

Sézary Syndrome in a Malay – Case Report and Literature Review

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ABSTRACT

Sézary syndrome is a rare form of primary cutaneous T cell lymphoma. It is a distinct systemic variant of mycosis fungoides, marked by erythroderma, lymphadenopathy and circulating cerebriform lymphocytes in the peripheral blood. We report a case of Sézary syndrome in a 61-year-old Malay man with a five-year history of indurated plaques, ulcers and tumours on the head and trunk, with characteristic findings on physical examination, skin biopsy, electron microscopy, immunophenotyping and peripheral blood film. A literature review on Sézary syndrome is presented.

Keywords: erythroderma, lymphadenopathy, cerebriform lymphocytes, mycosis fungoides, tumours

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INTRODUCTION

Mycosis fungoides (MF) and Sézary syndrome (SS) are the most common variants in the spectrum of cutaneous T-cell lymphoma. MF was first described by Alibert in 1806, as cutaneous tumours with a mushroom-like appearance. It primarily involves the skin at the early stages, with erythematous scaly patches and plaques. A definitive diagnosis of MF is often preceded by this “premycotic” phase whereby skin biopsies can be non-diagnostic. Over a variable period of time, it may progress to cutaneous tumours, and spread to the lymph nodes and viscera. SS is a leukemic variant of MF, characterised clinically by a pruritic exfoliative or infiltrative erythroderma, generalised lymphadenopathy, and the presence of atypical T-cells (Sézary cells) in the peripheral blood. Patients may present with all components of SS or may initially present with one component, and subsequently develop other clinical features of SS. The histological features of SS are similar to MF, with infiltration of malignant clonal T-lymphocytes in the dermis and epidermis, but this may not be present in all cases.



Fig. 1 61-year-old Malay man with multiple firm, plum-coloured, excoriated nodules on his face, scalp and neck.

Differentiation from erythroderma due to other causes like chronic dermatitis, psoriasis and drug eruptions can be difficult. Hence, histopathological examination of enlarged lymph nodes, and other studies using electron microscopy, immunophenotyping, T-cell receptor gene rearrangement help to confirm an early diagnosis of SS.

CASE REPORT

A 61-year-old Malay man with no known past medical history presented with a five-month history of rapidly enlarging nodules on his head, neck, trunk and groin. They were pruritic and nontender. Associated symptoms included low grade temperature, dry cough, loss of appetite, loss of weight and hair loss. According to family members, he has had rashes on his face for five years, but refused to seek medical advice. He presented this

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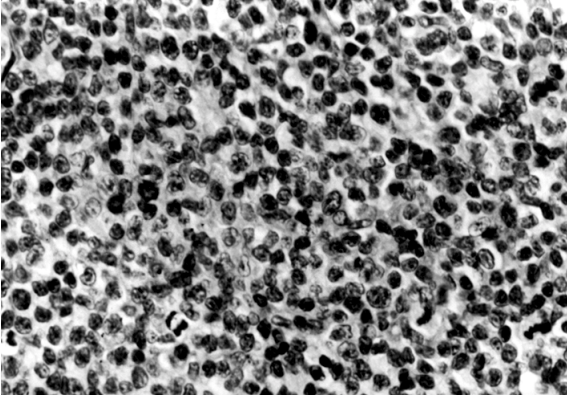


Fig. 2 Features show a malignant lymphoma composed of sheets of tumour cells with irregularly lobulated nuclei, scant cytoplasm and several mitoses (H + E x 600).

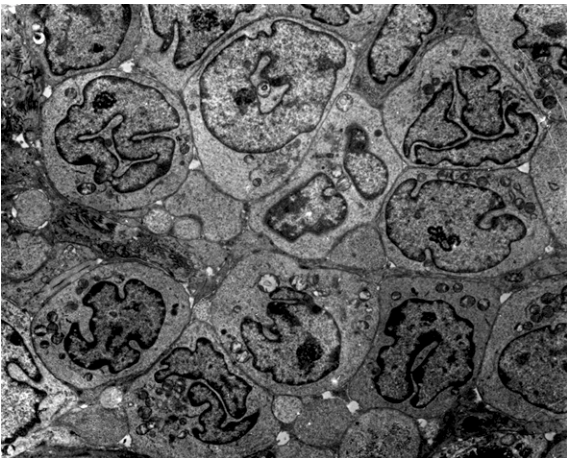


Fig. 3 Electron micrograph showing sheets of characteristic Sézary cells with large highly convoluted cerebriform nuclei (Uranyl acetate x 6300)

time because of intense pruritis and bleeding from the excoriated nodules.

