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Commentary

Contentious and Ambient-Aggressive NK Cell Leukaemia

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Aggressive NK cell leukaemia (ANKL) is an exceptional disorder simulating morphological and genetic features of extra-nodal NK/T cell lymphoma or diverse natural killer (NK) cell malignancies although an acute clinical representation and aggressive biological course may segregate the malignancy from various NK cell neoplasms. Cogent disease discernment is challenging and the condition demonstrates an unfavourable prognosis.

Aggressive NK cell leukaemia can be appropriately detected with pertinent morphological and immuno-phenotypic manifestations. Incrimination of bone marrow may be preponderant or subtle. Although cytological atypia is significant, a subset of neoplasms may be configured of bland neoplastic cells.

Epstein Barr virus infected (EBV+) aggressive NK cell leukaemia predominantly incriminates Asian population whereas EBV- aggressive NK cell leukaemia implicates diverse ethnic groups. Besides, aggressive NK cell lymphoma devoid of Epstein Barr virus (EBV-) infection is an infrequently discerned variant. The condition demonstrates a significant association with Epstein Barr virus infection although Epstein Barr virus encoded small RNAs (EBER) may be absent.

Aggressive NK cell leukaemia implicates peripheral blood, bone marrow, spleen or hepatic parenchyma [1,2].

Median age of disease emergence is 40 years. A specific gender predilection is absent [1,2].

EBV+ aggressive NK cell leukaemia demonstrates significant quantities of interleukin 10 (IL10) as induced by Epstein Barr virus encoded small RNAs (EBER) [2,3].

Interleukin 10 activates JAK/STAT pathway along with stimulation of STAT3 phosphorylation. Subsequent downstream activation of MYC engenders clonal cellular expansion. EBV- aggressive NK cell leukaemia induces unidentified mechanisms with consequent stimulation of STAT3 phosphorylation along with downstream activation of MYC with subsequent clonal cellular expansion [2,3].

EBV+ aggressive NK cell leukaemia is associated with chronic active infection with Epstein Barr virus. In contrast, EBV- aggressive NK cell leukaemia is accompanied by obscure infections or cellular modifications [2,3].

Array based comparative genomic hybridization (aCGH) analysis exhibits nonspecific cytogenetic features designated as:

- Gains within chromosomes 1q23.1-q23.2 and 1q31.3-q44
- Losses within chromosomes 7p15.1-q22.3 and 17p13.1.

Whole genome and exome sequencing along with next generation sequencing enunciates chromosomal mutations within pathways as

- JAK/STAT pathway comprised of STAT3, STAT5B, STAT5A, JAK2, JAK3, STAT6, SOCS1, SOCS3 and PTPN11
- RAS/MAPK pathway
- Epigenetic modifiers constituted of TET2, CREBBP, KMT2D, BCOR, SET2D or GFI1 genes
- RNA helicase (DDX3X)
- Cell cycle regulation and repair of DNA damage comprised of TP53, ASXL1, ASXL2, BRINP3 genes
- mRNA splicing with PRPF40B gene [2,3].

Aggressive NK cell leukaemia demonstrates cogent clinical symptoms as pyrexia, hepatosplenomegaly, lymphadenopathy and B symptoms as night sweats and loss of > 10% body weight [2,3].

Peripheral blood smear delineates intermediate to enlarged neoplastic cells imbued with moderate, basophilic cytoplasm lacking cytoplasmic granules, 'punched out' cytoplasmic vacuoles, markedly irregular nuclear contour, an open-ended nuclear chromatin and prominent nucleoli.

Upon cytological exam, neoplastic cells are permeated with moderate, basophilic cytoplasm devoid of cytoplasmic granules, 'punched out' cytoplasmic vacuoles, significantly irregular nuclear contour, an open-ended nuclear chromatin pattern and prominent nucleoli [2,3].

Upon microscopy, aggressive NK cell leukaemia demonstrates a prominent or subtle incrimination of bone marrow. Bone marrow delineates distinctive configuration of tumour infiltration designated as interstitial pattern or sinusoidal pattern [2,3].

Neoplastic cells of intermediate magnitude are pervaded with moderate cytoplasm, markedly irregular nuclei, condensed nuclear chromatin and conspicuous nucleoli.

Certain neoplasms are configured of bland neoplastic cells with minimal atypia.

Foci of apoptosis and necrosis are commonly observed.

Typically, geographic necrosis is absent, in contrast to extra-nodal NK/T cell lymphoma [2,3].

Aggressive NK cell leukaemia is immune reactive to CD2, cytoplasmic CD3 epsilon protein, CD56, perforin A, granzyme B, T cell intracellular antigen (TIA), Epstein Barr encoded small RNAs (EBER), PDL1, p53, BCL2 or MYC [5,6].

Aggressive NK cell leukaemia is immune non reactive to surface CD3, CD4, CD5 or T cell receptor alpha/beta (TCRαβ) and T cell receptor gamma/delta (TCRγδ) [5,6].

