Annals of Case Reports
Tharageswari S, et al. Ann Case Rep: 7: 866.
www.doi.org/10.29011/2574-7754.100866
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Case Report

Adamantinoma like Ewing Family Tumor of the Eighth Rib, A Rare Case Report and Review of Literature

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Citation: Tharageswari S, Sivakumar K, Kumaran PK, Ratan N, Sharma K. (2022) Adamantinoma like Ewing Family Tumor of the Eighth Rib, A Rare Case Report and Review of Literature. Ann Case Report 7: 866. DOI: 10.29011/2574-7754.100866

Received: 09 June 2022; **Accepted:** 13 June 2022; **Published:** 15 June 2022

Abstract

Ewing sarcoma is a rare malignant tumor of bone and soft tissue that occurs primarily in children and young adults. It belongs to the Ewing family of tumors that are characterized by uniform small blue round cells and specific translocation involving EWS gene located in chromosome 22. Adamantinoma like Ewing sarcoma (ALES) is a rare variant of Ewing sarcoma that shows small round cells with epithelioid differentiation and unlike classic Ewing sarcoma, it possesses a complex immunoprofile showing positivity for HMWCK, CK5/6, p63 and p40. This creates a diagnostic dilemma and difficulty in distinguishing it from epithelial carcinoma. We describe a case of Ewing Sarcoma with epithelial differentiation occurring in the 8th rib of an 18-year-old male patient. The tumor showed biphasic pattern, extensive areas of squamous differentiation with prominent keratinization and calcification along with areas showing small blue round cells. Immunohistochemistry demonstrated positivity for CK, p63, CK5/6, CD99, FLI1 and NKX2.2. FISH showed EWSR1 gene rearrangement. Morphological features and immunoprofile of ALES makes it prone to be misclassified as other tumors with epithelial differentiation like squamous cell carcinoma, basal cell adenocarcinoma and myoepithelial carcinoma. However, biphasic pattern of epithelial cells admixed with small blue round cells along with positivity for CD99, FLI1 and NKX2.2 and specific translocation involving the EWS gene aids in correct diagnosis.

Introduction

The Ewing family of tumors (EFT) are a group of malignant tumors of bone and soft tissue. They typically occur between 5 years to 30 years of age, 14 being the median age of presentation [1]. Ewing Sarcoma and Peripheral Primitive Neuroectodermal Tumor (PNET) are now considered to be the same tumor with variable differentiation and are characterized by specific translocation involving EWS gene in chromosome 22 with various Erythroblast Transformation Specific (ETS) like genes, FLI1 being the most common. Histologically they are characterized by sheets or vague lobules of small blue round cells with scant clear to eosinophilic cytoplasm, indistinct cell outline, dispersed nuclear chromatin and inconspicuous nucleoli leading to morphological overlap with other small blue round cell tumors like lymphomas, rhabdomyosarcoma, neuroblastoma and small cell osteosarcomasubsequen. Immunoprofile of Ewing sarcoma shows positivity for CD99, FLI1 and NKX2.2. Additionally, 10 to 30% of cases demonstrate positivity for CK8 and CK18. A rare variant of Ewing Sarcoma with morphological overlap with Adamantinoma

was first reported by Van Haelst in 1974. He described the case as either a poorly differentiated Adamantinoma or Ewing Sarcoma with squamoid differentiation. Later it was proven to be Ewing Sarcoma with epithelial differentiation by genetic confirmation due to the presence of EWSR1 gene rearrangement and was called as Adamantinoma like Ewing Sarcoma. ALES is a rare variant of Ewing Sarcoma that typically arises in bone or soft tissue in proximity to the bone. It is characterized by small blue round cells with epithelial differentiation that typically presents as clusters of epithelioid/basaloid cells with peripheral nuclear palisading surrounded by desmoplastic stroma. Frank squamous differentiation with keratinization can be seen focally. Unlike classic Ewing Sarcoma, ALES shows positivity with HMWCK, CK5/6, p63, p40 along with CK 8 and CK18. We describe a case of adamantinoma like Ewing Sarcoma occurring in 8th rib of an 18-year-old with extensive squamous differentiation, prominent keratinization and calcification.

Case Report

Clinical Details: An 18-year-old male patient presented with a painless swelling in the anterior chest wall for one month that was gradually increasing in size. CT imaging showed a lesion arising from the eight rib on the left side measuring 9 cm in greatest dimension. The lesion was infiltrative involving the adjacent soft tissue and showed internal calcification. Wide local excision of the mass was done.

