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ONLINE CASE REPORT

Botryoid Rhabdomyosarcoma of the Cervix

Case report with review of the literature

Bajpai Neha,[1] *Attibele P. Manjunath,[2] Shivarudraiah Girija,[2] Kumar Pratap[1]

سرطان العضلات المخزة العنقودي في عنق الرحم

تقرير حالة ومراجعة الأدبيات

باجباي نيها، أتيبيلي بالاكشا، مانجوناش، شيفارودرايا جيريجا، كومار براتاب

ABSTRACT: Botryoid rhabdomyosarcoma is an aggressive malignancy that arises from embryonal rhabdomyoblasts. It is commonly seen in the genital tract of female infants and young children. Due to the young age of affected patients, this malignancy poses a management challenge as the preservation of hormonal, sexual and reproductive function is essential. There is currently no consensus regarding management. However, treatment strategies for these tumours have evolved from radical exenterative surgeries to more conservative management options. We report a case of botryoid rhabdomyosarcoma in an adolescent girl presenting to Kasturba Hospital, in Manipal, India, in August 2007 with botryoid rhabdomyosarcoma of the cervix. She was treated with surgery and adjuvant chemotherapy. The patient remained healthy until eight months after the surgery. After acquiring a varicella zoster virus infection, she died due to septic shock and multiple organ failure. Awareness of such an uncommon lesion and its clinical implications is important to avoid misdiagnosis.

Keywords: Cervix; Rhabdomyosarcoma; Surgery; Chemoradiotherapy; Case Report; India.

الملخص: يعتبر سرطان العضلات المخزة العنقودي من السرطانات الشرسة والتي تنشأ من الأرومة العضلية الجنينية. غالبا مايتم تشخيص هذا الورم في الرضع والفتيات صغار السن. يمثل علاج هذا الورم تحديا كبيرا وذلك للحفاظ على الوظائف التناسلية والجنسية والهرمونية في هؤلاء المرضى صغار السن. ولا يوجد حتى الآن إجماع على العلاج الأمثل لهذا المرض. وبالرغم من ذلك فقد تطورت استراتيجيات العلاج من اجتثاث الأحشاء الجذري إلى اختيارات أخرى أكثر تحفظا. هذا تقرير حالة لسرطان العضلات المخزة العنقودي في فتاة مراهقة حضرت لمستشفى كاستوربا بمانيبال، الهند في أغسطس 2007 مصابه بسرطان العضلات المخزة العنقودي في عنق الرحم. تم علاج هذه الفتاة بالجراحة والعلاج الكيميائي المساعد. وقد ظلت الفتاة في حالة صحية جيدة لمدة 8 أشهر عندما أصيبت بعدوى فيروس الحماق النطاقي ثم توفيت بسبب صدمة إنتانية مع فشل العديد من أجهزة الجسم. من المهم زيادة الوعي بهذه الأورام غير الشائعة وآثارها السريرية لتجنب التشخيص الخاطئ.

مفتاح الكلمات: عنق الرحم؛ سرطان العضلات؛ الجراحه؛ العلاج الكيميائي الإشعاعي؛ تقرير حالة؛ الهند.

Rhabdomyosarcoma (RMS) affects the female reproductive tract and is one of the most common soft tissue sarcomas in childhood.[1] Sarcoma botryoides or botyroid RMSs are a polypoid variant of embryonal RMS, arising from embryonal rhabdomyoblasts and constituting approximately 3% of all RMSs.[1] The primary site of these tumours is closely related to the age of the patient; it is found in the vagina during infancy and early childhood, in the cervix during the active reproductive stage and in the *corpus uteri* for postmenopausal patients.[2] Although vaginal tumours are five times more common than the cervical type, the latter appears to have a better prognosis than the former.[3]

Botryoid RMS has a marked tendency for local recurrence after excision, often invading the adjacent organs.[4] The management of this tumour is challenging as it presents at a younger age; at this age, the preservation of hormonal, sexual and reproductive function is essential. There are many methods of surgical approach and variations in adjuvant therapy in the management of these tumours. Over the past few decades, there has been a dramatic change in management strategy, from radical and often mutilating exenterative surgeries to a more conservative approach with adjuvant chemotherapy.[1] This report describes the management of a young girl with botryoid RMS of the cervix.

