Sex cord tumors with annular tubules are known to originate from the sex cord of embryonic gonads that synthesize Sertoli cells, Leydig cells, granulosa cells, and theca cells of the ovarian stroma, while ovarian small cell carcinoma of the hypercalcemic type is a type of neuroendocrine tumor. Both these tumors are uncommon, potentially malignant neoplasms in children. We report the case of a sex cord tumor with annular tubules in an 11-year-old girl and a case of small cell carcinoma of the hypercalcemic type in a 10-year-old girl. We also discuss the prognosis and management of these tumors.

Key words: Sex cord tumors, Ovary, Annular tubules, Carcinoma, Hypercalcemia

Introduction

Before puberty, the majority of ovarian neoplastic lesions are germ-cell tumors. Sex cord tumor with annular tubules (SCTAT) is an infrequent malignant ovarian tumor in children. SCTAT is a distinctive ovarian neoplasm. The predominant component of which has morphologic features intermediate between those of the granulosa cell tumor and those of the Sertoli cell tumor. Small cell carcinoma of the ovary of the hypercalcemia type (SCCOHT) is an uncommon and aggressive ovarian tumor that primarily affects young women and that is rarely observed in premenstrual adolescents. SCCOHT is a kind of neuroendocrine tumor. We report a case of SCTAT in an 11-year-old girl, and a case of a SCCOHT in a 10-year-old girl. The diagnosis of these 2 cases of unusual malignant neoplasms of ovary had not been suspected before surgery.

Case reports

1. Case 1

An 11-year-old girl was admitted to our department for intermittent pelvic pain that had been standing for a year as well as menarche followed by irregular episodes of uterine bleeding. The pain was exacerbated by walking and improved slightly with nonsteroidal anti-inflammatory medications. She was initially evaluated by her general pediatrician. Abdominal ultrasound examination revealed an intraabdominal mass measuring 20 cm in diameter. The mass was intraperitoneal and was found to consist of a cystic neoplasm. No shadowing was visualized to suggest calcification (Fig. 1). On examination, her breast development was Tanner stage 3 and pubic hair was Tanner stage 2. Clinical signs of Peutz-Jeghers syndrome (PJS) were absent. Ovarian tumor markers, including α-fetoprotein (α-FP) and human chorionic gonadotropin (HCG) were within normal range. At laparotomy,
the right adnexa proved to be twisted but without necrosis. The tumor measuring 20 cm originated from the right ovary. It was a polycystic mass with a smooth surface filled with a clear yellowish fluid. The largest cyst measured 10 cm. The left ovary was grossly normal. No enlarged lymph nodes were found in the retroperitoneum. The omentum as well as the peritoneal surface were macroscopically unaffected. Tumor resection was carried out. Microscopic examination showed simple and complex ring-shaped tubules surrounding central hyaline material. The nuclei are located both at the periphery and centrally with intervening anuclear pale cytoplasm (Fig. 2A). Immunohistochemically, the tumor was strongly positive for calretinin (Fig. 2B), cytokeratin (Fig. 2C), vimentin and inhibin. Estradiol level in the cystic fluid was very high. A right salpingooophorectomy was performed 1 month later, because of the increased malignant potential of sex cord tumor with annular tubules. The patient had no event during 3 years of follow-up time.

2. Case 2

A 10-year-old girl was admitted to our department for acute abdominal pain. She had had an intermittent pelvic pain for 6 months without swelling or urinary frequency. There were no symptoms attributable to hypercalcemia. A history of weight loss could not be confirmed. On examination, the pelvis was tender without fever or any palpable mass. No features of precocious puberty were noted. Ultrasound examination showed a 6-cm solid right ovarian mass and ascites. There were no calcifications or lymphadenopathy (Fig. 3). An emergency laparotomy was performed revealing a necrotic right ovary due to torsion of an ovarian solid tumor. The left ovary looked normal and neither ascites nor adhesion was detected in the abdominal cavity. A right salpingo-oophorectomy was therefore performed. Histological and immunophenotypical studies concluded that it was a small-cell carcinoma of the ovary of the hypercalcemic type. Microscopy revealed prominent follicle-like spaces filled with eosinophilic fluid. Tumor cells were round and had scant cytoplasm (Fig. 4A). Immunohistochemistry is notable for pan-cytokeratin positivity and nuclear WT-1 staining. Pan-cytokeratin stain was positive (AE1/AE3/cytokeratin 7) (Fig. 4B, C). Subse-
quent laboratory tests revealed hypercalcemia (2.95 mmol/L). HCG, α-FP and cancer antigen 125 were normal. Chest X-ray, radionuclide bone scan and cerebral computed tomography scan were normal. The postoperative course was uneventful. In view of the highly malignant form of the tumor, the patient was given 6 courses of chemotherapy based on vinblastine (6 mg/m² intravenous [IV] over 30 minutes on day 1), cisplatin (90 mg/m² IV over 4 hours on day 1), and bleomycin (15 units/m² IV over 24 hours on day 2). Seven years after the initial surgery, the patient was free of recurrent disease (normal calcium level, negative staging including chest radiography and abdominal ultrasound).

Discussion

SCTAT represents 6% of sex cord stromal tumors and approximately 5% of all ovarian neoplasms. SCCOHT is a very rare tumor. A review of the literature notes only a few well-documented cases of SCCOHT in teenagers. SCTAT is known to originate from sex cord of embryonal gonads that make the sertoli cell leydig granulosa theca cell of the ovarian stroma, and the SCCOHT is a kind of neuroendocrine tumor.

