Mutation of KIT In Cellular Extraskeletal Myxoid Chondrosarcoma: A Case of And Literature Review

Chen Wang (l-morning@163.com)  
Shengli Clinical Medical College of Fujian Medical University

Zhijie You  
Fujian Provincial Hospital South Branch

Xiao-Yan Chen  
Fujian Provincial Hospital

Jie Lin  
Fujian Provincial Hospital

Yi-Juan Wu  
Fujian Provincial Hospital

Case Report

Keywords: KIT, EMC, NR4A3, EWSR1, Case report

Posted Date: September 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-824533/v1

License: ☛️️️️️️️ This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background: Extraskeletal myxoid chondrosarcomas (EMCs) have been recognised as genetically and biologically solid tumours. Only a few studies have discussed the role of CD117 in immunohistochemical (IHC) staining or the influence of the KIT gene in EMC. We herein present a novel case of cellular EMC exhibiting EWSR1-NR4A3 fusion, KIT exon 13 mutations and a strong diffuse expression of CD117.

Case presentation: A man presented with a fist-sized tumour on his left shoulder. Computed tomography (CT) revealed a tumour in the left thoracic and dorsal muscle space. The tumour was completely resected. Histologically, the tumour cells had a nodular structure and underwent infiltrative growth, with the invasion of the peripheral fat and muscle tissues. The tumour cells had uniform size, round nuclei with well-defined nucleoli and eosinophilic cytoplasm. Immunohistochemically, the tumour cells were positive for CD117, vimentin, CD56 and NSE and revealed focal expression for desmin, with negativity for myogenin, S-100, SYN, INSM1, CD34, STAT6, INI-1, Brachyury, ERG, TLE1, AE1/AE3, WT-1, CD99 and SMA. Next-generation sequencing revealed EWSR1-NR4A3 fusion and KIT exon 13 mutations. The patient had no further treatment after surgery, and no recurrence or metastasis in follow-up for nearly 2 months.

Conclusions: Molecular detection is an indispensable technique for the diagnosis of EMC, especially rare variants like cellular EMC. The KIT mutations noted in this case report may offer fresh insights regarding EMC treatment.

Background

Extraskeletal myxoid chondrosarcomas (EMCs) have been recognised as genetically and biologically solid tumours [1], and they comprise < 1% of all soft-tissue sarcomas [2]. Cellular EMCs account for ~ 29% of all EMCs [3] and share the same nodular structure with classic EMC; however, an abundance of compact tumour cells and a limited myxoid matrix characterises the cellular variant. EWSR1-NR4A3 fusion products are detected in about 62–75% of the patients with NR4A3 rearrangement [4–6]. Only a few studies have discussed the role of CD117 in immunohistochemical (IHC) staining or the influence of the KIT gene in EMC. We herein present a novel case of cellular EMC in the left shoulder of a 69-year-old man, who exhibited, along with EWSR1-NR4A3 fusion, KIT exon 13 mutations as revealed by next-generation sequencing (NGS). Moreover, the IHC staining results demonstrated strong diffuse expression of CD117. To our knowledge, this is the first report of KIT exon 13 mutations in cellular EMC.

Case Presentation

Six months before admission, a 69-year-old man noted a fist-sized tumour on his left shoulder without obvious fever, ulcer, night sweat, weight loss and other symptoms. Palpation: We noted a palpable
subcutaneous mass on the left side of the scapula, which was difficult to reach, with a clear boundary, poor mobility and no obvious tenderness.

**Computed tomography** revealed an irregularly shaped soft-tissue mass measuring $7.0 \times 5.4 \times 2.7$ cm in size, located in the left thoracic and dorsal muscle space, and the mass revealed a clear boundary and uniform density (Fig. 1A). The bone adjacent to the mass revealed slight absorption and destruction. **MRI confirmed** an irregularly shaped soft-tissue mass in the left thoracic and dorsal muscle space with long T1 and T2 signalling as well as the uniform low-signal intensity in T1WI (Fig. 1B, C) and high-signal intensity with fat suppression in T2WI (Fig. 1D). **During surgery,** a mass of approximately $7 \times 6 \times 3$ cm was located in the deep surface of the latissimus dorsi muscle, most of the capsule of the mass was complete, and some tissues adhered at the bottom near the scapula region and the mass was removed.

