Metastatic Alveolar Rhabdomyosarcoma to the Breast: Case Report and Literature Review

J. Putra¹, J. Kim², J.D. Peterson¹, F.B. De Abreu¹, K.E. Muller¹, G.J. Tsongalis¹ and X. Liu¹

¹Pathology Department, Geisel School of Medicine, Hanover, NH, Dartmouth Hitchcock Medical Center and Norris Cotton Cancer Center, Lebanon, NH 03756, USA
²Pediatric Hematology and Oncology Department, Children Hospital at Dartmouth, Lebanon, NH 03756, USA

Abstract: Alveolar rhabdomyosarcoma is one of the common subtypes of rhabdomyosarcoma with a poor prognosis. It usually occurs in early adolescents with predilection for the deep muscles of the trunk and extremities. Its distinct histological features and molecular biology characteristics are important to distinguish it from other similar entities including embryonal rhabdomyosarcoma. We report a case of an 18-year-old female with metastatic alveolar rhabdomyosarcoma to the breast. Gene sequencing revealed a TP53 gene mutation in exon 4 and the patient was tested negative for a germline mutation. Several alveolar rhabdomyosarcoma cases with metastasis to the breast have been reported in a similar patient population. Therefore, we believe that breast examination and imaging study should be part of routine follow-up in adolescent female patients with alveolar rhabdomyosarcoma. Finally, this case allows us to review the multimodal techniques to diagnose alveolar rhabdomyosarcoma with an emphasis on molecular analysis.

Keywords: Alveolar rhabdomyosarcoma, Breast metastasis, Gene sequencing.

INTRODUCTION

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in the pediatric population from birth to adolescents aged less than 20 years. It represents 5% of all malignancies in children with an annual incidence of approximately 4 cases per million people [1, 2]. Histologically, RMS is classified into embryonal, alveolar, botryoid, and pleomorphic subtypes [3]. Embryonal rhabdomyosarcoma (ERMS) and alveolar rhabdomyosarcoma (ARMS) constitute the majority of histological subtypes, comprising 80% of RMS cases.

These two major histological subtypes are seen in different demographic subgroups and each subtype shows distinctive clinical behavior and prognosis. ERMS is more frequently observed in younger children and it often arises in the head and neck region, paraspinous region, and genitourinary tract. Contrarily, ARMS has a higher frequency in adolescents and it is commonly seen in the extremities, trunk, and perineal region [3]. The overall prognosis of RMS has significantly improved due to the utilization of multimodal therapy, which has mostly influenced ERMS with 5-year survival rates of 70%. Meanwhile, the prognosis of ARMS has not changed significantly over the last 30 years with 5-year survival rates of 40% [4].

Molecular classification of RMS has been used in conjunction with traditional histology to confirm the diagnosis. This distinction is essential for appropriate management and accurate prognostication. The classification is based on the molecular characteristics of the major subtypes of RMS. ERMS is associated with genomic instability and recurring allelic imbalances such as loss of heterozygosity at chromosome 11p15.5. Recurrent chromosomal translocations (t(1;13)(p36;q14) or t(2;13)(q35;q14)) are identified in more than 70% cases of ARMS. These translocations involve the FOXO1 gene on chromosome 13 and either PAX3 gene on chromosome 2 or PAX7 gene on chromosome 1 [5, 6].

Mutations of the tumor suppressor gene p53 (TP53), the most commonly mutated gene in human cancer, have also been associated with RMS [7]. The mutations are usually identified within exons 5-8, the region coding for the DNA binding domain. Recent studies have demonstrated the low prevalence of TP53 mutations in RMS and the lack of association between TP53 mutations and early-onset malignancy [8, 9]. We herein report an 18-year old female with metastatic ARMS to the breast and sequencing-proven TP53 mutation.

CASE REPORT

An 18-year-old Caucasian girl with a history of stage IV ARMS was seen at our institution for routine follow-up 10 months after completion of chemoradiotherapy.
There was no pertinent family history or other past medical history. Two years prior to her current presentation, she sought care for an enlarging mass (2.6 cm in greatest dimension) between her left thumb and index finger. Magnetic resonance imaging (MRI) showed a heterogeneously enhancing mass lesion with hyperintense appearance within the first metacarpal interspace. The differential diagnosis at that time included both benign and malignant soft tissue tumors. The mass was completely resected and histological examination revealed ARMS with focal anaplasia and lymphovascular invasion. Numerous bone metastases (spine, right iliac) were also identified on positron emission tomography (PET) scan.

