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Perspectives and Commentaries

Recent Developments in the Early Diagnosis of Mycosis Fungoides and Sézary's Syndrome

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MYCOSIS FUNGOIDES (MF) and Sézary's syndrome (SS), commonly referred to as the cutaneous T-cell lymphomas (CTCL), are closely related lymphomas of mature helper T-cells, that originate clinically in the skin. Classical MF usually appears with non-specific erythematous patches; with progression of the disease more infiltrated plaques and tumors may develop. The skin lesions may be the only manifestation of the disease for many years or, in some patients, even decades, before lymph node and visceral involvement eventually develop. SS is characterized by the presence of a pruritic exfoliate or infiltrative erythroderma, generalized lymphadenopthy, and the presence of atypical cells (Sézary cells) in skin, lymph nodes and peripheral blood. The clinical and histologic findings in the early cutaneous stages of MF and SS are often not diagnostic, and differentiation from chronic benign skin diseases may be extremely difficult. Similar difficulties are encountered in diagnosing early involvement of lymph nodes and peripheral blood by routine histological and cytological examinations. Early diagnosis of MF in the skin is important, since it provides the opportunity to treat these patients at an earlier stage of their disease. Treatment modalities currently used in MF patients with disease apparently confined to the skin include topical application of nitrogen mustard, photochemotherapy (PUVA) and total skin electron beam irradiation. Early demonstration of extracutaneous disease is even more important, since it generally indicates the presence of more aggressive disease, which may require systemic polychemotherapy rather than the above-mentioned therapies which are directed only at the skin.

In attempts to obtain more precise and objective criteria for the early diagnosis of MF and SS, investigators have used a number of special diagnostic techniques, including DNA cytometry, cytogenetic analysis, quantitative electron microscopy, monoclonal antibody studies, and very recently T-paper, we will review the results of some of these studies and discuss their clinical implications.

Feulgen–DNA cytophotometry was used by van

Feulgen–DNA cytophotometry was used by van Vloten *et al.* [1] on imprint preparations of skin biopsies of 430 patients clinically suspected of having early MF. An abnormal DNA histogram, which was defined by the presence of hypertetraploid cells, was found in 109 patients. During follow-up 102 patients developed MF, whereas 7 patients had lymphomatoid papulosis. From the 321 patients with normal DNA histograms, 34 developed MF, which may be due to sampling errors. Using flow cytometric analysis, Bunn *et al.* [2] analyzed the DNA content of lymph node and peripheral blood specimens from 46 patients with CTCL. Aneuploidy was detected in 32 of 46 patients studied, whereas control specimens from healthy volunteers or patients with chronic benign dermatoses contained only diploid cells. Aneuploidy was detected in 8 of 16 specimens scored as negative by cytologic and histologic examinations. The authors demonstrated a direct correlation between the results of DNA flow cytometry and chromosome abnormalities detected by G-banded cytogenetic analysis. These studies demonstrate that DNA flow cytometry and karyotype analysis

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are particularly useful in detecting early extracutaneous involvement with CTCL, and suggest that this occurs much earlier than can be assessed with routine cytology and histology.

Ultrastructurally, the neoplastic cells in MF and SS are characterized by the presence of deep and narrow (cerebriform) nuclear indentations, condensed chromatin along the nuclear membrane, and scanty cytoplasm poor in organelles. Since the first description of these cells in the peripheral blood of patients with SS by Lutzner *et al.* [3], many investigators have studied the usefulness of electron microscopy in the diagnosis of MF and SS. However, since cerebriform mononuclear cells (CMC) similar to those observed in MF and SS were found in benign skin diseases, and even in the peripheral blood of healthy donors [4], more objective criteria had to be searched for. Several groups performed quantitative ultrastructural studies to objectively define the degree of nuclear indentation of the lymphoid cells, which was expressed by the nuclear contour index, the nuclear shape index or the number of sharply angled indentations of these cells. These studies showed that the CMCs in CTCL have a higher degree of nuclear indentation than similar cells in reactive processes. Based on this difference criteria were developed allowing differentiation between CTCL and benign skin diseases. Such morphometric criteria have proved to be a major adjunct in the early diagnosis of MF and SS, both in the skin, lymph nodes and peripheral blood (for review, see Ref. [1]).