Physical examination revealed a cachectic man who was alert and oriented. He had a low grade temperature 37.8°C, a pulse of 108/minute, and a blood pressure of 120/70 mm Hg. There were multiple firm, plum-coloured nodules on his face, scalp, neck and trunk, ranging from 1 cm to 6 cm in diameter, with superficial excoriations and ulcerations (Fig. 1). Cervical, axillary and inguinal lymph nodes were visible and grossly enlarged. Hepatosplenomegaly and alopecia were present. Examination of the cardiovascular, respiratory and neurological systems were normal.

His laboratory tests were significant for leukocytosis 54,000/mm³ with 47% smudge cells, normocytic anemia 9.5g/dL, platelets 210,000/mm³, total protein 58g/L, albumin 28g/L, gamma glutamyl transferase 170U/L, alkaline phosphatase 302U/L, lactate dehydrogenase 3768U/L, uric acid 672umol/L, ionized calcium 1.14mmol/L, and a negative human immunodeficiency virus status. Peripheral blood film showed large acid phosphatase-positive lymphoid cells with irregularly-shaped nuclei and scanty

cytoplasm, with a CD4 positive, CD25 negative T-cell immunophenotype. Biopsy from the patient's back showed a dense infiltration of immature lymphoblastic cells with hyperchromatic, irregularly lobulated nuclei within the dermis (Fig. 2). Electron microscopy revealed characteristic Sézary cells with a highly convoluted cerebriform nuclei (Fig. 3). Trepphine bone marrow revealed lymphomatous involvement, consistent with peripheral T-cell lymphoma.

A diagnosis of Sézary syndrome was made. The patient was started empirically on intravenous ceftriaxone and cloxacillin to cover for sepsis and superficial bacterial skin infection. Given the aggressiveness of the disease, the lymphadenopathy, hepatosplenomegaly and bone marrow involvement, combination chemotherapy cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) was started. The patient responded remarkably with a decrease in tumour size, lymphadenopathy, and white cell count. Unfortunately, he developed nosocomial pneumonia with neutropenic sepsis day 11 post chemotherapy. Intravenous ceftazidime and gentamycin were started, but patient expired two days later from septic shock.

DISCUSSION

Mycosis fungoides (MF) and Sézary syndrome (SS) are a group of extranodal non-Hodgkin's lymphomas of T-cell origin with primary cutaneous involvement. They are distinguished from other cutaneous T-cell lymphomas (CTCLs) by their unique clinical and histopathological features. Both diseases result from the malignant transformation of helper T-lymphocytes with characteristic tropism for the epidermis. SS is a systemic variant of MF, marked by erythroderma, lymphadenopathy, pruritis, and circulating atypical cells in the peripheral blood⁽¹⁾.

SS is relatively uncommon. It is very rare in Asians. Only about 40 new cases are diagnosed each year in the United States, making up approximately 4% of all newly reported cases of CTCL⁽²⁾. Typically, SS affects middle-aged adults, with peak age at presentation of 55 years. There is a 2:1 male predominance and it occurs twice as often in blacks as in whites⁽²⁾. This is a rare disease, and a case may be seen once in two years in Singapore. Environmental and occupational exposure to solvents, chemicals and toxins, as well as the role of human T-lymphotropic virus type I (HTLV-I)⁽³⁾ have been suggested but not proven. The retrovirus HTLV-I has been etiologically linked to adult T-cell leukemia/lymphoma which is endemic in Japan and the Caribbean, and which often mimics SS⁽⁴⁾.

SS is characterised by generalised erythroderma, edema, and intense pruritis. Other major clinical features

include lymphadenopathy, hepatosplenomegaly, alopecia, onychodystrophy, keratoderma, and alopecia⁽⁵⁾. Patients may also have symptoms of fever, chills, weight loss and malaise. Pertinent laboratory findings include elevated white cell count ($> 15 \times 10^9/l$), hyperuricemia, and elevated lactate dehydrogenase. The skin can sometimes become infiltrated and give rise to plaque formation. This commonly occurs on the face, giving rise to leonine facies. The major route of extracutaneous spread is to regional lymphatics and the viscera⁽⁶⁾. Peripheral lymph nodes are the most frequent sites of extracutaneous involvement, followed by spleen, lung and liver. Despite circulating Sézary cells, the bone marrow is often negative for disease. However, autopsy studies have shown that involvement of any organ may occur in the final stages of disease⁽⁷⁾.

