

Case Report

Low-grade endometrioid carcinoma of the ovary associated with undifferentiated carcinoma: case report and review of the literature

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Abstract: The association of low-grade endometrioid carcinoma with undifferentiated carcinoma (UC) was first reported in endometrium carcinoma, termed with dedifferentiated carcinoma (DC). However, the coexistence of low-grade endometrioid carcinoma (LGEC) or serous carcinoma (LGSC) with UC has received minimal attention in ovary, and the behavior of this kind of neoplasm remains at further discussion. In this study, we reported a case of low-grade ovarian endometrioid carcinoma associated with UC and reviewed another four cases previously reported. We found a histological continuity between the LGEC and UC components in H&E section, which suggested a dedifferentiation from LGEC to UC components. In summary, this kind of pathological type has aggressive behavior and these patients have very poor prognosis regardless of the amount of undifferentiated carcinoma.

Keywords: Ovarian carcinoma, undifferentiated carcinoma, dedifferentiated carcinoma, low-grade endometrioid carcinoma

Introduction

Undifferentiated carcinoma (UC) of the female genital tract, mostly reported in the endometrium or ovary, is a clinically aggressive neoplasm accounting for 4% to 5% of all primary ovarian malignancies [1]. The association of low-grade endometrioid carcinoma (LGEC) with UC was first reported in endometrium carcinoma, termed with dedifferentiated carcinoma (DC) by Sliva et al [2]. Few publications have focused on the coexistence of low-grade endometrioid carcinoma (LGEC) or serous carcinoma (LGSC) with UC in ovary. In this report, we present a case of low-grade ovarian endometrioid neoplasm that is associated with UC, and four cases with follow-up data previously published are also reviewed here.

Case report

Clinical information

A 63-year-old postmenopausal Chinese woman without any notable past or familial history was

admitted to our hospital because of an abdominal mass for about half a month. Laboratory investigation showed a serum CA125 level of 542.5 U/mL (normal, < 35 U/mL). Levels of CA19-9 and HE4 (Human epididymis protein 4) were within normal limits. A pelvic ultrasound demonstrated a large cystic and solid mass (70 × 79 × 68 mm) filling the abdominopelvic space. No other neoplastic lesions were identified in the lungs, liver, gallbladder, and pancreas by chest X ray and abdominal ultrasound.

The patient consented to proceed with surgery and tumor samples were sent for intra-operative consultation. Frozen section revealed an adenocarcinoma in the right ovary and further tumor subtyping was deferred for permanent paraffin-embedded sections. The patient then underwent total hysterectomy with bilateral salpingo-oophorectomy, omentectomy, pelvic lymphadenectomy and appendectomy. After the operation, the patient received 2 courses of paclitaxel liposome (210 mg/m²) and carboplatin (300 mg/m²) or paraplatin (390 mg/m²) therapy. The patient could not tolerate the third

