CASE REPORT

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Primary ovarian primitive neuroectodermal tumor of the ovary

Tumor neuroectodérmico primitivo primario de ovario

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ABSTRACT

Primitive neuroectodermal tumor of the ovary is a rare and aggressive small round cell soft tissue sarcoma of neural origin that is usually associated with high morbidity and mortality. Immunohistochemistry is a useful adjunct in the differential diagnosis. We describe a case of a primitive neuroectodermal tumor of the ovary in a 21-year-old nulliparous patient who reported pain and increased abdominal circumference. Ultrasonography showed a solid-cystic heterogeneous tumor apparently originating from the left adnexa. Magnetic resonance imaging confirmed the presence of a tumor extending into the left iliac fossa without local organ involvement or regional or distant metastases. Tumor markers were all within the normal range. During laparotomy, a left ovarian tumor was observed with a normal right ovary. Left salpingo-oophorectomy was performed due the size of the tumor, right ovarian wedge resection, pelvic lymphadenectomy and omentectomy. Histopathologic examination revealed tumor composed of sheets of round cells. The tumor cells were positive for chromogranin A, synaptophysin, vimentin and neuron-specific enolase, which confirmed the diagnosis of a primitive neuroendocrine tumor of the left ovary originating from immature cystic teratoma. The patient refused postoperative chemotherapy.

Key words: Ovary primitive neuroectodermal tumor, Soft tissue neoplasm, Sarcoma; Immunohistochemistry.

RESUMEN

El tumor neuroectodérmico primitivo del ovario es un sarcoma de tejido blando de células redondas pequeñas, raro y agresivo, de origen neural que generalmente se asocia con una alta morbilidad y mortalidad. La inmunohistoquímica es un complemento útil en el diagnóstico diferencial. Se describe un caso de tumor neuroectodérmico primitivo del ovario en paciente nulípara de 21 años que refería dolor y aumento de la circunferencia abdominal. La ecografía mostró tumoración de contenido heterogéneo sólido-quística que aparentemente se originaba del anexo izquierdo. La resonancia magnética confirmó la presencia de tumoración que se extendía hacia la fosa iliaca izquierda sin afectación de órganos locales ni metástasis regionales o a distancia. Los marcadores tumorales estaban todos dentro del rango normal. Durante la laparotomía se observó tumoración de ovario izquierdo con ovario derecho normal. Se realizó salpingoforectomía izquierda debido al tamaño del tumor, resección en cuña de ovario derecho, linfadenectomía pélvica y omentectomía. El examen histopatológico reveló tumor compuesto por láminas de células redondas. Las células tumorales fueron positivas para cromogranina A, sinatrofisina, vimentina y enolasa específica de neuronas, lo que confirmó el diagnóstico de tumor neuroendocrino primitivo de ovario izquierdo, que se originaba de teratoma quístico inmaduro. La paciente rechazó la quimioterapia postoperatoria.

Palabras clave. Ovario, tumor neuroectodérmico primitivo, Neoplasias del tejido blando, Sarcoma; Inmunohistoquímica.

Introduction

In the first 2 decades of life, about 70% of ovarian tumors originate from germ cells and one third of these are malignant. These malignant tumors represent only 0.1% of ovarian neoplasms and those with neuroectodermal elements are even rarer[1].

Primary primitive neuroectodermal tumor (PNET) is a small round cell soft tissue sarcoma and shares many morphologic features with Ewing's sarcoma, based on the shared chromosomal translocation in EWSR1 (Ewing's sarcoma breakpoint region 1)[2]. Although it usually occurs in the soft tissues of children and young adults, primary cases have been

reported in visceral sites such as kidney, ovary, vagina, testis, uterus, cervix, urinary bladder, parotid gland, heart, lung, rectum, pancreas, and gallbladder. Those that occur in the ovary are relatively rare and are associated with high mortality[3]. A case of primitive neuroectodermal tumor of the ovary is presented.

