Leukemia cutis presenting as localized cutaneous hyperpigmentation

The usual clinical presentations of leukemia cutis include solitary infiltrated erythematous or violaceous plaques or nodules and multiple localized or generalized papules. On the other hand, cutaneous hyperpigmentation is a frequent finding in patients with malignancies, most of the cases because of chemotherapy or other drugs that the patient is taking. We present a case of cutaneous hyperpigmentation as the presenting sign of leukemia cutis. A 61-year-old male presented with cutaneous hyperpigmentation, which had appeared during the last chemotherapy cycle for treatment for biphenotypic leukemia. Cutaneous lesions consisted of bluish to brownish irregular well-defined discoloration of the skin involving the upper part of the trunk and the temporal regions of the forehead. The patient was asymptomatic and the skin was not infiltrated at all. However, histopathologic study showed nodular infiltrates involving the full-thickness of the dermis and destroying pre-existing adnexa. This infiltrate was composed of atypical basophilic cells with large hyperchromatic nuclei and scant cytoplasm. Immunohistochemical studies showed intense immunoexpression for CD43, CD68, CD45RO and myeloperoxidase within these cells. A diagnosis of biphenotypic leukemia cutis was established. In our review of the literature we have not found any report of cutaneous hyperpigmentation as the presenting manifestation of leukemia cutis.


Leukemia cutis is a poor prognosis sign in patients suffering from leukemia. The typical forms of presentation of leukemia cutis consist of solitary infiltrated erythematous plaques or nodules or multiple localized or generalized papules. Other less common forms of presentation include ulcers, chloroma and erythroderma with pruritus. On the other hand, cutaneous hyperpigmentation is a frequent finding in patients with malignancies. Most of these cases are because of chemotherapy or other drugs that the patient is taking. Usually, the clinical picture consists of generalized or localized symmetric irregular brownish discoloration of the skin, which seldom is symptomatic. The cutaneous hyperpigmentation starts few days after beginning with the chemotherapy and lasts for several days, fading away slowly in subsequent weeks. There are many chemotherapeutic drugs that may cause hyperpigmentation of the skin, being Busulfan, 5-Fluorouracil and Bleomicin the most frequent ones. Pathogenesis of this hyperpigmentation is unknown and it has been shown that it is not associated with melanocyte-stimulating hormone (MSH) or adrenocorticotropic hormone (ACTH) hyperfunction. We present a patient with biphenotypic leukemia who developed cutaneous hyperpigmentation during the last chemotherapy cycle. Cutaneous biopsy showed that the pigmentation was a consequence of
skin infiltration by leukemia cells. To our knowledge, this is the first described case of leukemia cutis presenting as skin hyperpigmentation.

Case report
A 61-year-old male, who had biphenotypic leukemia since 1 year ago, was receiving chemotherapy with Fludarabine, Citarabine and Topotecan. He had previously received four cycles of Cytarabine, Idarubicine and Mitoxantrone without any response. During the current chemotherapy cycle, he developed leukoneutropenia because of bone marrow suppression. Subsequently, treatment with wide-spectrum antibiotics including Ceftazidime, Amikacin and Vancomycin was administered for sepsis by coagulase-negative Staphylococcus aureus. He also developed a fungal pneumonia, which was treated firstly with Itraconazole and later on with Caspofungin. He was also receiving Aciclovir in a prophylactic way and granulocytic-colony stimulating factor for recovery of leukoneutropenia. In the last hospital admission, he developed cutaneous hyperpigmentation a few days before starting the new chemotherapy cycle. It consisted of a bluish to brownish irregular well-defined discoloration of the skin confined to the upper part of the trunk and the temporal regions of the forehead (Fig. 1). The patient was asymptomatic and the hyperpigmented skin was not infiltrated at all. With a clinical diagnosis of cutaneous hyperpigmentation because of chemotherapy, a skin biopsy was performed.

Histopathologic study showed nodular infiltrates involving the full-thickness of the dermis and destroying pre-existing adnexa (Fig. 2). There was a thin layer of spared papillary dermis. The epidermis showed no changes. The nodular infiltrates were composed of atypical basophilic cells with large and hyperchromatic nuclei and scant cytoplasm. Many individual necrotic cells and numerous mitotic figures could be seen in these nodular infiltrates. Immunohistochemical study showed intense immunoexpression for CD43, CD68 (KP-1), CD45RO (Fig. 3) and myeloperoxidase (Fig. 4) within the cells of the infiltrate, which were CD20 negative. The proliferation marker MIB1 was strongly positive in 50–75% of the nuclei of these cells and there was also intense immunoreactivity for p53 oncogen in many cells of the infiltrate. Fontana-Masson stain failed to show increased amount of melanin within the epidermis.

Fig. 1. Cutaneous hyperpigmentation involving. A) The temple and the temporal region of the forehead. B) The upper part of the trunk.