The patient received chemoradiotherapy following surgical excision of the primary lesion. She was enrolled in two clinical studies for patients with high-risk pediatric solid tumors. Her chemotherapy regimen included doxorubicin, cyclophosphamide, etoposide, ifosfamide, dactinomycin, irinotecan, vincristine, temozolomide, and cixutumumab. She also received radiation to the left hand, spine, and right iliac. Chemoradiotherapy was well-tolerated and completed 14 months after the diagnosis was initially made. Furthermore, she received tumor vaccination and recombinant human interleukin-7 protein (R-hIL-7) one month after the completion of chemotherapy.

Her first follow-up at our institution, which included physical examination, chest computed tomography (CT) scan, left hand MRI, and blood workup showed no evidence of disease recurrence. Physical examination and chest CT scan during her second follow-up revealed a 3.0 cm (greatest dimension) firm, round, mobile mass in her right breast.

Ultrasound-guided biopsy was performed and histological examination revealed microscopic features of ARMS. The lesion appeared highly cellular and consisted of small round blue cells with minimal cytoplasm (Figure 1). The tumor cells were diffusely immunoreactive for myoblast determination protein-1 (MyoD1) (Figure 2) and myogenin (Figure 3), which confirmed the diagnosis of metastatic ARMS. The patient underwent a simple mastectomy of the right breast (Figure 4), with negative resection margins.

Mutation analysis was performed on the mastectomy specimen. Genomic DNA was extracted from fresh tumor tissue at the time of excision and sequencing was performed using the Ion Torrent AmpliSeq™ Cancer Hotspot Panel and the Personal
Figure 4: Gross appearance of the right breast lesion (simple mastectomy).

Genome Machine (PGM) [10]. The test revealed a single point mutation of the TP53 gene (exon 4); no mutations were detected in hotspots of the other 49 genes tested. Because of the implications of TP53 mutations in hereditary cancer syndromes, the patient was tested for germline TP53 mutation and was negative. Immunohistochemical workup revealed that the tumor cells were strongly positive for p53, consistent with mutation, and negative for mouse double minute 2 homolog (MDM2) antibody.

Chromosomal analysis was inconclusive as the number of cells was below the laboratory standard for complete analysis. No clonal abnormalities were seen in the cells available for analysis.

The patient is doing well at the time of this writing, two months after she was found to have metastatic ARMS in the breast. She has been receiving cycles of chemotherapy, consisting of cyclophosphamide, temsirolimus, and vinorelbine, due to the recurrence. The patient has been receiving chemotherapy based on the recommendation from the Societe Francaise des Cancers et Leucemies de l’Enfant et de l’adolescent (SFCE) [11].

DISCUSSION

ARMS, the second most-common subtype of RMS after ERMS, is more frequently seen in older children and predominantly arises in the trunk and extremities. Its overall prognosis is worse than other subtypes of RMS. Our patient presented with a history of primary ARMS of the soft tissue in the left hand, diagnosed when she was 16-year-old. Casanova et al. reported poor outcome for patients with RMS of the extremities. More than half of the patients studied presented with widely-metastatic disease and only one-third survived [12]. Furthermore, a recent study showed that age was a strong, independent prognostic factor in RMS. Adolescents were reported to have a poor prognosis due to the higher frequency of ARMS subtype in this age group. Poor outcome is also associated with a specific chromosomal translocation, t(2;13), which is more frequently seen in adolescents with ARMS [13].

Breast involvement of RMS is relatively uncommon and it has been reported in approximately 6% of patients with metastatic disease [14]. D’Angelo et al. reported that all of the RMS patients who developed metastases in the breast in their study were adolescent girls with ARMS [15]. The increased risk of breast metastasis in this age group is associated with the increased vascularity of the breast during the pubertal development phase [16]. For these reasons, an accurate clinical and radiological or ultrasound evaluation of the breast has been suggested to be incorporated into the diagnostic workup in adolescent girls with ARMS [15].

