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CASE REPORT

CLINICAL BEHAVIOR OF UTERINE CERVICAL CARCINOMA IN AN IMMUNOCOMPROMISED RENAL TRANSPLANT RECIPIENT WITH LITERATURE ON THE INCIDENCE, PATHOGENESIS AND CLINICAL BEHAVIOR

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ABSTRACT: Incidence of malignancy is 2-31% in patients who had renal transplant. Due to advances in immunosuppression the incidence of graft versus host reaction and rejection of transplant are rare. Due to increase in survival of immune suppressed transplant patients, they are prone for acute immune disorders, infections and malignancies. Literature on cancer after kidney transplantation is limited. The incidence of malignancies in recipients of kidney transplantation patients is higher compared to general population. We report a case of 38 yrs old female renal transplant recipient who presented to us with carcinoma cervix. She had a very aggressive disease and rapid progression of malignancy in spite of aggressive treatment. Here we are discussing this case of renal transplant patient with cervical carcinoma with the review of literature about the incidence, pathogenesis and clinical behavior of cervical carcinoma in immunocompromised renal transplant recipients.

KEYWORDS: renal transplant, carcinoma cervix, incidence, clinical behavior, pathogenesis.

INTRODUCTION: Literature on cancer after kidney transplantation is limited to small single-centre studies and incomplete ascertainment of cases in large registries. The incidence of malignancies in recipients of kidney transplantation patients is higher compared to general population.[1]

Here we are discussing a case of renal transplant patient with cervical carcinoma in detail with the review of literature about the incidence, pathogenesis and clinical behavior of malignancy in renal transplant recipients with special emphasis on uterine cervical carcinoma.

Immune deficiency is a risk factor for some malignancies particularly for those with a known or suspected etiology. Meta-analysis showed that 20 out of 28 cancer types studied in HIV/AIDS patients and kidney transplant recipients, there is increase in the incidence of malignancy compared to general population.[2,3]

Standardized incidence ratios were very much higher in HIV/ AIDS patients than kidney transplant patients for Hodgkin's lymphoma (11 vs 4) non-Hodgkin's lymphoma (77 vs 80), Kaposi sarcoma (3640 vs 28) and anal cancer (29 vs 5). But vulval and vaginal malignancies (23 vs 6) are more in transplant recipient than in HIV/ AIDS patients.[2]

CASE DETAILS: A 38 yrs old female, renal transplant recipient presented to us 4 months after she underwent Wertheim's Hysterectomy at a Government General Hospital (Gandhi Hospital) in November 2012 for menorrhagia. Histopathological evaluation of the operative specimen revealed non-keratinizing squamous cell carcinoma confined to cervix not infiltrating the parametrium. The dissected left pelvic and right obturator lymphnodes, vagina, tubes and ovaries didn't show tumor

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deposits. She was diagnosed as FIGO stage IB 1 cervical carcinoma and referred to our institute for further management of her malignancy.

FIGURE 1: Histopathology of the cervical lesion showing non-keratinizing squamous cell carcinoma in low-power 10X (FIGURE 1a) and high power 40X (FIGURE 1b).

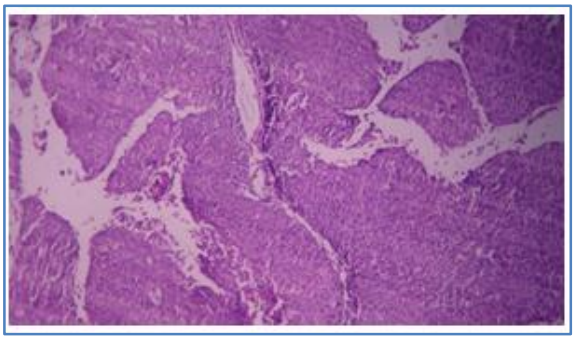

Fig. 1(a)

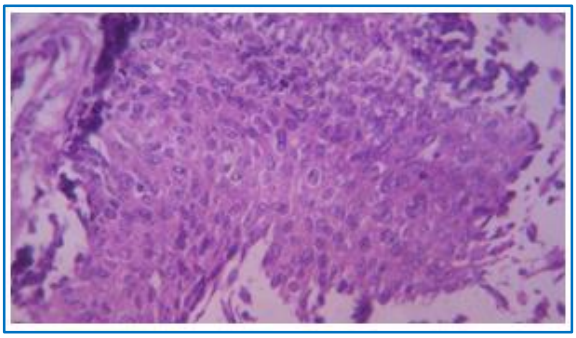

Fig. 1(b)

During post-op period she developed deep venous thrombosis of right lower limb (middle 1/3 femoral vein to the popliteal vein) after hysterectomy and treated with Heparin and Warfarin. Follow-up venous doppler study was normal.

