Acta Scientific CANCER BIOLOGY (ISSN: 2582-4473)

Volume 7 Issue 1 March 2023

Clinical Review

Gyration and Curlicue-Sézary Syndrome

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Received: December 13, 2022

Published: February 24, 2023

Erythrodermic cutaneous T cell lymphoma (CTCL) is constituted of primary cutaneous lymphomas which manifest erythroderma such as Sézary syndrome and erythrodermic mycosis fungoides.

Sézary syndrome is defined as a leukemic variant of cutaneous T cell lymphoma (CTCL) demonstrating erythroderma, generalized lymphadenopathy and clonal T cell proliferation. Clonal, neoplastic T cells are imbued with cerebriform nuclei (Sézary cells) and may disseminate within cutaneous surfaces, regional lymph nodes and peripheral blood.

Initially scripted by Albert Sézary in 1938, the exceptionally discerned Sézary syndrome (SS) may simulate clinically aggressive mycosis fungoides, especially the erythrodermic phase. Nevertheless, mycosis fungoides lacks a distinctive leukemic phase.

Sézary syndrome is contemplated to be distinct from mycosis fungoides and the syndrome may arise de novo. Besides, mycosis fungoides associated with erythroderma and regional lymph node enlargement may be nomenclated as Sézary syndrome preceded by mycosis fungoides. Although morphologically identical to mycosis fungoides, Sézary syndrome is devoid of specific features such as epidermotropism.

Sézary syndrome is a chronic condition wherein disease alleviation is challenging and treatment is directed towards controlling clinical symptoms and ameliorating quality of life [1,2].

Sézary syndrome represents ~5% of cutaneous T cell lymphomas and commonly emerges within sixth decade to seventh decade. The disorder is preponderant within Caucasian population and males wherein a male to female proportion of 2:1 is enunciated.

Mycosis fungoides and Sézary syndrome possibly arise due to chronic antigenic stimulation. Preliminary lesions of mycosis fungoides demonstrate enhanced dendritic cells and upregulation of antigen presenting cell (APC) ligands B7 and CD40 along with pertinent T cell costimulatory ligands CD28 and CD40L [1,2].

Mycosis fungoides and Sézary syndrome are engendered from specific cell of origin designated as cutaneous resident CD45RO+ effector memory T cell.

Antigen presenting dendritic cells may maintain survival and proliferation of clonal T cells and augmented specific human leukocyte antigen (HLA) class II alleles.

It is posited that cutaneous microbiomes as Chlamydia spp may contribute to disease pathogenesis on account of stimulation of clonal T cells [1,2].

Abnormalities within specific pathways as NFκB/JAK STAT activation, cell cycle dysregulation or apoptosis and structural dysregulation of DNA, thereby implicating gene expression may be encountered.

Erythrodermic mycosis fungoides and Sézary syndrome can be segregated with micro RNA expression profile.

Chemokine receptors such as CCR4 and CCR10 may contribute to homing of malignant T cells into diverse cutaneous surfaces with adherence to ligands situated upon endothelial cells, keratinocytes or Langerhans cells.

CCL17 is a predominant CCR4 ligand wherein elevated serum levels discerned within mycosis fungoides and Sézary syndrome

may decimate epidermotropism associated with Sézary syndrome. Decimated CD26 promotes inactivation of CXCL12, a CXCR4 ligand.

Characteristic response of T helper 2 (Th2) is enunciated within Sézary syndrome or tumour stage mycosis fungoides wherein overexpression of CD47 within Sézary cells pertains to Th2 cytokines such as interleukin 4(IL4), interleukin 7(IL7) and interleukin (IL13) [1,2].

Sézary syndrome is devoid of specific driver mutations. Somatic mutations confined to TCR/NFκB signalling, Th2 differentiation (ZEB1), cellular survival as JAK/STAT pathway, epigenetic regulation within DNMT3A, TET2, SMARCA4 genes, homologous recombination as with BRCA2 and cell cycle control as with TP53 is encountered. Activation of NOTCH1 signalling is accompanied by heterogeneous expression of genetic transcripts as upregulation of S100A4, S100A10, GATA3, Twist1, TOX, IL7R, CCR7 and CXCR4 and downregulation of ARID1A, SATB1, STAT4 and Fas gene.

Genomic complexity is exemplified although specific, reoccurring chromosomal translocations or genetic fusions are absent.

Cytogenetic abnormalities as gain of chromosome 17p11.2-q25.3 and 8q24.1-8q24.3 along with loss of chromosome 17p13.2-p11.2 and 10p12.1-q26.3 is enunciated.

Mono-allelic chromosomal deletion of PTEN situated upon genomic locus 10q23 is observed.

Sézary syndrome exhibits pathognomonic feature of mild to intense erythroderma which incriminates > 80% of body surface [1,2].

Uncommonly, initial clinical representation may be with alopecia or plaques as systemic symptoms are absent.

Advanced disease is associated with nail dystrophy, blepharo-conjunctivitis and ectropion.

