A profile of mycosis fungoides

Mycosis fungoides is the most common primary lymphoproliferative disorder of skin. The disease may be difficult to diagnose, particularly in the early patch and plaque stages, when it may resemble a chronic inflammatory dermatitis. The neoplastic cells of mycosis fungoides are CD3+ T cells, which are usually CD4+ T helper cells, and may or may not exhibit an aberrant immunophenotype, with loss of CD7 expression. A number of nonneoplastic conditions, including inflammatory dermatoses, may exhibit an identical immunophenotype, adding to the difficulty of early diagnosis. Often, the diagnosis becomes evident only after multiple biopsies, over a period of months to years. With disease progression, increasing epidermotropism and cytologic atypia are seen, allowing for more definitive diagnosis. With advanced-stage disease, skin tumors may form and neoplastic cells may spread to extracutaneous sites. The pathogenesis of mycosis fungoides is unknown.

In this issue, Tracey and colleagues (page 1042) apply gene-expression profiling techniques to mycosis fungoides, an approach that should significantly expand our knowledge of the disease. First, they identify a 27-gene expression signature, using cDNA microarray analysis on 29 cases of mycosis fungoides and 11 cases of inflammatory dermatoses, which distinguishes between the two. From this they extract a set of 6 genes whose expression can discriminate between mycosis fungoides and inflammatory conditions in 97% of cases. The set of 27 mycosis fungoides–expressed genes, which includes a number of genes involved in the regulation of signaling by tumor necrosis factor (TNF), may hold clues to the pathogenesis of the disease. Finally, through hierarchical clustering of the gene expression data, the authors define 2 main groups of mycosis fungoides cases, one of which includes those that are more aggressive, including cases with tumor-stage disease.

Gene-expression analysis by microarray techniques has been utilized to refine tumor classification for a number of malignant neoplasms, including large B-cell non-Hodgkin lymphoma and breast carcinoma. Tracey and colleagues have now applied this method to a T-cell lymphoma, providing us with a new set of markers that may aid in disease diagnosis, as well as providing a preliminary gene-expression-based tumor classification scheme for mycosis fungoides. Future gene-expression profiling studies, to compare mycosis fungoides with the related Sézary syndrome, other T-cell lymphomas, and benign mimics, such as pseudolymphomatoid drug eruption, will further advance this diagnostically challenging field.

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Prognostic staging in myeloma: in search of biology

For 30 years, clinicians relied on the Durie-Salmon staging system (Durie and Salmon, Cancer. 1975;36:842-854) to define risk in multiple myeloma (MM). In recent years the β2-microglobulin (β2M) and C-reactive protein (CRP) have added to the prognostic arsenal (Bataille et al, Blood. 1992;80:733-737). Despite their longevity, both staging systems are limited by an inability to segregate risk accurately in all cases, a particular problem in such a heterogeneous disease. Indeed, until recently prognostic prediction has been something of an irrelevance since all patients with symptomatic disease received essentially the same therapy. Lately, however, the landscape has changed and identification of accurate prognostic biomarkers has assumed increasing importance since therapeutic options may now vary widely according to disease biology.

In this issue, Terpos and colleagues (page 1064) take a step in this direction by examining the roles of the receptor activator of nuclear factor κB ligand (RANKL) and RANK/osteoprotegerin (OPG), which play a dominant role in osteoclast activation and probably in the bone disease common to MM patients (Mundy, Nat Rev Cancer. 2002;2:584-593). The authors demonstrate
that in 121 MM patients serum levels of sRANKL were elevated and correlated with bone disease. The sRANKL/OPG ratio was also increased and correlated with markers of bone resorption, osteolytic lesions, and markers of disease activity. More impressively perhaps, sRANKL/OPG ratio, CRP, and β2M were the only independent prognostic factors in multivariate analysis and, used together, defined a low-risk group having a 96% probability of survival at 5 years, as compared with 52% and 0% for the intermediate- and high-risk groups, respectively; a remarkable discriminatory power. The results suggest that the RANKL/OPG system is not only associated with MM bone disease but also impacts the biology of plasma cell growth as reflected by its influence on survival.

Predicting prognosis and defining therapy using novel biomarkers (as described herein), chromosome translocation status and gene expression profiles point the way to the future of MM care, but all require further study. Until confirmed in large prospective studies, user-friendly and sensitive prognostic tools such as the recently devised MM International Staging System (ISS), which employs β2M and albumin, deserve wide implementation, albeit with future refinement (Greipp et al, Hematol J. 2003;4:S42-S44).

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The MoAb reloaded? Is alemtuzumab the one?

Multiple myeloma remains an incurable B-cell malignancy whose victims survive a median of about 4 years. Over the past decade new therapies and supportive measures have provided incremental gains. No effective monoclonal antibody therapy exists for myeloma, but that is not for want of trying. Promising immunotherapeutic strategies involving CD38, CD20, and other antigens have been touted but did not succeed (Ellis et al, J Immunol. 1995;155:925-37; Maloney et al, Semin Hematol. 1999;36:30-33; Treon et al, Semin Oncol. 1999;26:97-106; Ozaki et al, Blood. 1999;93:3922-3930; Gemmel et al, Ann Hematol. 2002;81:119-123). These therapies failed because the antigens were not pan-specific myeloma cell antigens and, less commonly, because the monoclonals cross-reacted with similar epitopes present on other cell types (eg, spinal neurons), causing unanticipated toxicities. New candidates continue to be put forward (Satoh et al, J Clin Lab Anal. 2002;16:79-85). In this issue, Kumar and colleagues (page 1075) present flow-cytometric data regarding the CD52 antigen on clonal cells from patients with plasma cell disorders and suggest that clinical trials be developed to test the efficacy of alemtuzumab (Campath-1H), a humanized monoclonal antibody (MoAb) against CD52, in myeloma and primary systemic amyloidosis. Alemtuzumab antibodies recognize an epitope that consists of the C-terminal peptide and part of the glycosylphosphatidylinositol lipid anchor that binds CD52 to the cell membrane (Hale et al, Blood. 1983;62:873-882). CD52 is widely and densely expressed on human lymphocytes (T and B cells, monocytes, and some dendritic cells; Ratzinger et al, Blood. 2003;101:1422-1429) and in the male reproductive tract. Alemtuzumab is a human IgG1 that binds to all human IgG Fc receptors and activates both complement and antibody-dependent cellular cytotoxicity (ADCC). Over the past decade anti-CD52 immunotherapy has been used to prevent acute graft-versus-host disease and graft rejection in reduced intensity autologous hematopoietic cell transplantation, a time when ADCC may be enhanced. Risks of infectious complications and broad-spectrum prophylaxis would be important features of such a trial.

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A new von Hippel–Lindau disease

Molecular genetic analysis of inherited human disease has an exemplary record of informing our understanding of complex biologic processes. In keeping with this, recent studies of inherited erythrocytosis have provided important insights into physiologic mechanisms that govern oxygen homeostasis. Analysis of an apparently geographically restricted form of recessively inherited erythrocytosis, which is endemic...