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Diagnostic Significance of Cd117(C-Kit) in Ovarian Dysgerminoma

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Abstract
18 cases of dysgerminoma of the ovary retrieved from 1996 to 2005 from the Histopathology Department of Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan were examined.Tumor size ranges from 10 to 21cms in greatest dimension. Of the 18 cases, 17(94%) demonstrated immunoreactivity with CD117.

Introduction

The protoncogene C-Kit encodes a145-160 KDa type 3 transmembrane tyrosine kinase receptor known as C-Kit or CD117 [3-8]. The antibody recognizes extracellular domain and is expressed by a variety of normal and abnormal cell types. C-Kit is similar to platelet derived growth factor receptor family. The binding of stem cell factor, the ligand for this receptor leads to dimerization of C-Kit proteins leading to cell growth.

In normal cells, the CD117 antibody has been shown to label breast epithelium, germ

cells, melanocytes, stem cells and mast cells. In abnormal cells, aberrant expression is seen in testicular germ cells, endometrial carcinoma , papillary and thyroid carcinomas, small cell carcinomas, melanoma and ovarian epithelial carcinoma. It has also been shown to be an effective marker for mast cell disorders , gastrointestinal stromal tumors and immunotyping of blasts in human bone marrow.

The advent of therapies targeted to C-Kit have proven highly effective in treating some malignancies that over express this receptor such as gastrointestinal stromal tumors (GIST) and chronic myeloid leukemia(CML). Imitanib mesylate (Gleevec) is a tyrosine kinase inhibitor that specifically targets C-Kit, Abl and platelet derived growth factor receptor (PDGFR). It has been shown to be an effective treatment for patients with CML and GIST.

Ovarian dysgerminomas are rare ovarian tumors accounting for 1-2% of all ovarian cancer [1] but are the most common malignant germ cell tumors of the adolescent women in the first two decades of life. Despite availability of modern treatment options present, the most common complication is threat to the fertility of young patients.

Ovarian dysgerminomas are histologically and immunophenotypically shares features with its male counterpart that is testicular seminoma. There is a well documented and established role of CD117 in testicular seminomas [2] but there is a little data pertaining to its expression in ovarian dysgerminomas . Despite availability of Placental alkaline phosphatase(PLAP) and Cytokeratin(CK) immunohistochemical stains, accurate diagnosis of dysgerminoma is sometimes difficult. Therefore, a need for an immunohistochemical stain that is sensitive and specific for dysgerminoma is needed, so in this regard CD117 will serve this purpose.

Conventional treatment available for dysgerminomas are cisplatin and carboplatin based chemotherapy and radiotherapy, although the response of patients with these therapies is generally good but the most devastating and fatal complication is threat to the fertility of young females.

The identification of cellular C-Kit proteins that may be over expressed in this tumor could potentially leads to targeted therapies as seen in CML and GIST with less devastating side effects [3]. Therefore, we analyzed the immunohistochemical expression of CD117 in 18 cases of dysgerminoma of the ovary.

Materials and Methods

In all 18 cases of dysgerminoma of the ovary retrieved from 1996 to 2005 from the Histopathology Department of Shaukat Khanum Memorial Cancer Hospital. Formalin fixed paraffin embedded tissue specimens were available for all cases. Section 4 micrometer thick were cut from paraffin blocks and stained with hematoxylin and eosin for microscopic examination. This research was approved by Institutional Review Board. Additional paraffin sections of selected blocks were performed on an automated immunostainer. Immunohistochemical staining was performed. The expression of C-Kit was evaluated in a semiquantitative manner. Staining was graded as follows: Negative (no staining) , 1+ (1-10%), 2+ (10-29%), 3+ (30-50%) , or 4+(> 50%) . C-Kit is a transmembrane tyrosine kinase receptor so only membranous pattern of staining was interpreted as positive.

Results

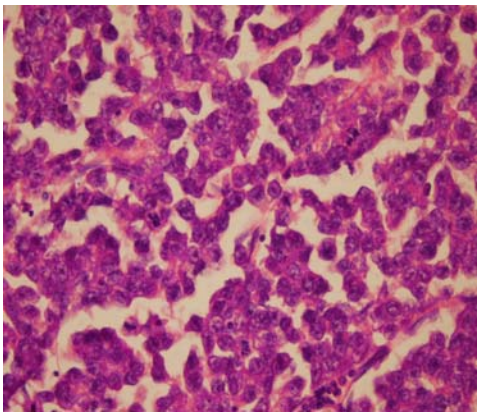
The 18 patients examined had a mean age of 23 years (range 16 to 29 yrs) . Tumor size range from 10 to 21cms in greatest dimension. Of the 18 cases examined , 17(94%) demonstrated immunoreactivity with CD117. In total, 11(61%) demonstrated 4 + staining; 3(16%) demonstrated 3+ staining; 1(5.5%) demonstrated 2+ staining; 2(11%) demonstrated 1+ staining ; 1(5.5%) demonstrated no staining with CD117.

Discussion

CD117 is expressed in vast majority of human malignancies including malignancies of the breast, endometrium, lung, gastrointestinal tract, genitourinary tract and hemopoeitic

system. Many studies have shown CD117 expression in endometrial carcinoma and gynaecological malignancies. Over expression of CD117 is well documented and well established in common germ cell tumor that is accounting for about in 50% of testicular seminomas. CD117 expression has not been successfully explored in ovarian dysgerminomas that is histologically and immunophenotypically similar to testicular seminomas. Because dysgerminomas constitutes only about 2% of all ovarian malignancies.

