THE JOURNAL OF
Obstetrics and Gynaecology Research

The official Journal of Asia and Oceania Federation of Obstetrics and Gynaecology
Japan Society of Obstetrics and Gynecology

doi:10.1111/j.1447-0756.2010.01449.x J. Obstet. Gynaecol. Res. Vol. 37, No. 7: 940–946, July 2011

Embryonal rhabdomyosarcoma of the uterine cervix in a 47-year-old woman

Glauco Baiocchi[1], Carlos Chaves Faloppa[1], Cynthia Aparecida Bueno de Toledo Osório[2], Lillian Yuri Kumagai[1], Elza Mieko Fukazawa[1] and Isabela Werneck Cunha[2]

Departments of [1]Gynecological Oncology and [2]Pathology, AC Camargo Cancer Hospital, Sao Paulo, Brazil

Abstract

Embryonal rhabdomyosarcoma (RMS) of the female genital tract usually occurs in the vagina during childhood. The uterine cervix as a primary site is rare, but is more frequent until the second decade of life. It usually has a good prognosis and the treatment is based on multidrug chemotherapy, radiotherapy and surgery. RMS accounts for <5% of all adult soft tissue sarcomas. Previous reports that included all primary sites showed a poorer five-year disease specific survival for adults with RMS when compared to the pediatric population. This difference has been attributed to a higher proportion of adverse prognostic clinical and pathological factors, and to inadequate treatment given to adults with RMS. A total of 115 patients with cervical embryonal RMS have previously been described; however, only 10 cases were reported in women older than 40 years. We present a 47-year-old woman treated with radical hysterectomy followed by adjuvant chemotherapy and review the current literature.

Key words: cervical cancer, embryonal rhabdomyosarcoma, VAC (vincristine, actinomycin D, cyclophosphamide) protocol.

Introduction

Rhabdomyosarcoma (RMS) is a highly malignant tumor that arises from the embryonal mesenchyma. It is the most common soft tissue sarcoma in childhood and young adults and accounts for 4–6% of all malignancies in this age group.[1] These tumors occur most commonly in the head and neck region, and the genitourinary tract is the second most common primary location, with nearly half being embryonal RMS.[2] The Intergroup Rhabdomyosarcoma Study (IRS) Group has reported a new classification of RMS and recognizes three major histological subtypes: embryonal, alveolar and undifferentiated.

The embryonal subtype is the most common and accounts for 58% of all RMS cases. Classic, botryoid and spindle cell variants comprise, respectively, 49, 6 and 3% of cases. It usually occurs in the vagina during infancy and early childhood with a mean age of three years.[3] The mean age at diagnosis of patients with embryonal RMS of the cervix is higher than patients with vaginal lesions.[4]

The botryoid type has a typical 'grape-like' appearance due to a layer of spindle cells pushing up beneath the mucosa in polypoid masses.[1] A combined modality approach to treat RMS using surgery, chemotherapy and radiotherapy has evolved over the past years and has improved survival rates to more than 60% for all stages and up to 90% for localized disease of any site, including genitourinary tumors.[2]

The clinical-pathological data of RMS have been studied through cooperative group trials that addressed the multimodality treatment for the pediatric population.[3] The successful multimodal approach has changed the surgical management of genital tract RMS in children. Primary chemotherapy plus surgery

Received: January 16 2010.
Accepted: July 21 2010.
Reprint request to: Dr Glauco Baiocchi, Departamento de Ginecologia, Hospital do Cancer AC Camargo, Rua Antonio Prudente 211, São Paulo 01509-010, Brasil. Email: glbaiocchi@yahoo.com.br

© 2011 The Authors
Journal of Obstetrics and Gynaecology Research © 2011 Japan Society of Obstetrics and Gynecology

and radiation therapy for local tumor control have taken the place of previous radical exenterative surgery and adjuvant chemotherapy, with no overall survival impact.[3,5,6]

Due to the rarity of RMS in the adult population, clinical and pathological features have been published only as case reports or small case series. Until now, 115 patients with cervical embryonal RMS were described,[2,4,7–12] but only 10 cases in women older than 40 years.[7–10,13,14] We present a 47-year-old woman treated with radical hysterectomy and adjuvant chemotherapy, and review the current literature.

