Sezary Syndrome: A Case Report and a Review of the Molecular Pathomechanism and Management

P P L Ng,*MBBS, MRCP (UK), C L Goh,**FAMS, M Med (Int Med), FRCP (Edin)

Abstract

Sezary syndrome, one of the cutaneous T-cell lymphomas, is a rare cause of generalised exfoliative dermatitis. We report a case of Sezary syndrome in a 64-year-old man who had persistent erythroderma for four years and who subsequently developed inguinal lymphadenopathy and marked leukocytosis. We review the pathomechanism and management of this rare condition.

Ann Acad Med Singapore **1998; 27:864-7**

Key words: Cutaneous T cell lymphoma, Erythroderma

Case Report

Our patient is a 64-year-old Malay man who first presented in July 1993 with a history of rash starting on the hands $1\,^1/_2$ years earlier progressing to generalised eczema 5 months prior to consultation. He was diagnosed to have generalised exfoliative dermatitis (GED). Full blood count and erythrocyte sedimentation rate (ESR) were normal and he was treated with topical steroids. He defaulted follow-up and was put on prednisolone 10 mg daily for a year by a general practitioner.

He was referred to us again in March 1995 for the problem of GED. This time he was diagnosed to have erythrodermic psoriasis and noted to have in addition, nail dystrophy, fissuring of the palms and scaling of the soles. Phototherapy (UVB) was commenced in May 1995 but was stopped after four treatments as his condition apparently worsened. He had persistent erythroderma and scaling despite topicals and was put on methotrexate (MTX) from September 1995 until February 1996. The scaling improved but he remained erythrodermic. In February 1996, he was noted to have erosions on the palms and MTX was stopped in view of possible toxicity. He refused phototherapy (PUVA) and was started on etretinate in April 1996 but he defaulted follow-up after 6 weeks.

Leukocytosis was noted since October 1995. Total white cell count was 20,000/mm³ with a differential count of 44% polymorphs, 50% lymphocytes, 1% monocytes, 1% basophils, 0% eosinophils and 4% atypical mononuclear cells. In January 1996, the total white blood cell (WBC) count was 27,600/mm³ just before

MTX was withdrawn. He defaulted follow-up in May 1996.

He was referred to us again in April 1997 and was noted by the referring doctor to have a WBC count of 31,000/mm³ and uncontrolled diabetes. He had been put on prednisolone 10 mg daily by his family physician the preceding 6 months for his skin condition. He also had diabetes mellitus for 7 years and was on tolbutamide.

On physical examination, the patient was afebrile. There was no pallor or jaundice. He was noted to have generalised erythema and scaling (Fig. 1). There was alopecia involving the scalp, eyebrows, beard area, axillae and pubic area. Several hypopigmented patches were noted over the vertex of the scalp and the upper chest as well as generalised skin atrophy. All nails were dystrophic with subungual hyperkeratosis. There were large, firm inguinal lymph nodes bilaterally each about 3 cm in diameter. Cervical, axillary and epitrochlear lymph nodes were not palpable. There was no hepatosplenomegaly. The rest of the clinical examination was normal.

Investigations revealed a haemoglobin of 13.1 g/dL, total WBC count of 25,500/mm³ (polymorphs 25%, lymphocytes 6%, monocytes 68%, eosinophils 0%, basophils 0%) and a platelet count of 248,000/mm.³ Erythrocyte sedimentation rate was 5 mm/h. Urea/electrolytes/creatinine and liver function tests were normal. Buffy coat revealed the presence of Sezary cells (Fig. 2). Initial skin biopsy showed a dense lichenoid infiltrate of lymphocytes and plasma cells consistent

