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Commentary

The Elementary Switch-Primary Cutaneous Gamma/Delta T Cell Lymphoma

Anubha Bajaj*

Department of Histopathology, Panjab University, A.B. Diagnostics, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University, A.B. Diagnostics, India.

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Primary cutaneous gamma delta T cell lymphoma is a peripheral T cell lymphoma derived from mature, post-thymic, cytotoxic gamma delta (γδa) T cells. Lymphoma incriminates dermis and subcutaneous tissue, akin to subcutaneous panniculitis-like T cell lymphoma and manifests an aggressive clinical course with an inferior overall survival. Indolent subsets delineate prolonged disease stage with subsequent progression into aggressive disease.

Foci of epidermotropism, neoplastic infiltration of dermis or panniculitis-like incrimination of subcutaneous tissue are variably observed wherein lesions may simulate mycosis fungoides and subcutaneous panniculitis-like T cell lymphoma.

The aggressive, peripheral, gamma delta (γδ) T cell lymphoma may manifest patches, plaques and tumour nodules. Mucosal and extracutaneous dissemination is frequent, as is possible emergence of hemophagocytic lymphohistiocytosis (HLH).

Instances with indolent biological behaviour may represent with self resolution of lesions, a disease spectrum which enunciates significant clinical, histologic and immuno-phenotypic concurrence with mycosis fungoides and extra-nodal NK/T cell lymphoma, nasal type.

Exceptionally, indolent clinical behaviour may simulate mycosis fungoides, lymphomatoid papulosis and subcutaneous panniculitis-like T cell lymphoma [1,2].

Subsets demonstrate spontaneous resolution of lesions or prolonged disease and subsequent disease progression.

Primary cutaneous gamma delta T cell lymphoma comprises of < 1% of cutaneous T cell lymphomas. Median age of disease emergence is 60 years although no age of disease emergence is exempt. An equivalent gender predisposition is observed.

Although no site of disease emergence is exempt, primary cutaneous gamma delta T cell lymphoma commonly incriminates gluteal region, thighs and lower extremities [1,2].

Of obscure aetiology, the exceptional primary cutaneous gamma delta T cell lymphoma may evolve in concurrence with precursor T cell dyscrasia and exemplify prolonged, indolent disease resembling mycosis fungoides or inflammatory panniculitides followed by progression of clinical disease.

Primary cutaneous gamma delta T cell lymphoma delineates clonal rearrangement of T cell receptor gamma chain which is indicative of the lymphoma when accompanied by nonspecific histologic features. Clones of neoplastic cells may persist within atypical lymphocytic lobular panniculitis and diverse T cell dyscrasias lacking features of cutaneous gamma delta T cell lymphoma.

Complex karyotype can be detected with single nucleotide pleomorphism (SNP) array comparative genomic hybridization (CGH) demonstrating gains and losses within chromosomal regions associated with RAS and PI3K/AKT/MTOR pathways along with MYC and PT53 signalling [1,2].

Primary cutaneous gamma delta T cell lymphoma manifests with patches, plaques and subcutaneous nodules. Red to violaceous neoplastic nodules may be associated with ulceration. Occurrence of mucosal or salivary gland lesions with focal neurotropism is documented. Regional lymph nodes, bone marrow or spleen are exceptionally incriminated.

Clinical symptoms as pyrexia, night sweats, weight loss, lymphadenopathy and splenomegaly may ensue, reminiscent of autoimmune panniculitis. Subsets may delineate antecedent autoimmune disease. Possible emergence of hemophagocytic lymphohistiocytosis (HLH) is enhanced.

Instances of indolent or prolonged disease with waxing and waning clinical course may be exemplified [1,2].

Primary cutaneous gamma delta T cell lymphoma may exhibit epidermotropism, diffuse infiltration of dermis and divergent subcutaneous involvement. Although variable, epidermotropism may simulate pagetoid reticulosis or mycosis fungoides with configuration of Pautrier's micro-abscesses. Nodular or diffuse configuration of neoplastic lymphocytic infiltrate incriminating dermis may extend between superimposed epidermis with a definitive Grenz zone and subcutaneous tissue.

Neoplastic lymphocytes appear as intermediate cells imbued with abundant pale, eosinophilic cytoplasm and elongated, irregular nuclei with conspicuous nucleoli.

Tumour infiltration of subcutaneous tissue is extensive and variable. Infiltrating lymphoma cells expand intra-lobular adipocytic zones. However, cellular internalization within adipocytes simulating circumscription of subcutaneous panniculitis-like T cell lymphoma may be encountered.

