CASE REPORT
A 42-year-old, multiparous female presented in Radiotherapy OPD, of PGIMS, Rohtak with complaints of continuous bleeding per vaginum for last three months with passage of clots. The patient had no other complaints. Her past medical and family history was not significant. On per vaginal examination there was a growth of 2x3 cm over lower lip. All vaginal fornice were free. Vaginal mucosa was smooth and no parametrial involvement observed. MRI pelvis showed bulky cervix with lesion 61 x 56 mm more on posterior and left side. Inferiorly lesion involves upper third of vagina (Table/Fig-1, 2).

Histopathological examination revealed it to be a poorly differentiated adenocarcinoma of cervix with focal areas of glandular differentiation and clinically staged as Ib2. Then the patient underwent pan hysterectomy, bilateral pelvic lymph nodes clearances with upper one third of vagina excised. On gross examination cervical lips show grey white polypoid growth measuring 6x5 x 3.5 cm. On microscopic examination revealed it as a large cell neuroendocrine tumour (Table/Fig-3&4). Lymphovascular invasion was present. On immunohistochemistry neurolose enolose, synaptophysin and chromogranin were positive (Table/Fig-5-7).

CECT scan of chest, abdomen and head was performed post surgery, showed no evidence of metastasis. Then the patient finally diagnosed on the basis of immunohistological markers to having large cell neuroendocrine tumour of cervix and again staged as Ib2 as per staging system for carcinoma of uterine cervix of Federation of Gynaecologists and Obstetricians (FIGO) [1].

Patient was given adjuvant external beam radiotherapy to whole pelvis in doses of 50 Gy in 5 fractions for 25 fractions and high dose rate brachytherapy 7 Gy to point A, in three fractions over three weeks. Chemotherapy with cisplatin 30

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mg/m² and etoposide 100 mg/m² on days 1-3 were given every three weekly concurrently with radiotherapy. Patient tolerated the treatment well. She was then planned for three more courses of chemotherapy. But after two weeks she complained of severe headache, vertigo and bilateral pedal edema. Her CECT skull shows an isodense lesion with surrounding hypodensity in left temporal parietal region and an enhancing lesion in right parietal region and cerebellum, suggestive of tumor metastasis to brain [Table/Fig-8, 9].

There was no evidence of local recurrence or metastasis to lung and liver. The patient was advised for biopsy from brain lesion but patient attendant denied. Keeping in view of poor general condition of the patient, she was given palliative radiotherapy to whole brain in 20 Gy in five fractions. Her condition deteriorated and she passed away six weeks after palliative treatment.

**DISCUSSION**

Neuroendocrine tumours represent 2% of female genital tract malignancies [2]. Primary large cell neuroendocrine carcinomas of cervix are rare with an incidence of approximately 0.087% - 0.9% [3]. Four subtypes of NECs are classified including atypical carcinoid tumour, typical carcinoid tumour, small cell neuroendocrine and large cell neuroendocrine.

Among them most are small cell and large cells tumours are extremely rare. LCNECs (Large cell neuroendocrine tumors) cervix usually have aggressive behaviour, high recurrence rate, tendency to metastasis despite aggressive multimodality treatment strategies even in early stages and therefore dismal survival.

Diagnosis of NEC of cervix is confirmed by histological and immunohistochemical analysis.

Histopathological criteria for the diagnosis of NEC of uterine cervix identical to criteria established for lung NEC tumours and they must have neuroendocrine differentiation for confirmation of diagnosis. These tumours are characterised as poorly differentiated, have high mitotic rate, extensive necrosis and lymphovascular invasion [4, 5]. Large cell NECs of cervix are often histologically misdiagnosed as they are usually mixed with other histological variant like carcinoid, atypical small cell carcinomas, poorly differentiated squamous cell carcinoma and adenocarcinoma [6].

Lymph vascular invasion, tumour sizes more than 4 cm, presence and number of lymph node metastases and advanced stage are considered as poor prognostic factors in such cases.

