γδ T-Cell Lymphomas

Philippe Gaulard, Karim Belhadj, and Felix Reyes

T-cell lymphomas expressing the γδ T-cell receptor (TCR) are uncommon, although their frequency may be underestimated. They show a broad clinicopathological spectrum. Besides precursor T-cell lymphoblastic leukemia/lymphoma, various post-thymic γδ T-cell neoplasms have been recognized. Among these, hepatosplenic γδ T-cell lymphoma constitutes the prototype of T-cell lymphomas expressing the γδ TCR and was listed as a provisional entity in the Revised European-American Lymphoma (REAL) classification. The recognition of this lymphoma subtype was further supported by the demonstration that the neoplasm results from a proliferation of nonactivated cytotoxic T cells and is associated with a recurrent cytogenetic abnormality, the isochromosome 7q. More recently, a few cases of hepatosplenic T-cell lymphoma with similar clinicopathologic features and αβ phenotype have been described that are thought to belong to the same entity, and the term "hepatosplenic T-cell lymphoma" is preferred in the current World Health Organization (WHO) classification. Most nonhepatosplenic γδ T-cell lymphomas occur in skin or in mucosal sites, a location that parallels that of normal γδ T cells. In contrast to hepatosplenic γδ T-cell lymphomas, they show an important clinical and morphological heterogeneity, have an activated cytotoxic phenotype, and are not believed to constitute a single disease entity.

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UNLIKE αβ T cells, human γδ T cells constitute only a small proportion (1% to 5%) of the lymphocytes that circulate in the blood and localize to most peripheral organs. γδ T cells are, however, more widespread within some epithelial-rich tissues, such as the intestine, and within sinusoidal areas of the splenic red pulp, where they represent up to 30% of the whole T-cell population.[8,10,31] Their development, which can be thymic-dependent or -independent, the absence of major histocompatibility complex (MHC) restriction, and their ability to recognize soluble protein and nonprotein antigens of endogenous origin also distinguish them from αβ T cells.[6] Their precise functions are not completely understood. Mature γδ T cells are cytotoxic cells that display strong MHC-unrestricted cytotoxic activity, a property reminiscent of natural killer (NK) cells. Both NK cell and γδ T-cell subsets express inhibitory MHC class 1 receptors and cytotoxic molecules including granzyme M,[6] which are features of cells participating in innate immune responses. Thus, γδ T cells appear to be early effectors in the immune response, providing a first line of defense in the epidermal and epithelial linings.[6,7,73]

γδ T cells have rarely been implicated in neoplastic lymphoproliferative disorders. Among T-cell neoplasms, the proportion of T-cell receptor (TCR) αβ versus TCR γδ malignancies differs according to the stage of differentiation of the tumor cells. Thus, a significant proportion of thymic—precursor T lymphoblastic leukemia/lymphoblastic lymphoma—neoplasms (up to 50%) express γδ TCR, whereas only a small percentage of post-thymic T-cell lymphomas are of γδ origin.[16,27,61] Among them, hepatosplenic γδ T-cell lymphoma is a distinct clinicopathologic entity, now recognized in the Revised European-American Lymphoma (REAL) and World Health Organization (WHO) classifications.[33,35] γδ T-cell lymphomas mainly with skin or mucosal localization[4,17,65] show many similarities to other forms of extranodal T- or NK cell lymphomas and may not constitute a single disease entity. In addition, occasional cases of large granular lymphocytes (LGL) leukemias or γδ peripheral T-cell lymphoma (PTCL) with nodal presentation have been reported.[17,45,57,58] Overall, mature γδ T-cell neoplasms appear to belong to the spectrum of cytotoxic tumors sharing a clinicopathologic presentation related to the tissue distribution and functional properties of normal γδ cells.[4]

In this chapter, we first describe the clinical, pathological, phenotypic, and genetic aspects of hepatosplenic γδ T-cell lymphoma, which constitutes the prototype entity among γδ neoplasms, and then review the main features of other nonhepatosplenic γδ T-cell lymphomas (Table 1).

Hepatosplenic γδ T-Cell Lymphoma

Definition and History

Hepatosplenic γδ T-cell lymphoma is an aggressive subtype of extranodal lymphoma, first recognized in

From the Département de Pathologie and EA2348, and the Service d'Hématologie Clinique, CHU Henri Mondor, AP-HP, Créteil, France.

Address correspondence to Philippe Gaulard, MD, Department of Pathology, Hôpital Henri Mondor, Créteil, France.

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Table 1. Main Clinical, Morphological, Phenotypic, and Genetic Features of γδ Peripheral T-Cell Lymphomas

