Int J Clin Exp Pathol 2017;10(8):8746-8750
www.ijcep.com /ISSN:1936-2625/IJCEP0053240

Case Report

A very rare adult case of cervical neuroblastoma

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Received March 19, 2017; Accepted April 21, 2017; Epub August 1, 2017; Published August 15, 2017

Abstract: Neuroblastoma is the most common malignancy in children, but it rarely occurs in adults, especially in the female genital system. Here, we report a case of a 28-year-old woman who was diagnosed with uterine cervical neuroblastoma. A microscopic examination revealed that tumor cells in the solid component were interspersed within an abundant fibrillary background and separated by thin fibrous septa that were composed of mats of neuropil. Immunohistochemistry showed that the cells were positive for vimentin and neuroendocrine markers, such as CD56, NSE, and synaptophysin. Clinical management of neuroblastoma must be tailored to the pathological diagnosis. Cases of neuroblastoma that originate in the cervix of an adult patient are rare, and few treatment strategies and chemotherapeutic protocols are therefore available. The case reported here provides information regarding our experience with a pathological diagnosis of such a cancer and the treatment protocol used to manage it.

Keywords: Neuroblastoma, uterine cervix, primary neuroectodermal tumor

Introduction

Neuroblastoma is a kind of tumor that originates from neural crest cells and involves the peripheral sympathetic nervous system. It is one of most common solid tumors among infants and children. Itusually originates in the adrenal medulla but can arise anywhere within the sympathetic nervous system. Neuroblastoma normally affects children during the first year of life and is very rare among adolescents and adults. The most common site of involvement is the abdomen (60%), which is followed by the thorax (15%), pelvis (5%) and cervical sympathetic chain (5%) [1]. It is extremely rare for neuroblastoma to originate in the female reproductive system. To our knowledge, there are few such reports in the literature, including one of a primary cervix neuroblastoma [2], one of a broad ligament of the uterus [3] andfour of primary ovarian neuroblastoma [4-7]. The normal treatment for neuroblastoma is surgery, chemotherapy or radiotherapy, and there is no standard treatment protocol for adult neuroblastoma.

Here, we describe a case of adult neuroblastoma that originated in the cervix of a 28-year-old woman who was diagnosed with uterine cervical carcinoma.

Case report

A 28-year-old woman, G1P1, was admitted to our hospital with abnormal, slight vaginal bleeding for 3 months. Her surgical history was unremarkable, and her medical history included hypertension. The physical examination confirmed that there was a large irregular mass that had invaded the cervix. A biopsy of the cervix revealed a small round-cell malignant tumor. A bone scan and pelvic CT did not show any evidence of metastatic disease. The patient then underwent a total abdominal hysterectomy, a bilateral salpingo-oophorectomy and a pelvic lymphadenectomy.

Grossly, the tumor was located in the cervix and was an endogenous growth of approximately 3 cm indiameter. A cut made at the surface of the tumor revealed that it was yellowish without hemorrhage or necrosis and relatively well circumscribed (**Figure 1**). The neoplasm was confined to the cervix and had not invaded any adjacent structures. The bilateral fallopian tubes and ovaries and the pelvic lymph nodes showed no evidence of malignancy.

Microscopically, the mass was vaguely nodular and interspersed within an abundant fibrillary background when viewed under low power.

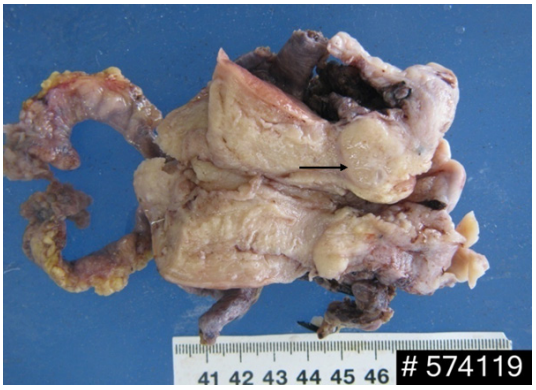

Figure 1. Gross appearance of a uterine cervical neuroblastoma. The arrow indicates the cutsurface of the cervical mass, which revealed a gray-white to yellow tumor that was relatively well-circumscribed.

