Primitive neuroectodermal tumor (PNET) of the uterine isthmus

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Summary

Primitive neuroectodermal tumors (PNETs) of the uterus are very rare. The histogenesis of these tumors is still unknown and the differential diagnosis includes a wide variety of tumor entities. We describe a rare case of a 68-year-old female who presented with persistent vaginal bleeding. Physical examination and CT-scan revealed a large tumor in the uterus. Macroscopically the tumor involved the uterine isthmus. Histological and immunohistochemical examination showed that the tumor fulfilled the diagnostic criteria set for PNET. Only a very small number of cases of PNETs of the uterus have been reported in the literature, thus no definitive conclusions concerning the therapeutic management and prognosis have been ascertained.

Key words: Uterine isthmus; Primitive neuroectodermal tumor; PNET.

Introduction

The term *primitive neuroectodermal tumor* (PNET) was first coined by Hart and Earle [1] in 1973 to describe a group of neoplasms thought to be derived from fetal neuroectodermal cells. These tumors consist of small round cells, and often show variable degrees of neural, glial and ependymal differentiation. They are classified according to their location and cell origin into central and peripheral PNETs. Central PNETs involve predominantly the central nervous system (CNS) and are derived from the neural tube, while peripheral PNETs occur outside the CNS, involving the sympathetic nervous system, soft tissue and bone, and are derived from the neural crest [2]. PNETs of the female genital tract are rare, most commonly arising in the ovary [3]. Only a few cases of PNET of the uterine corpus [2, 4-14] and cervix [15-18] have been previously reported in the literature. We present an additional case of PNET of the uterus, located at the uterine isthmus, infiltrating both the uterine corpus and the cervix.

Case Report

A 68-year-old woman gravida 0, para 0, presented with postmenopausal vaginal bleeding, persisting for almost three months. The patient was under daily medication due to an organic mental syndrome, taking daily citalopram hydrobromide and olanzapine. There was no family history of gynecological diseases. The patient reported never having sexual intercourse and this was confirmed by physical examination, with an intact hymen noted. On abdominal ultrasound examination a large mass in the uterine isthmus area was seen. Abdominal CT-scan followed, confirming the presence of this mass. Chest X-ray showed no significant abnormalities. The patient had no endocrine symptoms related to the tumor. Total abdominal hysterectomy with bilateral salpingo-oophorectomy followed. Intraoperatively, no evidence of intrapelvic or intra-abdominal tumor was noted. Post-operatively the patient was treated with radiotherapy. The patient is in good condition ten months after the initial diagnosis.

Pathology

Macroscopically, the uterus was slightly enlarged, measuring 11.5 x 7.5 x 7 cm. The ovaries and fallopian tubes were normal. The opened specimen revealed a large, soft, grayish-white polypoid tumor that occupied the isthmus, infiltrated the cervix, part of the uterine corpus, and measured 7 x 6 x 3 cm. Deep myometrial invasion was identified on serial sections of the tumor. There was no extension to the serosal surface. Microscopically, the tumor was composed of small- to medium-sized, ovoid- to spindle-shaped undifferentiated cells, with hyperchromatic nuclei and a narrow rim of eosinophilic cytoplasm. The mitotic activity ranged between 8 and 12 in 10 high-power fields. The tumor cells were arranged diffusely. No Homer-Wright-type rosettes were seen. The tumor involved the cervix, part of the endometrium, and almost totally invaded the myometrium (Figure 1). The rest of the endometrium was atrophic. The ovaries and fallopian tubes were histologically normal.

Immunohistochemical stains with the peroxidase-antiperoxidase method were performed, using antisera against the following antigens: pan-cytokeratin, epithelial membrane antigen, glial fibrillary acid protein, synaptophysin, chromogranin, smooth muscle actin, desmin, vimentin, S-100 protein, human chorionic gonadotropin, alpha-fetoprotein, neuron-specific enolase, HBA-71, CD34 and leucocyte common antigen. The most prominent finding was immunopositivity of the neoplastic cells for Ewing's sarcoma-related antigen, HBA-71 (CD-99) (Figure 2), and neuron-specific enolase. There were also small foci with slight positivity to vimentin. All other markers were negative (Figure 3). The morphological and immunohistochemical characteristics of the tumor suggested a primitive neuroectodermal tumor of the uterus (PNET), rather than any other type of neuroectodermal tumor, such as glioma or malignant mixed mullerian tumor.