Preliminary lesions may manifest extensive deposition of interstitial mucin, akin to lupus erythematosus panniculitis. Focal necrosis, macrophages ingesting debris and hemophagocytosis are commonly encountered. Foci of angiotropism, adnexotropism and vascular damage are frequent [1,2].

Primary cutaneous gamma delta T cell lymphoma expresses T cell receptor gamma (TCR γ), cytotoxic markers as T cell intracellular antigen 1 (TIA1), perforin or granzyme B. Immune reactivity to CD30 or CD56 is variable.

Primary cutaneous gamma delta T cell lymphoma is immune non reactive to TCR beta F1 or Epstein Barr encoded small RNAs (EBER). Variable decimation of mature T cell antigens as CD2, CD5 and CD7 is encountered. Neoplastic cells appear as CD4-/CD8- although occasional immune reactivity to CD8 is observed [3,4].

Primary cutaneous gamma delta T cell lymphoma requires segregation from neoplasms such as atypical lymphocytic lobular panniculitis (ALLP), extra-nodal NK/T cell lymphoma, hepatosplenic T cell lymphoma, hydroa vacciniforme-like T cell lymphoma, lupus erythematosus panniculitis, lymphomatoid papulosis (LyP), monomorphic epitheliotropic intestinal lymphoma, mycosis fungoides (MF), pagetoid reticulosis, peripheral T cell lymphoma not otherwise specified (NOS), pityriasis lichenoides, primary cutaneous acral CD8+ T cell lymphoma, primary cutaneous anaplastic large cell lymphoma, primary cutaneous CD4+ small/medium sized pleomorphic T cell lymphoproliferative disorder, primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma or subcutaneous panniculitis-like T cell lymphoma [3,4].

Category	Characteristics (age, incidence, gender, median survival)	Variants	EBV infection	Clinical features	Treatment
Hepatosplenic γδ T cell lymphoma	Young adults (35yrs), < 1%, male, < 2 years	None	Yes	Cytopenia, liver, BM, spleen and rare LN infiltration	CHOP-like regimen, allo-SCT. Relapses-bendamustine, bortezomib, lenalidomide, vorinostat
Primary cutaneous γδ T cell lymphoma	Adults, < 1%, none, 15 months	Aggressive, mycosis fungoides-like, subcutaneous panniculitis-like	No	Papule, plaque or nodule with ulceration, overlying epidermal necrosis	CHOP-like regimen, steroid, MTX, UV radiation, bexarotene
Mucosal γδ T cell lymphoma	> 48 years, NK, none, 1 - 1.5 years	GIT, nasal, pulmonary, laryngeal	Yes	HSM, nasal destruction, GI perforation, LN and BM rarely involved	CHOP-like regimen, allo-SCT
Gamma/delta T LGL leukaemia	45 - 75 years, 2 - 3%, none, indolent	None	Yes, few cases	Cytopenia, splenomegaly, BM involved	Steroids, MTX, cyclosporine, cyclophosphamide, fludarabine, pentostatin
Nodal gamma delta T cell lymphoma	NK < 2%, NK, < 1 year	None	Yes	LN, BM infiltration, HSM	CHOP-like regimen, allo-SCT

Table: *Classification of gamma/delta T cell lymphoma [2,3].*

LGL: Large Granular Lymphocyte; LN: Lymph Node; BM: Bone Marrow; GIT: Gastrointestinal Tract; HSM: Hepatosplenomegaly; allo-SCT: Allogeneic Stem Cell Transplant; MTX: Methotrexate; CHOP: Cyclophosphamide, Doxorubicin Hydrochloride, Vincristine Sulphate, Prednisone; UV: Ultraviolet Radiation; NK: Not Known.

Appropriate discernment of primary cutaneous gamma delta T cell lymphoma necessitates an intense clinical and pathological concordance. Exclusion of extra-cutaneous gamma delta (γδ) T cell lymphoma and mycosis fungoides is required.

Multiple surgical tissue samples obtained from various cutaneous sites within a variable duration for identification of clone-specific neoplastic cells is optimal for discerning the lymphoma, in contrast to evaluation of a singular surgical tissue sample.

Multiple tissue samples aid in establishing disease process with assessment of morphological findings progressing from an indolent to aggressive phenotype and occurrence of histologically heterogeneous, synchronous lesions [3,4].

