

LEUKEMIA CUTIS IN A PATIENT WITH ACUTE PROMYELOCYTIC LEUKEMIA – CASE REPORT

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Summary

Introduction. Leukemia cutis is a rare cutaneous leukemia-specific manifestation and is characterized by infiltrates with paraneoplastic leukocytes or their precursors located in the dermis, subcutaneous tissue, cutaneous annexes and blood vessels. Several terms have been used to describe the various leukemia cutis manifestations in acute myeloblastic leukemia: the granulocytic sarcoma, the monocytic sarcoma, primary extramedullary leukemia and the chloroma.

Clinical case. A 65-year old man from the urban area under evidence of the Hematology Department since August 2018 for acute promyelocytic leukemia (AML-M3 in the FAB classification) was consulted in the Craiova Dermatology Department in January 2019 for several nodular tumor masses that were firm, reddish, of 0.2-2 cm, well defined, located in the left inguinal, lumbar, anterior thorax and scalp areas. The tumor masses appeared 3 weeks ago. The patient received remission induction therapy with cytarabine, idarubicin and all-trans retinoic acid (ATRA), obtaining complete remission (blasts 2-3%), then he continued with consolidation treatment with cytarabine, epirubicin and ATRA. The histopathological aspect and the immunohistochemical staining are compatible with a myeloid sarcoma (extramedullary determination of acute myeloblastic leukemia). The immunophenotyping from marrow aspirate, repeated in the Hematology Department in February 2019 suggested a diagnosis of acute promyelocytic leukemia with positive residual disease which means a relapse. The cutaneous lesions have regressed after hematologic retreatment, with some leftover pigmented spots on the torso. The patient is currently under treatment with cytarabine.

Discussions. The incidence of cutis leukemia depends on the type of leukemia, with a frequency of 2-18% of cases in acute myeloblastic leukemia. The physiopathology that underlies the leukemic cell migration to the skin is not clear. Most cases of leukemia cutis in acute promyelocytic leukemia that were described in literature were associated with the use of ATRA, that is associated with a high incidence of extramedullary diseases as relapse after complete remission. There is the possibility that ATRA and anthracyclines may not reach the places where extra-medullary infiltrates occur. Clinically, LC can look like erythematous papules or nodules in 60% of cases. Because of the unspecific clinical aspect of the skin lesions, the cutaneous biopsy and the bone marrow biopsy are necessary for establishing the diagnosis. The prognosis of patients with LC is unfavorable, many also having other extramedullary presentations of leukemia. The treatment of leukemia cutis involves the treatment of the underlying disease.

Conclusions. Leukemia cutis is a skin marker of hematologic malignant disease but it is a rare manifestation in acute promyelocytic leukemia. Treatment with ATRA can induce leukemia cutis occurrence. The correct diagnosis of leukemia cutis creates the prerequisites for diagnosing the systemic disease and highlights the leukemia relapse, similar to our case.

Keywords. leukemia cutis, acute promyelocytic leukemia, diagnosis.

Received: 18.05.2019

Accepted: 7.06.2019

Introduction

Approximately 30–40% of patients with leukemia have a variety of unspecific cutaneous signs, including those related to bleeding, infections and eruptions due to the used cytostatic

agents as well as paraneoplastic lesions (leukemids). The specific skin signs of leukemia (leukemia cutis) are less frequent and they constitute infiltrates with paraneoplastic leukocytes or their precursors located in the dermis,

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subcutaneous tissue, cutaneous annexes and blood vessels.[1]

Several terms have been used to describe the various leukemia cutis manifestations in acute myeloblastic leukemia: the granulocytic sarcoma, the monocytic sarcoma, primary extramedullary leukemia and the chloroma. [2]

Case report

A 65-year old man from the urban area under evidence of the Hematology Department since August 2018 for acute promyelocytic leukemia was consulted in the Craiova Dermatology Department in January 2019 for several nodular tumor masses that were firm, reddish, of 0.2–2 cm, well defined, located in the left inguinal (Fig. 1), lumbar, anterior thorax (Fig. 2) and scalp areas (Fig. 3).

Past medical history: Acute promyelocytic leukemia diagnosed in August 2018; Mild left ventricular failure; Primary hypertension stage II.

Physical examination: Phototype II, normo-ponderal, pale skin and mucous membranes, scalp alopecia, liver with the lower margin 2 cm below the right costal margin.



