

Anaplastic Pelvic Carcinoma Secondary to Low-grade Endometrial Carcinoma

RAFAL WATROWSKI¹, JOCHEN MÖCKEL², THORSTEN VENZKE³,
CHRISTOPH JÄGER¹ and THOMAS BAUKNECHT¹

¹Department of Gynecology and Obstetrics, St. Josefskrankenhaus,
Teaching Hospital of the University of Freiburg, Freiburg, Germany;

²Institute of Pathology 'Dr. Möckel & Dr. Schneider', Freiburg, Germany;

³Institute of Pathology 'Dres. Hellerich, Venzke & Mattern', Freiburg, Germany

Abstract. *Background: Low-grade endometrial carcinoma has an excellent prognosis. The risk of secondary cancer after endometrial carcinoma is moderately increased and is mostly related to the field of postoperative radiation (small intestine, colon, vagina, and urinary bladder). Anaplastic (undifferentiated) pelvic carcinoma (APC) is rare and probably under-reported. To date, only one publication has reported six cases of APC that were secondary to low-grade endometrial carcinoma. Case Report: We have analyzed the fulminant course of APC—preceded by paraneoplastic arthritis—four months after hysterectomy and adnexectomy for low-grade endometrial carcinoma (endometrioid type, moderately differentiated, tumor diameter: 2 cm, infiltration depth 3 of 15 mm). The 73-year-old patient died five weeks after the diagnosis of the second malignancy. Conclusion: The prognosis of APC is poor and the limitations of the therapy result from aggressive tumor biology and rapid deterioration of the patients' general condition. Rheumatological symptoms can precede cancer diagnosis. Immunohistochemistry facilitates the differentiation between primary and secondary carcinoma.*

Although endometrial carcinoma (EC) is the most common carcinoma of the female genital tract, most patients do not die from this disease (1, 2). As many as 10-16% of EC, but only 2% of low-grade EC (including early-stage, grade 1 or 2, and endometrioid type), develop relapse (1-5). The median time-to-recurrence is 17 to 18 months (range=2 to 129

months) (2, 3). The mortality of relapsed EC is high (1, 4, 5). Cervical involvement predicts local recurrence, while lymph node status and tumor grade predict retroperitoneal recurrence (2). In patients with stage I–II endometrioid-type EC, involvement of lymphovascular space (LVSI) and infiltration into the outer one-third of the myometrium are predictors of distant hematogeneous failure (2, 3). The incidence of secondary cancer after EC is moderately increased (odds ratios=1.4-2.7). Secondary cancer develops more often after radiotherapy in organs related to the radiation field (small intestine, colon, vagina, and urinary bladder) (6). Anaplastic pelvic carcinoma (APC) is rare, probably under-reported, and has an extremely poor prognosis (7, 8). To date, six cases of APC, secondary to low-grade EC, supposed as 'de-differentiated' recurrences, have been described in a single publication (7).

Case Report

A 73-year-old Caucasian woman, gravida 3, para 3, body-mass index 26, non-smoker, having reached menopause at 56 years, with no history of hormonal replacement therapy, was brought to our attention. Her mother died of renal cell carcinoma. The patient had suffered for years from temporal lobe epilepsy, which was treated with valproic acid. In February 2008, she underwent diagnostic dilation and curettage because of post-menopausal bleeding and a thick (20 mm) endometrium on transvaginal ultrasound. Histology revealed an intermediate differentiated EC of the endometrioid type. The patient underwent midline laparotomy, peritoneal washing, total abdominal hysterectomy, and bilateral salpingo-oophorectomy. According to the histological grade and depth of the myometrial invasion, as determined intraoperatively, no lymphonodectomy was performed. The final histology (Figure 1A) confirmed an EC of the endometrioid type, moderately-differentiated (G2) tumor of 2 cm in diameter, with a polyp-like growth, and myometrial infiltration of 3 of 15 mm [stage

Correspondence to: Rafal Watrowski, Department of Gynecology and Obstetrics, St. Josefskrankenhaus, Teaching Hospital of the University of Freiburg, Sautierstr.1, 79104 Freiburg, Germany. Tel: +49 76127112601, Fax: +49 76127112602, e-mail: saraband@gmx.net

Key Words: Anaplastic carcinoma, endometrial cancer, secondary cancer, paraneoplastic arthritis.

