Int J Clin Exp Pathol 2013;6(8):1652-1657
www.ijcep.com /ISSN:1936-2625/IJCEP1304036

Case Report

Dedifferentiated endometrial cancer: an atypical case diagnosed from cerebellar and adrenal metastasis: case presentation and review of literature

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Received April 26, 2013; Accepted June 29, 2013; Epub July 15, 2013; Published August 1, 2013

Abstract: Dedifferentiated endometrial cancer (DEC) is microscopically characterized by the presence of high-grade areas emerging from low-grade tumour. DEC is an aggressive tumour even when the dedifferentiated component represents only 20% of the entire neoplasm. A proper histological diagnosis is essential to define the most appropriate therapeutic approach for these tumors, since they are characterized by a particularly aggressive trend and by an extremely poor prognosis. We report a single case of DEC associated with dedifferentiated and adrenal metastasis, for which the patient underwent both abdominal-pelvic and cerebellar surgery. Dedifferentiated carcinoma of the endometrium is a poorly recognized neoplasm since they have not been clearly defined the histological features discriminating this neoplasm from high-grade endometrioid adenocarcinoma. Revising existing literature we found 79 described cases of central nervous system secondary involvement and 13 cases where the onset of the disease was characterized by neurological signs and symptoms. We could only find two reported cases of adrenal metastases originating from endometrial neoplasia but in no case of dedifferentiated endometrial carcinoma previously described has been reported the concomitant adrenal-cerebellar involvement.

Keywords: Endometrial cancer, dedifferentiated features, cerebellum metastasis, adrenal metastasis, differential diagnosis

Introduction

The histological detection of dedifferentiated component in endometrial cancer is rare, occurring only in 9% of all endometrial carcinomas [1]. Silva et al. in a recent article did show that these tumors are often completely undetected or incorrectly classified as grade 3 endometrioid carcinoma according to FIGO guidelines [2].

Dedifferentiated endometrial cancer (DEC) is microscopically characterised by the presence of high-grade areas emerging from low-grade tumours. DEC is an aggressive tumour even when the dedifferentiated component represents only 20% of the entire neoplasm. Actually, FIGO system is based on architectural features, basically the amount of non-morular solid endometrioid component in cancer though it does not provide any details concerning histologic features of the solid tumor component.

A proper histological diagnosis is essential to define the most appropriate therapeutic approach for these tumors, since they are characterized by a particularly aggressive trend and by an extremely poor prognosis [3].

We report a single case of DEC associated with cerebellar and adrenal metastasis, for which the patient underwent both abdominal-pelvic and cerebellar surgery.

Case report

A 67 year old patient affected by essential hypertension pharmacologically treated, referred to the Emergency Unit for dysarthria, dysla-

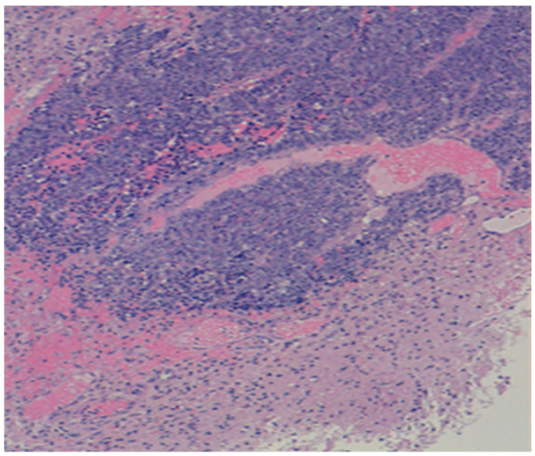

Figure 1. Cerebellum biopsy showing sheets of undifferentiated neoplastic elements organized to form solid nodules *(hematoxylin-eosin x 100).*

lia and balance disorders. From CT examination resulted to be present a hyper-hypodense lesion of about 30 mm in the left posterior superior region of the cerebellum, affecting both the fourth ventricle and the sylvian aqueduct. The findings where suggestive for malignancy, were confirmed also by brain MRI. The patient was subjected to suboccipital craniotomy for the excision of the mass.

Since the cerebellum histological diagnosis was suggestive for a secondary tumor of likely endometrial origin, a diagnostic hysteroscopy with biopsy was carried out, giving a diagnosis of G1 endometrioid adenocarcinoma, poorly differentiated with anaplastic regions and with an extensively necrotic dedifferentiated component.