Figure 1 – Leukemia cutis, lesions on the inguinal area

Disease history: the tumor masses appeared 3 weeks beforehand, first in the inguinal region. The patient was diagnosed with acute promyelocytic leukemia (AML-M3 in the FAB classification) in August 2018. He received remission induction therapy with cytarabine, idarubicin and all-trans retinoic acid (ATRA), obtaining complete remission (blasts 2-3%), then he continued with consolidation treatment with cytarabine, epirubicin and ATRA, in total 5 treatments.

The immunophenotyping from marrow aspirate (September 2018) describes 58% myeloid line CD45 precursor cells, the immunophenotype being compatible with the atypical promyelocyte; no co-expression of CD2 or CD56; CD33, CD13, CD64, CD117, CD9, MPO positive which are myeloid line markers. The FLT3-ITD (bad prognosis) and the NMP1 (good prognosis) mutations are absent.

mRNA Fusion detection test: PML-RAR alpha, t(15;17) (q24;q21) present – transcript bcr3, reference gene present.

We have excised a group of lesions from the lumbar region (Fig. 4) and the histopathological report showed: skin fragment with malignant tumor proliferation that is diffuse, compact, with medium cells, rounded and vesicular nucleus, barely visible nucleoli (blastic aspect), located in



Figure 2 – Leukemia cutis, lesions on the trunk



Figure 3 – Leukemia cutis, lesions on the scalp



Figure 4 – Clinical aspect after the excision of a group of lesions from the lumbar region for the histopathological examination

the dermis and hypodermis (with focal extension in the subcutaneous adipose).

Immunohistochemistry: tumor proliferation is of myeloid type, diffusely positive for MPO and for CD33 and it expresses CD34+ in isolated cells (1-2%)

The histopathological aspect and the immunohistochemical staining are compatible with a **myeloid sarcoma** (extramedullary determination of AML).

The immunophenotyping from marrow aspirate, repeated in the Hematology Department in February 2019, describes the presence of 24% precursor cells with an immunophenotype of atypical promyelocyte, with aberrant co-expression of CD9, and 13% monocytes. The results suggest a diagnosis of APL with positive residual disease which means a relapse.

The cutaneous lesions have regressed after hematologic retreatment, with some leftover pigmented spots on the torso. The patient is currently under treatment with cytarabine.

Discussions

Acute leukemia (AL) is a heterogeneous group of neoplastic diseases affecting the hematopoietic stem cells and cells that are partially directed to a certain cellular series, with stopping in an early stage of differentiation and clonal proliferation with immature cells (blasts) in the bone marrow and the extramedullary sites.

Blast cell proliferation results in the suppression of normal clones and the occurrence of the bone marrow failure syndrome, clinically expressed by anemia, infections and bleeding.

According to the cell of origin, AL is divided in two main categories: myeloid AL (AML) that results from the malignant transformation of the myeloid stem cell or its myeloid progenitor cells and lymphoblastic AL (ALL) that results from the malignant transformation of the lymphoid stem cell.

Confirming the diagnosis in AML is done according to the following tests: the bone marrow morphologic examination with the presence of at

least 20% atypical blasts and the dislocation of normal bone marrow; the peripheral blood examination (20% blasts being present); immunophenotyping and the molecular cytogenetic examination that specifies the type of leukemia. Patients that show recurrent genetic clonal anomalies such as t(8;21), t(15;17), inv(16), t(16;16) must be considered as having AML no matter the percentage of blasts.

Acute promyelocytic leukemia (APL) is the AML-M3 type under the FAB classification. This type of leukemia has the t(15;17) translocation, forming PML-RAR alpha, a fusion protein. Because of its peculiar biology, APL responds to treatment with ATRA, a reversing agent that induces the differentiation of leukemic promyelocytes into mature granulocytes. Yet, ATRA by itself doesn't lead to remission which is why it is associated with anthracyclines (idarubicin) during induction therapy or the association of ATRA, anthracycline and cytarabine may be used in high-risk cases. [3]

The FAB (French-American-British) classification of AML:

- M1 acute myeloblastic leukemia (no maturation) – the myeloblast cells prevail, promyelocytes are less than 3%;
- M2 acute myeloblastic leukemia (with signs of maturation) – myeloblast cells, promyelocytes >3%; t(8;21) is present;
- M3 acute promyelocytic leukemia – blast cells of promyelocyte type with cytoplasmic granulation >30%; t(15;17) translocation is present;
- M4 acute myelomonocytic leukemia – myeloblast cells > 20% and monoblast cells > 20%;
- M5a acute monocytic leukemia – blast cells without maturation, promonocytes/monocytes < 3%; monocytic M5b - blast cells with signs of maturation, promonocytes/ monocytes > 3%;
- M6 erythroleukemia – erythrokaryocytes > 30% and > 10% erythroblasts with many anomalies;
- M7 acute megakaryoblastic leukemia – megakaryoblast and micromegakaryocyte cells prevail, it can be associated with acute myelofibrosis;

- M0 undifferentiated acute leukemia - can be identified according to cytochemical criteria.[4]

According to this classification, our case has been set as AML-M3 subtype.

