CASE REPORT

Non Hodgkin T cell lymphoma: an atypical clinical presentation *

Linfoma não Hodgkin de células T citotóxico: uma apresentação clínica atípica

Paula Maio[1]
Raquel Vieira[3]
Fernanda Sachse[5]
Diogo Bento[2]
Ana Afonso[4]
Heinz Kutzner[6]

Abstract: Cytotoxic lymphomas comprise a spectrum of peripheral T-cell lymphomas that can have a initial or late cutaneous presentation. We describe a 46-year-old man from Cape Verde, with a dermatosis involving his face and trunk, consisting of monomorphic papules with a smooth surface and both motor and sensory polyneuropathy.The hypothesis of leprosy was supported by the clinical and initial hystopathological findings and the patient was referred to our hospital with suspected Hansen's disease. In the new skin and lymph node biopsies a lymphocyte population was identified whose immunohystochemistry study allowed the diagnosis of T-cell lymphoma with expression of cytotoxic markers. The patient was started on chemotherapy with initial remission of the skin lesions but, subsequently, progression of systemic disease.
Keywords: Cytotoxicity, immunologic; Leprosy; Lymphoma, T-Cell, cutaneous; Paraneoplastic polyneuropathy

Resumo: Os linfomas citotóxicos compreendem um espectro de linfomas de células T periféricos e linfomas Natural Killer que podem ter expressão cutânea primária ou secundária. Descrevemos o caso de um homem com 46 anos de idade, natural de Cabo Verde,com dermatose envolvendo a face e tronco constituída por pápulas monomorfas superfície lisa e polineuropatia sensitivo motora.A hipótese de Hanseníase foi colocada suportada por achados histopatológicos sugestivos sendo o doente referenciado à consulta de Doença de Hansen do nosso hospital. Em biopsia de pele e de gânglio identificou-se proliferação linfocitária cujo estudo imunohistoquímico permitiu o diagnóstico de linfoma T com expressão de marcadores citotóxicos. Iniciou quimioterapia verificando-se inicialmente remissão parcial das lesões cutâneas mas posteriormente a progressão da doença sistémica.
Palavras-chave: Citotoxicidade imunológica; Hanseníase; Linfoma cutâneo de células T; Polineuropatia paraneoplásica

INTRODUCTION

Cytotoxic cutaneous lymphomas are a group of lymphoproliferative disorders characterized by expression of cytotoxic proteins (TIA-1, granzyme A or B or perforin).[1,2] The diagnosis of these conditions can sometimes be clinically and histopathologically challenging.

CASE REPORT

We describe a 46-year-old, black male patient, born in Cape Verde. He first noted, months prior to presentation, a dermatosis that almost exclusively involved his face and trunk consisting of multiple small monomorphic papules with an erythematous smooth surface.[1,2] The patient reported dysesthesia at

Received on 12.10.2011.
Approved by the Advisory Board and accepted for publication on 16.01.2012.
* Study conducted at the Curry Cabral Hospital – Central Lisbon Hospital Center EPE (HCC- CHLN) – Lisbon, Portugal.
Financial Support: none
Conflict of Interests: none

[1] MD – Hospital Physician in Dermatology and Venereology at the Curry Cabral Hospital – Central Lisbon Hospital Center EPE (HCC- CHLN) – Lisbon, Portugal.
[2] MD – Hospital Attending Physician in Infectology at the Santa Maria Hospital – North Lisbon Hspital Center EPE (HSM- CHLN) – Lisbon, Portugal.
[3] MD – Graduate Hospital Assistant in Dermatology and Venereology at the Curry Cabral Hospital – Central Lisbon Hospital Center EPE (HCC- CHLN) – Lisbon, Portugal.
[4] MD - Graduate Hospital Assistant in Dermatopathology at the Curry Cabral Hospital – Central Lisbon Hospital Center EPE (HCC- CHLN) – Lisbon, Portugal.
[5] MD - Graduate Hospital Assistant in Dermatology at the Portuguese Oncology Institute (IPO) – Lisbon, Portugal.
[6] PhD – Professor of Dermatopatholgy, Graz Medical University – Graz, Austria.

the distal ends of both feet and paroxistical difficulty in mobilizing both feet. These symptoms suggested the existence of a sensory motor polyneuropathy.A cutaneous biopsy was performed motivated by these findings. The histopathological evaluation revealed perivascular and periadnexal inflammatory infiltration of nerve bundles with lymphocytic permeation which, with simultaneous findings of cutaneous involvement and sensory motor polyneuropathy, could be consistent with the diagnosis of leprosy. The patient was therefore referred for a consultation at the hospital regarding the possibility of Hansen's disease. The physical examination revealed a dermatosis involving the face and the upper torso that consisted of multiple infracentimetric monomorphic papules and plaques with a smooth erythematous surface (Figures 1 and 2). There was no hypoesthesia in relation to skin lesions. Examination of ganglionic chains revealed several adenopathies below the chin and in axillary chains. The adenopathies that were found were over one centimeter in diameter, with a hard consistency. Palpation of the abdomen revealed no masses or organomegaly.

