Peripheral T-cell Lymphoma

Raymond Liang

Abstract

Peripheral T-cell lymphoma (PTCL) is relatively uncommon in the Caucasian populations. A relatively high incidence of PTCL is, however, observed in many Oriental populations residing in places such as Hong Kong, Taiwan, Singapore and Japan. This difference in epidemiological pattern in different ethnic populations remains unexplained. Genetic predisposition may be important, but environmental factors, such as HTLV-I infection in Japan, may also contribute. A universally accepted pathological classification is still not available for PTCL. The disease is commonly seen in patients of advanced age, and there is a male predominance. Patients often have clinically advanced stage of disease at presentation. Systemic symptoms are common and the clinical course is often aggressive. PTCL is also characterised by its frequent extranodal presentations at sites such as skin, marrow, nose and liver. Patients sometimes present with atypical features, such as fever of unknown origin, liver failure or haemophagocytosis. A high index of suspicion is required for early diagnosis. The best management of PTCL remains uncertain. The prognosis is generally poor, particularly in those with stage IV disease. Their median survival is often less than 12 months. There is a desperate need to search for better treatment for PTCL and there is some evidence to suggest that more intensive and sequential chemotherapy regimens may improve the prognosis of these patients. High-dose chemotherapy with stem cell support may also be useful. Unfortunately, patients with PTCL are often very elderly and intensive therapy may not be possible. Younger patients who can tolerate more aggressive treatment appear to have a higher remission rate and better possibility of disease-free survival.

Introduction

Most malignant lymphomas are found to be of B-cell origin, and T-cell lymphomas are relatively uncommon except in some areas such as southwestern Japan and the Caribbean, where the human T-cell leukaemia/lymphoma virus I (HTLV-I) infection is endemic.[1] Some subtypes of T-cell lymphomas, including T-lymphoblastic lymphoma and the mycosis fungoides/Sézary syndrome, are well characterised. The others often carry relatively mature T-cell markers and are grouped together as peripheral T-cell lymphoma (PTCL). This heterogeneous group of peripheral T-cell lymphomas is poorly characterised. Despite the recent increase in awareness, there are still very scanty data on their epidemiology and aetiology and a lack of general agreement on the pathological classification. Their clinical behaviour is also poorly characterised. The optimal management of patients with PTCL remains to be determined and the prognostic factors further defined.

Epidemiology

Peripheral T-cell lymphoma is relatively uncommon in the Caucasian populations. For patients with non-Hodgkin's lymphoma (NHL), the proportion of PTCL in the Western countries is only around 10-20%.[1]

In Japan, the incidence of PTCL is as high as 70% in the southwestern region, where HTLV-I infection is endemic. Even in non-endemic areas such as Tokyo, the incidence of PTCL is as high as 40%. A relatively high incidence of PTCL is also observed in many Chinese populations residing in places such as Hong Kong, Taiwan and Singapore where, as in Japan, Hodgkin's disease and follicular lymphoma are relatively uncommon.[2]

Pathological Classifications

Widely accepted pathological classifications for NHL include the Working Formulation (WF) and the Kiel classification.[3,4] Unfortunately, T-cell lymphomas are not adequately classified under the WF. The Kiel classification has proposed a separate system for T-cell lymphoma but this has not yet gained universal acceptance (Table 1).[4] The recently proposed revised European-American classification also attempts to address this problem (Table 2).[5]

Table 1: Kiel classification for T-cell lymphoma

Low grade

Lymphocytic lymphoma
Mycosis fungoides or Sézary syndrome
T-zone lymphoma
Lennert's lymphoepithelioid lymphoma
AILD-like lymphoma
Pleomorphic lymphoma, small cell

High grade

Pleomorphic, medium/large cell
T-immunoblastic lymphoma
T-lymphoblastic lymphoma

Table 2 : Revised European-American Classification for T-cell neoplasms

(1) Chronic lymphocytic leukaemia
Chronic polymorphocytic leukaemia
Lymphocytic lymphoma
(2) Large granular cell leukaemia
T-cell/NK-cell
(3) Mycosis fungoides/Sézary syndrome