The myeloid sarcoma (the granulocytic sarcoma, chloroma, primary extramedullary tumor) is a rare extramedullary manifestation of AML comprised of malignant cells that are derived from the myeloid cells. The term of chloroma has been suggested by the greenish aspect due to myeloperoxidase production. The most frequent locations of the myeloid sarcoma include the skin, the lymph nodes, the testicles, the intestine.[5]

The cutaneous manifestation of granulocytic sarcoma is known as *leukemia cutis* (LC).

LC occurs in AML in 2–18% of cases. The incidence of LC is attributed to 25–30% of children with congenital leukemia. Unlike adults, the presence of LC in children doesn't worsen the prognosis.[6]

In most cases of LC, the systemic disease precedes the skin lesions (50–77%) or they occur simultaneously (23–38%). Yet in 7% of patients, the cutaneous manifestations occur before the bone marrow infiltration and before the systemic symptomatology (aleukemic leukemia or primary extramedullary leukemia).[7]

In a study since 1969–1986, LC was present in 18 out of 877 patients (2%) with AML. The FAB types included M2 (4 cases), M3 (1 case), M4 (10 cases) and M5 (3 cases). extramedullary locations at the skin level were present in 16 patients, including meningeal involvement in 6 cases. Two patients had LC before the leukemia diagnosis and the skin was the initial relapse location in 11 patients. Most patients were treated by palliative radiotherapy and/or chemotherapy. The prognosis was unfavorable with recurring relapses in the bone marrow and the skin. [8]

The pathogeny of leukemia cutis

The physiopathology that underlies the leukemic cell migration to the skin is not clear. Chemokines, integrin and adhesion molecules (ICAM-1) can play a role in the specific location of the leukemic cells. The expression of the CD56 molecule on the leukemic blast cells has been associated with extramedullary disease in AL in

patients with t(8;21). The role of this surface glycoprotein in the cell-cell or cell-matrix adhesion is taken into consideration. [9] Its role has also been supported by the constant skin involvement in the CD56+ cutaneous lymphomas.[10]

A study on 18 cases (patients with AML and LC) proved the presence of CLA (cutaneous lymphocyte-associated antigen) in 14 patients (78%).

Moreover, some authors noticed leukemic infiltrates in preexisting inflammatory lesions and cutaneous malignancies, suggesting that some chemotactic mechanisms may be involved. [11]

Up to 30-50% of patients with AML-M4 or M5 develop LC. Karyotype studies of the leukemic cells proved the presence of t(8;21) in these AML subtypes.

Other research studies have shown strong association between chromosome 8 aneuploidy and the presence of LC, but also with the presence of other cytogenetic anomalies such as chromosome 3 translocations, t(6;9). Chloromas are associated with t(8;21), t(9;11), inv(16).

The identification of the proteins coded by specific genes localized on these chromosomes may help in defining the responsible factors for developing LC.

Certain factors that may favor the occurrence of LC are taken into consideration. Thus, the use of ATRA in treating APL may predispose to an increased risk of extramedullary involvement, including LC, which is otherwise rare in APL.[12] LC that precedes a diagnosis of acute systemic leukemia in patients treated with chemotherapy for breast cancer has also been described.[13]

Most cases of LC in APL that were described in literature were associated with the use of ATRA, that is associated with a high incidence of extramedullary diseases as relapse after complete remission. There is the possibility that ATRA and anthracyclines may not reach the places where extramedullary infiltrates occur. We also recall that the intensity of chemotherapy is often reduced after ATRA treatment initiation and its biologic characteristics may favor relapsing. In addition to inducing differentiation in promyelocytes, ATRA can modify the expression of adhesion molecules, increasing the capacity of

leukemic cells to migrate to other tissues and may also promote the proliferation of keratinocytes, increasing the possibility of skin recurrence.

