CASE REPORT

Sézary syndrome: Unravelling the mystery behind erythrodermic manifestations - A case report

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SUMMARY

Sézary syndrome (SS) is a rare, aggressive leukemic variant of cutaneous T cell lymphoma (CTCL). It is often difficult to differentiate from benign inflammatory disorders such as atopic eczema, psoriasis and chronic eczema, especially in its early stages. The diagnosis relies heavily on a strong clinico-pathological association. Early diagnosis is crucial as inappropriate treatment, such as immunosuppressants, can lead to unfavourable outcomes. This article focuses on the diagnostic challenges faced and the subsequent management approach.

INTRODUCTION

Sézary syndrome (SS) is a rare leukemic variant of cutaneous T cell lymphoma (CTCL), characterised by the triad of erythroderma, generalized lymphadenopathy and neoplastic T-cells (Sézary cells) in peripheral blood.[1,2] Majority of CTCL (75%) can be classified as mycosis fungoides (MF) or SS.2 The relative frequency of SS as per World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) is 2%; whereas the 5-year disease-specific survival rate of SS is 36%.[1] Another multicentre registry study in Asia reported 0.6% of SS among peripheral T cells lymphoma.[3] MF and SS often share overlapping features clinically and histopathologically, yet are considered two distinct diagnoses with separate memory T cell subset.[2,3,4] SS manifests with severe symptoms, unfavourable response to treatment and poorer survival rate in comparison to MF.[5] Its rare manifestation as generalised erythroderma poses a diagnostic challenge and impacts patient management.[1] Herein, we present a rare case of SS presenting as generalised erythroderma, discuss the diagnostic challenges faced and the subsequent management approach.

CASE PRESENTATION

A 27-year-old male of Indian ethnicity was referred by a local clinic to a tertiary hospital for dermatology consultation and evaluation of a 10-year history of diffuse, pruritic hyper-pigmented skin eruptions. He had visited multiple general practitioners prior for this troubling condition as he was disabled by its severity and could not hold onto his job. The longstanding lesions initially commenced over the trunk as dermatitis-like lesions. The lesions gradually spread over his face, bilateral limbs, and flexural area with worsening thickness and pain over the past 2 years despite followed up under dermatology clinic. Sweating and sun exposure further aggravated the skin lesions. He had a history of childhood asthma and dry skin. There was no significant family history of any malignancy, autoimmune or familial disorder. The patient was an active smoker and a non-alcoholic drinker.

Despite multiple courses of topical creams and antibiotics, the skin eruptions persisted. During the first dermatology consultation, hidradenitis suppurativa and atopic dermatitis were diagnosed. He was started on topical emollients and doxycycline. After 6 months of treatment, his lesions waxed and waned. The surface of plaques increased with new nodules over his scalp, and he developed alopecia. Accompanied by systemic symptoms such as weight loss, anorexia and reduced effort tolerance, the clinical picture was intriguing.

On examination, he had generalised hyper-pigmented plaque-like and nodular lesions with scratch marks over his face, trunk, upper and lower limbs, accounting for about 95% of his body surface area. Diffuse alopecia and infiltration over facial skin were present (Figure 1). There was an absence of lymphadenopathy and hepatosplenomegaly. Other examinations were unremarkable.

The preliminary laboratory investigations showed an elevated white cell count of 17.3 109/L and lactate dehydrogenase level of 285 U/L. Peripheral blood smear showed leukocytosis with eosinophilia without any blasts seen, indicating a potential inflammatory or infectious condition. His total IgE was >5000 kU/L. The Viral screening panel was negative. Flow cytometry immunophenotyping of peripheral blood showed a small cluster of 3.5% aberrant T cells expressing c3, 3 dim, TCRab dim, 2 dim, 5 bright, 4 dim and lacking all other antigens including 7, 8, 26, 25, 30, cyTCL-1, 34 and nTdT alongside 47% cluster of eosinophils.