In this study, we analyzed 18 cases of ovarian dysgerminoma with anti C-Kit antibodies and found that, like seminomas, these tumors frequently exhibits immunoreactivity for CD117.



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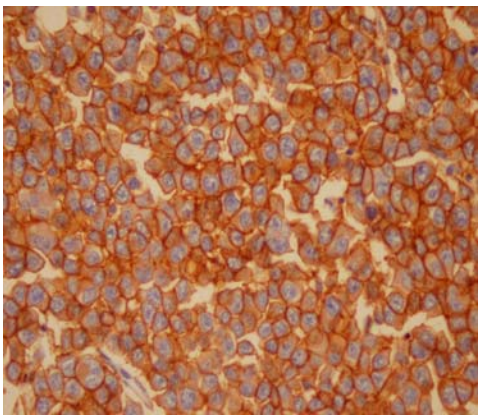

CD117 (positive)

Ovarian dysgerminomas need to be diagnosed accurately because its treatment and prognosis differs considerably from other ovarian neoplasms. Dysgerminomas has a better prognosis and greater sensitivity to available treatment modalities among all ovarian neoplasms. Cure rate approaches almost 95% employing conventional treatment options[18]

There are many entities that comes in the differential diagnosis of ovarian dysgerminomas. These includes solid variants of yolk sac tumor, embryonal carcinoma, granulose cell tumor, clear cell adenocarcinoma and metastatic carcinoma such as melanoma. Although these lesions can be distinguished morphologically but sometimes in difficult cases a clear differentiation among these is required for definitive diagnosis.

Immunohistochemical stains that are routinely being used are Placental Alkaline Phosphatase(PLAP) and Cytokeratin(CK). PLAP is routinely being used for diagnosing dysgerminomas but the main disadvantage being that its staining is also seen in primitive germ cell tumors and in benign lesions. Cytokeratin shows focal staining in ovarian dysgerminomas. There is another immunohistochemical marker OCT4 that shows positivity for dysgerminomas [9] but its expression is also seen in clear cell adenocarcinoma.CD117 staining may prove to be a useful marker for diagnosing ovarian dysgerminoma.

There are many studies that demonstrated CD117 expression in large number of human solid tumors. Ovarian neoplasms, let alone dysgerminoma in particular included small number of studies.

Sever et al [3] in his study demonstrated expression of CD117 (C-Kit) receptor in dysgerminoma of the ovary catering 29 cases of ovarian dysgerminoma. Klein et al [10]demonstrated lack of C-Kit protein (CD117) in mesenchymal tumors of the uterus and ovary. Tonary et al [11] demonstrated lack of expression of C-Kit in ovarian cancers is associated with poor prognosis. Kim et al [12]demonstrated expression and mutational analysis of C-Kit in ovarian surface epithelial tumors. Ramalingam et al [13] recently reported yolk sac tumors of the ovary often included in the differential diagnosis of

dysgerminoma, demonstrated no C-Kit expression. Went et al [14] demonstrated prevalence of C-Kit expression in human tumors as well as in dysgerminoma and gonadoblastoma. Khalifeh et al [7] demonstrated the impact of C-Kit and Ki-67 expression on patients prognosis in advanced ovarian serous carcinoma. M.R. Raspollini [15] demonstrated C-Kit expression and correlation with chemotherapy resistance in ovarian carcinoma.

There is a well documented data regarding C-Kit expression in seminomas, its male counterpart as Sakuma et al demonstrated alteration of C-Kit gene in testicular germ cell tumors. No doubt about that there are long list of studies exploring C-Kit expression in vast numbers of human malignancies even in gynaecological malignancies. Importance of CD117 expression in ovarian dysgerminoma cannot be overlooked.

With the advent of C-Kit targeted therapy with imatinib mesylate(Gleevec; Novartis) and the proven success of this drug in the treatment of Gastrointestinal Stromal Tumors (GIST) and Chronic Myeloid Leukemia (CML). C-Kit expression not only serves as a diagnostic tool but also have therapeutic implications.

There are many studies documenting imatinib mesylate usefulness in treatment of human malignancies. Joensun et al demonstated effect of the tyrosine kinase inhibitors STI571 in a patient with metastatic GIST[16]Mesters et al demonstrated stable remission after administration of the receptor tyrosine kinase inhibitor SU5416 in a patient with refractory acute myeloid leukemia[17]O Dwyer demonstated new therapeutic principles in Chronic Myeloid Leukemia [18].Brian et al recently demonstatred expression of imatinib mesylate targeted kinases in endometrial carcinomas[19].

Dysgerminoma is highly radiosensitive and cure rate approaches 95 % even when metastasis develop in patients. With advanced disease[20] Reproductive compromise is the most devastating side effect after usual treatment with conventional chemotherapy and radiotherapy. This is of utmost concern in patients with dysgerminoma keeping in mind the young mean age of patient presentation.

Although given the treatment of imatinib mesylate in CML and GIST, anti C-Kit compounds could prove to be an additional treatment option in patient with

dysgerminoma, allowing for conservative therapy with less devastating side effects on fertility of these patients.

It has been suggested , although not rigorously proven that tumor resistance to carboplatin based chemotherapy may result from exon 17 C-Kit gene mutations. Similarly as described earlier that Rapollini et al [15] demonstrated advanced serous ovarian carcinoma that expressed C-Kit was resistance to current chemotherapy regimen.

Dysgerminoma is a rare malignant germ cell tumor of the ovary in young females. Immunostain C-Kit may be useful in differentiating dysgerminoma from other ovarian neoplasm. With the success of C-Kit targeted therapies in GIST and CML. C-Kit expression in dysgerminoma may provide a new target for conservative fertility sparing therapy.

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