

Combination chemotherapy of doxorubicin and ifosfamide with proton beam therapy for myoepithelial carcinoma originating in the paraspinal region: A case report and literature review

SHUNICHI TOKI¹, TOSHIHIKO NISHISHO¹, RYO MIYAGI^{1,2}, YOSHIMI BANDO³, MIKA SAKAKI^{3,4}, YUSUKE DEMIZU^{5,6}, TOMOAKI OKIMOTO⁶ and KOICHI SAIRYO¹

¹Department of Orthopedics, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima 770-8503;

²Department of Orthopedics, Tokushima Prefectural Central Hospital, Tokushima 770-8593; ³Division of Pathology,

Tokushima University Hospital, Tokushima 770-8503; ⁴Department of Pathology, Takamatsu Municipal Hospital,

Takamatsu, Kagawa 761-8538; ⁵Department of Radiation Oncology, Hyogo Ion Beam Medical Center Kobe Proton Center,

Kobe, Hyogo 650-0047; ⁶Department of Radiology, Hyogo Ion Beam Medical Center, Hyogo 679-5165, Japan

Received June 23, 2022; Accepted September 16, 2022

DOI: 10.3892/mco.2022.2596

Abstract. Soft tissue myoepithelial carcinoma (MEC) is an extremely rare mesenchymal tumor that has a poor prognosis unless complete surgical resection is achieved. The present study reported a case of a 38-year-old woman with a tumor in the left paraspinal region at L2 to L3 with vertebral destruction. MEC was diagnosed based on molecular pathological examination of a biopsy specimen. Because curative surgery was expected to be difficult, a combination of chemotherapy with doxorubicin and ifosfamide and proton beam therapy as local therapy was performed, resulting in long-term survival for at least 7.8 years. To the best of our knowledge, this is the first case of soft tissue MEC for which classical cytotoxic chemotherapy and proton beam therapy were effective. Although surgical resection with negative margins is the mainstay of treatment for MEC, adequate doxorubicin-based systemic therapy and high-dose radiation therapy may be a feasible alternative in patients with unresectable or advanced MEC. Future studies on the relationship between molecular pathological features, including biomarkers, and the selection of therapeutic agents are warranted.

Introduction

Myoepitheliomas and mixed tumors of the head and neck are well known, particularly in the salivary glands (1,2).

Myoepithelial tumors of soft tissue were first described in 1997 and have since been increasingly reported (1). Although myoepitheliomas were initially thought to contain spindle or plasmacytoid cells growing in solid sheets, it is now believed that myoepithelial and mixed tumors are part of a spectrum of tumors with overlapping histologic appearance and similar clinical behavior (2). For example, soft tissue mixed tumors with ductal differentiation have rearrangements of *PLAG1* (encoded on chromosome 8q12), which are characteristic of salivary pleomorphic adenoma and carcinoma ex pleomorphic adenoma (3). In addition, rearrangement of the *EWSR1* gene (encoded on chromosome 22q), which occurs in nearly half of all myoepithelial tumors of soft tissue, skin, and bone, has been reported in up to 39% of primary salivary myoepithelial carcinomas (MECs) exhibiting clear cell morphology (3).

Soft tissue MEC is an extremely rare malignant neoplasm demonstrating myoepithelial differentiation, cords or nests of epithelioid, ovoid, or spindle cells with moderate or severe atypia, and a variably reticular architecture with chondromyxoid or collagenous/hyalinized stroma (2,4-6). The mainstay of treatment for localized disease has been surgical resection with adjuvant cytotoxic chemotherapy and/or radiation therapy (RT) (2,4,5,7). However, the relapse rate is approximately 30-45% (2,3). Furthermore, without appropriate chemotherapy, the 5-year overall survival rate was 14.6% in patients with locally advanced or metastatic disease who received systemic therapy (4).

To our knowledge, the case reported herein is the first case of MEC deeply seated in the trunk that was successfully treated by chemotherapy with cytotoxic agents and proton beam therapy (PBT).

