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Primary mesenchymal chondrosarcoma of the kidney without *HEY1-NCOA2* and *IRF2BP2-CDX1* fusion: A case report and review

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Abstract. Mesenchymal chondrosarcoma (MC) of the kidney is rare. To the best of our knowledge, the current report is the first case of a giant extraskeletal MC that arose primarily from the right kidney and mimicked renal cell carcinoma at the locally advanced stage (cT3bN0) with vena cava thrombus and multiple pulmonary arterial tumor emboli. Additionally, the literature on renal EMC is reviewed and the possibilities of oncogenic heterogeneity are discussed. A 64-year-old woman was admitted to Yamagata University Hospital for sudden onset of asymptomatic gross hematuria. CT revealed a 90 mm renal mass without calcification in the right kidney and tumor thrombus extending to the inferior vena cava. Radical nephrectomy with thrombectomy was performed. Lung metastasis was detected 2 months later. The patient received systemic chemotherapy, which was only marginally effective. She died of the malignancy 8 months after surgery. Microscopic examination of the tumor revealed typical histology of MC and a lack of *HEY1-NCOA2* and *IRF2BP2-CDX1* gene fusions in the tumor tissues. Not all MC patients may exhibit chromosomal alterations in the tumor, suggesting the presence of genetically heterogeneous pathways of MC oncogenesis. Further studies are required to confirm the present findings and reinforce the molecular diagnosis of MC.

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Abbreviations: MC, mesenchymal chondrosarcoma; EMC, extraskeletal mesenchymal chondrosarcoma; HEY1, hairy/enhancer-of-split related with YRPW motif 1; NCOA2, nuclear receptor coactivator 2; STAU2, staufen double-stranded RNA binding protein 2; ZFHX4, zinc finger homeobox 4; IRF2BP2, interferon regulatory factor 2 binding protein 2; CDX1, caudal type homeobox 1

Key words: mesenchymal chondrosarcoma, *HEY1-NCOA2* fusion, *IRF2BP2-CDX1* fusion, tumor thrombus

Introduction

Mesenchymal chondrosarcoma (MC) is a rare neoplasm and represents only 2 to 9% of all chondrosarcomas. Almost 24% of MCs originate from extraskeletal sites, such as head, neck, the extremities, and trunk. The kidney is an extremely rare origin of extraskeletal MC (EMC) (1). In a recent report from Japan (2), primary origins of MC were bone (58%) and soft tissues (42%). MC develops at various sites in the body, including the head and neck (12%), trunk (62%), and extremities (26%). The authors reported 5- and 10-year overall survival rates of 66 and 56%, respectively (2).

In the absence of specific tumor markers and radiographic findings, the diagnosis of MC largely depends on pathologic examination (3,4). The *HEY1-NCOA2* gene fusion is reported to be a specific chromosomal aberration for MC and may play a critical role in diagnosis due to its high sensitivity (3,5-7). Physiologically, HEY1 is considered to function mainly as a transcriptional repressor and *NCOA2* encodes a transcriptional coactivator protein for intranuclear receptors (7). Recently, an *IRF2BP2-CDX1* fusion gene was implicated as another candidate MC oncogene exclusive to the *HEY1-NCOA2* fusion gene (8).

We describe the first case of primary renal EMC mimicking renal cell carcinoma at the locally advanced stage (cT3bN0) accompanied by vena cava thrombus and multiple pulmonary tumor emboli. The microscopic pathology was typical of MC but the *HEY1-NCOA2* and *IRF2BP2-CDX1* gene fusions were not detected.

Case report

Clinical summary. A 64-year-old woman visited our clinic complaining of sudden onset asymptomatic gross hematuria and was hospitalized for further examination. Flank pain and fever were absent. Routine laboratory tests indicated no remarkable abnormality in hematology and urine cytology was negative. No past history was noted, except for liver cystectomy and right mastectomy.