Histological diagnosis of ARMS is an important step to differentiate it from other subtypes of RMS and other sarcomas. It typically has fibrovascular septa that outline clusters and nests of round blue (primitive looking) cells, morphologically resembling pulmonary alveoli. Cytologically, ARMS cells have large and round nuclei with central nucleoli and minimal cytoplasm. The diagnosis of ARMS does not depend on the amount of alveolar pattern which is seen; ARMS is diagnosed even when the alveolar pattern is focal, which can be diagnostically challenging. Differentiating ARMS from ERMS is particularly problematic when the tumor is solid and only focally contains an alveolar pattern. On the other hand, ERMS is histologically characterized by loose, paucicellular areas intermixed with dense, cellular areas, which is a phenomenon created by variable condensation of tumor cells, separated by mucin-rich myxoid stroma [3]. Immunohistochemistry is often critical to determine the cell lineage in poorly differentiated tumors. Myogenin and MyoD are particularly specific and useful in identifying tumors with myogenic differentiation. Diffuse and strong nuclear staining of both markers is seen in ARMS. ERMS, however, has a more heterogeneous staining pattern [3].

RMS has been associated with several environmental risk factors and genetic abnormalities.
These environmental exposures include paternal cigarette smoking, advanced maternal age, radiation exposure in utero, antibiotic use during pregnancy, and maternal recreational drug use [4]. Although most of the cases occur sporadically, RMS has also been associated with several familial syndromes such as Li-Fraumeni syndrome (LFS), neurofibromatosis, Beckwith-Wiedeman syndrome, and Costello syndrome [17-20].

Our patient had a somatic TP53 mutation, confirmed by negative result for germline mutation testing. Initially, TP53 gene mutation was detected using massive parallel sequencing. This result prompted genetic testing for germline TP53 mutations. A recent study reported that germline TP53 mutation had a frequency of 1 in 20,000 in the general population [21]. Germline TP53 mutations are seen in the majority of patients with LFS. Although the occurrence of germline mutation in patients with early-onset sarcoma is not significantly high (2.5–10%), this information is essential for prognostic data [22]. Compared to the general population, LFS patients are at greater risk of having multiple primary cancers. Out of all patients with LFS, those with early-onset tumor and RMS have the highest risk to develop multiple cancers [23]. In addition, a diagnosis of LFS would be essential for other family members as it is inherited in an autosomal dominant manner.

Cytogenetic testing is another important diagnostic tool in ARMS. Chromosomal analysis of our patient was inconclusive due to the inadequate number of cells for analysis. Although there were no abnormalities seen in the analyzed cells, clonal abnormalities could not be completely ruled out. Translocations t(2;13) and t(1;13) are common in ARMS which generate PAX3-FOXO1 and PAX7-FOXO1 fusion genes respectively. This biologic characteristic is important and useful to differentiate ARMS from its differential diagnosis such as ERMS. Williamson et al. suggested that histological diagnosis of ARMS should be coupled with fusion confirmation. They discovered the identical outcome between translocation-negative ARMS and ERMS. Thus, the molecular diagnosis is more reliable than the histological diagnosis to predict the prognosis of RMS [24].

In conclusion, ARMS has a poor prognosis despite the overall improved outcome of RMS. Older age at presentation, lesions in the extremities, and chromosomal translocation t(2;13) have been associated with poor outcomes. Due to the diagnostic challenges, histological evaluation should be combined with chromosomal and molecular analysis to determine the accurate diagnosis and prognosis.

ACKNOWLEDGEMENTS

The authors wish to thank the staff of the DHMC Molecular Pathology Laboratory and the Translational Research Program. The data presented in this manuscript was in part generated through the Department of Pathology Translational Research Shared Resource Laboratory of the Geisel School of Medicine at Dartmouth, the Dartmouth Hitchcock Medical Center and the Norris Cotton Cancer Center.

REFERENCES


Received on 25-12-2013 Accepted on 30-12-2013 Published on 31-12-2013

DOI: http://dx.doi.org/10.14205/2309-3021.2013.01.02.1

This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.