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Klinikinė praktika

Ovarian Dysgerminoma with Metastases in Supraclavicular Lymph Nodes Diagnosed in a 16-year-old Girl: Clinical Case and Literature Review

Kiaušidės disgerminoma su metastazėmis viršraktikauliniuose limfmazgiuose, diagnozuota 16 metų merginai: klinikinis atvejis ir literatūros apžvalga

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Background

Tumors of children reproductive system are rare, the most frequent among them is ovarian tumor. The most frequent histological type of ovarian tumor in girls and adolescents is germ cell tumor, with dysgerminoma being the most frequent of all. Symptoms are very non-specific, this is why these tumors are often diagnosed late. Dysgerminoma is a malignant tumor, thus if not treated, it may be potentially lethal.

Case report

We present a 16-year old patient, who has come to Vilnius University Hospital Santaros Klinikos, Children's unit, due to a sudden emergence of a growth above the left clavicle. The girl did not have any other specific complaints. Huge hard growth was founded during palpation of the abdomen. After the cancer marker test (alfa-fetoprotein – 1,9 kU/L, beta-human chorionic gonadotropin – 1231.0 U/L; lactate dehydrogenase – 2721.0 U/L; Ca125 – 665.8 kU/L), pelvic ultrasound examination, computed tomography and histological evaluation of the supraclavicular mass, dysgerminoma of the right ovary FIGO stage IV was diagnosed. The patient was treated with laparotomic oophorectomy and chemotherapy before and after surgery. Treatment was successful as 100% of tumor cells necrosis was achieved.

Conclusions

Girls and adolescents should be suspect to ovarian masses if they complains about abdominal pain, a growth in the abdominal area, disruptions of menstrual cycle or signs of premature puberty. Early diagnosis and treatment of ovarian dysgerminoma have a very good recovery rate in girls and adolescent.

Key words: ovarian tumors in girls and adolescents, malignant germ cell tumors, dysgerminoma, nonepithelial tumors.

Įvadas

Vaikų reprodukcinės sistemos navikai yra reti, būdingiausias iš jų – kiaušidžių navikas. Germinogeniniai navikai – dominuojantis mergaičių, ypač paauglių, kiaušidžių navikų histologinis tipas. Iš šių navikų dažniausia disgerminoma. Simptomai labai nespecifiniai, todėl navikai diagnozuojami vėlai. Disgerminoma – piktybinis navikas, todėl negydant prognozė gali būti letali.

Atvejo aprašymas

Į Vilniaus universiteto ligoninės Santaros klinikų Vaikų ligoninės priėmimo skyrių kreipėsi 16 m. pacientė dėl kairėje viršraktikaulinėje srityje staiga atsiradusio darinio. Kitų specifinių skundų mergina neturėjo. Čiuopiant pilvą aptiktas didelis kietas darinys. Atlikus vėžio žymenų tyrimus (alfa fetoproteinas – 1,9 kU/L, beta chorioninis gonadotropinas – 1231,0 U/L; lakatato dehidrogenazė – 2721,0 U/L; Ca125 – 665,8 kU/L), dubens organų ultragarsą, kompiuterinę tomografiją ir viršraktikaulinio darinio histologinį tyrimą, pacientei diagnozuota FIGO IV stadijos dešinės kiaušidės disgerminoma. Pacientei prieš operacinį gydymą ir po jo buvo atlikta laparatominė ovarektomija ir chemoterapija. Gydymas buvo sėkmingas – rasta 100 proc. naviko ląstelių nekrozė.

Išvados

Mergaitėms, ypač paauglėms, gali būti įtartas kiaušidžių darinys, jei skundžiamasi pilvo skausmu, dariniu pilve, nereguliariu mėnesinių ciklu ar ankstyva branda. Ankstyva mergaičių, ypač paauglių, disgerminomų diagnostika ir gydymas lemia labai gerą šių navikų prognozę.

Reikšminiai žodžiai: mergaičių, ypač paauglių, kiaušidžių navikai, piktybiniai germinogeniniai navikai, disgerminoma, neepiteliniai navikai.

