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**CASE REPORT**

# A rare T-cell lymphoma in an ankylosing spondylitis patient under immunosuppression with tumor necrosis factor inhibitor

## *Linfoma de células T num doente com espondilite anquilosante sob imunossupressão com inibidores de necrose tumoral*

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## Abstract

Lymphoproliferative disorders arising in a background of immune deficiency/dysregulation correspond to a spectrum of disorders ranging from non-noxious hyperplasias to aggressive lymphomas, mainly of B-cell type. We describe a case of an Epstein-Barr virus-positive T-cell lymphoma, with a cutaneous presentation and unusual pathological features in a patient under immunosuppression with infliximab. A 60-year-old patient, with a history of ankylosing spondylitis and autoimmune hemolytic anemia, treated with infliximab and low-dose prednisone since 2013, presented with a 7 cm ulcerated, well-demarcated tumor on his left lower back and a 20 cm scaly, well-demarcated erythematous patch in the left scapular region. A skin biopsy revealed a diffuse infiltration of the superficial and deep dermis by atypical, intermediate-size lymphocytes that expressed CD2, CD3, CD56, TIA-1, Granzyme B, TCRδ, and EBER. There was no evidence of epidermotropism, vasculotropism, or necrosis. The fluor-d-glucose positron emission tomography showed a large splenic, hepatic, bone marrow, and nodal uptake. A diagnosis of an extranodal NK/T-cell lymphoma in association with immunosuppression was rendered. With this article, we aim to add awareness to the difficulty of diagnosis, the careful use of immunomodulators, clinical suspiciousness, and surveillance of possible consequences warranted in all patients under prolonged immunosuppression.

***Keywords:*** γδ T lymphocytes. γδ T-cell lymphoma. Extranodal NK/T-cell lymphoma. Epstein-Barr virus. TNF- α inhibitors.

## Resumo

No espetro de patologias linfoproliferativas associadas a imunodesregulação/deficiência constam hiperplasias linfoproliferativas e linfomas agressivos, estes últimos predominantemente de células B. Descrevemos um caso de linfoma de células T, Epstein-Barr virus positivo, com apresentação cutânea e características histopatológicas ambíguas, num doente sob imunossupressão com infliximab. Paciente de 60 anos, com antecedentes pessoais de espondilite anquilosante e anemia hemolítica autoimune, tratado com infliximab e baixa dose de prednisolona, desde 2013. Apresentou nódulo cutâneo ulcerado, bem delimitado, com 7 cm na região lombar esquerda e placas eritematosas, bem delineadas, com 20 cm, na região escapular esquerda. A biópsia cutânea revelou uma infiltração difusa da derme superficial e profunda por linfócitos atípicos, de tamanho intermédio, que expressavam CD2, CD3, CD56, TIA-1, Granzima B, TCRδ e EBER. Não se observou epidermotropismo, vasculotropismo ou necrose.

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A FDG-PET/CT demonstrou hipercaptação esplénica, hepática, medular e nodal. Concluiu-se o diagnóstico de linfoma de células T/NK extranodal em contexto de imunossupressão. Com este artigo pretendemos alertar para a dificuldade diagnóstica, alta suspeição clínica e vigilância atenciosa necessárias em doentes com uso prolongado de imunossupressores.

***Palavras chave:*** Linfócitos de células T γδ. Linfoma de células T γδ. Linfoma de células T/NK extranodal. Vírus Epstein-Barr. Inibidores TNF- α.

## Introduction

Lymphoproliferative disorders arising in a background of immune deficiency/dysregulation (primary or acquired) correspond to a spectrum of disorders ranging from non-noxious hyperplasia to aggressive lymphomas[1].

In autoimmune disorders, the risk and type of lymphomas seem to be dependent on the immunomodulatory agent used, the dose, duration, and underlying immunosuppressive disorder[1].