Case report

A 38-year-old woman was referred to our department with a 4-year history of low back pain. Examination revealed tenderness of the L2 spinous process and left paravertebral muscles. Kemp's test was positive on the left side, but there

Correspondence to: Dr Toshihiko Nishisho, Department of Orthopedics, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan
E-mail: tnishisho@gmail.com

Key words: myoepithelial carcinoma, proton beam therapy, doxorubicin, ifosfamide, INI-1, EWSR1

was no sensory disturbance or muscle weakness in the lower extremities. Plain radiographs obtained at the first visit showed the canonical pedicle sign on the left side at L2 (Fig. 1A). Computed tomography (CT) revealed a massive neoplasm mainly in the left paraspinal area at L2-L3 with L2 vertebral destruction (Fig. 1B). Contrast-enhanced CT and magnetic resonance images showed a soft tissue mass measuring 118x101x83 mm with areas of heterogenous intensity and spread into the spinal canal (Fig. 1C and D). Incisional biopsy confirmed MEC (Fig. 2). Histologically, the tumor was a poorly differentiated malignant neoplasm composed mainly of cells having nuclear atypia with easily discernible nucleoli and an epithelioid morphology with abundant clear or pale cytoplasm associated with a prominent myxoid matrix. Immunohistochemistry revealed extensive positivity for epithelial membrane antigen (EMA) and focal positivity for S-100 protein with negativity for AE1/AE3 and glial fibrillary acidic protein (GFAP). Staining for INI-1 was negative with appropriate staining of vascular endothelial cells serving as the internal control, indicating that the product of this gene on the long arm of chromosome 22 was lost or deleted. The appearance and immunophenotype fit well with high-grade MEC, which was confirmed by outside consultation. FDG PET/CT showed that the tumor had a maximum standardized uptake value of 5.2. We anticipated that radical resection would result in considerable morbidity, so the patient was treated with a combination of doxorubicin and ifosfamide. After 4 courses, she showed a partial response based on Response Evaluation Criteria in Solid Tumors (RECIST) (Fig. 3A). Despite the tumor size reduction by chemotherapy, wide resection with clear margins was still difficult. Therefore, definitive local PBT of 70.4 Gy (relative biological effectiveness [RBE]) in 32 fractions was performed after 4 additional courses of systemic therapy (Fig. 3B), followed by another course of the same regimen. In total, 507 mg/mm² doxorubicin and 84.5 g/mm² ifosfamide were administered. The patient developed left L2-L3 nerve palsy 4.8 years later as late toxicity of PBT but could still walk independently. Retrospectively, we noted that collapse of the L2 vertebral body progressed during the first 6 months of chemotherapy, but no serious neurological disturbance occurred because it was possible to avoid the spinal cord and cauda equina as much as possible in PBT due to adequate dose distribution. As of this writing, she remains disease-free at 9 years after the initial diagnosis with an International Society Of Limb Salvage (ISOLS) score of 77% and a Toronto Extremity Salvage Score (TESS) of 67.2% (Fig. 3C and D).

Discussion

We report herein the first known case of MEC originating in the trunk treated by a combination of canonical cytotoxic chemotherapy and definitive PBT, which resulted in long-term survival for at least 9 years. To our knowledge, only 2 cases of paraspinal MEC with follow-up after surgery have been reported (6). In both of those cases, the margin status was microscopically positive (R1), suggesting that complete resection of paraspinal MEC would be difficult.