 * *Registrar*
** *Senior Consultant and Medical Director*
 National Skin Centre
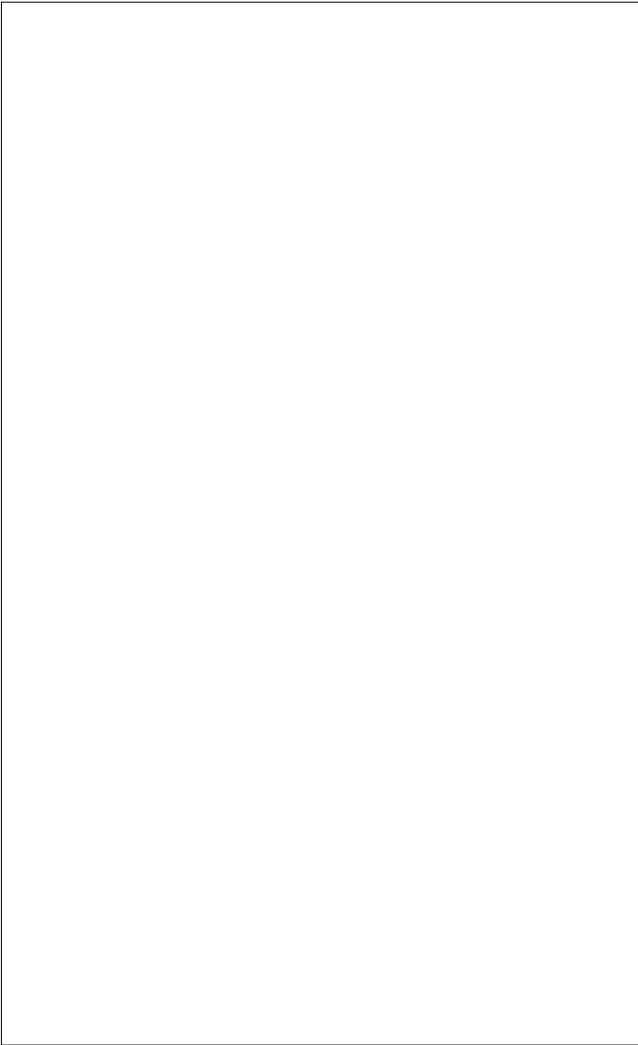*Address for Reprints: Dr Patricia Ng Pei Lin, National Skin Centre, 1 Mandalay Road, Singapore 308205.*

Fig. 1. Generalised erythema and scaling with patchy hypopigmentation and alopecia.

Fig. 2. Sezary cells with cerebriform nuclei in the peripheral blood film.

with lichenoid dermatitis (the pattern could go for Sezary syndrome but no atypical cells were seen).

A bone marrow trephine biopsy was performed which showed normocellularity with all three haemopoietic cell lines that disclose mature forms. A few atypical lymphoid cells were seen. Bone marrow aspirate showed quantitatively normal erythopoiesis but granulopoiesis was quantitatively decreased with 38% mature lymphocytes and 27% Sezary cells present. Peripheral blood film showed normocytic and normochromic erythrocytes, moderate leukocytosis with increased lymphocytes and Sezary cells. Flow cytometry was classical of Sezary syndrome with positive CD3, CD4 and CD5 together with CD7 deletion.

Right inguinal lymph node biopsy revealed a malignant lymphoid infiltrate resulting in effacement of the nodal architecture. The malignant medium-sized lymphoid cells showed coarse chromatin and enlarged irregular nuclei, a large number of which exhibited cerebrifor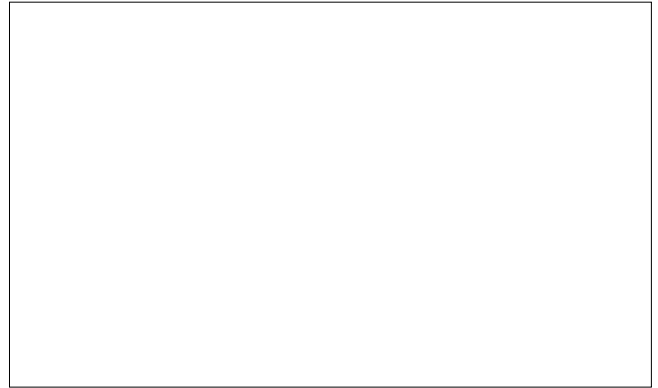m nuclei i.e. Sezary cells. Blast cells were not present. The background showed a fine arborising vasculature. The malignant cells stained for CD3, CD4 and UCHL1, confirming a T cell lineage.

He was diagnosed to have Sezary syndrome and was transferred to the Department of Haematology, Singapore General Hospital for staging and treatment. Repeat skin biopsy showed features consistent with Sezary syndrome. A dense band of lymphoid cells was seen just below the epidermis which were intermediate in size and had irregular nuclear contours with occasional larger cells with prominent nuclei. Epidermotropism was not prominent. Computed tomographic (CT) scan of the thorax, abdomen and pelvis showed no evidence of lymphadenopathy or hepatosplenomegaly.

