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REVIEW OF LITERATURE

PRIMARY LEIOMYOSARCOMA OF CERVIX: NOW IT COUNTS!

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ABSTRACT

Aim of the Study: To review and suggest treatment approach for Primary Leiomyosarcoma of cervix.
Material and Method: This literature review has been done to find out optimum management protocol for Primary Leiomyosarcoma of the cervix by search in PubMed Central, Embase, Cochrane, and Web of Science Central database. The obtained information, thus, has been classified as per Oxford Centre for Evidence Based Medicine (OCEBM) level of evidence, and National Comprehensive Cancer Network (NCCN) Categories of Evidence and Consensus. Current treatment scenario for sarcoma and its outcome will be discussed for treatment naive case of primary leiomyosarcoma of cervix based on systematic review, line listing of old reported cases and treatment evidence.
Results: Leiomyosarcoma of cervix, though, is rare malignancy, the number is steadily increasing. It generally occurs in the perimenopausal and postmenopausal population, mean age being 46 years. No specific risk factor has been identified so far. Diagnosis is confirmed by histopathology and immunohistochemistry. Prognosis corresponds to stage and grade of disease. Combined modality including surgery, radiotherapy and chemotherapy used in these patients has achieved better survival compared to any single modality.
Conclusion: Aggressive approach with combined modality including surgery, radiotherapy and chemotherapy need to be used in these patients to achieve better survival. Though, intensive literature search reveals lack of definitive guidelines for management of leiomyosarcoma of cervix, rising number of cases warrants to frame the guidelines.

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INTRODUCTION

Search Methodology

Search was made about "Management of leiomyosarcoma of the cervix" through various evidences in PubMed Central, Embase, Cochrane, and Web of Science Central database. The obtained information, thus, has been classified as per Oxford Centre for Evidence Based Medicine (OCEBM) level of evidence, and National Comprehensive Cancer Network (NCCN) Categories of Evidence and Consensus. Current treatment scenario for sarcoma and its outcome will be discussed for treatment naive case of primary leiomyosarcoma of cervix, based on line listing of old reported cases and treatment evidence.

Concept of Rare Disease

As per WHO, a rare disease is defined as any disease affecting fewer than 5 in 10,000 people. In this review, we will focus on leiomyosarcoma of cervix, with only a few cases being reported in the literature till date.

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RESULTS AND DISCUSSION

Epidemiology

Worldwide, cervical cancer is a major cause of morbidity and mortality among women. Squamous cell carcinoma is the most common histologic subtype of cervical cancer followed by adenocarcinoma. While squamous cell and adenocarcinomas account for the majority of invasive cervical tumors, other histologic subtypes including clear cell carcinoma, glassy cell carcinoma, neuroendocrine tumors, melanomas and cervical sarcomas also occur. (Wright *et al*., 2005; Fadare, 2006; Bansal *et al*., 2010; Khosla *et al*., 2013) Primary cervical sarcomas are rare neoplasms that have been poorly characterized. Owing to the relative infrequency of the disease, most of the available data on the natural history of cervical sarcomas are derived from case reports and small case series. The earliest description of sarcoma of the uterine cervix reportedly dates back almost five thousand years, yet until recently there have been no

universally accepted criteria for the diagnosis and classification of these neoplasms. Sarcomas of the uterine cervix are reported to constitute 0.4 to 1% of all cervical malignancies. (Wright *et al*., 2005; Bansal *et al*., 2010; Khosla *et al*., 2013) Based on SEER database between 1988 to 2005, Bansal *et al*, (2010) in largest series comprising 33074 patients of cervical cancer, identified 323 (approximately 1%) patients of cervical sarcoma. Of all cervical sarcoma cases, approximately 21% (67) were leiomyosarcoma of cervix. First case report of leiomyosarcoma of cervix is the one by Sturdy. (Sturdy, 1959) After 2005, less than twenty cases of leiomyosarcoma of cervix have been added to date. (Chargui *et al*., 2007; Sahu *et al*., 2008; Grover *et al*., 2009; Verma *et al*., 2011; Khosla *et al*., 2012; Dhull *et al*., 2013; Doshi 2013; Mehra *et al*., 2015; Bhatia *et al*., 2015; Thambi *et al*., 2016; Bhalekar *et al*., 2016; Aminimoghaddam *et al*., 2016; Zhiqiang *et al*., 2016) These should be differentiated from malignant mesenchymaltumors that can arise in the cervix, alveolar soft part sarcoma, malignant schwannomas, and osteosarcomas. (Fadare, 2006) For this tumour; due to lack of data on the natural history, histological criteria for diagnosis and treatment recommendations; there is lack of guidelines regarding treatment. Most of the reported cases in previous literature indicate that this may be an indolent tumour with a potential for cure if treated early. (Bansal *et al*., 2010)

