Sézary cell

M. J. Cyriac, Anu Kurian
Department of Dermatology and Venereology, Medical College, Kottayam, India.

Address for correspondence: Dr. M. J. Cyriac, Professor and Head, Department of Dermatology and Venereology, Medical College, Kottayam, Kerala - 686008, India. E-mail: drmjcyriac@hotmail.com

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Sézary cells (SC) (synonyms: mycosis cell, Lutzner cell, cerebriform lymphocytes, Atypia Cellules Monstreuses or monster cell[1,2]) are atypical lymphocytes with a grooved or cerebriform nucleus seen both in tissue and blood. They are characteristically seen in cutaneous T cell lymphomas including mycosis fungoides (MF). The Sézary cell is named after the French dermatologist Sézary A (1880-1956).[3] Sézary and Bouvrain described the leukemic variant of MF in 1938 where they identified the monster cells with atypical features. This variant is now known as Sézary syndrome. In 1968, Lutzner and Jordan[4] described the ultrastructural details of Sézary cells.

MORPHOLOGY

Three variants of Sézary cell are identified based on its size. The 'small cells' are less than 12 microns in diameter, 'large cells' are more than 12 microns and the 'very large cells' are more than 14 microns.[5] The nucleus, occupying at least four fifths of the cell, shows a variable surface contour ranging from mild indentations to gross cerebriform shape (Figure 1, 2).[6] The nuclear chromatin is condensed in a patchy distribution beneath the nuclear membrane. The nucleoli may be prominent. The cytoplasm is sparse and appears as a narrow rim around the nucleus. Mitochondria, often appearing clumped, rough endoplasmic reticulum, polysomes and cytoplasmic fibrils are seen. The cytoplasmic fibrils appear serpentine on electron microscopic examination.[7]

IMMUNOHISTOCHEMISTRY

Sézary cell is a malignant CD4+ helper T cell of the T helper 2 subset.[8] It produces cytokines (IL-4, IL-5 and IL-10) that enhance the differentiation and activation

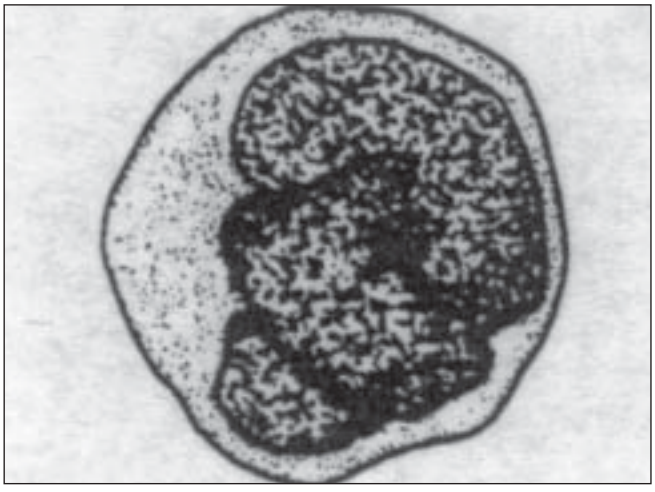

Figure 1: Sezary cell

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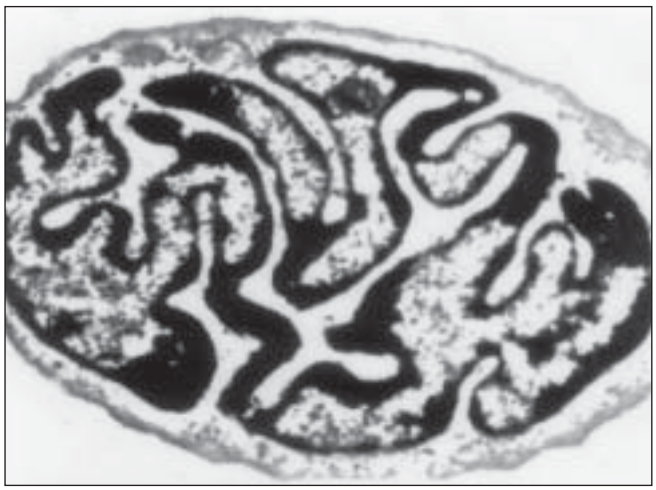

Figure 2: Convoluted nucleus of Sezary cell seen with electron microscopy

of eosinophils and suppress T helper 1 activity. The early lesion of mycosis fungoides retains the expression of both majority T cell markers like CD7 and Leu-8 (CD62L) which are present on most mature non-neoplastic T cells and pan T cells markers like CD2,CD3 and CD5 which are present on all mature non-neoplastic T cells. As lesions progress the earliest marker lost is a majority T cell antigen. Majority T cell markers may be lost in both MF and in 10-20% of inflammatory dermatoses. Pan T cell markers are less commonly lost in MF, but if they are lost then we can exclude the possibility of it being an inflammatory dermatosis. The absence of CD7 or Leu-8 within epidermis has been observed in mycosis fungoides, a feature absent in inflammatory lesions.[9-12]

Dipeptidyl peptidase IV (CD26) is found to be absent on circulating neoplastic cells in Sézary syndrome. The level of CD4+ CD26- T cell subpopulation correlates with the extent of peripheral blood involvement.[13] Recently CD158k marker has been demonstrated on Sézary cells.[14] This marker may prove useful as a tool for evaluation of circulating tumoral burden and in the follow up of patients with Sézary syndrome.