The mass had a soft consistency with a pale yellow appearance. The tissue specimen was then sent to the pathologist for analysis. **Gross examination:** The specimen comprised a block of tissues (2 blocks), which was $7.5 \times 5.1 \times 3.3$ cm in size, without a capsule and revealing a nodular cut surface, greyish-white colour and a glossy appearance (Fig. 2). **Microscopic examination:** The tumour cells were arranged in a nodular manner and revealed an infiltrating growth into the surrounding fat and muscle tissue (Fig. 3A). The nodules were separated by a large amount of fibrous tissues, and most (> 80%) were solid in texture and comprised round, slightly short spindle cells (Fig. 3B). The cells had uniform size, round nucleus, non-obvious entoblast and slightly stained cytoplasm; mitosis could be seen in high cellularity areas (Fig. 3C). Additionally, in a few nodules, the cells were loosely arranged and connected into a reticulated or crossed appearance in the myxoid stroma (Fig. 3D), with no necrosis within the tumour. It was difficult to distinguish EMC from other tumours with similar histological characteristics. The differential diagnosis of EMC refers to the differentiation between EMC and proximal-type epithelioid sarcoma, extrarenal malignant rhabdoid tumour, epithelioid angiosarcoma, malignant solitary fibrous tumour, extraosseous Ewing’s sarcoma, desmoplastic small round cell tumour, metastatic dedifferentiated chordoma, poorly differentiated synovial sarcoma and epithelioid malignant peripheral nerve sheath tumour. IHC staining plays an essential role in this process; thus, the detection of several markers was performed. The immunophenotype was positive for CD117 (Fig. 3E), Vim, CD56 (Fig. 3F) and NSE and showed focal expression for desmin, but was negative for myogenin, S-100, SYN, INSM1, CD34, STAT6, INI-1, Brachyury, ERG, TLE1, AE1/AE3, WT-1, CD99 and SMA. **NGS** was performed to detect tumour mutations. Integrative Genomics Viewer plots revealed genomic rearrangement involving *EWSR1*. The event comprised a translocation of a fragment from exon 1 to 7 of *EWSR1* and exon 2 to 5 of *NR4A3* (Fig. 4A). NGS detected a single-nucleotide variant (A to G) in exon 13 of *KIT* (Fig. 5). **Fluorescence in situ hybridisation (FISH)** confirmed the result of the *EWSR1-NR4A3* fusion gene. The representative FISH images with *EWSR1* and *NR4A3* revealed separately split red-green, which indicated *EWSR1-NR4A3* fusion (Fig. 6). A diagnosis of cellular EMC was confirmed in the patient based on the combined results of morphological, immunophenotype and molecular analyses.

**Discussion**
EMCs were first defined as a class of solid tumours by Enzinger et al. [1], and they constitute < 1% of all soft-tissue sarcomas [2]. EMCs are commonly seen in male adults, with a mean age of 50 years. Lesions are most frequently found in the deep soft tissues of the proximal extremities, especially the lower extremities; however, in some cases, EMCs can also affect the trunk, head and neck, abdominal wall, paravertebral soft tissues and bones [7–10].

Histologically, EMCs can be categorised into classical EMCs and two variants, cellular EMC and solid non-myxoid EMC [11]. Cellular EMCs account for ~ 29% of all EMCs [12] and share the same nodular structure with classic EMC; however, the cellular variant is characterised by an abundance of compact tumour cells and a limited myxoid matrix, with the tumour cells in round or polygonal shapes, enriched in hyperacidophilic or hypochromic cytoplasm and having well-defined, centred, or deviated nuclei. Immunohistochemically, vimentin expression exhibits a diffuse staining pattern, with the expression of S-100, CD117, syn and NSE differing from each other. Moreover, no antibody of relative specificity is detected, and in most cases, the expression level of ki-67 is < 10%. Ultrastructural studies reveal that EMC cells are rich in mitochondria and contain a well-developed Golgi apparatus, numerous smooth vesicles and dense core granules; synaptophysin expression is detected by immunoelectron microscopy, demonstrating the neuroendocrine differentiation of EMC cells [8, 13]. A recent study [14] reported positivity for INSM1 in up to 90% of EMC cases, which is considered evidence for the neuroendocrine differentiation of EMC cells; however, INSM1 expression was not detected in this case. In terms of molecular genetics, NR4A3 rearrangement is involved in ~ 90% of EMC cases but is absent in other types of sarcomas, which may facilitate the development of an EMC-specific technique for differential diagnosis. In patients with NR4A3 rearrangement, NR4A3 is mostly fused with EWSR1 (about 62–75%) [4–6] and less frequently with TAF15 (27%), TCF12 (4%), TFG and FUS. Other studies have reported HSPA8-NR4A3 translocation [15], a novel t(2;22)(q34;q12) EWSR1 translocation [16] and SMARCA2-NR4A3 fusion [17].

