Mycosis Fungoides

Dr. K. T. Chan

Date:	10 May, 2000
Venue:	Yaumatei Skin Centre
Organizer:	Social Hygiene Service, DH; Clinico-pathological Seminar

CASE SUMMARY

History

A middle-aged male with a 10-year-history of generalized pruritus involving the whole body was seen in a skin clinic. He denied any significant past medical or drug history. He had no known allergy. Previous skin biopsy performed over the abdomen in February 1999 showed features of lichen planus. He was treated with various topical steroids, emollients and antihistamines but the skin rash and the itchiness did not subside. In March 1999, the rash progressed. Two large plaques developed at sacral skin. They were mildly pruritic but rapidly enlarging. Due to the rapid growth, the tumour bled and ulcerated.

Physical examination

There were multiple erythematous lichenified papules and plaques over the upper limbs and the trunk. There was also erythroderma with extensive poikilodermatous changes affecting the abdomen, flanks, back, upper and lower limbs (Figure 1). Two large plaques measured 4x4.5 cm^2 and 1x1.8 cm^2 were noted at the sacrum (Figure 2). There was no palpable lymph node or hepatosplenomegaly.

Investigations

A second skin biopsy was performed on the tumour and the histology showed mycosis fungoides. Investigations at Oncology Unit showed that he had normal complete blood count, liver function tests and renal function tests. The hepatitis B serology was normal. Serum immunoglobulin level of IgG, IgE, IgA, IgM, HTLV-1 status, chest X ray and bone marrow biopsy were all normal. CT abdomen and pelvis showed bilateral inguinal lympadenopathy without hepatosplenomegaly. A fine needle lymph node aspiration and cytology (FNAC) showed suspicious

