JOURNAL OF CLINICAL ONCOLOGY CORRESPONDENCE

Cancer of Unknown Primary or Unrecognized Adnexal Skin Primary Carcinoma? Limitations of Gene Expression Profiling Diagnosis

TO THE EDITOR: Chiang et al[1] are correct that gene expression profiling in patients with cancer of unknown primary (CUP) can be useful and in some instances complements immunohistochemistry in determining the primary cancer site or tissue of origin in these patients. However, the case presented is probably not CUP, but illustrates well one of the limitations of gene expression profiling in patients with suspected CUP.

The patient described was a man with a nodule on the right lower eyelid that had been present for at least 9 months. Biopsy showed an adenocarcinoma, and multiple (18) immunohistochemical (IHC) stains were performed on the biopsy specimen, but they did not suggest a specific primary site. Additional clinical evaluation showed no evidence of a primary tumor site. The gene expression profiling assay (Tissue of Origin Test; Pathwork Diagnostics, Sunnyvale, CA) strongly supported breast cancer as the cell of origin. It is much more likely that this patient had a primary adnexal skin carcinoma (sweat gland or hair follicle) arising from his lower eyelid. Adnexal carcinomas can be easily mistaken for metastatic adenocarcinoma and occasionally show IHC staining that is very similar to that of breast cancers as well as salivary gland cancers.[2] Furthermore, consistent with similar protein synthesis, there seems to be some degree of overlap of the gene expression profiles of breast, adnexal skin, and salivary gland carcinomas. These tumor types share some common embryologic lineage and the morphology of these tumors at times can be nearly identical.[2]

When only one site of neoplasm is identified in a patient suspected of having CUP, the possibility of an unusual primary tumor mimicking metastatic disease should always be considered.[3] Skin adnexal carcinomas are rare neoplasms and are not included in the panel of tumors that are recognized by any of the three commercially available gene expression assays that are designed to determine the tissue of origin. The fact that the patient is a man who presented with a solitary lesion on his right eyelid and no other clinical evidence of metastatic disease would make an occult primary breast cancer with a metastasis to the eyelid exceedingly unlikely. However, the gene expression profile of an adnexal skin carcinoma would most likely list breast as a high probability. The gene expression assay reports often mention the possibility of cross reactivity in some clinical settings. It is possible that additional IHC staining with p63 and cytokeratin 5/6, if positive, would further substantiate the diagnosis of a skin adnexal carcinoma.[4] Most patients with adnexal skin tumors are best treated by excision, and their prognosis is considerably better than that of patients with metastatic carcinoma.

Regardless of the true tissue of origin of the tumor, the points made by the authors regarding gene expression profiling in CUP were insightful and valid. Recently, the outcome or survival of patients with CUP has been improved by site-specific therapy directed by a molecular assay diagnosis compared with empiric chemotherapy regimens.[5]

Gene expression profiling also has limitations. The assays are 85% to 90% accurate in predicting the primary tumor site, as confirmed by studies with known primary cancers, and this was referenced by the authors. Several different tumors may share, to some extent, gene expression profiles and may result in an incorrect diagnosis, not truly representing the tissue of origin of the neoplasm. The case presented by the authors most likely represents such an example. Gene expression profiling assays that are designed to determine the tissue of origin do not have every neoplasm necessary for comparison in their panels of known tumors. If a patient has a cancer that is not in the panel, there is a higher likelihood of an inaccurate diagnosis.

The entire clinicopathologic setting needs to be considered when interpreting the results of gene expression profiling diagnosis in patients with CUP. Clinical judgment remains an important element in the interpretation of molecular diagnostic testing.

F. Anthony Greco
Sarah Cannon Cancer Center, Sarah Cannon Research Institute, Nashville, TN

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** F. Anthony Greco, bioTheranostics **Research Funding:** None **Expert Testimony:** None **Other Remuneration:** None

REFERENCES

1. Chiang WM, Kapadia M, Laver NV, et al: Cancer of unknown primary: From immunohistochemistry to gene expression profiling. J Clin Oncol 30:e300-e302, 2012
2. Wick MR, Ockner DM, Mills SE, et al: Amologous carcinomas of the breasts, skin and salivary glands: A histologic and immunohistochemical comparison of ductal mammary carcinoma, ductal sweat gland carcinoma, and salivary duct carcinoma. Am J Clin Pathol 109:75-84,1998
3. Greco FA, Hainsworth JD: Cancer of unknown primary site, in DeVita VT Jr, Lawrence TS, Rosenberg SA (eds): DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology (ed 9). Philadelphia, PA, Lippincott, Williams and Wilkins, 2011, pp 2033-2051
4. Qureshi HS, Ormsby AH, Lee MW, et al: The diagnostic utility of p63, CK 5/6, CK 7 and CK 20 in distinguishing primary cutaneous adnexal neoplasms from metastatic carcinomas. J Cutan Pathol 31:145-152, 2004
5. Hainsworth JD, Rubin MS, Spigel DR, et al: Molecular gene expression profiling to predict the tissue of origin and direct site-specific therapy in patients with carcinoma of unknown primary site: A prospective trial of the Sarah Cannon Research Institute. J Clin Oncol 31:217-223, 2013

DOI: 10.1200/JCO.2012.47.1615; published online ahead of print at www.jco.org on February 25, 2013