As described above, the tumour cells, in this case, had a nodular structure and underwent infiltrative growth, with the invasion of the peripheral fat and muscle tissues. There were abundant fibrous tissues between the nodules, most of which were identified as solid nodules (> 90%) and comprised of round or fusiform cells. The tumour cells had uniform size, round nuclei with well-defined nucleoli and eosinophilic cytoplasm, and their nuclear fission was 2/10 HPF. The nodular structure partly resembled that of classic EMC, but the tumour cells were loosely arranged, forming reticular or crosswise layers in the myxoid matrix. Local necrosis was observed. It's a huge challenge to diagnose this tumor because of the lack of specificity in morphological features. There are many soft tissue tumours with similar morphology to this tumour The main differential diagnosis includes cellular EMC, proximal-type epithelioid sarcoma, extrarenal malignant rhabdoid tumour, epithelioid angiosarcoma, malignant solitary fibrous tumour, extraosseous Ewing's sarcoma, desmoplastic small round cell tumour, metastatic dedifferentiated chordoma, poorly differentiated synovial sarcoma and epithelioid malignant peripheral nerve sheath tumour. IHC staining plays an essential role in this process. In this case, the IHC staining results suggested that the patient was diffusely positive for CD117, vimentin, CD56 and NSE, focally positive for
desmin, with a ki-67 level of ~40% and negative for other markers. Despite the effectiveness of IHC staining, a definitive diagnosis of EMC cannot solely depend on positive IHC results for CD117, vimentin, CD56 and NSE as specific markers, but it gave us a diagnosis clue at least, so NGS was performed in the tumor, and a site specific to EWSR1 exon 7-NR4A3 exon 2 fusion was subsequently identified. Based on this, a diagnosis of cellular EMC was confirmed by considering the combined results of the morphological, immunophenotype and molecular analyses.

Interestingly, along with EWSR1 exon7-NR4A3 exon2 fusion, the NGS detected KIT exon 13 mutations; moreover, it was noted that the IHC staining results demonstrated a strong diffuse expression of CD117. Only a few studies have discussed the role of CD117 in IHC staining or the KIT gene in the diagnosis of EMC. Hornick et al. [18] reported that 2 of 20 patients tested positive for CD117 (one focally positive case and one diffusely positive case), without clarifying the expression intensity or detection of the KIT gene. In the study by Subramanian et al. [19], based on IHC and ISH (In Situ Hybridization) tests, 8 of 19 EMC patients were focally positive for CD117, and 6 of 11 EMC patients were diffusely positive for CD117, but the expression intensity or scope was not discussed; the diffuse positive cases (6/11) underwent screening of KIT exons 9, 11, 13 and 17 for mutations, and the results suggested that there were no mutations in these exons. The IHC staining results in the study by Stacchiotti et al. [20] suggested the presence of CD117 expression in 6 of 9 EMC cases, including four cases of weak focal expression of CD117, while the western blot test results in the same study indicated the KIT expression without phosphorylation; yet, no KIT gene analysis was conducted. Subsequently, Urbini et al. [21] reported the case of an EMC patient (1/20) with KIT exon 11 mutations, which, apart from this paper, is the only reported EMC case with KIT gene mutations; however, no IHC staining results were provided in the study. In this case, the presence of KIT exon 13 mutations was established based on the NGS and morphological findings, i.e. abundant tumour cells, scarce myxoid stroma and strong diffuse expression of anti-CD117 antibody in tumour cells. We consider that CD117-positive (CD117⁺) cellular EMC might have a higher frequency of KIT gene mutations. EMC subtypes were not elaborated in the above-mentioned studies, which involved patients without KIT gene mutations but who tested positive for anti-CD117 antibody or those with KIT gene mutations before anti-CD117 antibody testing. Moreover, to the best of our knowledge, no study has explored the association of anti-CD117 antibody and the KIT gene with EMC subtypes. Therefore, it is necessary to study more EMC cases positive for anti-CD117 antibody and cellular EMC cases positive for CD117.

