Sezary Syndrome

Dr. W. K. Tang

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CASE SUMMARY

History

A 75-year-old gentleman complained of generalized itchy erythematous rash since 1997. The rash was mainly distributed on the anterior chest and back, with less involvement of the limbs. No particular precipitating factors including drug or sun exposure could be recalled by the patient. He consulted a private doctor and was treated as dermatitis. His past medical history was unremarkable. He was seen in Social Hygiene Service since May, 1999 for worsening of the skin rash for two months.

Physical examination

Generalized confluent erythema with nodules and plaques were noted over the trunk. There was no ulceration (Figure 1). He also had facial erythema and ectropion. The scalp and nails were spared. No lymphadenopathy or fever was noted.

Investigations

Peripheral blood smear showed atypical lymphoid cells. White cell count was 8.4×10^9/l and haemoglobin was 12.2g/dl. There was mild renal impairment (urea - 8.1mmol/l, creatinine - 154 ㎜ol/l) and liver function was normal.

A skin biopsy was performed which showed dense band-like atypical lymphocytic infiltrate in the reticular dermis. Cell size ranged from medium to large with cerebriform nuclei, mixed with some large cells with more vesicular nuclei contouring large nucleoli. Mitosis were frequent (>2 per high power field). Epidermotrophism was not prominent.

Bone marrow biopsy showed mildly hypercellular, abnormal lymphoid infiltrate with varied distribution (constituting about 100% of the nucleated cells in some areas). The lymphoid cells were medium to large in size

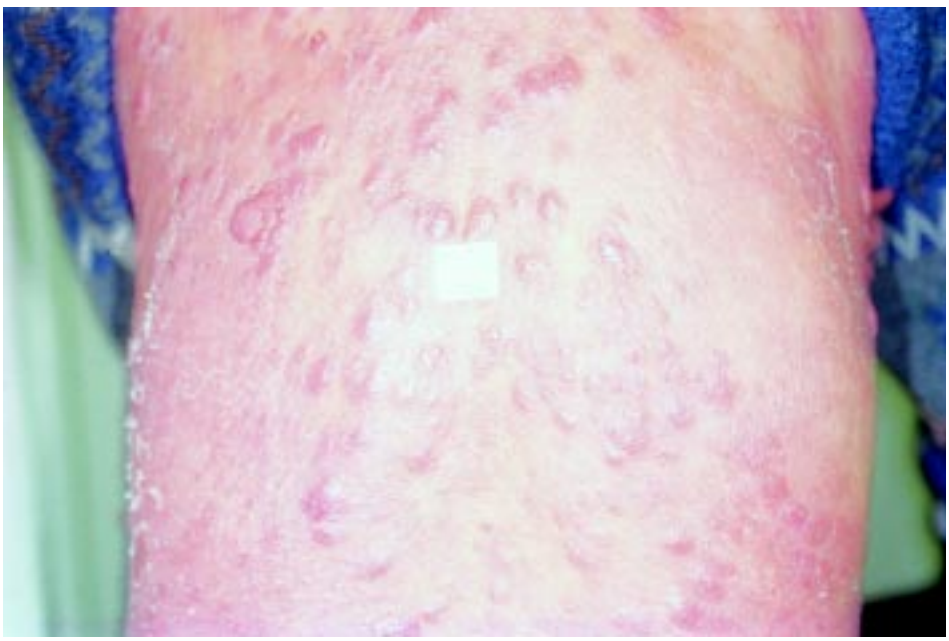

Figure 1: Confluent erythema, nodules and plaques over the trunk

with high nuclei/cytoplasm ratio and clumped chromatin. Peripheral blood also showed lymphocytosis with many abnormal lymphoid cells (43% of white blood cells).

Immunotyping of abnormal cells expressed CD3, CD4, and CD5. B-cell markers and HTLV1 antibodies were negative.

Diagnosis

The diagnosis of cutaneous T-cell lymphoma (CTCL) of the Sezary syndrome type was made.

Management

A trial of chlorambucil together with prednisolone was given initially. Later they were replaced by a combination of chemotherapeutic agents- vincristine cyclophosphamide, and prednisolone. The patient developed chest infection and succumbed before further staging investigations could be done.

REVIEW ON SEZARY SYNDROME

Cutaneous T-cell lymphoma (CTCL) is generally classified as a type of non-Hodgkin's lymphoma, and it represents a spectrum of diseases composed of malignant clonal helper T-lymphocytes of the CD4 phenotype.

CTCL is the most common type of primary cutaneous lymphoma, representing 65% of cases of cutaneous lymphoma. It is subdivided into different variants. Approximately 5% of new cases of CTCL belong to Sezary syndrome. It represents the leukemic variant of CTCL.

Etiology

The cause of the CTCL-MF/SS is largely unknown. The human T-cell lymphotropic virus type-1 (HTLV-1) was suggested as it had been found to have a causal relation to adult T-cell leukemia/lymphoma. And the HTLV-1-like retroviral particles have been found in Langerhans cells, B-lymphocytes, and the blood of some CTCL patients. However, most CTCL patients are negative for the virus and the known HTLV-1 epidemiologic patterns have not been observed in CTCL.[1] Some groups have found serologic evidence of the Epstein-Barr virus in CTCL patients, suggesting a possible role in the pathogenesis.[2] Other implicated risk factors include genetic predisposition, radiation exposure, and pre-existing malignancies, although there are little supporting data. Immunosuppression as a risk factor for CTCL has been suggested, since cases of CTCL were found in patients infected with the human immunodeficiency virus,[3] in organ transplant patients, and in treated lymphoma patients.

