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Case Report

Dedifferentiated endometrioid adenocarcinoma: An under-recognized but aggressive tumor?☆

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Introduction

Uterine cancer is the most common form of gynecologic cancer in the United States. It is estimated that 47,130 new cases will be diagnosed and 8010 uterine cancer related deaths will occur during 2012 in the United States (Siegel et al., 2012). The most common histological type is endometrioid adenocarcinoma, comprising 80% of cases (Clement and Young, 2002). Less commonly seen are serous, clear cell, and undifferentiated carcinomas. Patients with undifferentiated carcinomas may have a coexisting low-grade endometrioid adenocarcinoma, which suggests a process of dedifferentiation and classifies these tumors as a dedifferentiated (undifferentiated) endometrioid adenocarcinoma (Silva et al., 2006). The low-grade component in these tumors is typically grade 1 or 2 by the Federation of Gynecology and Obstetrics (FIGO) grading system. Dedifferentiated endometrioid adenocarcinomas may often be mistaken for more common forms of endometrial cancer and are therefore thought to be under-recognized. There is still a lack of information regarding its typical clinical presentation and clinical course. Reports to date suggest that this is an aggressive form of cancer even when the undifferentiated component represents only 20% of the entire neoplasm (Silva et al., 2006). We describe a case of dedifferentiated endometrioid adenocarcinoma that initially presented with multiple bone metastases, and for which imaging did not show any evidence of intraabdominal disease.

Case

A 62-year-old postmenopausal woman presented to the emergency room after a fall that resulted in acute exacerbation of right shoulder pain. She first noticed this pain three weeks prior, but could not identify any inciting factors. In the emergency room, an X-ray was obtained that showed a proximal humeral facture with lytic lesions in the surrounding bone (Fig. 1). She was placed in a sling and discharged with outpatient follow-up. As part of her workup, a computed tomography (CT) scan of the chest, abdomen, and pelvis was obtained and revealed multiple pulmonary nodules, necrotic-appearing mediastinal and hilar lymph nodes, a left adrenal nodule, a mass within the T10 vertebral body with epidural extension and spinal cord compression, and multiple bony lytic lesions. Bony lesions were noted throughout the T1 and T10 vertebral bodies, left ileum, right ileum, left femoral head, and left acetabulum. The pelvis was notable for a fibroid uterus, but was otherwise unremarkable. There was no pelvic lymphadenopathy or ascites.

One week later, she presented to the emergency room with rapid onset of lower extremity weakness. She was admitted with a diagnosis of spinal compression and initiated on dexamethasone to prevent further neurologic compromise. Magnetic resonance imaging (MRI) demonstrated a large T11 lesion with extensive epidural extension, a T2 lesion expanding into the prevertebral and ventral epidural space, and numerous other lesions throughout her spinal column (Fig. 2). Neurosurgery took her to the operating room for decompression and performed a T10–T12 laminectomy, tumor resection with T11 vertebrectomy, T9–L1 fusion and reconstruction with titanium cage and bone matrix allograft.

The pathology specimen showed a poorly differentiated adenocarcinoma. It was strongly positive for estrogen receptors, progesterone receptors, and Pax 8, suggesting an endometrial or breast cancer. On further interview, the patient reported five months of intermittent vaginal bleeding and a left breast mass. Bilateral mammography was negative. Pelvic ultrasound revealed fibroids with poor visualization of the endometrial lining. Pathology from dilation and curettage was notable for a well-differentiated endometrioid carcinoma and an associated undifferentiated carcinoma, suggesting dedifferentiated endometrioid adenocarcinoma (Fig. 3). Histopathological and immunostaining features