Malignant cells that were separated by thin fibrous septa were observed to have formed mats of neuropil (**Figure 2**). The tumor cells were small and regular and had round, deeply staining nuclei that were slightly larger than those in the lymphocytes arranged around the cervical gland. There was little cytoplasm, and cytoplasmic outlines were poorly defined. The nuclei of the tumor cells formed Homer-Weigh rosettes and were arranged around a central area that was filled with a fibrillary material. Mitotic cells were easily seen. An exhaustive examination of multiple sections obtained from the tumor failed to reveal any ganglion cell differentiation or any other neuronal differentiation.

Immunohistochemistry showed that the cells were positive for vimentin and neuroendocrine markers, such as CD56, NSE, and synaptophysin. The tumor cells were negative for epithelial markers, such as AE1/AE3, CK7, EMA, and CK5/6, and negative for CD99, Nf, S-100, LCA, p63 and p16, and HMB45. However, they were focally and weakly positive for c-kit and GFAP (**Figure 3**). These histological features and immunohistochemical findings were consistent with those observed in neuroblastoma.

After surgery, the patient underwent three cycles of chemotherapy and whole pelvic radiotherapy. There was nosign of recurrence or metastasis at a 12 months follow-up after the surgery.

Discussion

Neuroblastoma currently represents 7% of all childhood malignancies, corresponding to approximately 1 case per 100,000 children per year. However, only 1 case per 10 million adults is diagnosed per year [8-10]. This disease can arise anywhere in the sympathetic nervous system and frequently occurs in the adrenalgland or sympathetic ganglia, where it arises in a paraspinal location in either the retroperitoneum or chest.

While neuroblastoma is rare in adult patients, it is important to consider small-, round-, blue-cell tumors as a differential diagnosis. The differential diagnosis for our case included Ewing's sarcoma/primary neuroectodermal tumor (PNET), lymphoma, poorly differentiated squamous carcinoma and adenocarcinoma, and small-cell endocrine carcinoma. Moreover, it could also have represented a metastatic tumor.

It is often difficult to distinguish between neuroblastomas and PNET using pathology. Our patient's diagnosis of adult neuroblastoma was made based on the morphological features ofthe neuropil in addition to negative CD99 staining and positive CD56 staining, which ruled out Ewing's sarcoma/PNET. Lymphoma is similar to neuroblastoma in that it presents as sheets of cytologically malignant small cells that do not show evidence of glandular or squamous differentiation. The absence of lymphoid markers, such as LCA, virtually excludes a diagnosis of lymphoma. With regard for poorly differentiated squamous carcinoma, adenocarcinoma and small-cell endocrine carcinoma, there was no evidence of keratinization, intercellular bridges or glandular differentiation and the fact that the cells were negative for epithelial markers excluded these diagnoses.

In our case, there was no evidence of a primary tumor anywhere according to our investigations, intraoperative data and the patient's lack of a previous history of neuroblastoma or ganglio neuroblastoma. Metastatic neuroblastoma could therefore be excluded. Hence, we considered this case to have a primary uterine cervical origin. Additionally, in some cases, the primary origin of the neuroblastoma remains unknown.

A previous study demonstrated that MYCN oncogene amplification is rare in adult neuroblastoma but is observed in 20-30% of pediatric neuroblastomas [4]. However, cytogenetic and MYCN amplification were not performed in

