A Rare Case of Primary Cutaneous Ewing’s Sarcoma Diagnosed by Cytology Sampling: Case Report and Review of the Literature

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Abstract:
Ewing sarcoma (EWS) is an uncommon malignancy of the family of small blue round-cell tumors, with several known translocations involving EWSR1 and the ETS family transcription factors. EWS occurs in bone and soft tissue but rarely in skin. Radiological imaging and clinical presentation are not specific enough to conclude the diagnosis of extraskeletal cutaneous Ewing’s sarcoma (CES). In a few small studies, there have been reports of better CES prognoses than other EWS types. Tissue sampling (tissue biopsy or aspiration cytology) and enough immunohistochemistry (IHC) and translocation molecular genetic studies must be done together to make a final diagnosis. We present a case of a 73-year-old female who presented with a cutaneous cheek lesion that was initially misdiagnosed as a benign adnexal tumor. IHC and cytogenetic tests eventually confirmed the tumor’s diagnosis of CES after two recurrences. The definitive diagnosis was based solely on fine needle aspiration (FNA) material.

Keywords: Ewing sarcoma, Cutaneous, Small blue round cells, Molecular, Translocation

Introduction:

Ewing’s sarcoma (EWS) is primarily a skeletal malignancy, but there are incidences of extraskeletal occurrences that can be cutaneous or subcutaneous. They make up 12–20% of all EWS.1 Unlike their skeletal counterpart, extraskeletal cutaneous Ewing’s sarcoma (CES) tends not to derive from the pelvic area, to be in more women than men, to occur in non-European ancestry individuals, and to show up at later ages.2 Also, their prognosis appears promising, as they are usually detected in early stages with low rates of metastases.3,4 Post-resection, the treatment for CES is the same as for other Ewing's sarcomas, but with less intense chemotherapy and possibly little to no radiation.4 EWS diagnosis can be difficult. It cannot be established with a single test; instead, it requires the combined results of immunohistochemical analysis, fluorescent in situ hybridization (FISH), and molecular testing. Cytologically, all EWS are comprised of small, round cells with hyperchromatic nuclei and scant cytoplasm. They are a member of the small blue round cell tumor family (SBRCT). However, relevant IHC studies with CD99 and FLI1 are non-specific and can be positive in other tumors. In addition, FISH analysis for the characteristic fusion of EWSR1 (Ewing sarcoma region 1) in conjunction with FLI1 (Friend leukemia virus integration 1) at translocation 11,22 can yield inconclusive results.5 So, immunohistochemical characteristic stains for CD99 and FLI1 and RT-PCR testing for the translocation can help substantiate the diagnosis.6

EWS is an uncommon malignant small blue round cell tumor (SBRCT) that has been shown to affect all ages, mainly peaking during adolescence and young adulthood. The susceptibility to developing EWS is due to a translocation of the Ewing Sarcoma breakpoint region 1 (EWSR1) on chromosome 22 and an ETS-type gene.7 EWSR1, a DNA-binding domain, would form a chimeric protein with EWSR1, an RNA-binding protein involved in high-frequency transcription.8 EWSR1 plays a part in both benign and malignant tumor growth. It interacts with mesenchymal, neuroectodermal, epithelial, and myoepithelial cells. If problems are found in chromosome regions, there is a higher chance that oncogenesis will start.8 We present a case of cutaneous Ewing’s sarcoma that was initially misdiagnosed as a benign adnexal tumor. Cytology sampling of the tumor was sufficient to establish an accurate diagnosis of CES.

Case Presentation:

We received an overseas surgical pathology consultation case of a 73-year-old female with a recurrent mass of the left upper cheek. This was the second recurrence after two prior excisions. The primary tumor was described as a 2 cm slow-growing, crusty, painless, plaque-like lesion in
The left upper cheek; size was reported to be about 3x2 cm. After a biopsy diagnosis of a benign adnexal tumor at the referring institute, the lesion was excised. Seven months later, the patient experienced a recurrence at the same site. An excisional biopsy revealed a recurrence of the same tumor. Nine months later, the patient underwent another local recurrence. The patient refused an additional surgical biopsy but accepted a fine needle aspiration (FNA) of the new recurrence. We received no further details regarding the prior excisions. The information we received included that the patient reported having significant cardiovascular abnormalities in addition to moderate hypertension. She underwent a total hysterectomy when she was 55 for an unknown condition. No family history was provided.