B-cell lymphomas are the most frequent lymphomas associated with immunodeficiency states, whether primary or secondary[1]. Hepatosplenic T-cell lymphoma (HSTCL) is the most frequently reported subtype among the T-cell non-Hodgkin lymphomas associated with exposure to immunosuppressive agents[1].

We present a case of an atypical cutaneous presentation of a systemic extranodal NK/T-cell lymphoma in a patient with ankylosing spondylitis on long-term therapy with tumor necrosis factor-alpha (TNF-α) inhibitor and prednisone.

## Case report

A 60-year-old patient, with a history of ankylosing spondylitis and autoimmune hemolytic anemia, under treatment with infliximab and low-dose prednisone for the past 9 years, was referred to the Hematology Department of our Hospital, for a suspected cutaneous lymphoma. On clinical observation, he presented with a 7 cm ulcerated, well-demarcated lesion on his left lower back and in the left scapular region with a 20 cm erythematous, and scaly patch with two infiltrated 4 cm plaques within it (Fig. 1). On palpation, there were no detectable lymphadenopathies or hepato-splenomegaly. The lesions had a 6-month evolution gradually transitioning from patches to plaques and tumours. A skin biopsy of the tumor phase (and later from the plaque phase), performed in the hospital of origin, was reviewed in our pathology department for a histopathological diagnosis. We observed a diffuse infiltration of the superficial and deep dermis by atypical, intermediate-size lymphocytes, with dispersed chromatin (Fig. 2). The neoplastic lymphocytes, evaluated in paraffin-embedded tissue, expressed CD2, CD3, CD56, TIA-1, Granzyme B, and TCRδ and negativity for CD4, CD5, CD7, CD8, CD20, CD30, BCL6, CD278, TCRβ, and PD-1 (Fig. 3). *In situ* hybridization analysis with EBER revealed nuclear positivity in all neoplastic cells. There was no evidence of epidermotropism, vasculotropism, or necrosis.

Due to the ambiguous features of the case a diagnosis of a γδ T-cell lymphoma, Epstein-Barr virus (EBV)-positive was suggested.

We pursued an investigation to determine whether it was a systemic or a primary cutaneous T-cell lymphoma.

A 2-deoxy-2-[18F] fluor-d-glucose positron emission tomography/computed tomography (FDG-PET/CT) and a bone marrow trephine were performed for disease staging. The FDG-PET/CT revealed a stage IV lymphoma with diffuse hypermetabolism of supra- and infra-diaphragmatic lymph nodes, skin, subcutaneous fat, bone marrow, and homogenous hepatosplenomegaly, with the spleen measuring approximately 16 cm.

The bone marrow trephine revealed a diffuse, massive interstitial infiltration of medium-sized T-cell lymphocytes, positive for CD3, CD2, CD45, CD56, and TCR ãä by flow cytometry, compatible with infiltration of the bone marrow by a ãä T-cell lymphoma, and identical to the previously described on the skin (Fig. 4). An identical clonal rearrangement of the T-cell receptor delta gene was detected both in the bone marrow and in the biopsy of the skin lesion.

Plasma EBV DNA levels were 88642UI/mL.

In addition, an identical clonal rearrangement of the T-cell receptor delta gene was detected both in the bone marrow and in the biopsy of the skin lesion.

The authors, based on the histological and immunological features of the skin biopsy and bone marrow involvement, together with the systemic nodal and splenic uptake granted a diagnosis of a systemic γδ T-cell lymphoma, EBV-positive, favoring a diagnosis of an extranodal NK/T-cell lymphoma, with cutaneous involvement and probable association with immunomodulating therapy.