Introduction

Tumors of children reproductive system are rare [1], the most frequent among them is ovarian tumor [2]. About half of all ovarian masses founded in juvenile and adolescent girls are neoplastic [1, 3, 4]. It accounts for 2.6/100 000 cases every year [5]. Approximately 10–20% of all neoplastic masses are malignant [1–4, 6–14]. Malignant ovarian tumors constitute 1–2 percent of all children's malignant tumor cases and 3% of girl's malignant tumor cases [2, 4, 7–10, 12]. Unlike adult females, juvenile and adolescent girls often have tumors of non-epithelial origin [2], they comprise as much as 80% of all tumors [2, 8, 9]. The most frequent among them are germ cell ovarian tumors (60–80% of all non-epithelial ovarian tumors) [1, 2, 4, 8, 14]. Young girls with ovarian tumors generally have a better survival rate than older women [2]. The 5 year overall survival (OS) of patients with malignant tumors of all stages is 98.5% (95% confidence interval (CI): 95.6–100%), 5 year event free survival (EFS) is 84.5% (95% CI: 76.5–93.5%) [16]. The survival of patients with early stages of malignant tumors after surgery and adjuvant chemotherapy (with platinum) is 90% [13]. The 5 year survival of patients with the first stage tumors is 95.6%, with advanced stage tumors – 73.2%, total survival rate (all tumors) is 89.4% [2].

Case report

16 year old patient arrived to Santaros Klinikos of Vilnius University Hospital, Children's unit, with a sudden formation above the left clavicle. The girl complained about frequent defecation (1–2 times daily), weight loss (9 kg per 2 months), dry cough (for about 1 month), and general weakness (for about 2 weeks). The examination results were as follows: pale skin, visible and palpable, painless and immobile formation above the left clavicle (4x4 cm). The patient was coughing irritably, vesicular breathing pattern on both chest sides was heard during the auscultation, and there was no crepitation. There was a visible abdominal asymmetry, and a palpable, large (30x30x35 cm) and hard formation in the abdomen, slightly on the right

side. Laboratory test results showed: alfa-fetoprotein (AFP) – 1,9 kU/L, beta-human chorionic gonadotropin (beta-hCG) – 1231.0 U/L; lactate dehydrogenase (LDH) – 2721.0 U/L; Ca125 – 665.8 kU/L. Liver and kidney function was normal, C reactive protein (CRP) was 54,6 mg/L. Pelvic ultrasound (US) examination showed a large (46x28x18 cm), solid, heterogeneous (with liquid spaces and calcinates) formation, growing out of the right ovary, and free fluid inside the abdomen. Computed tomography (CT) was used to verify the US examination findings, the results were as follows: supraclavicular pathological masses, pathological masses in the posterior mediastinum, bilateral pleurisy and fluid in the pleural space; pathological formation in the abdomen and pelvis: it's size was 27.24x25.51x13.25 cm, the tumor was lobulated, consisting of two big nodes, it had necrotic zones and calcinates; hepatosplenomegaly; free fluid in the abdominal cavity. Germ cell ovarian tumor with metastases in the supraclavicular lymph nodes was suspected. Following a biopsy of the supraclavicular lymph nodes, the suspicion was confirmed. No metastases were found in the bone marrow. The patient was diagnosed with dysgerminoma of the right ovary FIGO stage IV. The patient was prescribed chemotherapy treatment – three cycles of BEP (cisplatin / etoposide / bleomycin). Later beta-hCG, LDH and Ca125 decreased till 5.9 U/L, 418.0 U/L and 169.9 U/L, respectively. CT also was repeated after chemotherapy: there were no pathological masses left in the left supraclavicular area; the ovarian tumor and lymph nodes conglomerates in the posterior mediastinum and the retroperitoneal space showed a partial response to the treatment – 50% reduction; hepatosplenomegaly persists; pleural and abdominal cavity fluids were no longer present. The decision was made to operate the patient. During the laparotomy, the right ovary and the affected part of the right fallopian tube were removed. The hardened and enlarged para-aortic lymph nodes of the retroperitoneal space were removed as well. Results of the histological examination showed: dysgerminoma of the right ovary; metastases of dysgerminoma in the supraclavicular lymph nodes; full post-therapeutic regression of ovarian dysgerminoma and metastases in the supraclavicular lymph nodes: 100% post-therapeutic cell necrosis and fibrosis. An immunohistochemical examination showed that 100% of the tumor cells were positive for CD117 and Salla4 markers. The 4th chemotherapy course was applied after the laparatomic oophorectomy. Then CT was repeated, and it showed active lymph nodes conglomerate, therefore it was decided to do relaparotomy. The para-aortic nodes of the retroperitoneal space were removed; histology showed necrotized cells of dysgerminoma metastases. The patient's five months duration treatment was successfully completed; long term follow-up was applied to prevent potential relapse.

