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

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Case Report

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Abstract

Background: Extraskelatal 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

Extraskelatal 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 data 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.

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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.

Figure 2

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

Figure 3

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.

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