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Case Report

Lower extremity pain as initial presentation of cervical cancer ☆

Savita V. Dandapani [a], Paulette Mhawech-Fauceglia [b], Suzanne Palmer [c], Michael Senikowich [a], Yvonne G. Lin [d,*]

[a] Department of Radiation Oncology, University of Southern California, Los Angeles, CA 90033, USA
[b] Department of Pathology, University of Southern California, Los Angeles, CA 90033, USA
[c] Department of Radiology, University of Southern California, Los Angeles, CA 90033, USA
[d] Department of Gynecologic Oncology, Obstetrics-Gynecology, University of Southern California, Los Angeles, CA 90033, USA

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Introduction

The diagnosis of bone metastases in cervical cancer defines advanced disease with a median overall survival of <1 year (Matsuyama et al., 1989; Abdul-Karim et al., 1990). The most common bones affected are the lumbar spine and pelvis; distal extremity metastases are rare, accounting for <5% of bone metastases (Ratanatharathorn et al., 1994; Rangarajan et al., 2010). High-dose palliative radiotherapy provides significant symptomatic relief in approximately 67% of cervical cancer patients (Matsuyama et al., 1989). The overall clinical and personal impact of osseous fractures for patients highlights the importance of clearly defining the management plan for osseous metastases in gynecological cancers.

We report a woman who presented with back and lower extremity pain, ultimately found to have cervical cancer. Despite multimodal therapy, the patient passed away 3 months after her initial presentation. This case report also reviews the biology of bone metastases and presents some emerging therapeutic options for these scenarios.

Case report

The patient was a previously healthy 36-year-old nulligravida woman who presented with isolated back and right leg pain (RLE) for two weeks. Imaging workup included X-ray and magnetic resonance imaging (MRI) of the spine, which demonstrated multiple vertebral body lesions with spinal canal extension at the T6 level (Fig. 1A); Tc99m bone scan redemonstrated the multiple spine and RLE lesions, including a large, distal right femoral lesion (Fig. 1B). Distal right extremity X-rays and MRI were obtained to exclude pathologic fracture at this site (Fig. 1C). An anterior cortex, lytic lesion with associated soft tissue component was seen, without associated fracture. A subsequent FDG-PET/CT (Fig. 1D) of the abdomen and pelvis demonstrated multiple organ lesions and lymphadenopathy. Because the etiology of the presumed diffuse metastatic disease was unclear, the patient subsequently underwent a CT-guided, core biopsy of the femur. Pathology revealed sheets of undifferentiated pleomorphic neoplastic cells with high nuclear/cytoplasmic (N:C) ratio, prominent nucleoli and numerous mitotic figures (Figs. 2A–C). The tumor cells stained strongly for cytokeratin (AE1/3) (Fig. 2D) and negative for CK7/CK20, S100, HMB45, synaptophysin, chromogranin, estrogen receptor (ER), progesterone receptor (PR), thyroid transcription factor-1 TTF1, CA125, renal cell marker, and calretinin. Because the primary site was still unidentifiable, excisional biopsy of the femur lesion was performed. Pathology showed rare areas of squamous differentiation among nests of tumor cells immunoreactive for p63 (Fig. 2E) and CK5/6 (Fig. 2 F), consistent with a poorly-differentiated squamous cell carcinoma from either the lung, head and neck or uterine cervix. A pelvic examination revealed a single 2-cm erosive lesion on her anterior cervix, and a cervical biopsy demonstrated a moderately-to-poorly differentiated squamous cell carcinoma.

Zoledronic acid was administered to slow the progression of the bone metastases, and surgical excision and internal fixation were performed to the femur. She also received palliative radiation therapy (20 Gy over 5 fractions to T4–T7 and 8 Gy in a single fraction to L5-sacrum). The patient received one cycle of systemic gemcitabine (1600 mg/m^2) with cisplatin (100 mg/m^2). Although the thoracic spine showed partial response to the palliative radiation on follow-up imaging (Fig. 1E), multiple, new diffuse bone and soft tissue metastases were found. The patient rapidly deteriorated and passed away before any further chemotherapy could be offered.