Case Report

In August 2007, a 14-year-old female was referred to Kasturba Hospital, a university hospital in Manipal, India, for treatment and management of botryoid RMS of the cervix. She presented with a mass protruding

[1]*Department of Obstetrics & Gynaecology, Kasturba Medical College, Manipal, India;* [2]*Department of Obstetrics & Gynaecology, Sultan Qaboos University Hospital, Muscat, Oman*

**Corresponding Author e-mail: manjunathattibele@gmail.com*

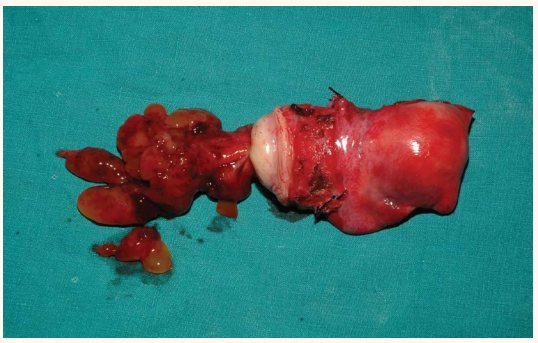

Figure 1: Hysterectomy specimen taken from an adolescent girl with botryoid rhabdomyosarcoma showing the grape-like polypoidal yellowish-red lesion connected to the cervix by a thin pedicle. The lesion was 4–5 cm in size.

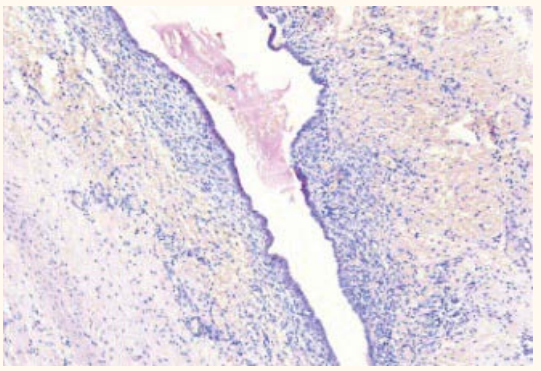

Figure 2: Haematoxylin and eosin histopathology stain demonstrating a prominent cambium layer overlying a malignant botryoid rhabdomyosarcoma at x10 magnification.

from the *introitus* which had been present for the previous six months and was particularly noticeable during menstruation. The patient also complained of a white discharge that was occasionally blood-stained. She did not have any significant medical or surgical history. General and systemic examinations were unremarkable. Upon local examination of the vulva, the mass was not apparent. However, on straining in a squatting position, a fleshy grape-like mass could be seen protruding from the vagina. It appeared reddish, friable and bled to the touch. An examination under anaesthesia revealed a reddish, smooth, glistening, polypoidal mass connected to the cervix by a thin pedicle. The *fornices* and both *parametria* were free of tumours.

A histopathological slide review performed at Kasturba Hospital confirmed the diagnosis of botryoid RMS. A metastatic work-up, including magnetic resonance imaging of the pelvis, computed tomography of the thorax and a bone scan, revealed that the disease was confined to the lower cervix. All routine preoperative laboratory parameters were normal.

Unfortunately, detailed descriptions pertaining to surgical interventions and histopathological prognostic factors of RMS cases were not available for many previously published case reports. Due to the limited data available in the literature regarding the outcome of patients managed conservatively, clinicians counselled the patient's parents about the condition and presented various management options. The parents opted for their daughter to undergo a hysterectomy. In August 2007, the patient underwent a type B1 radical hysterectomy under general anaesthesia. Intraoperatively, no lymph nodes were palpable and the upper abdomen was tumour-free with the botryoid RMS confined to the cervix. The uterus and cervix were removed with adequate margins along with the grape-like polypoidal yellowish-red cervix growth of 4–5 cm [Figure 1].

Postoperative histopathology revealed botryoid RMS of the cervix with no residual disease. All margins were free of tumours. Microscopy revealed a columnar and squamous epithelium overlying a malignant neoplasm [Figure 2]. The rhabdomyoblasts (strap cells) were visible [Figure 3]. No malignant cells were seen via peritoneal cytology.

