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Case Report
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Primary Malignant Germ Cell Tumor of the Uterus

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Abstract

Extra Gonadal Germ Cell Tumors (EGGCT) are germ cell neoplasms with morphologic, serologic and cytogenetic features similar to those seen in gonadal tumors, but occurring outside the gonads (ovary and testis). These tumors (EGCT) are rare and account for 1% to 5% of all germ cell malignancies. In adults, the most common locations of primary extra gonadal germ cell tumors by their frequency of occurrence are the mediastinum, retroperitoneum, sacrococcygeal and the pineal region. However, isolated cases of EGCT have been reported in other organs such as thyroid, pericardium, liver, bladder, breast, urachus and vulva. We describe a case of primary malignant germ cell tumor of the uterus, endodermal sinus type (yolk sac tumor) with hepatoid differentiation. Immunohistochemistry showed strong positive staining for PLAP, AFP, HEPPAR-1 and GPC3. HCG stain was positive in the large multinucleated tumor cells. ER and PR were negative. Endodermal sinus tumors with predominant or pure hepatoid patterns are extremely rare and occur more frequently in the ovary. The presence of a hepatoid differentiation confers aggressive behavior and poor prognosis. Recognition and distinction between this entity and other primary endometrial tumors is important to provide appropriate therapy for the patient.

Keywords: Extragonadal; Germ cell tumors; Endodermal sinus tumor; Hepatoid differentiation; Primary uterine tumor

Introduction

Germ cell tumors are subdivided into three categories; the first type is immature germ cell tumors, which represent a range of differentiation included immature germ cell (dysgerminoma), early embryonic development (embryonal carcinoma and polyembryoma), extra-embryonic differentiation (choriocarcinoma and yolk sac tumor) and immature somatic tissue (immature teratoma). The second is the matured germ cell tumor, typically composed of a wide range of somatic tissue from simple dermoid cyst to tumors with human form (homunculus). The third is benign cyst teratoma giving rise to a malignant neoplasm, such a squamous carcinoma, carcinoid, malignant struma ovarii (thyroid carcinoma) and other neoplasm. The first group predominates in young women under age 20, the second is most common in reproductive-age women and the third group is most common in postmenopausal women [1,2]. These tumors in women, commonly arise in the ovaries; however they have been reported in any mid-line structure including thyroid, retroperitoneum, mediastinum, pericardium and pineal region [3]. Here we report a case of malignant germ cell tumor, primary of the uterus, endodermal sinus tumor (yolk sac tumor) type with pure hepatoid differentiation. This is to our knowledge, the first case described in the uterus.

Case Presentation

A 63-year-old female complained and presented with irregular vaginal bleeding of two months duration. Past medical history was non contributory. An endometrial curettage was performed and interpreted as a high grade endometrial carcinoma. The patient underwent a total hysterectomy with bilateral salpingo-oophorectomy and regional lymphadenectomy. Determination of serum markers was not done because the clinical diagnosis was endometrial cancer.

Macroscopic examination showed that the uterus measured 7 cm × 3.5 cm and weighed 170 g. The endometrial cavity was filled by a 6.5 cm, soft, hemorrhagic, necrotic, polypoid mass attached to the left lateral endometrial wall that invaded less than 50% the myometrium. The depth invasion at that side was 0.9 cm out of a total myometrial thickness of 2.9 cm. The uterine serosa was unremarkable. In addition, a small intramural leiomyoma was identified. The left ovary had a 1.9 cm fibroma. The ovaries and the fallopian tubes were unremarkable.

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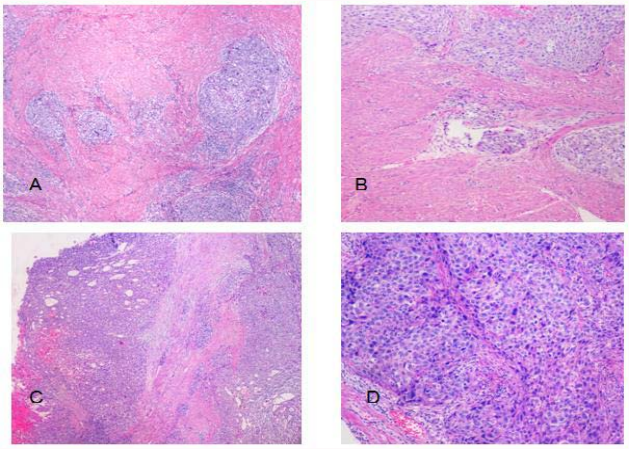

Figure 1: Uterine endodermal sinus tumor with hepatoid differentiation at microscopic examination (H&E). (A) Tumoral mass diffusely invading the myometrium. (B) Extensively invading vascular spaces. (C) Focal areas with patterns of acinar and microcystic formations. (D) Tumor cells large and pleomorphic, with moderate amount of granular cytoplasm and vesicular nuclei, resembling hepatic cells.