Discussion

In 2014 the World Health Organization (WHO) announced the new histological classification of ovarian tumors. In this classification, superficial epithelial ovarian tumors are classified into serous, mucinous, endometrioid, clear cell, Brenner, seromucinous, undifferentiated, mezenchymal and mixed epithelial-mesenchymal tumors. Non epithelial tumors are divided into sex cord-stromal and germ cell tumors. Among all histological types of tumors, benign, bordeline or malignant tumors are present [15]. Germ cell ovarian tumors are most commonly diagnosed in the first two decades of life, averagely at 16–20 years [16]. They account for as much as 70% of all ovarian tumors in women aged 10–30 years [1, 2, 4, 14]. 20–30% of germ cell tumors are malignant and represent 1–3% of all ovarian malignant tumors [4, 16, 17]. Malignant germ cell tumors include immature teratomas, dysgerminomas, yolk sac tumors, embryonic tumors, choriocarcinomas, poliembriomas and mixed tumors. Other rare malignant germinal tumors belong to the heterogeneous tumor group [18, 19]. Immature teratomas, dysgerminomas, yolk sac tumors and mixed tumors account for 90% of all germ cell tumors (dysgerminomas are the most common ones, 34% cases, immature teratomas make up 30% cases) [2, 16, 17]. Germ cell tumors are usually one-sided, discovered in the first stage and are susceptible to chemotherapy [2, 3, 6, 7, 9], their prognosis is very good [1.9]. 5 year OS is >95%, the best survival rate is in case of dysgerminoma, the worst one is in case of immature teratomas, yolk sac tumors and mixed tumors [17].

Clinical diagnosis of ovarian tumors consists of clinic, cancer markers, US, CT/MRI (magnetic resonance imaging) and intraoperative data. The final diagnosis

of tumor is determined only after the findings of the histological examination [17–21]. Ovarian tumor is differentiated from the primary neoplastic and non-neoplastic pathology of other organs (not ovaries). It should be kept in mind that ovaries may have secondary malignant tumors – i.e. metastases of tumors of other organs [18]. Ovarian tumors are usually asymptomatic in the early stages and are therefore diagnosed late. The most common symptom of ovarian tumors is abdominal pain. It can be accompanied by dyspepsia and disorders of urination or defecation. Menstrual disorders, signs of premature puberty or virilization are common. The tumor can be discovered by performing a bimanual examination *via* the rectum, vagina or abdominal wall. Cancer markers typical for dysgerminomas are: AFP, beta-hCG, LDH, Ca125 [17–21]. Ovarian masses are diagnosed with transabdominal and transvaginal pelvic ultrasonography [17–21]. CT and / or MRI with contrast are used for differential diagnosis and appropriate staging [4, 17, 20]. Dysgerminomas are large, solid, lobulated, hyper / neo-vascularized tumors of varied echogenicity. Multiplicity, septations and compartments of the tumor are common [22, 23]. Tumor cells are positive for Salla4, OCT3/4 and CD117 markers during an immunohistochemistry examination. In the future, these markers can be used for treatment with target therapy [18, 24, 25].

Gonadal dysgenesis is a risk factor for germ cell ovarian tumors. Gonadoblastoma is a rare sex cord-stromal tumor. A pure gonadoblastoma is a benign tumor, but in 50–60% of cases it contains malignant germinal tumor cells [17], most frequently it is dysgerminoma [26, 27]. Gonadoblastoma is most often associated with gonadal dysgenesis [1]. Mutations of 12p chromosome and c-kit gene in 4q chromosome are found in >80% of dysgerminoma cases. It is thought that the mutation of kit gene leads to development of more malignant tumor. It has been observed that the amplification of kit gene is directly related to the expression of the KIT protein in tumor cells [28, 29].

Surgery and chemotherapy are used to treat malignant ovarian tumors in girls and adolescents. The aim of the treatment is to leave as much of the healthy ovarian tissue as possible without compromising the radicallity of the treatment, since about 20% of cases are characterized by metachronous tumors in contralateral ovary [1, 6–9]. Laparotomic oophorectomy is the first-line treatment for the elimination of children's malignant tumors [7, 21]. During the operation a partial surgical staging is performed. The stage of the tumor is established according the FIGO classification [18, 19]. After the surgery adjuvant chemotherapy is prescribed to all patients except those with IA or IB dysgerminomas. First-line choice is 3/4 cycles of PEB (cisplatin / etoposide / bleomycin). The neoadjuvant chemotherapy may also be applied, when tumor is inoperable. After the treatment the patient should be monitored for a long time (at least 5 years) due to the potential for recurrence [13, 16, 18].

Conclusions

Malignant ovarian tumors in girls and adolescent is very rare pathology, however, if not treated, it may be potentially lethal. The most frequent tumors in this particular age group are the tumors of germ cells – dysgerminomas. Symptoms are very non-specific, this is why these tumors are often diagnosed late. Juvenile or teenage girl's complains about abdominal pain, a growth in the abdominal area, disruptions of menstrual cycle or signs of premature puberty, should rise a suspicion of ovarian tumor. Early diagnosis and treatment have a very good recovery rate [30, 31].

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