Case Report

SMARCA2/BRM-Deficient Undifferentiated/Rhabdoid Carcinoma of Unknown Primary Site

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Keywords

Cancer of unknown primary site · Undifferentiated · SWItch/sucrose nonfermentable · SMARCA2 · BRM

Abstract

Undifferentiated neoplasms of unknown primary sites are rare. It is difficult to identify their characteristics and determine the appropriate chemotherapy regimen to be used. Undifferentiated/rhabdoid carcinoma is reportedly associated with loss of SWI/SNF chromatin remodeling complexes, such as observed in SMARCA4-deficient tumors. However, little is known about SMARCA2/BRM-deficient tumors. A 48-year-old man presented with low back pain. Computed tomography (CT) revealed intraperitoneal lymph nodes and multiple bone metastases that invaded the thoracic and lumbar spinal canals. The primary tumor was not identified despite the standard diagnostic methods being used. CT-guided needle biopsy of right iliac bone metastasis showed that the tumor had an undifferentiated/rhabdoid morphology. Immunostaining revealed that the tumor was SMARCA2/BRM-deficient despite both SMARCB1/INI1 and SMARCA4/BRG being retained. We found no genomic alterations during domestic next-generation sequencing panel profiling, which can identify 114 genes. Thus, he was diagnosed with SMARCA2/BRM-deficient undifferentiated/rhabdoid carcinoma of an unknown primary site with multiple bone metastases and intraperitoneal lymph node metastasis. We administered radiotherapy to the thoracic and lumbar spine to improve cord compression, and carboplatin (CBDCA) and paclitaxel regimen was chosen as first-line chemotherapy, but this was discontinued due to an anaphylactic shock. We then selected the CBDCA and gemcitabine regimens; however, the patient did not continuously receive the regimen due to myelosuppression.

Radiation therapy effectively relieves pain and cord compression. To our knowledge, this is the first reported case of SMARCA2/BRM-deficient undifferentiated/rhabdoid carcinoma of an unknown primary site. Further studies are needed to improve SWI/SNF-deficient tumor identification methods.

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Introduction

Cancer of unknown primary site (CUP) is a histologically confirmed type of metastatic cancer for which clinicians cannot detect a primary lesion despite using a standard diagnostic approach. Undifferentiated neoplasms of unknown primary sites comprise approximately less than 5% of all CUP [1], and no appropriate chemotherapy regimen is available for their treatment. Recently, gene expression profiling has been useful to confirm some frequent alterations and support novel therapeutic approaches for the driver mutation in various cancers. In CUP, identification of molecular characteristics by a multiple gene assay triggers to assess the primary lesion and find appropriate molecular target agents.

In undifferentiated neoplasms, tumors with undifferentiated/rhabdoid morphology on pathological findings have been associated with abnormalities in SWItch/sucrose nonfermentable (SWI/SNF) chromatin remodeling complexes [2], which comprise multiple subunits (e.g., a BRG-encoding gene in SMARCA4, a BRM-encoding gene in SMARCA2, an INI1-encoding gene in SMARCB1, and ARID1A) [3]. SWI/SNF-deficient tumors include the following: SMARCA4-deficient thoracic sarcoma [4]; small-cell carcinoma of the ovary hypercalcemic type, which is deficient in SMARCA4 [5]; and malignant rhabdoid tumor, which is deficient in SMARCB1 [6]. However, little is known about SMARCA2/BRM-deficient tumors. In the present study, we report a case of SMARCA2/BRM-deficient undifferentiated/rhabdoid carcinoma of an unknown primary site.

Case Presentation

A 48-year-old man presented to a local hospital with complaints of low back pain. His medical history included hypertension, diabetes mellitus, and bronchial asthma. His hypertension was controlled with irbesartan 100 mg, bisoprolol 2.5 mg, amlodipine 5 mg, and diabetes mellitus with tofogliflozin 20 mg. Furthermore, his family medical history revealed no history of any malignant tumors. Computed tomography (CT) revealed swollen intraperitoneal lymph nodes and multiple bone masses in the spine, ribs, right scapula, left clavicle, sternum, bilateral ilia, left pubic bone, left ischium, and left femur. Spine magnetic resonance imaging showed invasion into the spinal canal at the Th4 and Th11 levels (shown in Fig. 1). The primary lesion was not found on CT, and upper gastrointestinal endoscopy and colonoscopy also did not reveal the primary tumor. He was suspected of having CUP and then referred to our hospital after 2 months of his first visit to the previous hospital. CT-guided needle biopsy of the right iliac bone metastasis was performed, and histopathological examination revealed diffuse growth of tumor cells with a high nuclear-cytoplasmic ratio. Moreover, some tumor cells with unevenly distributed nuclei were also observed. Scattered mitotic images of tumor cells were observed, and some tumor cells with large nuclei were included. Importantly, some tumor cells had rhabdoid features (shown in Fig. 2a, b). Immunohistochemistry revealed AE1/AE3, CK7, CK20 (focal), vimentin, and GATA3 positive markers but was negative for CDX-2, LCA, ALK, MUM1, HMB45, uroplakin II, and p63. Given these results, the pathologist ruled out urothelial

Fig. 1. STIR mode of the spine MRI showing the cord compressions in the Th4 and Th11 levels (arrows). STIR, short T1 inversion recovery; MRI, magnetic resonance imaging.