Abdomen-pelvis CT scan showed no pulmonary localization, but confirmed a widespread process occupying the whole uterine cavity without pelvic/aortic lymph nodes involvement, yet affecting the right adrenal gland.

The patient underwent laparotomy with removal of the uterus and adnexa, besides right adrenalectomy. Histological evaluation confirmed the presence of a dedifferentiated carcinoma infiltrating the full thickness of the myometrium, yet also spread to the parametrium and with associated metastases to the ovaries and to the right adrenal gland.

Microscopic examination of small cerebellar biopsies showed the presence of neoplasm

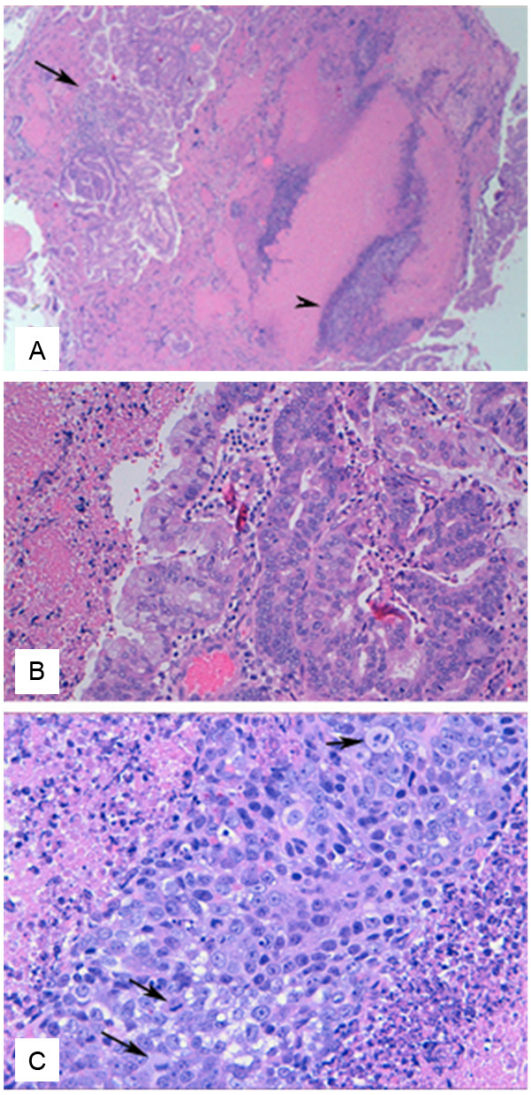

Figure 2. On low magnification, histological analysis of endometrial biopsy showing necrotic tissue, a proliferation of undifferentiated component and low-grade endometrioid carcinoma with glandular structures *(A: hematoxylin-eosin x 40. Arrow low grade of endometrial carcinoma, head of arrow undifferentiated component).* Low grade endometrial component on lager magnification *(B: hematoxylin-eosin x 100)* with evident glandular structures and undifferentiated component with monotonous medium-sized epithelial cells, organized to form solid sheets. The nuclei showed coarse chromatin, evident basophilic nucleoli and numerous mitotic figures (*C: hematoxylin-eosin x 400. Arrows mitotic indicate figures).*

characterized by sheets of neoplastic undifferentiated elements, (**Figure 1**). The immunohistochemical analysis then, showed these samples to be positive to keratin and negative to neuronal markers such as GFAP, fact which allowed to exclude primary cerebellar malignancy.

