New Advances in Dermatopathology: Part II

Surveying the latest research in dermatopathology on a variety of dermatological conditions, from merkel cell carcinoma to nephrogenic systemic fibrosis.

By Gary Goldenberg, MD

In last month’s article, I discussed research advances in dermatopathology related to malignant melanoma, from the D2-40 marker to the recent use of fluorescence in situ hybridization. In this second installment, I will examine the latest developments regarding various other tumors, such as merkel cell carcinoma, basosquamous carcinoma, basal cell carcinoma, and other adnexal tumors. I will also explore recent research and advances in inflammatory dermatoses and nephrogenic systemic fibrosis.

Merkel Cell Carcinoma

Merkel cell carcinoma is one of the more rare forms of skin cancer (Figure 1). However, recent data point to trends worth noting. The incidence of MCC is increasing, and this is especially true in immunosuppressed patients. A 2008 study described a previously unknown polyomavirus in MCC. The investigators found that eight out of 10 MCC patients had positive MCV sensitivity, compared to eight percent of control tissues from various body sites and 16 percent of control skin tissues. Polymavirus is a small double-stranded DNA virus with three types: avian, mammalian related to MuPyV, and mammalian related to simian virus 40 (SV40). The SV40 subgroup contains all human polyomaviruses. It tends also to be found in human brain and bone cancers, malignant mesothelioma, and non-Hodgkin’s lymphoma.

In a recent study reviewing 3,870 cases of MCC, investigators found that the most common sites for MCCs are the face, upper limbs, and shoulders. In addition, the study suggests that MCCs also appear to have a higher occurrence in men.

Take-Home Tips. Advances in dermatopathology help to shape the specialty of dermatology by opening new avenues of inquiry and understanding of a host of dermatologic conditions. Among recent studies discussed are advances in merkel cell carcinoma, basosquamous carcinoma, basal cell carcinoma, and other adnexal tumors. Also worth noting are recent studies in issues related to inflammatory dermatoses, such as distinguishing between dermatomyositis and systemic lupus erythematosus, the histologic features of psoriasis, and the latest on nephrogenic systemic fibrosis.
Tumors were stratified into less than or equal to 2cm and above 2cm. Survival rates for both unknown tumors and those less than or equal to 2cm vs. those greater than 2cm were statistically significant. Investigators concluded that white men over the age of 70 years old with tumors over 2cm in size did the worst.

A 2006 study evaluated MCC patients who underwent sentinel node biopsies (SLNB). Results showed that 32 percent of patients were SLNB positive. Of those, 52 percent of tumors greater than 2cm in size were SLNB positive, as compared to 29 percent of tumors less than 2cm in size. The three years’ follow-up recurrence rate was 60 percent for patients with positive SLNB, compared to 20 percent with negative SLNB. The three year relapse-free survival rate was 40 percent for patients with positive SLNB and 80 percent for patients with negative SLNB. However, a study the following year found no correlation between tumor thickness and disease-free survival.

Ber-EP4
Ber-EP4 is a monoclonal antibody to 34 and 39kDa glycopolypeptides found in most human epithelial cells. While its function is unknown, it is used to distinguish epithelial from mesothelial differen- tiation, such as adenocarcinoma vs. mesothelioma, for example. In a 2000 study, investigators examined Ber-EP4 and epithelial membrane antigen (EMA) expression in 75 tumors: basal cell carcinoma (39), squamous cell carcinoma (23), and baso- quamous cell carcinoma (13). Ber EP4 expression occurred in all BCCs and BSCs and none of the SCCs. By contrast, EMA expression occurred in 22 of 23 SCCs and in none of BCCs and BSCs. The authors concluded that BSC is a variant of BCC.

