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A Case of Primary Cutaneous Extraskeletal Ewing Sarcoma on the Abdomen

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Primary cutaneous extraskeletal Ewing sarcoma (EWS) is a primitive neuroectodermal tumor that usually occurs as a small, localized tumor on the trunk or extremities of young adults. The prognosis is typically reported to be quite favorable. It is extremely rare; only three cases of primary cutaneous EWS have been reported in Korea. In the first report, molecular genetic testing was not performed to make a definitive diagnosis. In the second report, reverse transcription polymerase chain reaction (RT-PCR) for *EWS-FLI1* gene arrangement was done, but the result was negative. Although RT-PCR and fluorescence *in situ* hybridization (FISH) were performed in the third report, none of the results were shown in the article. Considering that genetic testing is an essential diagnostic tool for certain diseases, such as some brain tumors, we report a case of primary cutaneous extraskeletal EWS, including the result of RT-PCR. A 36-year-old Korean female presented with a cutaneous mass on the abdomen. Histological evaluation revealed solid sheets of primitive, small, uniform cells with hyperchromatic nuclei and scant cytoplasm. Immunohistochemistry stains were positive for CD99 and FLI1. RT-PCR showed a t(11;22) *EWSR1* (Ewing sarcoma region 1)-*FLI1* (Friend leukemia virus integration 1) translocation.

Keywords: Ewing sarcoma, EWS protein, Fli-1 transcription factor, Reverse transcription polymerase chain reaction

INTRODUCTION

Ewing sarcoma (EWS) is a primitive neuroectodermal tumor that usually arises from the bone. A rare type of EWS that occurs in the cutaneous, subcutaneous, or soft tissues, called extraskeletal EWS, usually involves deep soft tissues (deep subcutaneous layer or muscles). Even less commonly, it is limited to the skin in a superficial location and is called primary cutaneous extraskeletal EWS[1].

Primary cutaneous extraskeletal EWS is one of a spectrum of neoplastic diseases known as the EWS family of tumors, which includes EWS, extraskeletal EWS, peripheral primitive neuroectodermal tumor (previously called peripheral neuroepithelioma), and malignant small-cell tumors of the thoracopulmonary region (Askin tumor)[2].

Primary cutaneous extraskeletal EWS is extremely rare. In a retrospective analysis of the Euro-Ewing99 database in France, only 2.7% of those with EWS (24/1,005 patients) were found to have cutaneous/subcutaneous EWS, and in 2015, only 91 cases were identified in the literature[3]. In Korea, there have been three reported cases of primary cutaneous EWS[4-6]. However, in the first report, molecular genetic testing was not performed to make a definitive diagnosis. In the second report, reverse transcription polymerase chain reaction (RT-PCR) for *EWS-FLI1* gene arrangement was done, but the result was negative. Although RT-PCR and fluorescence *in situ* hybridization (FISH) were performed in the third report, none of the results were presented in the article. Considering that genetic testing is an essential diagnostic tool for certain diseases, such as some brain tumors, we report a case of primary

cutaneous extraskeletal EWS, including the result of RT-PCR.

CASE REPORT

A 36-year-old Korean female with a history of type 2 diabetes mellitus presented with a cutaneous mass on the left lower region of the abdomen, which had been slowly growing for 3 years. She denied any history of local trauma or infection. Physical examination revealed a non-tender, soft, flesh-colored, deep nodule measuring 2.5 cm×1.5 cm without induration (Fig. 1A). A punch biopsy was performed. Histological evaluation revealed solid sheets of primitive, small, uniform cells with hyperchromatic nuclei and scant cytoplasm (Fig. 2A). Immunohistochemistry stains were positive for CD99 (Fig. 2B), FLI1 (Fig. 2C), and vimentin. Stains for pan-cytokeratin (pan-CK), leukocyte common antigen, neuron specific enolase, and S-100 were all negative. RT-PCR using formalin-fixed, paraffin-embedded tissues showed a t(11;22) *EWSR1* (Ewing sarcoma region 1)-*FLI1* (Friend leukemia virus integration 1) translocation (Fig. 2D). Complete blood counts, a blood chemistry, and urinalysis were performed and no specific findings were noted besides a HbA1c of 6.4%. The blood glucose level was 108 mg/dl. A whole-body positron emission tomography revealed no nodal involvement and no abnormal hypermetabolic lesion including bone marrow (Fig. 1B, C). A primary cutaneous extraskeletal EWS diagnosis was made, and the patient was referred to the department of oncology for further evaluation and treatment. We received the patient's consent form about publishing all photographic materials.

DISCUSSION

Extraskeletal EWS[7] was first described in 1969 as a paravertebral "round cell" tumor that histologically resembled EWS, and the first large series of extraskeletal EWS cases was published in 1975. These tumors were histologically identical as EWS, and cytogenetic studies later confirmed that they belonged to the same family as EWS arising from the bone, which is commonly called the EWS family of tumors[3].