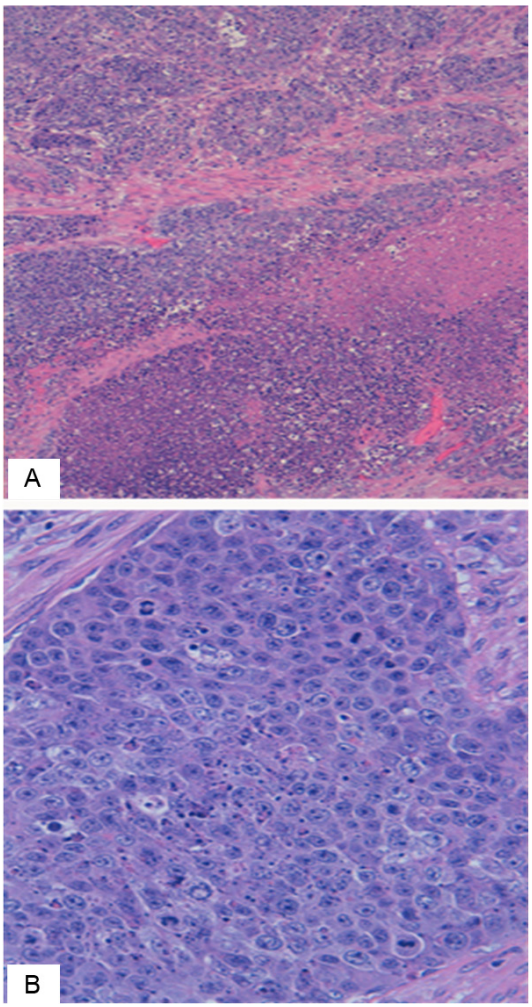

Figure 3. Histologically the neoplasm showing undifferentiated component with large necrotic areas invading myometrium *(A: hematoxylin-eosin x 100)* and on higher magnification the features undifferentiated carcinoma with with monotonous medium-sized epithelial cells, organized to form solid sheets. The nuclei showed coarse chromatin, evident basophilic nucleoli and numerous mitotic figures *(B: hematoxylin-eosin x 400)*.

Histological study of endometrial biopsy revealed the presence of necrotic tissue, a proliferation of undifferentiated component and low-grade endometrioid carcinoma with glandular structures (**Figure 2A**, **2B**).

Neoplastic elements of the solid component characteristically showed the same features of the neoplasm observed in the cerebellum: neoplastic elements were medium-sized, they were also present epithelial cells organized into solid nodules and sheets, in which all cellular elements basically showed same size and appearance.

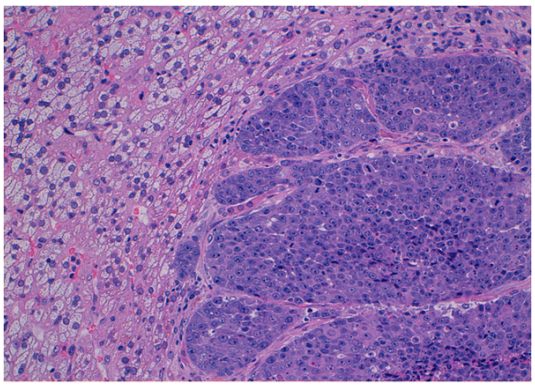

Figure 4. Metastasis of undifferentiated component in adrenal gland *(hematoxylin-eosin x 200)*.

Their nuclei presented coarse chromatin, with evident basophilic nucleoli and numerous mitotic figures (**Figure 2C**). Thus, final pathological diagnosis was that of dedifferentiated carcinoma of uterus.

The main lesion was located at the upper part of the uterine body and at its fundus. At the sectioning, the myometrium was entirely replaced by white neoplastic tissue that showed large necrotic areas. Histologically neoplastic tissue was composed only by undifferentiated carcinoma (solid component) with large necrotic areas invading the myometrium (**Figure 3A**, **3B**).

The examination of adrenal glands tissue revealed metastatic nodules and sheets of undifferentiated neoplastic matter with the same histological features observed in the uterine and cerebellar tumor masses (**Figure 4**).

The patient finely recovered after surgery, which allowed to start Carboplatin (AUC 5) and Taxol (175 mg/mq) adjuvant therapy 15 days later.

Discussion

Endometrial cancer is the most common invasive neoplasm of the female genital tract [4]. Undifferentiated carcinoma of the endometrium is a poorly recognized neoplasm since they have not been clearly defined the histological features discriminating this neoplasm from high-grade endometrioid adenocarcinoma [5].

The WHO defines undifferentiated carcinoma of the endometrium as a ‘‘malignant tumor of epi-

Table 1. Dedifferentiated endometrial cancer: age at diagnosis, Interval time from first diagnosis and metastasis, sites of metastatic involvement and survival, systematic review of literature

