GRANULOCYTIC SARCOMA FOLLOWING ACUTE MYELOGENOUS LEUKEMIA TYPE FAB-M5 ASSOCIATED WITH t(6;12) INVOLVING A REARRANGEMENT OF THE ETV6 LOCUS

RÉSUMÉ • Contexte : La leucémie myéloïde aiguë est un cancer qui affecte les cellules myéloïdes. Beaucoup de complications sont dues à cette condition, dont le sarcome granulocytaire. Dans le présent rapport les anomalies cutanées chez une patiente atteinte d’une leucémie myéloïde aiguë sont analysées. Description du cas : Un examen de la peau et une cytoponction des nodules comparées aux résultats d’une biopsie antérieure de la moelle osseuse confirment le diagnostic d’un sarcome granulocytaire. Une analyse cytogénétique révèle la présence de t(6;12) impliquant un réarrangement du locus ETV6. Conclusions : C’est l’unique cas de sarcome granulocytaire dû à une leucémie myéloïde type 5 avec t(6;12) impliquant un réarrangement du locus ETV6 rapporté dans la littérature. Il faut prendre plusieurs précautions pour établir ce diagnostic. Une combinaison de chimiothérapie systémique et thérapie de faisceau d’électrons ou PUVA pour traiter les lésions de leucémie cutanée résistantes à la chimiothérapie est nécessaire.

INTRODUCTION

Acute myelogenous leukemia (AML) is a cancer that affects myeloid cells. Several complications occur due to acute myelogenous leukemia of which is granulocytic sarcoma. This case report discusses the analysis of skin abnormalities in an acute myelogenous leukemia patient. Case description: Skin examination and fine needle aspiration of the nodules in comparison with previous bone marrow biopsy confirmed the diagnosis of myeloid sarcoma. Cytogenetic analysis showed t(6;12) involving a rearrangement of the ETV6 locus. Conclusions: This is a unique report of a case of granulocytic sarcoma following acute myelogenous leukemia type 5 with t(6;12) involving a rearrangement of the ETV6 locus. Several precautions should be made in diagnosing such conditions. A combination of systemic chemotherapy and local electron-beam therapy or PUVA to treat chemotherapy resistant leukemia cutis lesions is needed.

Keywords: acute myelogenous leukemia, leukemia cutis, granulocytic sarcoma, rearrangement

CASE DESCRIPTION

A 45-year-old woman with a history of dysmenorrhea, iron-deficiency anemia, and uterine leiomyomas status post total abdominal hysterectomy in July 2005, was diagnosed with M5 acute myelogenous leukemia (AML) in August of 2006, following weeks of fatigue and upper respiratory symptoms.

She had a difficult course with 7+3 daunorubicin and Ara-C induction chemotherapy including cardiomyopathy, enterococcal pneumonitis, and mucositis and furthermore failed to enter complete remission.

She presented for a second induction regimen in hopes of achieving remission and subsequently undergoing allogeneic hematopoetic stem cell transplant.

At this admission, she had several physical complaints, most notably large and extremely tender subcutaneous skin nodules over the anteromedial aspects of her arms and inferior neck consistent with prior veno-puncture sites. The patient reported that they primarily arose over a 48-hour period earlier that week. In addition, she had less tender, raised, discolored nodules on the dorsal aspect of her hands that had been present for a week to ten days (Figure 1.a)

Her skin exam revealed the following:

1) Fixed, raised, mildly tender 2 x 2 cm grey-brown lesions on the dorsum of the hands bilaterally, consistent with previous venopuncture sites.

2) Large, extremely tender multinodular subcutaneous lesions on the anteromedial arm from the elbow to the mid-humerus bilaterally and overlying the carotid sheaths on the inferior aspect of the neck bilaterally. These tender nodules were 2-3 cm in size and variably mobile.

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3) Small 1 x 1 cm palpable subcutaneous mildly tender, mobile nodules with no overlying discoloration on the left medial thigh, left anterior mid-forearm, and overlying the adductor pollicis dorsally. Mild bilateral medial ankle bruising, left forearm bruising, and bruising at IV sites bilaterally. Small dark spots were present on the dorsum of the feet.

To examine these nodules a fine needle aspiration of a subcutaneous nodule on the anteromedial arm was performed. Cytogenetic analysis including FISH (fluorescent in situ hybridization) was also performed.

**DISCUSSION**

The fine needle aspiration showed a loosely cohesive monomorphic population of medium-sized cells with scant cytoplasm (Figure 1.b). The nuclear features included coarse chromatin, small nucleoli, irregular folded nuclear membranes, and multilobated forms. More mature myeloid cells could also be found admixed with this population. By morphology alone, the findings were consistent with a hematopoietic neoplasm and suspicious for myeloid sarcoma [3-5].

