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Short Communication

The Connate Metarteriole-Intravascular Large B Cell Lymphoma

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Intravascular large B cell lymphoma is an exceptionally discerned, aggressive, extra-nodal, mature B cell lymphoma preponderantly confined to intravascular spaces or vascular lumens of miniature or intermediate vascular articulations. The lymphoma commonly arises within cutaneous surfaces or central nervous system and exhibits decimated overall survival. The frequently encountered classical variant demonstrates distinct neurological and cutaneous manifestations. Lymphoma cells circulating within peripheral blood are minimal to absent whereas large arteries or veins are devoid of infiltration by lymphoma cells. Characteristically, neoplastic lymphocytes singularly confined to vascular lumens of miniature to intermediate vascular articulations appear as enlarged cells permeated with vesicular nuclear chromatin and prominent nucleoli. Lymphoma cells appear immune reactive to pan B cell markers as CD19, CD20, CD79a and BCL2 along with MUM1.

Although considered as obsolete, intravascular large B cell lymphoma is additionally designated as malignant angioendotheliomatosis, angioendotheliomatosis proliferans syndrome, intravascular lymphomatosis or angioendotheliotropic lymphoma.

The infrequent intravascular large B cell lymphoma configures ~ 1% of B cell lymphomas. Generally, elderly population is incriminated with median age of disease emergence at 70 years. A slight male preponderance is observed [1,2].

Intravascular large B cell lymphoma selectively implicates vascular lumens of miniature vascular articulations, especially capillaries. Extra-nodal sites such as bone marrow may demonstrate sinusoidal or perivascular dissemination of neoplastic lymphocytes. Commonly, sites such as cutaneous surfaces, central nervous system, renal parenchyma, pulmonary parenchyma and endocrine glands may be incriminated whereas regional lymph nodes are exceptionally involved.

Of obscure aetiology, intravascular large B cell lymphoma manifests cellular localization within vascular lumens, a feature which is partially posited to occur due to lack of β_1 integrin (CD29) and intercellular adhesion molecule 1 (ICAM1) or CD54, molecules which are significant in engendering transmission and migration of lymphocytes across vascular configurations [1,2].

Classic or Western variant of intravascular large B cell lymphoma demonstrates a variable clinical representation with occurrence of few, mild symptoms as pyrexia of unknown origin, pain, organ-specific, localized symptoms or severe manifestations as multi-organ failure or B symptoms ~incrimination of central nervous system is indicated by appearance of heterogeneous symptoms as sensory or motor deficit, neuropathies, meningo-radiculitis, paraesthesia, hemiparesis, seizures or altered sensorium. ~cutaneous lesions are heterogeneous and comprised of painful, indurated erythematous eruption, cellulitis, peau d'orange, miniature, reddish, palpable spots, cutaneous nodules associated with or devoid of ulceration, tumours or erythematous, desquamated plaques. ~characteristically, regional lymph node metastasis is absent. ~incriminated subjects may manifest with disseminated intravascular coagulation inducing crucial haemorrhage following surgical tissue sampling [1,2]. Cutaneous variant is frequently discerned within Western population and occurs within young adults with a median age of disease emergence at 59 years. Singular or multiple cutaneous lesions are discerned along with sparing of additional sites The variant is minimally aggressive and associated with superior over-

all survival. Hemophagocytic syndrome-like variant is encountered within Asian population. The lymphoma manifests with multi-organ failure, hepatosplenomegaly or pancytopenia. Bone marrow infiltration is frequently discerned whereas cutaneous lesions or central nervous system involvement is exceptional. The aggressive variant is rapidly progressive with median survival of 2 months to 8 months [1,2].

Upon microscopy, neoplastic lymphoma cells configuring intravascular large B cell lymphoma may permeate vascular lumens of diverse organs. Neoplastic lymphocytes appear as enlarged cells incorporated with minimal cytoplasm, enlarged nuclei with elevated nucleo- cytoplasmic ratio and singular or multiple, prominent nucleoli. Morphologic spectrum of neoplastic lymphocytes varies from centroblasts to immunoblasts or plasmablasts although anaplastic lymphocytes are exceptionally discerned [2,3].Intravascular large B cell lymphoma delineates diverse patterns of tumour configuration designated as ~dis-cohesive pattern wherein neoplastic lymphoma cells preferentially accumulate within centric segment of vascular articulations and demonstrate a 'free floating' appearance ~cohesive pattern wherein neoplastic lymphoma cells may maximally permeate vascular lumens with partial occlusion. Appropriate assessment of vascular configurations may be challenging ~marginating pattern is infrequently discerned and is constituted of neoplastic lymphoma cells with preferential adherence to endothelium along with a vacant centric segment of intravascular lumen ~infiltration pattern as discerned within vascular articulations of bone marrow are denominated as pure intra-sinusoidal infiltration where neoplastic cells appear amalgamated within intra-sinusoidal spaces intra-sinusoidal infiltration with extravasation where neoplastic cells proliferate within intra-sinusoidal spaces and are accompanied by cellular extravasation diffuse interstitial infiltration where neoplastic cells demonstrate diffuse proliferation confined to the bone marrow [2,3].