The neurological examination did not reveal thickening or pain upon palpation of the nerve roots. There was slight hypoesthesia at the distal end of both feet, with diminished thermal, tactile and pain sensitivity.

The patient also reported weight loss of 12 kg(>10%) during the past year which had never been taken into consideration. The patient denied any other constitutional symptoms, including fever, anorexia and malaise.

The supplementary study revealed: normocytic normochromic anemia(10.4 g/dL), white blood cell count with lymphocytosis(3500) and thrombocytopenia (94000),VS 71mm in 1st hour, β2-microglobulin(8.0 mg/dL) and LDH(689 U/L) and negative results for HIV, HTLV, EBV.

PCR applied to a biopsy performed from the synovial tissue proved negative for *M. leprae*.

Body axial tomography showed severe ganglion involvement of the axillary and inguinal lymph nodes and mild splenomegaly with multiple small parenchymal nodules.
The skin biopsy revealed diffuse lymphoid infiltration in the dermis composed of CD3, CD4 positive T-cells, some of which had CD8 positivity (Figures 3, 4 and 5). The axillary lymph node biopsy identified a lymphocytic proliferation composed of small cells with CD2, CD3 positive cells and CD7, CD8, CD20 negative cells, and TIA expression allowing the diagnosis of T-cell lymphoma with cytotoxic expression (Figure 6). The study of T-cell receptors rearrangement by PCR confirmed the monoclonality of the cell

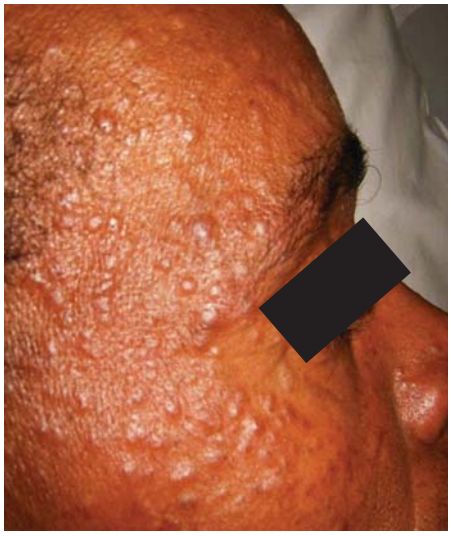

Figure 1: Clinical presentation. Multiple small monomorphic papules on the face

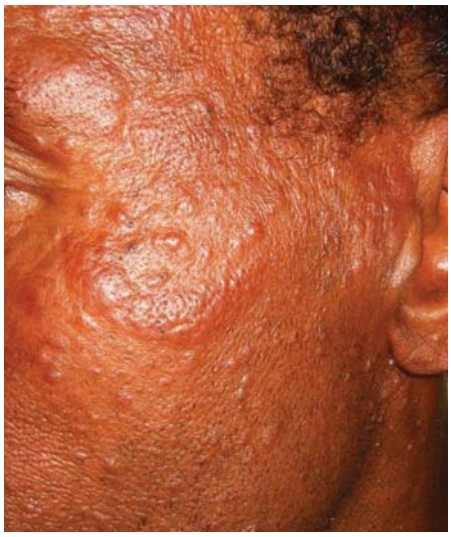

Figure 2: Clinical presentation (left sideof the face). Multiple small monomorphic papules and plaques slightly infiltrateds

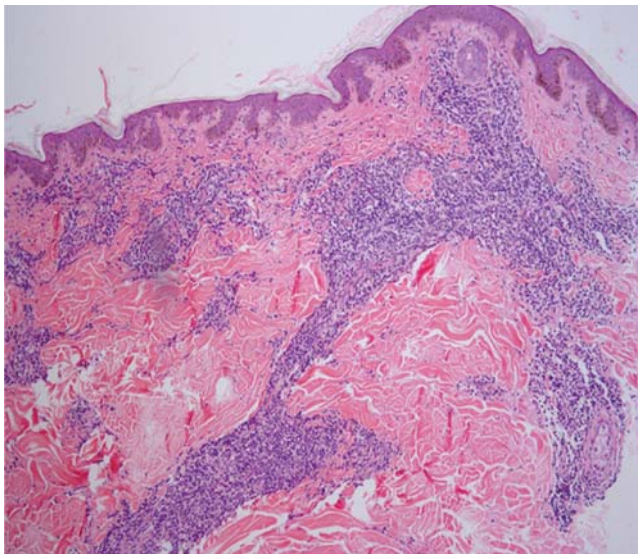

Figure 3: Hystopatology (H&E). Dermal intense and difuse infiltration of lymph cells

