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Citation

Penson, Richard, Annekathryn Goodman, Whitfield Growdon, Darrell Borger, Susanna Lee, and Esther Oliva. 2013. "Case 14-2013 — A 70-Year-Old Woman With Vaginal Bleeding." *The New England Journal of Medicine* 368, no. 10 (May 9): 1827-1835.

Published Version

DOI: 10.1056/NEJMcpc1209276

Permanent link

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Case 14-2013: A 70-Year-Old Woman with Vaginal Bleeding

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PRESENTATION OF CASE

A 70-year-old woman was seen in the gynecologic cancer center at this hospital because of vaginal bleeding.

Approximately 1 month earlier, the patient had noted a brown vaginal discharge; 18 days before she was seen in the gynecologic cancer center, vaginal bleeding had developed. During the week after the onset of bleeding, transabdominal and transvaginal ultrasonography of the pelvis revealed a normal-size uterus (5.9 cm in length). The endometrial lining was abnormally heterogeneous and thickened, measuring up to 1 cm. The kidneys and ovaries were normal. She saw her gynecologist, and an endometrial biopsy was performed. Pathological examination of the specimen showed a poorly differentiated malignant neoplasm, suggestive of malignant mixed müllerian tumor (carcinosarcoma).

Twelve days after the endometrial biopsy, the patient saw a gynecologic oncologist in the cancer center of this hospital. She reported no pelvic pain, change in appetite or weight, nausea, or vomiting. She was gravida 3, para 3, with normal spontaneous vaginal deliveries, and she had had laparotomies in the past for evaluation of endometriosis and primary infertility. Her last menstrual period had been 20 years earlier. Eleven years earlier, uterine bleeding had developed, which resolved after endometrial polypectomy. Ten years earlier, a diagnosis of infiltrating ductal carcinoma of the right breast had been made (T2N0); testing for estrogen receptor (ER) and progesterone receptor (PR) was positive, and immunohistochemical staining showed overexpression of human epidermal growth factor receptor type 2 (HER2). Treatment included lumpectomy with sentinel-lymph-node mapping; adjuvant chemotherapy with four cycles of doxorubicin, cyclophosphamide, and weekly paclitaxel, followed by radiation therapy; and the administration of tamoxifen for 4 years, followed by anastrozole.

The patient also had osteoporosis, hypercholesterolemia, and hypothyroidism. Medications included anastrozole (1 mg orally daily), risedronate, atorvastatin, levothyroxine, calcium supplements, glucosamine, chondroitin, aspirin, biotin, and a multivitamin. She was allergic to penicillin and codeine. She lived with her husband and did not smoke or drink alcohol. Her parents died of heart disease in their 90s, her maternal grandfather died of pancreatic cancer at 70 years of age, and a

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N Engl J Med 2013;368:1827-35.

DOI: 10.1056/NEJMcpc1209276

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maternal uncle died of liver cancer at 60 years of age; her brother, children, and grandchildren were healthy.

On examination, the patient was obese, the vital signs were normal, the uterus was small and mobile, and there were no vulvar, vaginal, or cervical lesions. The remainder of the examination was unremarkable. Routine laboratory tests, including measurement of the CA-125 level, chest radiography, electrocardiography, a cardiac stress test, and preoperative cardiac evaluation, were all normal.

Two weeks later, a diagnostic and therapeutic procedure was performed and additional management decisions were made.

DISCUSSION OF MANAGEMENT

Dr. Annekathryn Goodman: This 70-year-old woman presented with postmenopausal bleeding, and an endometrial-biopsy specimen showed a malignant tumor, probably carcinosarcoma. The underlying cause of abnormal vaginal bleeding is age-dependent. Ten percent of premenopausal women with abnormal bleeding have a malignant tumor. In contrast, 75% of women over 70 years of age with postmenopausal bleeding have cancer, and the risk rises with age in postmenopausal women.¹ Postmenopausal vaginal bleeding is the most common manifestation of carcinosarcoma. Patients with carcinosarcoma also frequently present with the classic triad of painful postmenopausal bleeding, an enlarged uterus, and prolapsed tumor visible at the cervical os; the triad was not seen in this patient.

