case report

Diffuse skin hyperpigmentation in CD30+ lymphoproliferation

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CD30+ T-cell lymphoproliferative disorders (LD) comprise two main groups of diseases: CD30+ LD of the skin and systemic anaplastic large cell lymphoma (ALCL). The main feature of these disorders is the expression of CD30. We present a patient with an unusual clinical presentation of CD30+ lymphoproliferative disease in a 54-year old Caucasian male who presented with generalized lymphadenopathy and pronounced skin hyperpigmentation. In the lymph nodes and skin, CD30+ lymphoproliferation (ALCL) was diagnosed. The Prussian blue staining identified that the pigment responsible for the skin color was hemosiderin. Chemotherapy was started but the patient's condition progressively worsened and he died a week after the first cycle. The complete color transformation of the entire skin due to hemosiderin accumulation is, to the best of our knowledge, the first reported observation in a CD30+ lymphoproliferation/ALCL patient. We speculate that hemosiderin-loaded macrophages resulted from the paraneoplastic process by some still unknown mechanism.

CD30+ T-cell lymphoproliferative disorders (LD) comprise two main groups of diseases: CD30+ LD of the skin and systemic anaplastic large cell lymphoma (ALCL). The main feature of these disorders is the expression of CD30.[1] CD30+ LD of the skin consist of the clinical and morphological spectrum of diseases with variable morphology and immunophenotype. These disorders include a range of diseases from clinically indolent lymphomatoid papulosis (LyP) to borderline cases and also the aggressive ALCL.[2] Much overlap can be found clinically between the diseases, and often histological examination is inadequate to distinguish between some types of LyP and ALCL.[3] Transformation of mycosis fungoides (MF) into ALCL can also pose some diagnostic difficulty. Anaplastic large T/null-cell lymphoma accounts for about 2% of all non-Hodgkin lymphomas. Discovery of the *t* (2;5) (p23q35) and the resultant frequent overexpression of the anaplastic lymphoma kinase-1 (ALK1) protein subdivided this entity into two main groups: ALK1+ and ALK1-ALCL. The diagnosis is made by the typical morphological picture and a T-cell or null-cell immunophenotype with CD30 positivity.[4] We report the case of a patient with an unusual clinical presentation of a CD30+ lymphoproliferative disease.

CASE

A 54-year-old white male was admitted to our hospital with generalized lymphadenopathy and pronounced skin hyperpigmentation (**Figure 1**). At admission, the physical examination revealed hepatosplenomegaly, generalized lymphadenopathy, and a low performance status (Eastern Cooperative Oncology Group score 3). The most prominent feature was his skin color. The whole skin was purple-brownish except for his palms and soles that were dry and atrophic with desquamation. On the back, he had multiple polypoid tumors, the largest being about 3 cm in diameter. The patient had complete alopecia, except in the pubic and axillary regions. He stated that his skin began turning brownish 18 months previously. In that period, he lost almost 50 kg of body weight. Three months before admission he noticed an enlarged lymph node in his right inguinal region. He felt tired with malaise. The largest lymph node, of approximately 6 cm in diameter, was in the left axillary region. The liver

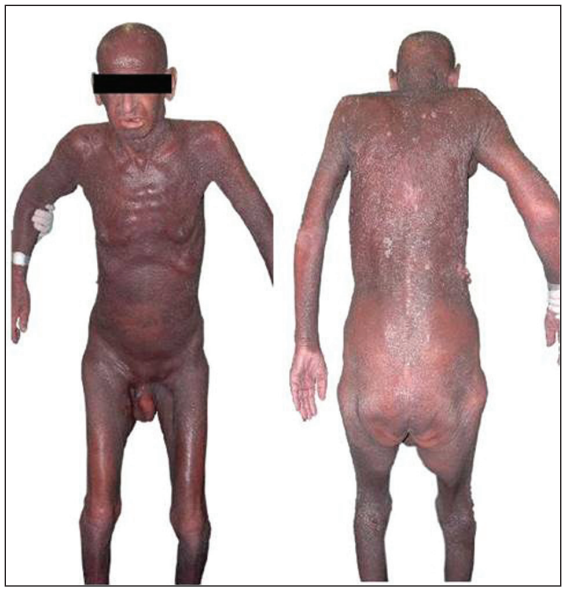

Figure 1. Pronounced skin hyperpigmentation.

Table 1. Laboratory test results.

