

Ovarian cancer transformation from adenocarcinoma to undifferentiated small cell carcinoma: A case report

ZUO PING HUANG, XING JING LIU, BIN XIN ZOU, QIAN SHEN, YING LIU and TAO ZHOU

Department of Oncology, The Affiliated Wujing Hospital of Guangzhou Medical College,
State Key Laboratory of Respiratory Disease, Guangzhou, Guangdong 510507, P.R. China

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Abstract. The ovaries contain cells that have the capacity for regeneration and cancer stem cells (CSC) that are capable of differentiating aberrantly from the homeostatic controls. The histology of ovarian cancer does not usually change in a patient. However, CSCs are the origin of a number of tumors. CSCs are known to exist in ovarian carcinomas and the expression of CD44, c-Kit and CD133 has been identified in such carcinomas. This study presents the case of a patient diagnosed with ovarian cancer with an abdominal mass who underwent surgery, eight cycles of gemcitabine-paclitaxel chemotherapy and irradiation. Pathological examination indicated a transformation from adenocarcinoma to undifferentiated small cell carcinoma. The expression of CD133 changed from negative to positive in ovarian carcinomas. The present case indicates that any histological changes observed in ovarian neoplasms originate from neoplastic stem cells. In addition, this case demonstrates the importance of repeatedly assessing therapy by tumor biopsy throughout the course of ovarian cancer treatment.

Introduction

It is widely accepted that the histology of ovarian cancer does not change in a patient. However, cancer stem cells (CSCs) are the origin of numerous tumors (1). Ovarian CSCs form spheroids and multicellular colonies that differentiate along epithelial, granulosa and germ cell lineages *in vivo* (2). CSCs have been shown to exist in ovarian carcinomas, and the expression of cluster of differentiation (CD)44, c-Kit and CD133 have been detected in these tumors (1). It appears that the histology of ovarian cancer would be change in the period

of therapy with CSCs existing. To the best of our knowledge, no studies currently exist regarding the transformation of ovarian cancer from one histology into another. In the present study, the ovarian cancer transformed from adenocarcinoma into undifferentiated small cell carcinoma, supporting the hypothesis that CSCs can differentiate into different types of mature neoplastic cells.

Case report

A 27-year-old female presented to The Affiliated Wujing Hospital of Guangzhou Medical College (State Key Laboratory of Respiratory Disease, Guangzhou, Guangdong, China) with an abdominal mass in April 2011. Computed tomography (CT) revealed a large intraperitoneal cystic mass and ascites. The patient presented with abdominal pain, but no fever. Complete blood count, and liver and renal function test results were normal. An ascites sample obtained by abdominocentesis tested positive for adenocarcinoma. The patient underwent surgery in June 2011, and multiple pelvic nodules, a large intraperitoneal cystic mass with ovarian involvement and an abdominal peritoneal implant, measuring 1.0 cm in diameter, were found. The inguinal and retroperitoneal lymph nodes were negative for cancer cell invasion. The pathological analysis of the mass indicated moderately-differentiated adenocarcinoma (Fig. 1). The patient was diagnosed with ovarian cancer, stage IIIB T3bN0M0, according to the International Federation of Gynecology and Obstetrics staging system (1988) (3). The patient was treated with combination chemotherapy consisting of platinum and paclitaxel. This chemotherapy regimen involved the administration of paclitaxel (120 mg, i.v.) followed by platinum (120 mg) every three weeks for six cycles. The treatment outcome was evaluated as a partial response after 18 weeks. The abdominal mass recurred, and the patient underwent surgery in June 2012. The pathology of the mass indicated a poorly-differentiated adenocarcinoma in February 2012 (Fig. 2). The ovarian carcinoma cells were negative for CD133 expression. The patient was treated with two cycles of gemcitabine-paclitaxel chemotherapy. Tumor biopsy results indicated an undifferentiated small cell carcinoma and positive CD133 expression in the ovarian carcinoma cells (Figs. 3 and 4). Positron emission tomography-CT revealed evidence of extensive metastatic disease in the neck, thoracic lymph nodes and liver, nodules

