CASE REPORT

# Peripheral T-Cell Lymphoma, Not Otherwise Specified – a case report and short literature review

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**ABSTRACT**

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is the most common subgroup of peripheral T-cell lymphomas (PTCL), and constitutes a diagnosis of exclusion. At presentation, most patients exhibit B symptoms and generalized lymphadenopathy, with or without concomitant extra-nodal involvement. We present a case of a man admitted to the hospital with B symptoms, generalized lymphadenopathy and a pruritic exanthema. Laboratory workup reveled persistent eosinophilia and malignant hypercalcemia. The excisional lymph node biopsy diagnosed PTCL-NOS, and the skin biopsy demonstrated a lichenoid dermatitis, compatible with the presumptive clinical diagnosis of a drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. The patient was treated with topical betamethasone with good overall response, and initiated the first cycle of chemotherapy before discharge. This case report describes a PTCL-NOS with a concomitant non-lymphoproliferative disease, the challenging diagnostic workup of the two diseases and reinforces the most important features of the lymphoproliferative neoplasm.

**KEYWORDS:** Peripheral T-cell lymphoma; PTCL-NOS; lymphadenopathy; DRESS syndrome

## INTRODUCTION

Peripheral T-cell lymphoma, not otherwise specified (PTCL-NOS) is the most common subgroup of Peripheral T-cell lymphomas (PTCL), and constitutes a diagnosis of exclusion. The pathogenesis of the disease is currently poorly understood, conditioning a shortage of reliable and effective treatments.

PTCL-NOS typically remain asymptomatic until the disease evolves into later and aggressive stages, making the diagnosis a challenge. At this point, the patient presents with generalized lymphadenopathy, eventually with extra-nodal involvements such as medullary or splenic. Cutaneous involvement is an uncommon feature.

We report a case of a PTCL-NOS with a concomitant drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome which, in this case, increased diagnostic complexity, followed by a discussion on the workup and etiologic investigation performed, and a short literature review on the topic.

## CASE REPORT

We present a 68-year-old male with a past medical history of ischemic stroke in 2015 (no sequelae) and hypertension, who presented in the Emergency Department with a 3-month history of asthenia and anorexia, as well as night sweats- sometimes accompanied with notion of fever- with 2 weeks. The patient also reported a maculopapular pruritic exanthema in the trunk and back that started 3 days before. There was no known history of immunosuppression or relevant epidemiological context.

The patient was chronically medicated with aspirin, atorvastatin and perindopril, and for the last 3 weeks, with oral terbinafine 250 mg for an onychomycosis, which was discontinued after 1 week allegedly because of an associated sickness sensation.

Physical examination revealed fever (38.9C), tachycardia, and hard, painless, immobile and multi-size (maximum 3-4cm) supraclavicular, axillary and inguinal adenomegalies. Initial laboratory workup revealed leukocytosis (with neutrophilia), increased cytocholestasis enzymes, and increased inflammatory markers. He was admitted in the Internal Medicine ward to continue etiologic investigation.

Since the admission, the patient maintained the B symptoms, with one daily fever peak despite optimal antipyretic treatment. He also developed purulent tonsillitis, with progressive odynophagia and solid dysphagia, initially interpreted as streptococcal, thus initiating treatment with clindamycin and later added ceftriaxone, due to poor response. The previously described exanthema evolved with centrifugal, from trunk and back to upper and lower limbs,