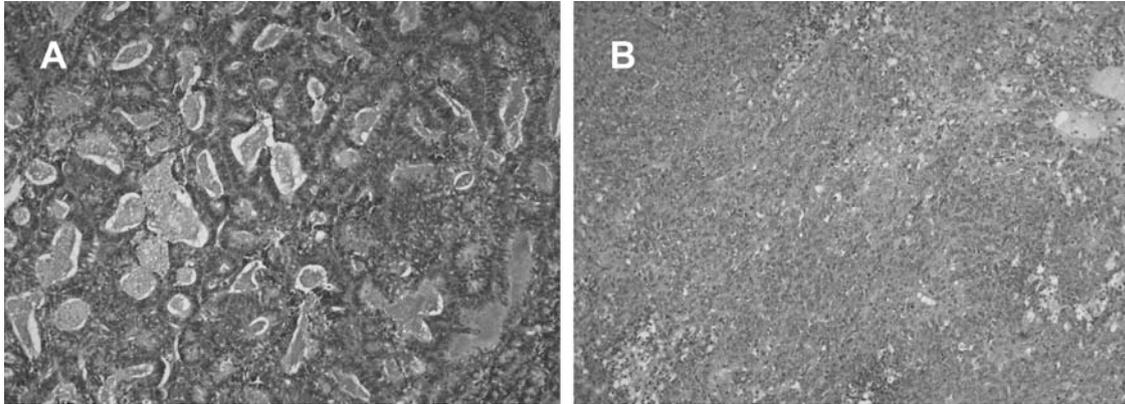


Figure 1. Hematoxylin and eosin staining, $\times 100$. A: Endometrioid adenocarcinoma, grade 2, with visible glandular formations. B: Solid growing anaplastic carcinoma, with enlarged bizarre nuclei and numerous atypical mitoses.

1 A with the new FIGO 2009 staging system, 1 B according to the FIGO 1988 staging (9)]. The lymphovascular space was not invaded and peritoneal washings were negative. The old FIGO stage II A was discussed [II A stage is no longer present in the 2009 FIGO classification (9)] because of the microscopic evidence of superficial spread to the cervical epithelium. Staining was positive for vimentin, estrogen receptor, and progesterone receptor. Staging investigations (chest X-ray and abdominal ultrasound) were negative. The patient received no postoperative radiation.

In May 2008 (10 weeks after operation), following complaints of 5 kg weight loss and joint pain in the upper extremities and knees, a "seronegative rheumatoid arthritis" (RA) was diagnosed. Remarkably, a panel of 23 rheumatologic autoantibodies and serological markers for Borrelia, Salmonella and Yersinia infection were negative. The patient received oral prednisone (20 mg daily). During this time, no liver, spleen, or para-aortic metastases were visible on ultrasound. In July 2008, the patient was admitted to our hospital because of further weight loss (10 kg from March to June), increased abdominal circumference, and discomfort in the lower abdomen. The serum concentration of carbohydrate antigen-125 (CA-125) was slightly elevated (67 U/ml), while the concentration of carcinoembryonic antigen (CEA) was within the normal range (0.3 ng/ml). On ultrasound and computed tomographic (CT) scan, multiple intra-abdominal tumor masses up to 10 cm in diameter were confirmed in the pelvis, middle abdomen, omentum, and abdominal wall, accompanied by ascites, disseminated liver metastases, enlarged mesenteric lymph nodes, and obstructive compression of the left ureter. A CT-guided core biopsy of the closest tumor (left iliac crest level) revealed an anaplastic carcinoma, with weak focal epithelial differentiation and necroses. Because of the confusing diagnosis, the specimens of the primary malignancy (low-grade EC) were re-examined by two pathologists from another pathological institute, and

