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Case Report

Pulmonary Artery Intimal Sarcoma in a Patient with Lynch Syndrome: Response to an Immune Checkpoint Inhibitor

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Keywords
Lynch syndrome · Immune checkpoint inhibitor · Intimal sarcoma

Abstract
Intimal sarcoma is an extremely rare mesenchymal tumor arising in the great vessels. To date, intimal sarcoma has not been reported in patients with Lynch syndrome (LS), even though this syndrome lacks DNA mismatch repair ability genetically and is prone to various malignancies. This patient was diagnosed with LS by the Revised Amsterdam Criteria II, and she suffered from intimal sarcoma in the left pulmonary artery. She had a germline missense variant of *PMS2* (c.1399G>A, pV467I) which is classified as a variant of unknown significance. In her intimal sarcoma, PMS2 expression was decreased. Additionally, it exhibited microsatellite instability and a high tumor mutational burden (69 mutations/Mb) which are features of mismatch repair deficiency, although *PMS2* (c.1399G>A, pV467I) missense is a variant of unknown significance. The metastatic lesions of intimal sarcoma in this patient responded heterogeneously to pembrolizumab, an immune checkpoint inhibitor. Cytotoxic agents and radiation were also effective for some metastatic lesions, but some lesions, including her liver metastases, were

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resistant. The hypermutable nature of the LS genotype might acquire resistance to an immune checkpoint inhibitor and other cytotoxic agents such as occurred with her liver metastases.

Introduction

Lynch syndrome (LS) is an autosomal dominant hereditary cancer syndrome [1]. The responsible genes for LS are mismatch repair genes including *MLH1*, *MSH2*, *PMS2*, and *MSH6* [1]. The loss of these genes' functions in a patient's germline induces LS. Mismatch repair deficiency (MMR-D) can induce carcinogenesis. Genetically, MMR-D induces microsatellite instability (MSI), resulting in frequent mutations in the tumor which is called tumor mutational burden (TMB)-high. MSI and TMB-high can be hallmarks of LS. LS can be diagnosed by phenotype according to various criteria. One criterion is the Revised Amsterdam Criteria II, which states that there should be at least three relatives with any LS-associated cancer. One should be a first-degree relative of the other two. At least two successive generations should be affected. At least 1 patient should be diagnosed before age 50. LS-associated cancers include colorectal cancer (CRC) as well as cancers of the endometrium, small bowel, ureter, or renal pelvis [1]. Clinically, LS-associated cancers with MSI and TMB-high are sensitive to immune checkpoint inhibitors (ICIs). However, some malignancies, such as lymphoma and neuroendocrine cancers, are rarely observed in patients with LS [2, 3].

Intimal sarcoma (IS) is an undifferentiated sarcoma frequently arising in the great vessels such as the pulmonary artery [4]. The incidence of this tumor in the pulmonary artery is 0.001% [5]. Additionally, sarcoma itself is very rare in LS with a frequency of approximately 1% [6]. To the best of our knowledge, this is the first report describing IS developing in a patient with LS. This report describes IS arising in the pulmonary artery with a new LS pedigree meeting Revised Amsterdam Criteria II, the genetic features of this new LS pedigree, and the responses to treatment.

Case Presentation

A 38-year-old woman complaining of dyspnea and fever was seen by her local doctor in September, 200X, and was transferred to this hospital. Chest computed tomography (CT) indicated a defect in the left pulmonary artery and a lung tumor (Fig. 1a–c). Vessel catheterization revealed obstruction of the left pulmonary artery by the tumor. Biopsy indicated that this tumor was composed of abnormal cells. In January, 200X + 1, the left pulmonary artery and the left lung were completely resected (Fig. 1d, e). Histopathological examination found that the resected tumor was vimentin (+), beta-catenin (+), CD99 (+), MDM2 (+), CDKN2A (+), CDK4 (+), PDGFR2 (+), desmin (partially +), smooth muscle actin (−), CD34 (−), Factor VIII (−), c-Kit (−), EMA (−), S-100 (−), cytokeratin AE1/AE3 (−), and the Ki-67 index was 35% (Fig. 1f–j). The tumor was diagnosed as an IS. The right lung artery was reconstructed with a graft (Fig. 1k). After rehabilitation, she was seen in consultation by this department in June, 200X + 1. At that time, CT examination showed that the tumor remained in the mediastinum around the aortic arch, and multiple metastases were found in the right lung, liver, brain, pelvic cavity, right hip joint, left quadriceps, and abdominal wall (Fig. 1l, m). She had suffered from CRC at age 15. She also had a family history of multiple types of cancer (Fig. 2). This situation met the Revised Amsterdam Criteria II, and she was diagnosed with LS. Next, MSI and MMR proteins were examined immunohistochemically in the primary tumor.