He was started on combination chemotherapy (cyclophosphamide, vincristine, prednisolone and methotrexate). He subsequently had intravenous catheter-related complications which included septicaemia and acute partial venous thrombosis of the right superior vena cava. He succumbed to septicaemia a few weeks after the second cycle of chemotherapy.

Discussion

We are reporting this case of Sezary syndrome as it is one of the rarer causes of GED, the common causes being psoriasis, atopic dermatitis, seborrhoeic dermatitis, contact dermatitis, chronic actinic dermatitis, pityriasis rubra pilaris and drug-related causes. Idiopathic causes account for about 12% to 32% of cases in several series of erythrodermic patients.[1-3] The presence of persistent erythroderma and inguinal lymphadenopathy in the presence of a markedly raised leukocyte count led us to suspect a more sinister cause of the erythroderma.

Cutaneous T-cell lymphoma (CTCL) is a heterogenous group of diseases, characterised by monoclonal expansion of malignant T cells, primarily helper T (CD4) cells, with mycosis fungoides and Sezary syndrome accounting for the majority of cases. Sezary syndrome is believed to be part of the spectrum of mycosis fungoides, an erythrodermic variant with circulating tumour cells

in the blood, which may arise *de novo* or from preexisting lesions histopathologically classical of mycosis fungoides.

Sezary syndrome, as originally defined, is characterised by the triad of erythroderma, lymphadenopathy and circulating atypical mononuclear cells (Sezary cells). Our patient had inguinal lymphadenopathy and long-standing erythroderma, as well as Sezary cells on peripheral blood film and in the bone marrow aspirate. The majority are elderly males. The clinical presentation of Sezary syndrome is a non-specific erythroderma, described as diffuse, bright red with scaling, which may be accompanied by fever, chills, loss of weight, malaise, insomnia secondary to overwhelming pruritus and poor temperature homeostasis. There may be scaling and fissuring of palms and soles, alopecia, ectropion, nail dystrophy and ankle oedema. Many of these features were present in our patient.

Diagnosis is made by skin biopsy and the finding of abnormal lymphocytes in the blood. Multiple skin biopsies may be needed because of the marked variability of epidermotropism and infiltrate density. This point is well demonstrated in our patient in which typical changes were only seen on repeat skin biopsy. Classically, there is perivascular accumulation of a large number of atypical mononuclear cells with convoluted nucleus in the dermis but there is usually less epidermotropism compared to mycosis fungoides.

The cutaneous affinity of this lymphoma is due to keratinocyte-T cell interaction. Intercellular adhesion molecule-1 (ICAM-1) and class II major histo-compatibility complex (MHC) are found on lesional keratinocytes but not on non-lesional keratinocytes in CTCL.[4] ICAM-1 affects T cell binding to both endothelial cells and keratinocytes and leads to T cell recruitment into the skin and epidermotropism. Lesional keratinocytes also produce more interleukin-1 (IL-1) which is a potent upregulator of ICAM-1 expression on endothelial cells. It also increases vascular permeability and enhances the effectiveness of other chemoattractants from keratinocytes, for example, IL-8.[5]

Southern blot analysis of T-cell receptor (TCR) gene rearrangements in leukaemic blood, involved lymph nodes, skin tumours and plaques of patients with CTCL revealed patterns consistent with the presence of a single neoplastic T cell clone.[6] With the introduction of polymerase chain reaction (PCR) which enhances sensitivity by about ten times, dominant T cell clones could also be demonstrated in early lesions.[7]

The classical Sezary cell has a serpentine and cerebriform nucleus with hyperdiploid DNA and chromosome count. There is difficulty in evaluating the relevance of the presence of Sezary cells in the peripheral blood and some believe that they may be reactive rather than malignant.[8] The malignant T cell in Sezary syndrome expresses the pan-T cell markers C2, CD3 and CD5 as well as CD45+RO+ and CD4+.[9] The early T-cell marker CD7 may be deleted[10] but is positive in about a third of patients. CD25 (IL-2 receptors) may be positive but are negative in at least half the cases.[11]

Kim et al[12] have reported several prognostic factors in erythrodermic mycosis fungoides/Sezary syndrome, namely, patient age at presentation (≥65 years), overall clinical stage and circulating Sezary cell count (≥5% of total lymphocyte count) which were associated with a worse prognosis in a multivariate analysis.