Case Report

A 47-year-old woman was referred to our institution in May 2009 with a recent history of a vaginal discharge and a fleshy mass protruding from the vagina.

Pelvic examination showed a 10 cm fragile, irregular, 'cauliflower-like' mass protruding from the cervical os and filling the vagina (Fig. 1). A biopsy confirmed a botryoid variant of embryonal rhabdomyosarcoma. In a low-power image, a polypoid architecture, characteristic cambium layer and myxoid stroma were found. Immunohistochemical staining were positive for myogenin, desmin, vimentin and Ki67; weakly positive for MyoD1 and negative for muscle-specific actin, CD10 and AE1/AE3 (Figs 2 and 3).

A CT scan of the chest and a full abdominal MRI (Fig. 4) were done and did not find any evidence of metastatic disease. The patient was initially treated with radical hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection.

The pathology demonstrated a 'grape-like' or 'cauliflower-like' tumor based on the endocervix that had more than 50% of depth infiltration and uterine isthmus extension (Fig. 1). Fifty lymph nodes were analyzed and no metastases were found.

As the patient had localized disease, confined to the site of origin and completely excised, she was staged as Group IA based on the IRS Group criteria.[15] The patient is currently receiving adjuvant treatment with chemotherapy, consisting of vincristine 1.5 mg/m^2, actinomycin D 0.5 mg/m^2, and cyclophosphamide 500 mg/m^2 (VAC) every three weeks, scheduled for 12 courses over the period of a year.[15]

Discussion

Histopathological characteristics

Well-differentiated RMS has some characteristics, such as rhabdomyoblasts, that may allow for a morphologic diagnosis without adjunct studies.[16] On the other hand, less differentiated RMS resembles other small, blue, round-cell tumors (SBRCTs). Of those cases (at least 20% of RMS), immunohistochemistry is required and essential for definitive diagnosis.[17] The most commonly used immunohistochemical stains for RMS differential diagnosis are based on cytoplasmic filaments such as desmin and muscle-specific actin or oxidative proteins such as myoglobin. However, desmin and muscle-specific actin are not specific to the myogenic lineage and myoglobin is usually expressed only in the late stages of myogenesis.[16]

Desmin has a very good sensitivity in the diagnosis of RMS; however, as its specificity is lower, the final diagnosis of RMS based solely on desmin staining cannot be done in a SBRCT.[18] Myogenin and MyoD1 belong to the MyoD family of myogenic helix-loop-helix transcription factors.[16,19] They play an important role in the myogenic differentiation pathway from mesodermal precursors into myoblasts, and in its

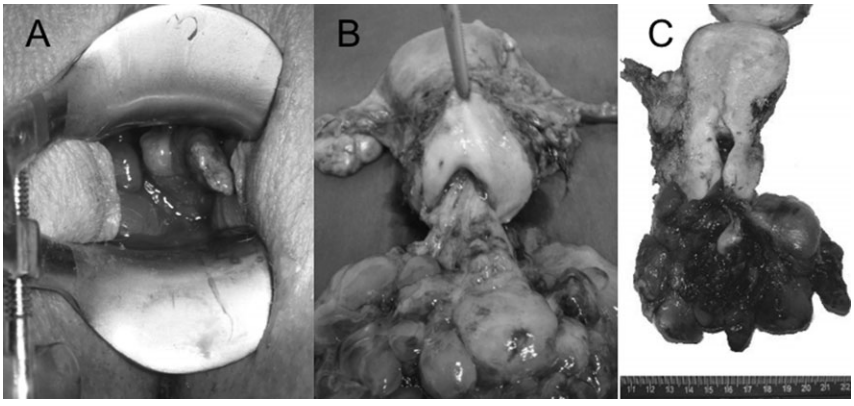

Figure 1 (A) Pelvic examination showed a 'cauliflower-like' mass filling the vagina; (B) radical hysterectomy specimen with the tumor protruding from the cervical os; (C) surgical specimen after coronal section demonstrating a tumor based on the endocervix that infiltrates more than 50% of the depth.