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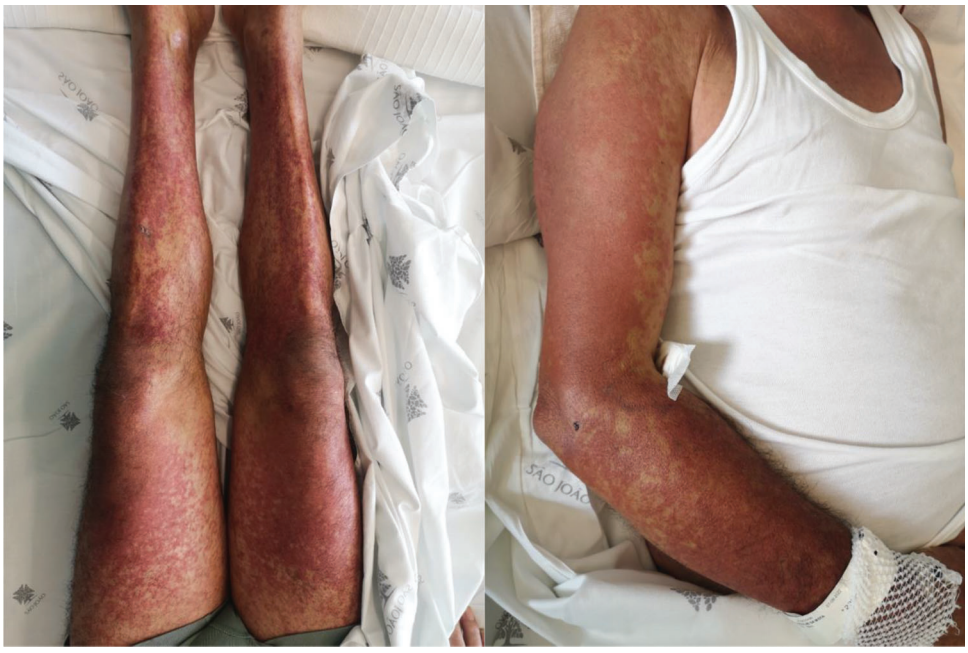

**Fig. 1.** Maculopapular coalescing and symmetric exanthema of the limbs. No blisters or vesicles observed, and negative Nikolsky sign.

symmetric and coalescing features; without blisters or vesicles and negative Nikolsky sign (Figure 1). There was an associated facial swelling without oral/ ocular/ genital mucosa involvement. Pruritus was controlled with antihistaminics.

At this point, laboratory findings were consistent with persistent leukocytosis, fluctuating between $12.00x10^9$/L and $18.00x10^9$/L leucocytes, with relative or absolute neutrophilia (max. $13.00x10^9$/L) but always with absolute eosinophilia (max. $3,52x10^9$/L); persistent cytocholestasis (max. AST 142 U/L, ALT 161 U/L, ALP 166 U/L, total bilirubin 1,92 mg/dL); increased lactate dehydrogenase (max. 798 IU/L); malignant mild hypercalcemia (max. 1,51mmol/L ionized calcium); and increased inflammatory markers (CPR always above 100mg/L). Peripheral blood smear, protein electrophoresis, immunoglobulin and free light chain analysis revealed no abnormalities. No proteinuria was observed. Serum and urinary immunofixation were negative. Serial blood cultures were also consistently negative. Serum virologic panel was strongly positive for HHV-6 (230,000 copies/mL) and CMV (5010 IU/mL); and slightly positive for EBV (500 cp/mL) and Parvovirus (<150 cp/mL). HIV, HBV, HCV, VZV antibodies were negative.

On the presumption diagnosis of a DRESS syndrome, the patient started empirical topical betamethasone, with overall good response over a 14-day period, until complete resolution of the dermatosis (Figure 2). Oral corticosteroids were not contemplated in order to avoid obscure a possible lymphoproliferative diagnosis. At this point, lymphoproliferative neoplasm with probable involvement of the Waldeyer ring was contemplated, since the patient responded poorly to the antibiotics. A scrape cytology examination of the tonsils revealed a nonspecific inflammatory necrotizing process. Tonsil EBV screening was positive. Serum antistreptolysin O was negative. Nonetheless, the course of antibiotic was completed.