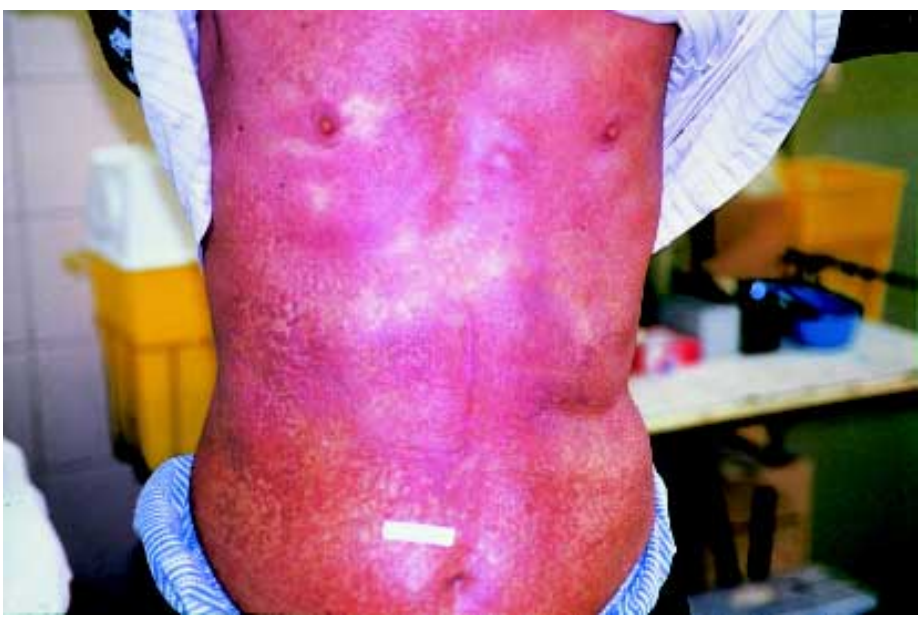

Figure 1: Florid poikiloderma and generalized erythroderma

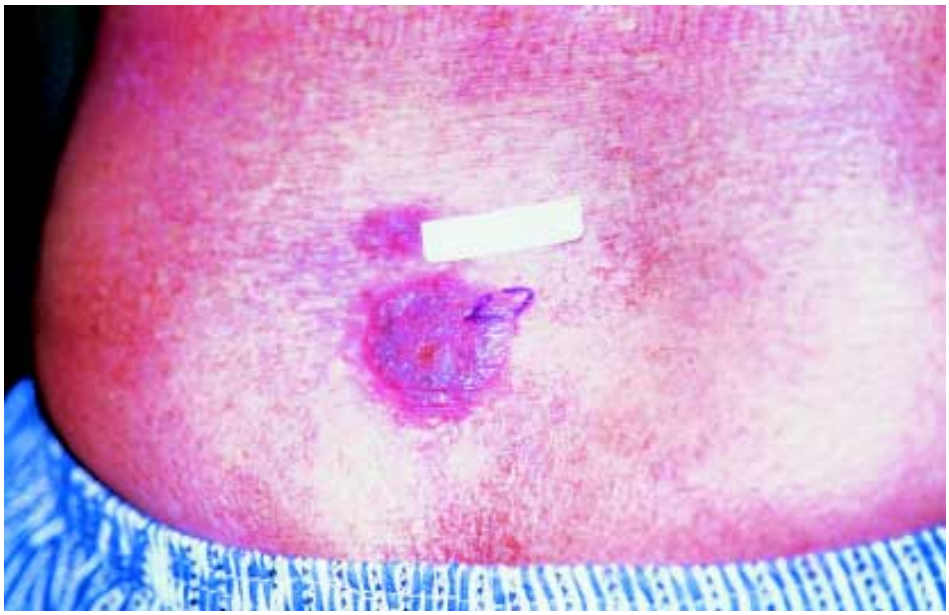

Figure 2: Two large erythematous plaques measured 4x4.5 cm^2 and 1x1.8 cm^2 located over the sacrum of the patient

malignant cells and suggested lymph node biopsy. In view of the clinical and radiological findings, the cutaneous T-cell lymphoma was staged as T4 N1 M0 (cutaneous tumour, generalized erythroderma with lymph node enlargement without systemic metastasis).

Treatment and progress

He was given palliative treatment for his advanced mycosis fungoides. Two fractions of local radiotherapy were given to the sacral tumours. He was then treated with total skin electron beam therapy (TSEBT). TSEBT was given for 30 seconds daily from Monday to Thursday afternoon every week. A total of 32 sessions of TSEBT were administered. Significant improvement was noted with disappearance of the sacral tumours after 10 sessions of TSEBT (two weeks of therapy). There were residual hyperpigmentation and hypopigmentation. The poikiloderma and generalized pruritus also resolved. Apart from xerosis, there was no reported adverse reaction. He did not receive any systemic chemotherapy or adjuvant therapy for his skin disease.

REVIEW ON MYCOSIS FUNGOIDES

Mycosis Fungoides (MF) is a form of cutaneous T-cell lymphoma (CTCL) in which the T-cell lymphoma primarily resides in the skin. In advanced stage, it can metastasize systemically to the lymph nodes, liver, spleen and the rest of the body. Mycosis fungoides was first described by a French dermatologist, Alibert who referred the disease as pain fungoide or framboesia mycoides ("mushrooms"). In 1915, Von Zumbusch described Sezary syndrome as a generalized form of MF with circulating atypical lymphoid cells in the blood.

Epidemiology

There are few epidemiological data on MF. It is a rare condition and the estimated incidence of MF is approximately 0.2 per 100,000 population per year. The difficulty of diagnosing early patch stage MF and the inclusion of parapsoriasis en plaques under MF had made the diagnosis of this condition inaccurate in the past.

Classification

There are a number of revised classifications of CTCL in the literature but they all have their limitations. The modified Kiel classification divided CTCL into high and low-grade lymphoma of T cell origin. The Working Formulation divided CTCL into ten categories: types A-J. Recently, the Revised European American Lymphoma (REAL) classification and the updated version of World Health Organization (WHO) – the REAL modification, segregated T-cell lymphomas, B-cell lymphomas, Hodgkin's disease, precursor cell and mature cell neoplasms.