(4) Peripheral T-cell lymphoma
medium cell
medium and large cell
large cell
lymphoepithelioid
hepatosplenic gamma-delta T-cell
subcutaneous panniculitic T-cell
(5) Angioimmunoblastic
(6) Angiocentric
(7) Intestinal T-cell
+/- enteropathy
(8) Adult T-cell leukaemia/lymphoma
(9) Anaplastic large cell
CD30+, T- and null cell types
Hodgkin's like

Pleomorphic T-cell lymphoma is one of the commonest types of PTCL. Similar histology is also seen in patients with Adult T-cell Leukaemia/Lymphoma complicating HTLV-I infection. For the HTLV-I - positive cases, the tumour often has a T-helper immunophenotype, and the disease is usually disseminated, involving liver, spleen, bone, skin, marrow and peripheral blood. Hypercalcaemia is common. The disease is often very aggressive.

Angioimmunoblastic lymphadenopathy (AILD)Ðlike lymphoma is another common type of PTCL. The disease is not always preceded by AILD. Histologically, it is characterised by the presence of angio-proliferation with polymorphous cellular infiltrates and interstitial amorphous deposits. Immunophenotypically, it can be of T-helper or T-suppressor type. Patients often present with disseminated disease involving liver, spleen, skin and marrow. Systemic symptoms are common. Infection is often present even at the time of presentation. Positive laboratory findings include hypergammaglobulinaemia, Coomb's positivity and positive anti-nuclear factor. Although it has been classified as a low-grade lymphoma under the Kiel classification, the disease is often clinically aggressive.

T-zone lymphoma is characterised by the presence of malignant T-cells located in the inter-follicular T-zone areas of the lymph gland. Marked epithelioid reaction is a constant feature of Lennert's lymphoepitheioid lymphoma. Both entities are uncommon. Again, although they are both classified as low grade under the Kiel classification, they can be clinically quite aggressive.

There are still many entities not included in the above-mentioned classifications for PTCL. Angiocentric lymphoma is a T-cell tumour characterised by marked angio-invasion and ischaemic tumour necrosis. Immunophenotypically, the tumour carries the markers of both T-cells and/or natural killer (NK) cells. Unlike the other PTCLs, T-cell receptor (TCR) gene rearrangement is often absent in these cases, which may suggest NK-cell origin of the tumour cells. The tumour affecting the nasal region is also sometimes called polymorphic reticulosis.

The Ki-1 (CD30) antigen is an activation-related antigen expressed in a small subset of large cells around the B-cell follicles. The Reed-Sternberg cells of HodgkinÕs disease usually stain positively for this antigen. The CD30 antigen is also found to have variable expression in a variety of T-cell tumours including mycosis fungoides, pleomorphic T-cell lymphoma, AILD-like T-cell lymphoma and Lennert's lymphoepithelioid lymphoma. Also, there is a distinct tumour called Ki-1 anaplastic large cell lymphoma which uniformly expresses the CD30 antigen in the tumour cells, and T-cell markers are also expressed in most of the cases. A characteristic t(2;5) translocation may be found on cytogenetic study. To the inexperienced, the tumour may histologically mimic carcinoma, malignant histiocytosis or Hodgkin's disease. Extranodal involvement such as skin or gastrointestinal tract is common, and the clinical course is usually very aggressive.

The confusion in the classification of PTCL is further complicated by an increasingly described entity: T-cell rich B-cell lymphoma.(6) This is basically a B-cell tumour which is overwhelmed by a T-cell reaction. As a clonal marker for T-cells is not available in immunophenotyping, the reactive T-cells may be mistaken for a malignant component while the truly malignant B-cells are inconspicuous. TCR gene rearrangement is usually absent, and the presence of clonal immunoglobulin gene rearrangement can usually confirm the diagnosis.(7)

Molecular Genetics

There has been more understanding in the pathogenesis of human lymphoma. Factors such as cytogenetic changes, molecular abnormalities, oncogenes and immune suppression may be important. However, most research work has been done on B-cell tumours. Our knowledge of T-cell malignancies remains scanty.