The disease proved to be highly refractory to several therapeutic regimens, including cyclophosphamide, doxorubicin, vincristine, prednisolone, rituximab,

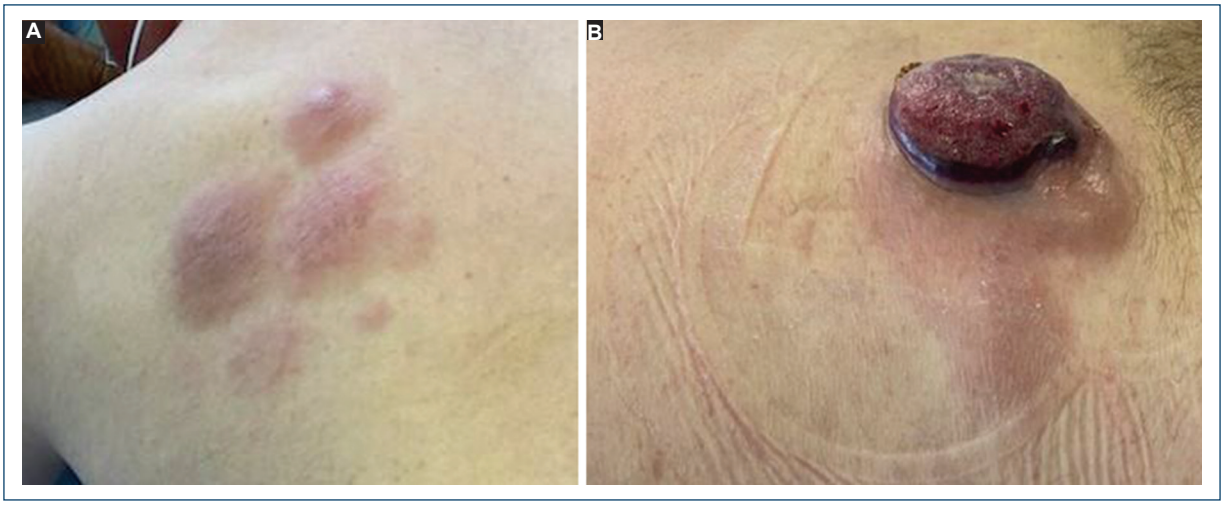


**Figure 1. A:** patient with a well-demarcated, erythematous, and scaly patch with two infiltrated plaques within it and **B:** an ulcerated and well-demarcated tumor on his left lower back.

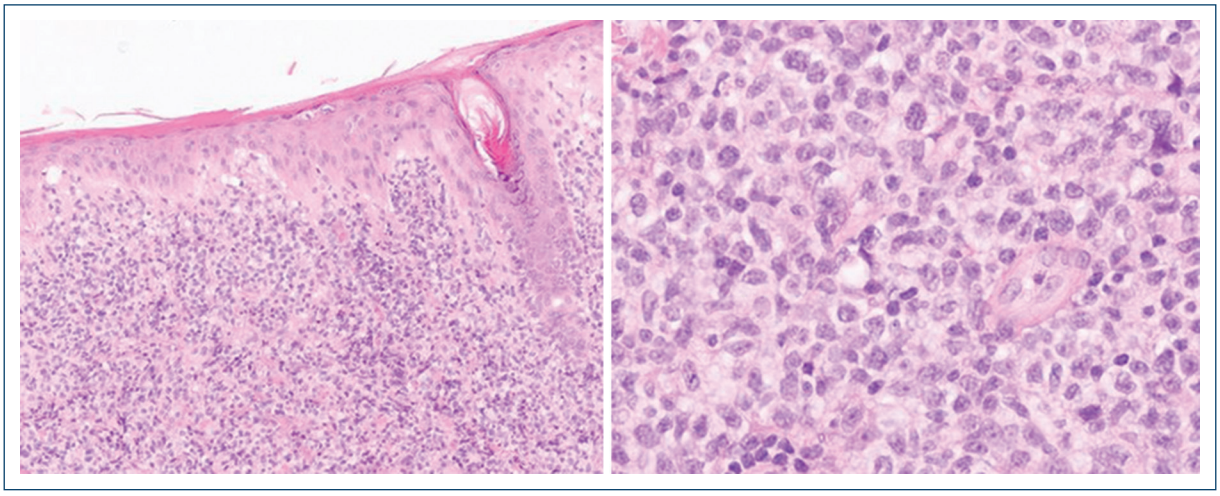

**Figure 2.** Infiltration of the dermis by atypical, intermediate size lymphocytes, with dispersed chromatin.

ifosfamide, carboplatin, etoposide and rituximab and hyperfractioned-cyclophosphamide, vincristine, doxorubicin, and dexamethasone. In addition to the refractoriness of the disease, several serious infectious complications were documented, as well as hematologic and gastrointestinal toxicity. Following this series of events, the patient died, 2 months after the initial diagnosis (Table 1).