Computed tomography (CT) of the abdomen revealed a giant mass (90x70x67 mm) in the mid to lower pole of the right

kidney. The tumor was hypovascular on contrast-enhanced CT images compared with adjacent normal renal parenchyma, although tumor vessels surrounding the mass were well-developed. In addition, the tumor was characterized as internally heterogeneous, free of calcification, and protruding into the inferior vena cava (IVC) through the right renal vein to form a tumor thrombus up to the level of the caudate lobe of the liver (Fig. 1). Tumor emboli were disseminated to pulmonary arteries, but no distant metastases were identified. The tumor presented with a high standardized uptake value of 12.00 at the maximum in positron emission tomography (PET)-CT. Magnetic resonance imaging (MRI) with delayed contrast-enhancement revealed the heterogeneous nature of the tumor. On plain MRI, the tumor had high, low, slightly low, and slightly low signal intensities on T2-weighted, T1-weighted, diffusion-weighted, and apparent diffusion coefficient mapping images, respectively. Histological examination using percutaneous needle-biopsied specimens of the tumor revealed that it contained atypical chondrocytes and spindle cells with high nuclear-to-cytoplasmic ratio, suggesting renal chondrosarcoma. Radical nephrectomy with intracaval thrombectomy was performed for the initial treatment for the tumor. We successfully en bloc resected the whole kidney and the attached IVC thrombus using an artificial heart-lung machine and clamping IVC just beneath the beginning of the hepatic veins in cooperation with vascular surgeons.

The results of the pathological investigation of the resected specimens are presented in Fig. 2. They had biphasic morphological components with transition zones between round and spindle-shaped hyperchromic tumor cells and contained cartilaginous islands with good differentiation (Fig. 2A and B). The spindle-shaped cells showed indistinct cytoplasmic borders, inconspicuous nucleoli, and a hemangiopericytoma-like pattern (Fig. 2C). Tumor cells invaded into small lympho-vascular structures, renal veins, and renal hilar fat tissues. No metastasis was microscopically confirmed in any of the 11 local lymph nodes surgically resected in total, including para-aortic/vena cava and renal hilar lymph nodes. Immunohistochemically, the tumor was positively stained with antibodies to vimentin, CD99, and Ki-67 (labelling index: 60-70%), without immunoreaction to epithelial membrane antigen, CD34, chromogranin A, and synaptophysin. Expression of S-100 protein was negative in mesenchymal spindle cells, but was slightly positive only in some chondroid cells (Fig. 2D). Based on these pathological features, the tumor was diagnosed as primary renal EMC.

Two months later, she experienced local recurrence and multiple lung metastases. Systemic chemotherapy was delivered and began with three courses of doxorubicin (30 mg/m^2 on day 1-2, every 3 weeks). This was followed by pazopanib (800 mg/day), but the therapy was discontinued due to drug eruption at day 11. Eribulin mesilate was delivered in two courses (1.4 mg/m^2 on day 1 and 8, every 3 weeks). The dose was reduced to 1.1 mg/m^2 in the second cycle because of neutropenia. Palliative irradiation of 20 Gy was given to de novo metastasis to the right 8th rib for pain control. The patient's condition gradually worsened and she finally died of the malignancy 8 months after surgery.

HEY1-NCOA2 and IRF2BP2-CDX1 gene fusion. Standard reverse transcription-polymerase chain reaction (RT-PCR) were used to detect the *HEY1-NCOA2* and *IRF2BP2-CDX1* chromosomal fusions, as described elsewhere (9). In brief, RNA samples were extracted from surgically resected and fleshly frozen MC tissues with mirVana™ miRNA Isolation kit (Life Technologies). Total RNA (2 μg) was reverse-transcribed in a 20 μl reaction volume using a cDNA Reverse Transcription Kit according to the manufacturer's instructions (Applied Biosystems). RT-PCR was run using 1 μl cDNA in a 50 μl PCR reaction using AmpliTaq Gold DNA polymerase (Applied Biosystems). Primers for *HEY1-NCOA2* fusion, *STAU2*, and *ZFHX4* are shown in Table I and Fig. 3A (all were purchased from Integrated DNA Technologies, IA, USA). The primers for *IRF2BP2-CDX1* were the same as reported previously (Integrated DNA Technologies) (8). The PCR conditions were 95˚C for 30 sec, 55-60˚C (according to the Tm of each primer provided from the manufacturer) for 30 sec, and 72˚C for 45 sec after initial denaturation at 95˚C for 2 min. Thirty-five cycles were run. RT-PCR of the housekeeping gene encoding β-actin was run on all samples to check the RNA quality. PCR products were checked using 2% agarose gel electrophoresis.

Table I. Primer sequences for PCR.