Generally, palms and soles appear thickened, scaly and fissured. Median duration of appearance of dermatologic symptoms prior to disease discernment is ~3.5 years. Erythroderma may be detected at ~ 1.7 prior to disease emergence.

Clinical representation with erythroderma along with circulating Sézary cells < 1 x 10^9/L is designated as pre-Sézary syndrome. An indolent clinical course or progression to Sézary syndrome may ensue. Pruritus is frequent. Systemic symptoms are generally absent whereas regional lymph node enlargement is observed. Bone marrow is incriminated in ~ 20% instances [1,2].

Sézary syndrome may be preceded by mycosis fungoides and appear disparate from de novo Sézary syndrome.

Upon microscopy, Sézary syndrome morphologically simulates mycosis fungoides. Occasionally, epidermotropism may be absent.

Diagnostic features may range from superficial or perivascular lymphocytic infiltrate and eosinophilic dermatitis along with or devoid of spongiosis. Configuration of atopic-like lesions or a lichenoid lymphocytic infiltrate may be exemplified. Pautrier's micro-abscesses are uncommon [1,2].

Peripheral blood demonstrates Sézary cells comprised of enlarged to intermediate atypical lymphocytes imbued with cerebriform nuclei. Few Sézary-like cells may be encountered within healthy individuals or diverse inflammatory cutaneous diseases.

Regional lymph nodes demonstrate complete effacement of architecture and replacement with a monotonous infiltrate of Sézary cells. Advanced disease stage may be accompanied by enlarged cells or blastoid cellular component [1,2].

Figure 1: Sézary syndrome demonstrating neoplastic lymphocytes imbued with moderate cytoplasm and convoluted, cerebriform nuclei with inconspicuous nucleoli [5].

Figure 2: Sézary syndrome delineating cutaneous infiltration of neoplastic lymphocytes incorporated with moderate cytoplasm and convoluted, cerebriform nuclei with inconspicuous nucleoli [6].

Staging of Sézary syndrome as per International Society of Cutaneous Lymphoma (ISCL) and European Organization of Research and Treatment of Cancer (EORTC) is designated as.

Cutaneous lesions

- T1: Limited patches, papules or plaques covering < 10% of cutaneous surface
- T1a: patch only
- T1b: plaque along with or devoid of patch
- T2: Patches, papules or plaques covering ≥ 10% of cutaneous surface
- T2a: patch only
- T2b: plaque along with or devoid of patch
- T3: Singular or multiple tumours ≥ 1centimetre magnitude
- T4: Confluence of erythema extending to ≥ 80% body surface area

Regional lymph nodes

- NX: Clinically anomalous peripheral lymph nodes devoid of histological confirmation
- N0: Clinically anomalous peripheral lymph node absent
- N1: Clinically anomalous peripheral lymph nodes, Dutch grade 1 or NCI LN0 to LN2
- N1a: clone negative
- N1b:-clone positive
- N2:Clinically anomalous peripheral lymph nodes, Dutch grade 2or NCI LN3
- N2a: clone negative
- N2b: clone positive
- N3: Clinically anomalous peripheral lymph nodes, Dutch grade 3 or 4 or NCI LN4
- N3a: clone negative
- N3b: clone positive

Visceral involvement

- M0: No visceral incrimination
- M1: Visceral incrimination with histopathological confirmation.

Peripheral blood involvement

- B0: Absence of significant blood involvement with ≤ 5% Sézary cells within peripheral blood
- B0a: clone negative
- B0b: clone positive
- B1: Minimal blood tumour burden with > 5% Sézary cells within peripheral blood, lacking criteria of B2
- B1a: clone negative
- B1b: clone positive
- B2: Elevated blood tumour burden with Sézary cells ≥ 1000/ µLitre within peripheral which are clone positive.

Sézary syndrome manifests as disease stage IVA1 as T1 to T4, N0 to N2, M0, B2 and beyond [2,3].

Updated ISCL/EORTC classification	Dutch system	NCI-VA classification
N1	Grade I: dermatopathic lymphadenopathy	LN_o: no atypical lymphocytes
		LN_1: occasional and isolated atypical lymphocytes(lacking clusters)
		LN_2: many atypical lymphocytes or in 3-6 cell cluster

N2	Grade II: dermatopathic lymphadenopathy, early mycosis fungoides(cerebriform nuclei> 7.5µm	LN_3: aggregates of atypical lymphocytes, nodal architecture preserved
N3	Grade III: partial effacement of nodal architecture, many atypical cerebriform mononuclear cells.	LN_4: partial/ complete effacement of nodal architecture by atypical lymphocytes or neoplastic cells
	Grade IV: complete effacement of nodal architecture	

Table 1: Histological staging of lymph nodes in mycosis fungoides and Sézary syndrome [2,3].

ISCL: International Society for Cutaneous Lymphomas, EORTC: European Organization of Research and Treatment of Cancer, LN: Lymph node.