She had renal transplant 9 yr ago for end-stage renal disease of unknown etiology. She is a known hypertensive on Amlodepine and post-renal transplant she has been on oral immunosuppresant agents, Prednisone 10mg and Azathioprine for 9 years.

Patient is a divorcee, lives with her parents. She was childless with para two, live zero.

FIGURE 2: CT scan of abdomen and pelvis showing bilateral small, shrunken kidneys in the abdomen.

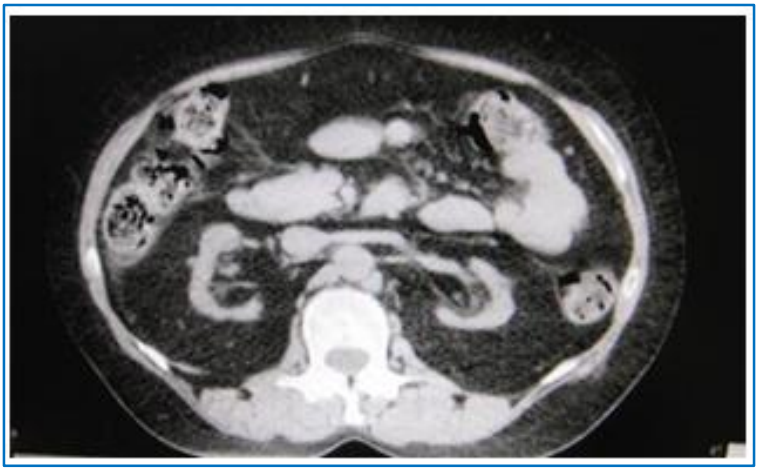

Fig. 2

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FIGURE 3: CT scan of abdomen and pelvis of the patient with the right transplanted kidney in the pelvis.

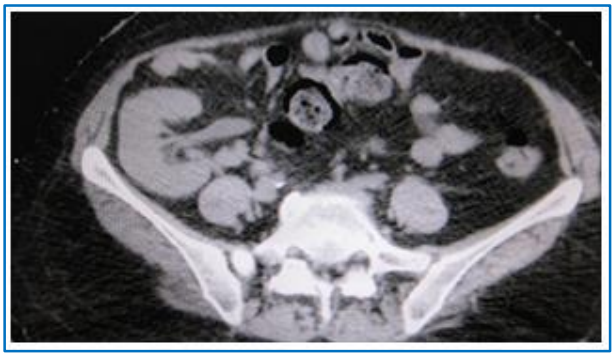

Fig. 3

Patient didn't receive any adjuvant treatment post-operatively as she had carcinoma cervix FIGO stage IB 1 with single transplanted pelvic kidney and surgery was done 4 months ago. Also the dissected pelvic lymph nodes were negative for malignancy and radiotherapy treatment was deferred. Literature was also reviewed and recurrence rates in such cases were less than 10% and radio therapy is indicated in high risk patients only. So patient was kept on close follow up.

During follow-up at 8 months, in September 2013, per vaginal examination revealed 1.5 x 1.5 cm growth over the vault and colposcopy showed condylomatous area over the vault extending on to all vaginal walls in the proximal half, mostly post vaginal wall suggestive of early invasive carcinoma. Biopsy of the lesion revealed large cell non-keratinizing squamous cell carcinoma from the vaginal vault.

FIGURE 4: Histopathology section from the vault lesion, showing large cell non-keratinizing squamous cell carcinoma in low power 10X (FIGURE 4a) and high power 40X (FIGURE 4b).