In a gastrointestinal stromal tumour, the location of KIT mutations is associated with its biological behaviour, with exons 11 and 13 mutations providing evidence regarding its malignant biological behaviour [22]. KIT exon 13 mutations are relatively rare, accounting for 0.8–4.1% of all KIT mutations, and patients with KIT exon 13 mutations benefit from sunitinib therapy [23]. A patient with EMC who had KIT exon 11 mutations and had never received sunitinib was reported to benefit from sunitinib therapy [21]. In this case, the patient experienced KIT exon 13 mutations but was not administered sunitinib; therefore, the therapeutic activity of sunitinib as part of the treatment for this patient remains unclear.
However, the findings of the preceding studies indicate that KIT mutations are potential targets for EMC treatment. Further studies with larger sample size and follow-up data are needed to verify this viewpoint.

Presently, wide surgical resection is the mainstay of treatment for patients with EMC, and opinions are mixed concerning the treatment of cellular EMC. The prognosis of EMC remains controversial. In the 1970s, Enzinger et al. \[1\] viewed EMCs as low-grade malignant tumours when they first introduced this class of solid tumours. Later, the long-term follow-up study of 10 patients with EMC by Saleh et al. \[24\] revealed that 70% of the patients with EMC had an average survival of 10 years. Meis-Kindblom et al. \[12\] reviewed 177 EMC cases treated by the Armed Forces Institute of Pathology and Sahlgren University Hospital over 20 years for analysing the biological behaviour and prognosis of EMC. They discovered that EMC had a rather long disease course and was prone to metastasis and local recurrence; moreover, the case-death ratio was relatively high, and the biological behaviour differed from that of other low-grade malignant soft-tissue sarcomas. The 10-year survival rate was 70% among the patients with EMC, and the prognosis of EMC was not associated with histological grade or proliferative markers but with the location and size of the tumour in elderly patients. In this case, it was only about 2 months after the surgery, so the significance of follow-up results were limited. We will continue to follow up.

In conclusion, molecular detection is an indispensable technique for the diagnosis of EMC, especially rare variants like cellular EMC. The KIT mutations that were reported in this case report may offer fresh insights regarding EMC treatment.

**Abbreviations**

EMC: Extraskeletal myxoid chondrosarcomas; IHC: Immunohistochemical; CT: Computed tomography; FISH: Fluorescence in situ hybridisation; ISH: In Situ Hybridization; NGS: next-generation sequencing; MRI: Magnetic resonance imaging; T1WI: T1-weighted image; T2WI: T2-weighted image

**Declarations**

**Authors’ contributions**

Chen Wang and Zhi-Jie You designed the study; Chen Wang acquired clinical data; Zhi-Jie You performed the pathological examination and image examination; Chen Wang and Zhi-Jie You wrote the manuscript; Jie Lin and Yi-Juan Wu performed the experimental operation and date analysis; Chen Wang and Xiao-Yan Chen revised the manuscript. All authors issued final approval for the version to be submitted.

**Availability of data and materials**

All data generated or analyzed during this case are included within the article.

**Ethics approval and consent to participate**
The need for ethics approval and consent was waived, since a consent for publication was obtained from the patient himself.

Consent for publication

Written informed consent for publication of the clinical details and/or clinical images was obtained from the patient himself. A copy of the consent form is available for review by the Editor of this journal.

Competing interests

The authors declare that they have no competing interests.

Author details

1 Department of Pathology, Shengli Clinical Medical College of Fujian Medical University, Fujian Provincial Hospital, Fuzhou 350001, Fujian, China

2 Department of Pathology, Fujian Provincial Hospital South Branch, Fuzhou 350028, Fujian, China

References

1. Enzinger FM, Shiraki M. Extraskeletal myxoid chondrosarcoma. An analysis of 34 cases. Hum Pathol. 1972 Sep;3(3):421–35. doi: 10.1016/s0046-8177(72)80042-x. PMID: 4261659.

2. WHO Classification of Tumours Editorial Board. WHO Classification of Tumours of Soft Tissue and Bone Tumours. Lyon: IARC Press; 2020. pp. 303–5.

3. Meis-Kindblom JM, Bergh P, Gunterberg B, Kindblom LG. Extraskeletal myxoid chondrosarcoma: a reappraisal of its morphologic spectrum and prognostic factors based on 117 cases. Am J Surg Pathol. 1999 Jun;23(6):636–50. doi:10.1097/00000478-199906000-00002. PMID: 10366145.

4. Wang WL, Mayordomo E, Czerniak BA, et al. Fluorescence in situ hybridization is a useful ancillary diagnostic tool for extraskeletal myxoid chondrosarcoma. Mod Pathol. 2008 Nov;21(11):1303–10. doi: 10.1038/modpathol.2008.114. Epub 2008 Jun 27. PMID: 18587326.

