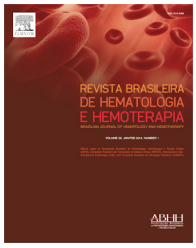
Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy

www.rbhh.org



Special article

Primary nodal peripheral T-cell lymphomas: diagnosis and therapeutic considerations

Luis Alberto de Pádua Covas Lage[a], *Tamara Carvalho dos Santos Cabral*[a,*], *Renata de Oliveira Costa*[b], *Marianne de Castro Gonçalves*[a], *Debora Levy*[a], *Maria Cláudia Nogueira Zerbini*[a], *Juliana Pereira*[a]

[a] *Faculdade de Medicina, Universidade de São Paulo (USP), São Paulo, SP, Brazil*
[b] *Centro Universitário Lusíada (UNILUS), Santos, SP, Brazil*

ARTICLE INFO

Article history:
Received 16 September 2014
Accepted 10 March 2015
Available online 7 June 2015

Keywords:
T-cell Lymphoma
Diseases classification
Immunophenotyping
World Health Organization
Antineoplastic combined chemotherapy protocols

ABSTRACT

Nodal peripheral T-cell lymphomas are a rare group of neoplasms derived from post-thymic and activated T lymphocytes. A review of scientific articles listed in PubMed, Lilacs, and the Cochrane Library databases was performed using the term "peripheral T-cell lymphomas". According to the World Health Organization classification of hematopoietic tissue tumors, this group of neoplasms consists of peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma-anaplastic lymphoma kinase positive (ALCL-ALK$^+$), and a provisional entity called anaplastic large cell lymphoma-anaplastic lymphoma kinase negative (ALCL-ALK$^-$). Because the treatment and prognoses of these neoplasms involve different principles, it is essential to distinguish each one by its clinical, immunophenotypic, genetic, and molecular features. Except for anaplastic large cell lymphoma-anaplastic lymphoma kinase positive, which has no adverse international prognostic index, the prognosis of nodal peripheral T-cell lymphomas is worse than that of aggressive B-cell lymphomas. Chemotherapy based on anthracyclines provides poor outcomes because these neoplasms frequently have multidrug-resistant phenotypes. Based on this, the current tendency is to use intensified cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP) regimens with the addition of new drugs, and autologous hematopoietic stem cell transplantation. This paper describes the clinical features and diagnostic methods, and proposes a therapeutic algorithm for nodal peripheral T-cell lymphoma patients.

* *Corresponding author at*: Rua Dr. Ovídio Pires de Campos, 225, 1° andar, PAMB, sala 61, Cerqueira César, 05403-010 São Paulo, SP, Brazil.
E-mail address: tamicarvalho@hotmail.com (T.C.d.S. Cabral).

http://dx.doi.org/10.1016/j.bjhh.2015.03.017

Introduction

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of malignancies of the immune system, encompassing more than 40 entities with specific clinical, morphologic, immunophenotypic, and molecular characteristics. In the Western World, NHLs originate from B lymphocytes in 85–90% of cases and from lymphoid T cells and natural killer cells (NK) in 10–15% of cases, while T-cell lymphomas represent a higher proportion of NHL cases in Asian countries, accounting for up to 25% of these neoplasms.[1]

T-cell malignancies derived from precursor or immature T cells originate from leukemia-lymphoblastic T-cell lymphoma. Otherwise, the NHLs that originate from mature T lymphocytes or NK cells are recognized as peripheral T-cell lymphomas (PTCL). The latter represent 12–15% of all NHLs and, according to the World Health Organization (WHO) Classification of Tumors, comprise 22 different entities categorized according to clinical presentation as primary nodal, primary extranodal, primary cutaneous, and disseminated or leukemic forms as summarized in Table 1.[1–3]

This review discusses the main clinical and therapeutic aspects of primary nodal PTCLs such as peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large-cell lymphoma-anaplastic lymphoma kinase (ALK) positive (ALCL-ALK$^+$), and anaplastic large-cell lymphoma-ALK negative (ALCL-ALK$^-$).

Table 1 – World Health Organization classification of peripheral natural killer (NK)/T-cell lymphomas.