Revised manuscript accepted for publication December 1, 2003

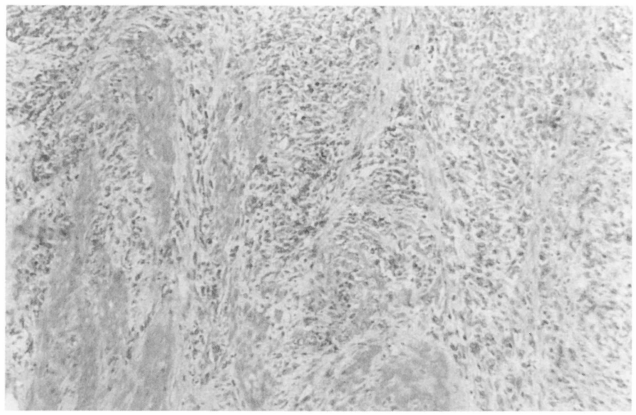

Fig. 1

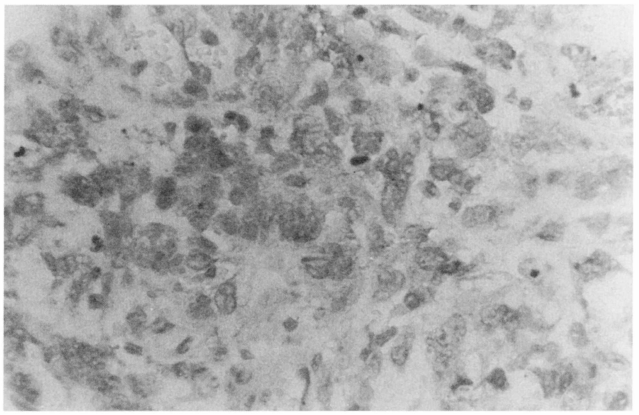

Fig. 2

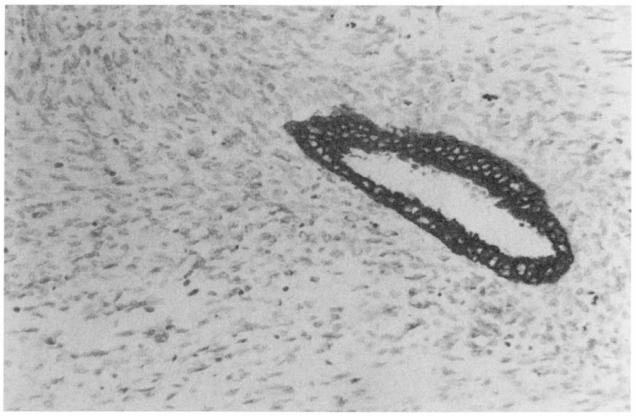

Fig. 3

Figure1. — Primitive neuroectodermal tumor invading the myometrium. The tumor consisted of small- to medium-sized, undifferentiated cells (H & E x 100).
Figure 2. — Positive staining with HBA-71 (CD99) in the cytoplasm of tumor cells (x 400).
Figure 3. — Immunostaining for pan-cytokeratin. Note the positive staining of endocervical glands surrounded by negative neoplastic cells (x 200).

Discussion

A very rare case of PNET arising from the uterine isthmus and infiltrating both the uterine corpus and the cervix is presented. Primitive neuroectodermal tumors of the female genital tract are very rare. Only 16 cases of PNET of the uterus have been previously reported in the literature [2, 4-14]. A pure PNET of the uterus was found in 11 of these cases, while in the rest of the cases only parts of the uterine tumor showed neuroectodermal differentiation [6, 12-14]. Five additional cases of PNETs and small cell tumors with neuroectodermal differentiation located in the uterine cervix have been previously reported [15-18]. However, due to pathological differential diagnostic problems, the actual number of PNETs of the uterus might be higher than that reflected in the literature [9].

Histologically, the differential diagnosis of PNETs should include tumors that show signs of neurogenic differentiation, as well as small round cell tumors, such as gliomas, uterine sarcomas composed of small cells, rhabdomyosarcomas, undifferentiated small cell carcinomas, malignant mixed mullerian tumors, immature malignant teratomas, neuroblastomas and malignant lymphomas. In all these cases not only the morphological characteristics, but also a panel of antibodies for immunohistochemical study is essential in reaching the correct diagnosis.

The histogenesis of primary PNETs is speculative. Several theories have been proposed: 1) PNETs of the uterus originate from fetal neural tissues after incomplete abortion or curettage [5, 6, 19]. However, it is worth noting with respect to this theory that the patient in the present case has never been pregnant, and neither was the patient in a previously reported case [11]. 2) PNETs of the uterus may represent teratomas with monodermal differentiation, as previously described in the ovary [3, 5, 8]. However immature teratomas of the uterus are extremely rare, and usually affect younger patients. On the other hand, in most of the reported cases of PNET of the uterus the patients have been postmenopausal, with only four cases presenting in adolescence [2, 4, 5, 11]. 3) The possibility of dedifferentiation of native neural elements has been proposed previously [5], but evidence is lacking. 4) Several authors [4, 8, 11, 15] have proposed that PNETs of the uterus originate from different, yet not differentiated pluripotent cell types: i) PNETs may be derived from displaced germ cells [4]. ii) Mesenchymal cells may be the progenitors of PNETs. iii) At least in some cases, the possibility of a mullerian origin of these tumors cannot be totally excluded [8, 11]. iv) PNETs may arise from aberrant neural crest cells [15].

In almost all previously reported cases of PNETs of the uterus, the patients presented with abnormal vaginal bleeding [2, 4-9, 11], and this was the initial presentation in the present case. Other reported clinical presentations were an enlarged uterus [4, 6, 7, 9] and a pelvic mass [4, 5]. Most patients were treated with total abdominal hysterectomy and bilateral salpingo-oophorectomy, and as in our case, received postoperative treatment - radiotherapy and/or chemotherapy. Concerning the prognosis of

uterine PNETs, though in some cases a dismal prognosis has been reported [4, 6-9], with death from disease occurring between six months and two years after the initial diagnosis, in other cases [2, 5, 6, 11] longer periods without evidence of disease, ranging between four and more than ten years, have been reported. The very small number of cases reported in the literature does not allow definitive conclusions to be drawn concerning optimal therapeutic management and prognosis.

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