A more practical and comprehensive classification of CTCL is the biologic categorization of T-cell lymphoma (Table 1) based on clinical behavior, genetic characteristics and course of diseases.[1] This divided CTCL into three main groups: (1) semi-malignant lymphoma, (2) indolent progressive malignant lymphoma and (3) aggressive progressive malignant lymphoma. Semi-malignant lymphoma consisted of small and large plaque parapsoriasis, lymphomatoid papulosis and circumscribed form of MF (for example, pagetoid reticulosis). The indolent progressive malignant lymphoma included MF and Sezary syndrome. Aggressive progressive malignant lymphoma included anaplastic large T-cell and B-cell lymphomas.

Clinical features

The clinical features of MF are characteristic with sequential development from premycotic patch stage to plaque and ultimately tumour stage. There are many clinical variants of MF, which include: bullous, follicular, granulomatous, pustular, hyperkeratotic, hyperpigmented, hypopigmented, adenoxtropic and purpuriform patterns. Sezary syndrome is characterised by generalized erythroderma, lymphadenopathy, and atypical lymphoid cells in the blood.

Diagnosis

The diagnosis of MF requires a high index of suspicion. It is not unusual that repeated skin biopsies are required before the final diagnosis is made. Histological and cytomorphological studies offer a diagnostic accuracy of 80%. Immunotyping and genotyping by Southern blot or polymerase chain reaction (PCR) can confirm the clonal nature of the proliferating cell type in the remaining 20%. PCR is an expensive and tedious procedure and is often unavailable. Recent advances in analysis of single cell with micro-dissection techniques more precisely identify the tumour cell and its original clone.[2]

Staging

For complete staging of MF the following are required: physical examination with mapping and photo-documentation of the skin lesions; skin biopsy with paraffin embedding, and with cryopreservation for phenotyping and genotyping; chest radiography, haematological work up, bone marrow and lymph node biopsy.

The Alibert-Bazin system classified MF into premycotic eczematous stage, plaque or infiltrative stage and tumour stage. Today most dermatologists dealing with MF use the TNM staging system, which realistically described the severity and prognosis of the condition (Table 2). Future staging systems with tumour burden index can hopefully reflect prognostically reliable categories of tumour mass.[3]

There is increasing evidence that the development of full-blown MF is a multi-factorial, stepwise, evolutionary process involving many single genetic mutations. It is unlikely that environmental factor like antigenic stimulation by contact antigens plays any role in the pathogenesis of the condition.

Treatment

Treatment of MF depends on the stage of the disease. Early aggressive treatment did not improve the long-term prognosis. The choice of treatment of MF is also affected by the age of patient, presence of concurrent systemic illness, availability of the treatment modalities and the patient's compliance.

Table 1. Biological categories of cutaneous lymphoma

	Semi-malignant lymphoma	**Malignant lymphoma**	
		Indolent	Aggressive
Clinical course (Spontaneous healing)	No	No	No
Potential systemic spread	No	May occur	May occur
Average survival time	Normal	5-10 years	<5 years
Potential fatal course	No	May occur	Always
Transformation to less differentiated form	No	May occur	Always
Clonality	No	May occur	May occur
Chromosomal alteration (Genetic instability)	No	May occur	Always

Currently for patients with early disease (papules, plaques), the treatment of choice is topical nitrogen mustard or PUVA with topical steroids. Patients with more advanced disease (skin tumours) should received treatment with soft X rays or total skin electron beam therapy (TSEBT). Patients with erythroderma and/or lymph node involvement may benefit from PUVA, extra-corporeal photophoresis or TSEBT. Unfortunately, the technique of extra-corporeal photophoresis is not available in Hong Kong. Other experimental therapies include: autologous bone marrow transplantation, high dose interleukin-2, cyclosporin A and administration of radio-labeled monoclonal bodies. Table 3 summaries the response rates of MF to various treatments.[4]

Topical nitrogen mustard induces a complete remission rate of 30-60%. Results are better in early than in advanced disease. However, relapses were seen in two third of cases.