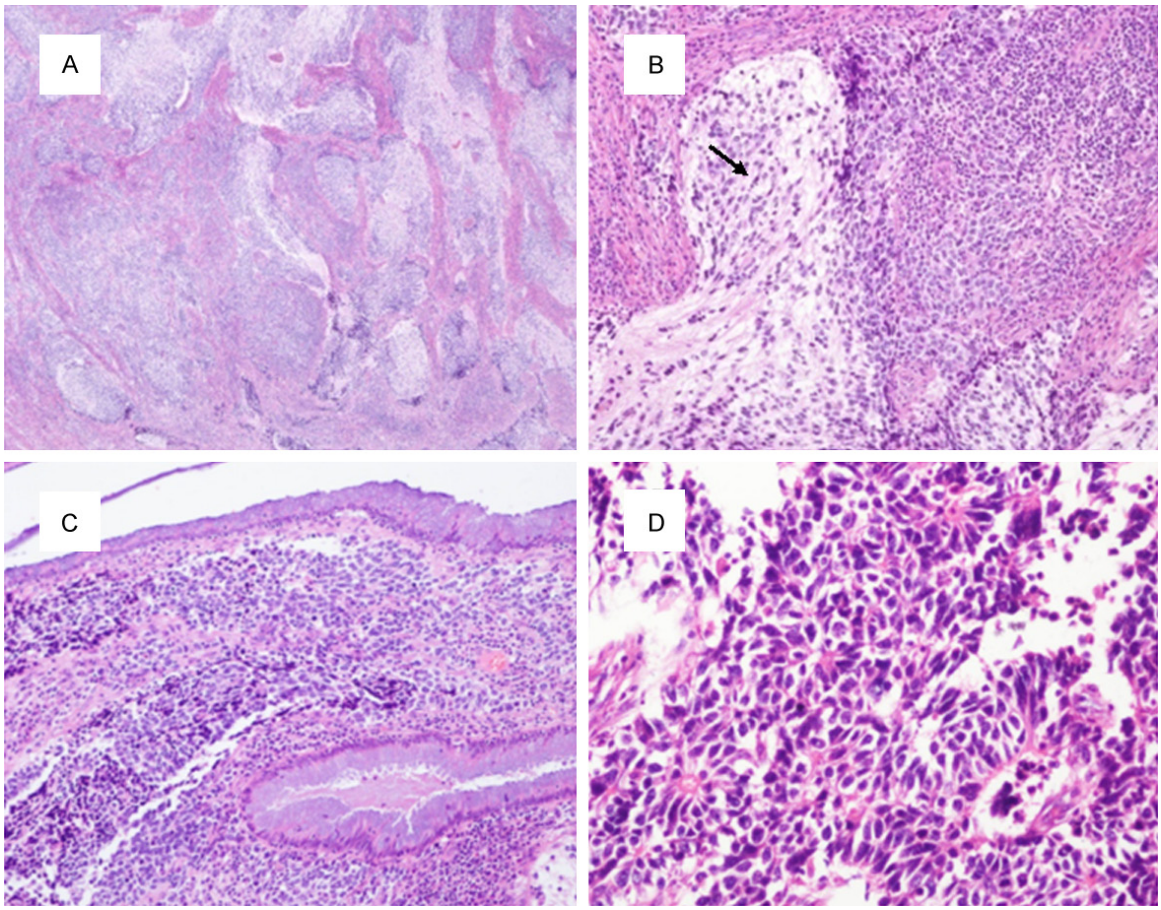

Figure 2. A: The mass had a lobular appearance and was interspersed within an abundant fibrillary background when viewed under low power (40×, H&E). B: Small, poorly differentiated tumor cells separated by fibrillary materialand mats of neuropil (arrow) were observed (H&E, 100×). C: Uniform malignant small-round cells arranged around the gland of the uterine cervix (H&E, 100×). D: The nuclei of the tumor cells formed Homer-Weigh rosettes, suggesting that the tumor was a neuroblastoma (H&E, 200×).

ourpatient, even though these may have contributed to the diagnosis.

A primary neuroblastoma of the uterine cervix was not described in the literature until 2007 [2], when Andreas Loeser and colleagues reported a recurrent case of neuroblastoma of theuterine cervix in an adult. However, two cases of small-cell tumors of the cervix that displayed neuroepithelial features have been described [11]. That study was the first to describe at the ultrastructural level the features of the cells in the cervix that are derived from the neural crest. Those authors suggested that it was possible for primitive neuralcrest cells (i.e., neuroblasts) to persist into adult life in proximity to peripheral nerves and nerve endings and that tumors could potentially originate from these cells to reside within the subepithelial connective tissue.

Because there is currently no treatment protocol for adult neuroblastomas, some previous reports have described strategies that were performed according to the pediatric guidelines. Although complete surgical resection is sufficient to treat low-risk and nonmetas tatictumors, combination therapy with radiotherapy and chemotherapy is necessary to treat disseminated and recurrent disease. To treat this case of cervical carcinoma, we chose classical chemotherapy and radiotherapy courses instead of previously reported therapies [3]. We also chose not to follow treatment protocols that have previously been established for children because a localized disease involves a more aggressive course in adults than in children. Then, C indicated that the standard chemotherapy protocols used for childhood neuroblastoma would not be effective in adults [12].