In only a few circumstances is surgery not the primary treatment for uterine cancer — when there is a desire to preserve fertility, when the operative risk is high, and when the disease is unresectable.² The goals of surgical treatment are excision of all disease with at least a 1-cm margin and staging of the tumor. The initial spread is to regional lymph nodes; therefore, standard treatment is a total abdominal hysterectomy and bilateral salpingo-oophorectomy with lymphadenectomy. Endometrial cancers have several potential patterns of spread: direct invasion and expansion of the primary tumor, lymphatic invasion, hematogenous spread, and intraperitoneal dissemination.³ Because metastasis is common, preoperative combination positron-emission tomography and computed tomogra-

phy (PET-CT) and a meticulous exploratory laparotomy are standard practice.

The big surgical questions for this patient are whether laparoscopy would allow for tumor staging and the extent of lymphadenectomy that needs to be performed. In one randomized study, laparoscopy was associated with substantially better overall quality of life and body image than was open surgery, and only 21% of the patients who underwent laparoscopy required conversion to laparotomy for full staging.⁴ Laparoscopic hysterectomy does not compromise the surgical management of uterine cancer.⁴

For this patient with carcinosarcoma, a highly malignant uterine tumor, laparotomy remains the standard of care. We generally follow the Mayo Clinic practice of not performing lymphadenectomy if uterine tumors are less than 2 cm in size, are grade 1 or 2, and invade less than 50% of the myometrium⁵; however, surgery for carcinosarcoma routinely includes lymphadenectomy. This patient underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic-node dissection, and omentectomy.

PATHOLOGICAL DISCUSSION

Dr. Esther Oliva: The original endometrial-biopsy specimen showed a high-grade endometrial carcinoma, with areas suggestive of associated malignant mesenchyme. These findings were consistent with a malignant mixed müllerian tumor (carcinosarcoma).

The patient subsequently underwent total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic-lymph-node dissection. The uterus measured 8.8 cm by 3.9 cm by 2.8 cm and weighed 78.4 g. An exophytic, ill-defined, tan-white mass (2.0 cm by 1.5 cm) was centered in the right fundus and involved the anterior and posterior walls. Sectioning showed that the tumor deeply invaded the myometrium. Microscopical examination showed that the tumor was composed of an intimate admixture of high-grade serous carcinoma and predominantly homologous sarcoma (Fig. 1A), with focal areas of chondrosarcoma (Fig. 1B). The malignant epithelial component deeply invaded the myometrium (to a depth of 2.1 cm in myometrium that had a depth of 2.3 cm) (Fig. 1C), and areas of lymphovascular invasion (stage IB) were noted (Fig. 1D). There was no evidence of tumor in the

ovaries, fallopian tubes, omentum, or four right and five left pelvic lymph nodes. All margins were free of tumor.

Diagnostic features of malignant mixed müllerian tumor include the finding of a biphasic malignant tumor that is composed of high-grade carcinoma (most commonly endometrioid or serous) and sarcoma that is typically homologous (arising from mesenchymal tissue normally found in the uterus), although in up to 50% of cases (including this case), the tumor has a heterologous component (most commonly rhabdomyosarcoma or chondrosarcoma). There is no transition between the epithelial and mesenchymal components.⁶ Tumor stage is the most important prognostic factor in these tumors,⁷ although histologic features also affect outcome. The finding of serous or clear-cell carcinoma is associated with a more aggressive course of the disease. Sarcomatous components adversely affect the overall prognosis for patients with stage I tumors (the 5-year survival rate is 30% among patients with heterologous elements as compared with 80% among patients with homologous elements); myometrial and lymphovascular invasion are also associated with a poor prognosis.⁷⁻⁹ This patient has all these adverse factors.