A biopsy of skin over his back presented with epidermotropism with Pautrier microabscess, a feature suggesting CTCL[4] (Figure 2). The atypical lymphoid cells expressed CD2, CD3, CD4, CD5, CD7 and GATA3 diffusely

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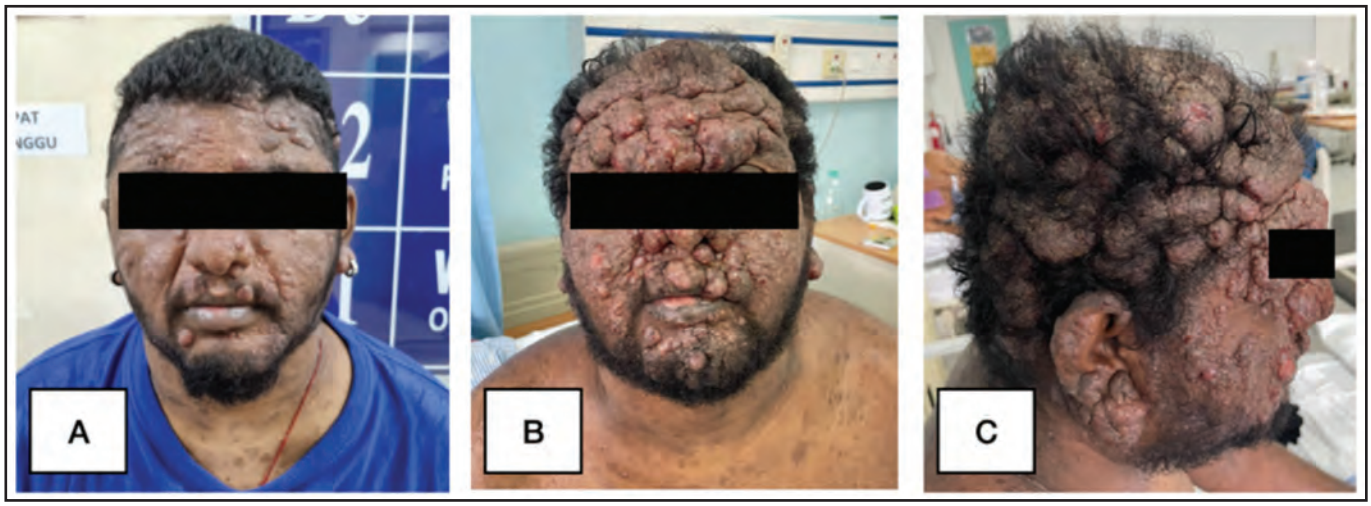

Fig. 1: Clinical images of the patient with cutaneous findings. A. 2 years ago (front view): Scattered plaques-like and nodular lesions over bilateral temporal region and nasolabial folds. B. Current (front view) : Infiltration over facial skin—leonine facies. C. Current (side view): Diffuse alopecia and nodules over scalp; infiltration over ears