Primer	5'→3'
HEY1_F1	CGAGGTGGAGAAGGAGAGTG
HEY1_F2	ACCGGATCAATAACAGTTTG
HEY1_R	CCCGAAATCCCAAACTCCGA
NCOA2_F	AGCTTTTCCCAGACACGAGG
NCOA2_R1	TCCTGGCTGAGGTATCAC
NCOA2_R2	AGTTGGGCTTTGCAATGTGA
STAU2_F	ACTCCCCCTTGTTCTCCAGT
STAU2_R	TGCCTGGTTATTGTCCGCTT
ZFHX4_F	CCGCTGATGACTGGACAACT
ZFHX4_R	GGTGTTGGTCTTCACCGCTA
βActin_F	CCTCGCCTTTGCCGATCC
βActin_R	GGATCTTCATGAGGTAGTCAGTC
IRF2BP2_F1	CAAGAGCCGCGGGTCTGGAGA
IRF2BP2_F2	GTCAACAGGCCCAAGACCGTGC
IRF2BP2_R	GTGTGGTCCGGTTGGAATGAGGTG
CDX1_F	CCGCAGTACCCCGACTTCTCCAG
CDX1_R1	GTTCAGTGAGCCCCAGATTGGCAG
CDX1_R2	TGATGTCGTGGGCCATCGGC

The overall results of RT-PCR are presented in Fig. 3B. The *HEY1-NCOA2* fusion gene was not observed in this patient. Instead of the fusion gene, intact *HEY1* and *NCOA2* genes were successfully detected. The presence of intact *STAU2* and *ZFHX4* genes, each of which should be deleted from the chromosome at the fusion of *HEY1* and *NCOA2* genes (Fig. 3A), was confirmed by RT-PCR in the patient's samples. Similarly, the *IRF2BP2-CDX1* fusion was not detected in the patient (Fig. 4). Taken together, these findings demonstrate that the *HEY1-NCOA2* and *IRF2BP2-CDX1* gene fusions were absent or were not located at the chromosomal breakpoints that were previously reported.

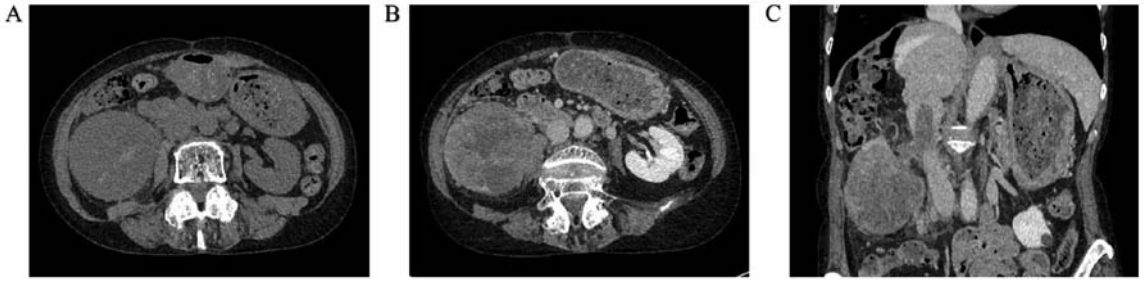

Figure 1. Abdominal computed tomography scan. (A) Plain computed tomography did not reveal calcification in the tumor. (B) The tumor was marginally enhanced and was heterogeneous. (C) The tumor thrombus extended into the IVC and reached the level of the caudal lobe of the liver. The right lobe of the liver had been previously resected. IVC, inferior vena cava.