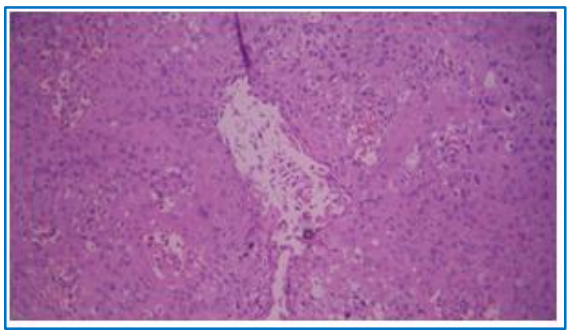

Fig. 4(a)

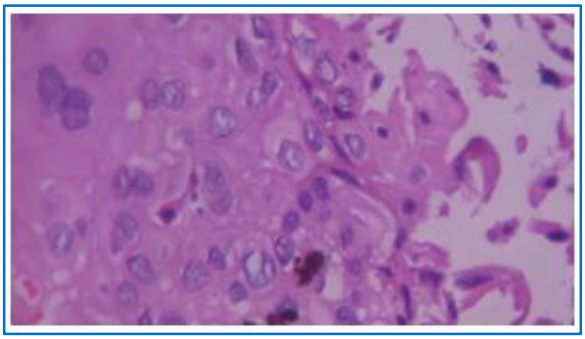

Fig. 4(b)

As patient had local recurrence, surgical oncologist was consulted and opined as an inoperable lesion. As it is local recurrence in the vault, patient received vaginal brachytherapy with vaginal cylinder, by Ir^{192} High Dose Rate brachytherapy by remote after loading technique and a dose of 6 Gray per fraction, prescribed at 0. 5 cm from the vaginal vault was delivered. A total of 5 fractions with 1 week between fractions were delivered.

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Colposcopy done 3 months after brachytherapy showed no evidence of the disease.

`During follow-up after 5 months in July 2014, she came with exertional dyspnea. Patient had bilateral palpable supraclavicular lymph nodes and CT scan chest showed multiple soft tissue density nodules and focal areas of ground glass appearance in both the lungs and mediastinal lymphadenopathy. In view of post-transplant status possibility of lymphoproliferative disorder had to be ruled out but ultra sound guided Fine Needle Aspiration Cytology from right supraclavicular lymphnode showed metastatic adenocarcinoma. Patient received 6 cycles of palliative chemotherapy with Inj Carboplatin and Inj Paclitaxel (last cycle in November 2014). She tolerated chemotherapy well.

After 1 month, in December 2014, patient came with bleeding per rectum. Per vaginal examination showed healthy vault. On per rectal examination, a soft growth was felt with finger blood stained. Patient underwent colonoscopy which revealed telangiectatic areas suggestive of radiation proctitis. Biopsy from ulcerated area of the rectum revealed inflammatory changes with no evidence of malignancy. CT scan abdomen showed thickened vault and CT Chest showed thin fibrotic bands noted in both lung fields. Patient was given symptomatic treatment for radiation proctitis and she responded well.

But in January 2015 patient came with headache and difficulty in walking. CT brain showed ring enhancing lesions with edema in the cerebellar vermis, bilateral fronto-occipital regions and 4th ventricle of brain. Patient received whole brain palliative radiotherapy for brain metastasis with external bean radiotherapy on Linear accelerator machine with a dose of 30 Gray in 10 fractions from 6-1-2015 to 19-1-2015. While on treatment she was complaining of severe bone pains with moderate relief with Morphine. A Technetium^{99m} bone scan was done which showed multiple bone metastases in the spine and in the pelvis. Patient was discharged home and 3 weeks later she succumbed to her disease at her residence.

DISCUSSION: The incidence of malignancies in recipients of kidney transplantation patients is higher compared to general population. A 3. 5 times to 5 fold higher incidence than the general population has been reported.[1,4] This higher incidence rate has been seen for many malignancies. The incidence of melanoma, leukemia, hepatobiliary tumors, cervical, and vulvovaginal tumors is 5-fold higher. Testicular and bladder cancer was about 3-fold, cancers of anogenital tract about 4- fold while kidney cancer about 15-fold and 20-fold increased for Kaposi's sarcoma, non-Hodgkin's lymphomas and non-melanoma skin cancers was observed. As rates of most malignancies are higher after kidney transplantation compared with the general population, cancer should continue to be a major focus of prevention in kidney transplantaion patients.[1,3]

The prognosis of transplant recipients diagnosed with cancer is much worse than patients without transplant. The data from Australian and New Zealand dialysis and transplant registry have shown that women with breast cancer have an excess mortality of 40 % compared to general population.[5] In the Dutch kidney transplant population, the median patient survival after the diagnosis of cancer was only 2.7 years, compared with an average survival of patients without cancer of 8.3 years.[6]

In patients with transplant the cancers are more aggressive and surgical, radiotherapeutic and chemotherapeutic management is also compromised as the patients are immunosuppressed. The reason for aggressive behavior of cancer and the pathogenesis of increased incidence of malignancy

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in immune suppressed renal transplant patients is not clearly understood. Different theories are proposed in the literature.

