Late Relapse of Embryonal Rhabdomyosarcoma, Botryoid Variant, of the Vagina

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Abstract

We report on two very similar cases of vaginal embryonal RMS, botryoid variant that relapsed 9 and 10 years after initial diagnosis, a few months after the menarche in both cases. A possible causal association with estrogen hormones is hypothesized, particularly for the second case described, in which estrogen receptors were negative in the primary tumor specimen and positive in the relapsing tumor specimen. Pediatr Blood Cancer 2008; 51:140–141.

Key words: chemotherapy; hormone receptors; menarche; rhabdomyosarcoma.

Introduction

More than 70% of patients with localized rhabdomyosarcoma (RMS) are currently expected to be relapse-free 5 years after their initial diagnosis [1]. Most treatment failures occur in the first 3–5 years after the diagnosis of the primary, while later recurrences are uncommon [2–4]. This article reports on two very similar cases of embryonal RMS, botryoid variant, of the vagina in two childrenaged 24 and 10 months and relapsing 9 and 10 years, respectively,after the initial diagnosis. The relapse occurred a few months after the menarche in both cases, suggesting a possible relationship with sex hormone status.

Case Report 1

A 24-month-old child was diagnosed with multifocal botryoid embryonal RMS of the vagina in November 1987. She was given chemotherapy (vincristine, adriamycin, cyclophosphamide and actinomycin-D) for 24 months, achieving a complete remission. No treatment for local control (surgery or radiotherapy) was administered. She had her menarche in June 1996 (at 11 years of age). Nine months later (112 months after the initial diagnosis), she presented to our Institute with transvaginal bleeding and evidence of a polypoid exophytic tumor on the vaginal introit. Further radiological investigation revealed a huge pelvic mass (9 cm x 7 cm in size). A biopsy was taken of the polypoid lesion and the histological diagnosis confirmed that it was a botryoid embryonal RMS. Immunocytochemical assessment of the estrogen and progesterone receptors was negative in the relapsed tumor cells.

The patient received second-line multi-drug chemotherapy (cisplatin/carboplatin, ifosfamide, etoposide, vincristine) with only minimal tumor shrinkage, followed by partial tumor resection and then radiotherapy (60 Gy). The tumor progressed locoregionally 10 months after the relapse had been identified, followed by hepatic, lung and brain metastases a month later. The patient died in May 1998.

Case Report 2

A 10-month-old child was diagnosed with botryoid embryonal RMS in June 1994 after transvaginal biopsy of a bleeding vaginal polypoid lesion 3 cm x 2 cmin size. Chemotherapy with ifosfamide, vincristine, adriamycin, and actinomycin-D was administered for 12 months and the tumor disappeared completely. Two months after stopping the treatment, multifocal vaginal nodules were identified during a vaginoscopy and another biopsy confirmed the recurrence. The patient was given second-line therapy with carboplatin, etoposide, vincristine and epirubicin, followed by brachytherapy (60 Gy), obtaining a second complete remission. In October 2005 the patient had her menarche (at 12 years of age). In November 2006, a vaginal polypoid lesion was detected. Multiple biopsies taken during a vaginoscopy led to the diagnosis of a multifocal vaginal relapsing RMS. Immunocytochemical assessment of the estrogen and progesterone receptors disclosed reactivity for progesterone receptors in both the initial and the relapsing tumor specimens, while estrogen receptors were negative in the primary tumor and positive in the tumor relapsing after the menarche.

Re-staging investigations ruled out metastatic lesions, so five courses of chemotherapy with cyclophosphamide, actinomycin-D and vincristine were administered, then the patient underwent surgery consisting of vaginectomy and hysterectomy. Multiple tumor foci were found in the vaginal wall. A biopsy of a tiny lesion in the perineum, close to the urethra, also showed tumor cells outside the vagina, so external beam irradiation up to 50 Gy was given to the perineum and pelvis. Maintenance chemotherapy with vinorelbine was then administered. The patient was still on maintenance treatment at the time of this report, with no macroscopic evidence of disease.

Discussion

Botryoid embryonal RMS of the vagina usually has a favorable prognosis (with a 10-year survival rate of 90%) [5]. This article describes two very similar cases of recurrent botryoid embryonal RMS of

the vagina sharing two particular features of potential interest, that is a very long interval before the recurrence, and a close association with the menarche, suggesting a close relationship with sex hormones.

Late relapses are known to occur in RMS, but they are by no means common. The Intergroup Rhabdomyosarcoma Study (IRS) group reported a median time to treatment failure of 1.1 years, ranging from 1 week to 9 years, in the IRS-III, IV-pilot and IV protocols, with 95% of all recurrences occurring within 3 years of the first diagnosis [2]. The same group also analyzed events occurring in the 1,160 patients treated between 1984 and 1997, who were event-free 5 years after their RMS was diagnosed, and they estimated a 5-year and 10-year recurrence rate of 2.4% and 2.7%, respectively (22 late relapses) [3].

