Successful Treatment of Nongestational Choriocarcinoma of Uterine Body in a Young Girl With Modified EMA-Cotherapy and thus Preserving Fertility - The First case in World Literature

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Abstract

Background: To describe the first case in world literature of Primary nongestational choriocarcinoma (NGC) of the uterine body as Primary NGC of female gestational tract has been described in the ovaries and is unusual in other genital sides.

Setting: An Academic Research Centre

Patient(s): A 21 year old unmarried girl who presented with continuous vaginal bleeding, fever of unknown origin with an abdominal mass eventually diagnosed as NGC of the uterine body.

Intervention(s): After 3 units of fresh blood transfusions and intravenous antibiotics two courses of methotrexate 1mg/kg (40mg) alternating with leucovorin 0.1mg/kg (4mg). Followed by Etoposide 100mg iv infusion x 5, Actinomycin D 0.5mg iv x 5 & methotrexate 40mg alternating with leucovorin 4mg iv x 4 doses followed 1 week later by cyclophosphamide 500mg in iv infusion and vincristine 1mg iv in saline (modified EMA-CO therapy).

Main Outcome Measures: Regression of tumour size clinically, on USG and MRI along with a negative urine pregnancy test and β-HCG becoming undetectable.

Result(s): Expulsion of the tumour from the uterine cavity.

Conclusions: Although very rare NGC should be considered in the differential diagnosis of any tumour presenting in the uterine cavity presenting as a solid deeply penetrating mass and a conservative approach of chemotherapy should be the treatment of option rather than jumping on to Total abdominal hysterectomy along with bilateral salpingo-oophorectomy (TAH with BSO) as the primary treatment especially in a young girl whose reproductive career is of vital importance for her future life.

Introduction

Choriocarcinoma that affects female genital tract is classified as either gestational (GC) or nongestational choriocarcinoma (NGC). GC is the result of pregnancy and is located in uterine corpus. Primay extrauterine Choriocarcinoma is very rare and is found mostly in the genital tract (tube, cervix, ovary, vagina) in patients with coincident or antecedent pregnancy. NGC of the uterine cervix has been reported (Talerman 2002, Bakyal et al 2003), however primary NGC of uterine body has never been reported. NGC of uterus is likely to arise from germ cells and therefore behaves like germ cell tumours. Additionally dedifferentiation of epithelial cells into choriocarcinoma can cause these tumours. In some instances these are mixed tumours comprising of epithelial elements and choriocarcinoma but in others, they may have completely lost their epithelial phenotype (Maesta et al 2005). Till date the primary NGC of uterine cervix had been treated by total abdominal Hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO) combined with combination chemotherapy. We report the first case in world literature of NGC of uterine body in a young unmarried girl which was successfully treated with a combination chemotherapy alone (modified EMA-CO therapy) (Newlands 2003, Hiramastu et al 2005) and its consequent expulsion from uterus and thereby salvaging uterus and preserving fertility of the patient.

Case Report

A 21 year old unmarried virgin girl, was seen for treatment regarding dysfunctional uterine bleeding of three months duration without any visible improvement. Initially, gynaecological examination and transvaginal ultrasonography (TVS) was not performed due to an intact hymen. A transabdominal ultrasonography (USG) done one month later showed an ill defined tumour in the uterine cavity extending beyond the myometrium and cell blocks taken from a transabdominal and perrectal biopsy at an oncology centre revealed villi...
which were lined by β-HCG expressing syncytiotrophoblasts(fig4and5). The smears also showed trophoblast cells but no cytotrophoblast cells and was reported as doubtful products of conception. At initial presentation to us the patient had severe anaemia, haemoglobin(Hb- 6.4gm%) with persistent irregular, almost continuous bleeding per vagina(p/v) and fever 102-104degree F. Her vaginal swab and urine cultured strept. pyogenes and pseudomonas aeruginosa, both of which were sensitive to a combination of cepferazone and sulbactum which was administered along with fresh blood transfusions to build up her general condition. Serumβ-Hcg was 30, 538miu/ml, however other germ cell and epithelial tumour markers were negative(a fetoprotein-2.931iu/ml,CEA-1.91ng/ml,CA19.9-3.48U/ml,CA15.3-17iu/ml,CA125-10.9iu/ml,5.progesterone was0.7ng/ml,pregnancy specific β-2glycoprotein IgM was neg(7.03)(-Nor<20units) .Abdominal ultrasound and colour Doppler revealed a makedly enlarged uterus 164x80x37mm with fundus reaching upto level of umbilicus, endometrial lining was not defined. An illdefined echogenic mass measuring 80mmx20mm was seen filling the endometrial cavity and invading the myometrium. Myometrium was heterogenous with tiny anechoic areas which filled with colour. On CFI large amount of colour flow was visualized on periphery of uterus.Cervix andboth ovaries were normal.(fig1)