The patient was classified as category 1A according to the staging classification criteria of the Intergroup Rhabdomyosarcoma Study Group (IRSG).[5] She received six cycles of postoperative adjuvant chemotherapy consisting of vincristine, actinomycin and cyclophosphamide (VAC) with the following regimen: 1.8 mg of vincristine weekly (at 1.5 mg/m^2) and 0.5 mg of dactinomycin (at 0.015 mg/kg/day), 1,200 mg of cyclophosphamide (at 1 mg/m^2) and 200 mg of mesna at zero, four and eight hours, respectively, every 21 days. The patient had episodes of neutropaenia which delayed the above treatment regimen on several occasions during the chemotherapy course.

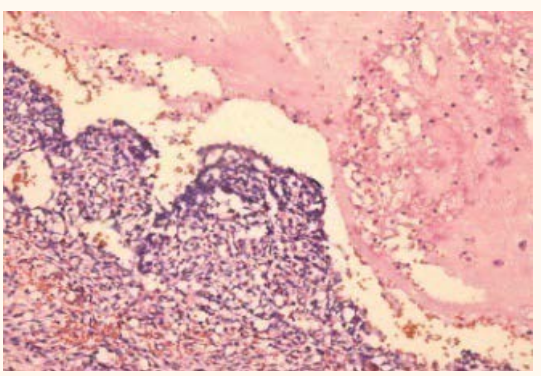

Figure 3: Haematoxylin and eosin histopathology stain showing the periglandular infiltration of the botryoid rhabdomyosarcoma tumour cells (rhabdomyoblasts or strap cells) at x10 magnification.

The patient was followed-up regularly. She appeared to be healthy until approximately eight months after surgery, when she acquired a varicella zoster virus infection while undergoing chemotherapy. This later progressed to pneumonia and septicaemia. She was transferred to an intensive care unit where she died due to septic shock and multiple organ failure.

Discussion

Botryoid RMS is a rapidly growing rare malignancy seen in infants and young children.[1] Although more than 100 nomenclatures exist for this tumour, the term 'sarcoma botryoides' was first used by Pfannenstiel in 1892.[6] The appearance of the botryoid RMS results when the tumour arises under the mucosal surface of the organs, which forces the growth to assume a typical grape-like structure. A distinct cambium layer beneath the epithelium is characteristic of botryoid RMS.[7] The patient reported here satisfied all three criteria essential for the botryoid variety of RMS (i.e. a polypoid appearance, an origin below a mucous membrane-covered surface and the presence of a cambium layer).[8] In order to avoid misdiagnosis and mismanagement, it is essential for clinicians to know of this uncommon disease, particularly common sites and the aggressive nature and clinical implications of the tumour.

The currently reported patient presented with a mass in the vagina, which is among the most common presenting complaints for those with RMS.[3] However, young children may present with vaginal bleeding or urinary or bowel symptoms.[3] Since the occurrence of benign polyps in the vagina or cervix is extremely rare in childhood, the authors recommend that any polypoidal mass found in a child be regarded as botryoid RMS unless proven otherwise.

Only a few case series and reports regarding the management of botryoid RMS of the female genital tract are currently available in the literature. Due to the rare occurrence of these tumours, there is limited literature on the evaluation of optimal therapy and a lack of level 1 evidence. Hence, there is no uniform consensus in the management approach to these tumours. Over the decades, there has been a paradigm shift in management strategies for botryoid RMSs. Although ultra-radical surgery like pelvic exenteration was considered the treatment of choice in the late 1960s, outcomes were often unsatisfactory. In the 1970s, limited surgery with adjuvant chemotherapy and/or irradiation showed improved survival. Surgical aggressiveness gradually reduced from mutilating exenterative procedures to simple local excisions.[9] The spectrum of surgical therapy now includes radical hysterectomies with or without lymphadenectomies,[2,3,7,10–14] hysterectomies,[3,15,16] vaginectomies,[16] cervicectomies,[3] polypectomies,[9,17–19] local excisions,[10,11,20] and diathermy loop excisions.[9] Botryoid RMSs are mostly either treated with surgery alone or with adjuvant chemotherapy and/or radiotherapy.[21]