Unit	Volume (normal range)
Hemoglobin	98 g/L (138-175 g/L)
C reactive protein	179.2 mg/L (< 5 mg/L)
Immunoglobulin G	22.4 g/L (7-16 g/L)
Immunoglobulin A	9.4 g/L (0.7-4.0 g/L)
Lactate dehydrogenase	341 U/L (< 241 U/L)
Ferritin	366 µg/L (20-250 µg/L)
Total bilirubin	22.2 µmol/L (3-20 µmol/L)
Aspartate transaminase	7 U/L (11-38 U/L)
Alanine transaminase	6 U/L (12-48 U/L)

was palpable 4 cm and spleen 3 cm under the costal margins.

Laboratory test results are shown in **Table 1**. The patient was anemic, while platelets and leukocytes with normal differential counts were in the normal range. Pathological and biochemical values included an increased C reactive protein and decreased values of aminotransferases. Hepatitis B and C, *Treponema pallidum* hemaglutination test, and HIV markers were negative. The patient's cardiopulmonary status was diminished, with restrictive-obstructive disorders of ventilation and left ventricular diastolic failure. Thyroid hormone values were normal. Brain CT and multidetector computerized tomography of the neck, thorax, and abdomen showed widespread lymphadenopathy and hepatosplenomegaly. The histologic assessment of the skin biopsy showed dense dermal

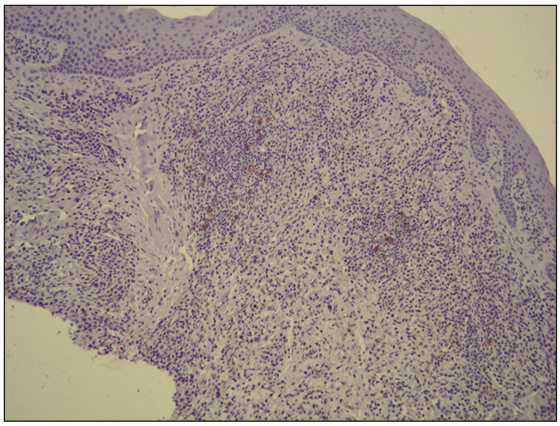

Figure 2. Skin biopsy showing CD30+ cells in dermis (anti-CD30 immunohistochemistry, 100×).

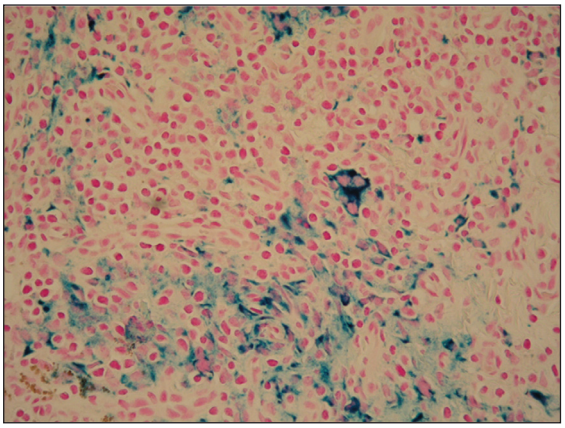

Figure 3. Hemosiderin in skin (Prussian blue staining, 400×).

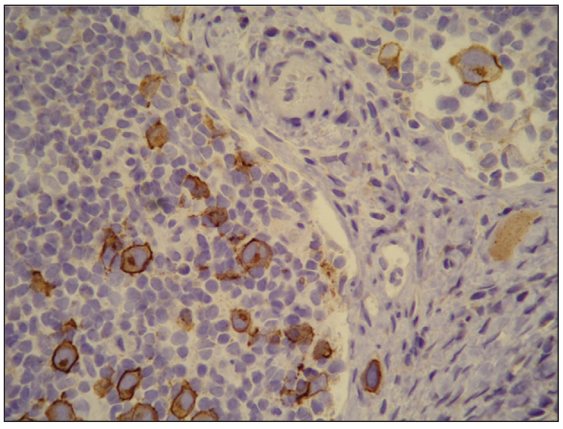

Figure 4. CD30+ cells in lymph node (anti-CD30 immunohistochemistry, 400×).

lymphocyte infiltration without epidermoptropism. The infiltrate mostly consisted of small lymphocytes and plasma cells. Within the infiltrate were observed large CD30+ anaplastic cells with moon-shaped nuclei that were negative for T- and B-cell marker epithelial membrane antigen, anaplastic lymphoma kinase 1, of anticytokeratin monoclonal antibodies AE1/AE3, CD15, CD20, CD56, and granzyme (**Figure 2**). Among the tumor infiltrates were numerous macrophages containing pigment. Prussian blue staining identified hemosiderin as the pigment responsible for the skin color (**Figure 3**). The histology of subcutaneous lymph nodes showed atypical large cells with moon-shaped nuclei, in smaller clusters or scattered. Immunohistochemically, tumor cells showed the same immunophenotype as those described in the dermis (**Figure 4**). The marrow trephine biopsy showed no CD30+ cells infiltrate.

