

Case Report

Clinicopathologic study of endometrial dedifferentiated endometrioid adenocarcinoma: a case report

Yan Shen¹, Ying Wang¹, Yuquan Shi¹, Jinsong Liu², Yixin Liu¹

¹Department of Pathology, Tianjin Central Hospital of Gynecology and Obstetrics, Tianjin, China; ²Department of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

Received November 30, 2011; accepted December 20, 2011; Epub January 1, 2012; Published January 15, 2012

Abstract: In 2006, dedifferentiated endometrioid adenocarcinoma (undifferentiated carcinoma associated with low-grade endometrioid carcinoma) of the uterus was first proposed. Dedifferentiated endometrioid carcinoma is part of the spectrum of undifferentiated carcinoma of the endometrium which is a highly aggressive tumor even when the undifferentiated component represents only 20% of the entire neoplasm. Therefore, accurate diagnosis and appropriate classification of this neoplasm are important in patient management. Lack of the recognition may lead to misclassification of dedifferentiated endometrioid adenocarcinoma as a pure endometrioid adenocarcinoma which is less aggressive. Only 4 papers have appeared in the literature so far on the topic of dedifferentiated endometrioid carcinoma. We report herein a first case of endometrial dedifferentiated endometrioid carcinoma in a 51-year old woman in Chinese population. We performed immunoperoxidase studies for 12 markers. Among them, cytokeratins, keratin 7, keratin 18, EMA, estrogen receptor (ER), progesterone receptor (PR), and vimentin show significantly differential expression between differentiated and undifferentiated area.

Keywords: Endometrium, dedifferentiated endometrioid adenocarcinoma, undifferentiated carcinoma, endometrioid adenocarcinoma

Introduction

Dedifferentiation was first described in bone and soft tissue tumors, then this phenomenon has been recognized in several epithelial malignancies, such as salivary glands, thyroid, pulmonary and kidney. It was until 2006 that dedifferentiated endometrioid adenocarcinoma (DEAC) of the uterus or ovary was described by the MD Anderson group for the first time [1]. It has been accepted that once dedifferentiation occurs, the neoplasm behaves in a more aggressive fashion. Therefore, it is important to accurately diagnose and appropriately classify this neoplasm and guide the clinical care of these patients.

DEAC of the uterus or ovary was defined as "combined undifferentiated and differentiated carcinomas". This tumor is characterized by the coexistence of an undifferentiated carcinoma (UC, a proliferation of medium size monotonous epithelial cells with no glandular differentiation growing in a patternless solid fashion) and low

grade endometrioid adenocarcinoma (most commonly FIGO grade 1 or 2). It is an aggressive tumor even when the UC component represents only 20% of the entire neoplasm [1]. This admixed carcinoma has not been widely recognized because the solid areas of UC have usually been misdiagnosed as solid of FIGO grade III endometrioid adenocarcinoma.

In this study, for the undifferentiated component, we used the definition proposed by Silva et al from the MD Anderson group, i.e., "a malignant epithelial neoplasm arising in the endometrium or ovary characterized by a total absence of nests, papillae, glands or trabeculae, lack of squamous or mucinous metaplasia, lack of a spindled growth pattern with a patternless solid, sheet-like growth of tumor cells, with absent or minimal neuroendocrine differentiation (<10%)" [1, 5]. We used the FIGO grading system for the endometrioid carcinoma, which is based on architectural features. Thus, grade 1 tumors have up to 5% of solid areas, grade 2

tumors have 6 to 50% of solid areas, and grade 3 tumors have more than 50% of solid areas of endometrioid adenocarcinoma. It was been emphasized that the cells in the solid areas of endometrioid adenocarcinoma should be similar to the cells in the glandular areas.

Here we report a recent case of DEAC of the uterus in Chinese population.

Case report

Clinical information

A 51-year-old woman complained that menstrual volume had been increased for 8 years. Physical examination showed the uterus enlarged slightly. Ultrasound demonstrated the endometrial thickness was significantly increased to 16.3 mm without extra uterine extension. She underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. After surgery, she was given vaginal radiation therapy and adjuvant chemotherapy including cisplatin, docetaxel and taxanes. The patient has been diagnosed for 11 months, her general condition was poor, but no evidence for recurrence.

