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Myeloid Sarcoma of the Skin in a Patient with Myelodysplastic Syndrome

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ABSTRACT We report the case of a 76-year-old woman who presented with asymptomatic extensive erythematous. Firm plaques were noted over the right cheek. Complete blood count was normal, as was a peripheral smear. An excision biopsy taken from the cheek showed infiltration of the dermis and hypodermis with atypical cells which were strongly positive for human leukocyte antigen (HLA-DR) and lysozyme and were moderately myeloperoxidase (MPO) enzyme. The results of immunohistochemical staining for CD34, CD117, CD3, CD4, CD8, CD20, CD23, CD56, and ALK-1 were negative. Bone marrow analysis indicated myelodysplastic syndrome RAEB 1 while cytogenetic finding showed tetrasomy 8. It was recommended that the patient undergo local radiotherapy of skin lesions, but she refused and was lost to follow-up.

KEY WORDS: skin; myeloid sarcoma; myelodysplastic syndrome

INTRODUCTION

Myeloid sarcoma (MS), also known as granulocytic/monoblastic sarcoma, extramedullary myeloid tumor, myeloblastoma, or chloroma was first described in 1811 by Burns (1) It was subsequently further described by King as consisting of tumors with a predominant green color that resulted from the presence of myeloperoxidase (MPO) (2). In 1966, Rappaport proposed the term "granulocytic sarcoma" (3). Eventually, in 2002, the term myeloid sarcoma was accepted by the World Health Organization (WHO) (4). According to the new WHO classification of acute myeloid leukemia (AML) MS has been recognized as separate entity (5). MS is an extramedullary lesion composed of myeloid-lineage blasts that typically form tumorous masses and may precede, follow, or occur in the absence of systemic acute myeloid leukemia (AML) (4,6). The associated clinical symptoms are largely dependent on the site of involvement. On the skin, lesions most commonly involve the torso, although the head and neck regions and extremities are also involved in many cases. MS of the skin is reported in 3% of patients with AML and less frequently in those with chronic leukemia. The reported incidence of MS may be overestimated if biopsy is not performed because the skin lesions involved in MS have overlapping features with those of inflammatory, neoplastic, and infectious lesions (6). Other sites of isolated MS include bone, periosteum, lymph nodes, and soft tissues, as well as the orbit, intestine, mediastinum, and epidural region, and the uterus and ovary (7-9). Here, a patient with cutaneous MS is presented.

CASE REPORT

A 76-year-old woman with a past medical history of hypertension presented with several asymptom-

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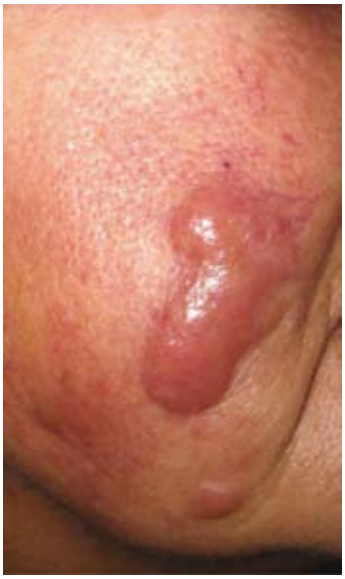

Figure 1. Erythematous, firm plaques over the right cheek.

atic facial red, plaque-like lesions on the right cheek (Figure 1) that had appeared 6 months before referral to our Department. These lesions started as multiple non-tender nodules that initially resolved spontaneously with scarring but subsequently recurred and progressed. Clinically, extensive erythematous, firm plaques were noted over the right cheek with no lymphadenopathy. Complete blood count was normal, as was a peripheral smear. An excision biopsy taken from the cheek showed infiltration of the dermis and hypodermis with atypical cells with abundant eosinophilic cytoplasm and large, oval, or cleaved nuclei (Figure 2). Immunohistochemical staining showed that the atypical cells were moderately positive for human leukocyte antigen (HLA-DR) (Figure 3, a) and myeloperoxidase (MPO) and strongly positive for lysozyme (Figure 3, b). The results of immunohistochemical staining for CD34, CD117, CD3, CD4, CD8, CD20, CD23, CD56, and ALK-1 were negative. Flow cytometry of the bone marrow showed blasts with a

