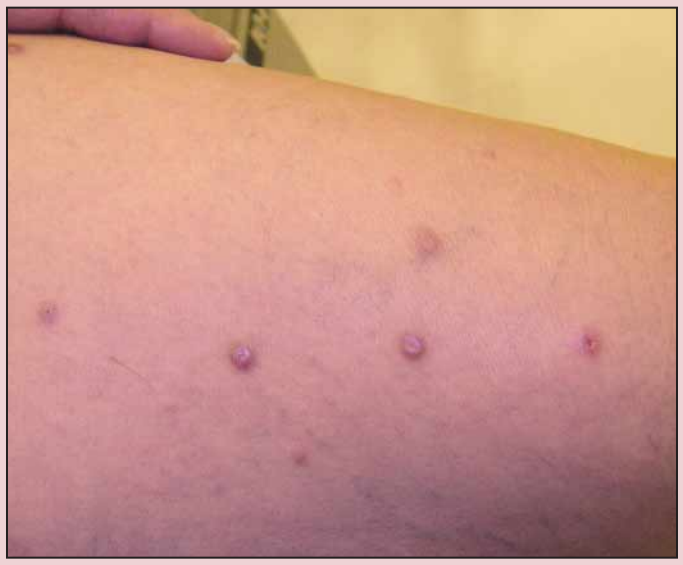
DERM DX

A 57-year-old Asian woman presented with a recent eruption of a dozen dull, erythematous papules and nodules on her extremities and numerous, well-demarcated, faintly erythematous patches on her chest and back. She had had symptoms of peripheral neuropathy for the past 10 years. What's your diagnosis?



QUEBEC CITY — The woman's origin from Singapore and her extensive history of living in nine countries from age 26 to 39 years until she immigrated to Canada was crucial in leading to her diagnosis of borderline lepromatous leprosy, Michael Kalisiak, M.D., reported at the annual conference of the Canadian Dermatology Association.

Her countries of residence included Iran, Trinidad, Scotland, United States, Indonesia, the Netherlands, and Norway, with brief periods in Kenya and Ecuador; some of these countries have an intermediate incidence of leprosy.

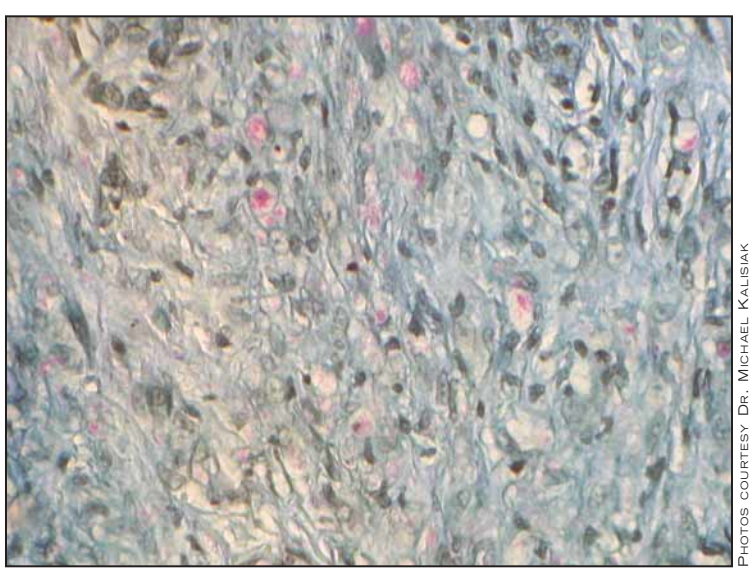
For 3 years prior to her skin manifestations, the patient visited neurologists for her neuropathic symptoms, which initially occurred as numbness and occasional pain in her left anterior thigh and later spread to her left hand and left and right lower legs. She also reported decreased grip strength in her left hand, according to Dr. Kalisiak, a second-year dermatology resident at the University of Alberta, Edmonton.

The neurologists discovered numerous motor and sensory deficits in those areas but excluded any common causes of neuropathy after extensive testing. They diagnosed her with idiopathic polyneuropathy.

On staining with hematoxylin and eosin, skin biopsies of the faint erythematous patches showed mild, nonspecific perivascular and periappendigeal infiltrate whereas biopsies from the nodules showed a heavy infiltrate in the deep dermis and beyond. Fite's stain revealed numerous lepra bacilli in the biopsy specimens (in red on biopsy of a nodule). Nasal scrapings were positive for acid-fast bacilli and polymerase chain reaction confirmed the presence of *Mycobacterium leprae*.

Dr. Kalisiak and his colleagues began daily treatment with 600 mg of rifampin, 100 mg of dapsone, 50 mg of clofazimine. The regimen also included gabapentin for neuropathic pain that will be continued for at least 1 year.

—Jeff Evans



PHOTOS COURTESY DR. MICHAEL KALISIAK

Melanoma Investigators Look Beyond Genetics

BY PATRICE WENDLING
Chicago Bureau

VIENNA — There are multiple genetic targets and combinations of therapies that hold great promise for changing the fate of melanoma patients, Christoph Höeller, M.D., said at the 10th World Congress on Cancers of the Skin.

