Case Report

Isolated Breast Relapse after Metastatic Alveolar Rhabdomyosarcoma in a Young Premenarcheal Girl: What Could Have Been Done?

Raymond N. Haddad^a Souad Ghattas^a Paul-Henri Torbey^b

^aHotel Dieu de France University Medical Center, Department of Pediatrics, Saint Joseph University, Beirut, Lebanon; ^bHotel Dieu de France University Medical Center, Division of Pediatric Oncology, Department of Pediatrics, Saint Joseph University, Beirut, Lebanon

Keywords

Rare disease · Alveolar rhabdomyosarcoma · Breast metastasis · Pediatric tumor

Abstract

Alveolar rhabdomyosarcoma (RMS) is one of the most common pediatric soft-tissue neoplasms. Breast involvement either as primary tumor or metastasis is extremely rare. Herein, we report a case of primary limb alveolar RMS with breast metastases in a young premenarcheal girl that relapsed only to the metastatic breast site after achieving complete response. Accordingly, we believe that investigations of the mammary glands should be part of the routine diagnostic workup in adolescent females with RMS. Local therapeutic measures to control breast disease, including surgery or radiotherapy has to be considered for better prognosis. Newer radiation modalities aiming at reducing side effects should be developed.

© 2019 The Author(s)
Published by S. Karger AG, Basel

Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue-sarcoma in childhood and adolescence [1, 2]. Although metastases can occur in almost 20% of RMS, especially in the

alveolar histological type, breast involvement is a very rare event with variable reported incidence, but may be problematic in treatment plans [3–5]. Breast metastases of RMS occur almost exclusively in adolescent females with dismal prognosis as in other metastatic RMS [6, 7]. Until this date, there is no consensus about the optimal treatment strategy for breast metastases in RMS because of the limited number of case series reported. We describe our experience with a young premenarcheal female patient who suffered from primary alveolar RMS of the thigh with regional pelvic lymph node involvement and distant localization in both breasts that relapsed only at the metastatic breast site and present a review of the literature about diagnostic and therapeutic implications.

Case Presentation

In February 2018, a 13-year-old premenarcheal female patient presented with bilateral violaceous breast masses. Nineteen months earlier, she was diagnosed with stage IV alveolar RMS of the left thigh with inguinal, pelvic and retroperitoneal lymph node involvement. Earlier, the patient underwent large but incomplete surgical resection of the primary limb mass (Fig. 1). Initial 18-fluorodeoxyglucose positron emission tomography (FDG PET) scan showed beside the thigh and pelvic masses, nodular activities of both breasts with a SUV max of 3. At that time, her puberty stage was Tanner II and no suspicious breast mass could be clinically detected. Patient was treated according to the French RMS 2005 protocol. She received 4 cycles of chemotherapy IVADo (Ifosfamide, Vincristine, Actinomycin and Doxorubicin) with good clinical and radiological response. Intensity-modulated concomitant radiotherapy was initiated 12 weeks after the initiation of chemotherapy and targeted the primary site and the involved regional lymph nodes. She achieved complete response (CR) in primary and all metastatic regions including both breasts and completed 5 cycles of chemotherapy using IVA (Ifosfamide, Vincristine and Actinomycin). Maintenance therapy with six months of weekly Vinorelbine (25 mg/m²) and daily oral Cyclophosphamide (25 mg/m²) followed. By the time the bilateral breast lump appeared (Fig. 2), our patient was disease-free and off-treatment for almost six months. Computed tomography (CT) scan (Fig. 3) and magnetic resonance imaging (MRI) of the chest showed bilateral heterogeneous lesions as well as enlarged lymph nodes in the axillary regions. Needle biopsy showed alveolar RMS. Complete workup was negative for other sites. She received second line chemotherapy with one cycle of Carboplatin and Etoposide but because of disease progression, chemotherapy was changed to TC (Toptecan and Cyclophosphamide). After achieving 6 courses of TC chemotherapy at 3 weeks intervals, MRI of the chest showed important regression of the bilateral breast tumors, and lymph nodes. FDG PET scan showed focal hyperactivity at the breast sites only with a SUV max of 2. At this point, the multidisciplinary pediatric oncology team strongly recommended local radiotherapy based on the fact that all initially involved fields previously irradiated were free of disease at relapse. This suggestion was rejected by the radiotherapy team due to the extent of the required radiotherapy fields and the potential high toxicity risks of breast irradiation at that young age. Instead, radical bilateral mastectomy with axillary lymph nodes dissection was successfully performed. One month later, a right sub-clavicular mass appeared. CT scan showed numerous sub-clavicular lymph nodes and pleural nodules. Ultrasound guided needle biopsy revealed alveolar RMS confirming a second metastatic relapse. The prognosis was considered very poor and the family preferred the palliative treatment option. The patient died of rapidly progressive thoracic metastases nine months after her second relapse.