Sézary syndrome demonstrates heterogeneous immune reactivity to T cell markers as CD3, CD4, T central memory phenotype as CD45RO, CD62L and CD197. Subsets may enunciate T naïve or stem cell memory T phenotype with expression of CD45RA. Besides, neoplastic cells are immune reactive to CCR4, CCR7, CD47, CTLA4, PD-1, NOTCH1, Syndecan-4 or TCRVβ. Aberrant expression of MHC class I killer immunoglobulin like receptor as KIR/CD158κ is encountered. The disorder is enriched with a population of CD26-, CD7- lymphocytes.

Sézary syndrome manifests decimated conventional T cell markers as

- CD2, CD5, CD7, CD8, CD25, CD26, CD30 or FOXP3. Aberrant decimation of CD7 or CD26 is commonly observed. Generally, B cell markers appear immune non reactive [3,4].

Sézary syndrome requires segregation from conditions such as non neoplastic erythroderma (pseudo erythroderma cutaneous T cell lymphoma), chronic actinic dermatitis, erythrodermic psoriasis, adult T cell leukaemia/lymphoma, leukaemia cutis or peripheral T cell lymphoma [3,4].

Characteristically, Sézary syndrome manifests erythroderma, generalized lymphadenopathy and clonal T cells aggregated within cutaneous surfaces, regional lymph nodes and peripheral blood accompanied by ≥one criteria designated as

- Absolute Sézary cell count ≥ 1 x 10^9/L
- Alternative diagnostic criteria as ≥ 40% of CD4+/CD7- T cells and ≥ 30% of CD4+/CD26- T cells as observed upon flow cytometry.

T cell receptor β constant region1 (TRBC1) is sensitive and specific for detecting clonal T cells with flow cytometry.

Expansion of CD4+ T cell population with proportionate CD4:CD8 ≥ 10 pertains to elevated absolute CD8 count and proportion may decimate following therapy.

Decimated ≥ T cell antigens may be exemplified.

Demonstration of T cell clonal population may be detected with southern blot or polymerase chain reaction (PCR).

Assessment of clonal T cell population with flow cytometry enunciating a constant chain of T cell receptor or TRBC1 is encountered.

Although variably employed, high throughput sequencing is a sensitive technique for diagnosing Sézary syndrome.

Cytogenetic demonstration of an abnormal cellular clone is diagnostic. Incrimination of bone marrow appears as a non definitive criteria of discerning Sézary syndrome [3,4].

Sézary syndrome is a chronic condition which defies alleviation.

Cogent therapy is aimed at controlling pertinent clinical symptoms and ameliorating quality of life.

Systemic therapies such as retinoids or bexarotene appear efficacious in curbing extra-cutaneous disease. Adoption of monotherapy is associated with moderate response to therapy. Nevertheless, chlorambucil can be combined with prednisone or low doses of methotrexate (MTX) can be employed.

Recombinant interferon α is adopted as a monotherapy or concurrently administered with retinoids [3,4].

Conventional chemotherapy applicable for treating Sézary syndrome is comprised of cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone (CHOP) or CHOP-like regimen. However, complete or persistent disease remission is exceptional.

Target therapy is constituted of agents such as alemtuzumab and anti PD1 or CD47/signal regulatory protein alpha (SIRPα) molecules.

Extracorporeal photopheresis (ECP) is adopted singularly or in combination with systemic therapy as first line therapeutic strategy and may induce long term remission.

Histone deacetylase inhibitors (HDACi) as vorinostat and romidepsin may demonstrate superior overall response rate.

Allogenic stem cell transplantation may be preceded by cutaneous electron beam radiation and may be associated with acute and chronic graft versus host disease in significant instances [3,4].

Therapeutic response of peripheral blood is assessed as

- Complete response (CR) wherein B2 converts into B0
- Partial response (PR) wherein minimally 50% reduction of tumour burden is encountered
- Progressive disease (PD) wherein B0 or B1 enhances to B2 with augmentation of absolute Sézary cell count ≥ 50% or B2 with augmentation of absolute count ≥ 50% or decimated response with augmented absolute counts ≥ $1x10^9$/L and ≥ 50% from nadir
- Disease relapse wherein elevated absolute Sézary cell count of ≥ $1x10^9$/L is concurrent with complete response (CR) [3,4].

Sézary syndrome exhibits an inferior prognostic outcome. Following initial disease discernment, median overall survival is ~ 3.1 to 4 years. Instances with visceral incrimination exhibit a median overall survival of ~ 2.5 years. Median mortality following disease discernment is ~ 3.5 years. 5 year overall survival varies from 18% to 37% and 10 year overall survival is up to 18%.

Syndrome with Sézary cells overexpressing CD47 is associated with inferior overall survival.

Factors contributing to inferior prognostic outcomes are

- Advanced age at initial diagnosis > 65 years
- Preceding mycosis fungoides
- Occurrence of TCR genetic rearrangement within cutaneous lesions or peripheral blood
- Disease manifesting elevated lactate dehydrogenase (LDH) levels at initial representation.

However, variation in quantifiable Sézary cells circulating within peripheral blood may not alter prognostic outcomes.

Proportionate emergence of secondary lymphoma within Sézary syndrome or mycosis fungoides is enhanced [3,4].

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5. Image 1 Courtesy: Plastic surgery key.

6. Image 2 Courtesy: Springer link.