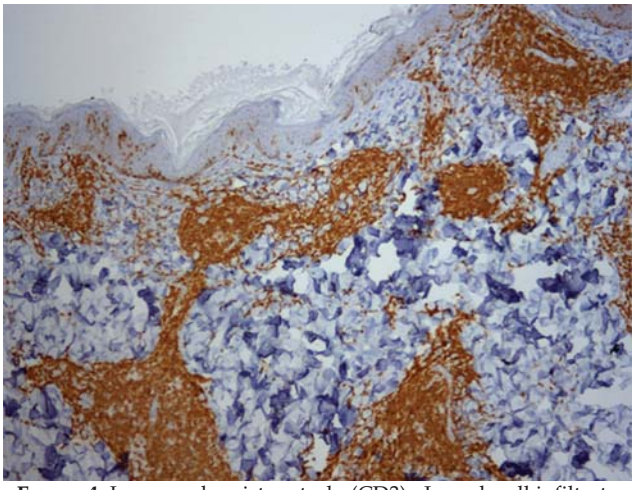

Figure 4: Immunochemistry study (CD3). Lymph cell infiltrate showing CD3 positivity

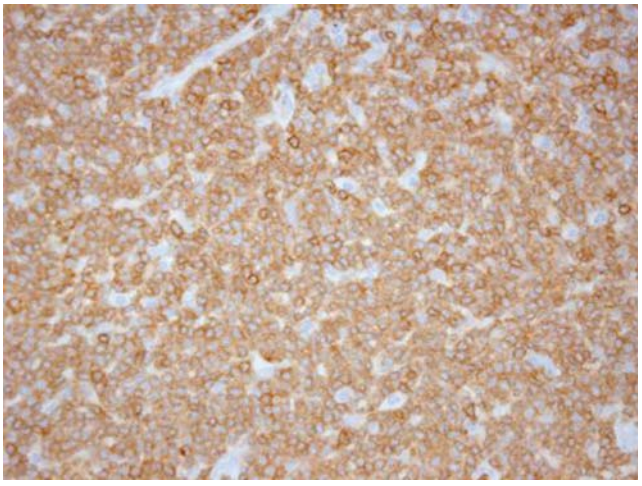

Figure 5: Immunochemistry (CD4). Lymph cells infiltrate showing CD4 positivity

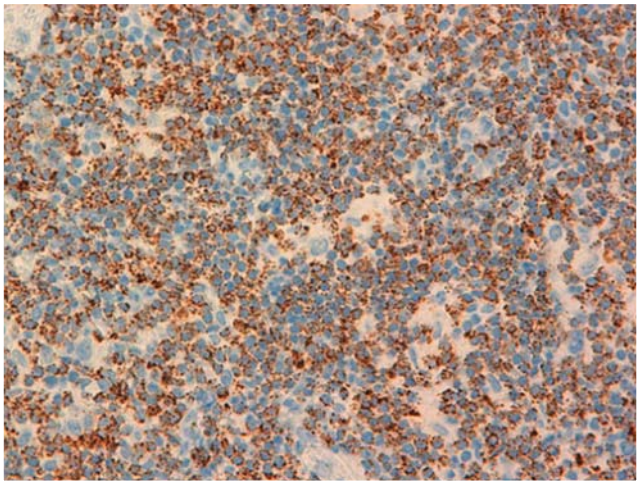

Figure 6: Immunochemistry study (TiA). The immunochemistry study showing a difuse infiltrate of lymph cells with cytotoxic expression (TiA+)

population based on the analysis of gamma genes.The absence of typical clinical lesions and the typical histological markers of Hansen's disease, the successively negative nasal smears and skin swabs, together with the PCR detection technique for *M. leprae,* allowed for the exclusion of a Hansen's disease diagnosis. The evaluation by a neurologist allowed a correlation between lymphoma and demyelinating neuropathy to be characterized as a rare paraneoplastic syndrome.

The patient was started on chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), which led to partial remission of the cutaneous lesions (Figure 6) but with subsequent loss of response. Second line therapeutic management with ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin) was then initiated with no noticeable clinical response. The patient was then started on a CMOPP chemotherapy regimen (cyclophosphamide, mechlorethamine, vincristine, procarbazine and prednisolone), but at 12 months follow-up there was invariable progression of the systemic disease, resulting in the patient´s death.

