

Window of lost opportunities: Time to consider a mandatory cervical cancer screening protocol??

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Abstract

We report 2 cases of carcinoma cervix treated at our institution where a window to detect malignancy at an early stage was available, yet missed.

Case 1: A 38 year old nulligravida, post-renal transplant patient, reported with abnormal discharge per vaginum and inter-menstrual bleeding. She was found to have Squamous Cell Carcinoma of Cervix Stage Ib2 on evaluation. A decision to start IMRT was taken. The patient didn't continue further treatment at our institute and was lost to follow up.

Case 2: A 47 year old lady presented with 4 months postpartum bleeding. She had undergone caesarean delivery post-IVF 6 months ago. She was found to have Squamous cell carcinoma Stage IIa on evaluation, for which she underwent Radical Hysterectomy with bilateral pelvic lymph node dissection. She received Postoperative radiotherapy along with Intracavitary Radiotherapy.

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Introduction

Cervical Cancer is the second most common cancer among women worldwide and the most common cause of cancer-related deaths among women in India; accounting for 26% of all cancer deaths (IARC 2009)¹. The current estimates indicate approximately 1, 32,000 new cases diagnosed and 74,000 deaths annually in India, accounting to nearly 1/3rd of the global cervical cancer deaths. Indian women face a 2.5% cumulative lifetime risk and 1.4% cumulative death risk from cervical cancer¹⁻². At any given time, about 6.6% of women in the general population are estimated to harbour cervical HPV infection. HPV serotypes 16 and 18 account for nearly 76.7% of cervical cancer in India.

The screening coverage in Asian countries is low and varies from 50 per cent in Singapore which has an existing Cancer Screening Programme to 2.6%-5% in India². Despite existence of national guidelines, the screening coverage in India is appalling and is mainly attributed to inequality between infrastructure, outsized population and lack of resources.

The ability to detect E6 and E7 oncoproteins offer new opportunities to improve the effectiveness of cervical cancer screening. High grade cervical disease and invasive cervical cancers have demonstrated high levels of these proteins. Recently available commercial tests measure oncogenic activity indirectly by detecting E6/7 mRNA in cervical cells. They have higher specificity compared to HPV DNA tests. Use of these

new markers may help to more accurately assess cervical cancer risk in HPV infected women and they are expected to become a valuable addition to the current testing toolkit.

Here we review a case of renal transplant patient who developed clinical cervical cancer seven years post transplant and the other in a lady who underwent in-vitro fertilisation (IVF). There is now consistent evidence that renal transplant recipients are three times more likely to develop cancers than the general population³. For non-skin cancers, the risk is greatest in cancers associated with viral infections, such as cervix *in situ*, vulvo-vaginal, and post-transplant lymphoproliferative diseases⁴. Cervical cancer is reported to be the commonest form of neoplasia, after skin cancer, in female transplant recipients⁵. The reasons for the increased risk of cancer are the duration and burden of immuno-suppression both before and after transplantation, exposure to specific viral infection and time on dialysis prior to transplantation⁶. It is highly unfortunate when transplant patients with functioning grafts die secondary to a malignancy.

The American Society of Transplantation (AST) acknowledged that the 'Optimal frequency of surveillance for ano-genital cancer among renal transplant recipients has not been established' but recommended at least annual examinations to prevent escape from the radar of surveillance⁷.

Assisted reproduction technology (ART) is a common recommendation with successively increased use and success rates for couples having subfertility problems. The risk of cancer among infertile women has been explored in many studies however the results are inconsistent. Since many women > 30 years of age are more likely to undergo IVF, Pap smear along with HPV testing becomes imperative.

Case Reports

We report two cases where a window to detect malignancy at an early stage was available, yet missed despite both patients being on regular follow up.

Case 1: Squamous Cell Carcinoma of Cervix Stage Ib2 in a renal transplant patient.

A 38 year old nulligravida patient was referred to our institute for complaints of intermenstrual bleeding and abnormal discharge per vaginum since two months. Renal transplant had been performed seven years ago for Chronic Renal Disease and she was on immunosuppressants (cyclosporine and prednisolone) since then. She had been screened with conventional cytology and no abnormality was detected prior to transplant. There was however no cervical cancer screening post- transplant. She was found to have Squamous Cell Carcinoma of Cervix Stage Ib2 on evaluation. Allograft kidney was noted in right iliac fossa on MRI. A decision to start IMRT was taken. The patient didn't continue further treatment at our institute and was lost to follow up.

