Oxyphilic clear cell carcinoma of the ovary with a minor clear cell component- case report with emphasis on the morphological diversity and histogenesis

Carcinom ovarian cu celule clare varianta cu celule oxifile asociat cu o componentă minoră cu celule clare - prezentare de caz cu discutarea diversității morfologice şi a histogenezei

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Abstract

This paper presents a case of oxyphilic clear cell carcinoma of the ovary in an old patient. Because of its histology and the association with peculiar patterns as hemosiderinic pigment, psammoma bodies, pseudo-papillary or follicular-spaces and grooved nuclei, this tumor is responsible for a significant proportion of differential diagnosis in ovarian pathology. Since ovarian clear cell carcinoma has a bad prognosis and is usually more resistant to systemic chemotherapy than other types, recognition of this entity from other primaries and metastatic oxyphilic cell tumors in the ovary is mandatory. The origin in endometriotic cysts or related lesions demonstrated by molecular biology and suggested in this case by the presence of hemorrhage and hemosiderin pigment may explain the good prognosis in early stages of the disease despite the fact that the tumor is poorly differentiated, grade three and always associated with atypia.

Key words: *clear cell carcinoma, ovary, oxyphilic cells*

Rezumat

Articolul prezinta cazul unei paciente de 70 de ani care a dezvoltat un carcinom ovarian cu celule clare varianta cu celule oxifile. Datorita aspectului morfologic particular si asocierii din punct de vedere microscopic cu prezenta pigmentului de hemosiderina, a corpilor psamomatosi, a aspectelor arhitecturale de tip peuso-papilar sau folicular precum si a celulelor tumorale cu nuclei cu incizura longitudinala aceasta tumora poate fi confundata cu numeroase alte leziuni ovariene. Carcinomul ovarian cu celule clare este asociat cu un prognostic ne-

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favorabil si este chimiorezistent, de aceea, diagnnosticul corect al acestei leziuni si diferentierea de alte leziuni ovariene asemanatoare primare sau metastatice este esentiala in vederea unui management corect al pacientei. Originea tumorii in focare de endometrioza ovariana sau leziuni asociate acesteia, demonstrata de catre studiile recente de biologie moleculara si sugerata in acest caz de prezenta focarelor de hemoragie si a pigmentului de hemosiderina ar putea explica un prognostic mai bun al acestui tip de tumora in stadii incipiente, in ciuda faptului ca tumora este slab diferentiata microscopic si intotdeauna asociata cu pleomorfism nuclear marcat.

Cuvinte cheie: *carcinom cu celule clare, ovar, celule oxifile*

Introduction

Clear cell carcinoma of the ovary is a rare tumor that accounts for less than 5% of all ovarian malignancies (1). It originates from the ovarian surface epithelium or endometriotic foci and microscopically it is characterized by a variety of patterns being composed of clear glycogen-rich or hobnail cells. Oxyphilic clear cell carcinoma of the ovary is a rare variant of clear cells carcinoma composed of large tumor cells with eosinophilic cytoplasm (2). Because of its histology, oxyphilic clear cell carcinoma of the ovary is responsible for a significant proportion of differential diagnosis in ovarian pathology. The main problems in differential diagnosis of this tumor will be highlighted in this paper together with its pathogenesis. Since ovarian clear cell carcinoma has a bad prognosis and is usually more resistant to systemic chemotherapy than other types, recognition of this entity from other primaries and metastatic oxyphilic cell tumors in the ovary is mandatory (3).

Case report

A 70 year old patient was admitted to the Surgery Department for nausea, vomiting, intestinal transit arrest and tenesmus. There were no urinary complaints or abnormal vaginal bleeding. CT scan revealed ascites and a large, complex pelvic mass which seemed to originate in the rectum and was infiltrating the right adnexum. On laparotomy, the perforation of the rectum associated with peritonitis was due to a 9 cm tumor infiltrating both the rectum and right adnexum. She underwent rectosigmoid resection together with right salpingo-oophorectomy and appendectomy.

Grossly, the right adnexum corresponded to a mass that incorporated both the ovary and the fallopian tube and was partly cystic with hemorrhagic foci. The sigma and the appendix were normal but the rectal serosa was infiltrated by the adnexal tumor.

Microscopically, the ovarian tumor invaded the capsule, tube and rectal wall and was composed of tumor cells arranged in large sheets, trabeculae or tubules (*Figure 1*).