Morphologically a large tumor mass was identified at the endometrial surface and that diffusely infiltrated the myometrium and vascular spaces (Figure 1A and 1B). The tumor was composed of cells growing in a predominantly solid pattern with focal areas of acinar and microcystic formations (Figure 1C). The tumor cells were large and pleomorphic, with moderate amounts of granular eosinophilic cytoplasm and vesicular nuclei, with clumped chromatin and prominent nucleoli resembling hepatic cells (Figure 1D). Eosinophilic, hyaline droplets were present within tumor cells and outside them. The tumor cells showed brisk mitotic activity with the presence of several atypical mitoses. Abundant karryorhectic bodies were present throughout.

Immunohistochemistry

Five micron sections were cut from the blocks for immunohistochemical analysis. A panel of commercially available antibodies was applied using the streptavidin-biotin-peroxidase technique and 3-3'-diaminobenzidine as a chromogen, using appropriate positive and negative controls. The tumor was stained for alpha 1-fetoprotein (AFP, Dako), Human Chorionic Gonadotropin (HCG, Dako), Placental alkaline phosphatase (PLAP, Biogenex), Hepatocyte Paraffin-1 (Hep-par-1, Dako), Glipican-3 (GPC3, Biomosaics), Estrogen receptor (ER, Leica), and Progesterone receptor (PR, Leica).

Tumor cells stained diffusely positive for AFP and PLAP suggesting poorly differentiated endodermal sinus tumor (yolk sac tumor). Additionally, the presence of diffuse strong staining for Hep-par-1 and GPC3 suggested the hepatoid differentiation [4]. HCG was focally positive. ER and PR staining were negative (Figure 2). Our final diagnosis was malignant germ tumor type endodermal sinus tumor (yolk sac tumor) with hepatoid differentiation.

Discussion

Extra Gonadal Germ Cell Tumors (EGCT) is relatively rare in frequency, accounting for 1% to 5% of all germ cell tumors. These tumors are thought to develop from germ cell precursors that become arrested during embryologic migration and survived in an ectopic location. Other pathophysiologic explanation that has been suggested is the possibility of metastatic spread from an undetected primary gonadal germ cell tumor which may have regressed spontaneously, most likely a "burned-out" tumor [5]. Histologically, extragonadal germ cell tumors comprise dysgerminomas (30% to 40%) and non-dysgerminomas (60% to 70%) in women. Non-dysgerminomas germ cell tumors include teratoma, embryonal carcinoma, endodermal sinus tumor (yolk sac tumor), choriocarcinoma and tumors with mixed histology. The tumors with even a small proportion of nondysgerminomas elements are classified as nondysgerminomas and are believed to have a more aggressive course than dysgerminomas [6]. In adults, the most common locations of primary extragonadal germ cell neoplasms by their frequency of occurrence are the mediastinum, retroperitoneum and cranium [6]. Very few cases have been reported primary in other organs such as thyroid, pericardium, liver, bladder, breast, urachus and vulva, between others [3,4,7-10]. We here report a case of primary malignant germ tumor type endodermal sinus tumor (yolk sac tumor) with pure hepatoid differentiation in the uterus, which is the first known reported in the literature.

Endodermal sinus tumor (yolk sac tumor) was first described as third most common type of ovarian germ cell tumors; it accounts for 1% of ovarian neoplasms and rarely originates in extraovarian sites. A variety of histological patterns such reticular, polyvesicular, papillary, solid; endometrioid and hepatoid have been described [11]. Prat et al. [12] described 7 samples of ovarian yolk sac tumors