In order to establish a definitive diagnosis, the patient underwent inguinal lymph nodule excisional biopsy. Histopathologic examination revealed a complete effacement of the nodal architecture by a diffuse infiltrate of medium-sized lymphoid cells with irregular and hyperchromatic nuclei, and large lymphoid cells with irregular and vesicular nuclei with prominent nucleoli (Figure 3A). The background was composed of small lymphocytes and clusters of epithelioid histiocytes, sometimes surrounding foci of ischemic necrosis. Numerous mitotic figures were present. Immunohistochemistry studies revealed that the atypical lymphoid cells expressed diffusely CD3 (Figure 3B), with partial loss of CD5 and multifocal expression of CD4, CD8, PD-1 and ICOS (CD278). These findings were consistent with PTCL-NOS. EBV-encoded RNAs in situ hybridization (EBER) was negative. Lymph node cultures and Ziehl-Neelsen histochemical staining were negative.

Bone marrow infiltration was discarded by biopsy. Medullary lymphocyte population immunophenotyping revealed CD4/CD8 inversion. Staging $^{18}$fluorodeoxyglucose positron emission tomography combined with computed tomography ($^{18}$FDG-PET/CT) showed high-grade metabolic lymphoproliferative disease with bilateral supra and infradiaphragmatic involvement, and likely splenic and Waldeyer-ring involvements (Figure 4).

Skin biopsy confirmed the clinical presumptive diagnosis of DRESS syndrome, revealing a lichenoid reaction pattern with epidermal changes including hyperkeratosis, infiltrating lymphocytes, vacuolar alteration of some of the basilar keratinocytes and scattered Civatte bodies. In the dermis there was a superficial perivascular and interstitial infiltrate, composed of small lymphocytes and histiocytes, with scattered eosinophils (Figures 5A and 5B). No atypical lymphocytes were observed, excluding lymphoproliferative involvement.

After the establishment of the definitive diagnosis, and since the patient was presenting with limiting B symptoms accompanied by dysphagia, he was transferred to the Hematology department to initiate treatment. He started the first cycle of chemotherapy regimen with CHOP

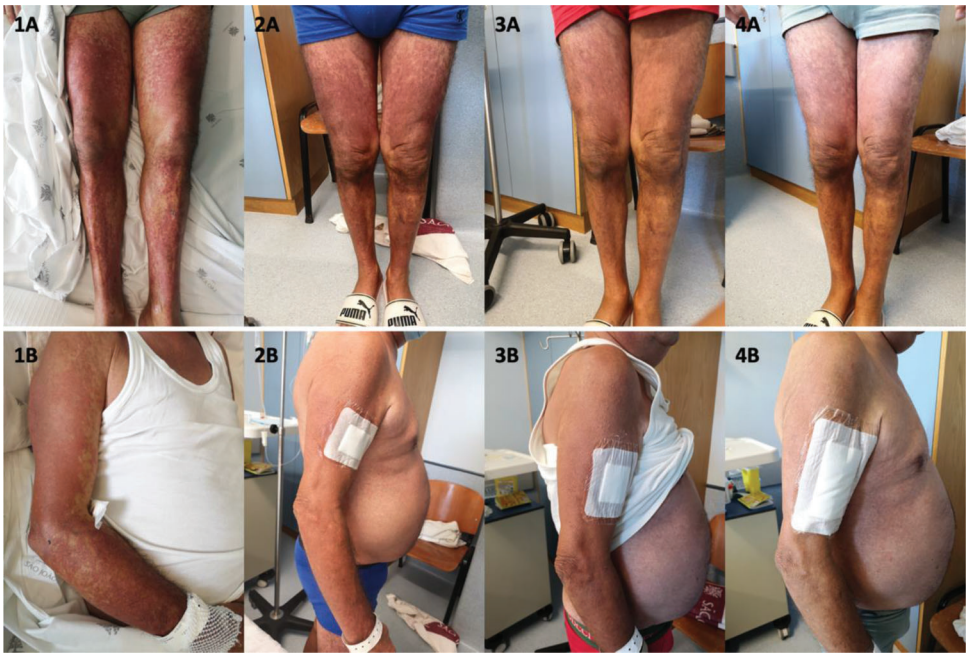


**Fig. 2.** Dermatosis evolution. Pre-treatment with betamethasone (1A/1B). Post-treatment: 2A/2B (fourth day); 3A/3B (seventh day); 4A/4B (eleventh day).