Compared to primary skeletal EWS (median age 14 years), primary cutaneous EWS has a slightly later onset and predominantly affects females (F/M=2.0; median age 17 years)[8]. Cutaneous and subcutaneous EWS most commonly present as a 2- to 3-cm-sized superficial mass on the trunk or the lower or upper extremities of young females, while EWS of the bone is most commonly observed in the upper extremities of males.

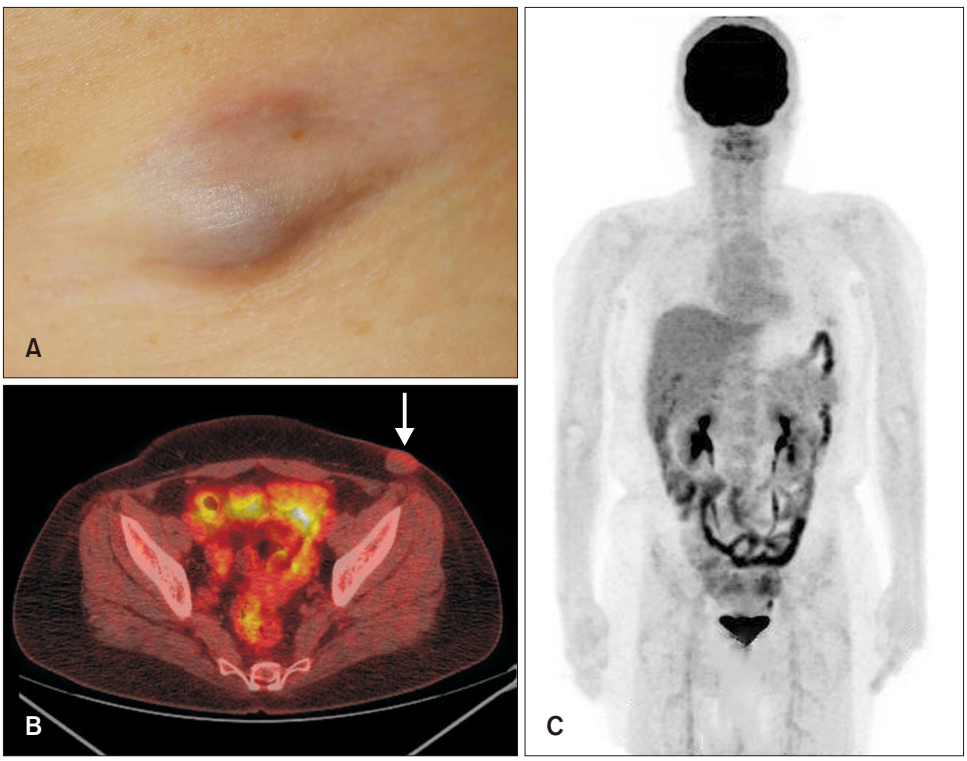

Fig. 1. (A) Clinical image of the left lower abdomen with a non-tender, soft nodule measuring 2.5 cm×1.5 cm without induration. (B) Positron emission tomography shows an area of increased uptake in the abdominal wall (arrow). (C) A positron emission tomography scan demonstrating negative metabolic activity.