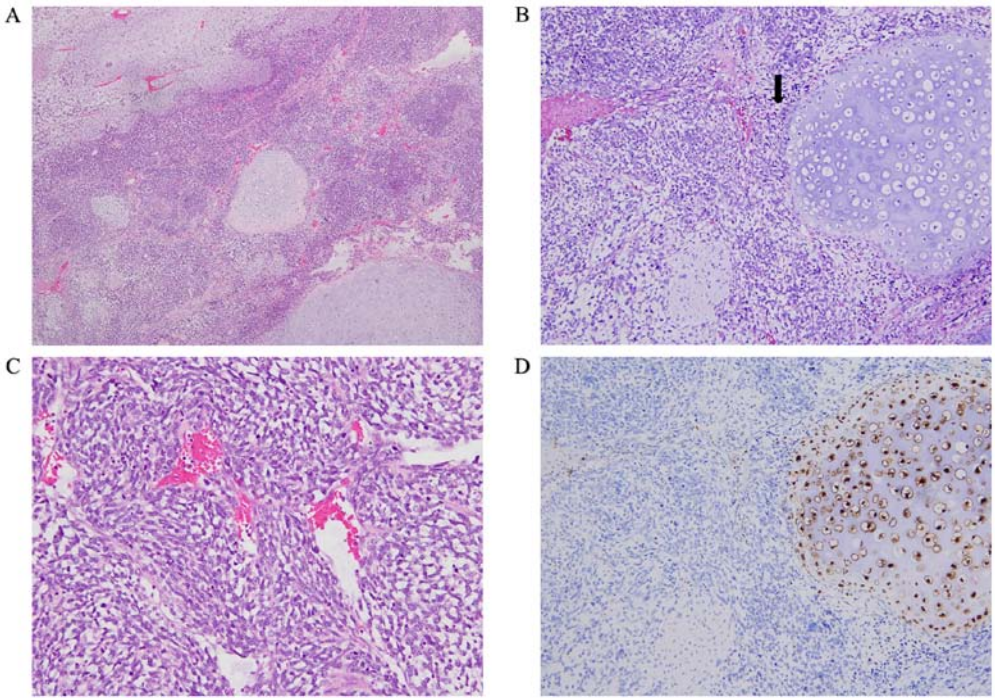

Figure 2. Microscopic examination of the renal tumor. (A) Islands of well-differentiated cartilage surrounded by hyperchromic cells are visible in a hematoxylin and eosin stained section (magnification, x40). (B) A transition zone was seen between cellular and cartilage components (arrow; hematoxylin and eosin; magnification, x100). (C) A hemangiopericytoma-like pattern was seen (hematoxylin and eosin; magnification, x200). (D) Immunoreaction to S-100 protein was positive in a cartilaginous island, but negative in the surrounding small tumor cells (magnification, x100). This microphotograph shows the same region in (B).

Discussion

Primary renal EMC is extremely rare (1). To our best knowledge, only 16 patients with renal EMC, including the present case, have been reported in the medical literature (Table II) (1,10-23). According to a review article on renal EMC (1), flank pain and hematuria are two most common clinical symptoms. Renal EMC occurs from children to elderly people with the peak incidence in the third decade, equally in men and women (1). No clinical differences in oncological behaviors are indicated between renal and non-renal origins of EMC (1). Despite a paucity of credible evidence for renal EMC, a favorable prognosis might be expected if the tumor is small, locally confined, and completely resected (1). Mimicking advanced renal cell carcinoma (cT3bN0), our case had tumor dissemination in pulmonary arteries at the initial presentation and early metastatic recurrence occurred in the bilateral lungs soon after radical nephrectomy with IVC thrombectomy.

MC is often difficult to diagnose because of the lack of specific findings. On clinical imaging, MC typically exhibits low CT attenuation with calcification and heterogeneous appearance, T1-low and T2-high/low intensities of MR signals, and strongly metabolic activity on PET-CT (4,24). These radiological findings are not specific to MC and its diagnosis entirely depends on histology. For this reason, MC is usually diagnosed with MC postoperatively. Renal MC is frequently misdiagnosed as renal cell carcinoma, renal pelvic cancer, or other rare malignant tumors, such as Wilms' tumor, in younger cases. In our case, the kidney tumor was initially suspected to be advanced RCC due to IVC thrombus and pulmonary tumor emboli. Low contrast-enhancement in CT and MRI and lack of remarkable findings of blood tests, including leukocyte and neutrophil counts, and serum levels of lactate dehydrogenase