© 2011 The Authors

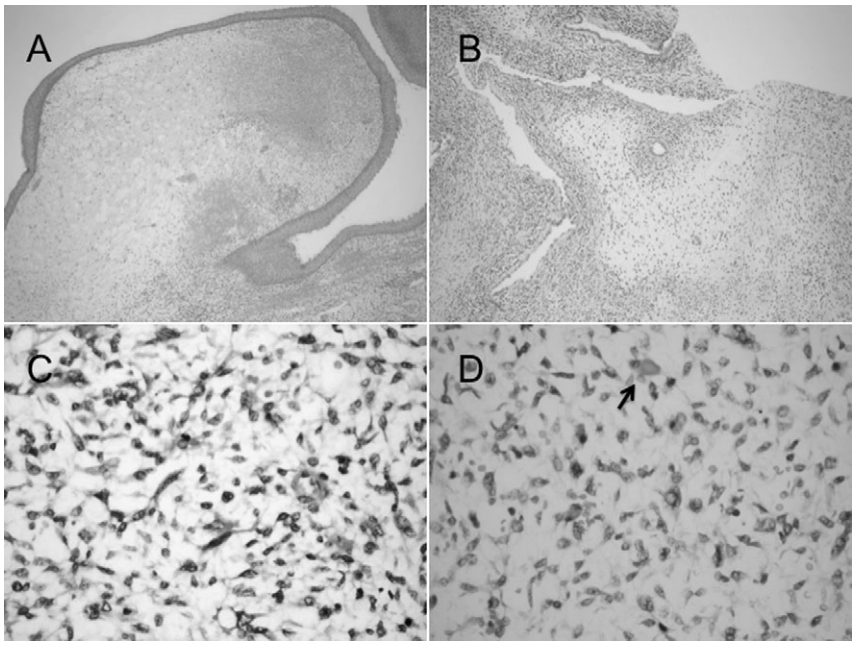

Figure 2 (A) Low-power aspect of botryoid rhabdomyosarcoma showing polypoid architecture (4×); (B) low-power aspect of myxoid stroma and characteristic cambium layer (10×); (C) small oval and spindle cells with high mitotic index (40×); (D) rhabdoid cells (arrow) in a background of edematous stroma.

consecutive differentiation into myotubes and skeletal myofibers.[20] Before differentiation, myoblasts express MyoD1, and myogenin is expressed after differentiation.[16,21–23]

Morotti *et al*.,[16] stated that MyoD1 and myogenin immunostains are the most useful assays to confirm the diagnosis of RMS. This may be correct, even without morphologic evidence of myogenic differentiation. Both have high sensitivity and specificity.

The present a case has a typical immunohistochemical profile, showing positive staining for myogenin, desmin and MyoD1.

Clinical characteristics

Rhabdomyosarcoma accounts for <5% of all adult soft tissue sarcomas.[24] In children, primary uterine cervix RMS accounts for 15% of cases. It is the third most common gynecologic site after vagina (54%) and uterine corpus (17%).[3,10] In adult patients, RMS might be considered in the clinical and histological differential diagnosis along with other uterine primary neoplasms such as carcinosarcoma, leiomyosarcoma, endometrial stromal sarcoma and adenosarcoma. Those may demonstrate skeletal muscle differentiation.[10]

Previous reports that included all primary sites, showed a poor five-year disease specific survival for adult RMS ranging from 20–40%;[25–30] however, a five-year overall survival of >85% has been achieved in children with gynecologic RMS.[3,6] This difference has been attributed to a higher proportion of adverse prognostic clinical and pathologic factors, and to inadequate treatment given to adults with RMS.[10,26]

Embryonal RMS has a five-year overall survival of 82% compared with 66% for non-embryonal variants[3,10] and these unfavorable variants are more frequent in adults.[3,10,26,27,29] When only the primary gynecological site is considered, uterine corpus RMS in children usually confers a worse prognosis when compared to vaginal, vulvar and cervical sites.[31] Ferguson *et al*.[10] have also shown in the adult female genital tract a better progression-free survival for the uterine cervix when compared to other gynecological sites, but with no impact in overall survival. The adult age also seems to be a prognostic factor. Patients between 16 to 20 years old may have a better prognosis than those patients older than 20.[27]

