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MINI REVIEW

Childhood Ovarian Malignancy

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Abstract Objective of this article is to appraise diagnostic aspects and treatment modalities in childhood ovarian tumor in background of available evidence. Literature search on Pubmed revealed various aspects of epidemiology, histopathological diagnosis, and treatment of pediatric ovarian tumor. 85 % of childhood tumors are germ cell tumors. The varied histopathological picture in germ cell tumors poses a diagnostic and therapeutic challenge. Immunohistochemistry and newer genetic markers like SALL4 and karyopherin-2 (KPNA2) have been helpful in differentiating ovarian yolk sac tumor from dysgerminoma, teratomas, and other pictures of hepatoid, endometrioid, clear cell carcinomatous, and adenocarcinomatous tissues with varied malignant potential. Before platinum therapy, these tumors were almost fatal in children. Fertility-conserving surgery with bleomycin, etoposide, and cisplatin has dramatically changed the survival rates in these patients. This modality gives cancer cure with healthy offspring to female patients with childhood ovarian tumor. Evidence also supports this protocol resulting in successful pregnancy rates and safety of cytotoxic drugs in children born to these patients.

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Introduction

This article addresses a clinical dilemma in diagnosis and management strategy for childhood ovarian malignancy. Conserving fertility, achieving the longest remission period, and balancing therapeutic doses and side effects of cytotoxic drugs in this age are the challenges. It is universally agreed that uterus and contralateral adnexa be preserved, complemented with bleomycin, etoposide, and cisplatin (BEP) therapy. As these tumors are rare and potentially malignant, all aspects of histologic diagnosis and treatment are considered. Search for text on Pubmed is presented in this article.

Gynecological malignancy accounts for 1–2 % of all pediatric cancer, age 1–15 years. The diagnosis is challenging due to varied histologic features. The incidence of ovarian masses in childhood is 2.6 cases per 100,000 girls per year, and 50 % are malignant; 85 % are germ cell tumors (GCT), 8 % epithelial cell carcinoma, and 5 % sex cord stromal tumors. Until mid of twentieth century, 10-year survival was poor in GCT. Ovarian yolk sac tumor (OYST) is a special variety comprising tissues derived from all three germ cell layers, and it is having a high malignant potential. Generally, 75 % of all ovarian malignancies are in clinical stage two to stage four at

diagnosis. On the contrary, GCT is diagnosed early due to appreciably fast growth in a female child. Mostly, it is in clinical stage one at diagnosis [1]. It is seen in right-sided ovary in less than 10 years age group and has good response to chemotherapy. The prognostic marker is typically high levels of serum alfafetoprotein (AFP) as high as 1000 ng/dl. Usually, children with less than 1000 ng/ml have better prognosis than those with higher values.

Etiology

Genetic origin of ovarian malignancy is present in 5–10 % of all cases, the childhood tumors are not exempted from it. BRCA 1 and BRCA 2 have already established linkage with breast and ovarian malignancy. KPNA2 is a candidate oncogene, estimated in different cancer tissues by microarray assay. Its validation by real-time polymerase chain reaction and Western blotting techniques documented higher expression in OYSTs. It is a potential candidate molecular and prognostic marker in all GCT [2]. A transcription factor GATA4 is also shown to be regulator for differentiation of yolk sac endoderm along with RUNX3 gene promoter [1]. But this has not yet received sufficient scientific proof. SALL4 is a stem cell marker essential to maintain pluripotency, self-renewal of embryonic stem cells, which is shown to be sensitive and highly specific marker for GCT [3]. The genetic correlation may be of much prognostic importance in future. To date, we very much rely on clinical, serological, and immunohistochemical markers.

Clinical Presentation

Abdominal pain is the commonest symptom (50–75 %). Occasionally, they can present with torsion, rupture, and hemorrhage with acute abdomen. Vaginal bleeding in a girl child can be a pathognomonic symptom and may be due to hormone-secreting tumor which is rare but can be confused with precocious puberty due to feminizing adrenal tumors and gonadotrophin-secreting lesions of pituitary. Most of the patients have clinically palpable non-tender mass and absence of ascites.

Pathology

The cut surface is tan, white, or gray with small cysts and areas of hemorrhage and necrosis. GCTs are almost always unilateral, solid or solid and cystic tumor, display a wide range of histologic pattern; as microcystic papillary, sinus, alveolar, glandular, papillary, myxomatous, macrocystic, hepatoid, primitive endodermal, and polyvesicular vitelline pattern. OYSTs show perivascular formations mimicking glomerulus (Schiller–Duval bodies) and eosinophilic globules which contain AFP. Yolk sac tumor shows five major patterns. A mixture of patterns is present in most tumors.

Radiological Diagnosis

Ultrasonography and CT can diagnose if tumor is solid or cystic and the lymph-vascular space invasion. The staging is final after laparotomy. Recently, some authors considered a score for preoperative evaluation to predict malignant potential as histopathological diagnosis is always postoperative. The features are maximum diameter of solid component on radiology, presence of sex hormone-related symptoms, and enhancement of flow in a septum or solid papillary projection on CT scan [4].