Lymphoma Type	Clinical Features	Cytology	Histopathology	Cell Type	Phenotype	Cytotoxic Profile	Genetics	Clinical Course	Proposed WHO Entity
Hepatosplenic	Splenomegaly, cytopenia, B symptoms, young adults	Monomorphic medium-sized	Sinuses: bone marrow, spleen; sinusoids: liver	Tγδ (Vδ1) (> Tαβ)	$CD3^+$, $CD2^+$, $CD5^-$, $CD7^{+/-}$, $CD56^+$, $CD4^-$/$CD8^-$	Non activated ($TIA1^+$, GrB^-)	Iso 7q ± trisomy 8, EBV^-	Aggressive	Hepatosplenic
T-LGL leukemia	Indolent, neutropenia, RA elderly	Lymphocytic (LGL), azurophilic granules	Bone marrow: interstitial (± sinus)	Tαβ >> Tγδ(Vδ1)	$CD3^+$, $CD8^+$, $CD57^+$	Activated ($TIA1^+$, GrB^+)	? EBV^-	Indolent	T-LGL leukemia
Cutaneous (subcutaneous ± panniculitis-like)	Subcutaneous nodules, extremities	Pleomorphic, variable	Subcutaneous ± dermic infiltrate, atypical lymphoid cells, apoptosis	Tαβ >> Tγδ (Vδ2)	$CD3^+$, $CD2^+$, $CD5^-$ (+) $CD4^-$/$CD8^-$ or $CD8^+$	Activated ($TIA1^+$, GrB^+)	? EBV^-	Aggressive	Subcutaneous panniculitis-like?
Nasal	Destructive nasal lesions,	Pleomorphic, variable	Angiocentrism, angioinvasion, necrosis	NK >> Tγδ(Vδ2)	$CD3^+$, $CD2^+$, $CD5^-$ (+) $CD4^-$/$CD8^-$	Activated ($TIA1^+$, GrB^+)	? EBV^+	Aggressive	Nasal NK/T
Gastrointestinal	Tumors (ulcerated) of the GI tract	Pleomorphic, variable	Variable	— (Vδ3 ?)	$CD3^+$, $CD2^+$, $CD5^-$ (+) $CD4^-$/$CD8^-$	Activated ($TIA1^+$, GrB^+)	?EBV^{+}*† $^-$	Aggressive	*
Nodal	Polyadenopathy, B symptoms	Variable	Variable (from angio-immunoblastic- to anaplastic-like)	—	$CD3^+$, $CD2^+$, $CD5^-$ (+) Usually $CD4^+$	Activated ($TIA1^+$, GrB^+)	? EBV^- (+)	Aggressive	†

*Some cases of gastrointestinal γδ T lymphomas are EBV-positive and could resemble nasal-type NK/T tumors; exceptional cases may correspond to enteropathy T-cell lymphomas.

†Exceptional cases of nodal γδ T lymphomas with ALK expression could correspond to anaplastic large cell lymphomas (?).

Abbreviations: LGL, Large granular lymphocyte; RA, rheumatoid arthritis; GI, gastrointestinal; GrB, granzyme B.

1990 on the basis of its uniform clinicopathologic aspects: hepatosplenic presentation without lymphadenopathy, and peculiar sinusal/sinusoidal pattern of infiltration of the spleen, liver, and bone marrow by the usually monomorphic medium-sized tumor cells of γδ phenotype.[20,26,27,38] Hepatosplenic γδ T-cell lymphomas are not common, but their incidence might be underestimated as their features are not typical for lymphoma, and due to the difficulty in assessing the γδ T-cell origin on routine specimens. According to the literature, they represent less than 5% of all peripheral T-cell lymphomas; a review of 45 documented cases emphasized the striking clinicopathologic features of hepatosplenic γδ T-cell lymphoma.[72] Additional possible cases were excluded because studies on γδ TCR, which rely on frozen tissue immunophenotyping, were not available. The recognition of this lymphoma subtype, listed as a provisional entity in the REAL classification, was further supported by the demonstration that the neoplasm results from a proliferation of nonactivated cytotoxic T cells and is associated with a recurrent cytogenetic abnormality, the isochromosome 7q.[33,35] More recently, a few cases of hepatosplenic T-cell lymphoma with sinusoidal infiltration and αβ phenotype have been described[43,46,64] that are thought to belong to the same entity, and the term "hepatosplenic T-cell lymphoma" is preferred in the current WHO classification.[35]

Clinical Features at Presentation and Diagnostic Strategy

Hepatosplenic γδ T-cell lymphoma has a male predominance and occurs in young adults with a median age of about 35 years,[55,72] although it has also been found in adolescents.[25,43,71] No geographical distribution has been recognized. Patients present with marked splenomegaly and most often hepatomegaly, but without lymphadenopathy.[14,55,72] Many have B symptoms including fatigue, fever, and/or weight loss, although these may be lacking at presentation. There may be abdominal pain. Thrombocytopenia is a constant feature, associated with anemia and/or leukopenia in about half of cases. Idiopathic thrombocytopenic purpura[24,72] or Coombs negative hemolytic anemia[43] may lead to the first symptoms of hepatosplenic T-cell lymphoma have been reported. An overt leukemic picture is rare at presentation and lymphocytosis uncommon. However, after careful examination of blood smears a minor population of atypical lymphoid cells can be identified in some patients.[68] The association with an hemophagocytic syndrome occasionally precipitates a fulminant clinical course.[2] Abnormal liver tests are an inconstant finding. Computed tomography scan shows absence of mediastinal and retroperitoneal lymphadenopathy. In our experience, bone marrow involvement, although often minimal (see below), is constant and results in advanced Ann Arbor stage IV disease in all

patients. Patients also frequently show elevated serum lactate dehydrogenase (LDH) levels and a performance status greater than 1. As a consequence, the majority of patients present with two or three adverse risk factors of the age-adjusted International Prognostic Index and belong to its high-risk group.