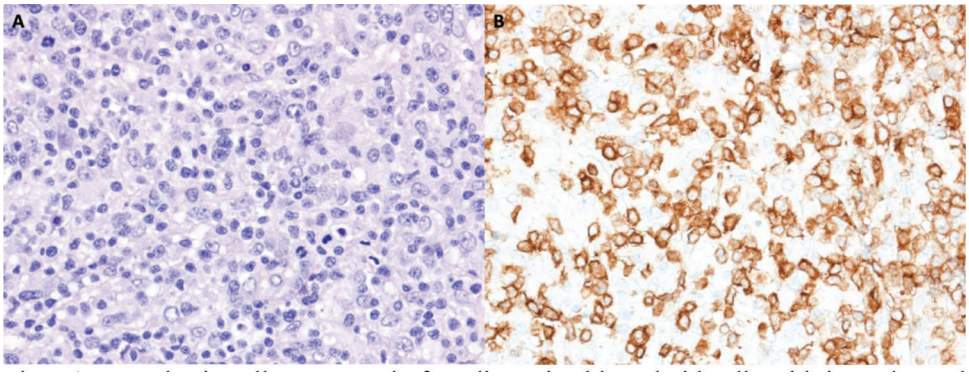


**Fig. 3.** A- Neoplastic cells composed of medium-sized lymphoid cells with irregular and hyperchromatic nuclei and large lymphoid cells with irregular and vesicular nuclei with prominent nucleoli. Numerous mitotic figures are seen (HE, 400x). B- Atypical lymphoid cells positive for CD3 (IHC, anti-CD3 Ab, 400x).

(cyclophosphamide, doxorubicin, vincristine and prednisone), and supportive therapy with filgrastim. At discharge, the patient was referred to a short-term Hematology appointment, prior to the beginning of the second cycle of chemotherapy.

## DISCUSSION

In this article we present a case of PTCL-NOS with a concomitant cutaneous non-lymphoproliferative disease.

PTCL, which represent 10-15% of non-Hodgkin lymphomas, are a group of neoplasms that arises from the proliferation of mature post-thymic lymphocytes. They are broadly categorized according to their presentation, and furtherly, based on their morphology, immunophenotype and genetics [1]. PTCL-NOS, the most common subtype of PTCL, is a heterogeneous entity with a poorly understood pathogenesis, thought to have origin in T-helper cells. Deregulation of signaling pathways, clonal expansion of T-cell receptors (TCR) rearrangements, and cytogenetic aberrations have been reported but, more recently, two possible biological variants, according to their T-helper-cell transcriptional program, with prognostic and therapeutics implications, are admitted. Nonetheless, the current limited knowledge on clinicopathologic, genomics and mutational profiles does not allow further subdivisions, making this entity a diagnosis of exclusion [1-3].

The clinical presentation of PTCL-NOS is usually advanced (stage III or IV, Lugano classification) and aggressive (intermediate to high International Prognostic Index (IPI) scores), more frequently affecting men between in the sixth and seventh decades of life at diagnosis. Most patients exhibit B symptoms and nodal involvement (typically generalized), but can also demonstrate extranodal or medullary involvements.