Even with adjuvant chemotherapy regimens, there is no uniform agreement in the management of these tumours. Most investigators have used a combination of two or three chemotherapeutic agents.[22,23] The most widely used chemotherapy regimen is VAC,[11] which was also used in the current case. VAC is the current gold-standard chemotherapy treatment. Phase II trials from Europe and the USA have shown that ifosfamide, as a single agent, is an active drug against RMS. In combination with other drugs, the response rate is even better. Irinotecan (a topoisomerase I inhibitor) also appears to have promising activity against RMS, with minimal haematopoietic toxicity.[21] There are variations in the type, dose and number of chemotherapy agents used. The number of cycles and the sequence of chemotherapy also differ.[10,18] There are even reports of neoadjuvant chemotherapy being used to shrink large tumours before operations.[11,16] Although in earlier reports radiotherapy was used as a treatment modality, it has since been abandoned as it is now generally agreed that these tumours are not radiosensitive and this therapy would interfere with ovarian function and cause pelvic contractions. It is hence generally reserved only for residual tumours.[23]

Copeland *et al*. conducted one of the largest case series on botryoid RMS of the female genital tract (n = 14) which showcased the evolution of treatment over a 30-year period.[24] The second largest series was carried out by Daya *et al*. who were the first to demonstrate a conservative approach in the management of these tumours with a favourable outcome.[3] Another series showed a successful outcome in 12 out of 14 cases treated via local excision followed by multidrug chemotherapy.[11] However, two patients in this series required radical hysterectomies to control the disease.[11] other reports have also shown favourable outcomes for cervical botryoid RMS patients who were treated via local resection and chemotherapy, with preservation of fertility.[9,17,18,20]

The progression to less extensive therapy over recent years is partly due to the response of this neoplasm to the VAC chemotherapy regimen.[24] It should be emphasised that successful therapy with limited surgery is applicable only for patients who fall into IRSG categories 1 or 2.[24] It is unknown whether localised well-differentiated lesions can be safely

treated with conservative surgery alone without the use of adjuvant therapy. Daya *et al*. reported favourable outcomes in four young patients with cervical botryoid RMSs who were treated only by polypectomy or cervicectomy without chemotherapy.[3] However, fatal recurrence with poor outcomes have been reported with the use of conservative surgery alone.[24] Therefore, postoperative chemotherapy should be administered even for IRSG category 1 patients with cervical botryoid RMS, regardless of the type of surgical intervention performed. Unfortunately, the optimal number of adjuvant chemotherapy cycles needed is unknown.

The role of histopathology in the prognosis of RMS cannot be underestimated. Although three varieties of RMS have been described (embryonal, alveolar and undifferentiated), the embryonal type is the most common and has a favourable prognosis, whereas the alveolar type is rare with a poorer prognosis.[8] Embryonal RMS of the cervix must be distinguished pathologically from adenosarcomas with heterologous elements, malignant mixed Müllerian tumours and low-grade stromal sarcomas as the optimal management strategies and clinical outcomes differ for each.[11] The tumour site, deep myometrial invasion,[3] and lymphatic invasion are important prognostic factors. Cervical RMSs have a better prognosis than similar tumours arising from other sites of the female genital tract.[9]

The survival rates for vaginal and cervical lesions are 60% and 96% respectively.[20] Overall survival has been reported as 79% in patients treated with surgery and adjuvant chemotherapy.[25,26] Although some patients may be cured by simple surgical procedures, the risk of recurrence and metastatic spread remains a concern.[1] The pelvis is the most common site of primary recurrence and the recurrence of this disease is rarely cured after definitive initial therapy.[24] There are reports of extensive metastasis to the lung with high mortality, despite surgery and chemotherapy.[1] Cervical botryoid RMSs invade and recur despite adjuvant chemotherapy,[9,11] and patients have died due to the recurrent disease.[3]