Multiple treatment modalities have been used in CTCL.[13,14] Sezary syndrome does not respond well to therapies which are potentially curable for early CTCL disease, that is, before the development of tumours, erythroderma or nodal involvement.

Topical nitrogen mustard useful in early CTCL disease rarely achieves complete remission in advanced disease.[15] Psoralen and ultraviolet A light (PUVA) is also not useful in Sezary syndrome although it has been reported to be effective in clearing erythrodermic mycosis fungoides without circulating atypical cells.[16] While total skin electron beam (TSEB) therapy has been shown to give complete response rates of 64% in erythrodermic patients,[17] a 3-year disease-free survival is rarely achieved, although a recent study has suggested a survival benefit for advanced CTCL patients who in addition to TSEB received adjuvant photophoresis or systemic chemotherapy.[18]

Photophoresis (extracorporeal photochemotherapy)[19] which involves oral psoralen ingestion followed by UVA irradiation of peripheral blood on two consecutive days at 4-weekly intervals was first described in 1987 as therapy for patients with advanced CTCL especially those with erythroderma. Recent studies have reported responses (either complete or partial) in Stage IV (erythrodermic) patients of between 50% and 55%.[20,21]

Single agent chemotherapy (including nitrogen mustard, cyclophosphamide, carmustine, methotrexate, bleomycin, doxorubicin, cisplatin, VP-16, corticosteroids and the newer purine analogues fludarabine, 2'-deoxycoformycin and 2'-chlorodeoxyadenosine) has been used.[22] A study on 2'-deoxycoformycin (DCF) in T cell malignancies showed patients with Sezary syndrome to have the best response (62%) with complete remission in 3 of 16 patients.[23] The most data reported with single agents has been with MTX and it may be effective in advanced disease.[13,22] A recent study showed a 58% response rate among 29 patients with erythrodermic disease.[24] Combination chemotherapy has also been used but it is still unclear whether combination therapy is superior to single agents.[22] Combined modality therapy with both electron beam and combination

chemotherapy either sequentially or concomitantly has been used. There have been better response rates but in a randomised study, there was no statistically significant difference in survival.[25] Bioimmunotherapies such as IFN-α and retinoids have also been used either alone or in combination therapy. Recombinant IL-2 (a T cell growth factor) and IL-2 fusion toxin or a toxin-conjugated monoclonal antibody are among the novel therapies being tried in CTCL.[13]

Acknowledgement

REFERENCES

1. Nicolis G D, Helwig E B. Exfoliative dermatitis: a clinicopathologic study of 135 cases. Arch Dermatol 1973; 108:788-97.

2. Hasan T, Jansen J T. Erythroderma: a follow-up of 50 cases. J Am Acad Dermatol 1983; 8:836-40.

3. Sigurdsson V, Toonstra J, Hezemans-Boer M, van Vloten W A. Erythroderma—A clinical and follow-up study of 102 patients, with special emphasis on survival. J Am Acad Dermatol 1996; 35:53-7.

4. Griffiths C E, Vorhees J J, Nickoloff B J. Characteristerization of intercellular adhesion molecule-1 and HLA-DR expression in normal and inflamed skin: Modulation by recombinant gamma interferon and tumour necrosis factor. J Am Acad Dermatol 1989; 20:617-29.

5. Barker J N, Sarma V, Mitra R S, Dixit V M, Nickoloff B J. Marked synergism between tumour necrosis factor-alpha and interferon-gamma in regulation of keratinocyte-derived adhesion molecules and chemotactic factors. J Clin Invest 1990; 85:605-8.

6. Wood G S, Dummer R, Haeffner A, Crooks C F. Molecular biologic techniques for the diagnosis of CTCL. Dermatol Clin 1994; 12:231-41.

7. Wood G S, Tung R M, Haeffner A C, Crooks C F, Liao S, Orozco R, et al. Detection of clonal T-cell receptor γ gene rearrangements in early mycosis fungoides/Sezary syndrome by polymerase chain reaction and denaturing gradient gel electrophoresis. J Invest Dermatol 1994; 103:34-41.