HISTOGENESIS

The site of origin of Sézary cell has not been determined. Large numbers of these cells are seen in the dermis in MF and Sézary syndrome. Epidermotropism is noted more markedly in mycosis fungoides as compared to Sézary syndrome. It has been shown that these atypical cells are in fact actively dividing in the dermis itself, the dermis forming a home to these cells. The cells appearing in the peripheral blood are probably an overspill phenomenon.[15] The observations that these cells cannot be demonstrated in abnormal amounts in bone marrow and that they tend to disappear when skin lesions resolve support this theory.

It is believed that the evolution of mycosis fungoides starts with the aggregation of circulating T helper cells in the papillary dermis. This is followed by a selection phase where cells with a T helper 2 cytokine profile predominate and are then transformed into a clonal population by various cytokines. The final stage is the dissemination phase in which the neoplastic cells dedifferentiate without the need of the skin microenvironment. The critical step in the cascade seems to be the commitment to the T helper 2 subtype. Once switched to the T helper 2 profile the cytokines produced suppress immunosurveillance by the cytotoxic T lymphocytes and the natural killer cells allowing for unremitting stimulation of the T helper cells by the autocrine loop and by antigen presenting cells.[16]

A higher incidence of Sézary syndrome is seen with occupational exposure to industrial solvents and in those employed in the petrochemical, textile, manufacturing and construction industries.[17] Recently, the Human T cell lymphotropic virus I /II have been implicated although molecular analyses have been inconclusive.[18]

LABORATORY DIAGNOSIS

In blood smear Sézary cells appear as mononuclear cells with grooved nuclei and cytoplasmic vacuoles, which can often be stained with Periodic Acid Schiff reagent. Glycogen is responsible for staining in some, but not in all of the vacuoles.[19] These cells can also be recognized by Giemsa or Wright staining methods. Some Sézary cells are the size of normal lymphocyte while others are much larger. Based on the

cytomorphology Sézary syndrome has been classified by the International Society for Cutaneous Lymphomas (ISCL) as:

1. Small cell variant: more than 80% of SC are small cells
2. Large cell variant: more than 20% of SC are very large cells
3. Mixed cell variant: an intermediate number of large SC and small SC

Patient with very large SC in the blood have a worse prognosis that those without.[20] Smears are not a particularly sensitive method of quantifying the number present.[21] It must be realized that it is not necessary to have a raised total lymphocyte count for the diagnosis to be made and in such situations unless the tail of the smear or the buffy coat is specifically examined for the atypical cells, the diagnosis may easily be missed. At least 100 lymphocytes are counted to determine the percentage of cells showing Sézary phenomenon. Lutzner, et al compared the ultrastructure of the abnormal cells in the skin, lymph nodes and peripheral blood of patients with Sézary syndrome and found that the cells were similar.[22] Ultrastructural morphometry has been used to distinguish Sézary cells in blood from normal lymphocytes and reactive lymphocytes.[23]

CLINICAL SIGNIFICANCE

In mycosis fungoides the Sézary cell is considered malignant based on following criteria:

1. They are present in skin lesions and viscera
2. Have abnormal number of chromosomes and abnormal karyotypes including marker chromosomes[24]

Diagnosis of Sézary syndrome as originally described requires the presence of the triad of erythroderma, lymphadenopathy and 10% or more of atypical mononuclear cells in the peripheral smear. Many experts now consider a circulating Sézary cell count which exceeds 1000 cells/cumm as characteristic of Sézary syndrome and the prognosis to be worse in patients with circulating Sézary cell counts of >5% of total lymphocyte count. The term pre Sézary syndrome is used if cell count is < 1000 cells/cumm with erythroderma, although others believe that presence of Sézary cell by itself is significant irrespective of the number.[25-27]

Blood criteria to define Sézary syndrome as recently proposed by ISCL are the following:

- An absolute Sézary cell count of 1000 cells/cumm or more
- An increase in CD3 or CD4 positive cells resulting in a CD4/CD8 ratio of 10 or more
- Aberrant expression of pan T cell markers by flow cytometry, deficient CD7 expression
- Increased relative or absolute lymphocyte counts with evidence of a T cell clone in the blood by Southern blot or PCR technique
- Chromosomally abnormal T cell clones[5]

Although Sézary cell is the pathological hallmark of cutaneous T cell lymphoma, its significance has been brought into dispute as similar atypical mononuclear cells have been described in a variety of other skin disorders (Table 1). The conditions include lichen planus, discoid lupus erythematosus, psoriasis, vasculitis, actinic keratosis,[6] actinic reticuloid,[15] dilantin hypersensitivity syndrome and erythrodermic follicular mucinosis. Whether CD4+ CD7- T cells present in the epidermis and the dermis represent the neoplastically transformed cell population can be determined using the panel of antibodies to the variable regions of T cell receptor (TCR beta chain).[9] Although chromosomal characteristics/DNA content of the Sézary look-alike cells in benign dermatoses is yet to be studied, such studies of Sézary cell reveal abnormal number of chromosomes and abnormal karyotypes pointing towards its malignant nature.

Table 1: Conditions where Sezary cell look-alikes are reported

1. Actinic reticuloid
2. Actinic keratosis
3. Dilantin hypersensitivity syndrome
4. Discoid lupus erythematosus
5. Erythrodermic follicular mucinosis
6. Lichen planus
7. Psoriasis
8. Vasculitis

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News and Announcements

5th East Zone Dermacon

The 5th east zonal conference of IADVL is going to be held at Patna on the 18th & 19th of December 2004.
For details please contact the following:

Dr. Amar Kant Jha Amar Dr. P. K. Roy
Org sec 06122287772,
Prafull Plaza 09431095458,
Makhaniya kuan,
Patna - 800004.
Mobile 06123116298