Correspondence to: Miss. Bin Xin Zou, Department of Oncology, The Affiliated Wujing Hospital of Guangzhou Medical College, State Key Laboratory of Respiratory Disease, 268 Yan ling lu, Guangzhou, Guangdong 510507, P.R. China
E-mail: 331743043@qq.com

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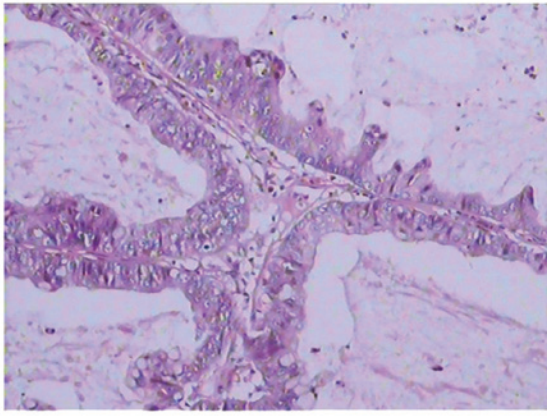


Figure 1. Pathology indicating moderately-differentiated adenocarcinoma.

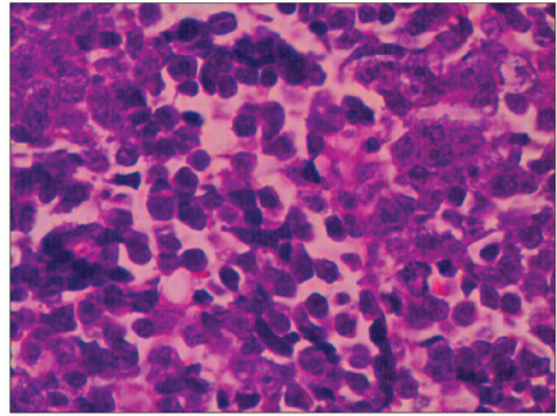


Figure 3. Tumor biopsy results indicating undifferentiated small cell carcinoma.

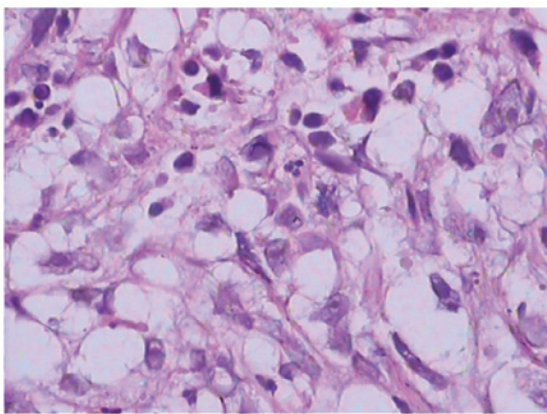


Figure 2. Pathology indicating poorly-differentiated adenocarcinoma.

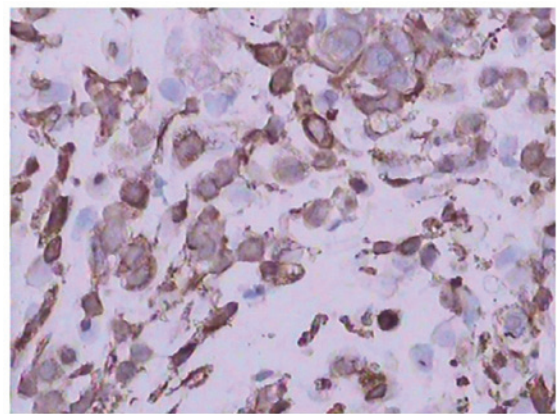


Figure 4. Positive cluster of differentiation 133 expression in the ovarian carcinoma cells.

along the diaphragm, and multiple pelvic nodules (Fig. 5). Whole abdomen irradiation was administered at a dose of 46 Gy (23 fractions) in May 2012, however, the patient succumbed to the disease in September 2012.

Written informed consent was obtained from the patient's parents for publication of this study. The study was approved by the Ethics Committee of the Affiliated Wujing Hospital of Guangzhou Medical College.