8. Bendelac A, O'Conner N T J, Daniel M T, Boitard C, Michel C, Laroche C, et al. Nonneoplastic circulating Sezary-like cells in cutaneous T-cell lymphoma. Cancer 1987; 60:980-6.

9. Sterry W, Mielke V. CD4+ cutaneous T-cell lymphoma show the phenotype of helper/inducer T cells (CD45RA-, CDW29+). J Invest Dermatol 1989; 93:413-6.

10. Wood G S, Hong S R, Sasaki D T, Abel E A, Hoppe R T, Warnke R A, et al. Leu/CD7 antigen expression by CD3+ T-cells: Comparative analysis of skin and blood in mycosis fungoides/Sezary syndrome relative to normal blood values. J Am Acad Dermatol 1990; 22:602-7.

11. Kaudewitz P, Josimovic-Alasevic O, Dianantstein T, Eckert F, Klepzig K, Burg G. Soluble IL-2 receptor serum levels in cutaneous T-cell lymphoma: correlation with clinical stage and IL-2 receptor status in cutaneous infiltrates. J Invest Dermatol 1988; 91:386-7.

12. Kim Y H, Bishop K, Varghese A, Hoppe R T. Prognostic factors in erythrodermic mycosis fungoides and the Sezary syndrome. Arch Dermatol 1995; 131:1003-8.

13. Diamandidou E, Cohen P R, Kurzrock R. Mycosis fungoides and Sezary syndrome. Blood 1996; 88:2385-409.

14. Duvic M, Lemak N A, Redman J R, Eifel P J, Tucker S L, Cabanillas F F, et al. Combined modality therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 1996; 34:1022-9.

15. Vonderheid E C, Tan E T, Kantor A F, Shrager L, Micaily B, Van Scott E J. Long-term efficacy, curative potential, and carcinogenicity of topical mechlorethamine chemotherapy in cutaneous T cell lymphoma. J Am Acad Dermatol 1989; 20:416-28.

16. Abel E A, Sendagorta E, Hoppe R T, Hu C H. PUVA treatment of erythrodermic and plaque-type mycosis fungoides. Ten-year follow-up study. Arch Dermatol 1987; 123:897-901.

17. Hoppe R T. The management of mycosis fungoides at Stanford: standard and innovative treatment programmes. Leukaemia 1991; 5(suppl 1):46-8.

18. Wilson L D, Licata A L, Braverman I M, Edelson R L, Heald P W, Feldman A M, et al. Systemic chemotherapy and extracorporeal photochemotherapy for T3 and T4 cutaneous T-cell lymphoma patients who have achieved a complete response to total skin electron beam therapy. Int J Radiat Oncol Biol Phys 1995; 32:987-95.

19. Edelson R, Berger C, Gasparro F, Jegasothy B, Heald P, Wintroub B, et al. Treatment of cutaneous T-cell lymphoma by extracorporeal photochemotherapy. N Engl J Med 1987; 316:297-303.

20. Duvic M, Hester J P, Lemal N A. Photophoresis therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 1996; 35:573-9.

21. Zic J, Arzubiagac C, Salhany K E, Parker R A, Wilson D, Stricklin G P, et al. Extracorporeal photophoresis for the treatment of cutaneous T-cell lymphoma. J Am Acad Dermatol 1992; 27:729-36.

22. Bunn P A Jr, Hoffman S J, Norris D, Golitz L E, Aeling J L. Systemic therapy of cutaneous T-cell lymphomas (mycosis fungoides and the Sezary syndrome). Ann Intern Med 1994; 121:592-602.

23. Mercieca J, Matutes E, Dearden C, MacLennan K, Catovsky D. The role of pentostatin in the treatment of T-cell malignancies: analysis of response rate in 145 patients according to disease subtype. J Clin Oncol 1994; 12:2588-93.

24. Zackheim H S, Kashani-Sabet M, Hwang S T. Low-dose methotrexate to treat erythrodermic cutaneous T-cell lymphoma: Results in twenty-nine patients. J Am Acad Dermatol 1996; 34:626-31.

25. Kaye F J, Bunn P A Jr, Steinberg S M, Stocker J L, Ihde D C, Fischmann A B, et al. A randomized trial comparing combination electron-beam radiation and chemotherapy with topical therapy in the initial treatment of mycosis fungoides. N Engl J Med 1989; 321:1784-90.