Although not necessary in MEC, RT is often used in an adjuvant setting. A systematic review found that 163 (32.3%) of 505 cases of MEC (including cases originating in a salivary

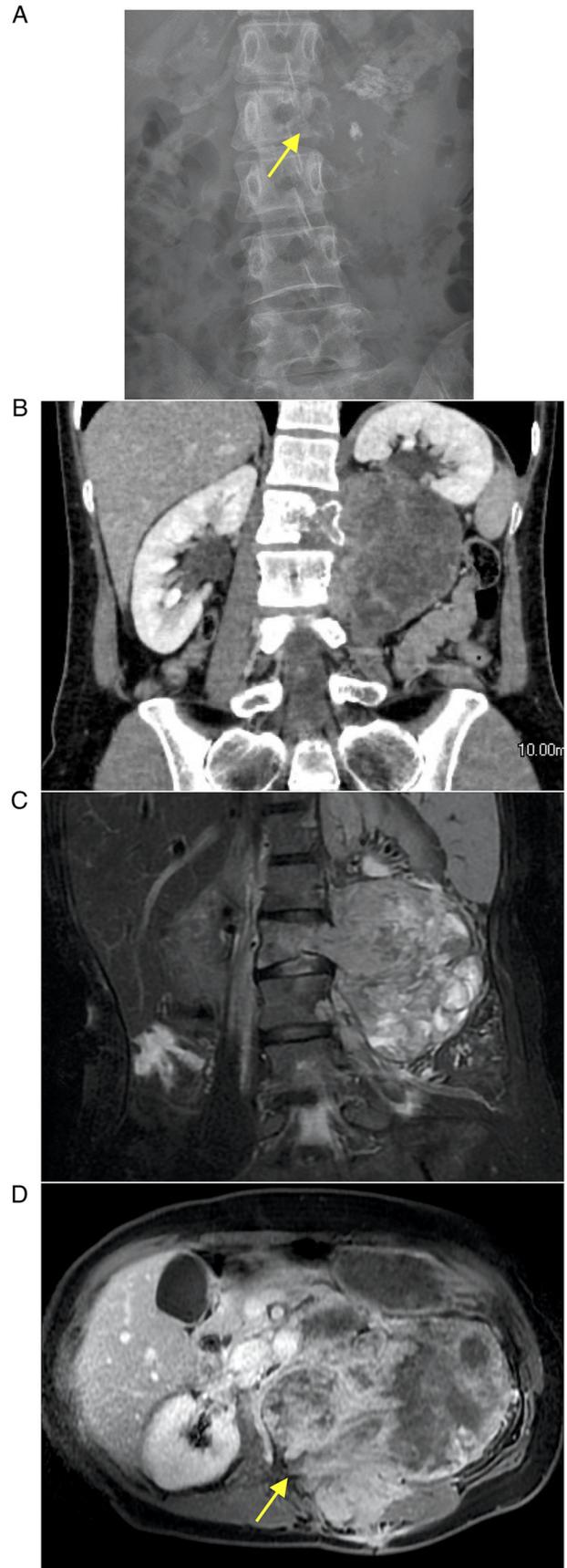


Figure 1. Imaging findings at the time of the initial diagnosis showed (A) canonical pedicle sign on the left side of the vertebra at L2 on a plain radiograph (arrow), (B-D) a massive neoplasm located mainly in the left paraspinal region at L2-L3 and destruction of the L2 vertebra on (B) computed tomography and (C and D) magnetic resonance imaging, and (D) invasion of the tumor into the spinal canal (arrow).