## Discussion

γδ T lymphocytes are tissue-restricted cytotoxic lymphocytes accounting for < 5% of the adult T-cell population. They are crucial in immunosurveillance and are mainly lodged in the skin, sinusoids of the liver, red pulp of the spleen, and the intestinal mucosa[2].

Persistent, dose-dependent, treatment with infliximab has been shown to promote the expansion of clonal γδ T-cells *in vivo* and induce proliferation *in vitro*[3]. Furthermore, patients with inflammatory bowel disease or psoriasis seem to have a higher baseline frequency of γδ T-cells when compared to the general population, and, when treated with thiopurines or methotrexate in association with infliximab, demonstrate an even higher baseline frequency and a lower threshold for their expansion[3].

**Table 1.** Clinicopathologic features of extranodal NK/T-cell lymphoma in a patient with ankylosing spondylitis receiving TNF-α inhibitors

| Age/gender | Associated immune disease | Involved organs | Immunomodulator | IHQ-panel | EBV status* | Treatment | Survival+ | Status |
|---|---|---|---|---|---|---|---|---|
| 60 M | Ankylosing spondylitis | Skin, liver, spleen, bone marrow, supra and infra diaphragmatic lymph nodes | Infliximab + prednisone | CD2+, CD3+, CD4-, CD5-, CD7-, CD8-, CD30-, CD56+, TIA-1+, Granzyme-B+, TCR-δ+, TCR-θ-. | +† | CHOP R-ICE HYPER-CVAD | 2 mo | Passed away |

*EBV status determined by *in situ* hybridization with EBER probe.
†Nuclear positivity in all neoplastic cells. Survival+ represents time, in months (mo), from diagnosis. R-ICE: rituximab, ifosfamide, carboplatin, etoposide.




**Figure 3.** The neoplastic lymphocytes expressed diffuse positivity for **A:** TCR-δ, **B:** TIA-1, and **C:** granzyme B. **D:** *in situ* hybridization analysis with EBER revealed nuclear positivity in all neoplastic cells.

In the literature, so far, seven cases of T-cell lymphomas in association with TNF-α inhibitors have been documented, in patients with ankylosing spondylitis[4-8]. Curiously, the predominant histological subtype is *Mycosis fungoides*/Sezary syndrome. Other types include subcutaneous panniculitis-like TCL, HSTCL, angioimmunoblastic T-cell lymphoma, and one case of anaplastic large-cell lymphoma, also with a cutaneous presentation[4-9].

The description of extranodal NK/T-cell lymphomas, in patients on infliximab therapy, is extremely rare[10-12].

In our case, the cutaneous manifestation of extranodal NK/T-cell lymphoma presented after a 9-year immunosuppression treatment, with infliximab and low-dose prednisone, for ankylosing spondylitis. The systemic presentation, with nodal involvement, also favors this diagnosis over other γδ T-cell lymphomas, such as HSTCL.

This case represents a diagnostic dilemma with clinical, morphological, immunohistochemical, and prognostic overlap to other γδ T-cell lymphomas.

The differential diagnosis includes of a cutaneous γδ cytotoxic T-cell lymphoma is included extranodal NK/T-cell lymphoma (by definition EBV-positive), primary cutaneous γδ T-cell lymphoma (by definition EBV-negative), and cutaneous involvement of an HSTCL (by definition EBV-negative).

