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Metastasizing uterine tumor resembling ovarian sex cord tumor (UTROSCT)

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Summary

An enigmatic category of uterine mesenchymal neoplasms is descriptively referred to as uterine tumors resembling sex cord-gonadal stromal tumor. First described by Clement and Scully in 1976, they were subsequently subcategorized in 1) endometrial stromal tumors with sex cord-like elements (ESTSCLE) and 2) mural uterine tumors resembling ovarian sex cord tumors (UTROSCT). In the first subcategory, the prognosis depends on the type, grade, and stage of the underlying stromal neoplasm, while in the second one, a low-grade malignant behavior has been postulated on the basis of occasional local recurrences. Here, the authors report a new case of metastasizing UTROSCT in an 83-year-old Caucasian woman, providing a literature review, and emphasizing its metastatic potential. This tumor entity shows a variable immunohistochemical profile with possible co-expression of sex cord (inhibin, calretinin, WT1, MART1/melanA), epithelial, smooth muscle (actin, caldesmon), and miscellaneous markers, such as estrogen or progesterone receptors. For this aberrant expression of immunohistochemical markers, the final diagnosis of metastatic UTROSCT appears a diagnostic challenge. Finally, the authors detected the cdkn2a ($p16^{INK4a}$) expression in about half of the neoplastic cells; this finding suggests a possible involvement of the CDKN2A gene in the genesis of an aggressive tumor clone, as observed in other uterine sarcomas.

Key words: Uterine tumor resembling ovarian sex cord tumor (UTROSCT); Metastasis; Histology; Immunohistochemistry; Inhibin; MART1/melanA; cdkn2a ($p16^{INK4a}$) protein

Introduction

Cellular mesenchymal tumors of the uterus can be subdivided in two main categories, the smooth muscle tumors (highly cellular leiomyoma, cellular intravenous leiomyomatosis, leiomyosarcoma) and the endometrial stromal tumors (endometrial stromal sarcoma). Other rare densely cellular tumors, which may occur in the uterus, are undifferentiated uterine sarcoma, embryonal rhabdomyosarcoma, primitive neuroectodermal tumor, lymphoma, small cell or anaplastic carcinoma [1]. A further enigmatic category of uterine mesenchymal neoplasms, often highly cellular, is descriptively referred to as uterine tumors resembling sex cord-gonadal stromal tumor. First described by Clement and Scully in 1976 [2], they were subsequently subcategorized in 1) endometrial stromal tumors with sex cord-like elements (ESTSCLE) and 2) mural uterine tumors resembling ovarian sex cord tumors (UTROSCT). In the former subcategory, the sex cord counterpart constitutes a minor component of the endometrial stromal neoplasm, whereas in the latter, it is the predominant or exclusive component. In the first subcategory, the prognosis depends on the type, grade, and stage of the underlying stromal neoplasm, while in the second one a low-grade malignant behavior has been postulated on the basis of occasional local recurrences [3]. Here, the authors report a new case of metastasizing UTROSCT, providing a literature review, and emphasizing its metastatic potential.

Case Report

An 83-year-old Caucasian woman was admitted to the emergency room for marked asthenia due to sideropenic microcytic anemia. In the medical history, a hysteroannessiectomy, dating back about 15 years ago, for UTROSCT was reported. In order to understand the anemia's origin, the patient was submitted to abdominal sonography, which revealed a 3-cm solid nodule in the context of the aponeurosis of the left external oblique muscle. The subsequent computed tomography confirmed the presence of the lesion, characterized by inhomogeneous contrast enhancement, and disclosed a further mass, 3.2 cm in size, placed on the right anterosuperior pararenal fascia, with analogous contrastographic appearance. In the suspicion of malignancy, a core biopsy was performed and sent for histopathological characterization. Besides routinely hematoxylin and eosin (H&E) stain, the bioptic material was subjected to further immunohistochemical investigation. More in detail, after deparaffinization, hydration, endogenous peroxidase blocking, and heat-induced antigen retrieval, the tissue sections were incubated for 30 minutes at room temperature with anti-Ki67 (clone MIB-1, 1:75), anti-inhibin (clone R, prediluted), anti-calretinin (clone SP65, prediluted), anti-estrogen receptor (clone SP1, prediluted), anti-MART1/melanA (clone A103, prediluted), anti-smooth muscle actin (clone 1A4, prediluted), anti-caldesmon (clone E89, prediluted), anti-desmin (clone DE-R-11, prediluted), anti-cytokeratin (clone MNF116, prediluted), anti-chromograninA (clone LK2H10, prediluted), anti-S100 (clone 4C4.9, prediluted), anti-DOG1 (clone SP31, prediluted), anti-CD10 (clone SP67, prediluted), anti-CD34 (clone QBEnd/10, prediluted), anti-CD45 (clone RP2/18, prediluted), anti-CD99 (clone O13, prediluted), anti-CD117 (clone 9.7, prediluted), and anti-cdkn2a ($p16^{INK4a}$, clone E6H4, prediluted). Biotinylated sec-