Case report

The patient was 21 years old, nulliparous, who came to the office for presenting diffuse abdominal pain, of mild to moderate intensity and of approximately 2 weeks of evolution, accompanied by an increase in abdominal circumference. The patient reported irregular menstruation in the last 12 months. She denied alterations in bowel habits, palpitations, tachycardia or sweating. She also denied a history of hypertension, diabetes mellitus or any significant personal history of neoplasms or cancer.

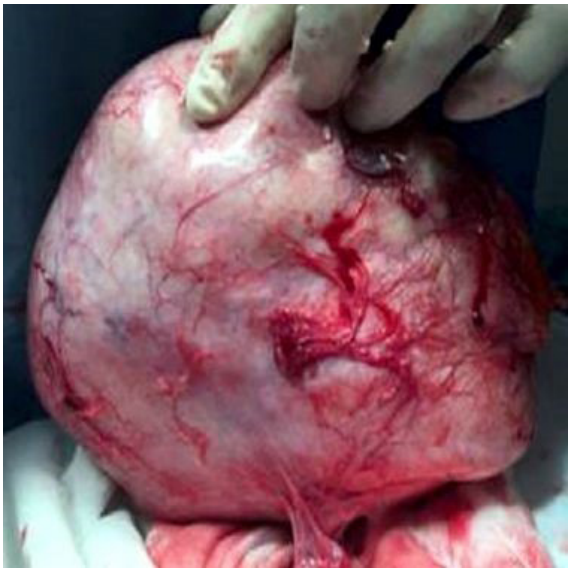
On physical examination, cardiac and thoracic evaluation were normal. Abdominal examination revealed a large abdomino-pelvic tumor, about two centimeters above the pubic symphysis, of regular shape of approximately 13 x 10 centimeters on the left side of the abdomen and attached to adjacent structures. The gynecological examination showed no alterations, a closed cervix without genital bleeding, and rectal examination revealed the presence of a tumor corresponding to the left adnexa without lesions of the rectal mucosa.

Ultrasound evaluation showed a tumor with a smooth surface and complex heterogeneous content with some solid and other cystic portions of approximately 11 centimeters in diameter and apparently originating from the left adnexa. Magnetic resonance imaging confirmed the presence of the tumor with solid and cystic structures, which extended through the left iliac fossa without local organ involvement or regional or distant metastases. Tumor markers (CA-125, alpha-fetoprotein, lactate dehydrogenase and human chorionic gonadotropin) were within normal limits, as were hematologic, electrolyte, renal and hepatic functionalism, and coagulation tests. Plain radiographs of the skull, thorax and long bones were within normal limits. Upper endoscopy and rectosigmoidoscopy showed no alterations. The possibility of ovarian teratoma was suspected.

During exploratory laparotomy, the left ovary showed a smooth surface tumor measuring approximately 15 x 12 x 10 centimeters with a normal right ovary accompanied by 500 mL of free fluid in the cavity. No retroperitoneal lymph node enlargement or peritoneal disease was observed. The cecal appendix, uterus and ovaries showed no signs of infiltration. Pathologic evaluation of the frozen sections during surgery was compatible with immature teratoma of the ovary. Left salpingo-oophorectomy was performed due to the size of the tumor, right ovarian wedge resection, pelvic lymphadenectomy and omentectomy, because the patient wished to preserve fertility, despite the potential risks of the tumor.