The sole characteristic of SCTAT is based on histological finding along with the existence of simple and complex annular tubules, like in our patient. Immunohistochemical analysis frequently reveals the expression of vimentin, cytokeratin and inhibin. Tumor markers (HCG, α-FP) were negative for germ cell tumors. SCTAT was documented as an estrogen- and progesterone-secreting tumor. Menometrorrhagia followed by persistent amenorrhea and a pelvic mass are important clinical features. There are 2 forms of tumors: SCTAT associated with PJS that manifests itself as typically bilateral, multifocal, with small cysts and SCTAT without PJS in which the tumors generally present as large and unilateral neoplasms. In our first case...
lethargy, and coma and associated cardiac disturbances. Hypercalcemia may cause serious sequelae, including hypotonia, nausea and vomiting might be related to hypercalcemia. Severe symptoms like abdominal pain and a palpable mass. Symptoms like diagnosis in more than 60% of cases with SCCOHT. In fact, hypercalcaemia is present at the time of diagnosis. SCCOHT are suggestive of a heritable predisposition to SCCOHT, in young women. The combination of hypercalcemia and an ovarian mass in premenarchial girls should awaken the suspicion of SCCOHT. Radiological features are not specific as in sex cord tumor with annular tubules. According to the literature, prognosis of this tumor is extremely poor compared to other ovarian malignancies in children. Metastatic tumors have been shown to have a very diverse effect on survival. Treatment approaches have included surgery usually followed by adjuvant chemotherapy, radiotherapy or both. The optimal surgical approach is unknown, but, as the disease is unilateral in 99% of cases, it seems unnecessary to perform a bilateral salpingooophorectomy and hysterectomy. Unilateral oophorectomy associated with chemotherapy was widely applied. All long-term survivors, in the literature, received the combination of cisplatin and etoposide. However, it is impossible to clearly distinguish the effects of chemotherapy and radiotherapy and to determine their individual influence on survival. Thus, the use of radiotherapy remains questionable. Our patient received 6 courses of chemotherapy based on vinblastine, bleomycin and cisplatin without radiotherapy and with good outcome. Factors related to better outcome, in the literature, are age (>30 years), normal preoperative serum calcium, tumor size (<10 cm), and absence of large cells. Long-term prognosis of this tumor in pediatric patients is unknown as there are sparse data in the literature.

SCCOHT is highly aggressive malignant tumor occurs mostly in young women. The case studies of familial clustering of SCCOHT are suggestive of a heritable predisposition to SCCOHT, but the genetic etiology had yet to be characterized. Histogenesis of SCCOHT and the mechanism of development of the hypercalcemia are unknown. Histologically, the typical pattern is diffuse follicle-like sheets of small, closely packed cells with scant cytoplasm. The large cell variant consisting of the majority of cells with abundant cytoplasm is rare. As in epithelial ovarian carcinomas, CA-125 could be a very useful marker.

The immunohistochemical staining pattern typical for tumor cells in SCCOHT is positive for epithelial markers (cytokeratin positive, epithelial membrane antigen), INI-1, WT-1, calretinin, CD10, and p53. Due to the often nonspecific morphology, other high grade neoplasms must be excluded, especially germ cell tumors, like dysgerminoma (negativity of HCG and α-FP). Our report had provided specific morphology and updated immunohistochemistry and the hypercalcemia had evoked the diagnosis. In fact, hypercalcaemia is present at the time of diagnosis in more than 60% of cases with SCCOHT like in our patient. The general symptoms are nonspecific and include an abdominal pain and a palpable mass. Symptoms like nausea and vomiting might be related to hypercalcemia. Severe hypercalcemia may cause serious sequelae, including hypotonia, lethargy, and coma and associated cardiac disturbances.
calcemic type: a case report. J Pediatr Surg 2012;47:588-92.
4. Podczaski E, Kaminski PF, Pees RC, Singapuri K, Sorosky JI. Peutz-Jeghers syndrome with ovarian sex cord tumor with annular tubules and cervical adenoma malignum. Gynecol Oncol 1991;42:74-8.
5. Ishikawa H, Kiyokawa T, Takatani T, Wen WG, Shozu M. Giant multilocular sex cord tumor with annular tubules associated with precocious puberty. Am J Obstet Gynecol 2012;206:e14-6.
6. Shen K, Wu PC, Lang JH, Huang RL, Tang MT, Lian LJ. Ovarian sex cord tumor with annular tubules: a report of six cases. Gynecol Oncol 1993;48:180-4.
7. Yinon Y, Beiner ME, Gotlieb WH, Korach Y, Perri T, Ben-Baruch G. Clinical outcome of cystectomy compared with unilateral salpingo-oophorectomy as fertility-sparing treatment of borderline ovarian tumors. Fertil Steril 2007;88:479-84.
8. Estel R, Hackethal A, Kalder M, Munstedt K. Small cell carcinoma of the ovary of the hypercalcemic type: an analysis of clinical and prognostic aspects of a rare disease on the basis of cases published in the literature. Arch Gynecol Obstet 2011;284:1277-82.
9. Schleef J, Wagner A, Kleta R, Schaarschmidt K, Dockhorn-Dworniczak B, Willital G, et al. Small-cell carcinoma of the ovary of the hypercalcemic type in an 8-year-old girl. Pediatr Surg Int 1999;15:431-4.
10. Young RH, Oliva E, Scully RE. Small cell carcinoma of the ovary, hypercalcemic type: a clinicopathological analysis of 150 cases. Am J Surg Pathol 1994;18:1102-16.
11. Harrison ML, Hoskins P, du Bois A, Quinn M, Rustin GJ, Ledermann JA, et al. Small cell of the ovary, hypercalcemic type: analysis of combined experience and recommendation for management. A GCIG study. Gynecol Oncol 2006;100:233-8.