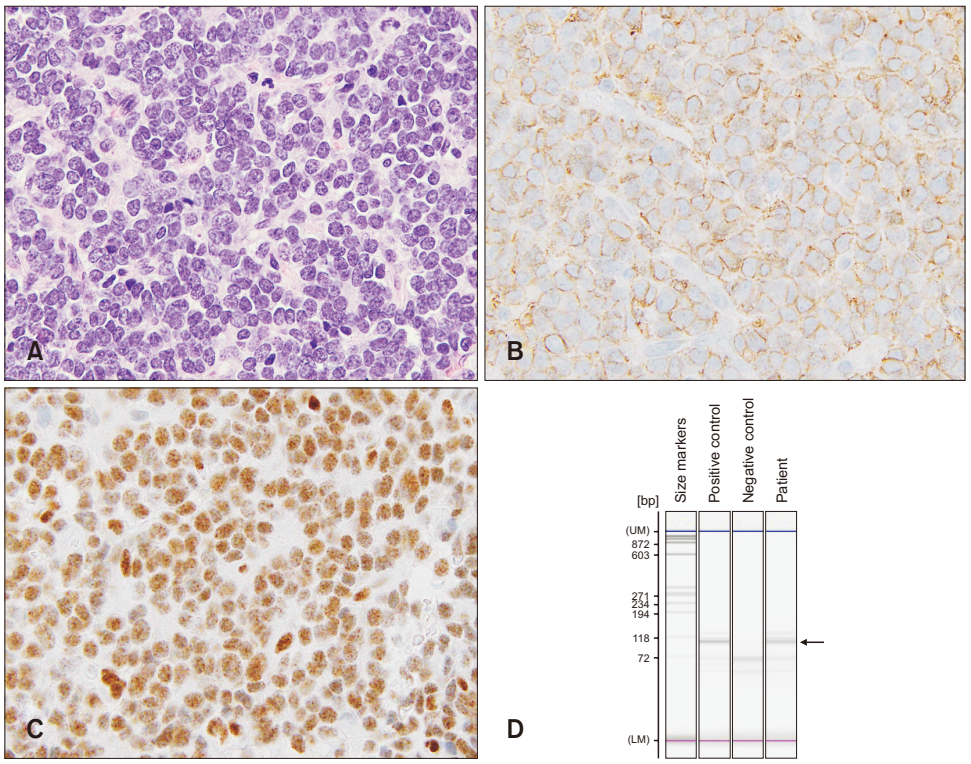

Fig. 2. (A) Histopathological images show sheets of primitive, small, round cells (H&E, original magnification: ×400). (B) CD99 immunoreactivity shows a membranous pattern (original magnification: ×400). (C) FLI1 immunoreactivity is observed (original magnification: ×400). (D) Reverse transcription polymerase chain reaction (RT-PCR) for the detection of the *EWSR1-FLI1* transcript. The lane patient is the RT-PCR product obtained from the patient's tumor RNA, and the band corresponds to an *EWSR1-FLI1* fusion transcript (arrow).

Primary cutaneous EWS is superficial and usually small at presentation with an initial size of less than 5 cm in 78.5% of cases and an initial volume of less than 200 ml in 96% of cases[3].

EWS is a primitive, undifferentiated neoplasm showing sheets of uniform, small, round, blue cells with hyperchromatic nuclei and scant cytoplasm, which are evident due to the presence of abundant glycogen. The appearance of EWS is similar to that of other small, round, blue cell tumors, including Merkel cell carcinoma (MCC), lymphoma, poorly differentiated adnexal tumors, leukemia, small cell lung carcinoma, and neuroblastoma[1]. These tumors can therefore be difficult to diagnose when examined by light microscopy alone. Consequently, a combination of immunohistochemistry and molecular diagnostic techniques is necessary for differential diagnosis.

Immunohistochemically, the vast majority of the EWS family of tumors show strong positive results as depicted by the membranous pattern following staining with CD99, a 32-kDa cell surface glycoprotein encoded by the *MIC2* gene and a sensitive diagnostic marker for the EWS family of tumors. However, CD99 staining lacks specificity as the expression of this antigen has been documented in many other tumors, such as lymphoblastic lymphoma, synovial sarcoma[1,9]. Although FLI1 is a variable histochemical marker for EWS, it is also positive in lymphoblastic lymphoma[10]. Additionally, epithelial differentiation (pan-CK expression) is detected in 20% of the EWS family of tumors, thus complicating the differential diagnosis with other superficial small round cell tumors with CK immunoexpression, such as MCC/neuroendocrine carcinomas, undifferentiated carcinoma, synovial sarcoma, rhabdomyosarcoma, epithelioid sarcoma, cutaneous disseminated malignant rhabdoid tumor, and myoepithelial carcinoma[1].

Therefore, a final diagnosis is only possible through molecular confirmation (FISH and/or RT-PCR) of the translocation specific to the sarcoma in question. Approximately 90% to 95% of cases of the EWS family of tumors show the reciprocal translocation t(11;22)(q24;q12), which results in the fusion of the *EWSR1* gene with the *FLI1* gene at 22q12. For 5%~10% of cases, the *EWSR1-ERG* translocation t(21;22) (q22;q12) is present. In the remaining cases, *EWSR1* or *FUS* fuses with other ETS and non-ETS family genes, such as *ETV1*, *ETV4*, *ERG*, *NFATC2*, *SMARCA*, or *SP3*[11]. In our case, RT-PCR using formalin-fixed, paraffin-embedded tissues revealed a t(11;22) *EWSR1-FLI1* translocation (Fig. 2D).

Primary cutaneous EWS is rare and currently treated in

the same way as EWS of the bone using extensive surgery, radiotherapy, and multi-agent chemotherapy. However, with the good overall prognosis of primary cutaneous EWS, increased consideration has been given to less aggressive treatment regimens, such as surgery without systemic chemotherapy[2]. The overall survival for primary cutaneous EWS is reported to be approximately 91% at 10 years, while that for primary bone EWS ranges from 39% to 68% at 5 years[2]. However, cases of primary cutaneous EWS with poor outcomes have also been reported. Machado et al.[12] reported six cases of superficial EWS family of tumors. Follow-up of three cases revealed the following: one case of lung metastases with death at 2 years, one case of multiple metastases with death at 5 months, and one case of local recurrence at 18 years. Therefore, prospective clinical trials are necessary to identify the appropriate population for treatment with surgery alone versus resection with intensive or less intensive chemotherapy.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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