The Italian cooperative group reported a median time to recurrence of 17.8 months (range 1.7 months–12 years), and 95% of the relapses within 5 years of the initial diagnosis [4]. In our single-institutional experience of 475 RMS patients treated over a 30-year period, we recorded 232 relapses, occurring 1–144 months after the first diagnosis (median time to recurrence: 11 months), but—apart from the two patients described here—we had only one other relapse occurring more than 5 years after the initial diagnosis.

The two cases described here are peculiar not only for the very long time elapsing before their recurrence, but also because they shared the same particular clinical characteristics as concerns the histotype, the tumor site of origin and the possible association with sexual hormone status: both recurrences occurred a fewmonths after the girls' menarche. This prompted us to explore hormone receptor expression by the tumor cells: while the immunocytochemical analysis of estrogen and progesterone receptors was negative in the first case, the second was positive for progesterone receptors in both initial and relapsing tumor specimens, with estrogen receptors testing negative in the primary tumor specimen and positive in the relapsing tumor specimen.

It is naturally hard to say whether the rise in estrogen level coinciding with puberty—combined with the presence of receptors on

the relapsing tumor—could have played a part in the tumor's recurrence. The peculiar features of these cases, and of the second one in particular, might point to a relationship between hormone status and tumor progression. As we know, the pathogenesis ofRMS is still not clear and there are no well-established risk factors for this disease: genetic predisposition (i.e., Li-Fraumeni syndrome, neurofibromatosis type 1), ionizing radiation, chemical carcinogens and oncogenic viruses have rarely been associated with the onset of RMS [5–8]. A possible association between the progression of RMS and estrogen/progesterone stimulation has already been suggested in a case that has some features similar to our two cases: a young woman previously treated for parameningealRMSrelapsed 25 years later, 3 months after starting hormone replacement therapy with estrogen and progesterone; here again, the primary specimen was steroid receptor negative, while the recurrent tumor was positive [9].

In conclusion, our report describes two similar cases of botryoid embryonal RMS of the vagina relapsing several years after the first diagnosis and a few months after the patients' menarche. A causal association between these recurrences and estrogen hormones may be hypothesized. Reports of other similar cases are needed, of course, to confirm such a relationship, but our findings might suggest that a clinical and radiological follow-up longer than is usually recommended for other RMS cases might be indicated for patients with RMS of the vagina.

References

1. Wexler LH, Meyer WH, Helman LJ. Rhabdomyosarcoma and the undifferentiated sarcomas. In: Pizzo PA, Poplack DG, editors. Principles and practice of pediatric oncology, 5th edition. Philadelphia, PA: Lippinco--tt Williams & Wilkins; 2006. pp. 971–1001.

2. Pappo AS, Anderson JR, Crist WM, et al. Survival after relapse in children and adolescentswith rhabdomyosarcoma:Areport from the Intergroup Rhabdomyosarcoma Study Group. J Clin Oncol 1999; 17:3487–3493.

3. Sung L, Anderson JR, Donaldson SS, et al. Late events occurring five years or more after successful therapy for childhood rhabdomyosarcoma: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group. Eur J Cancer 2004; 40:1878–1885.

4. Mazzoleni S, Bisogno G, Garaventa A, et al. Outcomes and prognostic factors after recurrence in children and adolescents with nonmetastatic rhabdomyosarcoma. Cancer 2005; 104:183–190.

5. Leuschner I, Harms D, Mattke A, et al. Rhabdomyosarcoma of the urinary bladder and vagina.Aclinicopathologic study with emphasis on recurrent disease: A report from the Kiel Pediatric Tumor Registry and the German CWS Study. Am J Surg Pathol 2001; 25: 856–864?

6. Diller L, Sexsmith E, Gottlieb A, et al. Germline p53 mutations are frequently detected in young children with rhabdomyosarcoma. J Clin Invest 1995; 95:1606–1611.

7. Gripp KW, Scott CI, Jr., Nicholson L, et al. Five additional Costello syndrome patients with rhabdomyosarcoma: Proposal for a tumor screening protocol. Am J Med Genet 2002; 108:80–87.

8. Ferrari A, Bisogno G, Macaluso A, et al. Soft-tissue sarcomas in children and adolescents with neurofibromatosis type 1. Cancer 2007; 109:1406–1412.

9. Zacharin M, Waters K, Chow CW, et al. Recurrent rhabdomyosarcoma after 25 years: A possible association with estrogens and progestogen therapy. J Pediatr Haematol Oncol 1997; 19:477–481.