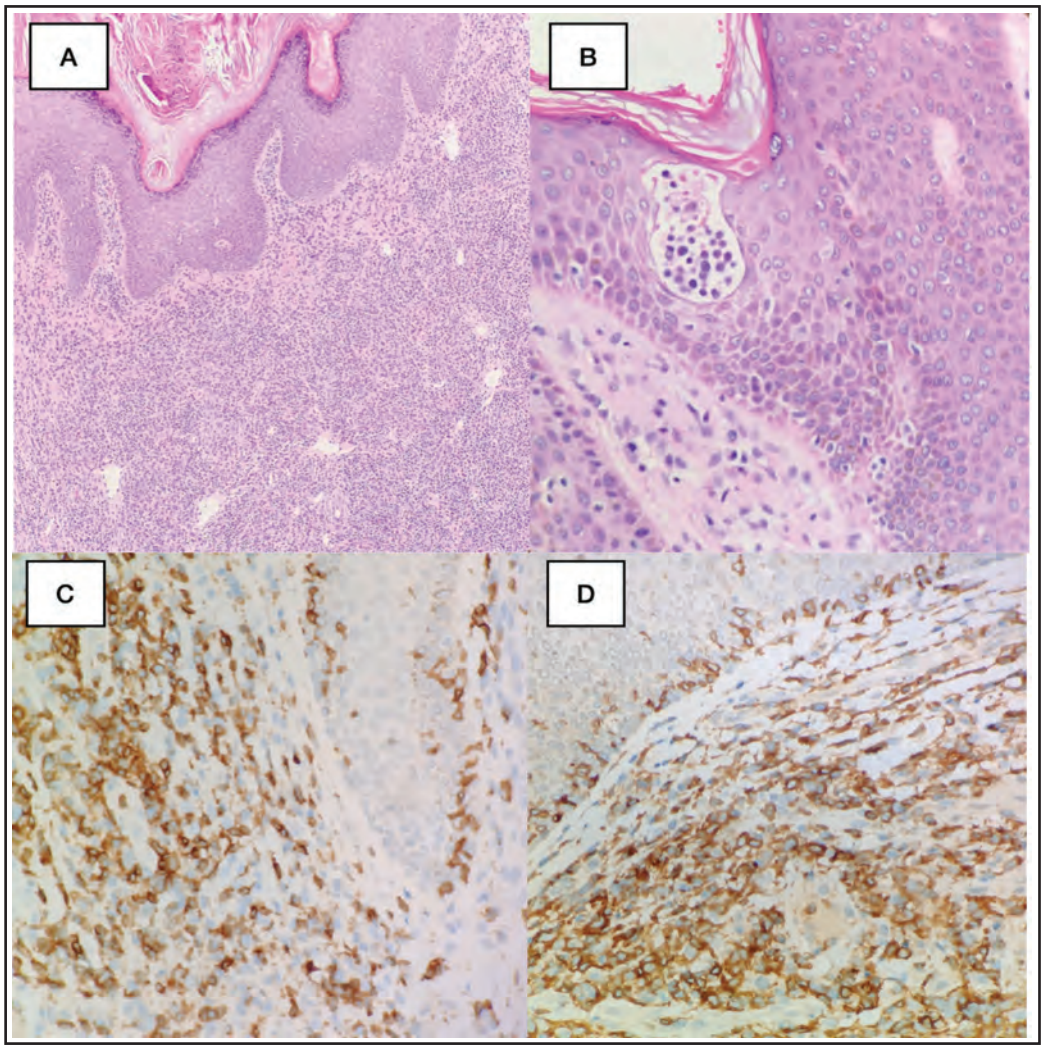

Fig. 2: Histological findings from the skin biopsy. A.Diffuse lymphoid infiltrates in the dermis along with occasional epidermotropic lymphocytes(H&E with 100× magnification). B. The case showing Pautrier microabscess (H&E with 400× magnification). C. Neoplastic CD3-positive T-cells can be seen in the epidermis and dermis (CD3 immunostain 400× magnification). D. Neoplastic CD4-positive T-cells can be seen in the epidermis and dermis (CD4 immunostain 400× magnification)

(Figure 2). There was a smaller number of those cells expressing BCL6, CD8, CD30, CD56, T1A1 and PD1. The cells stained negative for CD10, CD20, CD21, EBER (ISH), MPO, TDT and granzyme B. The Ki67 proliferative index was reported to be about 30%. Computed tomography of thorax, abdomen and pelvis revealed multiple skin thickening and nodules, but no visceral organ involvement, hence the tumour, node, metastasis, and blood (TNMB) staging was determined to be stage 3A T4N0M0B0.[1]

Collectively, the clinical and histopathological features were suggestive of SS.