5. Hinrichs SH, Jaramillo MA, Gumerlock PH, et al. Myxoid chondrosarcoma with a translocation involving chromosomes 9 and 22. Cancer Genet Cytogenet. 1985 Jan 15;14(3–4):219–26. doi: 10.1016/0165-4608(85)90187-6. PMID: 3967207.

6. Flucke U, Tops BB, Verdijk MA, et al. NR4A3 rearrangement reliably distinguishes between the clinicopathologically overlapping entities myoepithelial carcinoma of soft tissue and cellular extraskeletal myxoid chondrosarcoma. Virchows Arch. 2012 Jun;460(6):621–8. doi:10.1007/s00428-012-1240-0. Epub 2012 May 9. PMID: 22569967; PMCID: PMC3371325.

7. Tateishi U, Hasegawa T, Nojima T, et al. MRI features of extraskeletal myxoid chondrosarcoma. Skeletal Radiol. 2006 Jan;35(1):27–33. doi:10.1007/s00256-005-0021-0. Epub 2005 Oct 12. PMID: 16220270.
8. Goh YW, Spagnolo DV, Platten M, et al. Extraskeletal myxoid chondrosarcoma: a light microscopic, immunohistochemical, ultrastructural and immuno-ultrastructural study indicating neuroendocrine differentiation. Histopathology. 2001 Nov;39(5):514 – 24. doi: 10.1046/j.1365-2559.2001.01277.x. PMID: 11737310.

9. Demicco EG, Wang WL, Madewell JE, et al. Osseous myxochondroid sarcoma: a detailed study of 5 cases of extraskeletal myxoid chondrosarcoma of the bone. Am J Surg Pathol. 2013 May;37(5):752–62. doi: 10.1097/PAS.0b013e3182796e46. PMID: 23588370.

10. Kilpatrick SE, Inwards CY, Fletcher CD, et al. Myxoid chondrosarcoma (chordoid sarcoma) of bone: a report of two cases and review of the literature. Cancer. 1997 May 15;79(10):1903-10. doi: 10.1002/(sici)1097-0142(19970515)79:10<1903::aid-cncr10>3.0.co;2-z. PMID: 9149016.

11. Meis-Kindblom JM. Cellular(solid) variant of extraskeletal myxoid chondrosarcoma[A]. Proceedings from the Xth International Congress of the International Academy of Pathology Meeting[C]. Nice, France. October 1998.

12. Meis-Kindblom JM, Bergh P, Gunterberg B, et al. Extraskeletal myxoid chondrosarcoma: a reappraisal of its morphologic spectrum and prognostic factors based on 117 cases. Am J Surg Pathol. 1999 Jun;23(6):636–50. doi: 10.1097/00000478-199906000-00002. PMID: 10366145.

13. Oliveira AM, Sebo TJ, McGrory JE, et al. Extraskeletal myxoid chondrosarcoma: a clinicopathologic, immunohistochemical, and ploidy analysis of 23 cases. Mod Pathol. 2000 Aug;13(8):900-8. doi: 10.1038/modpathol.3880161. PMID: 10955458.

14. Yoshida A, Makise N, Wakai S, et al. INSM1 expression and its diagnostic significance in extraskeletal myxoid chondrosarcoma. Mod Pathol. 2018 May;31(5):744–752. doi: 10.1038/modpathol.2017.189. PMID: 29327709.

15. Urbini M, Astolfi A, Pantaleo MA, et al. HSPA8 as a novel fusion partner of NR4A3 in extraskeletal myxoid chondrosarcoma. Genes Chromosomes Cancer. 2017 Jul;56(7):582–6. doi:10.1002/gcc.22462. Epub 2017 May 4. PMID: 28383167.

16. Batsis ID, Offenbacher R, Rybinski B, et al. Systemic manifestations of extraskeletal myxoid chondrosarcoma associated with a novel t(2;22)(q34;q12) EWS translocation in a child and a review of the literature. Pediatr Hematol Oncol. 2018 Oct-Nov;35(7–8):434–441. doi: 10.1080/08880018.2018.1557766. Epub 2019 Feb 18. PMID: 30776935.

17. Wei S, Pei J, von Mehren M, et al. SMARCA2-NR4A3 is a novel fusion gene of extraskeletal myxoid chondrosarcoma identified by RNA next-generation sequencing. Genes Chromosomes Cancer. 2021 Jun 14. doi: 10.1002/gcc.22976. Epub ahead of print. PMID: 34124809.