The cytology FNA sample we were received had cytology smear slides stained with DQ and H&E stains and formalin-fixed paraffin-embedded cell block cytology material. The sample was adequate for cytomorphology studies and further studies such as immunohistochemistry (IHC) and molecular analyses. A cytomorphological examination revealed a cellular specimen showing small, round, blue cells with little cytoplasm and round to ovoid, hyperchromatic nuclei. Mitotic figures were not common. The cellblock preparation showed moderate necrosis and pseudorosettes formation (Figures 1A,B,C). Another possible diagnosis was rhabdomyosarcoma, melanoma, clear cell sarcoma, malignant rhabdoid tumor, malignant primitive neuroectodermal tumor, or poorly differentiated adnexal tumor. These all have this type of cytomorphology. Figure 2A shows that CD99 stained solid and diffuse nuclear membranes, and Figure 2B shows that FLI1 strongly stained tumor nuclei. The tumor cells were negative for lymphoid markers (LCA, CD3, CD 20), epithelial markers (AE1/AE3, and Cam-5.2), and muscular markers (desmin and myogenin). The tumor cells were also negative for chromogranin-A, WT-1, and CD34. The tumor cells showed 40% nuclear staining with the proliferation index Ki-67. The molecular study using FISH and confirmed with RT-PCR testing for the translocation revealed a t(11;22) (q24;q12), which led to the fusion of EWSR1 and FLI1. These features confirmed the diagnosis of extraskeletal cutaneous Ewing's sarcoma.

The submitting institution reported no evidence of other body involvement, including a negative bone marrow aspiration biopsy. The mass was surgically excised, but it was reported that the tumor focally involved the surgical margins. The patient refused additional surgery for margins and received adjuvant chemotherapy with vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide in addition to radiotherapy. She was followed up for 32 months with no evidence of recurrence or metastasis.

EWS encompasses a group of tumors characterized by molecular and cytogenetic similarities. EWS is the second most common primary bone malignancy; it is an aggressive tumor of adolescents and young adults, constituting 10% to 15% of all bone sarcomas, and rarely manifests as soft tissue (extraskeletal EWS) or cutaneous EWS (CES). Other terminology used in the literature for EWS includes Ewing's sarcoma of bone, extraskeletal Ewing sarcoma, CES, and adamantinoma-like Ewing sarcoma. Other terms no longer recommended include primary neuroectodermal tumor (PNET) and Askin tumor (EWS arising in the chest wall).

The incidence of Ewing's sarcoma in the United States is between 10 and 15 years of age, with 30% of the cases arising in children under 10 and 30% in adults over 20. EWS carries a male predominance with a male-to-female ratio of 3:1. From an ethnic perspective, the Caucasian population is more frequently diagnosed than the Black, Asian, or Hispanic populations. Primary CES, a rare subset of EWS, is illustrated by retrospective analysis of the Euro-Ewing99 database in France, as only 2.7% of all reported ES (24/1,005 patients) cases. CES displays stark epidemiologic differences compared to EWS; its occurrence exhibits a female predominance and delayed age of incidence (F/M = 1.9; median age 21.5 years), bares a similar ethnic prevalence to EWS but differs in location with the primary tumor affecting the extremity (48.5%) and trunk (39%). To date, CES has no known association with modifiable risk factors; however, non-modifiable factors such as age, sex, ethnicity, and genetic susceptibility remain factors known to the Ewing Sarcoma family of tumors.

CES most commonly presents as a 2- to 3-cm superficial mass of soft consistency on young females' trunks or lower/upper extremities. On the other hand, EWS presents more often in the upper extremities of males. The diagnosis can be confirmed through fine needle aspiration cytology, immunohistochemistry, cytogenetics, and molecular genetics of translocations. EWS of the bone and CES share similar molecular and cytogenetic characteristics through membranous expression of CD99 and an EWSR translocation on chromosome 22. Imaging tests for CES can be carried out; however, they could be more diagnostically helpful compared with EWS of the bone. EWS is a mall round cell sarcoma showing gene fusions involving one member of the ETV family of genes (usually EWSR1) and a member of the E26 transformation specific (ETS) family of transcription factors. American pathologist James Ewing (1866–1943) first described the tumor as diffuse endothelioma of bone. Over several decades, two primary considerations regarding the origin of EWS have emerged: neural crest stem cells and mesenchymal stem cells.
Histologically, classical EWS shows characteristic features of SBRCT, including uniform small round cells one or two times the size of lymphocytes, round nuclei, inconspicuous nucleoli, and indistinct cytoplasmic membranes. They usually display sheet-like growth patterns or islands separated by dense fibrous tissue. There is also a subset with neuroectodermal differentiation (Homer-Wright pseudorosettes). While not pathognomonic, immunohistochemical staining of the MIC2 (CD99 antigen) on histology supports Ewing Sarcoma. Therefore, the best diagnostic test is a cytogenetic analysis, which verifies the existence of a t(11;22) or other associated translocations. The most common translocation is t(11;22) (q24;q12), resulting in EWSR1-FLI1 fusion (~85%–90%), while the second most common is t(21;22) (q22;q12), resulting in EWSR1-ERG fusion (~5%–10%). The differential diagnosis of SBRCTs is comprehensive and includes rhabdomyosarcoma, Ewing’s sarcoma, medulloblastoma, small cell osteosarcoma, lymphoblastic lymphoma, blastematous Wilms’ tumor, and small cell desmoplastic tumor. EWS is distinguished from several other malignancies with the help of IHC studies. EWS is usually positive for CD99, NKX2.2, Vimentin, nuclear staining with EWSR1-FLI1 fusion (FLI1), nuclear staining with EWSR1-ERG fusion (ERG), and PAS that highlights cytoplasmic glycogen diastase sensitive). EWS is usually negative for LCA/CD45, Desmin, Myogenin, MyoD1, WT1, TTF1, and Chromogranin.