Some areas presented a pseudopapillary architecture that was due to necrosis and others consisted of follicular-like spaces (*Figure 2*).

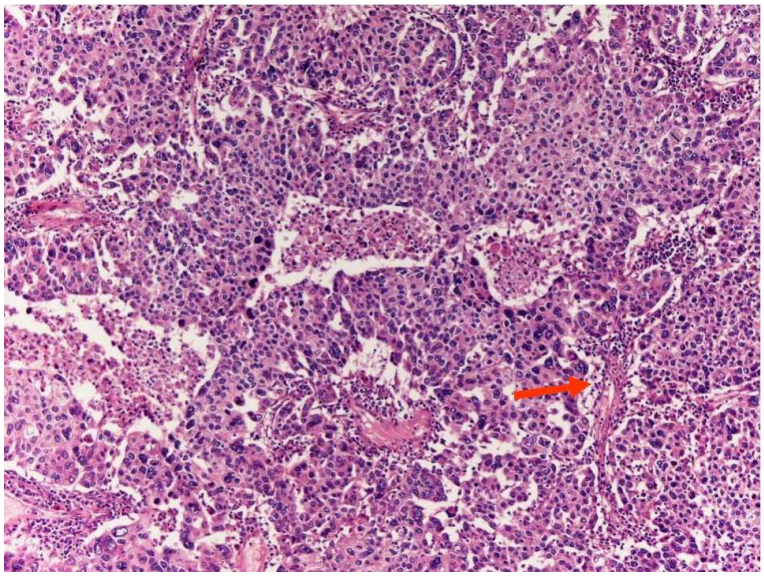

Figure 1. Tumor cells arranged in large sheets, separated by thin fibrovascular septa, and with areas of necrosis, x100, H-E.

The majority of the tumor cells were round or oval, with large amount of conspicuously granular eosinophilic cytoplasm and vesicular or hypercromatic nuclei. Some nuclei presented grooves, others marked pleomorphism with one or more eosinophilic nucleoli (*Figure 3)*.

Sporadic giant cells were also seen. The tumor cells were separated by thin fibrovascular septa infiltrated by neutrophils with focal areas of hemorrhage and hemosiderin pigment (*Figure 4)*.

Foci of clear tumor cells were visible in limited areas, representing less that 10% of the tumor area. Some other areas were composed of small undifferentiated tumor cells with scanty cytoplasm and round pleomorphic vesicular nuclei. Occasional psammoma bodies were seen. Mitotic activity was moderate. Immunohistochemically, the tumor cells were positive for CK 7, CA125 and antimitochondrial antibody (*Figure 5).*

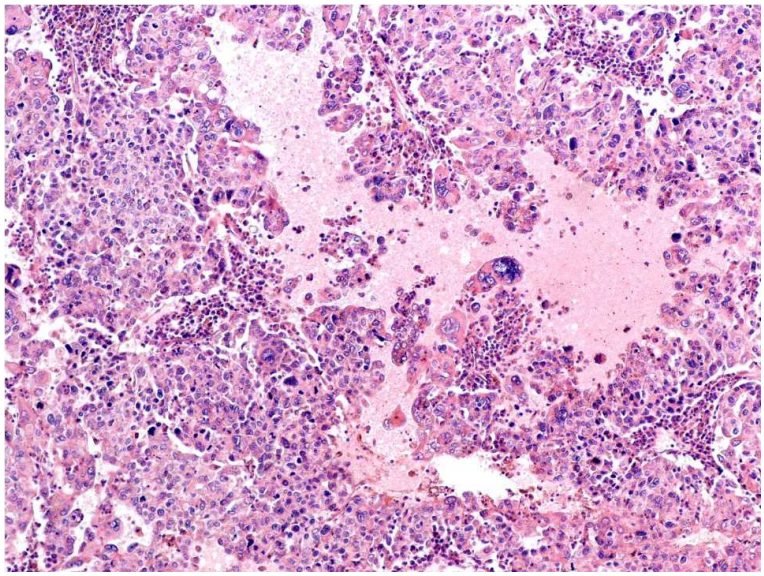

Figure 2. Areas with follicular-like spaces, x100, H-E.