In the majority of previously reported cases, the diagnosis of the disease was based on histopathological and immunohistochemical findings obtained after splenectomy and/or liver biopsy. However, in view of the constant and characteristic pattern of bone marrow involvement,[28,68] bone marrow biopsy should now be the recommended first step in the diagnostic strategy of the disease, thus avoiding splenectomy to procure tissue. Furthermore, since the γδ T-cell phenotype cannot be reliably determined on routinely fixed material, diagnosis also requires frozen tissue specimens for TCRδ1 staining or alternatively flow cytometry on marrow cell suspension.

Morphology

The neoplastic cells are usually monomorphic small to medium-sized, with a round/oval or slightly irregular nucleus showing slightly dispersed chromatin and inconspicuous nucleoli. The cytoplasm is pale, somewhat abundant, and most often does not show azurophilic granules on smears or imprints. Pleomorphism is very limited within a single case. Mitotic figures are rare. Cells are located preferentially in the sinusoids of the liver, the cords and sinuses of the splenic red pulp, and the sinuses of the bone marrow.

At splenectomy, the spleen is usually massively enlarged (commonly 1,000 to 3,500 g) and discloses an homogeneous red-purple cut surface with no identifiable gross lesions, and no hilar lymph node enlargement. Histopathology shows marked reduction or complete loss of the white pulp, but the red pulp is diffusely invaded by a more or less dense infiltration consisting of usually monomorphic medium-sized lymphoid cells. The neoplastic cells are present within the cords and, to a variable extent from case to case, the sinuses of the red pulp (Fig 1) Dilated sinuses filled with sheets of neoplastic cells can be observed. Histiocytes may be numerous. Rare cases show features of hemophagocytosis at presentation or during the course of the disease. Hilar lymph nodes, although usually not significantly enlarged, commonly show some involvement confined to sinuses or perisinusal areas, without destruction of the normal lymph node architecture.[11]

Histological involvement of the liver is constant, resulting in hepatomegaly without nodules in more than half of patients at presentation. Liver infiltration always shows a sinusoidal pattern, which can produce pseudopeliotic lesions.[26] A mild portal and periportal lymphomatous infiltrate may also be observed but is not predominant.

Bone marrow involvement, seen in about two thirds of patients, appears to be constant when biopsies are carefully assessed by a combined histological and immunohistochemical approach. Characteristic is a typical, if not specific, sinusoidal pattern of infiltration, the recognition of which appears to be a very useful diagnostic criterion. Initial bone marrow specimens are commonly hypercellular with trilineage hyperplasia, and may be confused with myelodysplastic or myeloproliferative syndrome. Marrow lymphoma infiltration is discrete, often subtle, and difficult to recognize in routine hematoxylin and eosin (H&E)-stained sections, requiring immunohistochemistry for its demonstration; selective or predominantly sinusal infiltrate is composed of atypical small to medium-sized lymphoid cells forming files or aggregates within more or less dilated sinuses, which is strongly highlighted by CD3 immunostaining (Fig 2A and B).[14,28,40,68] Together with the peculiar sinusal distribution in the bone marrow, the demonstration of a $CD3^+$, $CD5^-$, $TIA1^+$ phenotype appears characteristic, if not specific, of hepatosplenic T-cell lymphoma.

Careful examination of aspirate smears may help to identify this minor population of atypical lymphoid cells, which are sometimes described as blast-like cells and may contain fine cytoplasmic granules. Above all, it allows immunophenotyping on fresh cell suspension by flow cytometry, enabling the characterization of the γδ origin of the neoplastic cells in most cases.

Cytological variants, such as large cell or blastic appearance, have occasionally been observed at diagnosis but usually occur progressively during the course of the disease.[20,23,47,68] Their tissue distribution is not distinctive but at a late disease stage, the pattern of bone marrow involvement has a tendency to become more intense, diffuse, and interstitial, not only sinusal, and the neoplastic cells become larger.

Immunophenotype and Genotype

The neoplastic cells have the phenotype and genotype of γδ T cells. The general pattern of expression of T-cell antigens is $CD3^+$, $CD2^+$, $CD5^-$, $CD7^{+/-}$. As normal γδ cells, they are $CD4^-/CD8^-$ or more rarely $CD4^-/CD8^+$ and most cases exhibit the CD56 NK cell–associated marker but are $CD57^-$. They may express CD16. Like most T-cell lymphomas, hepatosplenic γδ T-cell lymphomas show a clonal rearrangement of the TCR γ gene, as demonstrated by polymerase chain reaction (PCR) studies used in routine practice. As expected for γδ T cells, Southern blot or PCR studies demonstrate a rearrangement, usually biallelic, of the TCR δ chain.[38,53] It is noteworthy that γδ lineage commitment does not exclude the presence of TCR β gene rearrange-

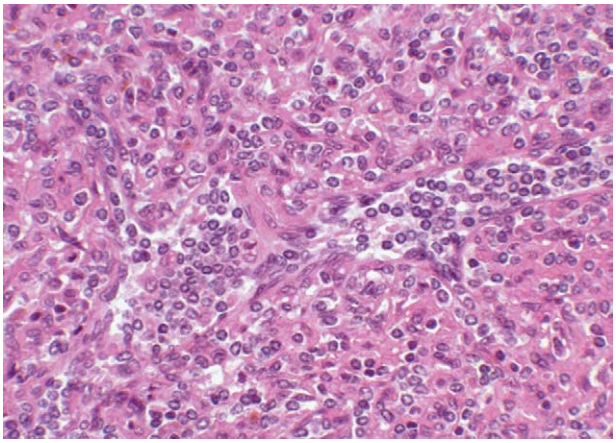

Figure 1. Histopathology of the spleen in hepatosplenic γδ T-cell lymphoma: at a high magnification, presence of an atypical infiltration of the cords and the sinuses by monomorphic medium-sized lymphoid cells.

