

CLINICAL VIGNETTE

Squamous Cell Cancer of Unknown Primary with Bone Marrow Metastases

Evangelia Kirmis, M.D.

A 46-year-old female presented with three months of left-sided neck lymphadenopathy. She was treated with several courses of antibiotics for a putative upper respiratory infection. The lymphadenopathy persisted, and the patient reported a 10-pound weight loss over the prior two months and overall malaise. A fine needle biopsy was performed but was non-diagnostic. She had an excisional biopsy which demonstrated a metastatic poorly-differentiated carcinoma with glandular and squamous differentiations. Additionally, the pathology noted a distinct 7 millimeter nodule of tumor cells within the node, which although similar to the rest of the tumor demonstrated larger cells with more prominent nucleoli and more mitotic activity. This nodule was strongly TTF-1 positive, focally CK7 positive and negative for p63 and high molecular weight cytokeratin. Conversely, the rest of the tumor cells were negative for CK7 and TTF1 and positive for p63 and high molecular weight cytokeratin. The remaining immunostains demonstrated a similar staining pattern in both subsets of tumor cells. Unfortunately, no clear primary was discernible based on pathology alone. Positron emission tomography-computer tomography (PET/CT) showed hypermetabolic nodes in the level 2 and 3 areas of the left neck as well as within the left parotid gland. The imaging was otherwise unremarkable. Esophagogastroduodenoscopy was unremarkable as was laryngoscopy with random biopsies.

Her medical history was otherwise minimal. She had a history of gastroesophageal reflux controlled with a proton pump inhibitor. She was originally from India and travelled back frequently. She lost her husband to esophageal cancer a few years prior to presentation. She did not use tobacco, alcohol, or illicit drugs. There was no family history of malignancy.

No clear primary cancer could be determined. While the full presentation was concerning for advanced squamous cell cancer (metastatic carcinoma of unknown primary), given her young age, she was given the benefit of the doubt and treated with curative intent for a primary head and neck cancer. She proceeded with chemoradiation with cisplatin since this was the only scenario where she was still potentially curable. Repeat imaging after treatment demonstrated no evidence of disease. Unfortunately, she was lost to follow-up over the next six months until she presented to the emergency room with weight loss, low grade fevers, and intense back and right arm pain. Labs were unremarkable except for a mild anemia. Magnetic Resonance Imaging of the lumbar spine and right upper extremity both showed a diffuse, heterogeneous abnormal marrow signal with associated patchy abnormal enhancement. It was felt consistent with red marrow

replacement in the setting of her anemia versus a diffuse marrow infiltration. PET/CT showed no abnormalities beyond diffusely increased activity in the marrow.

Bone marrow biopsy demonstrated metastatic, poorly differentiated squamous carcinoma similar to her original lymph node biopsy. She was started on palliative chemotherapy.

Metastatic spread of tumor cells to the bone marrow is hematogenous.¹ Review of the literature demonstrates no specific reports of a similar presentation of squamous carcinoma in only the lymph system and bone marrow. While reports of squamous cell cancer in the bone marrow have been described, they are usually associated with clear primary lesions and/or much more widely metastatic disease.^{1,2} Such was not the case in the patient above, whereby even with multiple tests over almost a two-year span, the primary was never determined. There were no similar reports of strictly marrow involvement with squamous cell carcinoma. Bone marrow-only disease or small primaries have been described in the setting of bone marrow metastases, but these reports seem to more likely attributed to metastatic adenocarcinomas of the breast, prostate, and lung.^{2,3,4}

The patient above had a fairly classic presentation for bone marrow involvement. Bone pain is one of the most common symptoms reported in prior case series as well as weight loss and fatigue.^{2,4} All of these symptoms were noted in the patient above upon her presentation of metastatic disease. Anemia as noted with her is commonly seen before other cytopenias, and in some reports is seen in almost all cases of metastatic bone marrow involvement.^{2,3,4} Other common indicators include elevated alkaline phosphatase, hypercalcemia, leucoerythroblastic changes, and pathologic fractures.^{2,3} While treatment with chemotherapy is recommended, patients may have more issues with cytopenias due to poor marrow reserve with cancer infiltration and noted fibrosis.^{1,2} Bone marrow involvement has also been reported as a poor prognostic indicator.¹

Given the poor prognosis for patients with solid tumors and bone marrow or bone involvement, a lot of research has been dedicated to better understanding the pathogenesis of spread. The bone marrow microenvironment has been an area of interest to determine mechanisms to decrease cell stability and growth at these metastatic sites. Most recently bisphosphonates and RANK ligand inhibitors have been evaluated as a way of preventing bone metastases.⁵ The above

case highlights an atypical presentation of metastatic squamous cell cancer, and the need for more research to prevent bone and marrow metastases.

REFERENCES

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