Ann Arbor staging of Non Hodgkin's Lymphoma [2,3].

- stage I with involvement of singular lymph node region ~stage IE with involvement of singular extra-lymphatic organ or site
- stage II with involvement of ≥2 lymph node regions on one side of diaphragm ~stage IIE with localized involvement of an extra-lymphatic organ or site and ≥ one lymph node region upon one side of diaphragm stage III with involvement of lymph node regions on opposite sides of diaphragm ~stage IIIS with involvement of spleen ~stage IIIE with involvement of extra-lymphatic site

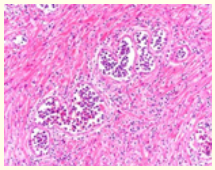

Figure 1: Intravascular large B cell lymphoma impacted with enlarged lymphoma cells with scant cytoplasm, vesicular chromatin and prominent nucleoli surrounding by connective tissue and elastic tissue fibres [5].

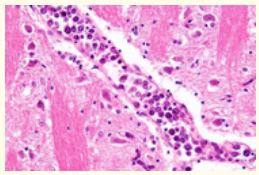

Figure 2: Intravascular large B cell lymphoma enunciating vascular impaction with enlarged lymphoma cells imbued with minimal cytoplasm, vesicular chromatin, prominent nucleoli and circumscribing connective tissue and elastic tissue fibres [6].

- stage IV with diffuse or disseminated involvement of ≥one extra-lymphatic organ or tissue along with or devoid of associated lymph node involvement. Occurrence of systemic symptoms within preceding six months are designated as fever, night sweats or >10% loss of body weight. Absence of systemic symptoms is designated 'A' whereas presence of systemic symptoms is denominated as 'B' within Ann Arbor staging of non-Hodgkin's lymphoma. Incriminated extra-nodal sites are designated as ~M+ with involvement of bone marrow ~L+ with involvement of pulmonary parenchyma ~H+ with involvement of hepatic parenchyma ~P+ with involvement of pleura ~O+ with involvement of bone ~D+ with involvement of cutaneous and subcutaneous tissue.

Characteristically, intravascular large B cell lymphoma manifests with stage IV disease upon initial representation [2,3].

Intravascular large B cell lymphoma is immune reactive to pan B cell markers as CD20, CD79a, PAX5 with reactive BCL2. Majority (~95%) of lymphomas depict a non germinal centre phenotype with immune reactive MUM1/IRF4. Besides, immune reactivity to CD5 or CD34 ensues. Substantial instances express PDL1. Epstein

Barr virus (EBV) or human herpes virus 8 (HHV8) are exceptionally discerned.

The lymphoma is immune non reactive to CD10, CD30, cyclin D1 and BCL6 [3,4].

Intravascular large B cell lymphoma exhibits clonal rearrangements of immunoglobulin genes, genetic mutations of MYD88 L265P, CD79b Y196 and mutations as engendered within neoplastic lymphocytes constituting activated B cell diffuse large cell lymphoma (DLBCL).

Intravascular B cell lymphoma necessitates segregation from neoplasms such as lymphomatoid granulomatosis, primary central nervous system lymphoma, diffuse large B cell lymphoma, central nervous system vasculitis, diverse lymphomas representing as intravascular lymphoma such as extra-cavitary primary effusion lymphoma or various T cell and NK/T cell lymphomas [3,4]. Intravascular large B cell lymphoma can be appropriately discerned with surgical tissue sampling of incriminated, enlarged organ. Commonly, a randomly obtained cutaneous tissue sample in conjunction with bone marrow biopsy appears confirmatory. Incriminated subjects frequently depict anaemia, leukopenia, thrombocytopenia and unexplained hypoxemia. Serum albumin levels are decimated whereas serum lactate dehydrogenase (LDH) and ferritin levels are elevated [3,4]. Upon plain radiography, incriminated pulmonary parenchyma demonstrates nodules and ground glass appearance. Enlargement of various organs as liver, spleen, kidney or adrenal glands is a frequent accompaniment of the disorder. Magnetic resonance imaging (MRI) of brain exhibits hyper-intense lesions confined to the pons, nonspecific white matter lesions, infarct-like lesions or meningeal enhancement. Positron emission computerized tomography (PET/CT) is optimal for discerning bone marrow involvement [3,4]. Intravascular large B cell lymphoma is appropriately treated with chemo-immunotherapy in association with additional central nervous system oriented therapy [3,4]. Intravascular large B cell lymphoma demonstrates a median overall survival of 105 months whereas 5 year survival is ~50% to 60%. Adoption of precise chemotherapy is associated with a median overall survival of 135 months [3,4].

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5. Image 1 Courtesy: Science photo library.

6. Image 2 Courtesy: Wikipedia.com.