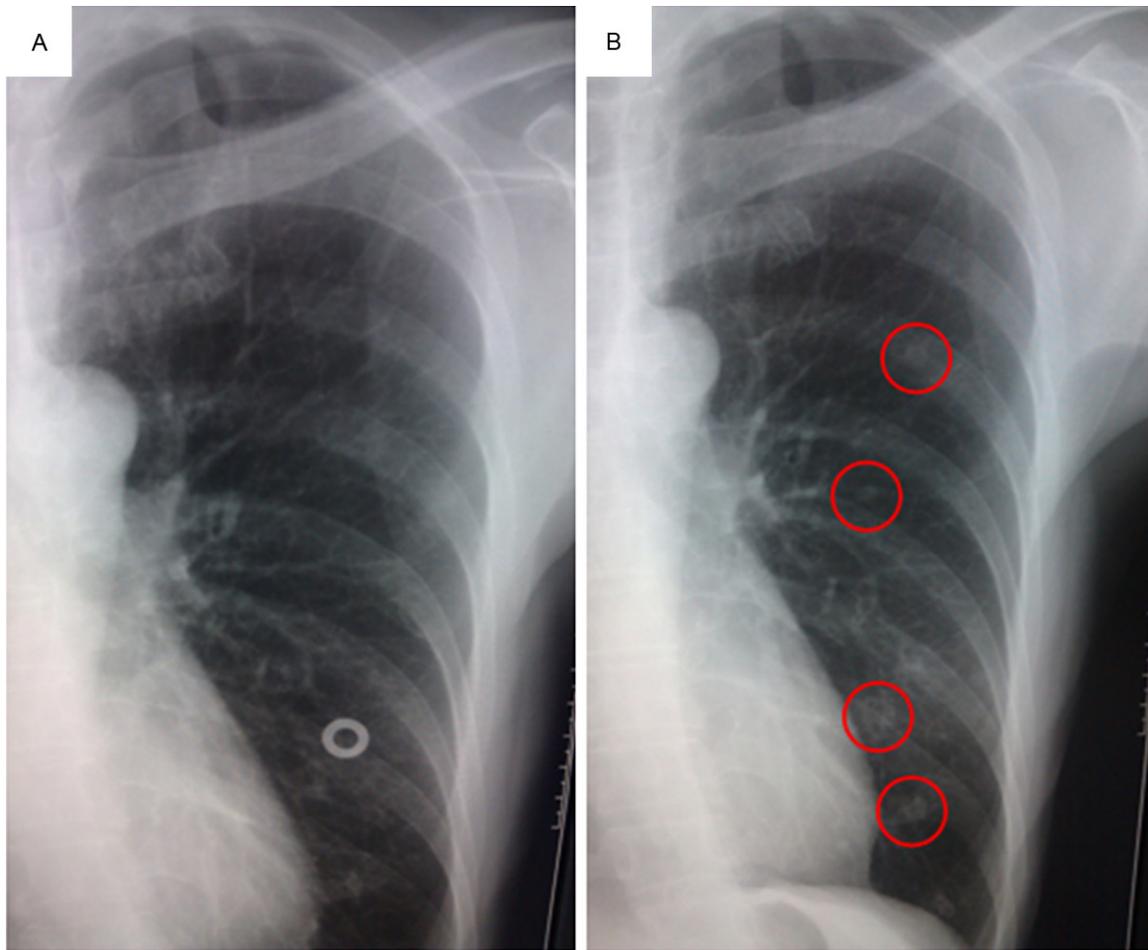


Figure 1. The comparison of X-ray photograph of the chest before surgery (A) and after surgery for one month (B), the metastases foci were indicated by red circles.

course of chemotherapy because of poor physical condition. Computed tomography (CT) scan and chest X ray showed several scattered enhancing foci (likely metastasis) in liver and both lungs (**Figure 1**) one month after surgery, and metastases foci in kidney after five month. The patient died seven month after surgery.

Pathology findings

Macroscopically, the right ovary specimen showed a mass with focal rugged surface. The mass was $9.5 \times 7 \times 6$ cm and the cut surface showed a both solid and cystic components. The solid part was about 6.5 cm in maximum diameter with soft yellowish gray appearance. The multilocular cystic contained clear fluid in some cysts and mucus in another cysts, the thickness of cyst wall ranged from 0.2 cm to 0.8 cm.

Microscopically, the tumor was composed of both LGEC and UC (**Figure 2A, 2B**). The percentage of LGEC and UC in this tumor was estimated as about 30% and 70%, respectively. The UC component lack of glandular differentiation. Instead, it is composed of diffuse sheets of neoplastic cells with enlarged and markedly atypical nuclei, often with prominent nucleoli, and moderate to abundant cytoplasm (**Figure 2C**). High mitotic rate and large areas of necrosis were observed. Vascular invasion was found in the H&E section (**Figure 2D**) and proved by CD31 stain (**Figure 2E**). Lymphovascular invasion or perineural invasion was not observed in H&E section or D2-40 staining section. The LGEC exhibited a mixed papillary and glandular architecture (**Figure 2A, 2B**) with bland nuclei and little mitotic activity. The morphological transition from papillary proliferation to glandular proliferation lined by columnar epithelium

