Immunostaining Can Help Classify Paget Disease

BY BRUCE JANCIN
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AMSTERDAM — A panel of immunohistochemical stains, including human epidermal growth factor receptor 2/neu and CDX2, is useful in distinguishing extramammary Paget disease that is limited to the skin versus the subset of secondary extramammary Paget disease that is associated specifically with concurrent or future anogenital cancer, Dr. Jared Abbott said at the 11th World Congress on Cancers of the Skin.

Other investigators have postulated that the triad of cytokeratin 7 (CK7), CK20, and BRST-2 immunohistochemical stains is broadly useful in distinguishing extramammary Paget disease (EMPD) that is limited to the skin—known as primary EMPD—from all forms of secondary extramammary Paget disease, but Dr. Abbott did not find this to be the case in his own large series. Indeed, caution should be exercised in relying upon the triad of immunostains for this purpose, said Dr. Abbott of the Mayo Clinic, Rochester, Minn.

EMPD is an uncommon condition occurring primarily in the elderly, with more women than men affected. It arises as a cutaneous adenocarcinoma with a proclivity for sites rich in apocrine glands. Patients with EMPD often present with a prominent solitary plaque lesion in the anogenital or vulvar region. The lesion is erythematous, eczematous, and often pruritic. The course is often locally aggressive, with frequent recurrences.

The classic histopathologic findings of EMPD consist of clusters of epithelial cells with pagetoid extension throughout the epidermis, often accompanied by a superficial lymphocytic inflammatory infiltrate, he said at the congress, which was sponsored by the Skin Cancer Foundation and Erasmus University.

The distinction between primary and secondary EMPD is clinically important because the prognoses are entirely different. Primary EMPD, which accounts for at least three-quarters of cases, has a good prognosis, whereas secondary EMPD has a very poor prognosis because the skin disorder is often accompanied—or, in the months to come, followed—by a gastrointestinal or genitourinary malignancy. Unfortunately, primary and secondary EMPD can't be differentiated based upon histopathology. "Their [hematoxylin and eosin stains] look exactly alike," Dr. Abbott explained.

Percentage of Patients With a Positive Immunostain

	Primary EMPD (n = 45)	Secondary EMPD (n = 16)
Androgen receptor	20%	0%
BRST-2	44%	25%
CDX2	2%	31%
CK7	100%	100%
CK20	22%	56%
Cyclin D1	73%	56%
HER2/neu	69%	50%

Note: Based on a study of 61 patients with extramammary Paget disease (EMPD).
Source: Dr. Abbott

Elsevier Global Medical News

Other investigators have turned to immunohistochemical staining patterns in an effort to make the distinction. It has been reported that primary EMPD is often CK7- and BRST-2 positive and CK20 negative, whereas secondary EMPD is BRST 2 negative, CK20 positive, and equivocal in terms of CK7.

To see if he could verify this finding, and to assess the utility of some newer immunohistochemical stains, Dr. Abbott studied excisional biopsy specimens from 61 Mayo Clinic patients with EMPD. The median age at diagnosis was 73 years, and 44 patients were women. A total of 45 patients had primary EMPD. The 16 with secondary EMPD, as determined during a median 4-year follow-up, consisted of seven patients with anorectal carcinomas, four with prostate cancer, and five with urothelial cell cancer.

All patients in both the primary and secondary EMPD groups were CK7 positive, so that was of no help, he said. In addition, CK20, BRST-2, androgen receptor, and cyclin D1 did not prove to be of much assistance in distinguishing primary from secondary EMPD. (See box.)

In contrast, HER2/neu and CDX2 were quite helpful in separating primary from secondary EMPD involving anorectal malignancy. Five of the seven patients with lower GI cancer stained positive for CDX2, and all seven were HER2/neu negative. Unfortunately, no staining pattern proved useful in identifying patients with prostate or urothelial cell cancer.

The finding that more than two-thirds of patients with primary EMPD were HER2/neu positive, and that the positivity rate was even higher among those with recurrent primary EMPD, raises the intriguing possibility that Herceptin (trastuzumab) might be an effective therapy in these individuals, although that has never been studied, Dr. Abbott said. ■

Anti-TNF-α Efficacy in Trials Not Achieved in Real-World Scenarios

BY DENISE NAPOLI
Assistant Editor

Good clinical response and rheumatoid arthritis remission following treatment with tumor necrosis factor–α blockers is much rarer on the community level than results from randomized clinical trials, with their many exclusion criteria, would seem to indicate, according to results from an Italian group of researchers.