MRI Abdomen (fig2 and fig3) showed the same mass in uterine cavity causing its enlargement with distortion of internal architecture occupying almost whole of pelvis. It was heterogeneously hyperintense on T2W images and hypointense on T1W images with both solid and cystic components. Small foci showed blooming suggestive of haemorhage, seen to involve both myometrium andendometrium with disruption of junctional zone anteriorly andreaching up to anterior abdominal wall, superiorly till pelvic inlet, inferiorly it was causing mass effect on urinary bladder, however fat planes were well maintained. Rest of abdominal viscera were normal.

MRI Brain and Chest were normal With a positive pregnancy test in a virgin girl and a solid huge tumour deeply invading uterine myometrium, a tentative diagnosis of nongestational choriocarcinoma of uterine body was made considering the histopathological reports of syncytiotropho blast from the tumour biopsy and a positive pregnancy test as well as β-HCG levels of 30,588 and no attempts were made to take a repeat biopsy in view of her poor general condition. Although no such case could be found in literature we decided to give her methotrexate(1mg/kg) alternating with folinic acid(0.1mg/kg). Although NGC is supposed to be treated like high risk gestational trophoblast neoplasia GTN(Schlareth et al1980) the patients poor general condition and anaemia weighed heavily against such chemotherapy(cisplatinum,bleomycin,vinblastine). Two courses of methotrexate resulted in some tumour regression and negative urine pregnancy test(UPT) but repeated bouts of continuous bleeding p/v persisted, so it was decided to give highly modified EMA-CO therapy-where patient received actinomycin-D 0.5mgivx5days,etoposide 100mg iv infusionx5days and methotrexate 1mg/kg/alternating with leucoviron 0.1mg/kg/IM and then one course of cyclophosphamide 500mg iv and vincristine 1mg iv in saline was given although we tried to avoid cyclophosphamide initially because of its adverse effects on future fertility. As the patient developed stomatitis with mildly altered transaminases methotrexate had to be decreased till side effects were reversed. By the time 2nd course of EMA therapy was given patient developed gradually shrunken uterine size which decreased and became intrapelvic so that by the time a repeat examination under anaesthesia (EUA) was planned and a repeat endometrial biopsy was taken to be able to take tissue for genetic studies, tumour had considerably regressed andhence a dilatation and curettage was planned after permission from mother for the same but although tissue was sent for karyotyping and histopathology examination, no reports were obtained despite our repeated requests for the same to decide further management for which we had to repeat a MRI which revealed the increased myometrial penetration had considerably decreased and a junction could now be demarcated between myometrium and endometrial mass at places unlike earlier MRI’s, and till patient felt pain in back and was thus instructed to collect the tumour in formalin, once she expelled the tumour at home. The expelled tumour (fig6) on gross revealed a single greyish white soft tissue mass measuring 9cmx5cmx4.5cm.C/S-was congested, solid to firm in consistency with microscopic examination (fig7)showing a relatively circumscribed noncapsulated lesion composed of a degenerated infarcted tumour mass composed of syncytiotrophoblast tissue separated by bands of fibrous stroma with varying thickness and marked vascularity. Few small bits of basal decidualized stroma along with lympho neutrophilia infiltrate was seen which was reported as expelled tumour consistent with post treatmentchanges in a nongestational choriocarcinoma. This tumour was screened for HCG, but with negative results. Subsequently patient was given three courses of
methotrexate alternating with leucoviron and has been followed for two years post chemotherapy and is normally cycling with normal uterus and ovaries.