In this case, an angiodestructive growth pattern and necrosis, common and desirable features of an extranodal NK/T-cell lymphoma, were not observed[1]. Furthermore, involvement of the bone marrow is rare

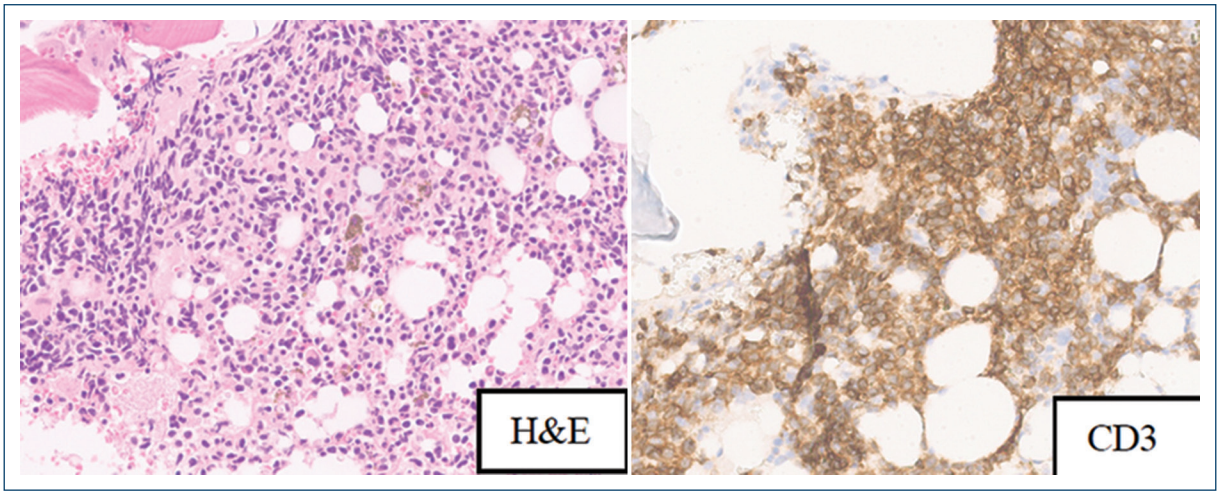


**Figure 4.** Diffuse interstitial involvement of the bone marrow by CD3-positive neoplastic lymphocytes.

in extranodal NK/T-cell lymphoma. On the other hand, HSTCL is an EBV-negative lymphoma, although rare reports of EBV positivity, as a secondary event of reactivation of the virus, have been reported[1]. HSTCL usually presents with an intrasinusoidal infiltration of the bone marrow and absence of nodal disease[1]. Rare EBV positivity has also been described in primary cutaneous γδ T-cell lymphoma[2], but a systemic disease at diagnosis is extremely rare for a primary cutaneous γδ T-cell lymphoma[13].

For all the above, the histological diagnosis of this case is particularly challenging and emphasizes the importance of a complete clinical history, including past or current medication, and illustrates the difficulty of adequately classify EBV-positive γδ T-cell lymphomas according to the current standardize classification of haematolymphoid tumors. We reinforce the need to further expand and review the classification of these entities.

The cautious use of immunomodulators, including TNF-α inhibitors, high clinical suspicion, and surveillance of possible consequences of prolonged immunosuppression, is warranted to avoid a rapid fatal disclosure associated with the risk of an aggressive lymphoma[14,15].

## Conclusion

The histological diagnosis of this case is particularly challenging and emphasizes the importance of a complete clinical history, including past or current medication, and illustrates the difficulty of adequately classify EBV-positive©™ T-cell lymphomas according to the current standardize classification of haematolymphoid tumors. We reinforce the need to further expand and review the classification of these entities.

The cautious use of immunomodulators, including TNF inhibitors, high clinical suspicion, and surveillance of possible consequences of prolonged immunosuppression, is warranted to avoid a rapid fatal disclosure associated with the risk of an aggressive lymphoma[14,15].

## Funding

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## Conflicts of interest

None.

## Ethical disclosures

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this study.