Gross findings

The uterus was attached with macroscopically unremarkable fallopian tubes and ovaries, measuring 11 × 8 × 5.5 cm. Endometrium of the right uterine corner presented as a fleshy and decayed grey-white plaque, measuring 3.5 × 3 × 0.9 cm. The surface of plaque was shaggy and irregular. On sectioning, the tumor had invaded superficial myometrium, measuring 0.5 cm. The remaining endometrium was unremarkable.

Microscopic findings

In this case, the better-differentiated component was composed of low-grade (FIGO grade 1 to 2) endometrioid carcinoma which constituted 80% of the total tumor volume. The UC component (20% of the entire tumor) was characterized by the solid growth of tumor cells, without any evidence of gland formation, trabecular or nested growth pattern. The cells in the UC had a monomorphic appearance, presented as sheets of dyshesive round to ovoid cells with prominent eosinophilic nucleoli, coarse chromatin, signifi-

cant atypia and numerous mitotic figures, which was separated by delicate fibrovascular septa. Compared with the cells in the areas of endometrioid adenocarcinoma, they showed more variation in their size and shape. Foci of tumors presented marked nuclear pleomorphism or vague spindling cells, but they were in a background of uniform cells as described above and no overtly sarcomatous component was proved. The transition between these two components was abrupt with a sharp border (Figure 1A-F).

The endometrium was associated with complex atypical hyperplasia. Both undifferentiated components and differentiated components had infiltrated less than one-half of the myometrial thickness. The cervical stroma was involved by the differentiated component. No lymph node or ovarian metastases were found. According to the FIGO system, this case presented at FIGO stage II.

Immunohistochemical results

Using the EnVision method, immunoperoxidase studies were performed for the following markers: cytokeratins, cytokeratin 7 (CK7), cytokeratin 18 (CK18), epithelial membrane antigen (EMA), ER, PR, P16, vimentin, synaptophysin (Syn), chromogranin A (CgA), SMA and desmin. The differentiated components expressed strongly and diffusely positive with cytokeratins, CK7, CK18, EMA, ER and vimentin. On the contrary, the adjacent undifferentiated areas are negative for EMA and ER expression, weakly for vimentin expression. Cytokeratins, CK7 and CK18 are focally positive (<5%), but the intensity was strong. In addition to these markers, PR, P16, CgA, Syn, SMA and desmin showed a consistent expression between the differentiated and undifferentiated areas. It meant that P16 was focally positive, CgA, Syn, SMA and desmin were negative in both areas. Only PR showed a lower positive rate in the undifferentiated areas than in the differentiated areas (Figure 1G-J).

Discussion

Since 2006 DEAC (UC associated with low-grade endometrioid carcinoma) of the uterus or ovary was proposed by Silva et al [1]. DEAC is part of the spectrum of UC of the endometrium or ovary. The presence of even a small undifferentiated component in tumors appears to be asso-