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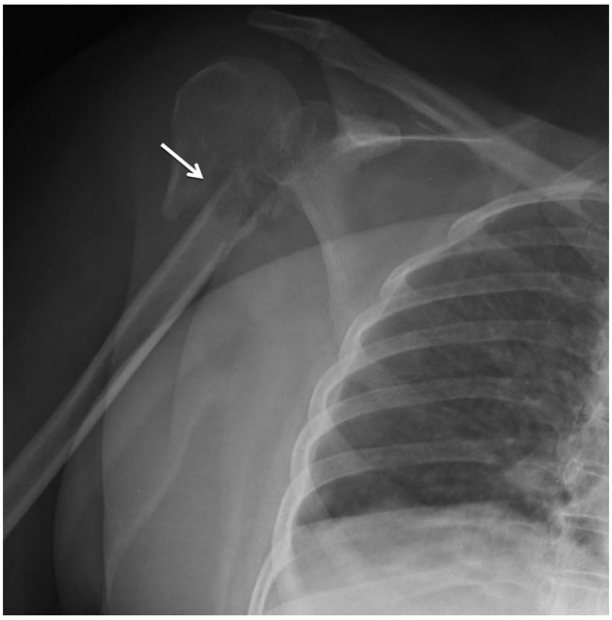

Fig. 1. Shoulder X-ray obtained on initial presentation showing a proximal humeral facture with lytic lesions in the surrounding bone (arrow).

of the dedifferentiated uterine carcinoma were similar to those in the specimen from T11. CA-125 was elevated to 264.

Two weeks after her initial surgery, she began radiation therapy. Over the course of two weeks, she received 3000 cGy of radiation therapy in 10 fractions to C5–T2 and the right humerus. Due to inadequate healing at the site of spinal fusion, radiation therapy to T10–T12 was deferred until six weeks after her initial surgery, after which she received another 3,000 cGy in 10 fractions. She remained wheelchair bound and her Gynecological Oncology Group performance status was estimated to be 3–4. This precluded her from chemotherapy and she was therefore started on a regimen of megace alternating with tamoxifen (Fiorica et al., 2004). Due to leukocytosis and deep venous thromboses, she was readmitted to the hospital 6 weeks after initiating hormonal therapy. Imaging studies showed progression of disease, including a new compression of the T2 vertebral body and widespread nodal and pulmonary metastatic disease. CA-125 had risen from 264 to 789. The patient and her family elected to discontinue treatment and transfer to home hospice given the rapid progression of disease.

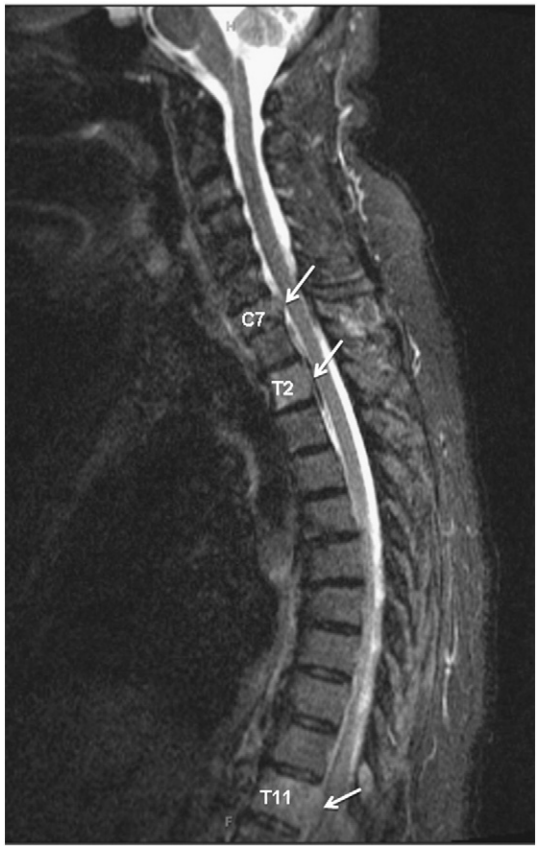

Fig. 2. Magnetic resonance T2 STIR image showing metastatic lesions at the C7, T2 and T11 vertebral bodies with epidural extension (labeled, arrows). Note this has resulted in a pathologic compression fracture at C7 and mild cord compression at T11.