The Gruppo Italiano per lo Studio delle Early Arthritis study (GISEA) enrolled 1,257 patients who had longstanding rheumatoid arthritis (RA) and who started therapy with tumor necrosis factor–α (TNF-α) blockers. The original aim of the study was to pinpoint predictors of remission in longstanding arthritis patients treated with TNF-α blockers.

However, in the process, the researchers uncovered an unexpected finding: only 682 (54%) of patients experienced even the minimally acceptable improvement in their symptoms after 6 months of treatment with a TNF-α blocking agent. Specifically, these 682 patients were the only ones to experience at least a 0.25 improvement in their Health Assessment Questionnaire score (HAQ), which is considered the cutoff point for a clinically meaningful response.

Of the patients who dropped out, 32% cited inefficacy and 14% cited adverse events, including skin reactions, infusion reactions, and gastrointestinal problems.

Even at the outpatient clinics, only half of the patients reached a clinically meaningful result as defined by an HAQ improvement of 0.25, wrote the researchers.

"Therefore, patients in clinical practice are not representative of those recruited in clinical trials, and certainly do not reach the outcomes that have been provided in [randomized controlled clinical trials]. Among these, remission was observed in a small percentage of patients with a long disease duration," they added.

The most likely interpretation for this discrepancy—randomized trials' extensive exclusion criteria—could "seriously influence not only the safety issue in general, but also the final clinical outcomes in aggressive and severe disease at the community level," the study investigators noted (J. Rheumatol. 2007;34:1670-3).

Of the 682 patients who were studied further, only 591 (47% of the whole cohort) had both a 0.25 improvement in HAQ scores and underwent regular bimonthly assessments of clinical and laboratory measures.

In this cohort of 591 patients, 404 (68%) were women, and the mean age was 53 years.

Overall, 32% of the men and 24% of the women achieved remission, a difference that was statistically significant and which prompted the authors to speculate that "male patients with RA seem to benefit more from anti-TNF-α strategies than do female patients." ■

Gout Treatment Patterns Vary Widely From Best Practices

BY DENISE NAPOLI
Assistant Editor

Just 25% of suspected gout patients had arthrocentesis for crystal analysis, despite the fact that the procedure remains the "gold standard" for diagnosis of the disease, according to a report by Dr. Danielle Petersel and Dr. Naomi Schlesinger.

Furthermore, of the 184 patients diagnosed with gout in one 400-bed hospital over a 2-year period from 2002 to 2004, only 38% received a rheumatology consultation, reported Dr. Petersel and Dr. Schlesinger, of the Robert Wood Johnson Medical School at New Brunswick, N.J. "The diagnostician was likely to be the admitting physician for these patients," they wrote.

Of the 184 patients, the average age was 71 years (with a range from 40 to 96 years). All were male.

Another important finding was that a combination of anti-inflammatory agents was taken by 52% of patients, despite a lack of evidence in the literature supporting the use of combination therapy.

In fact, wrote the authors, "Combination therapy potentially puts the patient at risk of increased morbidity/mortality due to the combined effects upon the kidney." Indeed, renal failure was present in 65% of patients with acute gout. Nevertheless, prednisone and colchicine were given in 23% of cases; nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine were given in 16%; and a steroid with an NSAID was administered in 13% of patients. Indomethacin was the most commonly prescribed NSAID (J. Rheumatol. 2007;34:1566-8).

Additionally, despite evidence that using the urate-lowering drug allopurinol to cut serum urate levels to less than 6 mg/dL is beneficial and leads to the dissolution of urate crystals and regression of tophi, only 27% were treated with the drug. "Even when it was taken, [serum urate] was not lowered to [an] SU goal of 6 mg/dL," reported the researchers.

Rather, in 60% of patients treated with allopurinol, SU level was greater than 6 mg/dL.

"Practice patterns vary widely and support the need for education of health care professionals taking care of patients with gout," concluded the authors.

"In our study, all patients were male, which may suggest that the cohort was somewhat biased. Long-term prospective, placebo-controlled studies are needed to establish guidelines for the diagnosis and treatment of gout," they added. ■