On pathology examination, the tumor had a smooth external surface, with a bluish-violet color and no signs of surface rupture (Figure 1). On section it was homogeneous and brownish, with some areas of cystic appearance (the largest measured 3 centimeters) with hemorrhagic content and homogeneous appearance. In the histological study, neural tissue and immature cartilage were found, with few mature elements. A 10-millimeter cellular focus composed of solid complexes with a high concentration of small cells with hyperchromatic oval nuclei, scarce cytoplasm and some rosettes, organized in lobules and divided by fibrovascular septa with a trabecular pattern was observed (Figure 2). The immunohistochemical test showed positive reaction for CD99, chromogranin A, synatrophysin, vimentin and neuron-specific enolase (Figure 3) and negative for desmin, chromogranin, cyto-

Figure 1. Macroscopic image of the ovarian tumor.



keratin and inhibin. The definitive diagnosis was primitive neuroendocrine tumor of the left ovary, originating from immature cystic teratoma (IC classification of the International Federation of Gynecology and Obstetrics). The right ovarian specimen, pelvic lymph nodes and omentum showed no evidence of neoplastic disease.

There were no intraoperative complications, the postoperative period was uneventful, and the patient was discharged after 5 days. Treatment with adjuvant chemotherapy was advised, but the patient refused any further treatment. No recurrence of the tumor has been reported after 2 years of follow-up.

Discussion

PNET is composed of immature neuroectodermal tissue, accounts for 3 to 6% of solid tumors and 1.4 to 8.8% of malignant processes. Most tumors occur between the second and third decade of life, at a slightly younger age than the well-differentiated form of neuroectodermal tumors and are more common in males. In a large number of cases, it is seen along the central axis, particularly in the soft tissue or bone of children and young adults, being the second most frequent sarcoma in these groups[4]. It is considered a distinct form within the Ewing's sarcoma / TNPP family because it has many similarities in histomorphology, immunohistochemistry and molecular biology. Both tumors result from reciprocal translocation of the long arms of chromosomes 11 and 22 and are located at different stages of neural differentiation. Regardless of origin, they are highly aggressive and rapidly metastasize to lung and bone[5].

Figure 2. Histologic findings of primary ovarian primitive neuroectodermal tumor. (A) Nodular lesion with round and oval cells. Hematoxylin-eosin stain, 20X. (B) Solid areas with clusters of small round cells separated by fibrovascular septa and areas of focal necrosis. Hematoxylin - eosin stain, 100X.

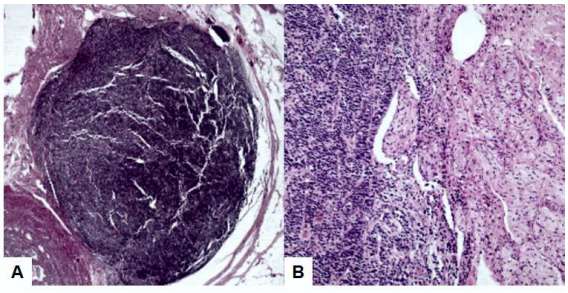
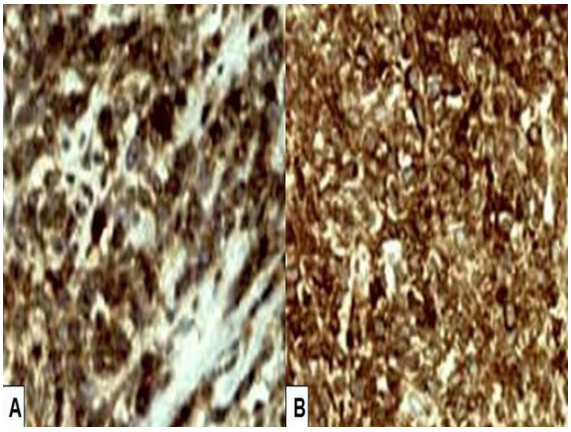


Figure 3. Immunohistochemical staining. A) Positive staining for CD99. B) Positive staining for neuron-specific enolase.



Accurate diagnosis is key to optimal management and prognosis in cases of PNET. The most frequent clinical manifestation is pain, enlargement and sometimes fever, weight loss, anemia, and leukocytosis. Physical examination often reveals abdominal and/or pelvic tumor accompanied by abdominal pain[6]. Imaging studies, such as computed tomography, show heterogeneous tumors originating from soft tissues and provide important information on tumor size, involvement of adjacent structures and presence of metastases.