Histopathological Diagnosis

Schiller–Duval bodies, which consist of fibro-vascular papillae covered by columnar tumor cells projecting into glands or cystic spaces lined by cuboidal cells, are characteristic and diagnostic of YST. Rare patterns include a hepatoid pattern composed of sheets or trabeculae of large cells with central vesicular nuclei with prominent nucleoli and abundant granular eosinophilic cytoplasm. Ovarian hepatoid yolk sac tumor is a highly aggressive tumor, and most patients exhibit recurrence or die of disease within 2 years of diagnosis. The endometrioid-like variant can be mistaken for endometrioid carcinoma. Intestinal pattern can mimic a primary or metastatic mucinous tumor. Malignant endodermal cells within YST express AFP. Small, bland, enteric glands lined by columnar and goblet cells are found in 50 % of YST and may be admixed with mucinous carcinoid tumor. Myxoid stroma stellate cells which stain with cytokeratin and vimentin are prominent in 25 % of YST.

Immunohistochemistry and Diagnostic Patterns

The most important immunohistochemical finding in YST is positivity for AFP. GCTs are cytokeratin positive but epithelial membrane antigen (EMA) negative. Lack of staining for EMA and positive staining for AFP differentiate GCT from clear cell carcinoma (CCC). CD 15 is usually strongly positive in CCC but negative in EST. Small or large zones of hepatoid differentiation in YST having positive staining for anti-hepatocyte antibody mimic hepatoid carcinoma.

It is important for pathologist to be aware that YSTs may mimic endometrioid adenocarcinoma and CCC. The

distinction is important for the clinical management of patients with these tumors. AFP staining is focal in most YSTs, and so absence of staining does not rule out this diagnosis. GLYPICAN3 and SALL4 in YSTs are important as AFP is positive in only 60 % of cases. Glypican and SALL4 are specific stains for GCT. SALL4 is more diffusely staining nuclear marker and is closely associated with metastatic OYST [3]. KPNA2 is overexpressed and is associated with uncontrolled ascitic fluid, suboptimal cytoreductive surgery, and resistance to initial chemotherapy. The low expression of KPNA2 was significantly associated with high survival rates [2].

An Overview of Management Protocols

Till 1970, cyclophosphamide was popular drug in therapy of ovarian malignant tumors. Generally, childhood tumors turned fatal due to lack of postoperative intensive care and hesitation in using cytotoxic drugs in infants and children specially in Indian setting. After 1971, cisplatin came in practice and showed its beneficial effect in ovarian cancer. From this time till date, surgery with BEP regimen is standard protocol with almost cancer cure for GCTs.

In as early as 1982 and 1989, there are reports of patients of GCT treated with combination of cisplatin, vinblastin, and bleomycin with the longest remission of 33 months in 88 % of cases [5, 6]. BEP combination with or without conservative surgery resulted in 81 % remission rate in studies conducted in last decade of 20th century [7–9]. Some reports advocate advantages of surgery alone and reserve chemotherapy for relapse. Gradually, BEP results showed its efficacy in achieving long remission periods and fairly adequate drug tolerance. A review of 47 patients with fertility-sparing surgery and cisplatin regimen had good prognosis, documented by Japanese study in last two decades of twentieth century [10, 11].

Experiences with Fertility-Sparing Surgery and BEP

In advanced stage disease, fertility-conserving surgery with adjuvant BEP has 72 % survival for 36 months and is as effective as radical surgery [12]. Children (median age 18 years) with OYSTs, undergoing conservative surgery and cumulative high-dose combination chemotherapy (BEP), had 90 % survival at 6 years, gave birth to children, and showed no adverse effect of chemotherapy on ovarian function [13]. de La Motte Rouge et al. [14] reported 84 cases without ascites having 84 % five-year survival with favorable serum AFP decline rate, with fertility-conserving surgery and not radical surgery. Only combination of BEP is the best reported therapy for GCT of vagina where surgery is not amenable in very young children (mean age 18 months) [15].

Effect of BEP Chemotherapy on Menstruation, Pregnancy, and Offspring

Five-year survival rate was 84 % for GCT, with 35 babies born without any adverse effect on menstrual function, pregnancy, and offspring [16]. A Malaysian report shows less favorable outcome in endodermal sinus tumors as compared to GCT as long as fertility is considered if treated with conservative surgery and BEP [17]. Chang YW et al. [18] in February 2013 reported an 18-year follow up in 13-year-old girl treated with same protocol having disease free long period and naturally occurring successful pregnancy.

Vomiting is the only adverse side effect of BEP. FIGO stage at diagnosis, residual disease after surgery, and declining AFP levels are prognostic markers in GCT. Before the advent of combination chemotherapy, GCT was almost universally fatal. Addition of Cisplatin to combination regimens improved survival rates very much even for advanced stage tumors. In fact, the credit of long remission periods, conservation of fertility, and menstruation is the boon of Platinum Era. A girl child would be considered lucky to have GCT of ovary than any other one if at all she has to have a malignant tumor.

Conclusion

Childhood ovarian malignancy is as such rare, but it poses a clinical challenge due to its varied histologic nature and fatal outcome. Immunohistochemistry has revolutionized the diagnosis and dilemma due to mixed picture of germ cell tumors. BEP therapy with fertility-conserving surgery is the gold standard resulting in long remissions and successful pregnancy

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