Children with locoregional RMS have a well-established treatment regimen, combining surgery, radiation and multiagent chemotherapy with vincristine, dactinomycin and cyclophosphamide.[3,31] Although prospective studies are lacking in the adult population and no standard treatment has been established, there are encouraging results from retrospective studies with multiagent chemotherapy based on pediatric guidelines, with improved survival and response rates of >80%.[10,25,26]

Organ-preserving procedures as trachelectomy, local excision and polypectomy have been reported in

© 2011 The Authors
Journal of Obstetrics and Gynaecology Research © 2011 Japan Society of Obstetrics and Gynecology

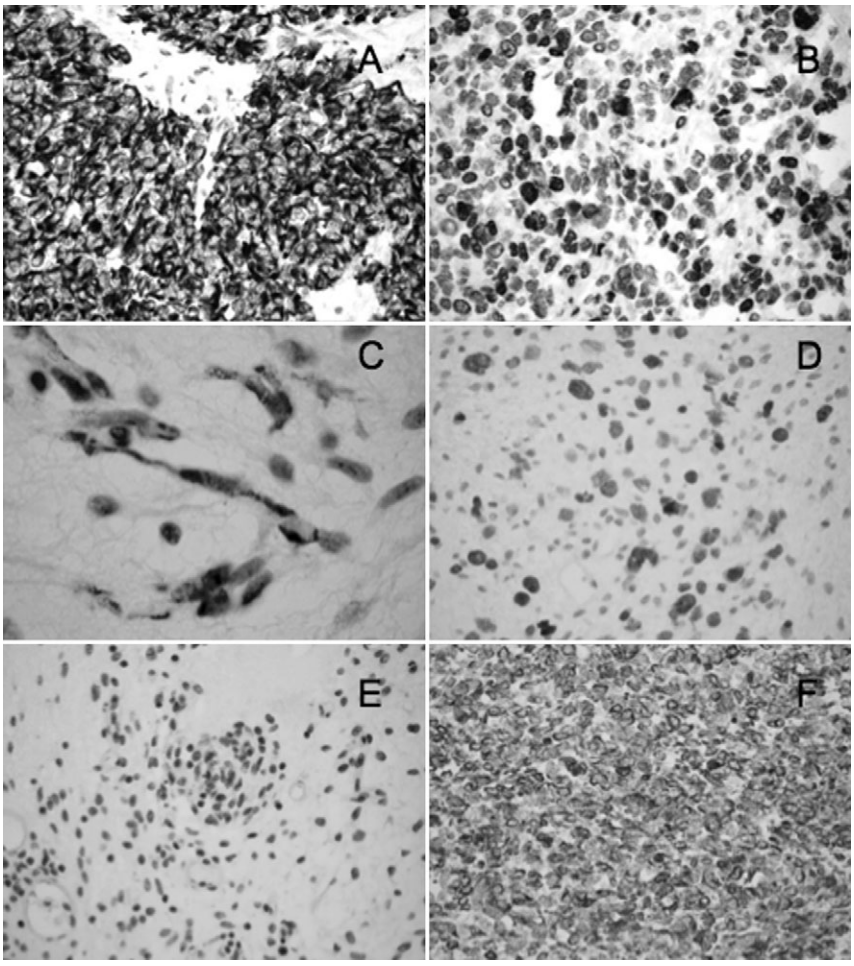

Figure 3 (A) Strong cytoplasmic immunohistochemical desmin staining (40×); (B) immunohistochemical nuclear staining of myogenin (40×); (C) cytoplasmic spindle cell staining of desmin (100×); (D) immunohistochemical nuclear staining of Ki67 showing a high proliferative index (40×); (E) weakly positive staining of MyoD1 (40×); (F) strong cytoplasmic staining of vimentin (40×).