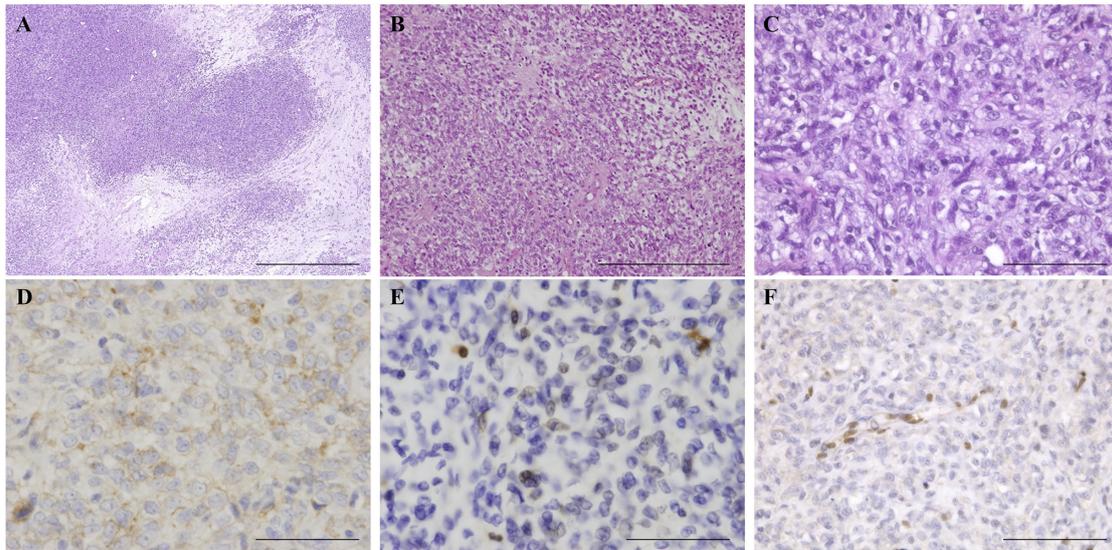


Figure 2. Histology and immunohistochemical staining of the myoepithelial carcinoma. (A-C) Hematoxylin-eosin staining reveals tumor cells showing a solid growth pattern with focal myxoid stroma (A, scale bar, 1,000 mm; B, scale bar, 500 mm; C, scale bar, 100 mm). Tumor cells show extensive positivity for (D) epithelial membrane antigen (scale bar, 100 mm), (E) strong focal positivity for S-100 protein (scale bar, 100 mm), (F) and loss of INI-1 immunoreactivity (scale bar, 100 mm).

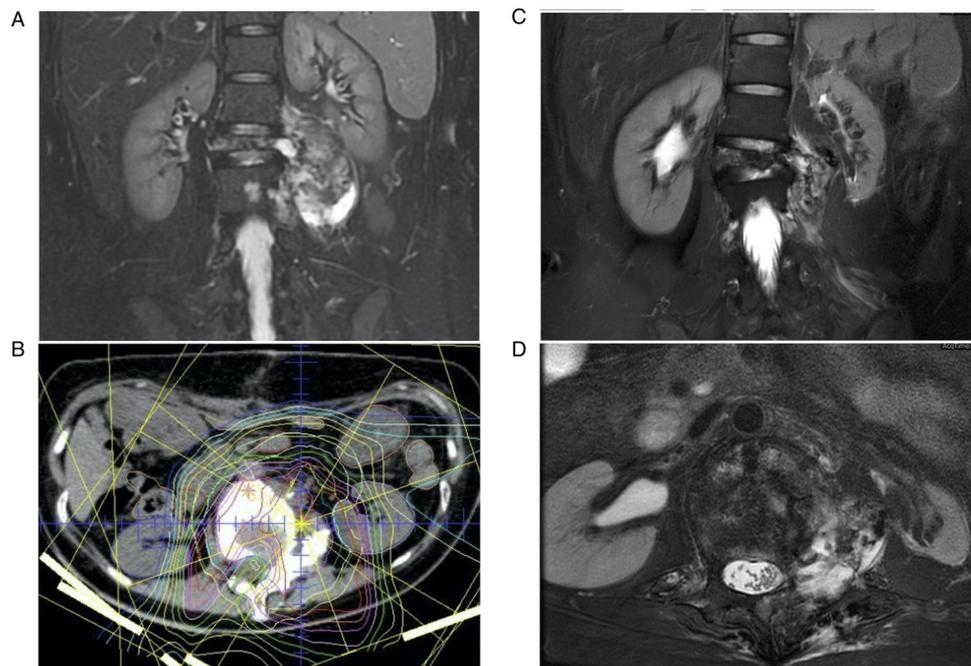


Figure 3. (A) After 4 courses of doxorubicin and ifosfamide, a partial response was seen on MRI. (B) Dose distribution of proton beam therapy. (C and D) MRI at the most recent follow-up 7.8 years after the initial diagnosis shows no evidence of relapse. MRI, magnetic resonance imaging.