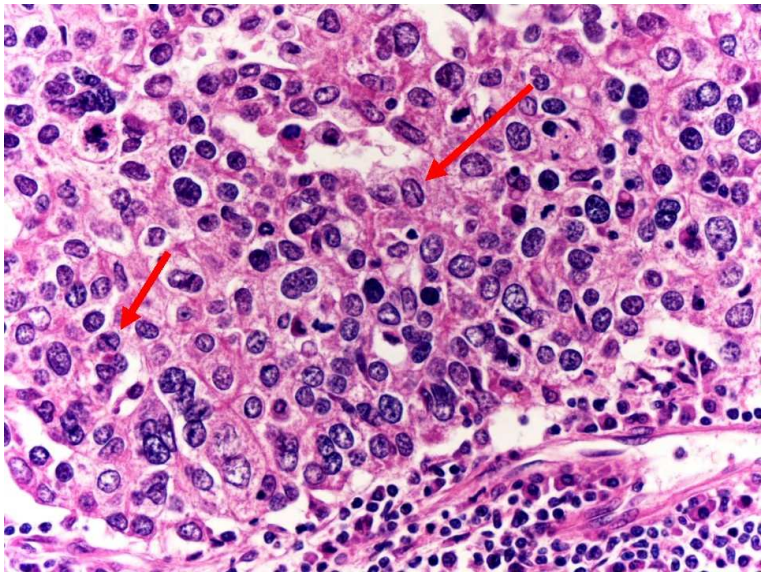

Figure 3. Marked pleomorphism with one or more eosinophilic nucleoli; some nuclei presented grooves, x400, H-E.

The tumor cells were negative for cytokeratin 20, vimentin, calretinin, AFP, HEP PAR1, ER and PR. A final diagnosis of a stage III oxyphilic clear cell carcinoma of the ovary was established. The patient eventually received 6 cycles of chemotherapy (Carboplatin, AUC 5, and Cyclofosfamide 600 mg/m2).

Discussion

Clear cell carcinoma of the ovary was first described by Schiller in 1939 and designated as mesonephroma in order to describe its presumptive origin from mesonephric rests in the female genital tract but did not discriminate clear cell carcinoma from yolk sac tumour (4). It was Teilum's paper in 1954 in which yolk sac tumors of germ cell origin were separated from clear cell carcinoma for the first time, and the latter was recognized as a distinct entity (5). In 1967 Scully and colleagues demonstrated the müllerian origin proposed by De Santo some years before due to the fact that more than 50% of the cases were associated with pelvic endometriosis (6, 7). Usually most of the clear

cell carcinomas present as early stage (I-II), are frequently associated with a large pelvic mass which may account for their earlier diagnosis and rarely occur bilaterally (8).

The oxyphilic type of clear cell carcinoma of the ovary is even rarer. In 1987 Young and Scully were the first ones to describe this variant of clear cell carcinoma of the ovary in a paper in which nine cases were characterized by a prominent component of tumor cells with abundant dense non-granular eosinophilic cytoplasm, were associated with the classical pattern of clear tumor cell in all cases and with a minor adenofibromatous component in four cases (9). None of the cases were evaluated by electron microscopy or immunohistochemistry and were considered as a different variety from oncocytic adenocarcinoma (9, 10).

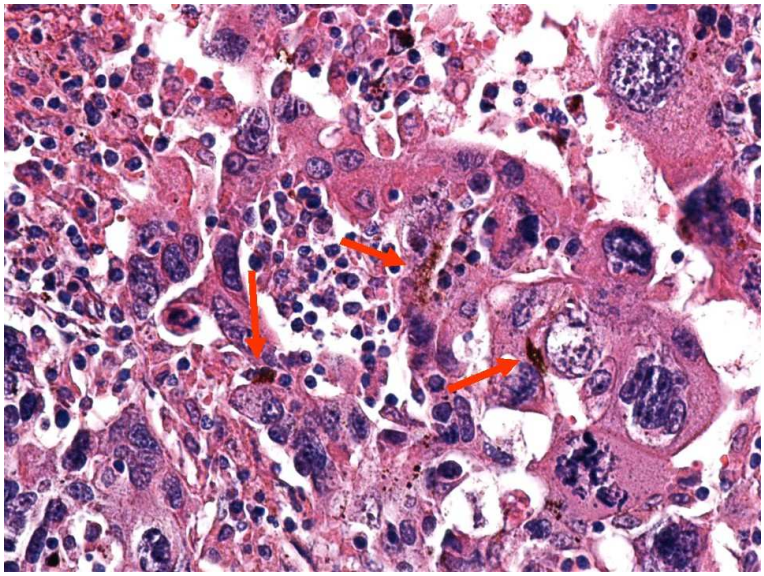

Figure 4. Some tumor cells contain hemosiderin pigment, x400, H-E.