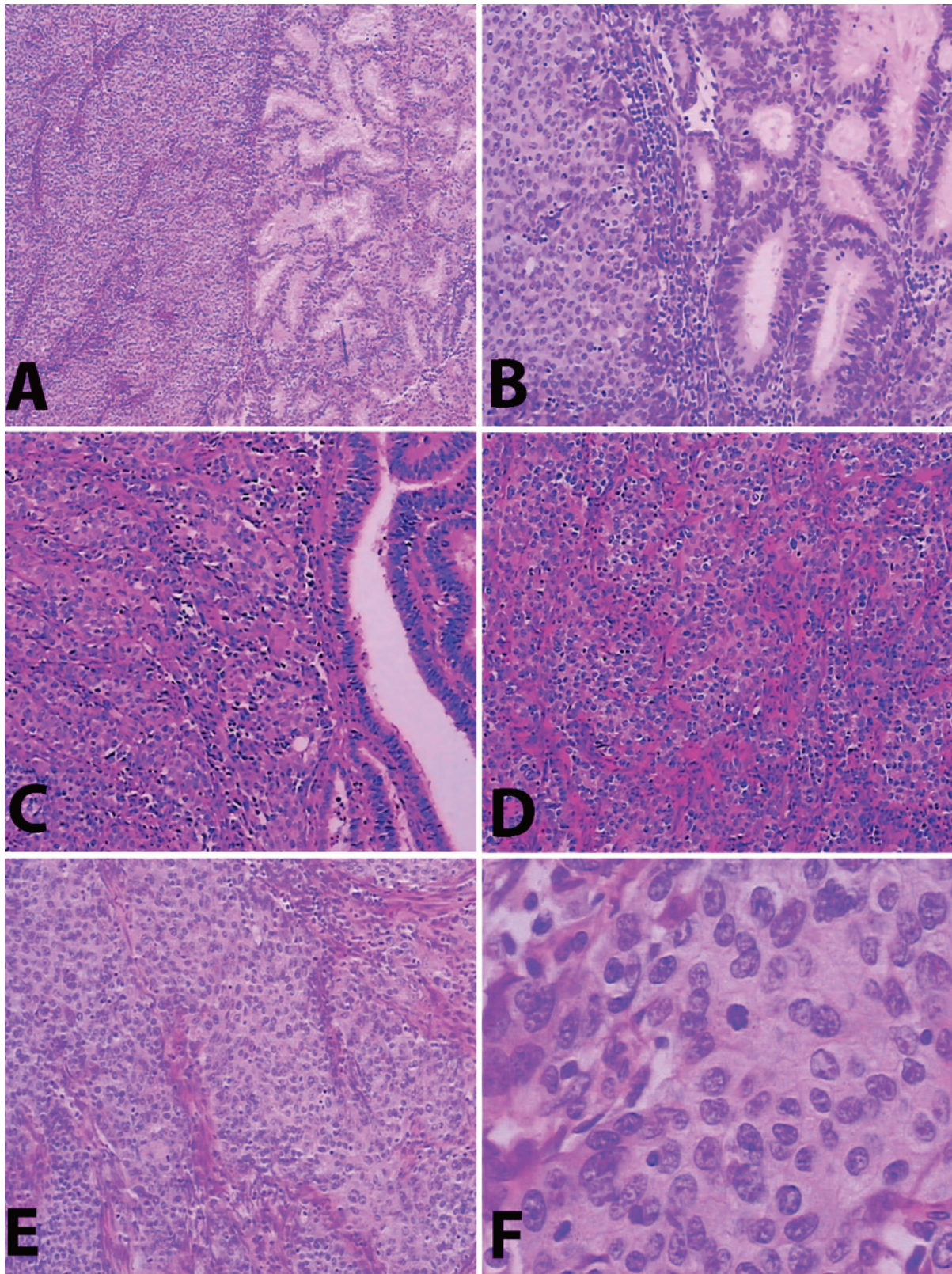


Figure 1: (Continued to next page)