To exclude other diseases with possibly similar skin presentation, further diagnostic procedures were undertaken. Porphyria was excluded, as porphyrins and its precursors were normal. Gene tests for Wilson disease (ATP7B mutations) were negative. CT and Magnetic resonance imaging of the brain excluded pineal gland tumor and the skin biopsy excluded acanthosis nigricans. Addison disease was excluded as cortisol levels were high and diffuse skin hyperpigmentation was not because of melanin. Hemochromathosis was excluded based on the ferritin value, liver biopsy, and finding of normal sequences of human *hemochromatosis* protein gene, also known as *HFE* genes (Cys282Tyr and His63Asp loci). Chemotherapy with etoposide-vincristine-doxorubicin-cyclophosphamide-prednisone (EPOCH) regimen was started; however, the patient's condition progressively worsened, complicated with gram-positive sepsis, and he died a week after the first cycle. The autopsy showed bilateral hydrothorax, bronchopneumonia, and hypertrophy of the heart. The abdominal lymph node taken at the autopsy showed hemophagocytosis inside the sinuses and a small number of scattered CD30 positive cells.

DISCUSSION

This patient with CD30+ lymphoproliferation had an unusual clinical presentation. His skin color gradually and completely turned into purple-brownish over a year and a half. CD30+ lymphoproliferation (ALCL) was diagnosed. With a variety of diagnostic tests, we excluded some of the most frequent conditions that could cause such skin presentation (e.g., porphyria, pineal gland tumor, acanthosis nigricans, hemochromathosis, and Addison disease). For such prominent skin hyperpigmentation, transformed MF (tMF) should be considered in the differential diagnosis.[5] However, because the patient was admitted to our hospital in a very late stage of the disease, we could have not distinguished between ALCL with skin progression and tMF. Also, considering his clinical course, it is most likely that this was neither LyP nor primary cutaneous ALCL. Skin pigmentations are frequently seen in skin lymphomas, but in most cases they are localized. Even in hyperpigmented MF, pigmentation is not so diffuse but rather consist with multiple areas of marked hyperpigmentation. It is crucial to mention that in hyperpigmented MF, the pigment is usually melanin and only rarely hemosiderin (melanoerythroderma).[6] Hemosiderin in macrophages can also be responsible for pigmentations in some cases of erythrodermic Sézary syndrome.[7] The complete color transformation of the entire skin because of macrophage accumulation of hemosiderin is, to the best of our knowledge, the first reported observation in the CD30+ lymphoproliferation/ALCL patient. We speculate that in this case it was the result of a paraneoplastic process by, according to our knowledge, a still unknown mechanism.

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REFERENCES

1. Kempf W. CD30 lymphoproliferative disorders: Histopathology, differential diagnosis, new variants and simulators. J Cutan Pathol 2006;33 Suppl 1:58-70.
2. Bekkenk MW, Geelen FA, van Voorst Vader PC, Heule F, Geerts ML, van Vloten WA, et al. Primary and secondary cutaneous CD30+ lymphoproliferative disorders: A report from the Dutch Cutaneous Lymphoma Group on the long-term follow-up data of 219 patients and guidelines for diagnosis and treatment. Blood 2000;95:3653-61.
3. El Shabrawi-Caelen L, Kerl H, Cerroni L. Lymphomatoid papulosis: Reapprasial of clinicopathologic presentation and classification into subtypes A, B and C. Arch Dermatol 2004;140:441-7.
4. Armitage JO, Longo DL. Malignancies of Lymphoid Cells. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw-Hill; 2005. p. 653.
5. Cerroni L, Rieger E, Hödl S, Kerl H. Clinicopathologic and immunologic features associated with transformation of mycosis fungoides to large cell lymphoma. Am J Surg Pathol 1992;16:543-52.
6. Cerroni L, Gatter K, Kerl H. An illustrated guide to skin lymphoma. Maden: Blackwell Publishing; 2004. p. 26-7.
7. Kohler S, Kim YH, Smoller BR. Histologic criteria for the diagnosis of erythrodermic mycosis fungoides and S?zary syndrome: A critical reappraisal. J Cutan Pathol 1997;24:292-7.