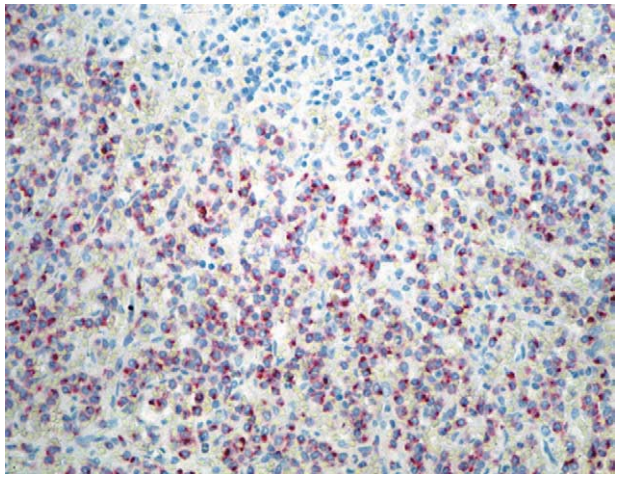

Figure 3. Neoplastic cells involving the spleen in hepatosplenic γδ T-cell lymphoma disclose granular staining for the TIA1 cytotoxic molecule. Note that the neoplastic cells surround residual white pulp, which is TIA1$^-$.

ment. Indeed, unproductive rearrangements of the β chain have been reported in hepatosplenic γδ T-cell lymphoma[18,38] following the same observation in normal γδ T cells.

All cases have a cytotoxic phenotype, as shown by the presence of granular cytoplasmic TIA1 staining (Fig 3) usually of nonactivated type since the great majority of cases do not express the other cytotoxic molecules granzyme B and perforin.[9,14] The presence of serine protease granzyme M is consistent with a derivation from lymphocytes involved in innate immunity.[41] Cytotoxic activity has been demonstrated in a few cases.[71] Neoplastic cells are also negative for CD25 and CD30 activation antigens. Expression of killer immunoglobulin-like receptors and of CD94/NKG2A was reported in one case.[32] By definition, the malignant cells express on frozen sections the γδ TCR, as shown by the βF1$^-$/TCRδ-1$^+$ phenotype. However, a loss of γδ TCR expression has occasionally been observed at progression, resulting in a "TCR-silent" βF1-/TCRδ-1$^-$ phenotype. The majority of hepatosplenic γδ T-cell lymphomas appear to derive from the subset of γδ T cells having rearranged the Vδ1 gene as revealed by molecular studies and positive staining with the δTCS−1 antibody.[18,27,38,53] Rare cases of PTCL with an αβ TCR phenotype (βF1$^+$/TCRδ-1$^-$) have the same clinicopathologic and cytogenetic features[43,46,64] and are considered to be a variant of the more common γδ form of the disease, according to the WHO classification.[35] Since frozen or fresh material is required to determine

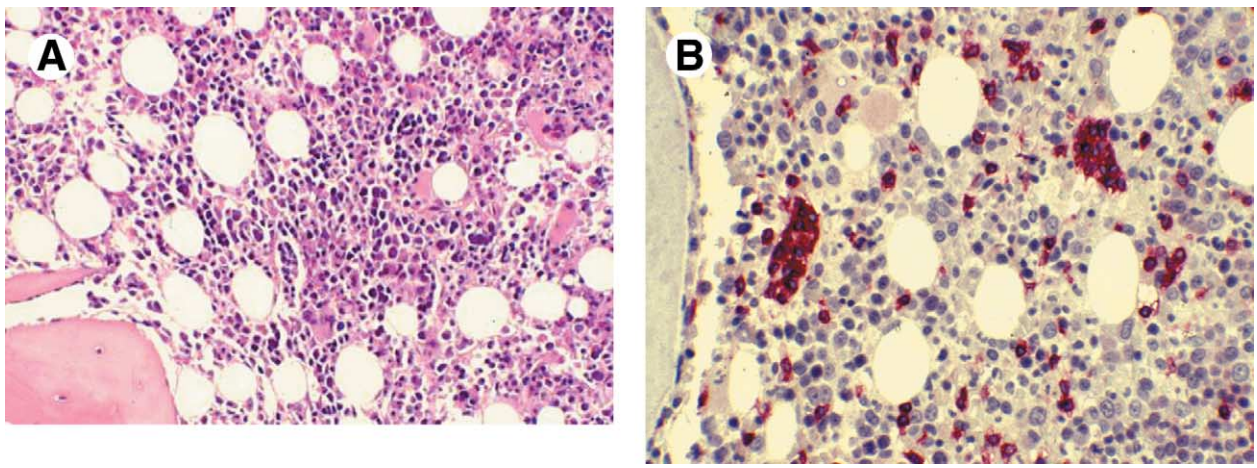

Figure 2. At presentation, the bone marrow in hepatosplenic γδ T-cell lymphoma is usually hypercellular and exhibits a mild elective sinusal infiltrate composed of medium-sized lymphocytes (A) strongly highlighted by CD3 staining (B).

expression of the γδ TCR, the diagnosis of hepatosplenic T-cell lymphoma of γδ T-cell origin cannot be reliably established in routinely fixed paraffin-embedded tissues, which results in a diagnosis of hepatosplenic T-cell lymphoma of undetermined αβ or γδ lineage. In such situations, flow cytometric analysis on marrow aspirate smears are recommended. Indeed, the relative incidence as well as the potential clinical impact of γδ or αβ immunophenotype among hepatosplenic T-cell lymphomas has yet to be determined.