In our case, a fine needle aspiration (FNA) biopsy was used to diagnose EWS. It is sufficient to do FNA biopsies with IHC and molecular testing, especially when cellblock cytology is prepared, to diagnose EWS, especially when typical cytologic features are present. Cytology and radiography provide a conclusive, less invasive, safe, and less expensive technique to diagnose suspicious lumps, previously accessible only by surgical biopsy techniques. As a result, cytologists are increasingly called upon to diagnose disease in a specimen procured under image guidance for different organs. Rather than causing delay, cytology facilitates timely diagnosis and management, an integral part of a multimodal approach to various tumor diagnoses. Several studies have already shown that cytology specimens alone, including cellblock preparation, can definitively diagnose tumors in multiple organs before surgery to remove them. In cytology preparations, the cytological characteristics of surgical biopsy specimens are easily identified, especially by experienced cytopathologists.

Typically, CES is treated with surgical resection with sufficient safe margins, and then the five-drug chemotherapy regimen for the EWS family (vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide) is used. There is limited efficacy of immunotherapeutic approaches. Favorable prognostic factors include a complete pathologic response to neoadjuvant chemotherapy, small tumor size, superficial location, and easily and completely resected masses. Early recurrence, metastasis, and a tumor in a difficult-to-resect anatomic position are all considered unfavorable prognostic markers. The submitting institution reported that the tumor focally involved the surgical excision margins for our patient, but she refused additional surgery. She received adjuvant radiation therapy, and at 32 months since the diagnosis, there was no evidence of recurrence or metastasis.

Extraskeletal cutaneous Ewing’s sarcoma is a rare Ewing’s sarcoma with a reported favorable prognosis compared with other types of EWS. Due to its cutaneous location and non-specific clinical presentation and imaging findings, CES can be misdiagnosed as other benign or malignant tumors. Here, we present a case that was initially misdiagnosed as a benign adenexal tumor with two later recurrences. Combining tissue sampling, immunohistochemistry, and molecular cytogenetic studies is essential for the definitive diagnosis of CES. We must report such rare cases to raise clinicians’ awareness and include the possibility of CES in the differential diagnosis of cutaneous lesions. Our case also shows that adequate cytology sampling with cell block preparation can definitively diagnose most tumors without invasive surgical sampling. Cytology sampling is sufficient for complete analysis, including immunohistochemistry and molecular cytogenetic studies.

**Figures:**

**Figure-1: Cytology diagnosis of Ewing sarcoma**

1A: Cytology cellblock preparation showing sheet-like growth pattern and islands separated by dense fibrous tissue and admixed with blood (Cellblock H&E stain x20)
1B: Cytology smear preparation showing cellular smear with scattered pseudorosettes (yellow arrow) (Papanicolaou stain X20)
1C: Cytology smear preparation showing round nuclei, inconspicuous nucleoli, scant cytoplasm, and pseudorosettes (yellow arrow) (Diff-Quik stain X60)
Figure 2: Immunohistochemistry studies
2A: Tumor cells diffusely positive for CD99, membranous staining
2B: Tumor cells are diffusely positive for FLI1, nuclear staining, and a yellow arrow pointing to pseudorosettes

Acknowledgements:

Special thanks to MD Candidates Isabella Korchony, Jotty Francois Fils, and Nicole Jaycox for their assistance in preparing manuscript images and reviewing the final manuscript.

Submitted: March 21st, 2024 | Accepted: April 9th, 2024 | Published: April 18th, 2024

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