LGEC associated UC in ovary

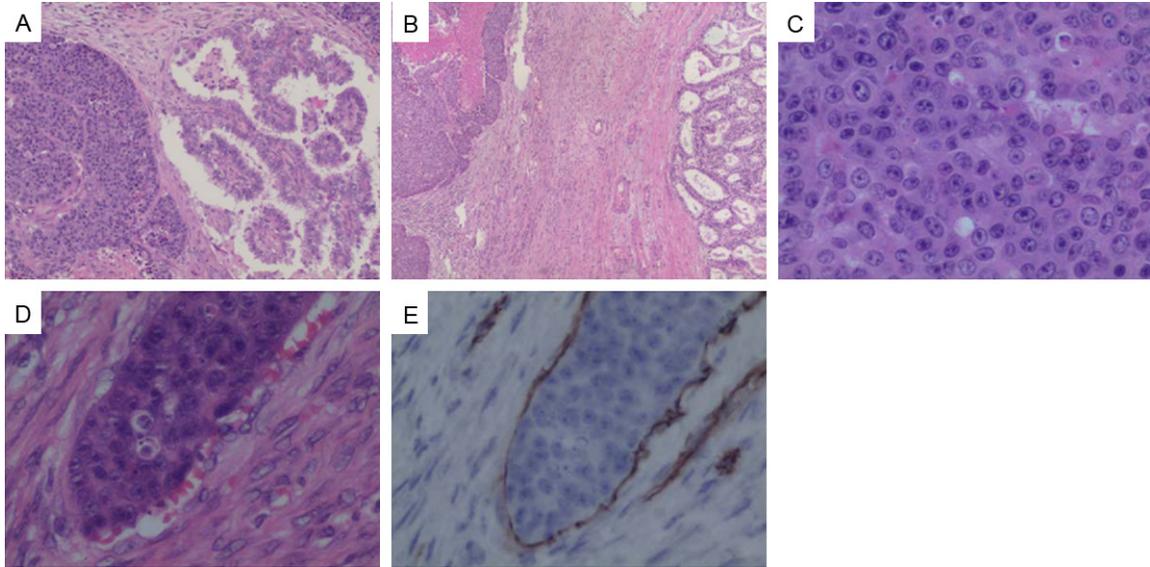


Figure 2. The tumor showed an admixture of well-differentiated endometrioid carcinoma (EC, G1) and undifferentiated carcinoma (UC) (A and B). The EC exhibited a mixed papillary (A) and glandular architecture (B) with bland nuclei and little mitotic activity. The component of UC was composed of diffuse sheets of cells without glandular differentiation (left panel in A and B), often with prominent nucleoli, and moderate to abundant cytoplasm (C). Vascular invasion was found in the H&E section (D) and be proved by CD31 stain (E). (A, B) H&E, 100 \times ; (C-E) H&E, 400 \times .

