDN when the diagnosis was made on a cutaneous biopsy specimen without a leukemic phase and $CD4^+CD56^+$ leukemia when the disease was diagnosed from blood workup of a leukemic phase [5]. In spite of the heterogeneous nomenclature used, the clinical presentation is quite constant. The majority of patients present with asymptomatic solitary or multiple skin lesions (particularly nodules and plaques) with a typical reddish-brown or brown color [6], and diagnosis often relies on skin histology coupled with immunohistochemistry [1, 4, 5]. The differential diagnosis includes skin localizations of myelomonocytic disorders, natural killer cell lineage tumors, and pleomorphic T-cell lymphomas [5]. Low-level bone-marrow involvement is often seen at presentation or soon after [1, 4, 6, 7]. Immunohistochemistry and flow cytometric analysis are essential tools for making the diagnosis and for evaluating new markers of disease; in particular, the adaptor protein CD2AP [8], BDCA-2 (CD303), and BDCA-4 (CD304) [1] were recently identified. Lymphadenopathy or splenomegaly or both are frequent. Cytogenetic analysis often shows a complex karyotype [1, 4, 5–7] or recurrent genomic aberrations combined with deletions of tumor suppressor genes [9]. The overall prognosis is dismal, with a

median overall survival duration of 12–14 months, irrespective of the initial pattern of disease [7].

Treatment

Although most cases of pDCL show an initial response to multiagent chemotherapy, relapses occur in the vast majority of patients after a median of 9–11 months, mostly affecting bone marrow, skin, and the central nervous system (CNS) [4, 5, 7]. Effective therapies have not been established yet, and to date allogeneic HSCT seems to be the only curative option [4, 7, 10]. Nonetheless, because the majority of patients are elderly, alternative therapeutic strategies must often be considered [10]. The frequent occurrence of CNS relapses suggests adopting, as induction treatment, intensive acute lymphoblastic leukemia-like regimens with intrathecal prophylaxis [7]. The use of RT has been only occasionally reported [5, 11, 12], mostly for the treatment of localized lesions or in the consolidation phase.

Conclusion

Here, we report on a patient affected by multiple cutaneous localizations of pDCL treated with RT plus HT. As described, this treatment did not avoid systemic evolution of the disease but did successfully resolve the skin lesions and prevent their relapse, thus suggesting that RT combined with HT may have a relevant role in the treatment and relapse prevention of skin lesions [13, 14], rather than merely symptom palliation. HT as an adjunct to RT has been a focus of interest in cancer management. Heat at temperatures of 42°C–43°C may be directly cytotoxic to tumor cells or inhibit repair of sublethal damage after radiation. Blood flow is often impaired in tumor relative to normal tissues, and HT may lead to a further increase in blood flow and augment heat sensitivity. At temperatures of 40°C–41°C (mild hyperthermia), HT can improve tumor oxygenation and increase the radiosensitivity of cancer cells [15]. Although, to the best of our knowledge, RT has been successfully used in only one additional case [6], our experience indicates that, in combination with HT, it may offer an effective and safe therapeutic option for skin lesions. Nonetheless, such treatment should be considered, whenever possible, in association with systemic interventions. In fact, according to the literature, even isolated cutaneous lesions should be treated early with intensive chemotherapy regimens (plus intrathecal prophylaxis) in order to avoid disease progression [7].

Author Contributions

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Supervision: Giampiero Girolomoni

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