A multidisciplinary approach was taken in the management of the patient in order to minimise the side effects of the long-term treatment and improve quality of life.[4,5] He was started on standard combination therapy of chemotherapy oral Methotrexate 10mg once a week and oral prednisolone 20mg OD.[2,6] There was limited response to oral chemotherapy. First cycle of intravenous infusion of methotrexate treatment was complicated by septic shock secondary to methicillin-sensitive *Staphylococcous aureus* bacteraemia. Subsequently, he was switched back to low-dose oral methotrexate. Ultraviolet phototherapy (Psoralen plus Ultraviolet A), an effective adjuvant therapy was started alongside with skin-directed topical treatments for symptom control.[4-6] His condition remained stable on this regime; however, he has yet to achieve a complete skin clearance. He was planned for total skin electron beam therapy, with future plans for subcutaneous interferon and brentuximab vedotin as the next steps in management.

DISCUSSION

This case highlights the importance of recognising uncommon presentations of SS. The common non-classic signs of SS were palmoplantar keratoderma, onychodystrophy, alopecia, leonine facies, and ectropion. Erythroderma, although a rare presentation, should be considered in patients with long-standing, progressive skin lesions and systemic symptoms.[8] Unless there is an exacerbation of pre-existing dermatoses, the final diagnosis of erythroderma depends on the individualised evaluation of clinical, biochemical, and histological findings of each patient. A 12-year-prospective study by Miyashiro and team reported the most common aetiology of erythroderma is eczema (20.7%), followed by psoriasis (16.8%), SS (12.3%), drug eruption (12.3%), atopic dermatitis (8.7%) and MF (5.5%).[9] The prevalence of CTCL can be as high as 18% in patients with erythroderma, not including the idiopathic erythroderma (16.8%) that may represent a pre-SS or not yet diagnosable erythrodermic CTCL.[9]

Erythroderma in SS can develop with or without the background of pre-existing cutaneous lesions.[4] The diagnosis of SS is challenging, particularly in the early stages. SS can masquerade as benign inflammatory disorders.[9] Patients may have other dermatologic symptoms (nonspecific dermatitis, poikiloderma or erythroderma) for years to decades, diagnosing as MF/SS.[5] It is difficult to further differentiate between SS and erythrodermic CTCL.[9,10] This can be due to clonal T cells occasionally being present in benign skin conditions and older subjects secondary to the ageing process. Furthermore, not all SS patients fulfil the criteria of CD4: CD8 ratio ≥ 10 at presentation.[9] In such cases, it is crucial to have unequivocal identification of Sézary cells in blood or skin.[10] It is strongly recommended for clinicians to be highly suspicious of CTCL and lower threshold to proceed with skin biopsy over the most indurated area after stopping topical treatment for >2 weeks in these patients, if the clinical course raised suspicion with the initial skin biopsy, is nondiagnostic.[5]

Immunostaining of specimens and flow cytometry of peripheral blood can aid in clonal cell detection to facilitate the accurate diagnosis of SS.[5,9] In SS, clonal T cells are generally CD3+CD4+ and CD8-.[2,4,5] The loss of CD7 and/or CD26 is highly specific for SS.[2] In contrast, MF have immunophenotypic characteristics of skin-resident effector memory T cells (CCR4+, CCR7–) compared to SS's phenotype of circulating central memory CD4+ T cells.[4,5] Alternatively, clonal gene rearrangement of T-cell receptors in skin or blood for clonality.[4,5]

The treatment of SS is stage-dependent; thus, early recognition can guide therapeutic strategy and potentially improve prognosis.

CONCLUSION

SS can present with a myriad of clinical manifestations.5 Recognising the atypical manifestation is key for early diagnosis and appropriate prompt management.5 Furthermore, standardising the evaluation of erythrodermic patients is the first step to better define the management and understand the evolution of this severe skin condition.[1] This case highlights the implication of taking into consideration SS in the diagnosis of erythroderma.

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ETHICAL CLEARANCE

Ethical clearance has been obtained from NMRR Secretariat (NMRR ID-23-02134-8R3). Informed consent was obtained from patient/ patient's family members in line with COPE standards for his/her images and other clinical information to be reported in this journal. Due efforts are made to conceal their identity.

DECLARATIONS

The authors declare no conflict of interest.

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