CLINICAL VIGNETTE

Breast Cancer Metastases: When to Biopsy?

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An 80-year-old female with a history of breast cancer presented to discuss current therapy. Her history began about seven years prior when imaging confirmed a new right-sided breast mass and extensive right axillary lymphadenopathy. She underwent mastectomy and axillary lymph node dissection with a 5 centimeter tumor that was estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, and human epidermal receptor 2 (HER2)-negative. Fifteen of twenty-nine lymph nodes were positive with metastatic disease. Given her age, chemotherapy was deferred, and she proceeded with radiation treatment. She started letrozole without any significant issues.

She did well for about five years when she presented with right hip pain and a rising tumor marker. A computed tomography (CT) scan of her hip confirmed a destructive 6.6 centimeter bone lesion. Positron emission tomography (PET) confirmed metastatic osseous disease to the right acetabulum extending into the right ischium and the L3 vertebral body. She also had hypermetabolic disease within the right axillary lymph nodes consistent with metastatic disease. She underwent palliative radiation treatment to the right hip with resolution of her pain. Her systemic therapy was now changed to tamoxifen. Her tumor marker decreased on the new endocrine therapy but by six months began to rise. Repeat PET/CT imaging demonstrated a small, new liver lesion; unchanged right axillary lymph nodes; and progression of her osseous disease.

She was changed to letrozole and palbociclib with dramatic improvement in her tumor marker. She had some early significant cytopenias requiring delays in treatment and transfusions, but with reduction in dose, she required less support. She continued to do well on treatment for about eight months but eventually had a rise in her tumor marker. PET/CT showed resolution of her right axillary lymphadenopathy, improvement in her metastatic bone disease but progression of her liver metastases.

Biopsy of her metastatic disease had been deferred until this point given the patient's age, other comorbidities, and initial high risk hormone-positive breast cancer, but given the dramatic differences in disease response, a liver biopsy was performed. Pathology was consistent with breast primary but now demonstrated ER-negative, PR-negative, and HER2-positive disease.

It can be difficult to know when to re-biopsy patients with metastatic disease. In the case above, she initially presented with bone-only disease from which it can be difficult to obtain good tissue and subsequent disease was too small to safely assess. However, there was a clear discrepancy in disease response on the final PET/CT suggesting something had changed. Furthermore, her liver disease was more pronounced, lending to a safer and more informative biopsy target.

In one prospective study of 121 patients, prognostic markers from repeat biopsies of metastatic lesions were compared to those from their original primary tumor biopsy.[1] They demonstrated that core biopsy was more effective for tissue assessment than fine needle aspiration, thoracentesis, or paracentesis.[1] Furthermore, core biopsies from bone yielded less adequate tissue.[1] When receptors were compared from metastatic biopsies to the original disease pathology report, discordance was found ~37% of the time.[1] HER2 changes occurred in ~10% of patients, while ER and PR differences were noted in 16% and 40% of patients, respectively.[1] The findings of progesterone differences have been noted in other reports and associated with downregulation after prior endocrine therapy.[2] None of twenty-three patients with triple negative disease had a change in receptor status.[1] A review of retrospective and prospective studies showed that almost all documented a change in ER status ranging from 14-40% of patients.[2] Differences in HER2 status in this same review again showed a lower percentage of change ranging 0-37% across studies.[2]

There is no clear answer for why prognostic markers between primary and metastatic tumors are conflicting. Discrepancies in quality of biopsy samples and lab analysis can certainly impact findings.[1,2] As alluded to above, fine needle aspirations and bone biopsies do not provide as reliable sampling.[1,2] Heterogeneity of tumors can make a small sampling misleading to the bulk of pathology.[2,3] Furthermore, selection for resistant clones may occur after exposure to targeted therapies (e.g., endocrine treatment or trastuzumab), and these resistant clones are more likely to lead to metastatic deposits.[2,3]

It should also be noted that prior studies have indicated different patterns of metastasis for the various subtypes of breast cancer.[4] ER-positive breast cancers have a high predilection for bone.[4] ER-negative/HER2-positive breasts were more likely to metastasize to the brain than ER-positive/HER2-positive disease.[4] Triple negative disease often metastasized to the lung and was less likely to travel to liver and bones.[4]

The main reason to consider re-biopsy is for possible changes in treatment paradigm and potentially impact on survival. However, the latter has been hard to study since randomized trials would be difficult to arrange. Certainly biopsy of metastatic deposits should always be considered when the biopsy results would change the staging or treatment plan. The study by Amir *et al.*[1] estimated that treatment plans changed in about 14% of patients. One report questioned whether treatment plans should change since a single lesion biopsy may not represent the disease as a whole.[3]

In the presented case, clinically it appeared that she had two different clones. While endocrine therapy was significantly controlling the majority of her disease, her liver disease was growing in a contrary manner. In considering her future treatment, it had to be effective for both her putative ER-positive/HER2-negative and ER-negative/HER2-positive clones. Thus, the change to chemotherapy with anti-HER2 medications. The patient again had a response in all areas of disease after change in treatment.

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