Although malignant mixed müllerian tumors were initially classified as sarcomas, the latest World Health Organization classification includes them in the category of endometrial carcinomas, since these tumors display genetic alterations that are common to both the epithelial and the mesenchymal components.^{10,11} These alterations include a high frequency of *TP53* mutations, multiple chromosomal gains and losses, up-regulation of the AKT- β -catenin pathway (AKT is also known as protein kinase B), amplification of *HER2*, microsatellite instability, and *KRAS* mutations.¹² This tumor is an example of stable epithelial-to-mesenchymal transition, a process of cellular transdifferentiation in which epithelial cells lose polarity and cell-to-cell contacts, reorganize their cytoskeleton, lose expression of epithelial markers, and acquire expression of mesenchymal markers. Epithelial-to-mesenchymal transition results from complex signaling, including, but not limited to, the switching of cadherin subtypes, gain of expression of mesenchymal markers, and activation of signaling pathways such as transforming growth factor β , notch, and hedgehog.¹³

Figure 1. Hysterectomy Specimen (Hematoxylin and Eosin).

The malignant mixed müllerian tumor is composed of high-grade serous carcinoma, with a pseudoglandular architecture, and high-grade homologous sarcoma (Panel A). Heterologous sarcomatous elements represented by chondrosarcoma are also present (Panel B). The epithelial component has invaded the myometrium (Panel C) and some of the lymphatic spaces (Panel D).

DISCUSSION OF MANAGEMENT

Dr. Richard T. Penson: The term “carcinosarcoma” was originally described by Rosenstein in 1883, and the term “malignant mixed müllerian tumor” was introduced by Sternberg and colleagues in 1954.¹⁴ In the past few years, the designation of carcinosarcoma has been favored by the Gynecologic Oncology Group (GOG).

Carcinosarcoma requires an integrated approach that spans multiple medical disciplines, but the optimal therapeutic approach for this patient has not been clearly defined. The consider-

Figure 2. Abdominopelvic CT Images after the Administration of Oral and Intravenous Contrast Material.

A coronal reconstruction image (Panel A) and axial images (Panels B and C) show a retroperitoneal soft-tissue mass (arrows) encircling and occluding the inferior vena cava. New subcentimeter liver lesions (arrowheads) are also seen. These findings suggest tumor recurrence.

ations include whether to use radiation, whether to use adjuvant chemotherapy, and which specific chemotherapy regimen to use (if the decision is made to use chemotherapy). Radiation therapy has been shown to reduce the rates of local recurrence in the pelvis but does not increase survival among patients with carcinosarcoma.¹⁵⁻¹⁷ Adjuvant chemotherapy has not been shown to have an effect on recurrence rates or progression-free or overall survival among patients with carcinosarcoma.¹⁷ Hormonal therapy is of no use for this patient, since estrogen and progesterone receptors do not control tumor growth, even though they are typically present in patients with carcinosarcoma.

To maximize the potential therapeutic effect for a patient such as this one who has high-risk disease, we have typically used a combination of doxorubicin, paclitaxel, and carboplatin with growth-factor support, administered for three cycles and followed by radiation therapy. The benefit of this strategy over the standard six cycles of carboplatin and paclitaxel is unknown; however, there is increasing support for the standard six-cycle strategy because of the lack of benefit of more intense chemotherapy for patients such as this one with metastatic disease, as shown in study GOG-209 (ClinicalTrials.gov number, NCT00063999).^{18,19}

Dr. Goodman: The patient was treated with six cycles of adjuvant carboplatin and paclitaxel, followed by brachytherapy (total dose, 2100 cGy) to the vault of the vagina. CT of the chest, abdomen, and pelvis 1 month after the completion of therapy revealed no evidence of cancer in the chest or upper abdomen but did reveal soft-tissue densities in the pelvis that were thought to be resolving postoperative inflammatory changes.

Eleven months after the completion of chemotherapy, the patient was admitted to another hospital with a 3-day history of dyspnea and leg edema.

Dr. Susanna I. Lee: On presentation at the other hospital, CT of the abdomen and pelvis after the administration of intravenous contrast material (Fig. 2) showed occlusion of the inferior vena cava by a circumferential retroperitoneal soft-tissue mass measuring approximately 4 cm in maximal dimension and extending from below the renal veins to the confluence of the common iliac veins. Two lesions measuring approximately 5 mm in greatest dimension were apparent in the liver.