Discussion

There is an apparent risk of cervical cancer in patients on immunosuppressive therapy. There is an 11-14 fold higher risk of cervical carcinoma-in-situ and 1.6-5.7 fold higher risk of invasive cancer in such patients. Immunosuppressive treatment may also increase the risk of progression of preinvasive condition. A number of studies have corroborated this⁸⁻¹⁰. The use of HPV DNA testing to complement cytological screening may be particularly advantageous in transplant recipients who have a higher incidence of HPV infection than the general population. Additionally, the value of vaccination in older women is less clear with no evidence of protection against disease caused by oncogenic virus to which there has been previous exposure. Although theoretically the vaccine should be safe in transplant recipients, there is no data confirming the efficacy of the vaccine in the end-stage renal disease patients⁵.

Treating cervical cancer with a pelvic kidney is a therapeutic dilemma. Radical hysterectomy can be done up to FIGO stage IIA. Anatomic alterations in the pelvis may occur post such transplant of kidney in the iliac fossa (right iliac fossa in this case), disruptions of normal anatomic relations of ureter with surrounding organs and changes in vascular structure due to anastomosis of renal vessels. Therefore prior renal transplant may complicate radical hysterectomy and lymphadenectomy in patients with cervical cancer. When the parametrium is involved, the reduced tolerance of the kidney limits the use of radiation. Hence complete dose of conventional radiation cannot be given. Mobilisation of transplanted kidney out of field of radiation is also not much of an option due to development of adhesions¹¹.

We have tried to highlight the difficulties in treatment approach and the importance of close clinical follow-up including regular gynaecologic screening for cervical premalignant and malignant lesions. In conclusion, we suggest that annual Pap smear supplemented with HPV testing should be mandatory in post transplant patient to detect and treat pre-invasive lesions of the cervix.

Case 2: Squamous cell carcinoma Stage IIA in a patient who underwent IVF.

A 47 year old lady presented to our department with complaints of postpartum bleeding for 4 months. She had conceived with the help of IVF with ovum donor and delivered twins by C-section. She had a history of ectopic pregnancy for which salpingectomy had been done and a daughter who expired in a road traffic accident at the age of 18.

On evaluation, she was found to have Squamous Cell Carcinoma of the Cervix Stage IIA for which she underwent Radical Hysterectomy with bilateral pelvic lymph node dissection. Her histopathology report showed a 4x3.5x2 cm³ poorly differentiated squamous cell carcinoma, involving both lips of cervix and extending to involve posterior flap of vagina and lower uterine segment. Lymphovascular permeation was not seen. Anterior and posterior cut ends of vagina were free of tumor. Parametrium, bilateral ovaries, fallopian tumor and bilateral pelvic lymph nodes were free of tumour. She received post-operative radiotherapy (PORT) along with intracavitary radiation. She was disease free for 13 months. Subsequently she developed dyspnea on exertion, with heaviness in chest associated with weight loss of 6-7 kgs over one month. Chest x-ray showed pleural effusion. Pleural fluid cytology and cell block were negative for malignancy. CT Thorax showed pleural effusion with tiny nodule. Intercostal drainage was done. Repeat pleural fluid cytology was positive for atypical cells suggestive of malignancy. Pleural biopsy showed non keratinizing squamous cell carcinoma. Recurrence was treated with six cycles of paclitaxel plus carboplatin. She has been disease free for six months.

Discussion

Relatively few studies have been published on the cancer risk of women who have undergone IVF. Studies from Australia indicated a transient increase in the risk of having breast or uterine cancer diagnosed in the first year after treatment but there was no increase in the overall incidence of breast, ovarian or uterine cancers. A previous study from Sweden, of women who underwent IVF up to 2001 found no increased risk for cancer with the exception of the risk for ovarian cancer, which was already increased prior to the first IVF treatment. The risk for cervical cancer was shown to be lower in IVF recipients¹³. Another study reported similar findings¹³. In addition, human papilloma virus

(HPV) infection has been found to be closely associated with CIS of the cervix, and HPV infection was found to be significantly less frequent in IVF women than in controls¹⁴. HPV positivity was more common than cytological abnormalities, making HPV a better test to screen such patients.

The incidence of cervical cancer depends on sexual behaviour, and it is possible that infertile women or their partners engaged in different sexual behaviour from the control women. Furthermore, this difference could be explained by surveillance bias, as it is likely that IVF women are used to visiting their gynaecologists regularly and thus more Papanicolaou smears are taken, which enabled earlier treatment of cell atypia. Low parity in infertile women may also be one of the factors responsible for lower incidence as high parity is associated with cervical cancer. Also women who chose IVF treatment might be more aware of risks or be more health conscious at the time of conception as compared with non-IVF women.

If a woman succumbs to cervical carcinoma post IVF, she would leave behind an unattended child, which would have significant social implications of its own. We suggest that at least routine screening guidelines for cervical cancer must be followed in patients undergoing in vitro fertilisation i.e. a woman who has never been screened should undergo a Pap test and also HPV testing if possible before starting the IVF procedure.

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