Comment

Endometrioid adenocarcinoma of the uterus is a frequent neoplasm and is usually found in pure form with a favorable prognosis. Undifferentiated carcinomas are less common and thought to occur in only 9% of endometrial carcinomas (Altrabulsi et al., 2005). Until a case series published by Silva et al. (2006), the association of these two types of tumors had received little attention in the literature and was thought to have little clinical significance. However, more widespread recognition of this tumor is important because it likely has a poor prognosis. The series described by Silva et al. is still the largest case series to date, and provided follow-up information for 12 patients with dedifferentiated endometrioid adenocarcinoma of the uterus. Of these patients, 7 were dead of disease (3–60 months), 4 were alive with progression of disease (6–8 months) and 1 was without any evidence of disease (104 months). Irrespective of the amount of undifferentiated carcinoma present, these neoplasms exhibited aggressive behavior. Furthermore, histologic changes seen in recurrent tumors suggested that the presence of an undifferentiated carcinoma admixed with endometrioid adenocarcinoma was a result of dedifferentiation (Silva et al., 2006). Based on mutational analysis of several genes including TP53, we have shown the clonal relationship between the well-differentiated endometrioid carcinoma and the undifferentiated carcinoma from the same patient in the majority of cases (Kuhn, unpublished). These findings are consistent with those found in our case. Not only were the endometrioid adenocarcinoma of the endometrium and the undifferentiated carcinoma in our patient admixed, but the histology from the metastases were most consistent with the undifferentiated component derived from the endometrial sample. Although undifferentiated carcinomas have been reported to lose ER and PR expression, expression of ER and PR in both undifferentiated carcinoma and well-differentiated endometrioid carcinoma suggests that de-differentiation during tumor progression does not affect ER and PR expression in this particular case (Tafe et al., 2010 Jun). As a result, retained ER and PR expression in undifferentiated carcinoma may serve as tissue biomarkers to suggest that the metastatic lesions are derived from either breast or gynecologic origin.

Given subtle differences in histologic appearance, dedifferentiated endometrioid adenocarcinoma may be mistaken for a high-grade endometrioid adenocarcinoma, malignant mixed mullerian tumor, or unclassified sarcoma. In the FIGO system, tumors are graded by the proportion of solid endometrioid components within a tumor, without further distinction based on histologic features. As a result, dedifferentiated endometrioid adenocarcinoma may be incorrectly classified as a FIGO grade 3 endometrioid adenocarcinoma. This may explain why the 5-year survival for grade 3 endometrioid carcinoma, ranges so widely, from 40 to 70% (Silva et al., 2007). In the Silva et al., 2006 analysis, many cases of dedifferentiated tumors were initially designated as FIGO grade 2, but exhibited unusually rapid progression (Silva et al., 2006). The implications of this may be profound, given the prognostic, and therefore potential treatment, differences between FIGO grade 2, grade 3, and dedifferentiated tumors.