A major focus of targeted therapies has been the protooncogene for Bcl-2, which is linked to chemoresistance, a problem in melanoma patients.

Antisense oligonucleotide therapy targeting Bcl-2 mRNA has increased tumor cell apoptosis and tumor response. But it has still not significantly improved the overall survival of these patients.

Small molecule inhibitors of Bcl-2 are entering phase I and phase III trials, and Bcl-2 RNA interference (RNAi) is in preclinical evaluation. But there's more to targeted therapies than Bcl-2, he said.

Dr. Höeller and colleagues at the Medical University of Vienna recently found that clusterin, a glycoprotein implicated in many cellular functions including apoptosis, varies in expression between melanocytes and melanoma cells (J. Invest. Dermatol. 2005;124:1300-7).

In tissue samples, 45% of melanomas stained positive for clusterin, whereas only 18% of nevi stained positive.

Antisense oligonucleotides directed against clusterin mRNA also significantly decreased the survival of human melanoma cells in mice in the presence of cytotoxic drugs, suggesting that downregulation of clusterin may be helpful in overcoming drug resistance in melanoma.

Mcl-1, another member of the Bcl-2 family that has been found to contribute to chemoresistance in melanoma in vivo, has potential for antisense therapy or combination therapy.

Combined Mcl-1 antisense oligonucleotides plus dacarbazine treatment led to significantly reduced mean tumor weight in severe combined immunodeficiency mice, compared with animals treated with saline plus dacarbazine or control oligonucleotide plus dacarbazine (J. Invest. Dermatol. 2003;120:1081-6).

Other treatment strategies include the use of histone deacetylase inhibitors such as tributyrin, sodium butyrate, and phenylbutyrate.

Histone deacetylase inhibitors are now in phase II studies, having been shown to be active against melanoma cells in in vivo and in vitro models, Dr. Höeller said at the meeting, which was cosponsored by the Skin Cancer Foundation.

Finally, he noted that bortezomib (Velcade), which is approved for patients with multiple myeloma and has a chemosensitizing effect when administered with other antitumoral drugs, may be useful in melanoma.

In a separate presentation, Eva-Bettina Bröcker, M.D., of the University of Würzburg (Germany), reported on a vaccine that targets the protein survivin.

Survivin is normally active only in growing embryos or rapidly dividing cells, but is turned on in a variety of malignancies.

It has become an increasingly popular target because downregulation or loss of expression of survivin is associated with impaired tumor progression.

Among five stage IV melanoma patients vaccinated with the human leukocyte antigen–A2 restricted survivin (96-104) epitope, four patients mounted strong T-cell responses to the epitope as measured by enzyme-linked immunospot assay (Vaccine 2005;23:884-9). ■

Promising Approaches Are on Horizon for Treating Nonmelanoma Skin Cancer

VIENNA — Imatinib, a protein-tyrosine kinase inhibitor indicated for chronic myeloid leukemia and certain stages of gastrointestinal stromal tumors, has shown clinical activity against dermatofibrosarcoma protuberans, Jens Gille, M.D., reported at the 10th World Congress on Cancers of the Skin.

DFSP, a rare and locally aggressive cutaneous tumor, is typically treated with wide surgical excision. Imatinib (Gleevec) could be used to improve the effectiveness of surgery or as an alternative treatment for unresectable DFSP, said Dr. Gille of Johann Wolfgang Goethe University in Frankfurt, Germany.

In a study of 10 people with DFSP, imatinib 400 mg twice daily resulted in a complete clinical response in four patients with locally advanced disease and a partial response in four patients with local disease and in one with metastatic disease (J. Clin. Oncol. 2005;23:866-73).

DFSP is often associated with a translocation between chromosomes 17 and 22. No clinical response was seen in one patient with metastatic disease whose tumor lacked this translocation, suggesting that variants of DFSP without the translocation may not respond to imatinib.

Imatinib, other tyrosine kinase inhibitors, and T4 endonuclease V are among the promising therapeutic avenues being pursued for nonmelanoma skin cancer. The epidermal growth factor receptor tyrosine kinase inhibitors, gefitinib (Iressa) and erlotinib (Tarceva), are approved for advanced non–small cell lung cancers, and have potential for squamous cell carcinomas of the skin, he said.

Two phase II trials of gefitinib are underway in patients with squamous cell carcinoma and topical therapies on the horizon include T4 endonuclease V, a bacterial DNA repair enzyme that increases the rate of repair of sunlight-induced DNA damage in human cells, Dr. Gille said at the congress cosponsored by the Skin Cancer Foundation.

Dr. Gille also noted that the effectiveness of cyclooxygenase-2 inhibitors in nonmelanoma skin cancer remains to be determined. Two skin trials were halted in 2005 after concerns were raised about the safety of several COX-2 inhibitors.

The trials were evaluating the effectiveness of celecoxib (Celebrex) in 60 patients with basal cell nevi and in 240 patients with sun-damaged skin. Analyses of the available data from both trials could be out later this year, he said.

—Patrice Wendling