conversely, the specimens of the secondary malignancy were cross-checked by two gynecological pathologists from the first institute. Two weeks later, a re-laparotomy, with removal of bulky tumors (omental cake: 400 g, pelvis: 200 g), and multiple biopsies were performed. Histology revealed a "large cell, undifferentiated, in solid formations and pseudo-rosettes growing malignancy, with in size and chromatin highly varying, leptochromatic and mitotic active nuclei, accompanied by extensive, partially hemorrhagic necrosis". The tumor lacked any glandular differentiation (Figure 1B). Extensive immunohistochemistry was conducted with a panel of 27 markers (Table I), which supported the diagnosis of APC, being positive only for vimentin and Ki67, and focally positive for epithelial membrane antigen (EMA). On the third postoperative day, the patient reported pain in the right abdominal wall. A palpable tumor (6 cm) appeared on the CT scan as a postoperative hematoma or an abscess; in reality, it was a rapidly growing APC metastasis of the right *rectus abdominis* muscle. On the seventh postoperative day, the Karnofsky index of the patient fell to 50%. The intended chemotherapy with carboplatin was considered unsafe for the patient. The postoperative course became complicated with ileus, bilateral pleural effusions, hypokalemia, hypoalbuminemia with anasarca, thrombocytopenia, and impaired wound healing. In August 2008, the patient refused all but palliative treatments and requested to be discharged. She died two weeks later, five weeks after the diagnosis of APC and five months after the operation for low-grade EC.

Discussion

In 2006, Silva *et al.* first described well- or intermediately-differentiated ECs with a 20-90% component of undifferentiated carcinoma. Those tumors have been termed 'de-differentiated carcinomas' (7) or 'combined undifferentiated and differentiated carcinomas' (8). The presence of even a small anaplastic

Table I. Immunohistochemical characteristics of the primary and secondary tumor.

Marker	Primary tumor	Secondary tumor
Vimentin	Positive	Positive
Antigen Ki-67	Not available	Positive (80%)
Epithelial membrane antigen (EMA)	Not available	Weakly positive
Pan-cytokeratin (AE1+AE3)	Focally positive	Negative (singular cells positive)
Mast/stem cell growth factor receptor (CD117)	Not available	Negative (singular cells positive)
Neuron-specific enolase (NSE)	Not available	Nonspecific/ negative
Neutral endopeptidase (NEP, CD10)	Not available	Nonspecific/ negative
Cytokeratin high molecular weight (HMW)	Not available	Negative
Cytokeratin 7	Positive	Negative
Cytokeratin 18	Positive	Negative
Cytokeratin 20	Positive	Negative
Estrogen receptor	Positive	Negative
Progesterone receptor	Positive	Negative
Carcinoembryonic antigen (CEA)	Focally positive	Negative
Cd45ra molecule (LCA)	Focally positive	Negative
Pan T-cell marker CD 3	Focally positive	Negative
Pan B-cell marker CD 20	Focally positive	Negative
B-Cell-associated antigen CD 79a	Focally positive	Negative
Melanoma marker HMB-45	Focally positive	Negative
Tumor necrosis factor receptor superfamily, member 8 (CD30)	Not available	Negative
Alpha-actin	Not available	Negative
Melan A	Not available	Negative
S-100 protein	Not available	Negative
Myogenic differentiation-1 (Myo D1)	Not available	Negative
Desmin	Not available	Negative
Phospholipase-A2 activator protein (PLAP)	Not available	Negative
Human epidermal growth factor receptor-2 (C-ERBB-2)	Not available	Negative