Cytogenetics

By conventional cytogenetics and fluorescent in situ hybridization (FISH) in approximately 40 cases,[74] most γδ hepatosplenic lymphoma have been characterized by the presence of an isochromosome 7q [i(7)(q10)]. This lesion has occasionally appeared as the sole karyotypic abnormality, suggesting the primary role of this recurrent characteristic in the pathogenesis of the disease.[3,13,36,70,74] In contrast, isochromome 7q in other hematological malignancies is generally considered as a secondary aberration associated with tumor progression. In addition to trisomy 8 and loss of chromosome Y, an increased number of 7q signals has been found in progressive cases of hepatosplenic γδ T-cell lymphoma, indicating a tendency to multiply the i(7)(q10) chromosome during evolution of the disease.[34] i(7)(q10) has also been found in hepatosplenic cases with αβ phenotype.[43,46,64]

Viral studies have failed to demonstrate any association with human T-lymphotropic virus (HTLV)-1 and -2, human immunodeficiency virus (HIV), and human herpesvirus (HHV)-8. Only one case has been reported in a patient positive for HHV-6.[44] The vast majority of cases do not show Epstein-Barr virus (EBV) association, with the exception of rare instances with cytological features of transformation, suggesting that EBV might be involved secondarily.[2,49]

Postulated Cell of Origin

The normal cell counterpart is not clearly identified. Hepatosplenic γδ T-cell lymphoma is believed to derive from the subset of immature non activated cytotoxic γδ T cells, showing predilection homing in the splenic red pulp.[8,10] Most γδ hepatosplenic T-cell lymphomas seem to originate from the Vδ1 subset.[27,38,53]

Clinical Course

As recently reviewed,[72] treatment options have shown considerable heterogeneity, including (in addition to splenectomy performed for diagnostic purposes) corticosteroids, alkylating agents, anthracycline-containing CHOP-like regimens, purine analogues, and autologous and allogeneic hematopoietic stem cell transplantation. From available reports and our experience as well, it appears that the disease has a highly aggressive course with only very few, if any, long surviving patients. In our preliminary report of 15 cases,[55] 70% responded to a first-line treatment consisting of a CHOP-like regimen (cyclophosphamide, doxorubicin, vincristine, prednisone) but all experienced early relapse, despite consolidative high-dose therapy with stem cell transplantation in six cases. In this series, all patients have died and the median survival time was 12 months. Thus, therapeutic strategies that have cured a significant proportion of other aggressive subtypes of lymphoma, such as diffuse large B-cell lymphoma, have been ineffective in hepatosplenic γδ T-cell lymphoma, and efficient treatment modalities have yet to be defined. Recently, individual reports have suggested the efficacy of 2′-deoxycoformycin (pentostatin).[1,29] The mechanisms of the resistance to therapy are unknown and may contrast with the relatively low percentage of proliferating cells as well as the apoptotic index.[52]

Relapses or disease progression occur in initially involved sites, such as spleen (when splenectomy has not been performed), bone marrow, and liver, but do not result in lymphadenopathy, thus reinforcing the special homing of neoplastic cells. In exceptional cases, relapses may also involve other extranodal sites, such as skin or mucosae and meninges. B symptoms and cytopenia, particularly thrombocytopenia, parallel disease activity[14] (personal observation). As the disease progresses, leukemic pictures may occur.[63] A "blastic" transformation is frequently seen during the course of the disease with neoplastic cells that become larger and/or more pleomorphic or acquire a blast appearance. During progression, phenotypic changes may occur, such as loss of γδ TCR leading to a "TCR-silent" phenotype (βF1$^-$/TCRδ-1$^-$).[20]

Clinical Context

Intriguingly, a number of hepatosplenic γδ T-cell lymphoma cases have been reported in the setting of chronic immune suppression or prolonged antigen stimulation, especially in patients receiving long-term immunosuppressive therapy for solid organ transplantation.[23,37,40,55,56,63] From these observations and in view of the functional properties of normal γδ T cells, chronic antigen stimulation in the setting of immune defect has been postulated in the pathogenesis of the disease. As an example, expansion of γδ T cells is observed in peripheral blood of kidney transplant recipients[69] and in vitro studies have shown that human γδ T cells display an allo-

reactive response to various leukocyte antigen molecules.[22]