Discussion

This case is being reported not only for it being the first case in world literature of nongestational choriocarcinoma of uterine body but also for the diagnostic and therapeutic challenges it presented with reports of rhabdomyosarcoma on MRI scan by the radiologist for a solid tumour in uterine cavity deeply invading myometrium and pathologists reporting as products of conception and patient being posted for a TAH with BSO without any conclusive diagnosis as her continuous bleeding was a big problem in the face of falling haemoglobin in a young unmarried virgin girl.

Normally genetic studies are required to establish the nongestational origin of primary choriocarcinoma of uterine cervix/body, which is generally lacking in case reports. Although we tried to check nongestational origin by taking tissue under GA after controlling her general condition with chemotherapy and though tissue was sent for both karyotyping and DNAPCR using PC-STR techniques (Maesta et al 2005) since no tumour tissue got cultured and only decidual tissue was reported and the report was not obtained even after patient had expelled tumour 10 days following biopsy and hence couldn’t repeat any further attempts for karyotyping. Since patient already had a perrectal biopsy and a histopathology report of syncytiotrophoblast it was not considered ethical to repeat the biopsy just for karyotyping purposes at that juncture. Nevertheless despite not having a karyotyping report the multiple features which point towards it being a nongestational choriocarcinoma besides the history of her being an unmarried virgin girl and having a narrow tight introitus were

(I) very low $\beta$hCG levels fluctuating so much that on the day I had to give chemotherapy a check UPT was negative and I had to reconfirm that the histopathology slides were of same patient in contrast to $\beta$-Hcg in lakhs seen in conventional highly deeply infiltrating choriocarcinoma or even a conventional pregnancy equivalent to 26weeks pregnant uterus size which the tumour had attained and all through the period I saw levels never exceeded 1250miu/m level even before the start of chemotherapy although we had one report from outside of 30,538miu/ml and that also was not in lakhs

(II) One doesn’t see a gestational choriocarcinoma being expelled as such a circumscribed tumour from vagina as seen in this case. Although most germ cell tumours are treated by a combination of bleomycin, cisplatinum and etoposide(Brewer et al 1999), even for resistant nongestationalchoriocarcinomas similar treatment is recommended(Schlareth et al 1980) and although we first got cisplatinum etc we thought patients general condition didn’t permit the use of the same and hence trial of a highly modified EMA-CO therapy use doesn’t take away the nongestational origin. There was a discrepancy regarding diagnosis from the pathologist who reported as products of conception saying that villi are not seen in choriocarcinoma and as per Chew and Ratnam 1996, the terminology villous and avillous choriocarcinoma has not been universally adopted and if this tumour was not choriocarcinoma what else could be such a highly infiltrating solid tumour in uterine cavity be which revealed syncytiotrophoblasts. Such tumours are very well known to arise from totipotential germ cells even in males. Hence the important lessons this case teaches both in the diagnostic and therapeutic field is if one comes across such challenging cases where nobody else has seen a similar case and there is lot of pressure from the relatives as well as your colleagues to choose the easier option of chopping away the uterus to control the uncontrollable bleeding it is better to atleast try to think of the long future the girl has ahead of her and consider preservation of fertility rather than straight removal of uterus in such a young girl which is very rare as all previous patients reported earlier with NGC even in cervix have been in perimenopausal or menopausal patients or an occasional patient where choriocarcinoma coexisted with serous carcinoma of uterine endometrium (Horn et al 2000) but never primarily in uterus that too in a young girl.

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Illustrations

Illustration 1

Colour Doppler abdusg Of Tumor

Illustration 2

Saggital Section Of MRI Of Tumor
Illustration 3

Coronal Section Of MRI Of Tumor

Illustration 4

Syncytio Tropho Blasts
Illustration 5

HCG Staining Of Syncytio

Illustration 6

Tumor
Illustration 7

MICR Exam Syncytio Post Chemotherapy
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