* Corresponding author at: Gynecologic Oncology, Obstetrics-Gynecology, USC Norris Comprehensive Cancer Center, Women's Cancer Program, 1441 Eastlake Ave, Suite 7419, Los Angeles, CA 90033, USA. Fax: +1 323 442 7436.
E-mail address: ylinliu@usc.edu (Y.G. Lin).

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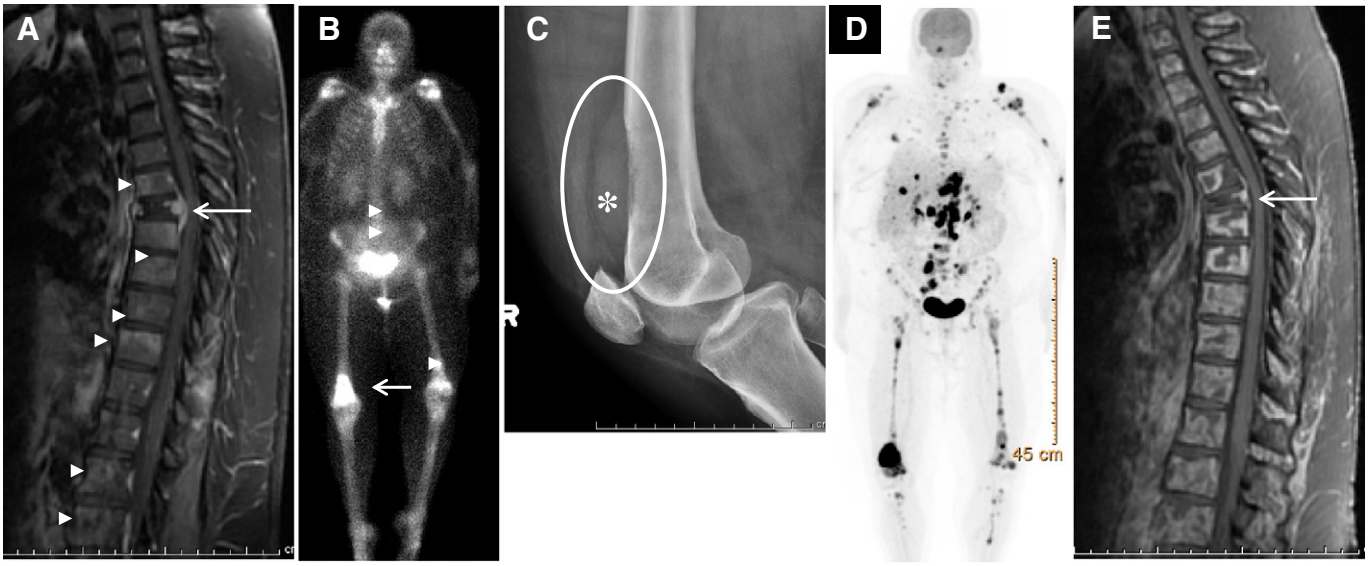

Fig. 1. MRI of the thoracic spine (A) shows multilevel vertebral body lesions (arrowheads), and compression fracture of the T6 vertebral body associated with epidural extension (arrow); 99 mTc Bone Scan (B) demonstrates extensive spine and extremity bone lesions (arrowheads), including right femur (arrow); right knee X-ray (C) and MRI (not shown) were obtained to exclude a pathologic fracture. An anterior cortex, lytic lesion with associated soft tissue component (*) was seen. No fracture was demonstrated; FDG-PET/CT (D) revealed multiple lymph nodes, liver and renal metastases and confirmed osteolytic metastases throughout the spine and extremities. Post therapy MRI (E) demonstrates decreased epidural metastasis (arrow) at site of focused radiation; however the remainder of the spine is now diffusely involved.