Another study evaluated Ber-EP4 expression in BCCs (28 samples), microcystic adnexal carcinomas (MAC, 13 samples), and desmoplastic trichoepithelioma (DTE, 16 samples). The percentage of stained cells in BCCs was 100 percent positive, in MACs zero percent positive, and 75 percent positive in DTEs. The stains were also measured for intensity, with 78.6 percent of BCCs measuring strong, compared to just 18.7 percent of DTEs as strong. (Figure 2)

Inflammatory Dermatoses Update
Systemic lupus erythematosus (SLE) vs. dermatomyositis (DM). The histopathology of cutaneous lesions of dermatomyositis (DM) can be difficult to distinguish from acute cutaneous lesions of systemic lupus erythematosus (SLE). This was the premise of a recent study examining 45 biopsies to categorize histologic findings of DM and to determine if skin biopsy specimens of DM
and SLE could be distinguished by light microscopic examination. The most consistent findings of DM were perivascular inflammation (93 percent), vacuolar alteration at the dermal-epidermal junction (80 percent), increased dermal mucin (61 percent on H&E and 97 percent with colloidal Fe stain), and basement membrane thickening (61 percent with PAS stain). Investigators noted that the histological grading of SLE skin biopsies was nearly identical to that of DM. In addition, the correct histopathologic diagnosis of DM or SLE was made in 11 of the 20 patients.

Given the difficulty of distinguishing acute cutaneous lesions of systemic lupus erythematosus from dermatomyositis, the researchers concluded that clinicopathologic correlation is important for making a diagnosis of DM or SLE.

Psoriasis. A new study has shed light on the histologic features of psoriasis before and after acitretin. Investigators evaluated histologic features and immunohistochemical stains for 17 patients with psoriasis with at least 10 percent BSA and previous failure or relapse with PUVA, methotrexate, and/or cyclosporine. Psoriasis Area and Severity Index (PASI) scores were 13.2 and 5.35 before and after treatment, respectively. Suprapapillary plate thickness stayed the same, although the epidermal/suprapapillary thickness ratio was significantly higher before treatment. In addition, CK10 positivity was lower and a thicker basal cell layer was seen in the epidermis before treatment. CK19 was negative in all cases. The investigators concluded that acitretin therapy improved histological and immunohistochemical features typical of psoriasis. They noted that suprapapillary plates are not thin in psoriasis, but the epidermal/suprapapillary thickness ratio is increased.

Psoriasis has also proven difficult to distinguish from certain eczematous dermatoses, which was the basis for another study. Researchers evaluated the histologic features of palmoplantar non-pustular psoriasis, as compared to patients with eczematous dermatitis. Results showed that vertical alternation of parakeratosis and orthokeratosis was more common in psoriasis and overlap of some histologic features, including full thickness spongiosis, and eosinophils in upper dermis.

Another study looked at expression of hypoxia inducible factor 1 (HIF-1) alpha in psoriasis and psoriasiform dermatitis. HIF-1 alpha is a proinflammatory cytokine that stimulates cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and human homeo box-2 (HOX-2). HIF-1 alpha has a role in the maintenance of oxygen and energy homeostasis and it also plays a central role in the stress response beyond hypoxia. Findings suggest that HIF-1 alpha may stimulate vascular endothelial growth factor (VEGF) and enhance angiogenesis. This appears to be important in the pathogenesis and progression of psoriasis.
Nephrogenic Systemic Fibrosis Update

Among recent findings related to nephrogenic systemic fibrosis (NSF), two particular studies stand out. In a 2005 study, investigators compared histologic findings in NSF and scleromyxedema (SMX), performing immunohistochemical staining for CD34, factor XIIIa, CD31, smooth muscle actin, CD68, and procollagen-I, and colloidal iron. Overall, NFD and SMX showed similar expression for all markers except procollagen-I, which showed increased expression in SMX. Although the researchers did find some immunophenotypic differences, the study did not demonstrate microscopically characteristic features that can be easily used diagnostically to distinguish NFD from SMX.

Another study examined the role of transglutaminases in the pathogenesis of NSF. Transglutaminases are calcium-dependent enzymes that cross-link glutamine and lysine residues of proteins. They form transglutaminase isopeptide bonds when activated and are especially important for tissue remodeling. Moreover, transglutaminases can be activated by gadolinium. The results indicate that the dermal fibroblasts and histiocytes of NSF express transglutaminase-2, CD68, factor XIIIa, and transglutaminase isopeptide, suggesting increased expression and/or activation of transglutaminases in NSF.

Conclusion

These studies represent a small sample of some of the latest developments in dermatopathology, which are ongoing and ubiquitous. Piece-by-piece, these studies help clinicians to better understand and diagnose dermatologic conditions and hopefully lead to improved care for patients.

Dr. Goldenberg does not have any relevant relationships to industry.