gland) received RT, which was administered as neoadjuvant therapy in 3 cases, adjuvant therapy (median dose, 60 Gy) in 110, and radical treatment (median dose, 62 Gy) in 10 (7). According to a literature review of soft tissue MECs, 19 of 58 patients (32.8%) were treated with RT as initial therapy (8). An analysis of the Surveillance, Epidemiology, and End Results (SEER) registry data showed an overall survival benefit with adjuvant RT in high-grade MEC cases (9). However, to our knowledge, there has been only 1 reported case in which ion beam RT was used for MEC (10). That patient received PBT

at a total dose of 79.2 GyE in 36 fractions to treat a recurrent tumor in the maxillary sinus after initial maxillectomy and survived for 30 months without relapse. Given that report and our present case, PBT of over 70 Gy (RBE) could be a promising definitive local treatment for inoperable MEC.

There are limitations to systemic anticancer chemotherapy as treatment for MEC. Chamberlain *et al* reported a case series including 24 soft tissue MECs in adults treated by a multidisciplinary team at a single institution (4). Nine cases (37.5%) underwent chemotherapy, of which 5 cases (55.6%)

Table I. Summary of reported adult soft tissue myoepithelial carcinoma cases showing response for cytotoxic chemotherapy.

First author, year	Age, y	Sex	Primary site	Immunohistochemistry	Molecular analysis	Systemic treatment	Surgery	Radiotherapy	Outcome	(Refs.)
Noronha, 2006	37	F	Vulva	S100(+; few), CAM5.2(+), AE1/AE3(+; few), SMA(-), desmin(-), calponin(+; few)	(Unknown)	CDDP (PD) > CBDCA + PTX + GEM > CBDCA + PTX (CR)	Yes	Yes; Adj., 45 Gy/ 10.8 Gy	NED; 3.5 y	(11)
Rastrelli, 2013	61	M	Toe	(Unknown)	(Unknown)	CDDP + DXR (PD) > IFO (CR)	Yes	Yes; 50.4/ 64.8 Gy	NED; 3.0 y	(12)
Bisogno, 2014	7.8	F	Orbit	Cytokeratins(+), SMA(-), S100(-), INII (intact)	FISH (rearrangement): EWSR1(+)	ICpE + IVE (PR)	Yes	Yes; 41 Gy	NED; 5.1 y	(13)
Bisogno, 2014	0.5	M	Orbit	Cytokeratins(+), SMA(-), S100(-), INII (intact)	FISH (rearrangement): EWSR1(-)	ICpE + IVE (PR)	No	Yes; 36 Gy	NED; 0.9 y	(13)
Mourtzoukou, 2016	36	M	Neck	INI1(loss), EMA(+), S100(+), AE1/AE3(+), SMA(+), calponin(+)	FISH (rearrangement): EWSR1(-), FUS(-)	CBDCA + Cape. (PD) > DXR (PR)	Yes	Yes; Adj.	AWD; 3.4 y	(14)
Hoggard, 2017	34	M	Knee	EMA(+), S100(-), CAM5.2(+), AE1/AE3(+), desmin(+), GFAP(-)	WES: EWSR1 (22q12) locus rearrangement(-)	CBDCA + PTX (PR)	Yes	Yes; Adj., 66 Gy	CDF; >3.0 y ^a DOD; 4.1 y	(15)
Chamberlain, 2019	33	M	Neck	(Unknown)	(Unknown)	CBDCA + Cape. (PD) > DXR (PR)	Yes	Yes; Adj.	AWD; 10 mo	(4)
Shenoy, 2020	21	M	Kidney	(Unknown)	FISH: EWSR1- POU5F1	VDC/IE (PR)	No	No	CDF; 7.8 y	(16)
Present case	38	F	Paraspinal	INI1(loss), EMA(+), S100(+), AE1/AE3(-), SMA(+), GFAP(-)	(Unknown)	DXR + IFO (PR)	No	Yes; PBT, radical, 70.4 Gy (RBE)		