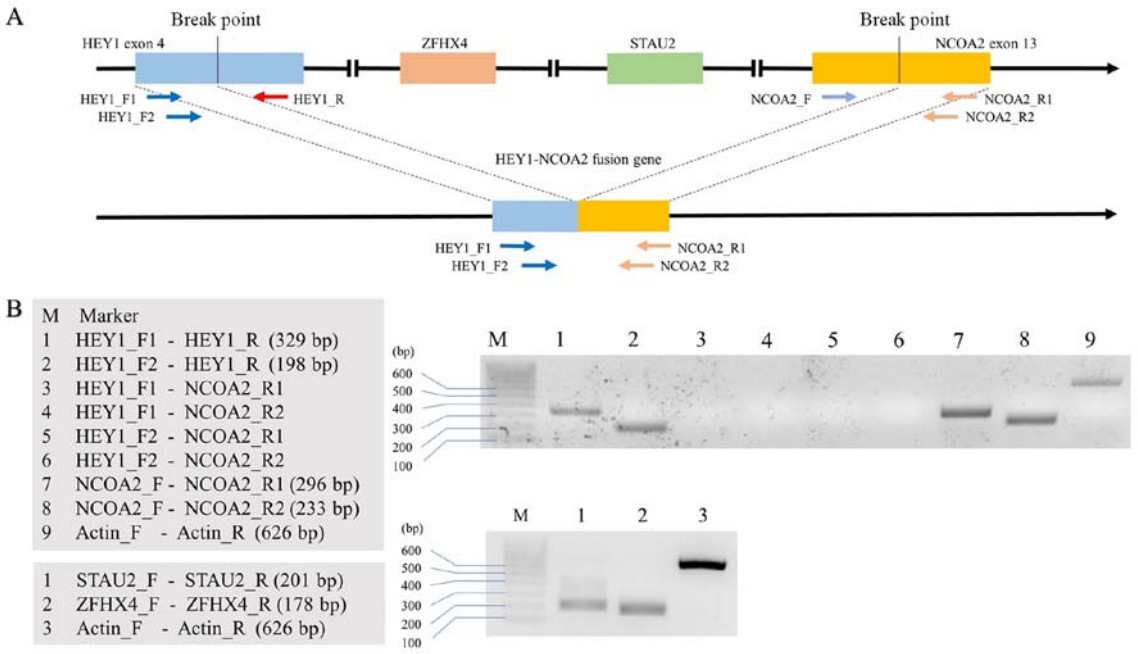

Figure 3. RT-PCR analysis of the *HEY1-NCOA2* fusion. (A) *HEY1* and *NCOA2* gene structures. The upper panel displays the wild type. *HEY1* and *NCOA2* genes are located on chromosome 8q. The *STAU2* and *ZFHX4* genes are located between them. The lower panel displays previously reported fusion genes. (B) Results of RT-PCR. The fusion gene was not detected. The actin band was clearly evident. Normal *NCOA2*, *STAU2* and *ZFX4F* genes were detected. The results affirmed the absence of the fusion gene because those genes should be deleted if *HEY1* and *NCOA2* genes fuses at a certain breakpoint, and also indicated the success of RT-PCR. RT, reverse transcription; *NCOA2*, nuclear receptor coactivator 2; STAU2, staufen double-stranded RNA binding protein 2; *ZFHX4*, zinc finger homeobox 4; *HEY1*, hairy/enhancer-of-split related with YRPW motif 1.