Flow cytometry exhibits a prominent forward scatter (FSC) along with an enhanced cellular magnitude, as compared to intermingled, non neoplastic, reactive lymphocytes. Immune reactivity to CD2, cytoplasmic CD3 (cCD3), CD16, CD56 or CD94 is consistent. CD7 and CD8 are frequently reactive [5,6].

Additionally, surface CD3 (sCD3), CD4, CD5, CD57, killer Ig-like receptors (KIR) (CD158a-e), T cell receptor alpha/beta (TCRαβ) and T cell receptor gamma/delta (TCRγδ) appear non reactive [5,6].

Aggressive NK cell leukaemia requires segregation from neoplasms such as extra-nodal NK/T cell lymphoma or chronic lymphoproliferative disorder of NK cells (CLPD-NK) [5,6].

T cell prolymphocytic leukaemia
T cell large granular lymphocytic leukaemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK cell leukaemia
Systemic EBV+ T cell lymphoma of childhood
Hydroa vacciniforme-like lymphoproliferative disorder
Adult T cell leukaemia/lymphoma
Extra-nodal NK/T cell lymphoma, nasal type
Enteropathy-associated T cell lymphoma
Monomorphic epitheliotropic intestinal T cell lymphoma
Indolent T cell lymphoproliferative disorder of GI tract
Hepatosplenic T cell lymphoma
Subcutaneous panniculitis-like T cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T cell lymphoproliferative disorder
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous gamma/delta (**γδ)**T cell lymphoma
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T cell lymphoma
Primary cutaneous acral CD8+ T cell lymphoma
Primary cutaneous CD4+ small/medium T cell lymphoproliferative disorder
Peripheral T cell lymphoma not otherwise specified (NOS)
Angioimmunoblastic T cell lymphoma
Follicular T cell lymphoma
Nodal peripheral T cell lymphoma with TFH phenotype
Anaplastic large cell lymphoma ALK+
Anaplastic large cell lymphoma ALK-
Breast implant-associated anaplastic large cell lymphoma

Table: *World health organization classification of mature NK/T cell neoplasms [4].*

Aggressive NK cell leukaemia can be appropriately discerned with bone marrow biopsy, surgical tissue sampling from diverse organs along with computerized tomography (CT) scan, assessment of peripheral blood smear and analysis with flow cytometry employed for possible incrimination by the leukaemia [5,6].

Generally, aggressive NK cell leukaemia enunciates neutropenia, anaemia, thrombocytopenia, elevated serum lactate dehydrogenase (LDH) levels, elevated liver functions tests, disseminated intravascular coagulopathy or hemophagocytic syndrome [5,6].

Aggressive NK cell leukaemia can be appropriately treated with allogeneic hematopoietic stem cell transplantation (SCT), a manoeuver which ameliorates survival outcome for a certain duration. However, consensus based chemotherapeutic regimen for managing the leukaemia is absent [5,6].

Precise chemotherapeutic regimens adopted to manage aggressive NK cell leukaemia are comprised of

- Dexamethasone, methotrexate, ifosfamide, etoposide and L-asparaginase (SMILE)
- L-asparaginase, methotrexate and dexamethasone (AspaMetDex)
- Etoposide, ifosfamide, dexamethasone and L-asparaginase (VIDL).

Prognostic outcomes are inferior and aggressive NK cell leukaemia delineates a median survival of < 2 months, in spite of commencement of intensive chemotherapy [5,6].

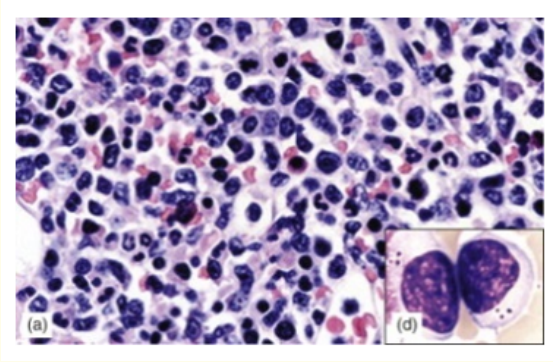

Figure 1: *Aggressive NK cell leukaemia demonstrating an infiltrate of intermediate cells with moderate cytoplasm devoid of granules, irregular nuclei and prominent nucleoli [7].*

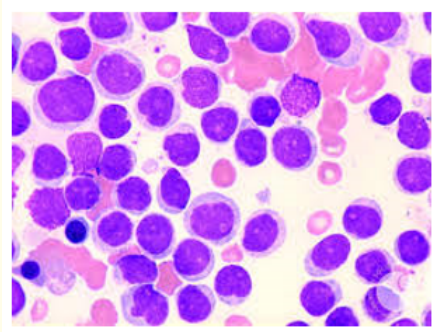

Figure 2: *Aggressive NK cell leukaemia delineating medium sized cells imbued with moderate basophilic cytoplasm with absence of granules, punched out cytoplasmic vacuoles, irregular nuclei and prominent nucleoli [8].*

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7. Image 1 Courtesy: Science direct.
8. Image 2 Courtesy: ASH.com.

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