Histopathology, Immunohistochemistry and FISH: Grossly the tumor was unencapsulated and infiltrative showing grey, tan, firm areas admixed with focal areas of necrosis (Figure 1). Microscopically, the tumor demonstrated a biphasic morphology. Extensive foci of epithelial islands showing squamous differentiation, prominent keratinization and calcification (Figure 2) were seen admixed with a few areas of undifferentiated cells with scant cytoplasm, round nuclei, dispersed chromatin and inconspicuous nucleoli (Figure 3). Immunohistochemistry showed diffuse positivity for CK, CK 5/6 (Figure 4) and p63 in the epithelial component and positivity for Vimentin, CD99 (Figure 5) and NKX2.2 (Figure 6) in the undifferentiated small round cell component. FISH analysis demonstrated EWSR1 rearrangement (Figure 7). Based on the morphology and immunohistochemical profile, a diagnosis of ALES was strongly suspected which was confirmed by FISH demonstrating EWSR1 gene rearrangement.

Figure 1: Gross- Infiltrative tumor with grey tan areas admixed with necrosis.

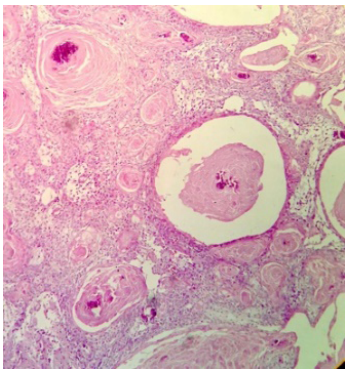

Figure 2: Epithelial islands showing squamous areas with keratinization.

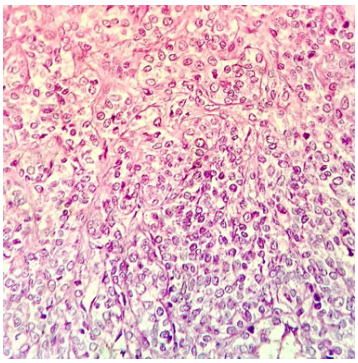

Figure 3: Sheets of undifferentiated small round cells.

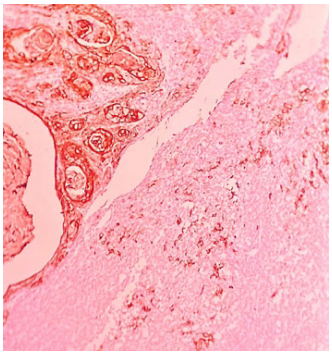

Figure 4: ALES- CK5/6 Strong Positive.

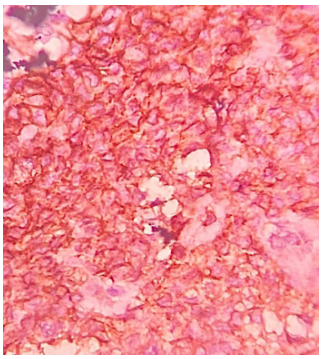

Figure 5: ALES- CD 99 Strong membranous positivity.

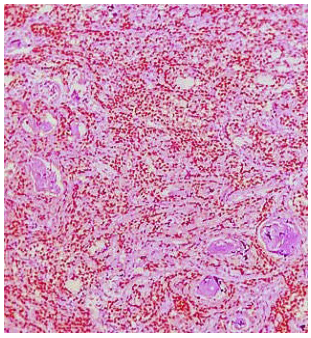

Figure 6: ALES-NKX2.2 Strong nuclear positivity.

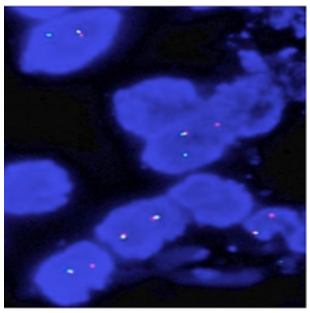

Figure 7: FFPE-FISH on interphase cells showing EWSR1 translocation.

Materials and Methods

The specimen was serially sliced at 1 cm intervals and fixed overnight in 10% neutral buffered formalin. Representative sections from the tumor area were taken and processed routinely. Sections of 3micron thickness were taken and stained with Hematoxylin and Eosin stain. Antigen retrieval for immunohistochemistry was done by heat induced epitope retrieval method. FISH for EWSR1 rearrangement detection was done using Zyto Light SPEC EWSR1 break apart probe.