Malfunction of the cellular immune response following either HIV-induced depletion or iatrogenic inhibition of CD4-lymphocyte activation, enhances the progression of HPV-induced cervical lesions to malignancy. This is based on the study done by Karl Ulrich et al.[7] Low-grade lesions among HIV-infected and allograft recipients progressed more often than among controls during a 3-year period. Also recurrent lesions after destructive treatment were seen more frequently among patients than among controls. Patients with CD4-lymphocyte count of less than 400 per microlitre for more than 3 years suffered from progressive lesions.[7]

The higher incidence of HPV infection and high-risk HPV genotype infection in transplant patients with functioning grafts, have been implicated in the aggressiveness of such infection in immune suppressed patients.[8] It is seen that in renal transplant recipients, HPV DNA was positive in 62.8% patients and among these 59% had high-risk HPV genotype. So there is a high incidence of HPV infection in renal transplant recipients and mostly high-risk HPV genotype infection.

So HPV test is useful to monitor patients at higher risk of anogenital malignant neoplasms by identifying the cytological anomalies at an earlier stage.[8]

Cervical condylomas and intraepithelial neoplasia of the cervix in immune suppressed renal transplant patients have been found to be high risk factors for malignancy.[9] The incidence of cervical condylomas in renal transplant recipient women was about 8.5% and 4.5% of these women developed cervical neoplasia. The lag time from transplantation to the diagnosis of the condyloma was 22.4 months and for transplantation to the diagnosis of cervical neoplasia was 38 months. So immunosuppression should be included among the high-risk factors in the development of cervical neoplasia.[9]

The incidence of cervical cancer in transplanted patients is 2 to 3 times more than the age and gender matched population. Cancer screening is recommended in transplant patients. There is lack of data regarding the immunogenicity and effectiveness of HPV vaccination in Immune suppressed individuals.[5]

As our patient was on azathioprine since renal transplant, we reviewed the literature for azathioprine as an etiologic agent for malignancy. The incidence of various cancers, especially non-Hodgkin's lymphoma (NHL) is higher among patients who receive azathioprine for immune suppression after organ transplants than in the general population. A study done on 755 patients of inflammatory bowel disease on azathioprine for assessing the risk of neoplasia showed 2 cases of invasive cervical cancer. It was concluded that there is no substantial increase in the risk of cancer in patients on azathioprine.[10 5]

The clinical behavior of uterine cervical carcinoma in renal transplant recipients has been reviewed in the literature. The interval between the time of renal transplantation and the time of cervical carcinoma diagnosis was 38 months to 80.7 months in the literature.[9,4] In a study of 453 transplant patients only 5 were diagnosed with cervical carcinoma. Four of 5 patients tested positive for HPV and high risk HPV DNA. So higher incidence of cervical carcinoma is expected in renal transplant recipients, so appropriate surveillance is needed to ensure early detection and treatment of cervical carcinoma.[4]

CONCLUSION: Renal transplant patients on Immunosuppressive therapy with pelvic malignancies have therapeutic difficulties. They have aggressive clinical behavior, decreased treatment tolerance and worse survival.

As rates of most malignancies are higher after kidney transplantation compared with the general population, cancer should continue to be a major focus of prevention in kidney transplant patients.[1] Malfunction of the cellular immune response enhances the progression of HPV-induced cervical lesions to malignancy.[7] So HPV test is useful to monitor patients at higher risk of anogenital malignant neoplasms by identifying the cytological anomalies at an earlier stage.[8] Cervical condylomas and intraepithelial neoplasia of the cervix in immune suppressed renal transplant patients have been found to be high risk factors for malignancy.[9]

A higher incidence and aggressive behavior of cervical carcinoma is expected in renal transplant recipients, so appropriate surveillance is needed to ensure early detection and treatment of cervical carcinoma.

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