Hemophagocytic lymphohistiocytosis (HLH) manifests distinct diagnostic criterion as

- Pyrexia
- Splenomegaly
- Pancytopenia or bi-cytopenia implicating ≥ 2 lineages
- Hypertriglyceridemia or hypo-fibrinogenemia

- Minimal or absent NK cell activity
- Serum ferritin ≥ 500 µg/litre
- Soluble CD25 ≥ 2,400 units/millilitre
- Evidence of hemophagocytosis confined to bone marrow, spleen or lymph node.

Minimally five of aforesaid diagnostic criteria are required to establish the disease in the absence of genetic mutations associated with hemophagocytic lymphohistiocytosis [3,4].

Primary cutaneous gamma delta T cell lymphoma is generally resistant to radiotherapy and multi-agent chemotherapy. The lymphoma can be subjected to allogenic stem cell transplantation.

Besides, methotrexate or retinoid, analogue as bexarotene and narrow band ultraviolet B therapy can be optimally employed to treat the lymphoma [3,4].

Lesions associated with epidermotropism commencing with patch stage simulate mycosis fungoides and delineate an indolent clinical course, in contrast to lesions representing with plaques and nodules. Nevertheless, subsets may progress to an aggressive phenotype.

Majority of lymphomas represent with an aggressive clinical course. However, pertinent histologic features indicating a completely indolent clinical course as encountered within exceptional instances remain undefined. Morphological features which predict possible emergence of hemophagocytic lymphohistiocytosis remain obscure, although an adverse overall survival is observed in subjects devoid of the sequela. Primary cutaneous gamma delta T cell lymphoma manifests median disease survival of 15 months and 5 year overall survival of up to 33% [3,4].

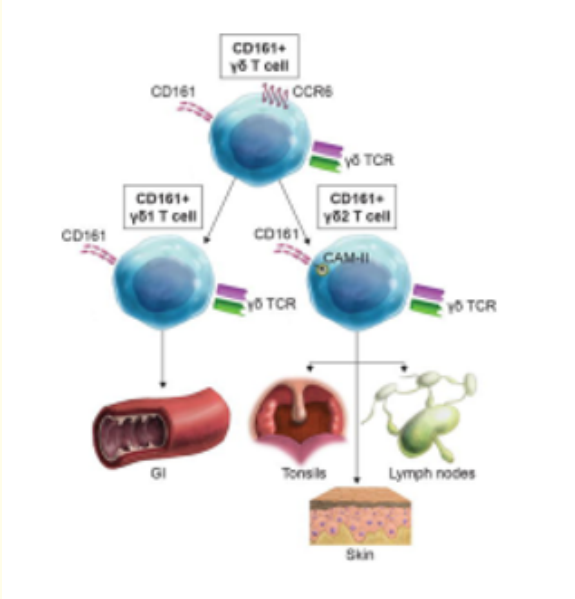

Figure 1: *Cutaneous gamma delta T cell lymphoma demonstrating variants of gamma delta molecules homing towards various subsites of disease incrimination [5].*

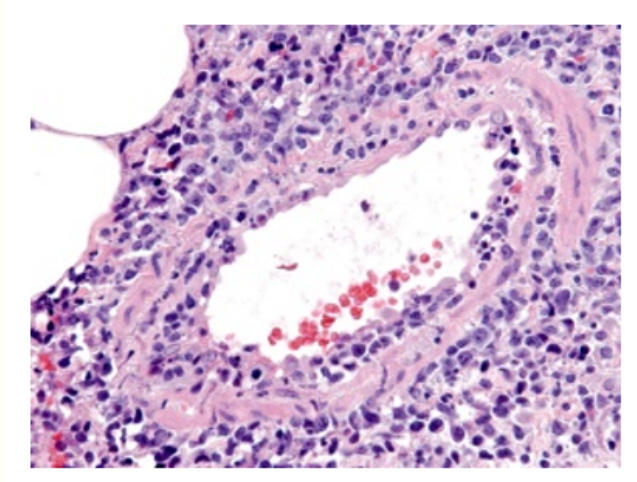

Figure 2: *Cutaneous gamma delta T cell lymphoma delineating infiltrate of neoplastic lymphocytes imbued with abundant pale cytoplasm, elongated, irregular nuclei with conspicuous nucleoli, manifesting dermal aggregates and circumscribing vascular articulations [6].*

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5. Image 1 Courtesy: Intech open.com.
6. Image 2 Courtesy: Pathology outlines.

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