component in an otherwise low-grade EC has been associated with a fulminant clinical course and a very short survival (range=0.5-20 months, median=6 months) (8). Most importantly, six out of 25 cases were metachronous APC after low-grade EC, localized in the retroperitoneum, pelvis, vagina, or liver (7). To the best of our knowledge, this has been the only publication to date that described a sequence similar to our case. Tafe *et al.* reported all 10 of their cases of 'de-differentiated' ECs to be synchronous. They appeared as large (>2 cm), necrotic, polypoid masses with diffuse involvement of the endometrium and mostly infiltrated the cervix (8). This presentation lacks, except for polypoid growth, similarity to EC in the present case. Undoubtedly, recognizing even a minor component of undifferentiated carcinoma in apparently low-grade EC is of eminent importance because of its dramatic impact on prognosis or misdiagnosis as poorly-differentiated EC or carcinosarcoma (8). It is unlikely that in the present case, four experienced pathologists had overlooked anaplastic components on 12 examined slides. Additionally, in relation to the highly aggressive tumor biology, a latency of four months until manifestation of the RA, would be difficult to explain. Nevertheless, it is possible that a patch of anaplastic cells was present in the primary tumor or developed from ectopic cells

of müllerian origin in other pelvic organs. Their rapid expansion could result from aggressive biology and immunological changes related to RA or steroid therapy. In particular, strong positivity for vimentin and Ki-67, and focal positivity for EMA were compatible with the undifferentiated carcinoma of endometrial origin (10). Immunohistochemistry facilitates differentiation between primary and secondary carcinomas. Generally, undifferentiated carcinomas of endometrial origin are likely to be positive for vimentin, focally (<10%) positive for pan-cytokeratin AE1/AE, cytokeratin 18, EMA or neuroendocrine markers, but negative for hormonal receptors, actin, desmin, or melanoma marker HMB-45 (8, 10).

The patient underwent standard primary surgery (hysterectomy, bilateral salpingo-oophorectomy, and peritoneal washings), and no postoperative radiotherapy. Was the omission of lymphadenectomy appropriate and was the absence of adjuvant radiotherapy justified? In patients with low-risk EC, lymphadenectomy increases morbidity and therapy costs without survival benefit; hence, hysterectomy with salpingo-oophorectomy alone is the appropriate surgical management and should be the standard care (11). Prospective studies indicate that postoperative radiotherapy can be omitted for low- and intermediate-risk ECs without loss of survival

(12). Oncological therapies can increase the risk for developing secondary cancer. However, our patient received no blood transfusion, no radiation, and no chemotherapy. Thus, in this case, the primary cancer therapy does not seem to be the probable trigger for secondary cancer. The coincidence of secondary APC with the onset of RA was remarkable. RA is a condition characterized by chronic inflammation with anti-self activity, associated with increased risk of developing hematological and renal malignancies (13). Paradoxically, women with RA are less likely to develop cervical or EC (standardized incidence ratio 0.86 and 0.66, respectively) (13). We suppose that rheumatoid symptoms reflect the development of cancer and should be regarded as 'paraneoplastic arthritis'. Paraneoplastic arthritis is difficult to distinguish from idiopathic, seronegative RA (14), as it can mimic RA with symmetrical polyarthritis and upper-extremity predilection (14, 15). The role of steroids as a possible trigger for APC in the present case will remain speculative since the steroid therapy of RA has rather been associated with reduced risk for some types of malignancies (lymphomas) (16). Additionally, the patient had been treated for years with valproic acid for epilepsy. It should be noted that a recent experimental study in cervical cancer shows that valproic acid suppresses tumor progression (17).

Conclusion

We are the second to report a case of metachronous APC after low-grade EC. It remains a matter of speculation whether the second tumor could be regarded as an early 'dedifferentiated' recurrence of EC. The prognosis of APC is extremely poor. Rheumatological symptoms can precede the diagnosis of cancer.