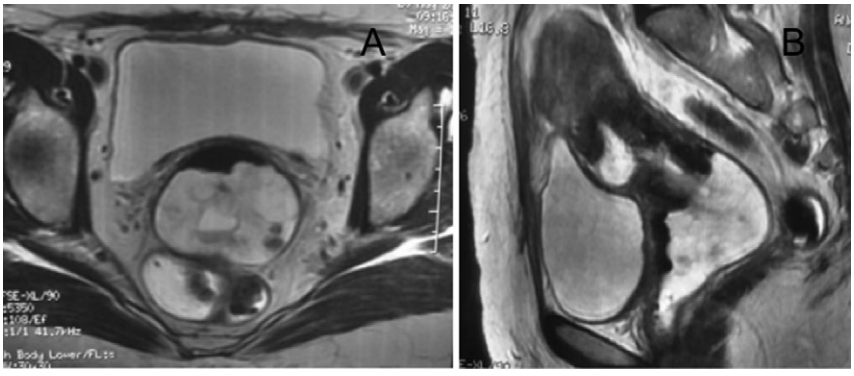

Figure 4 Axial (A) and sagittal (B) T2-weighted pelvic MRI shows a voluminous mass of endocervical origin filling the vagina without extension to the paracervical tissue.

young women.[32–36] From the 12 patients described, 11 were disease free after 1278 months. Four patients reported by Daya *et al*.[33] did not receive chemotherapy, but the indications were not stated. One death occurred in a patient with deep myometrial invasion submitted to hysterectomy after recurrence.[33] The favorable prognostic parameters were single polyp, embryonal histologic subtype, and localized disease without deep myometrial invasion. Those findings suggest that in a subgroup of young women with gynecological RMS,

© 2011 The Authors
Journal of Obstetrics and Gynaecology Research © 2011 Japan Society of Obstetrics and Gynecology

Table 1 Treatment data and clinical outcomes of the 10 patients aged >40 years with primary cervical rhabdomyosarcoma

Author	Age (years)	Staging (IRS Group)	Surgery	Radiotherapy	Chemotherapy	Outcome	Follow up (months)	Comment
Ober, 1971[14]	75	I	Polypectomy (3x) + vulvoperineal resection	14.4 Gy vaginal apex	–	DOD	96	Extension to uterine corpus
Brand, 1987[7]	48	I	TAH + BSO	54 Gy whole pelvis + 35 Gy vaginal apex (radium)	CPM (3 months)	NED	266	Radiotherapy after vaginal recurrence
Vlahos, 1999[13]	45	I	TAH + BSO + PPLND	–	–	DOD	4	Metastasis to abdomen
Miyamoto, 2004[8]	46	I	Polypectomy (× 2) + TAH + BSO	–	VCN + ACD	NED	45	–
Ferguson, 2007[10]	56	I	TAH + PPLND	–	VCN + ACD	NED	37	–
Ferguson, 2007[10]	51	I	TAH + BSO + PPLND	–	VCN + ACD + CPM + ADR	NED	7	–
Ferguson, 2007[10]	52	I	TAH + BSO + PPLND	Whole pelvis	–	DOD	17	Recurred after 9 months
Ferguson, 2007[10]	58	I	TAH + PPLND	25 Gy vaginal apex	–	NED	27	Previous BSO
Ferguson, 2007[10]	46	I	TAH + BSO + PPLND	–	–	DOD	12	Recurred after 7 months
Sanders, 2008[9]	47	I	RH + BSO + PLND	–	VCN + ACD + CPM	NED	14	–

ACD, actinomycin D; ADR, adriamycin; BSO, bilateral salpingo-oophorectomy; CPM, cyclophosphamide; DOD, died of the disease; IRS, Intergroup Rhabdomyosarcoma Study; NED, no evidence of disease; PLND, pelvic lymph node dissection; PPLND, pelvic and para-aortic lymph node dissection; RH, radical hysterectomy; TAH, total abdominal hysterectomy; VCN, vincristine.

© 2011 The Authors

the reproductive function may be able to be preserved; however, for women presenting with unfavorable prognostic parameters and where there are no fertility preservation concerns, radical surgery and adjuvant chemotherapy seems to be the most appropriate treatment.[2]

Only ten cases of uterine cervix RMS in women over age of 40 years have been reported (Table 1). Five patients did not receive chemotherapy after surgical treatment and just one did not recur after 27 months of follow-up.[10,13,14] From the five patients that received adjuvant chemotherapy, four were free of disease from 7 to 45 months.[8–10] One patient had local recurrence two months after the completion of chemotherapy, received radiation therapy and has no evidence of disease after 22 years of follow up.[7] We present here the 11th case. As the patient had extensive disease we opted to perform a radical hysterectomy. Lymph node dissection was also performed, although its role has no consistent data in literature. Our case is the second patient over 40 years of age[9] who was treated with radical hysterectomy followed by the IRS Group IV adjuvant chemotherapy schema.[15]