Authors	Number of patients	Age (years)	Interval time diagnosis and from first metastasis (months)	Other sites of metastasis involvement	Survival (months)
Salibi [7]	1	63	6	*Not reported*	14
Nakano [7]	1	77	26	*Chest, Abdomen*	4
Brezinka [7]	1	59	3	*Abdomen, chest*	0.75
Sawada [7]	1	43	1, 5	*None*	84
Kottke-Marchant [7]	3	59;	*Not reported*;	*Para-aortic Lymph node;*	38.5;
		43;	1;	*None;*	0.75;
		46;	*Not reported;*	*None;*	9;
De Porre [7]	1	65	21	*None*	1
Wronski [7]	2	70;	21;	*Chest;*	5.5;
		60;	90;	*Chest;*	0.23;
Ruelle [7]	2	64;	14;	*Chest and bone;*	9;
		63;	*Not reported;*	*Para-aortic Lymph node*	-
Martinez-Manas [7]	1	76	18	*None*	8
Petru [7]	4	59,5 (mean)	*Not reported*	*Pelvic Lymph node, ileum, colon*	17-171 (range)
Sewak [7]	1	63	48	*Chest*	6.5
Shiohara [7]	1	48	*Not reported*	*None*	38
Salvati [7]	2	62;	48;	*None;*	9;
		51;	*Not reported;*	*None;*	34;
Elliot [7]	1	51	2	*None*	30
N'Kanza [7]	1	61	*Not reported*	*Chest, abdomen, pelvis*	3
Lee [7]	1	54	96	*None*	0.2
Hacker [7]	1	64	216	*None*	0.8
De Witte [7]	2	67;	24;	*None;*	22;
		40;	*Not reported;*	*None;*	-
Cormio [7]	10	57 (mean)	24 (mean)	*Pelvis, lung, liver, bones*	1 (mean)
Gien [7]	8	66 (mean)	*Not reported*	*Not reported*	3.5 (mean)
Mahmoud-Ahmed [7]	10	50 (mean)	12 (mean)	*Not reported*	3.3 (mean)
J. C. Chura [7]	20	62 (mean)	24 (mean)	*Not reported*	2 (mean)
A. L. N'Kanza [8]	1	61	*Not reported*	*Suprarenal gland, Pelvis*	4
Kim JK [9]	1	64	*Not reported*	*Not reported*	*Not reported*
Farooq MU [10]	1	63	*Not reported*	*Bones*	none
Berretta et al. (our case)	1	67	-	*Suprarenal gland, cerebellum, pelvis*	4

thelial structure that is too poorly differentiated to be placed in any other category of carcinomas'' [6]. Such kind of neoplasm does not precisely match with current FIGO staging and risk factor scoring system parameters, for which reason it has to be considered a G3-type cancer. Dedifferentiated carcinoma is an uterine neoplasm characterized by the concurrent presence of both well differentiated (G1-G2) and undifferentiated tissue. The presence of undifferentiated tissue accounting for as little as 20% of total tumor mass, but even less than that, has to be considered an extremely unfavorable prognostic factor: for just one single case of dedifferentiated carcinomas out of 25, they could report a 104 month disease-/relapse-free time [2].

In this same context we may place the case we reported here, of a dedifferentiated carcinoma characterized at the time of diagnosis by the simultaneous presence of metastases to the central nervous system (cerebellum) and to the adrenal glands.

Central nervous system (CNS) metastases from endometrial cancers are quite rare. Revising existing literature (**Table 1**) we found 79 described cases of CNS secondary involvement (of which 63 as relapses after a variable disease-free interval ranging from 3 to 96 months), and 13 cases where the onset of the disease was characterized by neurological signs and symptoms [7-10].

We could only find two reported cases of adrenal metastases originating from endometrial neoplasia [11] but in no case of dedifferentiated endometrial carcinoma previously described has been reported the concomitant adrenal-cerebellar involvement.

In conclusion, the identification of the dedifferentiated component via an extensive sampling of the surgical specimen and a careful evaluation of the solid component especially in the case of low-grade neoplasms predominance. Identification of the dedifferentiated component is essential in order to prevent a yet ineffective surgical approach and to formulate a proper prognosis. In fact, a dedifferentiation ratio even lesser than 20% of total can lead to a significant worsening of the prognosis: we could therefore hypothesize that the failure in identifying this component could explain the discrepancy in terms of 5-year survival for patients with FIGO stage 1 cancer, as already reported by Mittal et al [12]. and Cormio et al [13]. These authors do report a survival rate ranging from 44% to 73%, but this marked variation to be likely considered as the result of the misdiagnosis of FIGO grade 3 undifferentiated carcinoma cases as endometrioid adenocarcinoma [14-17].

At present, based upon the poor existing data, for dedifferentiated endometrial cancer, similarly to genital or extra-genital Mixed Müllerian cancer [18, 19], are not defined neither the optimal surgical approach nor the role of any adjuvant therapy (chemotherapy and/or radiotherapy).

A multicenter, prospective analysis would be advisable.

Disclosure of conflict of interest

All authors declare no conflicts of interest.

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