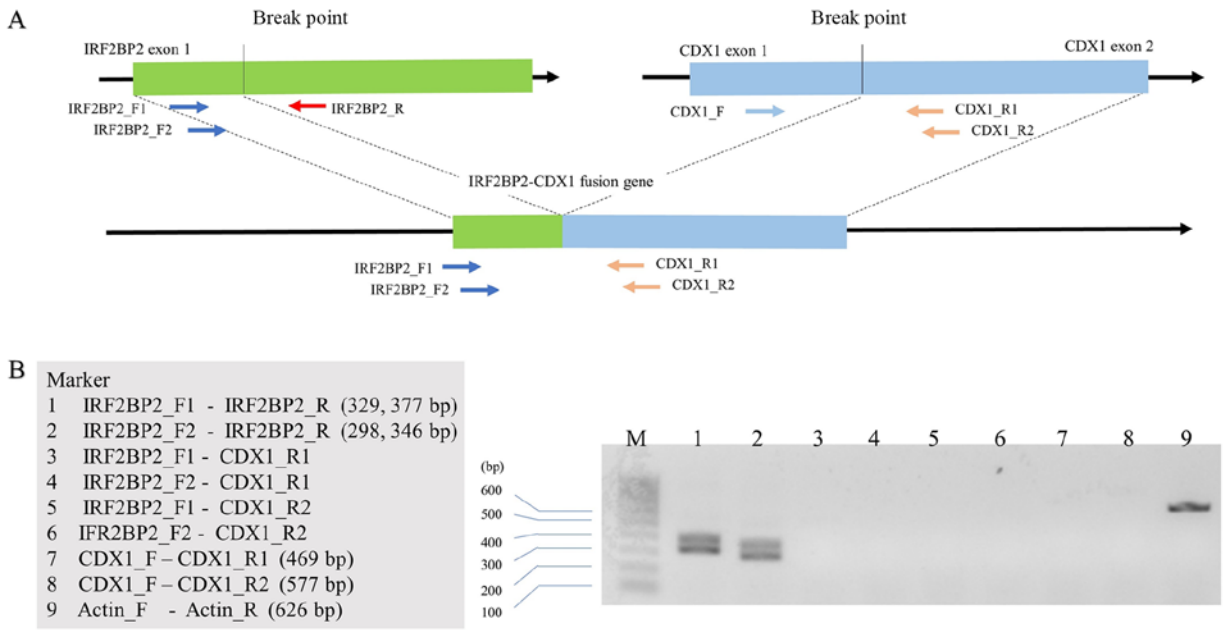

Figure 4. RT-PCR analysis of the *IRF2BP2-CDX1* fusion. (A) *IRF2BP2* and *CDX1* gene structures. The upper panel displays the wild type. *IRF2BP2* is located on chromosome 1q and *CDX1* is located on chromosome 5q. The lower panel displays previously reported fusion genes. (B) Results of PCR. The *IRF2BP2* and *CDX1* gene fusion was not indicated, despite the presence of the actin band. Normal *IRF2BP2* gene was detected as double bands reflecting its two isoforms. Normal *CDX1* was difficult to detect with RT-PCR possibly due to GC richness in the *CDX1* sequence. RT, reverse transcription; *IRF2BP2*, interferon regulatory factor 2 binding protein 2; *CDX1*, caudal type homeobox 1.

and C-reactive protein seem to be atypical for such advanced RCC. Percutaneous needle biopsy helped us to make an accurate pathological diagnosis and formulate sufficient treatment plans for the kidney tumor. However, not the all cases of MC could be successfully diagnosed with needle-biopsied specimens. Typically, MC histology shows a biphasic pattern, which consists of sheets of undifferentiated, round to spindle cell component, and islands of hyaline cartilage. The diagnosis in a small portion of biopsied tissues remains uncertain when the chondroid structures scattered within MC are not

Table II. Case series about MC of the kidney.

No.	Year	Author	Age	Sex	Calcification	Size (cm)	Metastasis[a]	Treatment	Follow	Outcome
1	1981	Pitfield J	61	M	+	12	-	-	2 m	Dead
2	1984	Malhotra CM	27	M	+	9	-	RTx, CTx, Mx	69 m	Alive
3	1991	Karanauskas S	15	M	+	ND	+	ND	ND	ND
4	2001	Gomez-B	52	F	+	8	-	-	1 y	Alive
5	2006	Kaneko T	61	F	+	2.5	-	-	6 y	Alive
6	2008	Dantonello TM	24	F	ND	10	-	NAC	1.3 y	Alive
7	2009	Buse S	23	F	+	7	+	AC, RTx	36 m	Alive
8	2012	Xu H	64	M	-	11	+	-	2 m	Dead
9	2014	Gherman V	67	M	-	30	-	-	9 m	Dead
10	2014	Tyagi R	22	F	-	6.5	+	CTx	ND	Alive
11	2015	Rothberg MB	16	F	+	15.2	+	ND	ND	ND
12	2015	Chen D	17	M	-	15	+[b]	CTx	10 m	Alive
13	2017	Salehipour M	22	M	+	9	-	ND	ND	ND
14	2017	Pani K	24	M	+	8.5	-	AC	6 m	Alive
15	2018	Valente P	35	M	+	20	-	-	18 m	Alive
16	-	Present case	64	F	-	9	-	CTx, RTx	8 m	Dead

[a]At the time of diagnosis. [b]Not proved pathologically. MC, mesenchymal chondrosarcoma; M, male; F, female; NAC, neoadjuvant chemotherapy; AC, adjuvant chemotherapy; CTx, chemotherapy; RTx, radiotherapy; Mx, metastasectomy; ND, no data; m, month; y, year.

Table III. Case series about gene fusion of MC.