Differential Diagnosis

Hepatosplenic γδ T-cell lymphoma should be distinguished from other lymphomas that commonly present with hepatosplenic disease and show infiltration of the splenic red pulp: mainly T-cell or NK cell neoplasms (aggressive NK-cell lymphoma/leukemia and T-cell LGL leukemia [T-LGL]) and, among B-cell neoplasms, hairy cell leukemia and splenic marginal zone lymphoma. Besides distinct clinical and biological features, the pattern of bone marrow infiltration differs in these entities, and bone marrow biopsy appears to be of value for the differential diagnosis of hepatosplenic T-cell lymphoma. The selective localization of tumor cells within the sinuses of the bone marrow is a characteristic feature of hepatosplenic γδ T-cell lymphoma, irrespective or αβ or γδ derivation, which contrasts with the dense interstitial and often paratrabecular nodules that characterize bone marrow involvement in most other B- and T-cell lymphoproliferative disorders. In T-LGL and in NK cell aggressive cell lymphoma/leukemia, however, the pattern of bone marrow infiltration may be subtle but differs from that observed in hepatosplenic T-cell lymphoma, being usually diffuse and interstitial without elective sinusal predilection. Only in T-LGL is some sinusal pattern observed[48] in addition to a diffuse interstitial lymphocytic infiltrate blending with hematopoietic cells. However, T-LGL is a chronic indolent lymphoproliferative disorder with clinical, cytological and phenotypic features that are clearly distinct from those observed in hepatosplenic T-cell lymphoma, including a common $CD3^+$, $CD8^+$, $CD57^+$ phenotype with expression of granzyme B.[45] Thus, in addition to the selective intrasinusal localization of neoplastic cells in the bone marrow biopsy specimens, the demonstration of a $CD3^+$, CD5−, $CD8^-$, $TIA1^+$, granzyme B phenotype provides a very strong, if not specific, indicator of hepatosplenic T-cell lymphoma.

Other γδ T-Cell Malignancies

γδ T-Cell Lymphoblastic Lymphoma/Leukemia

As mentioned above, a significant proportion (up to 50%) of precursor T-cell lymphoblastic lymphoma/leukemias express γδ TCR.[16,19,58,61] Their clinical and haematological features are similar to the αβ T acute lymphoblastic lymphoma/leukemia with a predilection for children and young adults, and leukemic and/or mediastinal presentation; αβ and γδ subtypes have a similar outcome. These tumors most likely represent the neoplastic counterpart of the normal γδ T cells residing in the thymus.

Cutaneous and Mucosal γδ T-Cell Lymphomas

Besides hepatosplenic γδ T-cell lymphoma, which constitutes the prototype of peripheral T-cell lymphoma expressing the γδ TCR and a large proportion of γδ T-cell lymphoma reported to date, malignant proliferation of γδ T cells can also occur in other extranodal sites (mainly skin and mucosa) and display a marked heterogeneity in terms of clinical presentation and histological features. Although still controversial, it has been proposed that these "non-hepatosplenic γδ T-cell lymphomas" constitute a subset of cytotoxic lymphomas with mucosal or skin localization.

Cutaneous γδ T-cell lymphomas. The frequency of γδ T-cell phenotype among cutaneous T-cell lymphomas is not clearly established, varying from 3% to 32% according to two large series.[54,65] Nearly all cases can be classified either as mycosis fungoides-like or subcutaneous panniculitis-like γδ T-cell lymphomas.[17] A small proportion of patients with γδ T-cell lymphomas primarily of the skin present with plaques, patches, or tumors and show histologic features consistent with mycosis fungoides, with perivascular or dermal infiltrate containing atypical irregular small lymphoid cells associated with marked epidermotropism. Some which show extreme epidermotropism and only a scant dermal infiltrate are reported as pagetoid reticulosis, a rare variant of mycosis fungoides.[5] In contrast to "classical" mycosis fungoides, which are $CD4^+$, mycosis fungoides-like γδ T-cell lymphomas are double-negative for CD4 and CD8. The prognosis of these rare tumors has not been established, but long-term survival has been reported.[4,14]

The majority of primary cutaneous γδ T-cell lymphomas show clinical and histological features reminiscent of subcutaneous panniculitis-like T-cell lymphomas.[4,30,42,54,59,65,66] In addition, a significant proportion of subcutaneous T-cell lymphomas (25% to 60%) are identified as being of γδ T-cell derivation.[66] Patients present with predominant involvement of the extremities with multiple subcutaneous nodules, some ulcerated and necrotic, without widespread dissemination to other sites except terminally. Systemic hemophagocytic syndrome can be observed.[30] Histologically, like αβ phenotype, they are characterized by a predominant subcutaneous infiltrate, with atypical lymphoid cells containing many apoptotic figures (Fig 4). However, some differences with classical subcutaneous panniculitis-like αβ T-cell lymphomas include a tendency for γδ cases to involve the reticular dermis, necrosis, and granulo-

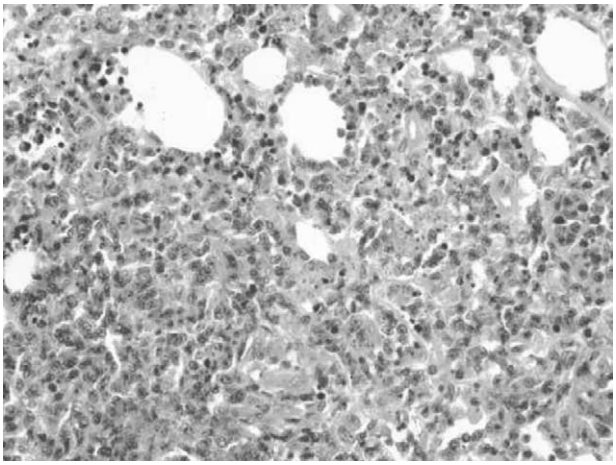

Figure 4. Subcutaneous γδ T-cell lymphoma: the atypical lymphoid cells densely infiltrate the subcutaneous tissue and contain many apoptotic figures.

matous reaction, as well as to display more aggressive clinical behavior. Several patterns of involvement in the skin (epidermotropic, dermal, and subcutaneous) can be observed within a single patient,[65,66] resulting in difficulty to classify such tumors within the WHO scheme. Lesions of cytophagic histiocytic panniculitis without evidence of lymphoma can precede the development of overt subcutaneous γδ lymphoma.