y, years; F, female; M, male; FISH, fluorescence *in situ* hybridization; WES, whole exome sequencing; CDDP, cisplatin; CBDCA, carboplatin; PTX, paclitaxel; GEM, gemcitabine; DXR, doxorubicin; IFO, ifosfamide; ICpE, ifosfamide, cisplatin and etoposide; IVE, ifosfamide, vincristine and etoposide; Cape., capecitabine; VDC/IE, vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide; Adj., adjuvant; PBT, proton beam therapy; NED, no evidence of disease; AWD, alive with disease; DOD, died of disease; CDF, continuous disease free; mo, months. ^aThe patient remains in radiographic remission 3 years from completion of chemotherapy.

were treated with doxorubicin alone or in combination as first-line treatment. According to RECIST, the best response to these doxorubicin-based regimens was a partial response in 1 patient, stable disease in 3, and progressive disease in 1. Review articles have shown that 18.8 to 36.2% of patients with MEC received chemotherapy, though it did not significantly decrease distant metastasis or local recurrence (7,8). Even among 11 children who received chemotherapy for metastatic or unresectable disease, a clinical response was seen in only 1 case (5).

Our literature review clearly identified only 8 cases of MECs in soft tissue, bone, skin, or organs excluding the salivary glands which showed a partial or complete response to some form of cytotoxic chemotherapy (Table I). Noronha *et al* reported a case with metastatic MEC primarily originating in the vulva that had a complete response to carboplatin and paclitaxel (11). Rastrelli *et al* similarly reported a case of metastatic MEC in which a complete response was achieved after locoregional and systemic therapy using continuous infusion of ifosfamide (12). Another man with a soft tissue MEC of the neck showed a partial response to 6 cycles of doxorubicin after progression on carboplatin and capecitabine (4). Two children who showed a partial response to combination chemotherapy were described by Bisogno *et al* (13). Furthermore, Mourtzoukou *et al* reported a 36-year-old man with metastatic MEC arising as a primary tumor within the soft tissue of the neck (14). Immunohistochemically, the tumor showed loss of INI1 with no rearrangement of either *EWSRI* or *FUS* on fluorescence *in situ* hybridization, and partial response was achieved by systemic administration of doxorubicin. Hoggard *et al* also reported a case of metastatic MEC showing partial response to carboplatin and paclitaxel with a disease-free interval of more than 3 years (15). In that case, molecular analysis of the tumor was notably negative for rearrangement of the *EWSRI* (22q12) locus. On the other hand, high-grade MEC harboring *EWSRI-POU5F1* fusion showed chemosensitivity to the VDC/IE regimen (vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide and etoposide) based on the protocol for Ewing sarcoma (16).

Including our case, 5 of the 9 patients shown in Table I were aged 30–40 years, and the regimens that proved effective were doxorubicin administered alone or in combination with ifosfamide (n=3), a combination of carboplatin and paclitaxel (n=2), and ifosfamide as a continuous infusion (n=1). MEC is prone to local recurrence, as well as distant and lymph node metastasis, even after complete surgical resection. Based on our case and a previous report (17), doxorubicin with an adequate total dose may provide a good long-term prognosis. Furthermore, the TREP project (*Tumori Rari in Eta Pediatrica*) in pediatric patients recommends the ICpE regimen (ifosfamide, cisplatin, and etoposide) with RT, which can be used as a clinical reference even in adolescents and young adults with MEC (13).

Rearrangement of the *EWSRI* gene occurs in nearly half of soft tissue MECs, and a small subset have alternative *FUS* rearrangements in lieu of *EWSRI* (3). Their fusion partners were reported to be *POU5F1*, *PBX1*, *ZNF444*, *KLF17*, *ATF1*, *PBX3* and *KLF15* (3,18–22). Moreover, among MECs lacking *EWSRI* rearrangements, a considerable subset that