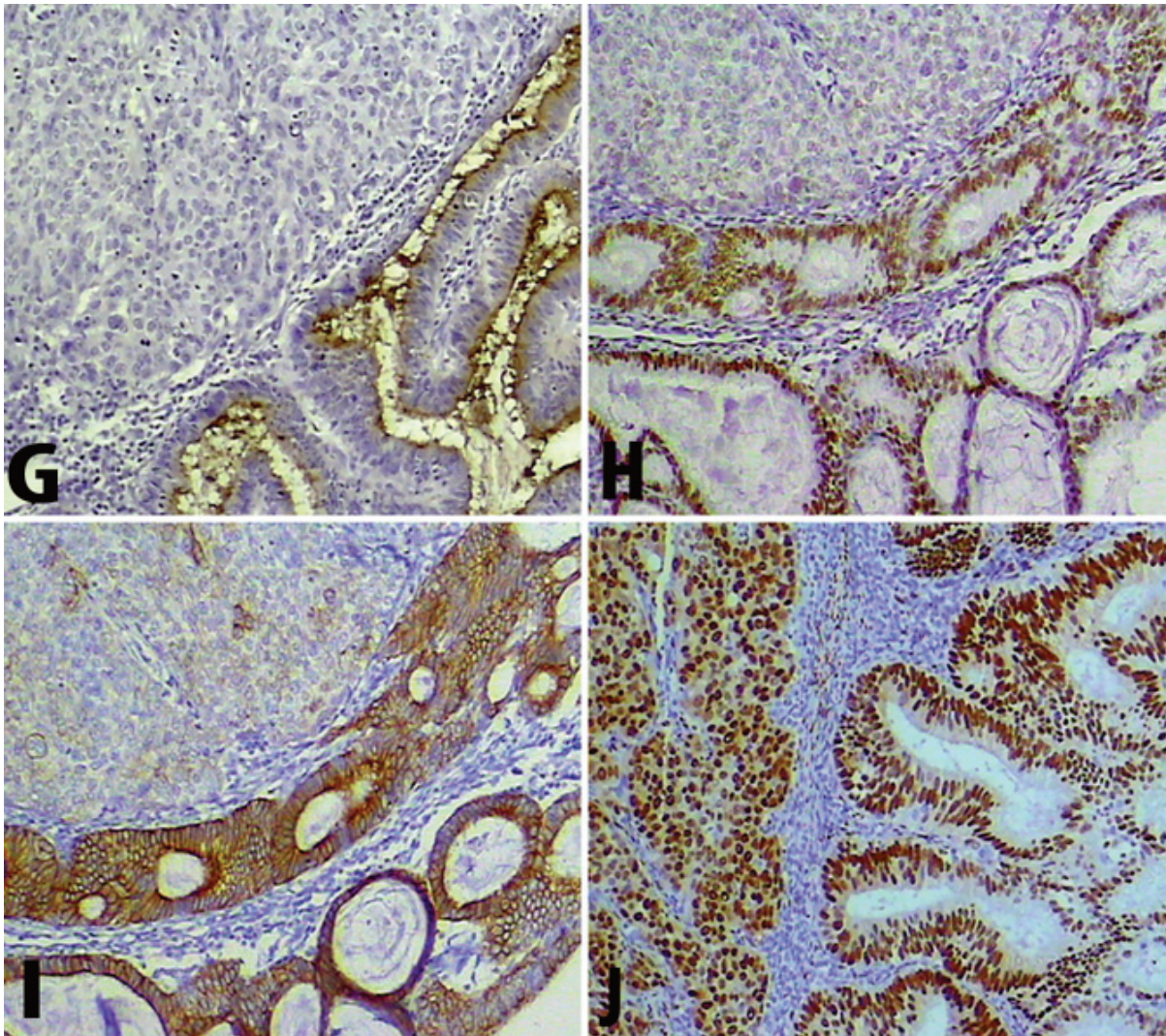


Figure 1. Dedifferentiated endometrioid adenocarcinoma (H&E, A-F). The tumor is composed of low-grade endometrioid carcinoma and undifferentiated carcinoma with a sharp border (A-C, A and B 40 $\times$, C 100 $\times$). In the undifferentiated areas, the tumor cells presented as sheets of dyshesive round to ovoid cells with prominent eosinophilic nucleoli, coarse chromatin, significant atypia and numerous mitotic figures, which was separated by delicate fibrovascular septa (D-F, D and E 100 $\times$, F 400 $\times$). Immunohistochemical features (EnVision, G-J, 100 $\times$). The differentiated components express strongly, diffusely positive with EMA (G) and ER (H), on the contrary, the adjacent undifferentiated areas show almost complete loss of expression of these markers. Strong, diffuse staining for cytokeratins is presented in the differentiated components, but with focal and strong staining in the undifferentiated areas (I). Both the differentiated and undifferentiated areas show strongly positive staining for PR, but the positive cells of the undifferentiated areas was much lower (J).

ciated with poor clinical outcomes [1]. Although recently pathological books and reviews on carcinomas of the uterine corpus have mentioned this type, due to lack of proper recognition, so far there are only 4 articles on the topic of DEAC [1-4]. Two of them are from the MD Anderson Cancer center of USA, the other two from two different hospitals in Italy, no report from Asia or

Chinese population.