Discussion

Histologically, ovarian neoplasms are epithelial tumors, germ cell tumors, sex cord stromal tumors and other tumors with the same underlying characteristics, and the histology does not change. Stem cells have the potential for multidifferentiation and proliferation, and can differentiate into various types of tissues, such as adipocytes, osteocytes and chondrocytes (4).

It is widely accepted that neoplastic stem cells can differentiate into different types of mature neoplastic cells. Multifactorial mechanisms for network formation result in tumorigenesis in cancers and sarcoma by the activation or deactivation of signaling pathways (5,6). In the present study, the pathology indicated a change from moderately-differentiated adenocarcinoma to poorly-differentiated adenocarcinoma, and to undifferentiated small cell

carcinoma. The expression of CD133 changed from negative to positive in the ovarian carcinoma cells. This indicated that the ovarian carcinomas possessed high proliferative potential and clonogenic efficiency, with stem-like characteristics.

We hypothesize that neoplastic stem cells can differentiate into several types of mature neoplastic cells, with synaptophysin as a marker for adenocarcinoma, small cell cancer and undifferentiated carcinoma, following chemotherapy. Tumor cells exhibit potential directional differentiation from one type of cell to another through cell transformation induced by cell signaling pathway activation or deactivation (2). This finding is supported by the previously reported dedifferentiation of mature goblet cells elicited by Wnt/ β -catenin pathway activation (7).

If a signal pathway is terminated or weakened by medicine or other interventions, such as pre-operative chemotherapy, radiation, its impaired function would be replaced by other signaling pathways (8). This is a likely cause of the change in malignant pathological type following treatment. In the present study, the mass was complete resected by surgery and no residual tumor tissue was left. The biopsy results showed a different pathology at all incidences of tumor progression following surgery or the different chemotherapy regimens. Considerable evidence supports the ability of neoplastic stem cells to differentiate into various types of mature tumor cells (1).

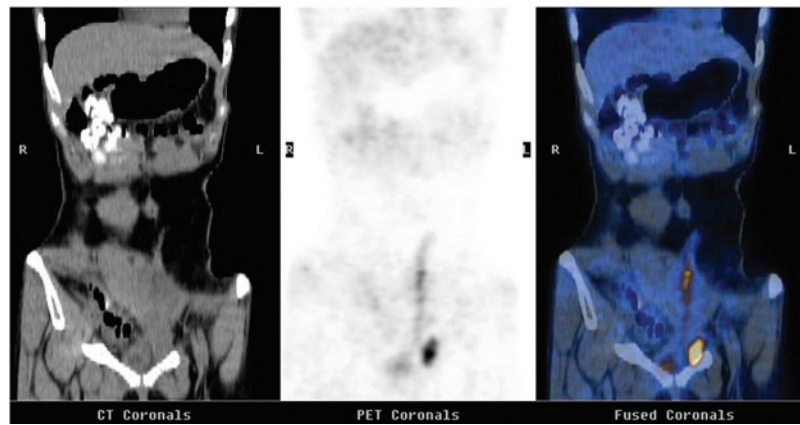


Figure 5. Positron emission tomography-computed tomography results revealing extensive metastatic disease in the neck, thoracic lymph nodes and liver, nodules along the diaphragm, and multiple pelvic nodules.

It is tempting to speculate that chemotherapy may result in differentiation into one particular type of mature tumor cell, which could lead to a shift in the phenotypical appearance. The neoplastic stem cell genotype and phenotype may evolve dynamically under the selective pressure of pre-operative chemotherapy, radiation, and targeted therapy (2).

In the present study, the malignancies exhibited pathological changes following chemotherapy. This finding is supported by previous observations of chemotherapy-resistant tumors that transformed from non-small cell lung cancer (NSCLC) into SCLC (9), which was attributable to a genetic or epigenetic event that concurrently led to a shift in phenotypic appearance. To the best of our knowledge, the genetic resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors has persisted, as EGFR genetic mutations resulted in the transformation of NSCLC to SCLC (10,11).

The present study indicated that epithelial tumors, germ cell tumors, sex cord stromal tumors and other tumors may histologically originate from neoplastic stem cells in ovarian neoplasms. This study also demonstrates the importance of repeatedly checking the appropriate therapy by tumor biopsy throughout the course of ovarian cancer progression.

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