Discussion

Breast involvement in RMS is very rare, both as primary or metastatic disease. Seventy cases of children and adolescents below 19 years of age with breast metastasis of RMS were reported from 1980 to 2014 [3]. Most of these metastatic breast cases occurred in post pubertal female patients. The reason for such a phenomenon remains unclear, but many potential contributing factors have been suggested [6]. The tendency of RMS to metastasize to breast in adolescent female patients is thought to be associated with the expression of insulin-like growth factor (IGF) receptors in the neoplastic cells. Breast epithelium and stroma are known to express growth factors IGF-I and IGF-II [8]. The rapidly increasing vascularity and the growing mammary tissue during the pubertal development phase is another hypothesis for the preferential metastasis to developing breast [9]. Yaren et al. reported even a case of breast metastatic RMS in a pregnant woman. This further supported the hypothesis that vascularity plays a significant role in the hematogenous spread of the disease [10].

Breast investigations are not included in the usual diagnostic work-up of young girls with alveolar RMS. We believe that meticulous physical examination of the mammary region should be performed at diagnosis and during follow-up and any suspicious breast lesion should be confirmed using breast ultrasound and MRI [11].

Treatment of patients with alveolar RMS and those with incompletely resected disease usually consists of chemotherapy followed by concurrent chemo-radiation [12]. Although alveolar RMS is a chemo-sensitive neoplasm, local progression and relapse are often responsible of treatment failure [13]. Radiotherapy was proven to be effective on metastases but the optimal dose and fractionation still need to be established [14]. In our patient, the primary tumor site was locally treated by incomplete surgical resection and radiotherapy, whereas the initial nodular metastatic lesions of the breast were not removed or irradiated due to the potential severe side effects. Despite complete response our patient relapsed only in the breasts while no recurrence was detected in other sites. Even after aggressive second line chemotherapy and radical surgical local treatment, disease rapidly progressed in the thorax. Would initial breast radiotherapy at the time of diagnosis have been sufficient for disease control? More clinical trials are needed to bring up further evidence [8, 13].

Treatment of breast metastases of RMS is extremely challenging. It is still unknown whether the criteria commonly used in adults may be adopted in pediatric patients. In particular, it is uncertain whether surgery can be complete and conservative or whether irradiation of the mammary regions in young pre-pubertal adolescents despite the high risk of secondary malignancies and growth sequelae should be preferred. D'Angelo et al recommended an aggressive surgical approach in single breast metastasis and more extensive use of radiotherapy for patients with multiple breast metastases [4].

In conclusion, because breast metastases of RMS are unusual, their treatment is not well established [7]. For these patients, the inability to eradicate occult microscopic residual disease remains a great challenge. Several cellular pathways seem to be involved in RMS pathogenesis and survival. Huh et al. pointed to a possible mesenchymal stem cell as the progenitor for alveolar RMS and the role of high-dose chemotherapy with stem cell rescue in high-risk patients [2]. Whether by targeting genetically quiescent cells with the administration of longer-duration maintenance therapy in patients with minimal residual disease, or by focusing on development of targeted therapies, newer treatment strategies are desperately needed if we are to end the well-intentioned but failed efforts of the past four decades [15].

Statement of Ethics

This study was reviewed and approved by the Saint Joseph University Research Ethics Committee. Written informed consent was obtained from the patient's legal representatives for the publication of this case report, including the photo of their child.

Disclosure Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding Sources

The authors have no financial relationships relevant to this article to disclose.

Author Contributions

RH designed the report and critically collected clinical data. RH and SG took the lead in writing the manuscript. PHT provided scientific contributions and critically revised the paper. All of the authors have read and approved the final version of the manuscript.

All authors listed meet the authorship criteria according to the latest guidelines of the international committee of Medical journal editors, and that all authors are in agreement with the manuscript.