Clinical presentations

Sezary syndrome is recognized by the classic triad of 1) generalized erythroderma, as a result of diffuse infiltration of the skin by neoplastic cells, 2) leukemia, and 3) lymphadenopathy. Patients may also have symptoms like fever, chills, weight loss and malaise. Other features include hepatomegaly, onychodystrophy, papulo-nodular lesions on the face (leonine facies), ectropion, alopecia, and palmo-plantar keratoderma. Early skin lesions may mimic eczema or papulo-squamous eruptions such as tinea corporis, secondary syphilis, or psoriasis. In fact, the latent period from the onset of the skin lesions to definite diagnosis was 4-10 years with a mean of 6 years. The smoldering and chronic subtypes of adult T-cell leukemia/lymphoma may also mimic MF/SS clinically and histologically.

Diagnosis

The diagnosis of Sezary syndrome is usually made by recognizing the characteristic clinical manifestations of the disease, routine histology and peripheral blood smear. Sezary cells can be detected in the peripheral blood in 90% of erythrodermic CTCL patients and up to 20% in those with plaque or tumor-stage disease, as well as in several benign dermatologic conditions. The definition of Sezary syndrome based on the number of circulating atypical lymphocytes remains controversial. Some researchers have arbitrarily used cutoffs of 5%, 9%, and 10% of the total leukocyte count as an indicator of the disease.[4] Others use an absolute count of 1,000 Sezary cells/mm^3 as diagnostic criteria.[5] As the disease progresses, the ratio of CD4(T-helper) lymphocytes to CD8(T-suppressor) lymphocytes becomes elevated by clonal expansion of the malignant CD4 lymphocytes. A CD4:CD8 ratio of >5 together with the morphology

of the nuclei of the atypical cells are more sensitive indicators in diagnosing Sezary syndrome. In general, Sezary cells lack CD7 molecules on their surface and are analogous to murine Th2 cells. Nevertheless, CD7 positive Sezary cells have been reported.[6]

The histologic features of erythrodermic MF and Sezary syndrome are even more subtle than the features of patch and plaque stage MF, thus rendering the histologic diagnosis more difficult. Since some cases initially resemble other chronic inflammatory dermatoses, frequently sequential biopsies are necessary before the diagnosis is made. In the case of adult T-cell lymphoma, HTLV-1 seropositivity and long-term follow up is needed in differentiating between it from MF/SS. In difficult cases, additional laboratory tests such as immunophenotyping, flow cytometry, and T-cell receptor (TCR) gene rearrangement analysis may help to establish the diagnosis.

TCR gene rearrangement (TCRGR) analysis, using Southern blot or polymerase chain reaction (PCR) methods, helps to confirm early or atypical CTCL when the histology is suggestive but not diagnostic.[7]

Prognosis

The prognostic factors mainly depend on the stage of the disease. Detection of the TCR rearrangement in lymph nodes is associated with an inferior survival rate.[8] A cohort study was conducted by Bernengo et al in Italy in 1998.[9] In this study a cohort of 62 SS patients were followed since 1975. The following variables were found by univariate analysis to be associated with a poor prognosis at the time of SS diagnosis:

- previous history of mycosis fungoides
- high number of circulating Sezary cells (SC) and CD4+ cells
- presence of large circulating SC
- abnormal LDH serum level
- presence of PAS-positive inclusions in the cytoplasm of circulating SC
- high CD4/CD8 ratio
- CD7 negative circulating SC phenotype

Patients with no or one adverse prognostic feature tend to run a slow disease course and a relatively favorable prognosis (five-year survival: 58%). Whereas patients with 2 or 3 adverse prognostic features tend to run an aggressive disease course not modifiable by traditional therapies (five-year survival: 5%).

Treatment

A stage-adapted approach to CTCL therapy is used. There are three main modalities of treatment available.

1) Skin direct therapies

Topical steroid, phototherapies (UVB, PUVA), total skin electron beam radiation and topical chemotherapy (mechlorethamine/nitrogen mustard and carmustine/BCNU) belong to this group. The skin direct therapies are able to induce remission as a monotherapy. Phototherapy and nitrogen mustard can be used as maintenance as well. A recent randomized study failed to show a survival benefit in patients with CTCL using aggressive combination chemotherapy and radiotherapy.[10] For limited disease (stage 0), a trial of glucocorticoids is indicated. If there is no response to glucocorticoids, PUVA is most commonly used, although some patients may respond to UVB therapy.

2) Biologic response modifiers

Interferon and interleukin-2 can be used in treating localized diseases. Photopheresis has been reported to induce remission in difficult cases. DAB-IL-2 (Chimeric fusion of diphtheria toxin and interleukin-2) is still experimental at this stage. In general, these treatment options are not very effective to induce remission on its own, therefore they are usually combined with skin directed therapies.

3) Chemotherapy

It is mainly reserved for advanced diseases as palliation. No regime has been shown to be curative, though adriamycin has been found to be a very effective single agent for palliative purpose. CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) is one of the safer and better tolerated regime for advanced disease. Chlorambucil and cyclophosphamide are most frequently used agents in daily low dose chemotherapy of CTCL. They are usually used in combination with steroid.

Learning points:

Sezary syndrome is diagnosed by a triad of erythroderma, leukaemia and lymphadenopathy. In early stage of the disease, close clinical and histopathological follow-up are needed. Treatment is largely palliative and is guided by the stage of the disease.

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