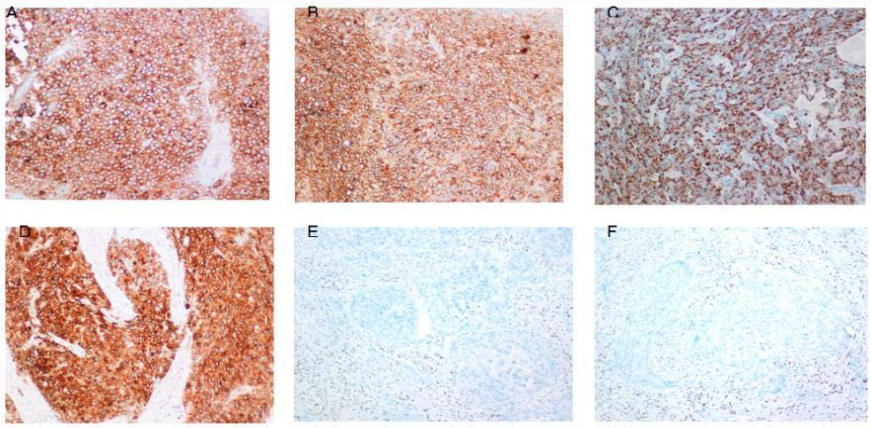

Figure 2: Immunohistochemistry analysis showed a strong and diffuse positivity to PLAP (A), AFP (B), Hep-par-1 (C) and GPC3 (D); and negative staining for ER (E) and PR (F) antibodies with adequate internal control.

that displayed a solid growth pattern reminiscent of a hepatocellular carcinoma and coined the term hepatoid yolk sac tumor for these lesions. The present case that we are describing also has uniform and diffuse hepatoid pattern as have been described in ovarian and extraovarian cases [13-16], however a predominant or pure hepatoid pattern is extremely rare. More commonly found, is the presence of foci of hepatoid differentiation, seen in up to 16% of ovarian yolk sac tumors [13]. Immunohistochemically, these tumors are positive to alpha 1-fetoprotein (AFP), hepatocyte paraffin-1 (Hep-par-1), glipican-3 (GPC3) and alpha-1-antitrypsin (AAT) all of which are normally synthesized by the adult or fetal liver [15,17]. The case here presented positivity for alpha-1-fetoprotein (AFP), hepatocyte paraffin-1 (Hep-par-1), glipican-3 (GPC3) and alkaline phosphatase activity (PLAP) as well. Estrogen receptors (ER), Progesterone receptor (PR) were negatives. ER and PR positivity are considered standard markers of endometrial adenocarcinoma [18]. Previously four cases of endometrial carcinoma (two with well and 2 with poorly differentiated areas) associated with foci of hepatoid differentiation have been reported [19-22]. The present case did not show features of a conventional endometrioid adenocarcinoma which further support our diagnosis.

There are three cases reported of the endodermal sinus tumor arising in the endometrium; the first was reported in 1980 in a 28-year-old woman, with positive to AFP. The second case showed the presence of Schiller Duval bodies and intra and extracellular hyaline globules which were Periodic-acid Schiff (PAS) positive [23-28]. The last case published in 1990 by Joseph et al. [29] showed the typical microscopic features of EST, with papillary, tubular, reticular and solid growth patterns; occasional Schiller-Duval bodies and many intracellular and extracellular PAS positive hyaline globules were seen. These last cases were positive for AFP as well [28,29]. None of them showed a hepatoid differentiation.

Ultra structurally, the endodermal sinus tumor with hepatoid differentiation contained numerous intracytoplasmic osmiophilic bodies of various sizes and densities. Intracellular and extracellular canaliculi are common. These spaces are lined by microvillis. The cells are attached to each other by desmosomes. The elevation in serum of AFP levels is not a unique feature of these types of tumors. Unfortunately, high AFP levels may also be associated with hepatoid carcinoma, hepatocelular carcinoma and ovarian carcinomas [13]. The presence of a hepatoid pattern confers an aggressive behavior and poor prognosis. Surgery combined with bleomycin, etoposide and cisplatin chemotherapy have dramatically improved the prognosis in the majority of cases, underlining the importance of recognition of this histopathological pattern. Survival is directly related to the International Federation of Gynecology and Obstetrics (FIGO) staging system at presentation. Measurements of serum AFP are useful to monitor tumor progression and response to treatment [12,16,30,31]. In our case, patient was not found to be eligible in any protocol and thus could not be followed up.

Conclusion

We here report a case of an endometrial germ cell tumor predominantly hepatoid type. The distinction between this entity and other endometrial tumors is important especially for treatment and prognosis.

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