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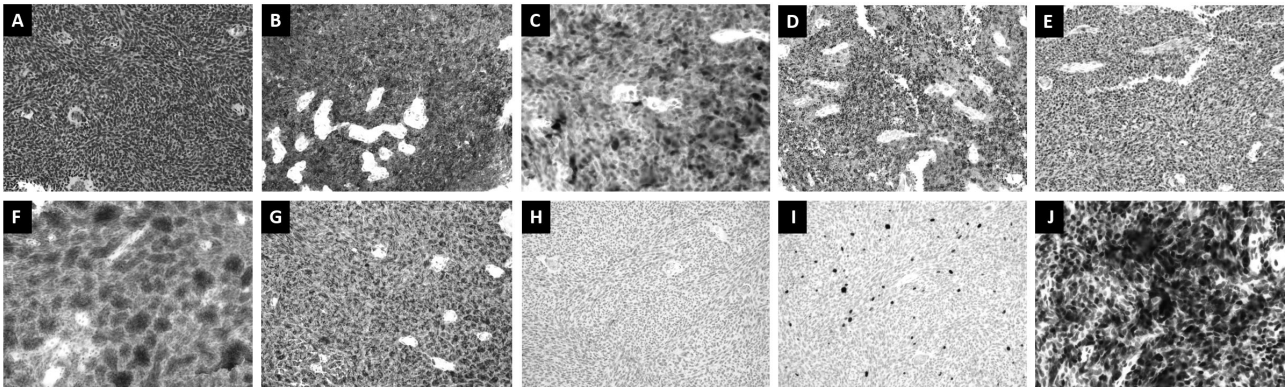

Figure 1. — Metastasizing UTROSCT (A, H&E, ×20): the neoplastic cells are variably immunoreactive for inhibin (B, ×20), calretinin (C, ×20), MART1/melanA (D, ×20), estrogen (E, ×20), smooth muscle actin (F, ×20), and caldesmon (G, ×20). No reactivity for desmin is observed (H, ×20). A rough MIB-1 labeling index is ascertained (I, ×20); about half of the neoplastic cells are positive for cdkn2a ($p16^{INK4a}$) protein (J, ×20).

ondary antibody was applied and the staining product detected with avidin-biotin complex against a hematoxylin counterstain. Detection of the staining reaction was achieved by an enzyme conjugated polymer complex adapted for automatic stainers, with 3-3'diaminobenzidine tetrahydrochloride as chromogen.

Results

On H&E, the lesion consisted of numerous slightly spindle cells, with monomorphic nuclei devoid of prominent nucleoli, arranged in a hemangiopericytomatous pattern (Figure 1, panel A). The neoplastic cells resulted strongly immunoreactive for inhibin (Figure 1 panel B), calretinin (Figure 1 panel C) and MART1/melanA (Figure 1 panel D), while a focal immunoreactivity for estrogen receptors (Figure 1 panel E), and smooth muscle actin (Figure 1 panel F) was detected. A diffuse staining for caldesmon was also ascertained (Figure 1 panel G); no reactivity for the remaining markers was observed, desmin included (Figure 1 panel H). The cytoproliferative activity (MIB-1 labeling index) was around 10% (Figure 1 panel I). About half of the neoplastic cells were positive for the cdkn2a protein (Figure 1 panel J). Merging the morphologic aspect with the immunohistochemical profile, a final diagnosis of metastasis from UTROSCT was formulated.

Discussion

UTROSCTs are very rare neoplasms, which usually occur in middle-aged women. The patients present with abnormal uterine bleeding and/or abdominal pain, together with an enlarged uterus [4]. The first metastatic case dates back to 2008, when Biermann *et al.* described in a female patient the development of obstructive ileus due to a large infiltrating tumor within the small bowel, with the same morphology and expression profile as the previous UTROSCT of the uterine corpus, diagnosed four years before [5]. In 2014, Umenda *et al.* reported two metastatic cases to pelvic lymph node and epiploic appendix, respectively [6]. In the same year, Mačák *et al.* described a further case of lymph node metastasis in the right iliac artery region [7]. In these cases, the final diagnosis can be achieved only through an accurate histopathologic examination. Numerous patterns of growth have been described, such as plexiform, trabecular, micro-/macrofollicolar, tubular, retiform, solid, and diffuse [8]. According to the present authors experience, the expression of 'haemangiopericytomatous pattern' can be also adopted. The neoplastic cells are small with round to ovoid nuclei; nuclear monotony, mild nuclear hyperchromasia, and inconspicuous nucleoli with scant eosinophilic cytoplasm are usually observed. Nuclear grooves are rare. Mitotic figures are infrequent, and necrosis is mostly absent [8]. These tumors show a variable and enigmatic immunohistochemical profile with possible co-expression of sex cord (inhibin, calretinin, WT1, MART1/melanA), epithelial, smooth muscle (actin, caldesmon), and miscellaneous markers, such as estrogen or progesterone receptors [9]. Immunoexpression for calretinin and at least for one of the other sex cord markers is required to establish a diagnosis of UTROSCT [10]. For this aberrant expression of immunohistochemical markers, the final diagnosis of metastatic UTROSCT takes the form of a diagnostic challenge. For example, in the present case, the tumor localization in the right anterosuperior pararenal fascia has imposed a differential diagnosis with an adrenocortical cancer, which commonly expresses MART1/melanA, inhibin, calretinin, and estrogens [11-13]. In these rare and difficult circumstances, the morphological aspect on H&E, in conjunction with the immunohistochemical evidence of neuroendocrine differentiation (synaptophysin, NSE) in adrenocortical cancers, avoids possible misinterpretations. The origin of UTROSCT remains unknown; a

genesis from endometrial stromal cells, adenomyosis, endometriosis, or multipotential cells within the myometrium has been proposed over the years [14]. For the first time in literature, the present immunohistochemical detection of the cdkn2a expression in about half of the neoplastic cells suggests a possible involvement of the CDKN2A gene in the genesis of an aggressive tumor clone, as observed in other uterine sarcomas [15]. Hysterectomy with or without bilateral salpingo-oophorectomy is usually the treatment of choice; although most UTROSCTs behave benignly, some locally recur or metastasize after many years, as the present authors report, therefore the entity is burdened by a metastatic potential. This biological attitude has to be considered in the clinical management of the patients and authorizes a long-term follow-up.

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