Irrespective of their clinical and histologic aspects, cutaneous γδ T-cell lymphomas are EBV-negative and display an activated cytotoxic profile, either $CD4^-/CD8^-$ or more rarely $CD8^+$.[66] Based on their immunoreactivity with a Vδ2 antibody, they are presumed to be derived from the subset of circulating γδ T lymphocytes, which also can be observed in normal skin.[4,53]

Despite the similarities of cutaneous γδ T-cell lymphomas with their αβ counterpart in most studies cutaneous γδ T-cell lymphomas generally have an aggressive clinical course, sometimes associated with hemophagocytosis. This is supported by the results of a recent series of 104 primary cutaneous T-cell lymphomas comprising 33 γδ T-cell lymphomas and 71 cases with an αβ T-cell phenotype, which showed that patients with subcutaneous involvement and γδ immunophenotype were associated with a more aggressive course with poorer survival than individuals with similar subcutaneous involvement and αβ immunophenotype.[66]

Mucosal γδ T-cell lymphomas. γδ T-cell lymphomas may develop initially in mucosal tissues of the nasopharynx, intestine, as well as occasionally in thyroid, larynx, lung, breast, or testis,[4,15,17,34,39,50,62,67] in agreement with the predilection of normal γδ cells for some epithelia and for mucosae.[31] Clinically, γδ T-cell lymphomas originating in the nasopharyngeal region usually present as destructive nasal lesions or midline facial tumors responsible for nasal obstruction and, like classical nasal NK cell lymphomas, are also preceded by a history of recurrent maxillary sinusitis. Those arising in the gastrointestinal tract display localized or multifocal lesions of the gut, which can even be revealed by peritonitis due to perforation.[4]

Despite localized disease at presentation, most mucosal γδ T-cell lymphomas show an aggressive clinical course, characterized by local recurrence and/or systemic or other mucosal localizations. Morphologically, the neoplastic γδ T cells vary in tumor size and shape among patients, ranging from predominantly

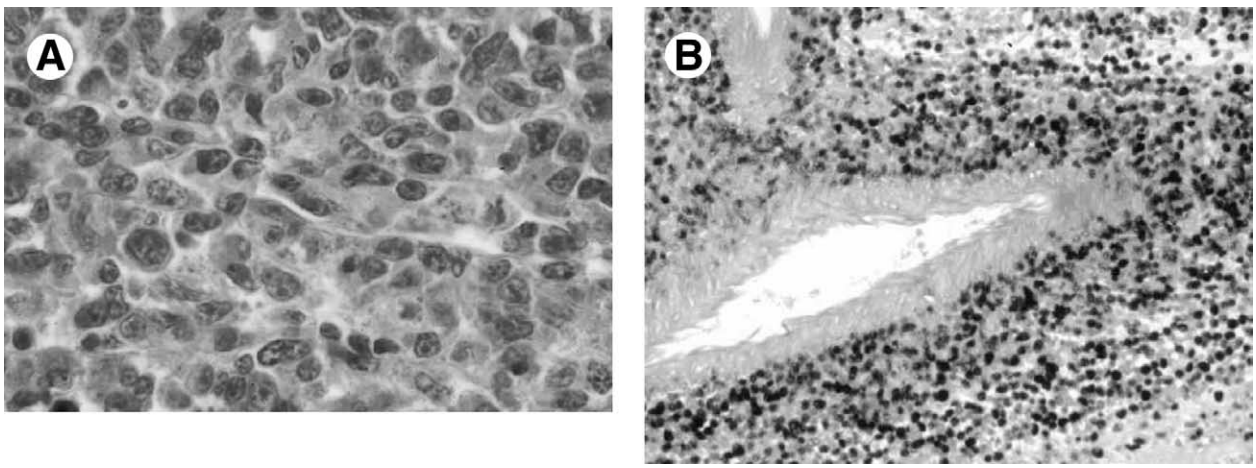

Figure 5. Example of a nasal NK γδ T-cell lymphoma showing (A) pleomorphic large cell cytology (at a high magnification); (B) neoplastic cells surrounding a vessel that contains EBV genomes as shown by in situ hybridization with EBER probes.