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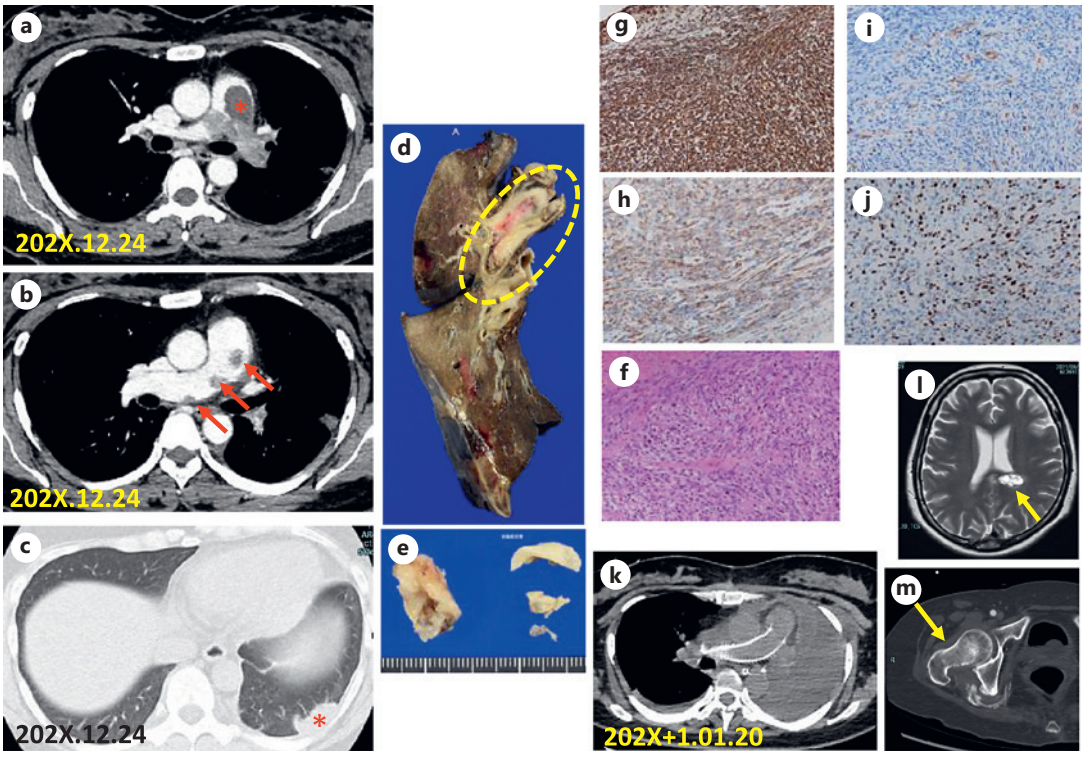

Fig. 1. Clinicopathological features. **a** Thoracic image CT. The red asterisk indicates the tumor in the left pulmonary artery. **b** Additional thoracic image CT. The red arrows indicate the tumors. **c** CT image of the lower lung. The red asterisk indicates the tumor in the left lung. **d** The resected tumor and the left lung. The yellow dashed circle indicates the tumor in the left pulmonary artery. **e** Tumors in the left pulmonary artery. **f** H&E staining of the tumor. Immunohistochemistry images of vimentin (**g**), beta-catenin (**h**), smooth muscle alpha (**i**), and Ki-67 (**j**). **k** Thoracic CT after surgery. CT image of the brain metastasis (**l**) and the right hip joint (**m**).

MSI-high was found as predicted (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000528682). While MSH2 and MSH6 proteins existed (Fig. 3a, b), PMS2 and MLH1 proteins were decreased (Fig. 3c, d). PD-L1 was also positive by clone 28–8 antibody (Abcam, Cambridge, UK) (Fig. 3e). The tumor proportion score was >90%. The cancer gene panel test of OncoGuideTM NCC Oncopanel System was performed on the primary IS as well as the lymphocytes. The results are shown in Table 1. The TMB was 69 mutations/Mb. *PMS2* (NM_000535.5, c.1399G>A, pV467I) was detected in the germ line among the MMR genes (online suppl. Fig. 2). Its allele frequency was 0.50. However, PMS2 (pV467I) is still classified as a variant of unknown significance (VUS) [7]. This *PMS2* (c.1399G>A) germline variant was confirmed by DNA sequencing (Falco biosystems). Based on these data, pembrolizumab (300 mg) was administered intravenously every 3 weeks beginning in June, 200X + 1. Stereotactic radiosurgery was also applied to the brain metastasis. Three months later, the effect was evaluated by CT with heterogenous results. The metastases in the lung and pelvic cavity had shrunk, but the metastases in the liver and abdominal wall had enlarged (Fig. 4a–d). Next, systemic chemotherapy was changed from pembrolizumab to paclitaxel + carboplatin, gemcitabine + docetaxel, and doxorubicin, sequentially. Paclitaxel + carboplatin and gemcitabine + docetaxel were effective on all metastases except for the liver. External beam radiotherapy was applied to the right hip joint (30 Gy/10 fractions) and stereotactic radiosurgery to the lateral ventricle lower horn of the brain metastasis (23 Gy/1 fraction). Radiotherapy was presumed to be able to control these lesions.