Monoclonal antibody studies on tissue specimens and cell suspensions of patients with MF and SS have firmly established the helper T-cell phenotype of the neoplastic cells in these conditions. It was hoped that these studies might also provide additional diagnostic criteria for the early diagnosis of these lymphomas. However, immunohistochemical studies on skin tissue sections of patients with early CTCL showed a staining pattern identical to that observed in many benign skin diseases, i.e. a predominance of (activated) helper T-cells, and varying numbers of $T8^+$ T-cells, $T6^+$ Langerhans cells and $HLA\text{-}DR^+$ macrophages [5]. Similar studies on lymph node sections also failed to differentiate between lymph nodes showing early involvement by MF and dermatopathic lymph nodes from patients with generalized benign skin diseases [6]. More recent studies have reported that some antigens are more (T9, T10) and other antigens (Leu-8, Leu-9) less frequently expressed in CTCL than in benign skin diseases [7, 8]. However, whether such gradual differences will be useful in the early diagnosis of MF and SS remains to be established. Finally, it has recently been demonstrated that the monoclonal antibodies BE1 and BE2, which were raised against the leukemic cells of a patient with CTCL, and were initially thought to react specifically with the malignant cells in MF and SS [9], are neither T-cell nor tumor cell specific, and therefore of limited value in differential diagnosis [1, 10]. Thus, it can be concluded that monoclonal antibody studies on tissue specimens have not yet provided useful criteria for the early diagnosis of MF and SS. In contrast, determination of the T4/T8 ratio in the peripheral blood of patients with erythroderma has been considered an important tool in the differentiation between SS and benign forms of erythroderma [11]. Similar studies in patients with MF have yielded conflicting results, which in part may be attributed to differences in patient selection. Recently, Larusso *et al.* [12] studied T4/T8 ratios in the peripheral blood of 15 MF patients with disease limited to the skin before and after photochemotherapy (PUVA). In comparison with patients with chronic benign skin diseases and healthy donors, the MF patients showed significantly elevated T4/T8 ratios before therapy. After PUVA therapy a marked decrease in T4/T8 ratios was observed in all but two patients who proved to be unresponsive to PUVA treatment. In the same patients these investigators measured the serum levels of beta 2-microglobulin (B2-m). B2-m is a low molecular weight protein synthesized by most nucleated cells, and constitutes the invariant chain of the human leukocyte antigens HLA-A, -B, -C. They found elevated levels of B2-m in untreated MF patients, but not in controls, which returned to normal in those patients achieving complete remission after PUVA therapy. These results suggest that determination of T4/T8 ratios and B2-m levels may be important in the early diagnosis of MF, as well as in monitoring response to treatment. It must, however, be emphasized that increased T4/T8 ratios may also be found in patients with atopic dermatitis. Since differentiation between early MF and atopic dermatitis may sometimes be difficult, additional studies will be necessary to establish the differential diagnostic value of this parameter.

The recent cloning of the genes encoding the T-cell receptor has provided useful markers of clonal T-cell proliferation. Using the Southern blot hybridization technique, Weiss *et al.* [13] analyzed the DNA of the beta T-cell receptor genes in lymph node specimens of patients with MF. Clonal rearrangements were not only found in all specimens showing definite histologic involvement, but also in 7 of 9 lymph nodes that were histologically not diagnostic for MF. This study suggests that the DNA hybridization technique is more sensitive than histologic and cytologic examinations to detect lymph node and peripheral blood involvement in patients with MF. Whether such studies

will also contribute to an early diagnosis of MF in the skin, has yet to be established.

In conclusion, the application of special diagnostic techniques in patients suspected of having CTCL, has provided useful criteria for the differentiation between early CTCL and chronic benign skin diseases. In addition, some of these studies have demonstrated that a proportion of patients with disease limited to the skin, as assessed by conventional methods, may already have disseminated disease. Whether such patients should receive systemic polychemotherapy rather than the commonly used cutaneous therapies (topical chemotherapy, PUVA, total skin electron beam irradiation), remains to be established.

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