The possibility of PNET should be considered as a differential diagnosis for ovarian tumors with unusual features, particularly if the patient is young. Lymphoblastic lymphoma, neuroblastoma, rhabdomyosarcoma, poorly differentiated synovial sarcoma, and Wilms' tumor are included among the differential diagnoses, because they are all small round cell tumors. The characteristic histology of PNET is composed of small cells with hyperchromatic, round or oval nuclei with scant cytoplasm. The cell lobules are separated by fibrovascular septa with some areas of necrosis[4]. Immunohistochemistry is essential to establish the diagnosis. The most commonly used diagnostic criteria are positivity for MIC2 glycoprotein (CD99) and at least two or more different neural markers positive and negative for lymphocyte common antigen and tumor immunohistochemistry markers to exclude lymphoma and small round cell myogenic tumors[7].

The concept of PNET is constantly evolving. Initially considered to be limited exclusively to the central nervous system and the most common malignant tumor in children, it is now recognized

that they also occur outside the central nervous system and are referred to in their central and peripheral variants. Although histologically similar, they represent clinical variants with different locations, immunohistochemical profiles and genetics[8]. The central variant is an embryonal tumor derived from the central nervous system, whereas the peripheral variant arises outside the central nervous system and expresses the chimeric EWS-FLI1 gene, which can be detected by CD99 immunohistochemical staining. Previous findings demonstrate that the majority of PNETs originating from testicular or ovarian germ cells have morphologic features of the central variety rather than the peripheral variety[9-11].

Ovarian PNET is highly aggressive and has a poor prognosis, especially in the presence of extraovarian dissemination. Because of its very low frequency, there is no consensus on the surgical approach or adjuvant therapy, such as chemotherapy and radiotherapy. The management of these cases is based on case reports and is largely extrapolated from the knowledge of transformed male germ cell testicular tumors[4,12]. The combination of surgery, radiotherapy and chemotherapy achieves increased survival and disease-free survival.

Chemotherapy is considered one of the most effective methods for treating metastatic tumors. However, it has been reported to be effective only during the first few cycles, as tumors develop resistance very quickly[10-15]. In the case of PNET arising from germ cell tumors, some authors recommend the use of chemotherapy based on bleomycin, etoposide and cisplatin[16]. However, other authors consider that, despite arising within germ cell tumors, these tumors are generally resistant to cisplatin-based treatment[17] and suggest chemotherapy with cyclophosphamide, doxorubicin, vincristine alternating with ifosfamide and etoposide[18]. Other authors have used chemotherapy targeting both PNET and germ cell tumor[19].

On the other hand, adjuvant radiotherapy is used in local recurrences, as well as for unresectable or incompletely resected tumors. A high initial complete response of 94% was observed in patients treated with chemotherapy plus local radiotherapy[1]. Because of the above, the prognosis is generally poor with a high mortality rate. The survival rate varies from 10 months to 3 years[4].

In the present case the decision was to perform conservative surgery plus chemotherapy according to the patient's age and fertility desires. There is evidence of the usefulness of fertility preservation surgery followed by chemotherapy for ovarian malignant germ cell tumors (even in advanced stages), with variable fertility rates[20,21]. One of the largest series of fertility preservation surgeries in patients with ovarian germ cell tumors reported a pregnancy rate of 76%[20]. Most of the patients in that series were in stage I of the International Federation of Gynecology and Obstetrics.

In conclusion, ovarian PNET is a rare type of germ cell tumor and should be considered in the differential diagnosis of malignant ovarian neoplasia, particularly in young women. The correct diagnosis of these atypical tumors should be made using available clinical and ancillary methods for their correct and timely treatment, due to the poor prognosis compared to other neoplasms. There is no consensus on the treatment strategy, although surgery, chemotherapy and radiotherapy are commonly used.

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