Fig. 2. HE stains and IHC of histopathology. Histopathology of biopsy for his right iliac bone metastasis (a, b); HE stains (c, d); IHC positive for SMARCB1 (INI1) and SMARCA4 (BRG1); IHC negative for SMARCA2 (BRM) (e).

carcinoma, sarcoma, malignant lymphoma, and malignant melanoma. Additional immune staining showed that SMARCB1 (INI1) and SMARCA4 (BRG1) were retained (shown in Fig. 2c, d), but SMARCA2 (BRM) expression was lost (shown in Fig. 2e). We used the OncoGuide™ NCC Onco-panel System (Sysmex Corporation), which facilitates the identification of variants of 114 cancer-related genes (Table 1) via next-generation sequencing (NGS) [7]. This gene panel test included SMARCA4 and SMARCB1, but not SMARCA2. No genomic alterations were found in the 114 genes included in the panel. Thus, he was diagnosed with SMARCA2/BRM-deficient undifferentiated/rhabdoid carcinoma of an unknown primary site with multiple bone

Table 1. Genes examined using the NCC Oncopanel test

Mutations and copy number alterations for all exons					Fusions
ABL1	CRKL	IDH2	NF1	RAC2	ALK
ACTN4	CREBBP	IGF1R	NFE2L2/Nrf2	RAD51C	AKT2
AKT1	CTNNB1	IGF2	NOTCH1	RAF1/CRAF	BRAF
AKT2	CUL3	IL7R	NOTCH2	RB1	ERBB4
AKT3	DDR2	JAK1	NOTCH3	RET	FGFR2
ALK	EGFR	JAK2	NRAS	RHOA	FGFR3
APC	ENO1	JAK3	NRG1	ROS1	NRG1
ARAF	EP300	KDM6A/UTX	NTRK1	SETBP1	NTRK1
ARID1A	ERBB2/HER2	KEAP1	NTRK2	SETD2	NTRK2
ARID2	ERBB3	KIT	NTRK3	SMAD4	PDGFRA
ATM	ERBB4	KRAS	NT5C2	SMARCA4/BRG1	RET
AXIN1	ESR1/ER	MAP2K1/MEK1	PALB2	SMARCB1	ROS1
AXL	EZH2	MAP2K2/MEK2	PBRM1	SMO	
BAP1	FBXW7	MAP2K4	PDGFRA	STAT3	
BARD1	FGFR1	MAP3K1	PDGFRB	STK11/LKB1	
BCL2L11/BIM	FGFR2	MAP3K4	PIK3CA	TP53	
BRAF	FGFR3	MDM2	PIK3R1	TSC1	
BRCA1	FGFR4	MDM4	PIK3R2	VHL	
BRCA2	FLT3	MET	POLD1		
CCND1	GNA11	MLH1	POLE		
CD274/PD-L1	GNAQ	MTOR	PRKCI		
CDK4	GNAS	MSH2	PTCH1		
CDKN2A	HRAS	MYC	PTEN		
CHEK2	IDH1	MYCN	RAC1		

metastases and intraperitoneal lymph node metastasis. To alleviate the symptom of cord compression, we performed radiation therapy to treat the thoracic and lumbar spine metastasis (30 Gy in 10 daily fractions of 3 Gy) before chemotherapy and left femur metastasis to prevent bone fracture (39 Gy in 13 daily fractions of 3 Gy) after about 1-month of the first visit to our hospital. We began administering a monthly subcutaneous injection of denosumab and selected carboplatin (CBDCA) and paclitaxel (CBDCA area under the curve [AUC] 5 on day 1 plus paclitaxel 175 mg/m² on day 1 every 3 weeks) as first-line chemotherapy after 3 weeks of radiation therapy. Owing to thrombocytopenia, CBDCA was reduced to an AUC of 4. The regimen was stopped due to an anaphylactic shock occurring immediately after paclitaxel administration. We selected a CBDCA and gemcitabine (GEM) regimen (CBDCA AUC 4 on day 1 plus GEM 750 mg/m² on day 1 every 3 weeks) as the second chemotherapy regimen. However, the patient did not continuously receive this regimen due to the recovery delay from neutropenia and thrombocytopenia. After 11 weeks of two courses of chemotherapy, CT revealed that the multiple bone metastases increased and enlarged, except for the irradiated lesion and the presence of brain, right axillary lymph nodes, and mediastinal lymph node metastases. The irradiated spine lesions showed osteoblastic bone formation (shown in Fig. 3). Due to the poor response to chemotherapy, the patient died of disease progression approximately 6 months after initiating first-line chemotherapy.