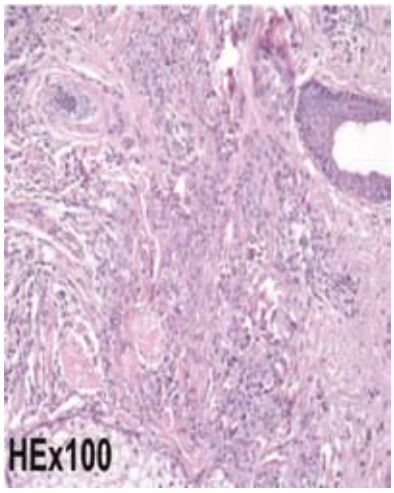

Figure 2. Infiltration of the dermis and hypodermis; hematoxylin and eosin ×100.

high expression of HLA-DR and CD117 present at 6%. Cytogenetics of the bone marrow aspirate revealed tetrasomy 8 (Figure 4). Finally, myelodysplastic syndrome (MDS) refractory anemia with excess blasts (RAEB-1) (International Prognostic Scoring System [IPSS] score 1.5, intermediate risk) (10) with MS was diagnosed. It was recommended that the patient undergo local radiotherapy of skin lesions, but she refused and was lost to follow-up.

DISCUSSION

MS usually occurs in patients with active AML or in patients with chronic myeloproliferative disease (MPD), in which it may occur as the first manifestation of blast transformation, AML relapse in previously treated patients, or in isolated MS in patients without bone marrow infiltration. It is rare for MS to be reported in patients with MDS. According to the WHO classification, MS is a separate entity from AML. In our patient with MDS, it could be speculated that a malignant myeloid clone of MDS (RAEB-1) evolved in subclone of MS clinically presented as cutaneous

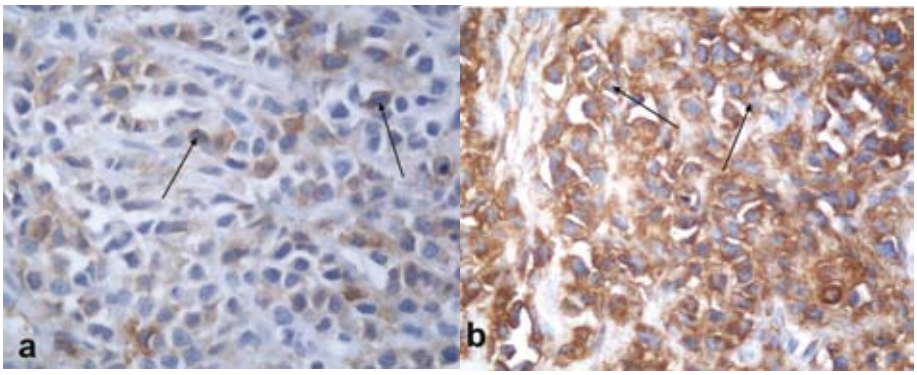

Figure 3. a, b: Tumor cells were positive for human leukocyte antigen (HLA-DR) and lysoyzyme.

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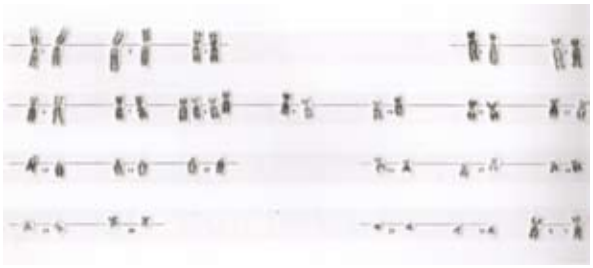

Figure 4. Karyogram: tetrasomy 8.

infiltration. In such cases the diagnosis is MS-AML. Cutaneous MS is often challenging to diagnose. In addition to clinical and histopathological findings, immunohistochemical studies are particularly important to distinguish MS from other hematological and non-hematological diseases. Myeloid cell markers include MPO, chloroacetate esterase, lysozyme, and CD43, and their presence may vary with the degree of tumor differentiation. The most sensitive myeloid markers are lysozyme and CD43, which produce positive staining in most tumor cells in both well-differentiated and poorly differentiated MS. As demonstrated in this patient, other immunohistochemical markers useful for diagnosis include CD56, CD68, and CD117, which are frequently positive in MS (4,6,11-13).