Clinical presentation

Patients with cervical leiomyosarcoma most commonly present in the perimenopausal and postmenopausal population, in their fourth to sixth decades of life;with abdominopelvic pain or mass in lower abdomen/ pelvic region, discharge or bleeding per vaginum or vaginal prolapse. (Wright *et al*., 2005; Fadare, 2006) The review finds abnormal vaginal bleeding as the most common presenting symptom. Compared to women with squamous cell and adenocarcinomas, patients with cervical sarcomas tend to be younger, have larger tumors, and have

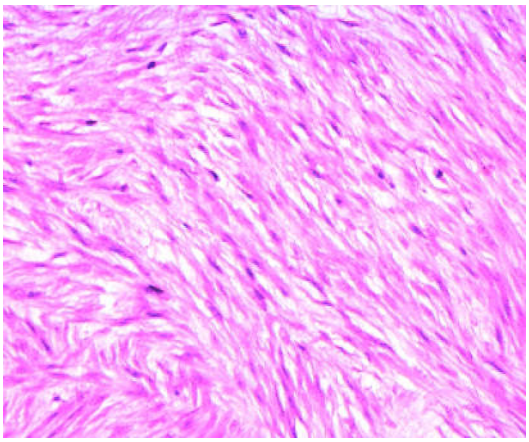

Figure 1. Pictomicrograph showing smooth muscle cells, with large pleomorphic nuclei and several mitotic figures

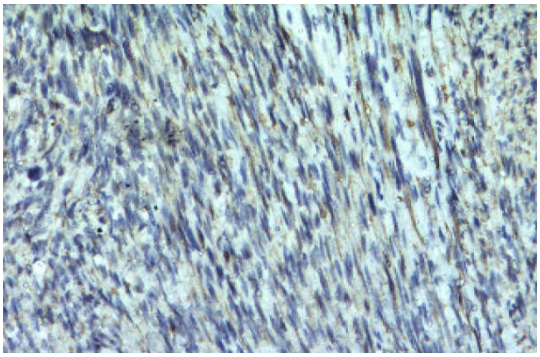

Figure 2a

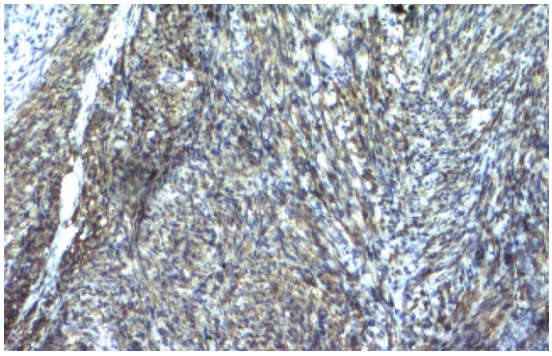

Figure 2b

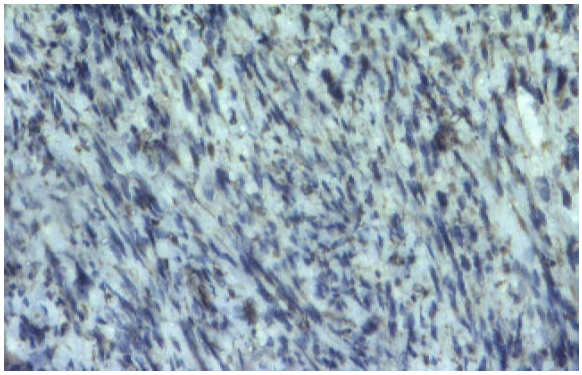

Figure 2c

Figure 2. IHC showing positivity for Desmin (a), SMA (b) and Vimentin (c)

more advanced stage disease ($p<0.05$ for all). (Bansal *et al*., 2010) We could trace youngest case report of paediatric patient aged less than 15 years (Lack, 1986) and eldest of 72 years. (Gotoh *et al*., 2001)