References

- 1 Egas-Bejar D, Huh WW. Rhabdomyosarcoma in adolescent and young adult patients: current perspectives. *Adolesc Health Med Ther*. 2014 Jun;5:115–25.
- 2 Huh WW, Skapek SX. Childhood rhabdomyosarcoma: new insight on biology and treatment. *Curr Oncol Rep*. 2010 Nov;12(6):402–10.
- 3 Kebudi R, Koc BS, Gorgun O, Celik A, Kebudi A, Darendeliler E. Breast Metastases in Children and Adolescents With Rhabdomyosarcoma: A Large Single-Institution Experience and Literature Review. *J Pediatr Hematol Oncol*. 2017 Jan;39(1):67–71.
- 4 D'Angelo P, Carli M, Ferrari A, Manzitti C, Mura R, Miglionico L, et al.; AIEOP Soft Tissue Sarcoma Committee. Breast metastases in children and adolescents with rhabdomyosarcoma: Experience of the Italian Soft Tissue Sarcoma Committee. *Pediatr Blood Cancer*. 2010 Dec;55(7):1306–9.
- 5 Oberlin O, Rey A, Lyden E, Bisogno G, Stevens MC, Meyer WH, et al. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. *J Clin Oncol*. 2008 May;26(14):2384–9.
- 6 Howarth CB, Caces JN, Pratt CB. Breast metastases in children with rhabdomyosarcoma. *Cancer*. 1980 Dec;46(11):2520–4.
- 7 Hays DM, Donaldson SS, Shimada H, Crist WM, Newton WA Jr, Andrassy RJ, et al. Primary and metastatic rhabdomyosarcoma in the breast: neoplasms of adolescent females, a report from the Intergroup Rhabdomyosarcoma Study. *Med Pediatr Oncol*. 1997 Sep;29(3):181–9.
- 8 Pareekutty NM, Bhagat M, Vora T, Qureshi SS. Rhabdomyosarcoma of the breast: report of two cases with the review of literature. *J Indian Assoc Pediatr Surg*. 2016 Apr-Jun;21(2):81–3.
- 9 Persic M, Roberts JT. Alveolar rhabdomyosarcoma metastatic to the breast: long-term survivor. *Clin Oncol (R Coll Radiol)*. 1999;11(6):417–8.
- 10 Yaren A, Guclu A, Sen N, Erdem E, Demirkan F. Breast metastasis in a pregnant woman with alveolar rhabdomyosarcoma of the upper extremity. *Eur J Obstet Gynecol Reprod Biol*. 2008 Sep;140(1):131–3.

Haddad et al.: Isolated Breast Relapse after Metastatic Alveolar Rhabdomyosarcoma in a Young Premenarcheal Girl: What Could Have Been Done?

- 11 García CJ, Espinoza A, Dinamarca V, Navarro O, Daneman A, García H, et al. Breast US in children and adolescents. *Radiographics*. 2000 Nov-Dec;20(6):1605–12.
- 12 Egas-Bejar D, Huh WW. Rhabdomyosarcoma in adolescent and young adult patients: current perspectives. *Adolesc Health Med Ther*. 2014 Jun;5:115–25.
- 13 Iniesta SL, Cereceda MT, Adams CS, Menor CE. Breast relapse after metastatic alveolar rhabdomyosarcoma: is it an incurable entity? *Indian J Med Paediatr Oncol*. 2016 Apr-Jun;37(2):119–21.
- 14 Skamene S, Abish S, Mitchell D, Freeman C. Radiotherapy is Important for Local Control at Primary and Metastatic Sites in Pediatric Rhabdomyosarcoma. *Cureus*. 2015 Nov;7(11):e388.
- 15 Wexler LH. Metastatic Rhabdomyosarcoma: Still Room for Improvement. *J Clin Oncol*. 2016 Jan;34(2):105–6.

Fig. 1. Magnetic resonance imaging of the left hip showing large ($30 \times 9.6 \times 8.8$ cm) masses at the root of the thigh and around the femoral vascular axes, pushing the bladder, extending upwards in the pelvis along the iliac vessels till the latero-aortic region and exceeding the midline to the right side.

Fig. 2. Enlarged bilateral breast masses appearing as a violaceous mass with distortion of the right nipple areolar complex.

Fig. 3. Computed tomography scan of the chest showing voluminous heterogeneous bilateral mammary masses occupying almost all the breasts, measuring 95 mm in the transverse axis. Bilateral diffuse skin thickening and axillary lymph nodes.