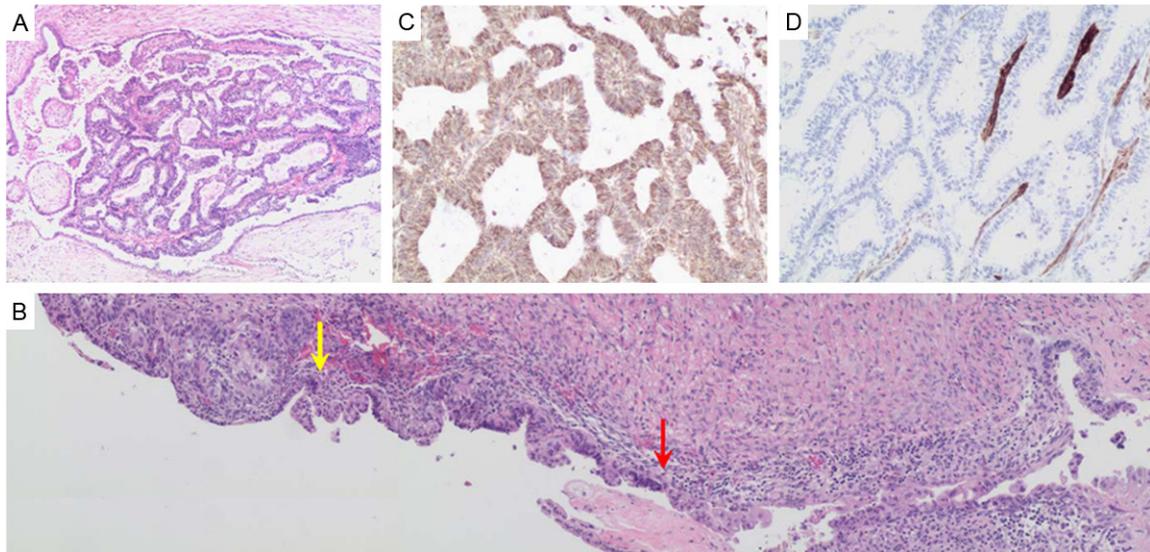


Figure 3. The morphological transition from the broad papillary structure to glandular structure lined with columnar epithelium. And the gland displayed low-grade cytologic features with sharp luminal margins and prominent sub- and supranuclear vacuolization (A). The progression was observed from endometriosis (the right of the red arrow) to atypical endometriosis (between the red and the yellow arrow) to LGEC (the left of the yellow arrow) (B). Vimentin was diffuse positive on the membrane of EC component (C). CD10 was focal positive in the stroma of EC part (D). (A) H&E, 40 \times , (B) H&E, 100 \times ; (C, D) IHC, 100 \times .

with sharp luminal margins were observed in some areas (**Figure 3A**). Progressions from endometriosis to atypical endometriosis to LGEC were also observed in the sections (**Figure 3B**). Detailed histologic examination

revealed histological continuity between the LGEC and UC components (**Figure 4**).

The neoplasm involved the serosal surface of the right fallopian tube and appendix and right