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained approval from the Ethics Committee for analysis and publication of routinely acquired clinical data and informed consent was not required for this retrospective observational study.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type

of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

## References


1. Alaggio R, Jong DD, Siebert R, Coupland ES, Naresh NK, Chan J. Lymphoid proliferations and lymphomas associated with immune deficiency and dysregulation. In: WHO Classification of Tumours Editorial Board. Haematolymphoid Tumours. 5th ed., Vol. 11. Lyon, France: International Agency for Research on Cancer; 2022.
2. Caudron A, Bouaziz JD, Battistella M, Sibon D, Lok C, Leclech C, et al. Two atypical cases of cutaneous gamma/delta T-cell lymphomas. Dermatology. 2011;222:297-303.
3. Kelsen J, Dige A, Schwindt H, D'Amore F, Pedersen FS, Agnholt J, et al. Infliximab induces clonal expansion of γδ-T cells in Crohn's disease: a predictor of lymphoma risk? PLoS One. 2011;6:e17890.
4. Deepak P, Sifuentes H, Sherid M, Stobaugh D, Sadozai Y, Ehrenpreis ED. T-cell non-Hodgkin's lymphomas reported to the FDA AERS with tumor necrosis factor-alpha (TNF-α) inhibitors: results of the REFURBISH study. Am J Gastroenterol. 2013;108:99-105.
5. Hruska JC, Bertoli JR, Young DY, Burkhart HP, Googe PB. Primary cutaneous anaplastic large cell lymphoma in a patient receiving adalimumab. JAAD Case Rep. 2015;1:56-9.
6. Kyong HJ, Mie JL, Seong RK, Ko WJ, Hyeon GY, Suk JC, et al. Angioimmunoblastic T cell lymphoma in an ankylosing spondylitis patient treated with etanercept. Mod Rheumatol. 2013;23:817-22.
7. Choi Y, Jeon SY, Yoo WH. Hepatosplenic T-cell lymphoma arising in a patient treated with tumor necrosis factor-α inhibitors for ankylosing spondylitis. J Clin Rheumatol. 2019;25:134-5.
8. Dauendorffer JN, Rivet J, Allard A, Bachelez H. Sézary syndrome in a patient receiving infliximab for ankylosing spondylitis. Br J Dermatol. 2007;156:742-3.
9. Miranda RN, Loo E, Medeiros LJ. Iatrogenic immunodeficiency-associated classical Hodgkin lymphoma clinicopathologic features of 54 cases reported in the literature. Am J Surg Pathol. 2013;37:1895-7.
10. Summers E, Samadashwily G, Florell RS. A unique presentation of an Epstein-Barr virus-associated natural killer/T-cell lymphoproliferative disorder in a white male adolescent. Arch Dermatol. 2011;147:216-20.
11. Chiaki M, Yasushi O, Azusa Y, Chisako I, Masashi A. Epstein-barr virus-associated natural killer/T-cell lymphoma in a patient receiving therapy with anti-tumour necrosis factor and thiopurine. Acta Derm Venereol. 2017;97:273-4.
12. Deneau M, Wallentine J, Guthery S, Gorman OM, Bohnsack J, Fluchel M, et al. Natural killer cell lymphoma in a pediatric patient with inflammatory bowel disease. Pediatrics. 2010;126:e977-81.
13. Lazar JA, Coupland ES, Akkari Y, Berti E, Pulitzer M, Guitart J, et al. Primary cutaneous gamma/delta T-cell lymphoma. In: WHO Classification of Tumours Editorial Board. Haematolymphoid Tumours. 5th ed., Vol. 11. Lyon, France: International Agency for Research on Cancer; 2022.
14. Subramaniam K, Yeung D, Grimpen F, Joseph J, Fay K, Buckland M, et al. Hepatosplenic T-cell lymphoma, immunosuppressive agents and biologicals: what are the risks? Intern Med J. 2014;44:287-90.
15. Pozadzides JV, Pro B. Editorial: hepatosplenic T-cell lymphoma and TNF-α inhibitors. Expert Rev Hematol. 2009;2:611-4.