Histopathologic features of the skin are similar in both MF and SS, as defined by the International Lymphoma Study Group. There is marked epidermotropism of atypical lymphocytes with convoluted cerebriform nuclei, which collect in clusters known as Pautrier's micro-abscesses in the epidermis, and in bandlike infiltrates in the upper dermis⁽⁸⁾. Circulating peripheral Sézary cells are seen in the majority of patients with erythroderma, in approximately 25% of patients with cutaneous tumours, and in 10% of patients with generalised plaques⁽⁹⁾. Electron microscopy of the buffy coat confirms the presence of the markedly convoluted cerebriform nucleus with a high nuclear to cytoplasmic ratio⁽¹⁾. Immunophenotyping of the Sézary cell reveals a CD4+ helper/inducer phenotype, while there may be a loss of mature T-cell antigens such as leu-8 and CD7⁽¹⁰⁾. T-cell receptor (TCR) gene rearrangement studies have proved to be useful in identifying the clonal nature of the disease⁽¹¹⁾.

The major causes of benign erythroderma that need to be differentiated from SS are psoriasis, atopic dermatitis, drug reaction, parapsoriasis, pityriasis rubra pilaris, and paraneoplastic cutaneous reaction to internal malignancies⁽¹²⁾. Differentiation requires consideration of clinical findings, together with histologic, immunologic, and molecular genetics studies. The presence of erythroderma with intense pruritis, along with atypical lymphoid bandlike infiltrate in the dermis or Pautrier's micro-abscesses, suggest but are not pathognomonic of SS. Additional analysis using ultrastructural and immunohistochemical studies, as well as TCR gene arrangement, will increase the sensitivity and specificity of detecting atypical circulating Sézary cells.

There are various staging classifications of CTCL, the standard being the Tumor, Node, Metastasis, Blood (TNMB) classification first proposed by the National

Cancer Institute in 1978. Each of these parameters bears prognostic value. SS has the poorest prognosis of all CTCLs, the median survival ranges from one to five years. The onset of symptoms may precede the diagnosis by several years, especially given the diagnostic difficulties with early erythematous lesions. The most frequent cause of mortality is infection, often originating from the cutaneous lesions themselves. *Staphylococcus* and *Pseudomonas* species are the most common organisms causing pneumonia or sepsis⁽¹³⁾. Herpetic infections have also been described in advanced disease⁽¹⁴⁾. Standard staging evaluation includes a careful examination of the skin (especially the scalp, palms, soles and perineum), skin biopsy, full blood count with Sézary cell analysis, screening chemistries, and chest radiography. Lymph node biopsies should be obtained if lymphadenopathy is present, since lymph node involvement affects both staging and prognosis.

There is no evidence that treatment prolongs the survival of patients with SS, but it is apparent that improved quality of life and increased disease-free interval can be obtained. The therapeutic options depend on the clinical stage of the disease. There are various therapeutic options for the treatment of CTCLs, but to date there have been no prospective controlled clinical trials done on patients with SS. From our literature review, the most reasonable treatment options in order of efficacy for erythrodermic and extracutaneous MF, as well as SS are extracorporeal photopheresis^(15,16), chlorambucil and prednisolone, cyclophosphamide/vincristine/prednisolone (CHOP)⁽¹⁷⁾ and low dose methotrexate⁽¹⁸⁾. PUVA alone or in combination with interferon alfa, systemic multiagent chemotherapy, electron beam irradiation, 2-deoxycoformycin, cyclosporin, anti-thymocyte globulin, and anti-T-cell monoclonal antibodies, have all been described in the therapy of SS⁽¹⁷⁾.

CONCLUSION

SS remains a challenging disease in terms of its proper diagnosis, etiology, classification, and treatment. It has a poor prognosis with estimated survival less than five years irrespective of therapeutic modality. In a patient who presents with erythroderma, the possibility of SS needs to be considered. There is not one test that is pathognomonic for the diagnosis of SS, instead a combination of histopathology, immunophenotyping, gene rearrangement studies, and clinical presentation help support the diagnosis. Importantly, one of the most common causes of mortality is infection, hence patients presenting with fever and/or chills need to be aggressively cultured and treated with appropriate antibiotics.

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