The high survival rates achieved for the pediatric population were not routinely reported for the adult population. There has been no final evidence that genital adult RMS has inherently different behavior than RMS occurring in children when both receive the same initial treatment. The evidence that RMS is also sensitive to chemotherapy in adults corroborates the current concept that adequate treatment should include surgery and multiagent chemotherapy, as proposed with the paediatric population. Radiation therapy may also be included in selected cases at higher risk of loco-regional recurrence.

Acknowledgment

The authors declare that there are no conflicts of interest.

References

1. Villella JA, Bogner PN, Jani-Sait SN, Block AM, Lele S. Rhabdomyosarcoma of the cervix in sisters with review of the literature. *Gynecol Oncol* 2005; **99**: 742–748.
2. Zeisler H, Mayerhofer K, Joura EA *et al*. Embryonal rhabdomyosarcoma of the uterine cervix: case report and review of the literature. *Gynecol Oncol* 1998; **69**: 78–83.
3. Arndt CA, Donaldson SS, Anderson JR *et al*. What constitutes optimal therapy for patients with rhabdomyosarcoma of the female genital tract? *Cancer* 2001; **91**: 2454–2468.
4. 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**: 452–455.
5. Andrassy RJ, Wiener ES, Raney RB *et al*. Progress in the surgical management of vaginal rhabdomyosarcoma: a 25-year review from the Intergroup Rhabdomyosarcoma Study Group. *J Pediatr Surg* 1999; **34**: 731–734.
6. Martelli H, Oberlin O, Rey A *et al*. Conservative treatment for girls with nonmetastatic rhabdomyosarcoma of the genital tract: a report from the Study Committee of the International Society of Pediatric Oncology. *J Clin Oncol* 1999; **17**: 2117–2112.
7. Brand E, Berek JS, Nieberg RK, Hacker NF. Rhabdomyosarcoma of the uterine cervix. Sarcoma botryoides. *Cancer* 1987; **60**: 1552–1560.
8. Miyamoto T, Shiozawa T, Nakamura T *et al*. 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.
9. Sanders MA, Gordinier M, Talwalkar SS, Moore GD. Embryonal rhabdomyosarcoma of the uterine cervix in a 41-year-old woman treated with radical hysterectomy and adjuvant chemotherapy. *Gynecol Oncol* 2008; **111**: 561–563.
10. Ferguson SE, Gerald W, Barakat RR, Chi DS, Soslow RA. Clinicopathologic features of rhabdomyosarcoma of gynecologic origin in adults. *Am J Surg Pathol* 2007; **31**: 382–389.
11. Scaravilli G, Simeone S, Dell'Aversana Orabona G *et al*. Case report of a sarcoma botryoides of the uterine cervix in fertile age and literature review. *Arch Gynecol Obstet* 2009; **280**: 863–866.
12. Ghaemmaghami F, Karimi Zarchi M, Ghasemi M. Lower genital tract rhabdomyosarcoma: case series and literature review. *Arch Gynecol Obstet* 2008; **278**: 65–69.
13. Vlahos NPM, Veridiano RNP. Cervical sarcoma botryoides. A case report. *J Reprod Med* 1999; **44**: 306–308.
14. Ober WB. Sarcoma botryoides of the cervix uteri: a case report in a 75-year-old woman. *Mt Sinai J Med* 1971; **38**: 363–374.
15. Crist WM, Anderson JR, Meza JL *et al*. Intergroup rhabdomyosarcoma study-IV: results for patients with nonmetastatic disease. *J Clin Oncol* 2001; **19**: 3091–3102.
16. Morotti RA, Nicol KK, Parham DM *et al*. Children's Oncology Group. An immunohistochemical algorithm to facilitate diagnosis and subtyping of rhabdomyosarcoma: the Children's Oncology Group experience. *Am J Surg Pathol* 2006; **30**: 962–968.
17. Qualman SJ, Coffin CM, Newton WA *et al*. Intergroup rhabdomyosarcoma study: update for pathologists. *Pediatr Dev Pathol* 1998; **1**: 550–561.
18. Gerald WL, Miller HK, Battifora H *et al*. Intra-abdominal desmoplastic small round-cell tumor. Report of 19 cases of a distinctive type of high-grade polyphenotypic malignancy affecting young individuals. *Am J Surg Pathol* 1991; **15**: 499–513.
19. Wright WE, Dac-Korytko I, Farmer K. Monoclonal antimyogenin antibodies define epitopes outside the bHLH domain where binding interferes with protein-protein and protein-DNA interactions. *Dev Genet* 1996; **19**: 131–138.
20. Venuti JM, Cserjesi P. Molecular embryology of skeletal myogenesis. *Curr Top Dev Biol* 1996; **34**: 169–206.