Molecular genetic changes seen in T-cell tumours are quite different from those of B-cell neoplasms. The translocations may involve one of the T-cell receptor genes and an oncogene, such as Ttg1, Ttg2, SCL, Lyl I and HOXII.(1)

Aetiological Associations

The different epidemiological pattern of PTCL in different ethnic populations remains unexplained.(8) Genetic predisposition may be important but environmental factors may also contribute. HTLV-I infection is the only definite aetiological agent associated with T-cell tumours identified so far. It is possible that other unidentified retroviruses may also be important.

The Epstein-Barr virus (EBV) has been known to be associated with many different diseases which are more prevalent in different populations (infectious mononucleosis in Caucasians, Burkitt's lymphoma in Africans and nasopharyngeal lymphoma in Southern Chinese). The virus has also been found to be associated with many other types of lymphoma including Hodgkin's disease, PTCL, polymorphic reticulosis and Ki-1 anaplastic large cell lymphoma as well as other cancers such as thymic tumour and gastric carcinoma.(8)

Nasal lymphoma is very uncommon in the West. However, it accounts for around 5% of all cases of diffuse aggressive lymphoma seen in Hong Kong Chinese.[9,10] The disease is also more commonly seen in many other Chinese populations and in Latin America. Nasal lymphoma affects males predominantly. The tumours usually have an aggressive histology and at least a fifth of them have definite histological features of "polymorphic reticulosis".[9,10] Most carry T-cell as well as NK-cell markers. However, TCR rearrangement is usually absent. Clonal EBV can be found in majority of the cases.[6] Two-thirds have disease clinically localised to the nose or the neighbouring lymph nodes at initial presentation. The disease is usually aggressive and local recurrence is common following initial response to intensive chemotherapy and local radiotherapy.[11]

Clinical Presentations

PTCL is seen predominantly in patients of advanced age, with a male predominance. Patients often have a clinically advanced stage of disease at presentation.[12] Systemic symptoms are common and the clinical course is often aggressive even for tumours classified as low-grade according to the Kiel classification.[13] PTCL is also characterised by its frequent extranodal presentations such as skin, marrow, nose and liver.[12] Patients may present with fever of unknown origin clinically mimicking some kinds of viral infection. When the liver is the predominant site involved, patients may present clinically with marked jaundice, fever and even liver failure. Marked coagulopathy may be present and hence prevents a liver biopsy for diagnosis. Also, patients may present with pancytopenia, and marrow biopsy may reveal the presence of haemophagocytosis. The tumour cells may sometimes be very occult and not obvious in the marrow. Other possible causes of haemophagocytic syndrome, such as infection, have to be excluded. A high index of suspicion is required for early diagnosis.

Management and Prognosis

The best management of PTCL remains uncertain.[14] Most series in the literature report only a small number of patients. There is an impression that the prognosis of PTCL is generally poor, particularly in those with stage IV disease. Their median survival is often less than 12 months. There is a need to search for better treatment for PTCL. Some evidence suggests that more intensive and sequential chemotherapy regimens may improve the prognosis of these patients.[13,14] Unfortunately, patients with PTCL are often very elderly and intensive therapy may not be possible. Younger patients who can tolerate more aggressive treatment appear to have a higher remission rate and better prognosis for disease-free survival.

Bone marrow transplantation has shown results similar to that of B-cell lymphoma for patients with T-cell tumours. Interferons have been used with some success in patients with mycosis fungoides but appear to be less effective in the more aggressive T-cell malignancies. Other more innovative approaches should be explored to improve the prognosis of this group of patients.[14]

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