show immunohistochemical loss of SMARCB1 (INI1) are characterized by homozygous deletions of *SMARCB1* (3). *SMARCB1* is a member of the SWI/SNF complex and is often lost in certain subtypes of sarcomas, including epithelioid sarcoma, malignant rhabdoid tumor, poorly differentiated chordoma, epithelioid malignant peripheral nerve sheath tumor, and MEC. This genetic feature appears in MECs rather than in benign myoepithelial neoplasms. In our review of MECs that responded well to treatment, loss of immunostaining for INI1 was noted in 2 cases and lack of *EWSRI* rearrangement in 2 cases. Although the two gene loci are close on 22q, the association between *EWSRI* fusions and *SMARCB1* perturbations remains unclear in MEC. Further research and elucidation of their downstream pathways may be helpful for better understanding the pathogenesis of myoepithelial neoplasms. More basic and clinical research is warranted to clarify the relationship between molecular genetic alterations and the clinical response to anti-tumoral agents in the effort to develop effective therapeutic strategies for patients with advanced MEC.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

ST made contributions to the acquisition and interpretation of data for this case, drafted the manuscript, and reviewed the literature. TN contributed to the concept and design of the case report, managed the therapeutic strategy, clinically treated the patient with chemotherapy and helped draft the. RM clinically treated the patient with chemotherapy and revised the manuscript critically for important intellectual content. YB curated the pathological data and revised the manuscript critically for important intellectual content. MS carried out pathological diagnosis, including immunohistochemistry, and revised the manuscript critically for important intellectual content. YD carried out PBT and revised the manuscript critically for important intellectual content. TO planned and carried out PBT and revised the manuscript critically for important intellectual content. KS made contributions to the conception of the case report and revised the manuscript critically for important intellectual content. ST and TN confirm the authenticity of all the raw data. All authors read and approved the final manuscript, and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and any associated images.

Competing interests

The authors declare that they have no competing interests.