In the current case, the patient died due to sepsis during the follow-up period. Her death was not due to persistence or recurrence of the botyroid RMS. There was no evidence of residual disease and no deep infiltration to the myometrium. Therefore, there was a good chance of prolonged survival had the patient not contracted the varicella infection. Moreover, in retrospect, she would have been an ideal candidate for a conservative surgical approach. The patient acquired the varicella infection while undergoing chemotherapy; however, it is difficult to determine whether the chemotherapy was the causative agent of the infection. The infection may be presumed to be due to the transient altered immunological status of the patient while undergoing chemotherapy and exposure to varicella infection in a prevalent area; Karnataka in South India is a high prevalence area for varicella infections, especially in adolescents.[27] Eight deaths have been similarly documented as a result of infection during management of genitourinary RMS in patients who received chemotherapy.[5] Therefore, due to the limited literature on this issue, an evaluation of infective morbidity and mortality rates during chemotherapy treatment would be of great value for future reports. However, due to the rarity of these tumours, it may not be feasible to conduct randomised controlled trials to demonstrate the most appropriate treatment approach.

Conclusion

RMS of the female genital tract is a rapidly growing rare malignancy seen in infants and young children. The most effective treatment for this tumour has still not been well established and is a subject of on-going investigation. Due to the lack of data pertaining to surgical interventions and histopathological prognostic factors of RMS cases, in addition to the diversity in management approaches, it is difficult to draw absolute conclusions regarding overall treatment outcomes. However, there has been an increasing tendency towards conservative therapy in recent years. From the available literature, it appears that limited surgery with adjuvant multi-agent chemotherapy is feasible in the treatment of early cervical RMS in young patients.

References

1. Bell J, Averette H, Davis J, Toledano S. Genital rhabdomyosarcoma: Current management and review of the literature. Obstet Gynecol Surv 1986; 41:257–63. doi: 10.1097/00006254-198605000-00001.
2. Atlante M, Dionisi B, Cioni M, Di Ruzza D, Sedati P, Mariani L. Sarcoma botryoides of the uterine cervix in a young woman: A case report. Eur J Gynaecol Oncol 2000; 21:504–6.
3. Daya DA, Scully RE. Sarcoma botryoides of the uterine cervix in young women: A clinicopathological study of 13 cases. Gynecol Oncol 1988; 29:290–304. doi: 10.1016/0090-8258(88)90228-4.
4. Cywes S, Louw JH. Sarcoma botryoides of the vagina: A report of two cases. S Afr Med J 1961; 35:911–17.
5. Ind T, Shepherd J. Pelvic tumours in adolescence. Best Pract Res Clin Obstet Gynaecol 2003; 17:149–68. doi: 10.1053/ybeog.2002.0345.
6. Pfannenstiel J. Das traubige sarkom der cervix uteri. Virchows Arch Path Anat 1892; 127:305–37.
7. Mousavi A, Akhavan S. Sarcoma botryoides (embryonal rhabdomyosarcoma) of the uterine cervix in sisters. J Gynecol Oncol 2010; 21:273–5. doi: 10.3802/jgo.2010.21.4.273.

8. Wenig BM. Undifferentiated malignant neoplasms of the sinonasal tract. Arch Pathol Lab Med 2009; 133: 699–712. doi: 10.1043/1543-2165-133.5.699.

9. Zanetta G, Rota SM, Lissoni A, Chiari S, Bratina G, Mangioni C. Conservative treatment followed by chemotherapy with doxorubicin and ifosfamide for cervical sarcoma botryoides in young females. Br J Cancer 1999; 80:403–6. doi: 10.1038/sj.bjc.6690370.

10. Behtash N, Mousavi A, Tehranian A, Khanafshar N, Hanjani P. Embryonal rhabdomyosarcoma of the uterine cervix: Case report and review of the literature. Gynecol Oncol 2003; 91:452–5. doi: 10.1016/S0090-8258(03)00539-0.

11. Dehner LP, Jarzembowski JA, Hill DA. Embryonal rhabdomyosarcoma of the uterine cervix: A report of 14 cases and a discussion of its unusual clinicopathological associations. Mod Pathol 2012; 25:602–14. doi: 10.1038/modpathol.2011.185.

12. Golbang P, Khan A, Scurry J, MacIsaac I, Planner R. Cervical sarcoma botryoides and ovarian Sertoli-Leydig cell tumor. Gynecol Oncol 1997; 67:102–6. doi: 10.1006/gyno.1997.4807.

13. Qiang JX, Takahashi O, Hatazawa J, Karube A, Ohyama N, Sato H, et al. Sarcoma botryoides of the uterine cervix: A case report. J Obstet Gynaecol Res 1998; 24:197–201. doi: 10.1111/j.1447-0756.1998.tb00075.x.