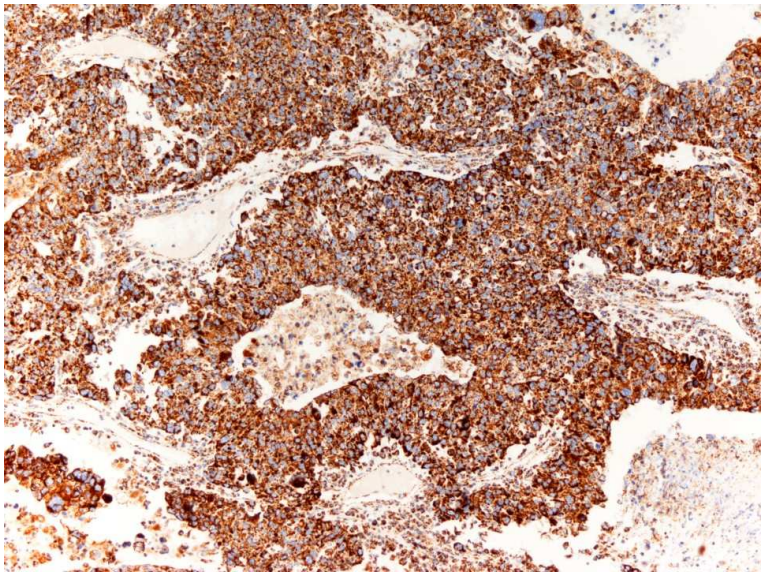

Figure 5. The tumor cells are positive for antimitochondrial antibody, x100.

Due to the rarity of the tumor, only occasional cases have been reported in the literature. To the best of our knowledge, this is the first case report of ovarian oxyphilic clear cell carcinoma in Romania.

Because of the presence of oxyphilic cells, the tumor can be frequently misdiagnosed since the ovary is the site of a wide range of tumors both of primary and metastatic origin.

Oxyphilic type of endometrioid carcinoma of the ovary was first described by Pitman and colleagues in 1994 (11). One of their tumors had an excess of mitochondria on electron microscopy as well as microfilaments, tonofibrils, a moderate amount of glycogen in combination with a moderate amount of rough endoplasmic reticulum that could also explain the eosinophilia of the cytoplasm. Authors concluded that oncocytic adenocarcinoma and oxyphilic type of endometrioid adenocarcinoma are the same and that a good sampling of the tumor would easily identifying the foci of classic endometrioid carcinoma (11).

Steroid cell tumor is another putative differential; the average age of patients with this neoplasm is

younger than that of patients with clear cell carcinoma, moreover, they have endocrine manifestations, usually androgenic. Microscopically, both tumors can share eosinophilic cells and atypia, but steroid cell tumor can contain lipofuscin pigment. Immunohistochemistry shows steroid cells positive for calretinin and α-inhibin but negative for antimitochondrial antibody and AFP.

Yolk sac tumor develops in young patients and has atypical histology. However in the hepatoid variant, cells have an abundant eosinophilic cytoplasm and are admixed with classic yolk sac pattern, with hyaline bodies and AFP-positivity.

Hepatoid carcinoma of the ovary, pure or associated with other epithelial neoplasms, is also characteristic in postmenopausal patients but the positivity for HEP PAR 1 is very useful (12).

Primary malignant melanomas of the ovary are extremely rare and most are associated with a benign cystic teratoma. Metastatic malignant melanoma is also uncommon; approximately 74 cases have been reported in the literature (13). Primary and metastatic melanoma are usually unilateral, associated with a poor prognosis and have similar morphology, being composed of mainly large tumor cells with abundant eosinophilic cytoplasm (but sometimes admixed with clear cytoplasm cells, small cells with scanty cytoplasm or spindle cells). They usually have melanin pigment and are immunohistochemically positive for S-100 protein and HMB-45 (14, 15).

Paraganglioma of the ovary is extremely rare, macroscopically appears as a yellow or brown tumor and is composed of large cells with eosinophilic cytoplasm arranged in nests. Immunohistochemically they are positive for neuroendocrine markers and negative for Cytokeratin (16).