References

- Kilpatrick SE, Hitchcock MG, Kraus MD, Calonje E and Fletcher CD: Mixed tumors and myoepitheliomas of soft tissue: A clinicopathologic study of 19 cases with a unifying concept. *Am J Surg Pathol* 21: 13-22, 1997.
- Hornick JL and Fletcher CD: Myoepithelial tumors of soft tissue: A clinicopathologic and immunohistochemical study of 101 cases with evaluation of prognostic parameters. *Am J Surg Pathol* 27: 1183-1196, 2003.
- Jo VY: Soft tissue special issue: Myoepithelial neoplasms of soft tissue: An updated review with emphasis on diagnostic considerations in the head and neck. *Head Neck Pathol* 14: 121-131, 2020.
- Chamberlain F, Cojocaru E, Scaranti M, Noujaim J, Constantinou A, Thway K, Fisher C, Messiou C, Strauss DC, Miah A, *et al*: Adult soft tissue myoepithelial carcinoma: Treatment outcomes and efficacy of chemotherapy. *Med Oncol* 37: 13, 2019.
- Gleason BC and Fletcher CD: Myoepithelial carcinoma of soft tissue in children: An aggressive neoplasm analyzed in a series of 29 cases. *Am J Surg Pathol* 31: 1813-1824, 2007.
- Rekhi B, Sable M and Jambhekar NA: Histopathological, immunohistochemical and molecular spectrum of myoepithelial tumours of soft tissues. *Virchows Arch* 461: 687-697, 2012.
- Giridhar P, Gupta P, Mallick S, Upadhyay AD and Rath GK: Impact of adjuvant therapy on survival in patients with myoepithelial carcinoma: A systematic review and individual patient data analysis of 691 patients. *Radiother Oncol* 140: 125-130, 2019.
- Kabarriti R, Quinn TJ, Ewart MR, Mehta KJ, Lomita C, Geller DS, Kalnicki S and Fox JL: Neoadjuvant radiation therapy for the management of myoepithelial carcinoma of the upper extremity. *Int J Cancer* 142: 854-862, 2018.
- Miccio JA, Oladeru OT, Yang J, Xue Y, Hoda ST, Ryu S, Stessin AM and Parker RI: Myoepithelial carcinoma: The role of radiation therapy. A case report and analysis of data from the surveillance, epidemiology, and end results (SEER) registry. *J Pediatr Hematol Oncol* 38: 274-278, 2016.
- Hata M, Tokuyue K, Shioyama Y, Nomoto S, Inadome Y, Fukumitsu N, Nakayama H, Sugahara S, Ohara K, Noguchi M, *et al*: Malignant myoepithelioma in the maxillary sinus: Case report and review of the literature. *Anticancer Res* 29: 497-501, 2009.
- Noronha V, Cooper DL, Higgins SA, Murren JR and Kluger HM: Metastatic myoepithelial carcinoma of the vulva treated with carboplatin and paclitaxel. *Lancet Oncol* 7: 270-271, 2006.
- Rastrelli M, Passuello N, Cecchin D, Basso U, Tosi AL and Rossi CR: Metastatic malignant soft tissue myoepithelioma: A case report showing complete response after locoregional and systemic therapy. *J Surg Case Rep* 2013: rjt109, 2013.
- Bisogno G, Tagarelli A, Schiavetti A, Scarzello G, Ferrari A, Cecchetto G and Alaggio R: Myoepithelial carcinoma treatment in children: A report from the TREP project. *Pediatr Blood Cancer* 61: 643-646, 2014.
- Mourtzoukou D, Zaidi S, Jones RL, Fisher C and Thway K: Soft tissue myoepithelial carcinoma metastatic to the cecum: Highlighting an unusual metastatic pattern and the need for diagnostic awareness. *Rare Tumors* 8: 6086, 2016.
- Hoggard TM, Henderson-Jackson E, Bui MM, Caracciolo J, Teer JK, Yoder S, Binitie O, Gonzalez RJ, Brohl AS and Reed DR: Myoepithelial carcinoma with RB1 mutation: Remarkable chemosensitivity to carcinoma of unknown origin therapy. *BMC Cancer* 17: 250, 2017.
- Shenoy N: Aggressive myoepithelial carcinoma with EWSR1-POU5F1 fusion highly responsive to Ewing sarcoma combination chemotherapy. *Cancer* 126: 5198-5201, 2020.
- Tian Z, Yang Y, Yang Y, Zhang F, Li P, Wang J, Yang J, Zhang P, Yao W and Wang X: High cumulative doxorubicin dose for advanced soft tissue sarcoma. *BMC Cancer* 20: 1139, 2020.
- Antonescu CR, Zhang L, Chang NE, Pawel BR, Travis W, Katabi N, Edelman M, Rosenberg AE, Nielsen GP, Dal Cin P and Fletcher CD: EWSR1-POU5F1 fusion in soft tissue myoepithelial tumors. A molecular analysis of sixty-six cases, including soft tissue, bone, and visceral lesions, showing common involvement of the EWSR1 gene. *Genes Chromosomes Cancer* 49: 1114-1124, 2010.
- Huang SC, Chen HW, Zhang L, Sung YS, Agaram NP, Davis M, Edelman M, Fletcher CD and Antonescu CR: Novel FUS-KLF17 and EWSR1-KLF17 fusions in myoepithelial tumors. *Genes Chromosomes Cancer* 54: 267-275, 2015.
- Flucke U, Mentzel T, Verdijk MA, Slootweg PJ, Creytens DH, Suurmeijer AJ and Tops BB: EWSR1-ATF1 chimeric transcript in a myoepithelial tumor of soft tissue: A case report. *Hum Pathol* 43: 764-768, 2012.
- Agaram NP, Chen HW, Zhang L, Sung YS, Panicek D, Healey JH, Nielsen GP, Fletcher CD and Antonescu CR: EWSR1-PBX3: A novel gene fusion in myoepithelial tumors. *Genes Chromosomes Cancer* 54: 63-71, 2015.
- Bodis S, Kroiss S, Tchinda J, Fritz C, Wagner U and Bode PK: Myoepithelial carcinoma of soft tissue with an EWSR1-KLF15 gene fusion in an infant. *Pediatr Dev Pathol* 24: 371-377, 2021.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.