© 2011 The Authors

Journal of Obstetrics and Gynaecology Research © 2011 Japan Society of Obstetrics and Gynecology

21. Davis RL, Weintraub H, Lassar AB. Expression of a single transfected cDNA converts fibroblasts to myoblasts. *Cell* 1987; **51**: 987–1000.
22. Montarras D, Pinset C, Chelly J *et al*. Expression of MyoD1 coincides with terminal differentiation in determined but inducible muscle cells. *EMBO J* 1989; **8**: 2203–2207.
23. Wright WE, Sassoon DA, Lin VK. Myogenin, a factor regulating myogenesis, has a domain homologous to MyoD. *Cell* 1989; **56**: 607–617.
24. Cormier JN, Pollock RE. Soft tissue sarcomas. *CA Cancer J Clin* 2004; **54**: 94–109.
25. Esnaola NF, Rubin BP, Baldini EH *et al*. Response to chemotherapy and predictors of survival in adult rhabdomyosarcoma. *Ann Surg* 2001; **234**: 215–223.
26. Ferrari A, Dileo P, Casanova M *et al*. Rhabdomyosarcoma in adults. A retrospective analysis of 171 patients treated at a single institution. *Cancer* 2003; **98**: 571–580.
27. Hawkins WG, Hoos A, Antonescu CR *et al*. Clinicopathologic analysis of patients with adult rhabdomyosarcoma. *Cancer* 2001; **91**: 794–803.
28. La Quaglia MP, Heller G, Ghavimi F *et al*. The effect of age at diagnosis on outcome in rhabdomyosarcoma. *Cancer* 1994; **73**: 109–117.
29. Little DJ, Ballo MT, Zagars GK *et al*. Adult rhabdomyosarcoma: outcome following multimodality treatment. *Cancer* 2002; **95**: 377–388.
30. Lloyd RV, Hajdu SI, Knapper WH. Embryonal rhabdomyosarcoma in adults. *Cancer* 1983; **51**: 557–565.
31. Raney RB, Anderson JR, Barr FG *et al*. Rhabdomyosarcoma and undifferentiated sarcoma in the first two decades of life: a selective review of Intergroup rhabdomyosarcoma study group experience and rationale for Intergroup Rhabdomyosarcoma Study V. *J Pediatr Hematol Oncol* 2001; **23**: 215–220.
32. Hays DM, Shimada H, Raney RB *et al*. Clinical staging and treatment results in rhabdomyosarcoma of the female genital tract among children and adolescents. *Cancer* 1988; **9**: 1893–1903.
33. 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.
34. Palazzo JP, Gibas Z, Dunton CJ, Talerman A. Sarcoma botryoides of the uterine cervix in young women: a clinicopathological study of 13 cases. *Virchows Arch A Pathol Anat Histopathol* 1993; **422**: 87–91.
35. Gordan AN, Montag TW. Case report – sarcoma botryoides of the cervix: excision followed by adjuvant chemotherapy for preservation of reproductive function. *Gynecol Oncol* 1990; **36**: 119–124.
36. Lin J, Lam SK, Cheung TH. Sarcoma botryoides of the cervix treated with limited surgery and chemo-therapy to preserve fertility. *Gynecol Oncol* 1995; **58**: 270–273.

© 2011 The Authors
Journal of Obstetrics and Gynaecology Research © 2011 Japan Society of Obstetrics and Gynecology