Ovarian metastases may take place before or many years after the diagnosis of the primary renal tumor and thus may be confused with primary ovarian tumors. On the other hand, metastases from the kidney are usually unilateral and especially in the tubulopapillary carcinomas type II they are characterized by an admixture of clear and oxyphilic cells forming multicystic or follicular-like spaces. Immunohistochemistry is crucial since the metastases from the kidney are CK7 negative but positive for CD 10 and AMACR (17).

Many other architectural patterns of clear cell carcinoma can be encountered, such as tubulocystic, solid, nested, trabecular or papillary, including the follicle-like spaces or the pseudopapillary patterns due to necrosis (16). The presence of a mixed architecture associated with papillary areas, psammoma bodies and hobnail cells can be mistaken with other primary ovarian tumors, such as serous or transitional cell carcinoma. In serous malignant tumors, the bilaterality of the tumor, the coexistence of the ciliated epithelial cells together with low mitotic index and characteristic immunohistochemical profile (serous carcinoma is diffusely and strongly positive for WT1 and ER and clear cell carcinoma for HNF-1beta) allows a correct diagnosis (18, 19).

Although most transitional cell carcinoma of the ovary have different cell types, a pseudopapillary pattern of oxyphilic clear cell carcinoma caused by necrosis and degeneration may impart at least a low-power resemblance between the two tumors. Immunohistochemistry combined with a good sampling is crucial to reach a final diagnosis.

Presence of follicular-like spaces overlaps with other tumors characterized by a follicular pattern such as oxyphilic struma ovarii (thyroglobulin-positive), small cell carcinoma (positive for CK, EMA, WT1 and neuroendocrine markers), granulosa cell tumor of both adult (lack of nucleoli and presence of grooves nuclei although in the luteinized granulosa cell tumor the cells lack the grooves) and juvenile type (immunohistochemistry using sex cord-stromal markers such as α-inhibin and calretinin can be used). Some of the nuclei in the present case had nuclear grooves that have not described before in the oxyphilic clear cell carcinoma of the ovary.

There are several theories regarding the pathogenesis of the tumor. Some papers admit the origin in the surface epithelium of the ovary while some others in the ovarian endometriosis.

Clear cell elements have been described admixed with every type of primary carcinoma of the ovary, with the endometrioid, mucinous and serous types being the most common (20-22). There are papers suggesting that clear cell carcinoma is an end stage appearance of many epithelial ovarian tumors.

Ovarian clear cell carcinoma has been reported also in association with endometriosis in the ipsilateral ovary in 5-38% of cases and in 50-70% when pelvic endometriosis is also taken into account (6). This wide variation is also due to the fact that endometriosis may be overrun by the tumor or not properly sampled. It has been noted in one study that 88% of clear cell carcinomas were preceded by an ultrasonographically detected endometrioid cyst (23). Two types of lesions can be encountered in endometriosis: the first one is characterized by cells with abundant eosinophilic cytoplasm and large hypercromatic nuclei lining the endometrioid cysts in a single layer and sometimes associated with acute inflammation. In the second type, large polygonal cells are associated with stratification and tufting of the epithelium. The cells in the second type may have an eosinophilic, clear, vacuolated cytoplasm or may contain intracytoplasmatic mucin. The nuclei are hypercromatic and pleomorphic. Two follow-up studies of patients with completely excised lesions revealed that all of them were alive, although in another study, one patient developed clear cell carcinoma 3 years later. These facts suggested a possible preneoplastic lesion, its neoplastic potential being indicated by the aneuploid genetic profile (24-26). On the other hand, most benign-appearing ovarian endometriotic cysts are monoclonal (27). LOH (loss of heterozygosity) is common in clear cell carcinoma and synchronous endometriotic lesions (28). Nuclear immunostaining for HNF-1beta was detected in clear cell carcinoma and endometrioid epithelium associated with clear cell carcinoma but also endometriotic cyst without neoplastic changes (29). Early differentiation into clear cell lineage may take place in ovarian endometriosis.

Conclusion

Oxyphilic type of clear cell carcinoma of the ovary is a lesion that can be misdiagnosed with other primary or metastatic tumors composed of oxyphilic tumor cells. The association with peculiar patterns as hemosiderinic pigment, psammoma bodies, pseudo-papillary or follicular-spaces and grooved nuclei represent a challenge for the pathologist.

The origin in endometriotic cysts or related lesions demonstrated by molecular biology and suggested in this case by the presence of hemorrhage and hemosiderin pigment may explain the good prognosis in early stages of the disease despite the fact that the tumor is poorly differentiated, grade three and always associated with atypia.

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