The WHO classification describes endometrial undifferentiated carcinomas as “malignant poorly differentiated endometrial carcinomas of lacking any evidence of differentiation” [5], without any further morphologic characteristics. The FIGO grading system of endometrial endo-

metrioid adenocarcinoma is based on architectural features, basically the amount of nonmucinous solid component in a tumor, no details about the histological features of the solid component. Therefore, the above vague definition about the appearance of the tumor cells in the solid areas can lead to misclassification of admixed carcinoma (i.e. DEAC) as a pure endometrioid adenocarcinoma. Subsequently, based on the FIGO grading criteria, it is misinterpreted as grade 1-3. If grade 3 nuclear features (marked nuclear polymorphism, coarse chromatin, prominent nucleoli) present in the majority neoplastic cells in architecturally grade 1 or 2 tumors, we usually increase their grade by 1. But the prognosis is significantly different between DEAC and high grade endometrioid adenocarcinoma.

In order to proper recognition of DEAC requires more attention to histological and cytological features of endometrial undifferentiated carcinoma. Recently, Silva et al has reported that selected endometrial undifferentiated carcinomas have reproducible morphologic features and provided the diagnostic criteria as mentioned before. It has been emphasized that the characteristic of UC is a distinctive, patternless proliferation of small to medium sized, uniform, dyshesive cells, sometimes with absent or minimal expression of neuroendocrine markers and foci of abrupt keratinization or rhabdoid cells [6]. Basing on this criteria, they reviewed 633 consecutive cases of endometrial adenocarcinoma in 2003 and 2004, documented that cases of UC of the endometrium represent 9% of endometrial carcinomas, which is much higher than the previously reported incidence of 1% to 2% [7]. The under recognition of UC could explain the above marked discrepancies of incidence. In their series 71% cases of UC were admixed with endometrioid adenocarcinoma. Therefore, DEAC is not rare. All cases of UC had uniformly poor prognosis, similar to that of pure serous carcinoma and worse than that of pure clear cell carcinoma [6]. The biologic behavior of DEAC is determined by its undifferentiated component; consequently it has the same rapid progression. In our case, the UC component constitutes 20% of the entire tumor, but abrupt keratinization or rhabdoid cells were not presented.

The immunohistochemical features of DEAC are that the differentiated components express strongly positive with keratins, EMA, ER and PR. On the contrary, the adjacent undifferentiated

areas show almost complete loss of expression of these markers [8] or focal staining for keratins and EMA, but the intensity was strong [1, 2]. In addition, these undifferentiated areas can express vimentin [2] and one or more than one neuroendocrine markers such as Syn, CgA and CD56, although is usually very focal (< 10%) [1]. In our case, the immunohistochemical result is similar to the MD Anderson group's finds except PR presents strongly positive in the differentiated and undifferentiated area, just positive rate was different between them.

The morphologic appearance of dedifferentiated endometrioid adenocarcinoma evokes very broad differential diagnoses, which are responsible for frequent misdiagnoses.

Endometrioid adenocarcinoma

The solid components in endometrioid adenocarcinoma are cohesive and often resemble poorly differentiated, nonkeratinizing squamous cell carcinoma. The nuclear features of tumor cells in both the glandular and the solid areas tend to be cytologically similar. The location of the nuclei was usually close to the basal portion of the cells. In contrast, the solid areas in DEAC are characterized by dyshesive cells that grow in a sheet-like pattern, at the same time, the cytologic features of the undifferentiated and differentiated components are distinct. Usually the differentiated components tend to be superficial, whereas the undifferentiated components are deep and invasive into myometrium [8]. The above two components often display an abrupt transition which resembles a collision tumor.

The use of immunohistochemical staining can assist in making this distinction. In the solid areas of DEAC, the expression of keratin and EMA is very focal (< 10% of the tumor cells, but the intensity is marked). In some cases the positive percent of EMA is maybe higher than keratin, but it doesn't present in our case. In contrast, keratin is more diffusely positive in the solid components of endometrioid adenocarcinoma than EMA.

Malignant mixed mullerian tumor (MMMT)

DEAC can be misdiagnosed as MMMT for its false appearance of biphasic. MMMT usually contains high-grade carcinoma, most frequently serous carcinoma. In contrast, the gland forming

components of DEAC are endometrioid and low grade. Meanwhile, the undifferentiated components of it consist of uniform, ovoid, epithelioid cells unlike the sarcomatous components of MMMT, which typically consist of pleomorphic spindle-cell proliferation and present heterologous elements.