References

- Lindahl B, Ranstam J and Willén R: Relapse of endometrial carcinoma: Follow-up of 272 patients with relapse. *Anticancer Res* 32: 3391-3395, 2012.
- Gadducci A, Cosio S, Fabrini MG, Fanucchi A, Barsotti C, Cristofani R, Greco C and Genazzani AR: Patterns of failures in endometrial cancer: Clinicopathological variables predictive of the risk of local, distant and retroperitoneal failure. *Anticancer Res* 31: 3483-3488, 2011.
- Gadducci A, Cavazzana A, Cosio S, DI Cristofano C, Tana R, Fanucchi A, Teti G, Cristofani R and Genazzani AR: Lymphovascular space involvement and outer one-third myometrial invasion are strong predictors of distant haematogeneous failures in patients with stage I-II endometrioid-type endometrial cancer. *Anticancer Res* 29: 1715-1720, 2009.
- Ueda Y, Matsumura Y, Egawa-Takata T, Miyake T, Miyatake T, Yoshino K, Fujita M, Matsuzaki S, Yokoyama T, Miyoshi Y, Yamasaki M, Enomoto T and Kimura T: Disease-free interval after primary treatment predicts prognosis of recurrent endometrial carcinoma. *Anticancer Res* 30: 4347-4352, 2010.
- Mariani A, Webb MJ, Keeney GL, Aletti G and Podratz KC: Endometrial cancer: Predictors of peritoneal failure. *Gynecol Oncol* 89: 236-242, 2003.
- Brown AP, Neeley ES, Werner T, Soisson AP, Burt RW and Gaffney DK: A population-based study of subsequent primary malignancies after endometrial cancer: Genetic, environmental, and treatment-related associations. *Int J Radiat Oncol Biol Phys* 78: 127-135, 2010.
- Silva EG, Deavers MT, Bodurka DC and Malpica A: Association of low-grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: A new type of dedifferentiated carcinoma? *Int J Gynecol Pathol* 25: 52-58, 2006.
- Tafe LJ, Garg K, Chew I, Tornos C and Soslow RA: Endometrial and ovarian carcinomas with undifferentiated components: Clinically aggressive and frequently underrecognized neoplasms. *Mod Pathol* 23: 781-789, 2010.
- Creasman W: Revised FIGO staging for carcinoma of the endometrium. *Int J Gynaecol Obstet* 105: 109, 2009.
- Altrabulsi B, Malpica A, Deavers MT, Bodurka DC, Broaddus R and Silva EG: Undifferentiated carcinoma of the endometrium. *Am J Surg Pathol* 29: 1316-1321, 2005.
- Dowdy SC, Borah BJ, Bakkum-Gamez JN, Weaver AL, McGree ME, Haas LR, Keeney GL, Mariani A and Podratz KC: Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial cancer. *Gynecol Oncol* 127: 5-10, 2012.
- Bertelsen K, Ortoft G and Hansen ES: Survival of Danish patients with endometrial cancer in the intermediate-risk group not given postoperative radiotherapy: The Danish Endometrial Cancer Study (DEMCA). *Int J Gynecol Cancer* 21: 1191-1199, 2011.
- Franks AL and Slansky JE: Multiple associations between a broad spectrum of autoimmune diseases, chronic inflammatory diseases and cancer. *Anticancer Res* 32: 1119-1136, 2012.
- Racanelli V, Prete M, Minoia C, Favoino E and Perosa F: Rheumatic disorders as paraneoplastic syndromes. *Autoimmun Rev* 7: 352-358, 2008.
- Bahat G, Kamali S, Saka B, Erten N, Karan MA and Tascioglu C: Paraneoplastic arthritis may mimic rheumatoid arthritis with symmetrical and upper extremity predilecting presentation. *J Clin Rheumatol* 15: 319-320, 2009.
- Hellgren K, Iliadou A, Rosenquist R, Feltelius N, Backlin C, Enblad G, Askling J and Baecklund E: Rheumatoid arthritis, treatment with corticosteroids and risk of malignant lymphomas: Results from a case-control study. *Ann Rheum Dis* 69: 654-659, 2010.
- Tsai C, Leslie JS, Franko-Tobin LG, Prasnal MC, Yang T, Vienna Mackey L, Fuselier JA, Coy DH, Liu M, Yu C and Sun L: Valproic acid suppresses cervical cancer tumor progression possibly *via* activating Notch1 signaling and enhances receptor-targeted cancer chemotherapeutic *via* activating somatostatin receptor type II. *Arch Gynecol Obstet* 288: 393-400, 2013.

Received October 5, 2013

Revised November 14, 2013

Accepted November 15, 2013