		HEY1-NCOA2			*IRF2BP2-CDX1*			
Year	Author	n	Positive	Positive ratio (%)	n	Positive	Positive ratio (%)	Assay
2012	Wang L	15	10	67	-	-	-	FISH, RT-PCR
2012	Nyquist KB	4	3	75	4	1	25	FISH, RT-PCR
2012	Nakayama R	10	8	80	-	-	-	FISH
2013	Fritchie KJ	6	6	100	-	-	-	RT-PCR
2014	Panagopoulos I	1	1	100	-	-	-	RT-PCR
2014	Andersson C	1	1	100	-	-	-	RT-PCR
2014	Moriya K	1	1	100	-	-	-	FISH
2015	Sajjad EA	1	1	100	1	0	0	RT-PCR
2015	Bishop MW	6	6	100	-	-	-	FISH
2016	Cohen JN	2	2	100	-	-	-	RT-PCR
2018	Folpe AL	3	3	100	-	-	-	RT-PCR
2018	Toki S	1	1	100	-	-	-	RT-PCR
Total		51	43	84	5	1	20	

MC, mesenchymal chondrosarcoma; RT, reverse transcription; FISH, fluorescence *in situ* hybridization; *NCOA2*, nuclear receptor coactivator 2; *IRF2BP2*, interferon regulatory factor 2 binding protein 2; *CDX1*, caudal type homeobox 1.

incidentally identified (3). This sampling error would be an intrinsic limitation in the histologic diagnosis of biopsied tissue.

Chromosomal aberration of *HEY1-NCOA2* fusion is reportedly specific to MC and can be a highly sensitive diagnostic tool (3,5,6). Table III presents 12 articles on the gene fusion in MC that were published in medical literature (3,5,6,8,25-32). The *HEY1-NCOA2* gene fusion is supposed to be absent in another histologic type of sarcoma (3,5,6), but its diagnostic sensitivity is not perfect (67-100%) despite the characteristic histology of MC (Table III). Interestingly, the *IRF2BP2-CDX1* gene fusion in MC may be exclusive to the *HEY1-NCOA2* fusion, suggesting heterogeneous oncogenesis of MC (8,28). In the present study,

we failed to detect the *HEY1-NCOA2* and *IRF2BP2-CDX1* gene fusions in renal EMC. Herein, CDX1 expression appeared to be absent in our case (Fig. 4). Specifically expressed in the intestines, CDX1 is a transcription factor to induce epithelial cell differentiation (33,34). In gastric, colorectal and hepatocellular carcinomas, CDX1 acts as a tumor suppressor and low expression of CDX1 are related clinically to poor prognosis of the malignancies (34). Thus, no expression of CDX1 might potentiate malignant nature in the present renal MC. Our results support the possible existence of another oncogenic mechanism in such fusion-negative cases, reflecting on the genetic heterogeneity in MC tumorigenesis to a typical microscopic phenotype.

It might be better to analyze *HEY1, NCOA2, STAU2* and *ZFHX4* gene expression using the adjacent or normal kidney tissues together with the renal MC for comparison (Fig. 3B). However, we were unable to do additional experiments due to the paucity of the freshly-frozen tissue samples left behind in store. This is a limitation in interpretation of the present results.

In conclusion, we report the first case of primary renal EMC, which progressed to form tumor thrombus in IVC and pulmonary arteries at diagnosis. On pathological inspection of surgical specimens, the tumor exhibited typical microscopic appearance of MC. However, the presence of the *HEY1-NCOA2* nor *IRF2BP2-CDX1* gene fusions in the tumor was detected by RT-PCR, suggesting the possibility of genetically heterogeneous pathways to MC oncogenesis. Further studies will be needed to confirm the present findings and reinforce the molecular diagnosis of MC.

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Availability of data and materials

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

Authors' contributions

AY contributed to conception and design of the study, acquisition of data, interpretation of data and drafted the initial and revised versions of the manuscript and is the corresponding author. OI did conception and design of the study, interpretation of data and assisted with the writing of several drafts of the manuscript. HI participated in analysis and interpretation of data especially for the technical aspects. TK and MY performed the histological examination of the tumor and revised the pathological section of study. SN contributed to the conception, design and intellectual content such as genomic abnormality and tumorigenesis. NT contributed to conception, design and supervision of the study and made final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the principles embodied in the Declaration of Helsinki and approved by the Ethical Committee of Yamagata University Faculty of Medicine (approval no. 28, 2019). Written informed consent for publication was provided by the patient.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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