Serous carcinomas

The presence of papillae and micropapillae, slit-like compressed spaces, background endometrial atrophy and architectural-cytological asynchrony can also provide clues to the correct diagnosis. DEAC lacks the above features.

Neuroendocrine carcinomas

As mentioned before, the undifferentiated components of DEAC can show focal neuroendocrine features and express neuroendocrine-related markers which is usually very focal (< 10%). In contrast, neuroendocrine carcinoma which is composed of large cell or small cell shows strong and diffuse staining (> 20%) for neuroendocrine markers [8].

High grade sarcoma

When undifferentiated components are the overwhelming majority of DEAC and the lack of focal expression of keratin or EMA can be misinterpreted as an evidence of sarcoma. Most sarcomas in the uterus are composed of spindle cells and have heterologous components. It is unusual for a sarcoma in the uterus to have only epithelioid cells, except for epithelioid leiomyosarcoma. In this situation, desmin, caldesmon, and SMA may help distinguish between them [9], or perform immunostains for keratin and EMA in another tumor block.

In summary, DEAC referred to UC associated with low-grade endometrioid carcinoma is part of the spectrum of UC of the endometrium, which pursues a more aggressive clinical course similar to UC. Undifferentiated components of it may be confused with solid areas of endometrioid adenocarcinoma, erroneously leading to the diagnosis of a less aggressive endometrioid adenocarcinoma. The possibility of DEAC must be kept in mind in the setting of a hard-to-classify endometrial neoplasm. As long as thought of it, this specific entity can be distinguished because of their overtly different morphologic and immunophenotypic features.

Address correspondence to: Dr. Yixin Liu, Department of Pathology, Tianjin Central Hospital of Gynecology and Obstetrics, Tianjin, China. Tel: 86-022-5828-7667, Fax: 86-022-5828-7026, E-mail: yixinliu66@yahoo.com.cn

References

- [1] Silva EG, Deavers MT, Bodurka DC, Malpica A. Association of low-grade endometrioid carcinoma of the uterus and ovary with carcinomas: a new type of dedifferentiated carcinoma? *Int J Gynecol Pathol* 2006; 25: 52-58.
- [2] Silva EG, Deavers MT, Malpica A. Undifferentiated carcinoma of the endometrium: a review. *Pathology* 2007; 39:134-138.
- [3] Vita G, Borgia L, Di Giovannantonio L, Bisceglia M. Dedifferentiated endometrioid adenocarcinoma of the uterus: a clinicopathologic study of a case. *Int J Surg Pathol* 2011; 19: 649-652.
- [4] Giordano G, D'Adda T, Bottarelli L, Lombardi M, Brigati F, Berretta R, Merisio C. Two cases of low-grade endometrioid carcinoma associated with undifferentiated carcinoma of the uterus (dedifferentiated carcinoma): a molecular study. *Pathol Oncol Res* 2011; [Epub ahead of print].
- [5] Silverberg SG, Kurman RJ, Nogales F, Mutter GL, Kubik-Huch RA, Tavassoli FA. Tumors of the Uterine Corpus. Tumors of the Breast and Female Genital Organs: World Health Organization Classification of Tumors. Edited by Tavassoli FA, Devilee P Lyon, France, IARC Press 2003; pp: 227.
- [6] Altrabulsi B, Malpica A, Bodurka DC, Bodurka DC, Broaddus R, Silva EG. Undifferentiated carcinoma of the endometrium. *Am J Surg Pathol* 2005; 29: 1316-1321.
- [7] Nonnett BM, Zaino RJ, Hendric K, et al. Endometrial carcinoma. Blaustein's Pathology of the Female Genital Tract. 5th ed. Edited by Kurman RJ, Ellenson LH, Ronnet BM. New York, Springer-Verlag, 2011, pp. 501-559.
- [8] Tafe LJ, Garg K, Chew I, Tornos C, Soslow RA. Endometrial and ovarian carcinomas with undifferentiated components: clinically aggressive and frequently unrecognized neoplasms. *Modern Pathology* 2010; 23: 781-789.
- [9] Prayson RA, Goldblum JR, Hart WR. Epithelioid smooth-muscle tumors of the uterus: a clinicopathologic study of 18 patients. *Am J Surg Pathol* 1997; 21: 383-391.