Fig. 2. A) Dense nodular infiltrates involving the full thickness of the dermis. B) Higher magnification showing atypical basophilic cells with large and hyperchromatic nuclei and scant cytoplasm.
along dermoepidermal junction and within papillary dermis, and S-100 protein immunostaining showed a normal number of dendritic melanocytes along dermoepidermal junction.

A diagnosis of leukemia cutis was established. The skin lesions faded away slowly, leaving a brownish residual pigmentation, as the patient went on receiving the chemotherapy cycle. However, he developed progressive respiratory insufficiency and cardiac failure and died shortly after.

**Discussion**

Leukemia cutis consists of generalized or localized infiltration of the skin by leukemic cells. It is considered a poor-prognosis sign with short survival after diagnosis. It is also possible to find cases with cutaneous infiltration by leukemic cells without detecting blasts in peripheral blood, a situation known as aleukemic leukemia cutis, which may precede months to years the appearance of leukemic cells in peripheral blood.

Leukemia cutis is more frequently seen in patients with acute myelomonocytic leukemia (M4), acute monocytic leukemia (M5), chronic lymphocytic leukemia and chronic myeloid leukemia. Our patient suffered from acute biphenotypic leukemia. This is a rare type of leukemia, in which leukemic cells express both myeloid and lymphocytic (either T or B) immunohistochemical markers. Leukemia cutis in patients with acute biphenotypic leukemia is an uncommon event, although some cases have been described in the literature.

The most usual clinical presentation of leukemia cutis consists of small reddish infiltrated papules or nodules. The typical location of the lesions is on the head or the upper trunk, although they may appear anywhere on the skin. Ulceration is also a frequent finding in specific leukemia cutis lesions. Perimealloar ulceration is a characteristic feature of chronic lymphocytic leukemia and chloroma is a frequent clinical manifestation of myeloid leukemia. Chloroma consists of a solitary nodule that, when excised, shows greenish color because of the oxidation of
myeloperoxidase, which is found in high concentration in this tumor.

Other less frequent forms of presentation of leukemia cutis include erythrodema and prurigo-like eruption with pruritus. Additional more rare forms of presentation of leukemia cutis include fingertip hypertrophy, chronic genital ulcer, circinate plaques in juvenile chronic myeloid leukemia, bilateral eyelid infiltration, leukemic vasculitis, sister Mary Joseph’s nodule, ulcers in herpes zoster scars, ecchymoses, ulcerative balanoposthitis, vaginal ulcers and psoriasis-like lesions. Our patient presented localized bluish hyperpigmentation of the skin of the upper trunk and temporal areas of the forehead and cutaneous lesions showed no infiltration of the skin from a clinical point of view. We have not found a previous description in the literature of cutaneous hyperpigmentation as the presenting sign of leukemia cutis.

Cutaneous hyperpigmentation in patients with malignancies is usually associated with chemotherapeutic drugs. The most common chemotherapeutic agents causing cutaneous hyperpigmentation include Busulfan, 5-Fluorouracil and Bleomycin. Cutaneous hyperpigmentation may be localized or generalized. The drugs that may develop generalized hyperpigmentation include Busulfan, Cyclophosphamide and topically administered 1,3 bis (2-chlorethyl)-1-nitrosourea. Localized hyperpigmentation may also be caused by several chemotherapeutic medications. Bleomycin causes hyperpigmentation on pressure sites, palms and soles, and it may also originate characteristic flagellated hyperpigmentation. Doxorubicin may also produce localized hyperpigmentation of the palms and soles, nail matrix and oral mucosa. 5-Fluorouracil may develop macular hyperpigmentation of the palms, soles and ears, as well as supravenous hyperpigmentation probably because of subclinical phlebitis. Thiopeta may be responsible for hyperpigmentation in occluded areas.

Our patient had received several chemotherapeutic drugs, which have been associated with different types of cutaneous hyperpigmentation. Cytarabine has been described as the drug causing cutaneous pigmentation and acral bullous erythema. Topotecan and Idarubicine can also induce nail hyperpigmentation and Mitoxantrone may be responsible for both cutaneous and nail hyperpigmentation. However, cutaneous hyperpigmentation of our patient mainly involved the upper chest and forearm and it has not been described in association with these drugs.

The pathogenesis of cutaneous hyperpigmentation because of chemotherapeutic drugs remains unknown, but it seems to be that it is not related with ACTH and MSH hormone hyperactivity. Histopathologic findings in drug-induced hyperpigmentation include increased amount of melanin in the basal layer of the epidermis with variable number of melanophages in the papillary dermis and normal number of melanocytes at dermoeidermal junction. In our patient, skin biopsy showed that the hyperpigmentation was consequence of leukemic infiltration of the skin. We have not found a previous report of leukemia cutis with cutaneous hyperpigmentation as the presenting clinical manifestation.

References
This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.