Fig. 3. The osteolytic lesion at the lumbar spine improved after radiation therapy.

Discussion/Conclusion

To our knowledge, this is the first report on SMARCA2/BRM-deficient undifferentiated/rhabdoid carcinoma of an unknown primary site. Similar to the present case, SMARCA4-deficient thoracic sarcoma is also frequently deficient in SMARCA2 [4], has an undifferentiated rhabdoid morphology [8], and has a poor prognosis [4]. Deleterious mutations of the SWI/SNF complex indicate tumor-suppressive function loss [9]. Tumors with SWI/SNF deficiency and undifferentiated rhabdoid morphology include small-cell carcinoma of the ovary hypercalcemic type and malignant rhabdoid tumor. Tumors with SWI/SNF deficiency and undifferentiated rhabdoid morphology have also been reported in the uterus [10] and gastrointestinal tract [11]. Tumors with reported SMARCA2 deficiency include non-small-cell lung cancer, prostate cancer, and gastric cancer [3]. Inactivating mutations in several SWI/SNF subunits have recently been frequently identified in various cancers. The importance of altered levels and/or aberrant function of SWI/SNF subunits in carcinogenesis is not fully understood. Approximately 15% of all cancers display numerous aberrations in SMARCA2 abundance or impairment, which may lead to cancer development or progression [12]. The relationship between SWI/SNF deficiency and undifferentiated rhabdoid morphology is unclear. SMARCA2-deficient undifferentiated/rhabdoid carcinoma was previously only seen in the gallbladder [13]. This reported case had a highly aggressive course, similar to that of our case.

Although the efficacy of the CBDCA and GEM regimens could not be assessed due to the low intensity of the treatment for myelosuppression in our case, both SMARCA2/BRM-deficient undifferentiated/rhabdoid carcinoma and SMARCA4-deficient thoracic sarcoma may be chemoresistant. SMARCA4-deficient thoracic sarcoma is refractory to many kinds of chemotherapy regimens, except for a transient response to Adriamycin-ifosfamide treatment in 1 case [4]. Presently, radiation therapy is very effective in preventing spinal cord compression and relieving lumbar pain. Thus, radiation therapy for symptom relief may be an effective treatment option.

Standard treatment for undifferentiated carcinoma of an unknown primary site has not yet been established. Some clinical studies on CUP have demonstrated the efficacy of combination chemotherapy, such as CBDCA and paclitaxel [14]. However, the results were unsatisfactory with poor overall survival of approximately 1 year, and we should improve the clinical outcome in CUP. A recent phase II study revealed that site-specific and targeted therapy based

on molecular profiling by NGS for CUP might improve clinical outcomes [15]. It is highly expected that treatment strategies for undifferentiated carcinomas of unknown primary sites will be decided based on the genomic findings of comprehensive genomic profiling to assess the primary site and explore possible targeted therapeutic agents. In addition, the association between genetic alterations and pathological findings will benefit the classification of CUP cases.

It has not been well known that undifferentiated carcinoma of the unknown primary site may include SWI/SNF-deficient tumor. SWI/SNF-deficient tumor is undifferentiated/rhabdoid morphology, aggressive clinical course, and refractory to the platinum agent. Thus, identifying this tumor from undifferentiated carcinoma of an unknown primary site is very important. Immunostaining for SMARCA4, SMARCA2, and SMARCB1 may be useful for diagnosing SWI/SNF-deficient tumors and the decision of clinical management, if the histopathological findings show undifferentiated/rhabdoid cells. We cannot control the progression of SWI/SNF tumors with the chemotherapy of the platinum doublet regimen. We expect the palliative effect of symptoms with RT. We should search for suitable molecular target agents with comprehensive genomic profiling or examine the effectiveness of immune therapy. We should collaborate with the pathologists to identify SWI/SNF-deficient tumors from poorly differentiated or undifferentiated carcinoma of the unknown primary site and to accumulate more cases and look for further findings to better establish an effective treatment strategy.

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Statement of Ethics

This article does not contain any studies with human participants performed by any of the authors. Our institutional Ethics Committee approved the use of his medical record for this case report. The patient provided written informed consent for the publication of this case report and all accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y.T. wrote the manuscript. Y.T. and A.T. managed the patient while in the ward. K.S., K.S., and Y.Y. provided some advice in clinical management. H.I., K.U., and M.U. were the pathologists who made the diagnosis of this tumor and made slides with histopathology pictures. T.M. and I.T. were the department heads and approved all medical decisions. All the authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author (Y.T.) upon reasonable request.

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