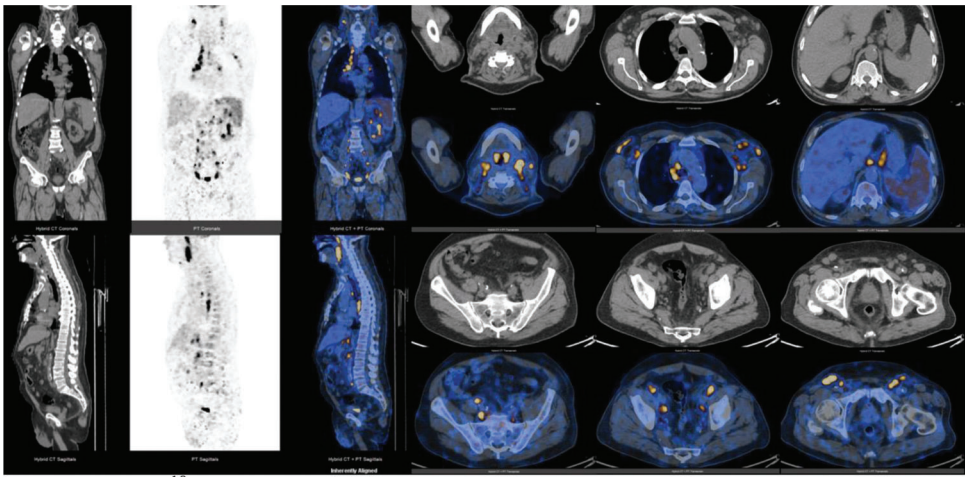

**Fig. 4.** Staging $^{18}$FDG-PET/CT demonstrating bilateral supra- and infradiaphragmatic lymphoproliferative involvement.

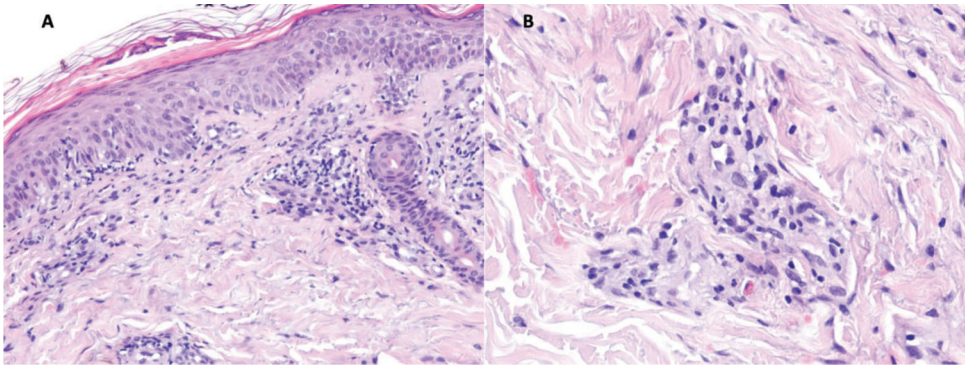


**Fig. 5.** A- Epidermis with hyperparakeratosis, infiltrating lymphocytes, vacuolar alteration of basilar keratinocytes and dermis with superficial perivascular and interstitial infiltrate of small lymphocytes and histiocytes (HE, 200x). B- Scattered eosinophils in the dermal infiltrate (HE, 400x).

Analytic features like anemia, lymphocytosis, eosinophilia, hypergammaglobulinemia or increased lactate dehydrogenase may be present [4-6].

Cutaneous involvement is not a frequent feature of PTCL-NOS. In our case, the clinical and temporal characteristics of the exanthema, with late presentation and the slow resolution, associated with the history of terbinafine usage, the presence of eosinophilia, the presence of increased cytocholestasis enzymes, and the HHV-6 and EBV positivity were clinically in favor of a DRESS syndrome (RegiSCAR score of 6 points). This was later confirmed by biopsy, thus excluding cutaneous lymphoproliferative involvement [7]. The authors admit that the observed eosinophilia might have had also a contribute from the lymphoproliferative neoplasm, since eosinophilia persisted for five weeks without improvement. In fact, the eosinophilia only resolved with the immunosuppression chemotherapy-induced, nonetheless oral corticosteroids would have also elicited a positive response in eosinophilia DRESS-induced.