Primary cutaneous lymphomas
Mycosis fungoides and Sézary syndrome
Primary cutaneous CD30$^+$ T-cell lymphoproliferative disease
- Primary cutaneous anaplastic large-cell lymphoma (C-ALCL)
- Lymphomatoid papulosis (LYP)
Primary cutaneous peripheral T-cell lymphomas (PTCLs)
- Gama-delta T-cell lymphoma
- CD8$^+$ aggressive epidermotropic cytotoxic
- CD4$^+$ small-medium
Nodal peripheral T-cell lymphomas (PTCL)
Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS)
Angioimmunoblastic T-cell lymphoma (AITL)
Anaplastic large-cell lymphoma (ALCL) anaplastic lymphoma kinase (ALK) positive
Anaplastic large-cell lymphoma (ALCL) ALK negative (provisional)
Extranodal peripheral T-cell lymphomas
Extranodal NK-T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma (EATL)
Hepatosplenic T-cell lymphoma (HSTL)
Subcutaneous panniculitis-like T-cell lymphoma (SPTCL)
Epstein–Barr virus (EBV)-positive T-cell lymphoproliferative childhood disorders
- EBV-positive T-cell lymphoproliferative childhood disease
- Hydroa vacciniforme-like
Widespread or leukemic
T-cell prolymphocytic leukemia (T-PLL)
T-cell large granular lymphocytic leukemia (T-LGL)
Chronic lymphoproliferative disorders of NK cells (provisional)
Aggressive NK-cell leukemia
Adult T-cell leukemia/lymphoma

Methods

A systematic literature search using PubMed, Lilacs (Literatura Latino-Americana e do Caribe em Ciências da Saúde), and the Cochrane Library databases was conducted to identify scientific papers related to the search term "peripheral T-cell lymphomas". Only papers focused on human subjects were included.

Clinical and epidemiological aspects

PTCL-NOS are represented by nodal or extranodal T-cell lymphomas not otherwise categorized as any specific entity in the current WHO classification. These tumors represent 60–70% of all PTCLs, and 5–7% of all NHLs. They occur more commonly in adults with a median age of 60 years and have a slight male predominance.[4–6] Although lymph node involvement predominates in the majority of cases, these lymphomas often disseminate to the bone marrow, liver, spleen, and other extranodal sites such as the skin and lung. They rarely have a leukemic presentation.[5,6] Patients often present with unfavorable clinical characteristics including B symptoms, elevated lactate dehydrogenase (LDH) levels, high tumor burden, advanced disease (Stage III or IV), and poor performance status.[5,6]

The AITL subtype is characterized by a specific clinical syndrome and polymorphic infiltrate involving lymph nodes, with proliferation of high endothelial venules in a tree-like pattern and irregular proliferation of follicular dendritic cells (FDC) with predominantly perivascular distribution. AITL represents the second most common subtype of PTCL (15–20% of cases) with its prevalence only being exceeded by PTCL-NOS. It occurs most commonly in elderly patients (aged 60–65 years), with a slight male predominance.[7]

Typical cases of AITL show acute or subacute systemic features that may mimic drug reactions or systemic infections. Clinically, AITL presents as small and generalized lymphadenopathy, hepatosplenomegaly, and constitutional symptoms. Maculopapular rash occurs in 50% of cases and paraneoplastic manifestations such as arthritis, vasculitis, serous effusions, and neurological manifestations are not uncommon. Laboratory features include eosinophilia, polyclonal hypergammaglobulinemia, elevated serum LDH and erythrocyte sedimentation rate (ESR), as well as circulating autoantibodies (cryoagglutinins, cryoglobulins, immune complexes, positive direct Coombs test) and paraneoplastic phenomena of an immune nature (hemolytic anemia, leukocytoclastic vasculitis, rheumatoid arthritis, and autoimmune thyroid disease).[1,4,7]

ALCL is a PTCL characterized by large polymorphic lymphoid CD30$^+$ cells with abundant cytoplasm and horseshoe- or kidney-shaped nuclei. The three recognized subtypes are ALCL-ALK$^+$, ALCL-ALK$^-$, and primary cutaneous anaplastic lymphoma.[8] ALCL-ALK$^+$ predominates in younger patients, with a median age of 30 years, and represents 3–5% of NHLs in adults and 30% of NHLs in children, with a male pre-