In 1994, Sergio Giralt et al. described 3 cases of APL treated with ATRA, that showed LC during relapse (2 men of 25 years, 35 respectively and a 45-year old woman). The men had nodules and the woman plaques.[14]

In 2012 a paper has been published that described a case of LC in a 46-year old man that showed a herpes zoster-like eruption and history of fever and fatigue for 2 weeks and who was later on diagnosed with APL, the patient died 2 weeks after therapy induction.[15]

Clinical aspects of leukemia cutis

Clinically, LC can look like erythematous papules or nodules in 60% of cases. The lesions are most frequently localized on the head, neck, torso and on traumatized areas or on scars (catheter areas, burns, decubitus ulcers, post herpes zoster scars, recent puncture areas). Cases of diffuse skin involvement have also been described. Lesions are purple, reddish or they can be of normal skin color.

Gingival hypertrophy by leukemic infiltration is found in 50% of cases of AML M4 and M5. [6,16] In AML, LC can also manifest itself as leonine facies.[17]

Other very rare and unspecific skin manifestations are: erythema nodosum, erythema annulare centrifugum, pyoderma gangrenosum, urticaria pigmentosa, guttate psoriasis, chronic paronychia, macular erythema. [18,19,20] In a patient with AML, LC took on the aspect of a Mary Joseph nodule.[21]

Positive diagnosis

In most patients the anamnesis includes leukemia. In those without leukemia medical history, finding the symptoms of the systemic disease is extremely important.

Because of the unspecific clinical aspect of the skin lesions, the cutaneous biopsy (the histopathological, immunohistochemical report) and the bone marrow biopsy are necessary for establishing the diagnosis.

The histopathological report has the following peculiarities:

- it differs depending on the type of leukemia;

- the epidermal involvement is absent or limited;
- in the dermis, nodular or diffuse infiltrate with leukemic cells, prevailing in the perivascular and periadnexal areas;
- the leukemic cells often infiltrate among the collagen fibers (in the reticular dermis), in the subcutaneous fat (along septate fibers) and in the blood vessel lamina (by infiltrating the wall leading to leukemic vasculitis);
- cells in AML are large with an oval, vesicular nucleus and basophilic cytoplasm. [22, 23]

Immunohistochemistry shows positive aspects for: lysozyme, MPO, CD34, CD33, CD68, CD15, CD117, CD56, CD43, CD14, CD3 and CD4, CD20.[5]

Differential diagnosis

LC must be differentiated from: cutaneous B-cell lymphoma, Non-Hodgkin lymphoma, pseudolymphoma, skin metastases of visceral cancers, the Sweet syndrome, urticarial vasculitis, post medication eruptions, pyoderma gangrenosum, neutrophilic hidradenitis.[24]

The prognosis of patients with LC is unfavorable, many also having other extramedullary presentations of leukemia.

Several studies show an aggressive evolution of the disease in patients with LC and brief survival. The survival rate at 2 years for patients with AML without LC is 30% and in AML with LC it is only 6%.[25]

Even patients with aleukemic leukemia progress toward systemic disease so for cases with LC, systemic treatment is needed fast.[23]

A study done by Baer shows that out of 18 patients with AML that had LC, 90% also had other extramedullary sites of involvement and in 40% of these, the meninges were involved.[26]

In a study (Shaikh et al.) on 5 patients with AML, all 5 deceased in 6 months after LC being diagnosed.[27]

Two cases are mentioned in medical literature where LC was a first sign of myelodysplastic syndrome transformation into AML.[28]

The treatment of leukemia cutis

LC is a local manifestation of an underlying systemic disease. Therefore, systemic chemotherapy must be administered. As regards aleukemic LC, since these patients have an unfavorable prognosis, treatment for leukemic clone eradication by using systemic chemotherapy and stem cell transplant after remission are recommended.

The treatment must be chosen depending on the type of leukemia and the patient's capacity to tolerate a certain combination of drugs.

Local treatment as electron beam therapy can be used in certain situations such as resistant or recurrent skin disease. Yet in most cases, reinduction systemic chemotherapy must be added. The collaboration between the hematologist, the oncologist and the dermatologist is necessary.[29]

Sorafenib, a tyrosine kinase inhibitor, proved efficient in treating LC in a patient with AML and with the FLT3+ mutation. Besides, sorafenib proved efficient in suppressing leukemic cells in mice with myeloid leukemia and with the FLT3 mutation.[30]

Conclusion

Leukemia cutis is a skin marker of hematologic malignant disease but it is a rare manifestation in acute promyelocytic leukemia.

Treatment with ATRA can induce leukemia cutis occurrence.

The correct diagnosis of leukemia cutis creates the prerequisites for diagnosing the systemic disease and highlights the leukemia relapse, similar to our case.

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Conflict of interest
NONE DECLARED

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