An excisional nodal or extra-nodal biopsy is crucial for the diagnosis of PTCL-NOS (and other lymphomas), which should be examined by a pathologist with hematopathology expertise. The diagnosis is made mainly considering the morphology and immunophenotype of the neoplasm [1,8]. PTCL-NOS classically has an aberrant T-cell phenotype consistent with loss of CD5 and CD7, CD4>CD8 (in nodal presentations is predominantly CD4+/CD8-), variable CD30 and CD56 expression, cytotoxic granule expression, and TCR genes clonally rearranged (mostly $\alpha\beta$). It does not also fulfill morpho-immunophenotypic features of the main differential diagnosis: nodal T-follicular helper cell lymphomas, anaplastic large cell lymphomas and EBV-positive lymphomas [1,9].

Laboratory analysis should include a complete blood count, a routine biochemistry and virologic screening for HIV, HTLV-1, HCV, HBV, and EBV. Peripheral blood smear is important for differential diagnosis, as well as bone marrow biopsy and/or aspirate for the differential diagnosis and staging [10]. Re-biopsy at relapse should be performed, if possible [8].

To assess the extent of the disease imaging studies should be performed. As computed tomography (CT) is widely available, it can be used first to support clinical findings and allow staging. Nonetheless, $^{18}$FDG-PET/CT is the preferred method for staging and restaging after end-of-treatment, with a superior sensitivity, as PTCL are FDG-avid neoplasms [8,11].

Outcomes are predicted preferentially by conventional IPI tool [12]. Our patient was a newly diagnosed, stage IV and high-risk IPI score (4 points) PTCL, that presented with a

concomitant DRESS syndrome, presumably terbinafine-induced. The particularly aggressive presentation and evolution, notably with evolving and sustained dysphagia with poor response to antibiotics, made us contemplate a very likely Waldeyer-ring involvement by the lymphoproliferative neoplasm, nonetheless a possible EBV contribute could not be ruled out since tonsil EBV screening was positive. Indeed, the overall perception of the authors was that the patient was admitted fully autonomous, and was later transferred to the Hematology department very debilitated, emaciated, with disuse myopathy and not tolerating solid nourishment, which could degenerate into an eventual fatal outcome.

Regarding treatment strategies, these are separated in newly diagnosed PTCL-NOS (with induction and consolidation phases) and relapsed/ refractory disease [6]. Inclusion in clinical trials, for both untreated and relapsed/ refractory patients, should be contemplated throughout the process [8,10].

Induction should be performed with CHOP, especially if the patient is older than 60 years old. Some variants, like adding etoposide (CHOEP) might improve event-free survival in younger patients, although conclusive data supporting its use is lacking and incremented toxicity is expected. CHOP dose-intensive strategies are not currently recommended [3,8,10]. High dose corticosteroids schemes may be used in frail patients, for symptomatic control, not otherwise eligible for intensive chemotherapy [13]. Other alternative treatments, including autologous hematopoietic stem cell transplant (aHSCT) may be used; nonetheless results regarding their benefit are sparse and conflicting [8,14-16]. There is no standardized treatment for relapsed or refractory disease. Chemotherapy recommendations should be made on an individual basis, and non-cross resistant multiagent chemotherapy should be offered [8]. Regardless, prognosis of relapsed PTCL-NOS is very poor with overall survival of a few months [17].

## CONCLUSION

PTCL-NOS are relatively rare lymphoproliferative neoplasms and typically have an aggressive clinical presentation. Diagnostic approach may be challenging, especially if more diseases are present. Rapid and explosive evolutions with possible airway compromise should prompt treatment initiation.

### Informed Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available, upon request, for review by the Editor-in-Chief of this journal.

### Conflict of interest statement

The authors have no conflicts of interest to report.

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