18. Hornick JL, Fletcher CD. Immunohistochemical staining for KIT (CD117) in soft tissue sarcomas is very limited in distribution. Am J Clin Pathol. 2002 Feb;117(2):188 – 93. doi: 10.1309/LX9U-F7P0-UWDH-8Y6R. PMID: 11865845.

19. Subramanian S, West RB, Marinelli RJ, et al. The gene expression profile of extraskeletal myxoid chondrosarcoma. J Pathol. 2005 Aug;206(4):433 – 44. doi: 10.1002/path.1792. PMID: 15920699.
20. Stacchiotti S, Pantaleo MA, Astolfi A, et al. Activity of sunitinib in extraskeletal myxoid chondrosarcoma. Eur J Cancer. 2014 Jun;50(9):1657–64. doi:10.1016/j.ejca.2014.03.013. Epub 2014 Apr 2. PMID: 24703573.

21. Urbini M, Indio V, Astolfi A, et al. Identification of an Actionable Mutation of KIT in a Case of Extraskeletal Myxoid Chondrosarcoma. Int J Mol Sci. 2018 Jun 23;19(7):1855. doi: 10.3390/ijms19071855. PMID: 29937513; PMCID: PMC6073125.

22. Lasota J, Wozniak A, Sarlomo-Rikala M, et al. Mutations in exons 9 and 13 of KIT gene are rare events in gastrointestinal stromal tumors. A study of 200 cases. Am J Pathol. 2000 Oct;157(4):1091–5. doi:10.1016/S0002-9440(10)64623-8.

23. Poveda A, García Del Muro X, López-Guerrero JA, et al. GEIS guidelines for gastrointestinal sarcomas (GIST). Cancer Treat Rev. 2017 Apr;55:107–119. doi: 10.1016/j.ctrv.2016.11.011.

24. Saleh G, Evans HL, Ro JY, et al. Extraskeletal myxoid chondrosarcoma. A clinicopathologic study of ten patients with long-term follow-up. Cancer. 1992 Dec 15;70(12):2827-30. doi: 10.1002/1097-0142(19921215)70:12<2827::aid-cncr2820701217>3.0.co;2-v. PMID: 1451062.

Figures
Figure 1

The computed tomography (CT) revealed an irregular-shaped soft tissue mass measuring 7.0cm × 5.4cm × 2.7cm in size located in the left thoracic and dorsal muscle space, and the mass showed clear boundary and uniform density (a), MRI confirmed the presence of an irregular-shaped soft tissue mass in the left thoracic and dorsal muscle space with long T1 (b) and T2 (c) signaling, as well as a uniformed low signal in T1WI (b) and a high signal with fat suppression in T2WI (d). The blue five-pointed star and arrow indicate the mass.
The specimen detected was a block of tissues (2 blocks), which was 7.5cm × 5.1cm × 3.3cm in total size, without capsule, showing nodular cutting surface, greyish white color and glossy appearance.
Histologic features of cellular extraskeletal myxoid chondrosarcoma. a, The tumor cells were arranged in nodular shape and showed an infiltrating growth into the surrounding fat and muscle tissue. b, The nodules were separated by a large amount of fibrous tissues. c, Cells showed uniform size, round nucleus, non-obvious entoblast, and slightly stained cytoplasm, mitosis could be seen in the high cellularity areas. d, In a few nodules, the cells were loosely arranged and connected into a reticulated or crossed appearance in the myxoid stroma. e, Immunohistochemically, the tumor cells were positive for CD117. f, positive for CD56.
Figure 4

Integrative Genomics Viewer (IGV) plots showing genomic rearrangement involving EWSR1. The event consists in a translocation of a fragment from the exons 1-7 of EWSR1 and the exons 2-5 of NR4A3. EWSR1- NR4A3 fusion was identified by DNA next-generation sequencing above and RNA next-generation sequencing below.

Figure 5

Sequencing reads of Kit were viewed by integrative genomics viewer. NGS detected a single nucleotide variant (A to G) in exon13 of KIT.

Figure 6
Analysis of EWSR1- NR4A3 fusion gene of the patient by fluorescence in situ hybridization (FISH). The representative FISH images with EWSR1 (left) and NR4A3(right) showed split red-green which indicating EWSR1- NR4A3 fusion.

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.

- CAREChecklist.docx