LGEC associated UC in ovary

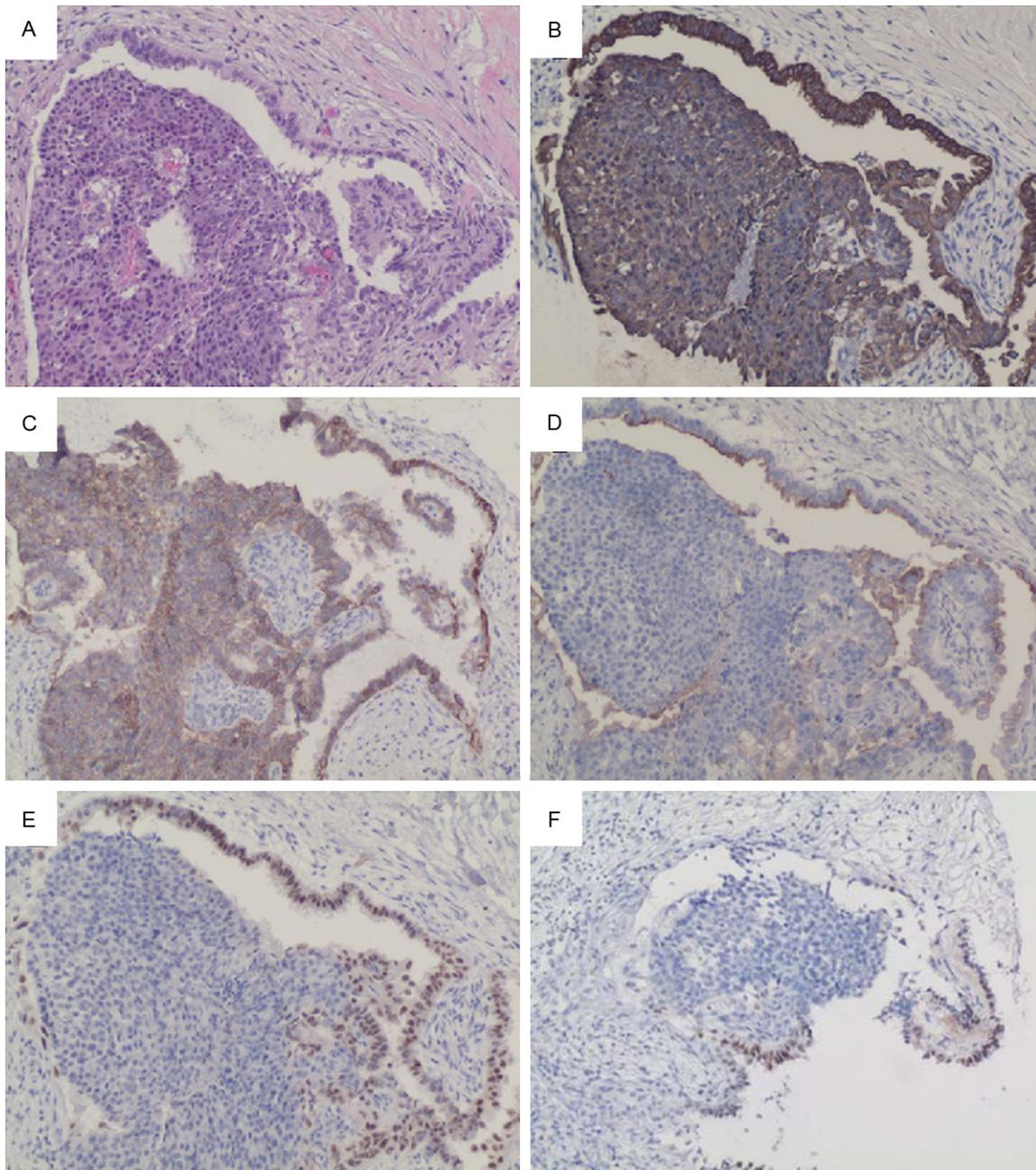


Figure 4. Histological continuity between the LGEC and the UC components (A). Both EC and UC component were immunoreactivity for CK8/18 (B) and Ber-EP4 (C), EMA expression (D) was more marked in EC than UC component. PAX-8 (E) and ER (F) were only expressed in EC component. (A) H&E, 100 \times ; (B-F) IHC, 100 \times .

side of pelvic wall. However, no metastasis was found in pelvic lymph nodes (0/10).

Immunohistochemistry

Deparaffinized sections were immunostained by streptavidin-peroxidase (SP) method. The primary antibodies used and the results of immunohistochemistry are summarized in **Table 1**.

Both LGEC and UC component were immunoreactive for CK8/18 and Ber-EP4. The LGEC component was stained more strongly for epithelial membrane antigen (EMA), E-cadherin and Vimentin than the UC component. PAX-8, CA-125, ER and PR were only expressed in LGEC component, CD10 were partially expressed in the stroma of LGEC component (**Figures 3C, 3D and 4**).

LGEC associated UC in ovary

Table 1. Antibodies used and summarized results of immunohistochemistry

Antibodies	EC	UC	Antibodies	EC	UC
CK8/18	+	+	E-cadherin	Strong +	Weak +
Ber-EP4	+	+	Syn	-	30% +
EMA	+	Focal +	P16	Patchy +	+
PAX-8	+	-	P53	-	-
CA-125	+	-	Ki-67	20-30% +	80% +
ER	40% +	-	TTF-1	-	-
PR	Focal +	-	CK20	-	-
Vimentin	+	Partial +	WT-1	-	-
CD10	Focal stromal +	-	PTEN	-	-

EC, endometrioid carcinoma; UC, undifferentiated carcinoma.

Discussion

According to the WHO criteria, UC of the ovary has been histologically defined as a tumor showing solid growth of pleomorphic cells with no differentiation or only small foci of differentiation [1]. Silva et al [2] reported that UC of the endometrium or ovary frequently showed immunoreactivity for both epithelial (i.e. cytokeratin and EMA) and mesenchymal (i.e. vimentin) markers. In our case, a portion of the neoplasm was composed of diffuse sheets of cells without any glandular differentiation. Both epithelial and mesenchymal differentiation (as confirmed by the diffuse immunoreactivity for CK8/18, Ber-EP4, focal for EMA and scattered for vimentin, respectively) were seen in the solid component; therefore, the histomorphology and immunohistochemistry profile of the solid component are consistent with UC. The other portion of the tumor showed a mixed papillary and glandular morphology displayed low-grade cytologic features with bland nuclei and little mitotic activity, which was difficult to be classified as LGEC or LGSC. After careful observation of the sections, endometriosis and the progression from endometriosis to atypical endometriosis to EC were also observed in the sections. In over one third of cases have led many to consider endometriosis is a likely precursor of endometrioid carcinoma [3]. Though the papillary structure was prone to consider as LGSC or serous borderline tumor (SBT), the broad papillae lined with columnar epithelium instead of numerous thin papillae with scanty fibrovascular core were support the diagnosis of EC. In addition, positive staining of ER, PR and vimentin, negative staining of WT-1, PTEN,