Ventilation–perfusion lung scans showed a low probability of pulmonary emboli. Ultrasonographic studies confirmed the presence of extensive deep venous thrombosis; CT of the chest with intravenous contrast material revealed no pulmonary emboli or lesions suspicious for metastatic disease.

Integrated whole-body ^{18}F -fluorodeoxyglucose (FDG) PET performed with concurrent CT of the chest, abdomen, and pelvis after the administration of intravenous contrast material (Fig. 3) 11 days later revealed marked FDG avidity in the retroperitoneal mass and liver lesions; the liver lesions had increased in size and number since the previous CT scan. A previously undetected focus of intense tracer uptake was seen in the L2 vertebral body, a finding that was consistent with metastasis. No intrathoracic metastases were seen.

PATHOLOGICAL DISCUSSION

Dr. Oliva: A CT-guided retroperitoneal (aortocaval) lymph-node biopsy was performed. The specimen consisted of fragments of collagenous tissue with scant poorly preserved carcinoma cells, findings consistent with recurrence of the malignant mixed müllerian tumor.

Dr. Whitfield B. Growdon: Genetic features of this patient's tumor may be important in the selection of additional treatment. The genetic differential diagnosis is greatly informed by the clinical type of uterine carcinoma. Clinical investigators group endometrial cancers into two types.²⁰ Of all endometrial cancers, 85 to 90% of cases are type I, which tend to be early-stage, with low-grade endometrioid histologic features, manifestation in patients who are young, and an excellent prognosis. In contrast, this patient has a type II cancer, which typically has a high histologic grade, a spectrum of histologic types (e.g., papillary serous carcinoma, clear-cell carcinoma, undifferentiated carcinoma, and carcinosarcoma), manifestation in older women, and aggressive behavior.^{11,21} Only 10 to 15% of uterine cancers are type II cancers, but they are responsible for 40 to 50% of deaths from endometrial cancer.^{22,23} As compared with endometrioid carcinoma, carcinosarcoma is twice as likely to be locally advanced and more than twice as likely to be metastatic at presentation.²⁴ These features most likely explain why carcinosarcoma is associated with a 5-year overall survival of 29%

Figure 3. Integrated Whole-Body FDG-PET and CT.

Frontal (Panel A) and lateral (Panel B) positron-emission tomography (PET) images show avid uptake of ^{18}F -fluorodeoxyglucose (FDG) by the retroperitoneal mass (white arrow) and liver lesions (arrowheads), as well as a hypermetabolic focus in the lumbar spine (black arrow). A contrast-enhanced CT image (Panel C) shows liver lesions (arrowheads) that had increased in size and number since the CT scan that was obtained 11 days earlier. Fusion of an FDG-PET scan and a CT image (Panel D) shows a previously undetected hypermetabolic focus in the L2 vertebral body (arrow), a finding that was consistent with metastasis.

as compared with the 85% rate observed among patients with endometrioid tumors.²⁵ Carcinosarcoma developed in this patient after she had received treatment with tamoxifen.²⁶ Two identified risk factors for the development of carcinosarcoma are radiation, which increases the risk by a factor of 8, and tamoxifen, which increases the risk by a factor of 2 to 7.^{27,28}

Specific genetic signatures that may have relevance to the treatment of this patient have been shown to be associated with type I and

mon in type I cancers, and alterations in *TP53* (encoding tumor protein p53) and *HER2* are more common in type II cancers. Activation of *PIK3CA* (encoding the phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha protein) through mutation or amplification is prevalent in both types.^{18,21,29} Recent data also show that 43% of carcinosarcomas harbor gain-of-function mutations in *PIK3CA* or *KRAS* in both the carcinomatous and sarcomatous compartments.³⁰ In light of these data, genetic testing of this patient's carcinosarcoma could reveal mutations that would direct her treatment toward innovative therapies targeting specific oncogenic pathways.