14. Scaravilli G, Simeone S, Dell'Aversana Orabona G, Capuano S, Serao M, Rossi R, et al. Case report of a sarcoma botryoides of the uterine cervix in fertile age and literature review. Arch Gynecol Obstet 2009; 280:863–6. doi: 10.1007/s00404-009-1022-3.

15. Miyamoto T, Shiozawa T, Nakamura T, Konishi I. Sarcoma botryoides of the uterine cervix in a 46-year-old woman: Case report and literature review. Int J Gynecol Pathol 2004; 23:78–82. doi: 10.1097/01.pgp.0000101147.41312.54.

16. Deligeoroglou E, Tsimaris P, Creatsa M, Athanasopoulos N, Creatsas G. Application of Creatsas vaginoplasty after radical surgical treatment of sarcoma botryoides. J Pediatr Adolesc Gynecol 2014; 27:93–5. doi: 10.1016/j.jpag.2013.12.004.

17. Gordon AN, Montag TW. Sarcoma botryoides of the cervix: Excision followed by adjuvant chemotherapy for preservation of reproductive function. Gynecol Oncol 1990; 36:119–24. doi: 10.1016/0090-8258(90)90121-Z.

18. Bernal KL, Fahmy L, Remmenga S, Bridge J, Baker J. Embryonal rhabdomyosarcoma (sarcoma botryoides) of the cervix presenting as a cervical polyp treated with fertility-sparing surgery and adjuvant chemotherapy. Gynecol Oncol 2004; 95:243–6. doi: 10.1016/j.ygyno.2004.06.049.

19. Rosenberg P, Carinelli S, Peiretti M, Zanagnolo V, Maggioni A. Cervical sarcoma botryoides and ovarian Sertoli-Leydig cell tumor: A case report and review of literature. Arch Gynecol Obstet 2012; 285:845–8. doi: 10.1007/s00404-011-2017-4.

20. Gruessner SE, Omwandho CO, Dreyer T, Blütters-Sawatzki R, Reiter A, Tinneberg HR, et al. Management of stage I cervical sarcoma botryoides in childhood and adolescence. Eur J Pediatr 2004; 163:452–6. doi: 10.1007/s00431-004-1469-y.

21. Agarwala S. Pediatric rhabdomyosarcomas and nonrhabdomyosarcoma soft tissue sarcoma. J Indian Assoc Pediatr Surg 2006; 11:15–23. doi: 10.4103/0971-9261.24632.

22. Arndt CA, Donaldson SS, Anderson JR, Andrassy RJ, Laurie F, Link MP, et al. What constitutes optimal therapy for patients with rhabdomyosarcoma of the female genital tract? Cancer 2001; 12:2454–68. doi: 10.1002/1097-0142(20010615)91:12<2454::AID-CNCR1281>3.0.CO;2-C.

23. Dayyabu AL, Adogu IO, Makama BS. Sarcoma botryoides, a management dilemma: A review of two cases. Int J Case Rep Imag 2014; 5:15–20. doi: 10.5348/ijcri-201458-CS-10044.

24. Copeland LJ, Gershenson DM, Saul PB, Sneige N, Stringer CA, Edwards CL. Sarcoma botryoides of the female genital tract. Obstet Gynecol 1985; 66:262–6.

25. Montag TW, D'ablaing G, Schlaerth, JB, Gaddis O Jr, Morrow CP. Embryonal rhabdomyosarcoma of the uterine corpus and cervix. Gynecol Oncol 1986; 25:171–94. doi: 10.1016/0090-8258(86)90098-3.

26. Brand E, Berek JS, Nieberg RK, Hacker NF. Rhabdomyosarcoma of the uterine cervix: Sarcoma botryoides. Cancer 1987; 60:1552–60. doi: 10.1002/1097-0142(19871001)60:7<1552::AID-CNCR2820600724>3.0.CO;2-W.

27. Girish PN, Shetty NJ, Shetty VH, Vaz GF. Study of the clinical patterns in varicella in a tertiary hospital at coastal Karnataka. Online J Health Allied Sci 2011; 10:6.