PUVA also achieved a high complete remission rate of 62% but without significant prospects for long-term disease free survival for patients. PUVA plus systemic interferon had been tried in advanced MF to improve prognosis in some cases.

TSEBT is the administration of high-energy electrons to a limited depth of skin for a short period of time. An overall 84% complete remission rate and a 10-year survival rate of 46% were reported using TSEBT for plaque stage disease. Those with more advanced disease, TSEBT could achieve remission rate at 40% but most patients at this stage may die of the disease within three years even with TSEBT. Relapse of advanced tumour stage MF may benefit from a second course of TSEBT.[5]

Technically, TSEBT should be carried out in a specialized treatment center with adequate experience

Table 2. The current TNM classification for CTCL

T1	Less than 10% involvement
T2	More than 10% involvement
T3	Patches plaques, tumours
T4	Erythroderma
N0	No lymph node enlargement
N1	Lymph node enlargement, -ve pathology for MF
N2	No lymph node enlargement, +ve pathology for MF
N3	Lymph node enlargement with +ve pathology
M0-M1	+/- Histological proven visceral organ involvement

Table 3. Response rates of mycosis fungoides to different treatments[4]

Modality	Response rate (CR+PR)(%)	CR rate (%)	Duration of responses (Months/m)	Authors
Topical nitrogen mustard	>70	30-60	1/3 of patients with CRs have long term response	Abel, Wood, Hoppe
Total skin electron beam therapy	-100	90 for limited plaque 70 for generalized plaque 40 for tumour	50% of patients with limited plaque and 25% of patients with generalized plaque have long term CRs	Abel, Wood, Hoppe
Interferon	55	17	4-28 m (median)	Bunn
Retinoids	58	19	3-13 m (median)	Bunn
Interferon and Retinoids	60	11	Not reported	Bunn
Single agent chemotherapy	62	32	3-22 m (median)	Bunn
Combination chemotherapy	81	38	5-41 m (median)	Bunn

NB: CR (complete remission), PR (partial remission)

of the therapy. A multidisciplinary approach should be adopted. A total dose of 28-32 Gy was supplied in cycles. 1-2 Gy could be given daily. Eyes, fingernails, toenails, hand and foot were shielded from the radiation to reduce possible clinical reactions.

TSEBT is contraindicated in patients with a platelet counts less than 100,000/ml or absolute granulocyte counts less than 1,500/ml. Haematologic toxicity should be monitored with weekly complete blood counts. Adverse reactions of TSEBT were few, which included skin hypopigmentation, hyperpigmentation, xerosis, telangiectasia, reversible nail dystrophy and alopecia. The development of secondary cutaneous malignancy from TSEBT is rare.

Learning points:

Total skin electron beam therapy (TSEBT) offers the best chance of cure for advanced stage MF at present.

References

1. Burg G. Cutaneous lymphoma. Curr Probl Dermatol 2000, 25-9.
2. Brauninger A, Hansmann ML, Strickler JG, et al. Identification of common germinal center B cell precursors in two patients with both Hodgkin disease and non-Hodgkin lymphoma. N Engl J Med 1999,340:1239-47.
3. Ness Schmid M, Bird P, Dummer R, et al. Tumour burden index as a prognostic tool or cutaneous T cell lymphoma: a new concept. Arch Dermatol 1999;135:1204-8.
4. Duvic M, Lemak NA, Redman JR, et al. Combined modality therapy for cutaneous T-cell lymphoma. J Am Acad Dermatol 1996;34:1022-9.
5. Becker M, Hoppe RT, Knox SJ. Multiple courses of high-dose total electron beam therapy in the management of mycosis fungoides. Int J Radiat Oncol Biol Phys 1995;32:1445-9.