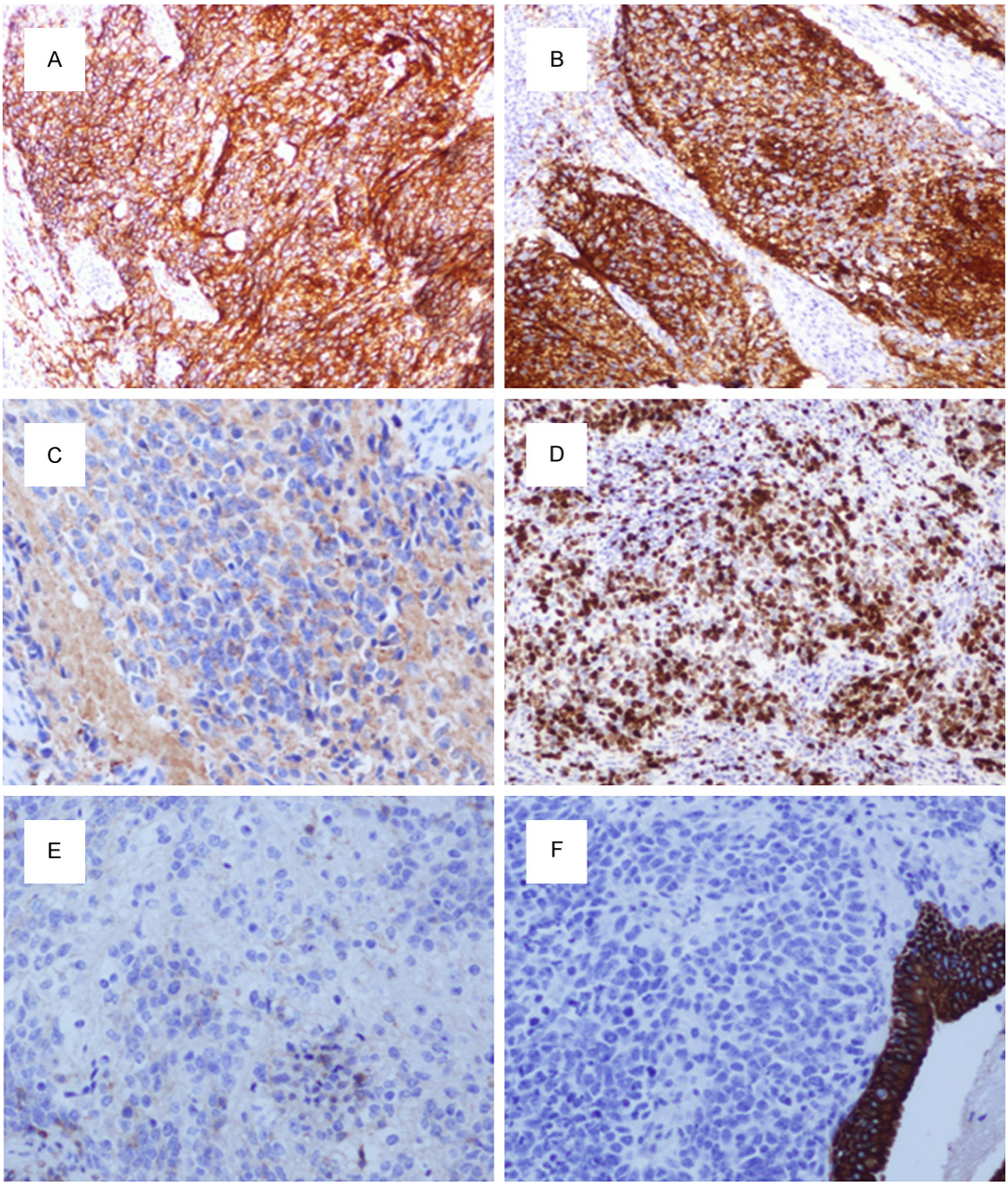

Figure 3. Immunohistochemistry showing small, nested, blue-round cells. A: CD56 at 200×; B: Synaptophysinat 200×; C: NSE at 200×; D: Ki67 at 100×; E: CD99 at 200×; and F: AE1/AE3 at 200×.

Although previous studies have concluded that adult neuroblastoma has a poorer prognosis than its pediatricvariant [4]. Conversely, Henry J et al. described the largest cohort of adult patients so far, and they argued that in all stage-matched categories, the prognoses for adult neuroblastoma patients were not significantly differentfrom those for pediatric neuroblastoma patients. Similarly, there was no significant difference in overall survival acrosspatients who received surgery or radiation, surgery and radiotherapy, or local therapy and chemotherapy [13].

We have reported this rare adult cervical neuroblastoma to share our methods for diagnosing

and treating this condition. The patient had an excellent response to treatment with typical chemotherapy and radiotherapy coursesfor cervical carcinoma, and no recurrence has been observed after more than one year. Further studies should be performed to reduce recurrence and improve clinical outcomes.

Disclosure of conflict of interest

None.

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