Etiological factors of these tumours are not well defined. However studies have been demonstrated association between human papilloma virus (mainly 16 and 18) with LCNECs of cervix ranging from 53-100% of cases [7]. Treatment of these tumours is similar to neuroendocrine carcinoma of the lung [7]. Therefore, the current multimodality strategies that include radical hysterectomy, chemotherapy and radiotherapy are considered the effective treatment protocols. It is now widely accepted that chemotherapy may be the corner stone of management due to characteristic of these tumour to have hematogenous or lymphatic spread resulting in distant metastasis with about 70% of the patients developing visceral metastasis, particularly to the lungs, liver and bone even in early stage [8,9]. Chemotherapy may be administered as
neoadjuvant, concurrent or adjuvant depending upon the stage and performance status and has also been performed with protocols based largely on agents active in NEC lung. Multiple agents have been used with different response rates. Those include cyclophosphamide, doxorubicin, vincristine, etoposide, cisplatin, carboplatin and irinotecan. Combination of cisplatin/carboplatin and etoposide promises better results on local or systemic control of NEC cervix.

In early stages the main component of treatment in tumor where size 4 cm or less is radical hysterectomy with regional lymphadenectomy. Adjuvant concurrent chemotherapy with or without radiation therapy to the primary site including regional nodes is generally recommended in addition to lymph node dissection. In cases where tumor size is more than 4 cm size neoadjuvant chemotherapy is strongly advocated followed by surgery. In advanced inoperable cases combination of chemotherapy and chemoradiation is the recommended treatment modality.

However aggressive multimodality treatment protocol has not been able to achieve a significant increase in survival rate. The median overall survival for stage I, II, III and IV was 19, 17, 3 and 1.5 months respectively, reported by Embry et al in a study [7].

Another treatment strategies to improve outcome have also have been investigated. Tangjitgamol et al., measured prevalence of estrogen receptor or progesterone receptor among LCNECs cervix, and evaluated the feasibility of applying hormonal treatment and found a very small portion of recruited patients (3 out of 24) expressed these hormonal receptors [10]. In another study Kajiwara et al., using the octreotide (somatostatin type 2A analog), to treat NECs, given that 3 out of 7 cases (2 out of 5 SCC and 1 out of 2 LCNEC) expressed SSTR2A receptors; however, this strategy has not been tested yet in a larger study [11]. Nonetheless, even early stage at presentation, no lymph node metastases and aggressive adjuvant treatment patient experienced early dissemination to brain in this case. A poor prognostic factor identified in the present case were size that was more than 4 cm and lymphovascular invasion. Moreover, neoadjuvant chemotherapy was not employed in this patient though the size of tumour was more than 4 cm as the patient was misdiagnosed with adenocarcinoma of cervix and underwent radical surgery as initial treatment modality. This probably could be a reason of early hematogenous metastasis further strengthen the impact of neoadjuvant chemotherapy on survival.

CONCLUSION

Large cell NECs cervix has distinct histological and immunohistological features and need to be considered in differential diagnosis of carcinoma cervix. Considering the aggressive disease course a close surveillance is required. Chemotherapy should be main component of treatment protocol. Though the success of this treatment is limited and no treatment protocol has been shown to improve survival even in early stages. Efforts should be taken for the understanding of molecular biology and identification of a number of molecular pathways which may serve as target for augmentation for radiation and chemotherapy response.

REFERENCES

AUTHOR(S):
1. Dr. Paramjeet Kaur
2. Dr. Anil Khurana
3. Dr. Ashok K Chauhan
4. Dr. Gajender Singh
5. Dr. Sant Parkash Kataria

PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Radiotherapy, Regional Cancer Centr, India.
2. Medical Officer, Department of Radiotherapy, Regional Cancer Centr, India.
3. Senior Professor, Department of Radiotherapy, Regional Cancer Centr, India.
4. Associate Professor, Department of Pathology, Pt BD Sharma, PGIMS, Rohtak, Haryana, India.
5. Professor, Department of Pathology, Pt BD Sharma, PGIMS, Rohtak, Haryana, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Paramjeet Kaur,
Department of Pathology, Pt BD Sharma, PGIMS, Rohtak-124001, Haryana, India.
E-mail: drparamjtkaur@rediffmail.com

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