In our case it was difficult to differentiate MS from blastic plasmacytoid dendritic cell neoplasm (BPDNC), another new entity of AML. Patients with BPDNC also usually present with asymptomatic solitary or multiple skin lesions that can be nodules or plaques. In addition, peripheral blood and bone marrow involvement can be minimal at presentation in these patients. Furthermore, 10-20% of patients with BPDCN develop AML, which can evolve from the underlying myelodysplasia (14). In our patient, myelodysplastic changes were confirmed, but cutaneous and marrow infiltrate cells were negative for CD56 and CD123 that are usually positive in BPDCN. The alternative differential diagnoses of extranodal NK/T cell lymphoma and mature T cell neoplasms were eliminated because the cells were negative for CD4 and ALK-1 staining (13,14). In line with our findings, published data indicate a wide spectrum of antibodies should be employed during immunohistochemical work-up of tumor tissue in cases of suspected MS. Correlation with past medical history is particularly important, because many patients have a concurrent hematological malignancy.

Tetrasomy, pentasomy, and hexasomy of chromosome 8 (polysomy 8) are relatively rare compared to trisomy 8, which is one of the most common recurring aberrations in myeloid hematologic malignancies. Two non-exclusive hypotheses have been proposed describing the mechanisms of tetrasomy 8 formation. The tetrasomic clone could be the result of a stepwise evolution from disomy to tetrasomy through an intermediate stage of +8 by 2 consecutive mitotic nondisjunctions or, alternatively, as a result of simultaneous nondisjunction of both homologs during a single cell division (15). Beyer et al [15] described a group of 117 patients with myeloid hematologic malignancies and polysomy 8. In this group, AML was diagnosed in 92 patients (83 tetrasomies, 8 pentasomies, and 1 hexasomy), MDS in 17 (12 tetrasomies, 4 pentasomies, and 1 hexasomy), and MPD in 8 (all tetrasomies). They designated polysomy 8 syndrome as a new clinical entity, representing a subtype of AML, MDS, and MPD and characterized by a high incidence of secondary diseases, myelomonocytic or monocytic involvement in AML, poor response to chemotherapy, and poor overall survival (6 months). It is interesting that as a group, patients with polysomy 8 were more likely to be elderly (especially those with MDS) and to present with skin infiltration. Polysomy 8 appears to constitute an adverse prognostic feature for survival of patients with AML, MDS, or MPD. However, the prognostic value of polysomy 8 diagnosis in our patient is questionable because the number of MDS patients with similar clinical findings is too small for any conclusion to be drawn.

The pathogenesis of skin invasion by leukemic cells has not yet been elucidated. However, it has been hypothesized that a predilection for cutaneous homing is directed by the presence of cell surface proteins such as blast neural cell adhesion molecules (CD56) and similar chemokine receptors that are shared by leukemic cells and normal memory T cells, both of which home to the skin. In our case, staining for CD56 was negative, but we did not analyze cutaneous lymphocyte antigen (CLA). CLA, which interacts with E-selectin and is also involved in T-cell homing to the skin, was found to be elevated in a small series of patients with acute myelomonocytic leukemia, a subset of AML. Presence of lymphocyte function-associated antigen-1, which interacts with endothelial intercellular adhesion molecule-1, could also explain the tropism of leukemic cells to the skin. Certain therapies, including all-trans retinoic acid, may change the expression of these cell adhesion molecules and facilitate the departure of these cells from the marrow and circulation to extramedullary sites (6,16).

The optimal treatment of patient with and MS has not been established thus far, since studies published to date have involved only small numbers of patients (8,17). According to WHO classification, MS should be treated as AML. The intensity of therapy depends on patient age and co-morbidities. For our patient we

suggest radioterapy, because bone marrow findings in the patient corresponded to MDS RAEB-1, as well as due to intermediate risk, only one local mass of MS, and patient age over 70.

CONSLUSION

In cases of diffuse cutaneous disease or in aggressive MDS, a systematic approach could be more appropriate because leukemic cells in the marrow will continue to reseed the skin if they are not eradicated. In such patients, radiotherapy can be added simply for rapid symptomatic relief of lesion-associated pain and pruritus. Identification of the underlying molecular basis for the migration of leukemia cells to specific sites will be critical in developing novel therapies.

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