Discussion

EFT are a group of malignant tumors of bone and soft tissue that occur predominantly in children and young adults between the age group of 5 and 30 years of age [1]. In 1918, a tumor composed of small blue round cells with rosetting arising from ulnar nerve was reported by Arthur Purdy Stout which was later found to be primitive neuroectodermal tumor (PNET). James Ewing in 1921 described first case of Ewing Sarcoma as an undifferentiated tumor arising from bones composed of undifferentiated small round cells. Over the years, a few extraskeletal tumors resembling Ewing sarcoma and neuroectodermal tumor occurring in bone were reported. Subsequently, in based on immunoprofile and molecular studies, they were identified as part of the same spectrum of tumors that originate from primitive mesenchymal cells with potential to differentiate into multiple lineages [2]. Around 85% of EFT show translocation between EWSR1 gene on chromosome 22 and FLI1 gene on chromosome 11, t(11;22) (q24;q12). Rest of the 15% tumors of this category, show translocation between EWSR1 gene with other ETS family genes that include ERG t(21;22)(q22;q12), ETV1 t(7;22)(p22;q12) and FEV t(2;22) (q13;q12) [3]. Adamantinoma like Ewing Sarcoma is a rare variant of Ewing Sarcoma that in addition to small blue round cells, shows epithelial differentiation. The epithelial component typically shows epithelioid/basaloid cells in nests with peripheral palisading surrounded by desmoplastic stroma. [1] Only focal squamous differentiation could be seen. First case of ALES was reported by Van Haelst in 1974 [4]. He described the case as 'highly malignant undifferentiated so-called Adamantinoma of bone clinically simulating Ewing Sarcoma'. Bridge et al [5] in 1999 confirmed it to be a variant of Ewing sarcoma by demonstrating the presence of chromosomal translocation t(11;22) between EWS gene and FLI gene. He called the tumor as Adamantinoma like Ewing Sarcoma, a rare variant of Ewing Sarcoma with "phenotypic drift". All the six cases described as ALES by Bridge et al occurred in bone or soft tissue in proximity to the bones of extremities. Morphologically they were composed of nests of epithelioid/basaloid cells showing peripheral palisading surrounded by stroma with striking desmoplasia. Only occasional cases showed a few frank squamous areas. Folpe et al [6], in 2005

described unusual variants of Ewing Sarcoma including ALES. He demonstrated the complex immunoprofile of ALES; for instance, unlike in classic Ewing Sarcoma HMWCK was expressed in all the cases of ALES. In 2008, Weinreb et al [7] reported an extraskeletal Ewing family tumor that occurred in lateral side of neck. Although the tumor showed squamous pearls and HMWCK positivity, the tumor was characterized by absence of desmoplasia and only occasional peripheral palisading with predominance of undifferentiated small cells. Also, unlike previously reported ALES, the case reported by Weinreb was reported at a site away from bone and soft tissue of extremities. They described the tumor as "Ewing sarcoma with complex epithelial differentiation" to emphasize the clinical and pathological differences between previously reported ALES and their case. In 2013, Kikuchi et al [8] reported a case of Adamantinoma like Ewing family tumor arising in relation to vagus nerve at the lateral side of neck. Morphologically the tumor was characterized by small blue round cells admixed with nests of HMWCK positive basaloid cells showing peripheral palisading and surrounded by desmoplastic stroma. A few areas with squamous differentiation were reported. Unlike other cases, Kikuchi reported spindle cell proliferation with transition between spindle cells and epithelioid cells in a few foci. He concluded that since the case occurred at a site away from bone and soft tissue of extremities as reported by Weinreb et al [7] but showed morphological features of typical ALES reported by Bridge et al [5] and Folpe et al [6] previously, they all represented a common spectrum of Ewing Sarcoma with epithelial differentiation. Till now, only a handful of cases of Adamantinoma like Ewing family tumor have been reported; most of them are in the head and neck region (sinonasal tract, thyroid, salivary glands etc.) showing morphological features of both typical ALES and Ewing tumor with complex epithelial differentiation. Our case is a rare occurrence of Adamantinoma like Ewing family tumor in the 8th rib that showed extensive squamous differentiation with prominent keratinization and calcification with only rare peripheral palisading and absence of prominent desmoplasia. We consider this case and the cases described previously as 'Adamantinoma like Ewing Sarcoma' and 'Ewing Sarcoma with complex epithelial differentiation' to represent a common spectrum of Ewing family tumor with epithelial differentiation.

Conclusion

To conclude, Adamantinoma like Ewing Sarcoma represents a rare variant of Ewing family of tumors that occur predominantly in bone and adjacent soft tissue of extremities as well as in head and neck region and show variable epithelial differentiation with a complex immunological profile, making them prone to be easily misdiagnosed. CD 99 and NKX2.2 should be included in the evaluation of poorly differentiated and undifferentiated tumors that occur in children and young adults in order to clinch this rare, aggressive variant of Ewing family of tumors that shows epithelial differentiation. Positivity for relevant immunohistochemistry markers demonstrating both components should be followed by molecular studies for EWSR1 gene rearrangement to precisely identify and subclassify Adamantinoma like EFT.

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