and focal stromal immunoreactivity for CD10 were also consistent with EC. Thus, histopathological diagnosis of low-grade endometrioid carcinoma (Grade 1) associated with undifferentiated carcinoma was made.

To our knowledge, in the English literature there have been less than five published cases of low-grade ovarian carcinoma associated with UC, which was summarized in **Table 2**. As shown in **Table 2**, this type of malignancy has aggressive behaviors and

these patients have very poor prognosis, but the patient survival was not in proportion to the amount of UC [2, 4]. Silva et al [2] conceived that even when the UC represented only 20% of the entire tumor, the neoplasm had an aggressive behavior. In our case, the lung metastases were detected right after only one month of surgery, signifying the rapid progression of the disease. Therefore, the recognition of UC in an otherwise low-grade carcinoma of ovarian (such as endometrioid carcinoma (EC), serous borderline tumor (SBT), LGSC et al) is extremely important because it indicates aggressive behavior.

Miyai et al [5] reported a case of massive intra-abdominal UC derived from a tiny well-differentiated EC of the ovary. Allelotype analysis using 24 polymorphic markers located on 12 chromosomal arms showed that the intra-abdominal UC and ovarian adenocarcinoma components had a high concordance rate (88%) of allelic patterns lineage. Sliva et al [2] also reported 6 cases of UC were diagnosed in recurrence lesion (vagina, pelvis or liver) after the resection of an EC from the endometrium or ovary. It is important to be aware of the possibility of transformation because the histological features of the recurrence tumor are different from those of the primary lesion. So far the best accepted explanation for the transformation is that the undifferentiated component arises from low-grade carcinoma through a process of dedifferentiation. The phenomenon of dedifferentiation has been recognized in several tumors including endometrium carcinoma [6-9] and thyroid cancer. But, no histological continuity between these components has

LGEC associated UC in ovary

Table 2. Summary of the reported cases of undifferentiated carcinoma associated with low grade ovarian carcinoma

Case	Age (y)	Tumor pathological type	Tumor stage	Follow-up	Recurrence/metastases
Silva et al [2]	NA	EC (G2) (40%) + UC (60%)	IV	DOD 12m	NA
Silva et al [2]	NA	EC (G1) (70%) + UC (30%)	IV	DOD 5m	NA
Silva et al [2]	NA	EC (G1) (20%) + UC (80%)	I	DOD 28m	NA
Boyd et al [4]	41	SBT + LGSC + UC	IV	DOD 6m	NA
Our case	63	EC (G1) (30%) + UC (70%)	IV	DOD 7m	Lung, liver and kidney

EC, endometrioid carcinoma; G, grade; UC, undifferentiated carcinoma; SBT, serous borderline tumor; LGSC, low-grade serous carcinoma; DOD, died of disease; m, months; NA, not available.

been reported to suggest an origin of the UC from low grade carcinoma. In our case, after detailed histological examination, we found a focal histological continuity between the LGEC and UC components in H&E sections, and immunostaining results also provide support for the presence of two separated LGEC and UC components that are next to each other (**Figure 4**).

In summary, the tumor of ovary with UC pathological type has high aggressive behavior and these patients have very poor prognosis regardless of the amount of undifferentiated carcinoma. As a pathologist, it is important to be aware of the possibility of transformation because the histological features of the recurrence tumor are different from those of the primary lesion.

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Disclosure of conflict of interest

None.

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