Dr. Darrell R. Borger: To personalize cancer treatment, it is becoming increasingly important for the clinical evaluation to include highly multiplexed tumor genotyping. This is particularly relevant to this patient, in whom recurrent metastatic disease developed after she had received standard treatment and for whom an alternative treatment was being sought. Testing for this patient was performed with the use of a cancer-gene mutational platform that has been expanded to simultaneously query for 160 site-specific mutations across 15 cancer driver genes (SNaPshot Multiplex System, Applied Biosystems).³¹ The panel emphasizes known activating point mutations of oncogenes that are relevant for targeted therapeutics. The testing was performed in a laboratory certified under the Clinical Laboratory Improvements Amendments and is fully validated as a clinical test that is routinely used in our institution to guide treatment decisions. To date, 61 patients with uterine carcinoma have been tested and mutations have been identified in 37. We have observed that the mutational profiles of uterine adenocarcinomas and uterine carcinosarcomas overlap at least partially (Fig. 4A).

The initial formalin-fixed, paraffin-embedded endometrial-biopsy sample from this patient was obtained for mutational profiling. The specimen consisted of a large aggregate of tissue fragments containing 60% tumor, providing an ideal sample for robust evaluation of somatic mutations. Total nucleic acids were extracted from the tumor portion and then evaluated with the use of our SNaPshot clinical genotyping platform. A prominent peak was observed in the *PIK3CA* assay that evaluated nucleotide position 3140 (Fig. 4B). An A→G base substitution was identified, resulting in a change of histidine to arginine at

type II cancers. Alterations in *KRAS*, *PTEN* (encoding the phosphatase and tensin homologue), and *CTNNB1* (encoding β -catenin) are more com-

amino acid position 1047. This *PIK3CA* His1047Arg mutation has been previously identified in uterine carcinosarcomas³⁰ and is known to activate phosphoinositide-3-kinase (PI3K) activity, leading to activation of the downstream AKT pathway.^{32,33}

DISCUSSION OF MANAGEMENT

Dr. Goodman: The patient's extensive thrombus was managed by vortex thrombectomy (en bloc aspiration of the thrombus), as well as infrarenal placement of an inferior vena cava stent and suprarenal placement of an inferior vena cava filter, with bilateral venoplasty. Anticoagulation was complicated by a subdural hematoma in the left frontal, parietal, and temporal region, without mass effect and with no neurologic sequelae.

A series of randomized, controlled trials has defined the standard of care for metastatic carcinosarcoma as either an inpatient regimen of ifosfamide with paclitaxel or an outpatient regimen of carboplatin with paclitaxel; these regimens are being compared in the randomized trial GOG-261 (NCT00954174).³⁴ This patient wanted to prevent alopecia, so she was treated with three cycles of carboplatin and pegylated liposomal-encapsulated doxorubicin hydrochloride, a regimen shown to be effective in patients with ovarian cancer and less likely than carboplatin with paclitaxel to cause alopecia.³⁵ A fourth cycle, of carboplatin alone, was given, owing to a shortage of the doxorubicin. Despite therapy, the patient's performance status deteriorated, the CA-125 level rose to 968.4 U per milliliter (reference range, <35.0), the alkaline phosphatase level was 925 U per liter (reference, 30 to 100), and a PET-CT scan showed progression of disease in the retroperitoneum, liver, and spine and new metastases in the lungs. Worsening back pain developed. Chemotherapy was discontinued, and the patient was treated with zoledronic acid and palliative radiation to the lumbar spine with a total of eight fractions of 3.5 Gy, totaling 28 Gy.

Dr. Penson: Current therapeutic approaches for patients with carcinosarcoma are woefully inadequate, and the emphasis should perhaps not be on phase 3 clinical trials but instead on expanding the understanding of the underlying biology of this disease, to identify new targets for therapeutic intervention. The hope for targeted therapy has so far been disappointing, with thalidomide, imatinib, and sorafenib all having a response rate

of 0 in patients with carcinosarcoma.³⁶⁻³⁸ Although HER2-targeted therapy was initially promising, clinical trials of single-agent therapy have been disappointing.³⁹