Diagnosis

The current approach is to simply extrapolate diagnostic criteria for corpus uteri tumors and apply them to their cervical counterparts, incorporating various combinations of cytological atypia, coagulative necrosis and mitotic activity to predict their malignant potential. Diagnosis is established by combination of radiology, histopathology and immunohistochemistry. Abdominopelvic ultrasonography may show hypoechoic lesion arising from cervix, suggestive of cervical fibroid. CT scan of abdomen and pelvis may give appearance of solid heterogeneously enhancing mass lesion, whereas MRI may clearly delineate extent of soft tissue mass arising from cervix. Microscopic examination revealsthe tumor mass arising from cervix, composed of oval to spindle shaped cells arranged in fascicles and sheets; having pleomorphic, hyperchromatic blunt nuclei (cigar shaped) and showing nuclear atypia with moderate amount of eosinophilic cytoplasm (Figure 1). (Fadare, 2006; Verma *et al*., 2011) Final diagnosis of Leiomyosarcoma of uterine cervix can be made on immune-histochemical(IHC) stains, which show neoplastic cells positivity for Smooth Muscle Actin (SMA), Vimentin & Desmin (Figure 2a-c) and negativity for HMB-45 and CK (excluding melanoma and MMMT). (Fadare, 2006; Verma *et al*., 2011) They display a spectrum of morphologic subtypes microscopically, similar to that seen in their corpus counterparts, including the myxoid variant, epithelioid variant, cases with abundance of xanthomatous cells and conventional types as well.

Differential diagnosis

Malignant mesenchymaltumors that can arise in the cervix include leiomyosarcoma, endocervical stromal sarcoma, embryonalrhabdomyosarcoma (botryoid type), alveolar soft part sarcoma, malignant schwannomas, and osteosarcomas. Primary cervical sarcomas are rare, of which the most common is leiomyosarcoma. (Fadare, 2006)

Management

Presently the management of uterine corpus is extended and applied to their cervical counterparts due to scarcity of literature of LMS of cervix. Surgical management includes abdominal hysterectomy with bilateral salpingo-oophorectomy. Given the low incidence of lymph node involvement, pelvic lymphadenectomy is indicated in cases with lymph node metastasis only. Adjuvant radiotherapy is used expecting preventionof local recurrence and chemotherapy is indicated in cases with metastasis. Postoperative adjuvant pelvic radiotherapy may reduce the risk of local recurrence in patients with early-stage disease; however, it cannot prevent the development of recurrent disease in distant sites. Several retrospective studies suggested improved local control, without any improvement in overall survival, in patients with uterine LMS who were treated with postoperative adjuvant pelvic irradiation. (Mahdavi *et al*., 2009; Sampath *et al*., 2010) In a prospective, randomized, multicenter Phase III study of uterine sarcomas, comprising 103 patients of uterine LMS, postoperative pelvic radiotherapy did not improve disease-free or overall survival. (Reed *et al*., 2008) External beam radiation therapy (EBRT) 50 Gy/25 fraction/ 5weeks along with three courses of vaginal cuff high dose rate (HDR) brachytherapy of 6 Gy each over a total duration of three weeks is usual consideration. Role of adjuvant chemotherapy is empirical and based on the finding that uterine sarcoma tend to metastasize early. Chemotherapeutic regimens include-Vincristine, Cyclophosphamide, Ifosfamide, Doxorubicin, Gemcitabine or Docetaxel in different combinations. Response rate as good as 30.3% has been reported. (Sutton *et al*., 1996) Integrated approach with combination of surgery, chemotherapy and radiotherapy has been preferred approach in most cases and has shown better outcomes. (Bansal *et al*., 2010; Verma *et al*., 2011; Lack, 1986) Follow-up can be done with CT scan and the post-treatment contrast-enhanced magnetic resonant scan of the abdomen and pelvis. Chest X-ray should be done with keen concern for lung metastasis.

Conclusion

Leiomyosarcoma of uterine cervix is a rare disease and diagnostic confirmation is based on pathological and immunohistochemical profile. Because therapeutic measures have been widely discordant among the reported cases, their true natural history and any variations in their malignant potential are not readily evaluable, the ideal approach for these malignant tumours is the team work between the surgical oncologist, the pathologist, the radiation and the medical oncologists for optimising the results for the best interest of the patient, although the effectiveness of radiation therapy and chemotherapy is debatable, and the lack of large series makes the conclusions insecure.

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