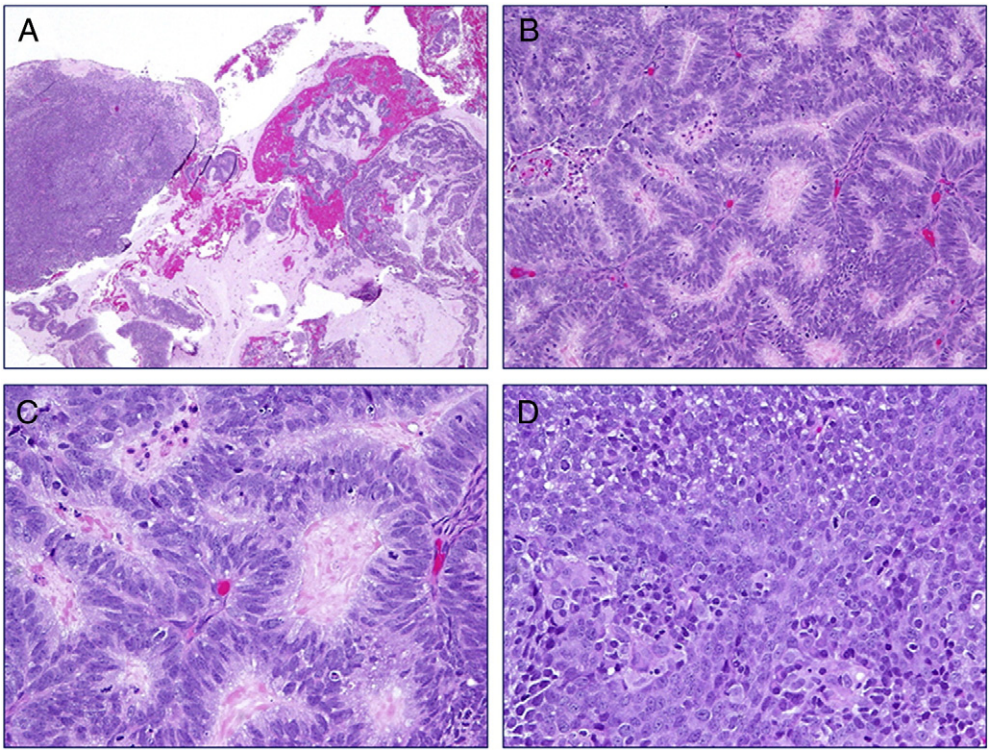

Fig. 3. Morphological features of the endometrial curettage specimen (hematoxylin and eosin stain). A. A low magnification demonstrates both low-grade (glandular pattern) and high-grade (solid pattern) components of the carcinoma. B. The low-grade carcinoma exhibits the classical glandular pattern, forming a confluent pattern. C. A high magnification demonstrates tumor cells forming glands. D. A high magnification view shows solid growth of the high-grade carcinoma without forming glands. The tumor cells appear poorly differentiated as compared to the tumor cells in C.

When dedifferentiated endometrioid adenocarcinoma metastasizes, the majority of metastases are comprised of only the undifferentiated component. Our case exhibits the same behavior, but is unique in the unusual distribution of bone metastases with lack of involvement in pelvic structures. In endometrial cancer, when metastases occur, they are typically found in the lymph nodes, ovary, omentum, peritoneum, liver, or lung. Bone metastases are less common and are estimated to occur in less than 15% of women with metastatic endometrial cancer (Albareda et al., 2008). However, data are limited to single-institution case reports. Even in dedifferentiated endometrioid adenocarcinoma, most metastases occurred in the pelvis or abdomen. There were no reported cases of bony metastases, leave alone those that initially presented with pathologic fractures (Silva et al., 2006). Vizzelli et al. (2012) most recently compiled cases of endometrial cancer presenting as bone metastases and noted the bones of the appendicular skeleton, such as the tibia, femur, calcaneus, and fibular and humerus, to be the most typical bony structure affected. Based on a PubMed search from 1950 to the present, using keywords including “endometrial neoplasms” and “bone neoplasms”, there have only been 4 prior cases of endometrial cancer presenting with spinal metastases, and none in combination with lytic lesions in the humerus, as seen in the current case.

In conclusion, two lessons can be gleaned from this case. The first is that the recognition of dedifferentiated endometrioid adenocarcinoma of the uterus is important because it has prognostic and potentially therapeutic implications. A focus of undifferentiated carcinoma may be confused with the solid component in an endometrioid adenocarcinoma. This would erroneously result in the diagnosis of a less aggressive tumor, and potentially result in providing suboptimal therapy. Second, although bony metastases are rare in endometrial cancer, it is important to consider when a patient with endometrial cancer presents with joint pain.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Conflict of interest statement

The authors have no conflicts of interest to report.

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