Without the patient’s clinical history of AML, additional studies to narrow the differential could be used. With enough material obtained by aspiration, ancillary studies to confirm the diagnosis would include the demonstration of myeloperoxidase and/or lysozyme staining and flow, or immunohistochemistry studies [6,7]. In this case, comparison of the aspiration with the patient’s prior bone marrow biopsy revealed a similar population of cells by morphology, supporting a diagnosis of myeloid sarcoma (Figure 1.c).

The WHO defines three types of granulocytic sarcomas: blastic, immature and differentiated [6]. Depending on the differentiation of the myeloid cells, cytoplasmic granules, or occasionally, Auer rods may be appreciated. In this case, the tumor was immature, although this differentiation is not clinically relevant [8]. The patient’s cytogenetic analysis, including FISH, showed t(6;12) involving a rearrangement of the ETV6 locus.

Leukemia cutis is a localized or disseminated skin infiltration of leukemic cells. It is usually a sign of systemic disease dissemination or the relapse of an existing leukemia [9]. It can manifest at any age, but is more common in people over 50 years old. It has no sex preference although it has been reported more with males. The incidence varies depending on the type of leukemia.

Leukemia cutis has been reported in both acute and chronic leukemia, in the leukemic phase of non-Hodgkin’s disease, as well as hairy cell leukemia [9]. It has also been reported in cases of aleukemic leukemia (acute leukemia...
confined to the skin) [10], as well as a result of chemotherapy and/or radiotherapy for other malignancies such as breast adenocarcinoma [11] and non-Hodgkin’s lymphoma.

Granulocytic sarcoma represents extramedullary myeloid tumor [9,12]. The characteristic green appearance of the tissue is due to the presence of the enzyme myeloperoxidase, prompting a synonymous name, chloroma [10,13]. It can involve multiple sites, including bone, lymph nodes and skin and most commonly presents concurrently with hematopoietic disease (AML, CML, MDS) [11]. It may be the initial manifestation of leukemic disease, sometimes preceding the diagnosis by years. The incidence of granulocytic sarcoma in patients with AML is 3-5% [14]. Cytopathologic analysis of AML patients with granulocytic sarcoma have rarely been re-reported in the literature. However, it appears that patients with t(8;21)-associated AML type 2 are more prone than others to develop granulocytic sarcoma. Indeed, 4.5-38% of patients with t(8;21)(q22)x22) developed granulocytic sarcoma [15,16]. Therefore, to the best of our knowledge, this is the first report of a case of granulocytic sarcoma following AML type 5 with t(6;12) involving a rearrangement of the ETV6 locus.

On physical examination, the pattern of presentation is variable and may overlap with other inflammatory eruptions. The most common lesions are small papules (2-5 mm), nodules, or plaques. Leukemia cutis lesions are always palpable, indurated, firm, psoriasiform, or lymphomatoid papulosis-like lesions, but usually are not tender. These lesions are commonly more pink or darker than normal skin [5]. They may be localized or disseminated and can be hemorrhagic when associated with thrombocytopenia. Similar lesions’ morphologies occur with different types of leukemia [5].

It is most important to differentiate leukemia cutis from disseminated infections in immunocompromised or neutropenic patients, especially in cases of bacterial sepsis like Staphylococcus aureus, Pseudomonas aeruginosa, fungemia such as Candida and Aspergillus, and viral infections like herpes simplex and varicella zoster. It is also important to rule out neutrophilic dermatosis such as Sweet’s syndrome and pyoderma gangrenosum, as well as adverse cutaneous drug reactions, transfusion-associated graft versus host disease, vasculitis, and erythema multiforme.

Hematologic studies with complete analysis of the bone marrow aspirate, peripheral blood smear, cutaneous histology and immunophenotyping are needed to make the diagnosis. A careful assessment of the peripheral blood smear and bone marrow aspirate should be made if cutaneous findings precede any systemic manifestations. Leukemic cells are usually present in the peripheral blood smear, except for aleukemic leukemia cases. Bone marrow aspirate confirms the diagnosis and defines the type. Touch preparation from a skin biopsy along with clinical findings might be sufficient for rapid diagnosis of leukemia cutis.

Prognosis is directly related to the systemic disease, except for the cases of therapy-induced leukemia cutis, which might carry a worse prognosis. For patients with underlying myelodysplastic syndrome or myeloproliferative disease, the development of granulocytic sarcoma represents blast transformation [6].

Therapy is usually directed towards the leukemia itself. In some cases this might not treat the cutaneous lesions effectively, thus warranting a combination of systemic chemotherapy and local electron-beam therapy or PUVA (for chemotherapy resistant LC lesions). Certain attention should be made toward the therapy-related aleukemic leukemia cutis, as it is an aggressive disorder resistant to conventional antineoplastic treatment approaches.

REFERENCES