small to medium-sized cells to large pleomorphic neoplasms (Fig 5A) Epitheliotropism is common. Necrosis, angiocentrism, and angioinvasion are particularly but not exclusively observed in the EBV-positive nasopharyngeal lymphomas. Immunophenotypically, tumor cells express CD3 and CD2, whereas CD5 is commonly lost and CD7 variable. Most cases are $CD4^-/CD8^-$. Expression of CD56 is inconstant except in nasal lymphomas. They show an activated cytotoxic phenotype (positive for TIA1, granzyme B, and perforin). γδ lymphomas in the nasopharyngeal region as well as occasional cases reported in the larynx or gastrointestinal tract demonstrate EBV association (Fig 5B). In the latter cases, LMP-1 expression suggests that EBV plays a role in their pathogenesis. In view of the clinical and immunomorphologic resemblance of the nasopharyngeal γδ T-cell lymphomas to typical nasal NK cell lymphomas, it has been proposed to group all lymphomas occurring in this region and expressing T-cell markers as well as EBV association into one category termed "nasal-type NK/T-cell lymphoma."[35] Furthermore, a context of gluten-sensitive enteropathy has been described in at least one case of gastrointestinal γδ T-cell lymphoma which was shown to express CD103 molecule and which occurred in a patient with celiac sprue,[4] thus indistinguishable from the entity named "enteropathy-associated T-cell lymphoma." γδ T cells account for a significant proportion (5% to 15%) of intraepithelial lymphocytes, which are cytotoxic cells in a resting state in normal human intestine but are activated and increased in celiac disease.[12]

Overall, it appears that mucosal and cutaneous γδ T-cell lymphomas represent a proliferation of functionally mature cytotoxic activated T cells that express the cytotoxic proteins granzyme B and perforin, able to induce apoptosis.[4,66] The distribution of these lymphomas strongly reflects the localization of normal γδ T lymphocytes, which play a role in host mucosal and epithelial immune responses.[6,73] It is remarkable that many mucosal γδ T-cell lymphomas are described in the context of chronic antigenic stimulation and/or prolonged immune suppression, with patients showing hypogammaglobulinemia or selective immunoglobulin A deficiency or T-cell deficiency responsible for recurrent opportunistic pulmonary infections.[4,17,51]

γδ T-LGL Leukemia

The great majority of T-LGL are derived from αβ T cells,[45] but rare cases of γδ T-cell phenotype have been reported.[17,45,57,58] They mimic in their presentation the αβ counterpart with pronounced neutropenia, frequent anemia and rheumatoid arthritis, and an indolent course. They differ in their phenotype, usually $CD4^-/CD8^-$ and may show an atypical cytological appearance with lack of cytoplasmic granules in a proportion of cases. Like hepatosplenic γδ T-cell lymphoma, most investigated cases express Vδ1 chain, and γδ T-LGL might result from a chronic reactive proliferation of a γδ subpopulation with limited functional properties.

γδ T-Cell Lymphomas Occurring in Lymph Nodes

γδ T-cell lymphomas showing disseminated nodal involvement without extranodal tumor sites are rare.[11,17,21,58] The histological appearance of these primary nodal γδ T-cell lymphomas is not uniform, ranging from angioimmunoblastic-like features to large pleomorphic or even anaplastic morphology. They may exhibit a $CD4^+/CD8^-$ phenotype, reminiscent of the minor subset (1% to 4%) of normal $CD4^+$ γδ T cells. A few cases of anaplastic large cell lymphomas expressing the ALK protein might be derived from this γδ T cell subset.[21] Like the great majority of γδ T-cell lymphomas, nodal γδ T-cell lymphomas resist therapy and have a very poor prognosis.

Conclusions

The ontogeny of γδ T cells, the mechanisms involved in their activation, as well as their precise functions remain incompletely understood. It is known that normal γδ T cells comprise several subsets with different homing within the splenic red pulp, skin, and epithelia, in agreement with the predilection of γδ T-cell lymphomas to present as splenic, cutaneous, or mucosal diseases. γδ T-cell neoplasms were thought to be very rare. However, some recent studies have indicated that the incidence of γδ T-cell neoplasms may be relatively high compared with the frequency of the TCR γδ phenotype in T cells from normal peripheral blood (1% to 10%) and lymph nodes (2% to 4%).[17]

The classification of γδ T-cell neoplasms is still a matter of debate. Indeed, it appears that neoplasms composed of γδ T cells may mimic their αβ or NK cell counterparts, occurring in the same sites and with the same cytotoxic properties, indicating that site of origin and functional properties might be more important than the precise phenotype for the definition of entities among T-cell and NK cell lymphomas. Only hepatosplenic γδ T-cell lymphoma has been defined as a distinct entity, deriving from functionally immature cytotoxic T cells with a nonactivated $TIA1^+$, but granzyme B– and perforin-negative profile. However, cases with the same aspects but with an αβ phenotype may occur and the WHO classification proposed to group the αβ and γδ immunovariants as "hepatosplenic T-cell lymphoma."[35] Mucosal and cutaneous γδ T-cell lymphomas are regarded as a subset of

activated cytotoxic T-cell lymphomas with heterogeneous clinicopathologic aspects. Based on clinical, pathologic, and molecular features in common with other T- cell αβ or NK cell lymphomas, a proportion of non-hepatosplenic T-cell lymphomas were considered to belong to different disease entities, such as nasal-type NK/T-cell lymphomas, subcutaneous T-cell lymphomas, or enteropathy-type T-cell lymphoma. However, the recent finding that, irrespective of the clinicopathologic aspects, γδ immunophenotype has important prognostic implications in cutaneous γδ T-cell lymphomas, raises the question of whether cutaneous and mucosal γδ T-cell lymphomas should be regarded as separate subtypes in the future.[17,66] In this respect, the search for specific karyotypic abnormality(ies) might be important. Finally, further studies are needed to define precisely the roles of chronic antigen exposure and impairment of the immune system—conditions frequently observed in patients with γδ neoplasms irrespective of the clinicopathologic aspects—in the pathogenesis of γδ T-cell lymphomas.

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