Given the presence of *PTEN* mutations in carcinosarcoma, the phase 2 clinical trial of deforlimus includes patients with carcinosarcoma; also, an increasing number of patients with *PIK3CA* mutations have access to phase 1 and phase 2 clinical trials involving PI3K and AKT.⁴⁰ Antiangiogenic agents show promise in endometrial cancer, and trials of the new agent trebananib (formerly AMG 386) may enroll patients with carcinosarcoma. We had one patient who did exceptionally well on the histone deacetylase inhibitor belinostat (PXD101), with carboplatin and paclitaxel.⁴¹ Carcinosarcomas have loss of imprinting, which leads to biallelic overexpression of insulin-like growth factor II (IGF-II) and concomitant overexpression of IGF-IR.⁴² Also, carcinosarcoma is a vivid example of epithelial-to-mesenchymal transition; therefore, hedgehog inhibitors, such as vismodegib and saridegib (IPI-926), are interesting treatment candidates.

There were limited options for this patient who did not have a response to platinum therapy. Treatment with weekly paclitaxel was perhaps her best chance of clinical benefit (although it was a small chance), and hospice or a clinical trial were reasonable alternatives. She was not eligible for a phase 2 clinical trial of E7080, an oral antiangiogenic agent that targets vascular endothelial growth factor receptor 2, because she had had a "stroke" within the previous 6 months, despite our petitioning that it was not a stroke but an iatrogenic subdural hematoma. She signed a consent form for SNaPshot analysis and 1 month later returned to consider participating in a phase 1 clinical trial of an experimental PI3K inhibitor (NCT01219699). Unfortunately, her health had declined precipitously; she was predominantly confined to bed and had jaundice and hypotension (96/61 mm Hg). Results of liver-function tests had worsened substantially, with the aspartate aminotransferase level rising from 60 to 251 U per liter (reference range, 9 to 32), and the bilirubin level from 0.4 to 2.1 mg per deciliter (6.8 to 35.9 μ mol per liter) (reference range, 0.1 to 1.0 mg per deciliter [1.7 to 17.1 μ mol per liter]). As a result, she was ineligible to enroll in the clinical trial of the PI3K inhibitor BYL719. She elected to enroll in hospice, met the palliative care

team, and died at home with her family 2 weeks later, 22 months after the initial diagnosis.

Dr. José Baselga (Medical Oncology): Carcinosarcomas are unique in that they have abnormalities in both the PI3K and the RAS pathways, in contrast to other tumors, such as breast cancer. This provides the opportunity to consider experimental therapy involving a combination of inhibitors of both pathways. In assessing the usefulness of mTOR (mammalian target of rapamycin) inhibitors in the clinical trials involving patients with endometrial cancers, are you sure that the dosing and schedule were optimal?

Dr. Penson: I agree that the newer targeted agents show more promise. Older rapamycin-based analogues at inadequate dose and suboptimal schedule have not been a fair trial of this class of agents for the treatment of endometrial cancer. However, the randomized phase 2 trial GOG-248 was halted after only 22 participants enrolled in the group assigned to receive temsirolimus and alternating megestrol acetate and tamoxifen, because of excess thromboembolic events and myocardial infarctions.⁴³ The issues are that the older agents have more toxic effects

than new agents and that the population of patients with endometrial cancer is more obese and older than the population of patients involved in breast cancer studies and thus is at greater risk for complications. Prescreening and selection of patients with relevant molecular abnormalities may further improve efficacy in these trials.

ANATOMICAL DIAGNOSIS

Malignant mixed müllerian tumor (carcinosarcoma) of the uterus, with a *PIK3CA* mutation.

This case was discussed at Cancer Center Grand Rounds.

Dr. Penson reports receiving payment from Apotex for providing expert testimony in a case of *Aventis Pharma S.A. v. Apotex Inc.*; payment for serving on scientific advisory boards from Genentech, AstraZeneca, Lifecore Biomedical, BioMarin Pharmaceuticals, Clovis Oncology, and Seattle Genetics; and grant support through his institution from ImClone Systems, Endocyte, AstraZeneca, Eisai Pharmaceuticals, and Amgen. Dr. Borger reports receiving consulting fees from Leerink Swann, Prous Science, and Bio-Reference Laboratories. Dr. Oliva reports providing expert opinions in legal cases on behalf of patients or physicians. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Dror Michaelson for help with organizing the conference.

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