DISCUSSION

The heterogeneous cutaneous clinical presentation of T-cell lymphomas, together with the frequent occurrence of nonspecific histological findings in cutaneous biopsies, creates significant diagnostic difficulties. The cutaneous lymphoma classification is also a challenge, in addition to the problem that until a few years ago there was no consensus between the WHO and the EORTC (European Organization for Research and Treatment of Cancer). [1,3] The new classification allows for more uniformity regarding both the diagnosis and therapeutic approach to these lymphomas.[4]

In the case of our patient, there was already systemic involvement at the date of diagnosis, and in these circumstances this lymphoma could not be classified as primary cutaneous T-cell lymphoma. These lymphomas are characterized by a transient partial response to chemotherapy and by its association with a poor prognosis. The demyelinating neuropathy has been otherwise described since lymphomas have been reported to occasionally involve the peripheral nervous system. This damage is more often caused by non-Hodgkin T-cell lymphomas, the cells of which can infiltrate the nerve sheath and cause axonal damage, or by an autoimmune process where antineuronal antibodies are directed against intracellular antigens. [5,6]

Furthermore our patient's lymphoma exhibited cytotoxic behavior characterized by the expression of molecules such as TIA, perforin and granzyme B. The expression of these molecules is of great diagnostic use and helps the dermatologist to classify lym-

phoma; however, the use of these markers lacks clinical and phenotypic specificity.[7] The surface markers expressed in malignant T-cells: CD2, CD3, CD4, CD25 and CD52 were the first therapeutic targets to be identified. However, the presence of these receptors, even in normal T-cells, implies that therapy with monoclonal antibodies or immunotoxins inevitably results in different degrees of immunosuppression. New classes of therapeutic agents have emerged, particularly those that act by inhibiting histone deacetylase(HDAC).[8,9] These molecules are intended to induce apoptosis in malignant T-cells. Immunomodulators such as interferon and toll-like receptor agonists (TLR), also have a particularly important role in the treatment of primary cutaneous lymphomas (CTCL).[9] While most classical cytotoxic drugs have limited effectiveness in the treatment of lymphomas, agents that inhibit the metabolism of purine and pyrimidine (nucleoside analogues) seem to have some additional efficacy in cases of T-cell lymphoma.[9,10] Clinical trials currently underway will better define therapeutic strategies for these lymphomas.

We stress the importance of this case due to the uncommon clinical presentation, in particular the simultaneous neurological and skin involvement that required a thorough investigation of multiple differential diagnoses. This may ultimately result in a later diagnosis of Non-Hodgkin's peripheral T-cytotoxic lymphoma. ❑

REFERENCES

1. Slater DN. The new World Health Organization-European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas: a practical marriage of two giants. Br J Dermatol. 2005;153:874-80.
2. Kanavaros P, Boulland ML, Petit B, Arnulf B, Gaulard P. Expression of cytotoxic proteins in peripheral T-cell and Natural Killer cell Lymphomas: Association with extranodal site, NK or T gamma delta phenotype, anaplastic morphology and cd30 expression. Leuk Lymphoma. 2000;38:317-26.
3. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th edition; France: IARC; 2008. 439 p.
4. Paulli M, Berti E. Cutaneous T-cell lymphomas (including rare subtypes). Current concepts. II. Haematologica. 2004;89:1372-88.
5. Kelly JJ, Karcher DS. Lymphoma and peripheral neuropathy: a clinical review. Muscle Nerve. 2005;31:301-13.
6. Blaes F, Tschernatsch M.Paraneoplastic neurological disorders. Expert Rev Neurother. 2010;10:1559-68.
7. Massone C, Chott A, Metze D, Kerl K, Citarella L, Vale E, et al. Subcutaneous, blastic natural killer (NK), NK/T-cell, and other cytotoxic lymphomas of the skin: a morphologic, immunophenotypic and molecular study of 50 patients. Am J Surg Pathol. 2004;28:719-35.
8. Garcia-Herrera A, Song JY, Chuang SS, Villamor N, Colomo L, Pittaluga S, et al. Nonhepatosplenic γδ T-cell lymphomas represent a spectrum of aggressive cytotoxic T-cell lymphomas with a mainly extranodal presentation. Am J Surg Pathol. 2011;35:1214-25.
9. Erter J, Alinari L, Darabi K, Gurcan M, Garzon R, Marcucci G, et al. New targets of therapy in T-cell lymphomas. Curr Drug Targets. 2010;11:482-93.
10. Piccaluga PP, Agostinelli C, Tripodo C, Gazzola A, Bacci F, Sabattini E , et al. European T cell Lymphoma Study Group.Peripheral T-cell lymphoma classification: the matter of cellular derivation. Expert Rev Hematol. 2011;4:415-25.

MAILING ADDRESS:
Paula Maio
Rua da Beneficência, 8
1069-166 Lisbon,
Portugal.
E-mail: paulamaio@gmail.com

How to cite this article: Maio P, Bento D, Vieira R, Afonso A, Sachse F, Kutzner H. Non Hodgkin T cell lymphoma: an atypical clinical presentation. An Bras Dermatol. 2012;88(2):264-7.