Discussion

A review of the English literature in PubMed from 1946 to 2012 with search terms of "gynecological cervical cancer," and "bone metastases" to identify cases with pathological fracture, distal extremity bone metastases of unknown primary revealed 51 reports in the indexed literature.

Unusual distal extremity bone metastases from previously undiagnosed cancers are rare, and not previously reported for newly diagnosed cervical cancer. Bone metastases of unknown primary in women are typically attributed to occult breast cancer which portends a more favorable prognosis compared to other visceral malignancies. On the other hand, recurrent cervical cancer after prior treatment involving central (e.g., calvarium, vertebrae) and distal (e.g., extremities) osseous lesions has been reported (George and Lai, 1995; Dewdney and Selvarajah, 2010; Mohanty et al., 2010).

The earliest series of skeletal metastases from recurrent cervical cancer suggest that the lumbar spine and pelvic bones were the most common sites, and only 1.5% developed metastases to the proximal long bones (Matsuyama et al., 1989). Despite palliative radiation (30 Gy/10 fractions) followed by cisplatin-based chemotherapy, survival was uniformly less than 1 year. A subsequent series concluded that the likelihood of bone metastases increased with advanced stage, and survival after detecting the bone metastasis averaged only 6 months (Abdul-Karim et al., 1990). A review of autopsy reports from that series identified previously undiagnosed bone metastases in 18% of patients suggesting that bone metastases may be under diagnosed (Abdul-Karim et al., 1990). Across nearly all series, most patients received palliative radiation (range of 16 Gy in 4 fractions; 55 Gy in 25 fractions, and most common regimen 30 Gy in 10 fractions) and 70% reported pain relief.

The predilection for bone metastases to the lumbar spine and the pelvic bones is thought to occur from hematogenous spread or via Batson's plexus (Abdul-Karim et al., 1990). Most authors seem to agree that the degree of differentiation predicts the likelihood of bone metastases with poorly differentiated tumors faring the worst (Abdul-Karim et al., 1990). Interestingly our patient's tumor in the pathological fracture was poorly differentiated, whereas the primary cervical lesion was moderately differentiated non-keratinizing. Aside from histologic morphology, no biomarkers exist to better predict likelihood for osseous metastases.

Chemotherapy options for metastatic cervical cancer typically include a cisplatin-based doublet; however, bone penetration by these agents is generally poor (Ratanatharathorn et al., 1994). New treatments for bone metastases from breast cancer may be evaluated for cervical cancer patients. Currently, patients with bone metastases from breast cancer are treated with a bisphosphonates and/or the RANK-ligand inhibitor, denosumab, to slow and decrease the number of skeletal-related events and fractures (NCCN, 2012). Although cancer was historically regarded as organ-specific, most people now appreciate that biochemical processes and signaling pathways are likely shared among solid cancers. Thus, research on metastatic breast cancer could guide new treatment considerations for cervical cancer. Emerging targets currently under investigation for bone metastases in breast cancer (e.g., Cathepsin K, c-Src, sclerostin, or specific integrins) should be investigated for cervical cancer patients as well (Coluzzi et al., 2011). The proto-oncogene, c-Src, has already been implicated in translational studies in breast cancer as predictive of skeletal metastases versus visceral metastases and may represent a candidate therapeutic target to explore in cervical cancer. Dasatinib is a small molecular multi-tyrosine kinase inhibitor of the Src-family kinases (among other targets), and has shown efficacy in prostate cancer with bone metastases. Bone sialoprotein, a marker originally identified and validated as a predictive marker for skeletal metastases in breast cancer, has also been found to be highly expressed in primary invasive squamous cell cervical cancers and may help to identify patients at higher risk for skeletal metastases (Detry et al., 2003). In this patient's case the burden of the disease was not able to be controlled, and her case highlights the need for better treatments for bone metastases in gynecological cancers.

Conflict of interest statement

Suzanne Palmer is a research consultant for Halt Medical.
The other authors declare that there are no conflicts of interest.

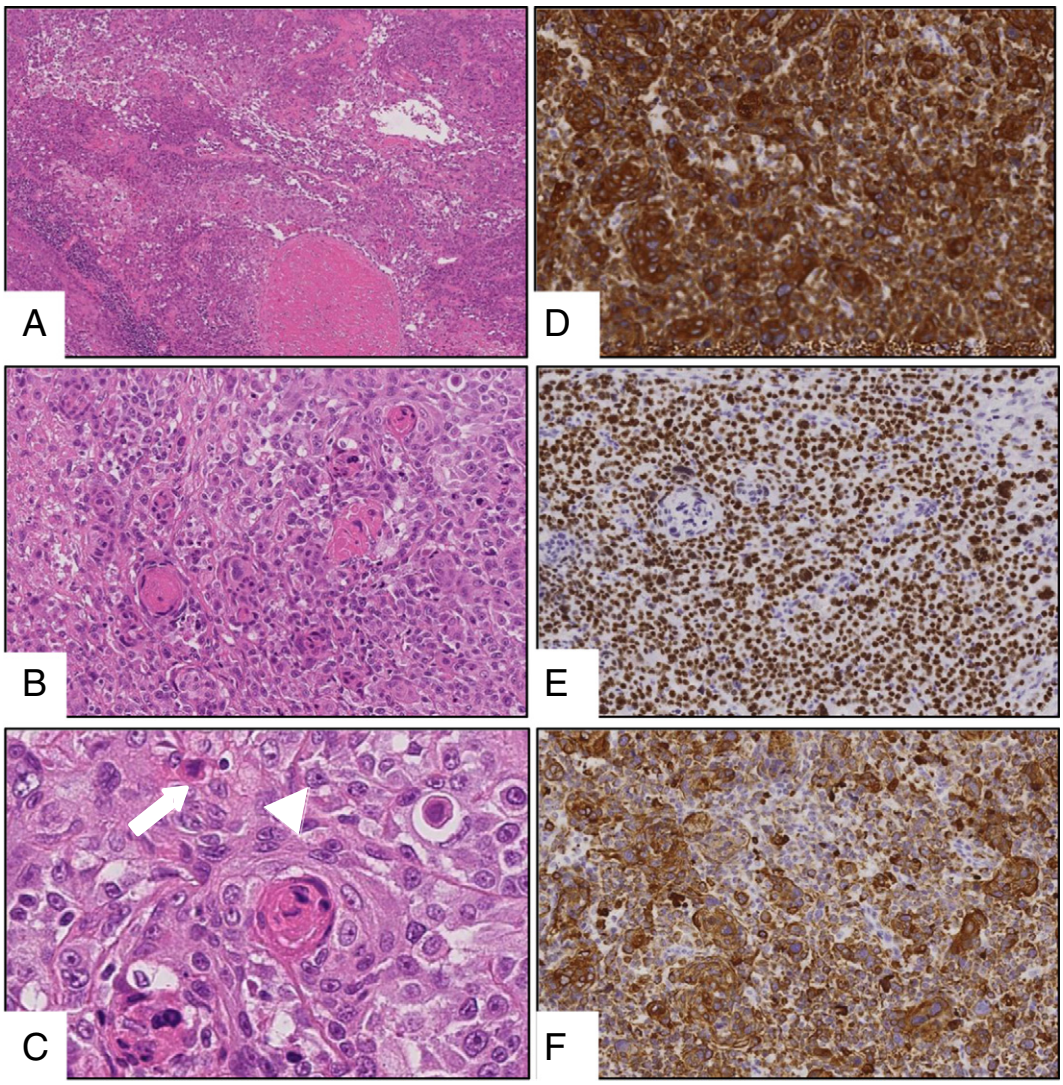

Fig. 2. Representative immunohistochemical staining images of tumor from femur bone biopsy. Hematoxylin and eosin (H&E) of initial femur biopsy at 4× (A), 10× (B), and 40× (C) magnification. Triangle head indicates nucleoli and arrow indicates mitotic figures. (D) AE 1/3. (E) p63 staining. (F) CK 5/6.

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