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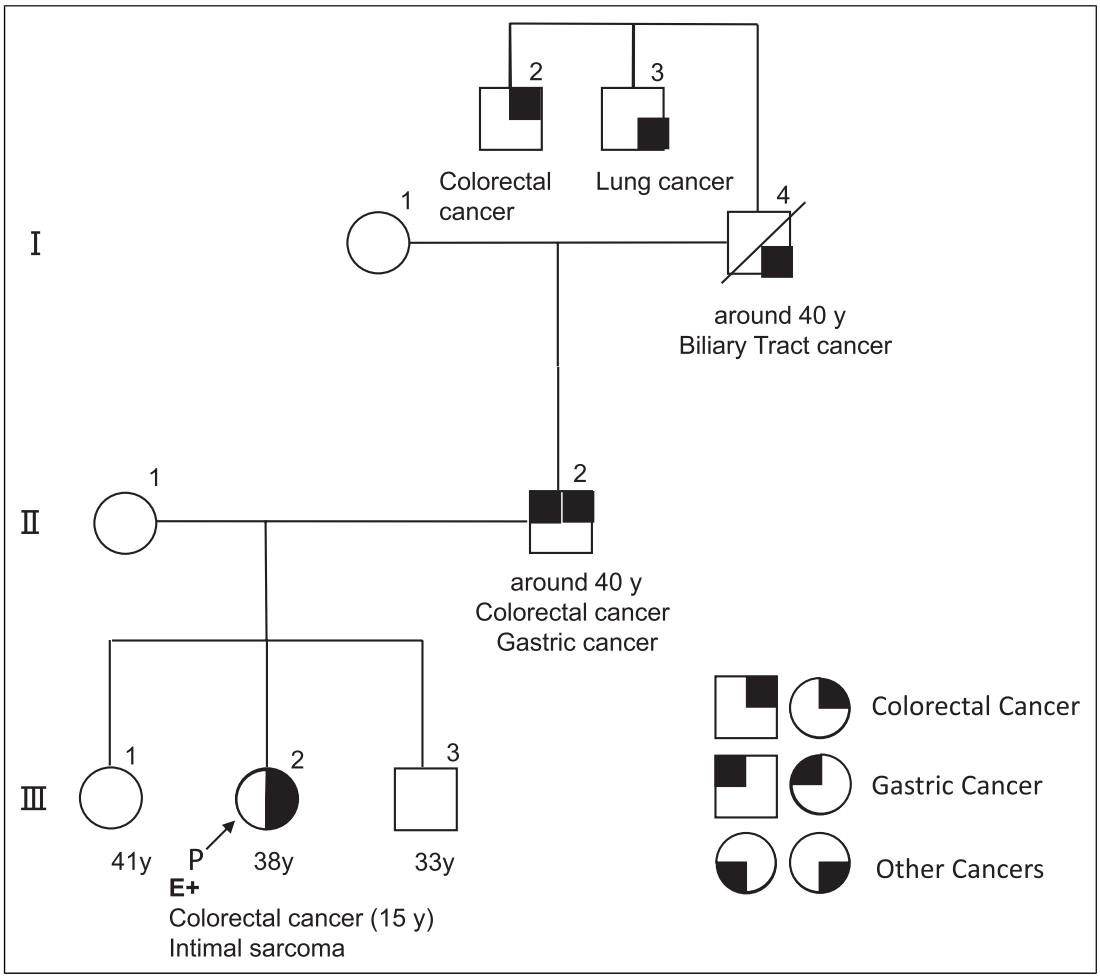

Fig. 2. Family tree of the pedigree. Each closed quarter of rectangle and quadrant indicates cancers in the figure. The proband (P) tested for bearing of the germline variant *PMS2* (c.1399G>A, pV467I) is indicated as E+.

Although these treatments exhibited some clinical benefit, the patient died in March, 200X + 2, 17 months after the onset of clinical disease.

Discussion

This report documents a new LS family in Akita, Japan. The genetic testing of the patient indicated the presence of PMS2 (c.1399G>A) in her germline. This variant has not been reported in the database previously, but *PMS2* (c.1399G>T) has been reported [7]. These two missense variants have a similar effect on amino acid translation resulting in PMS2 (pV467I). PMS2 (pV467I) has been reported 7 times in the Clinical Variations database [7]. This variant has been recognized as a VUS in 6 of the 7 cases (3 were detected in patients with LS). Of the 7 cases, 1 was a benign variant of the 7 which has been related to LS [7]. Including this patient in the database, this variant is related to LS in 4 out of 5 cases. In the COSMIC database, a missense substitution occurs most frequently (25%) in the *PMS2* gene [8]. In another report, 28 missense mutations were identified in 105 *PMS2* variants (26.7%) [9]. According to the Tohoku Medical Megabank Organization, Tohoku University, the allele frequency of this *PMS2*

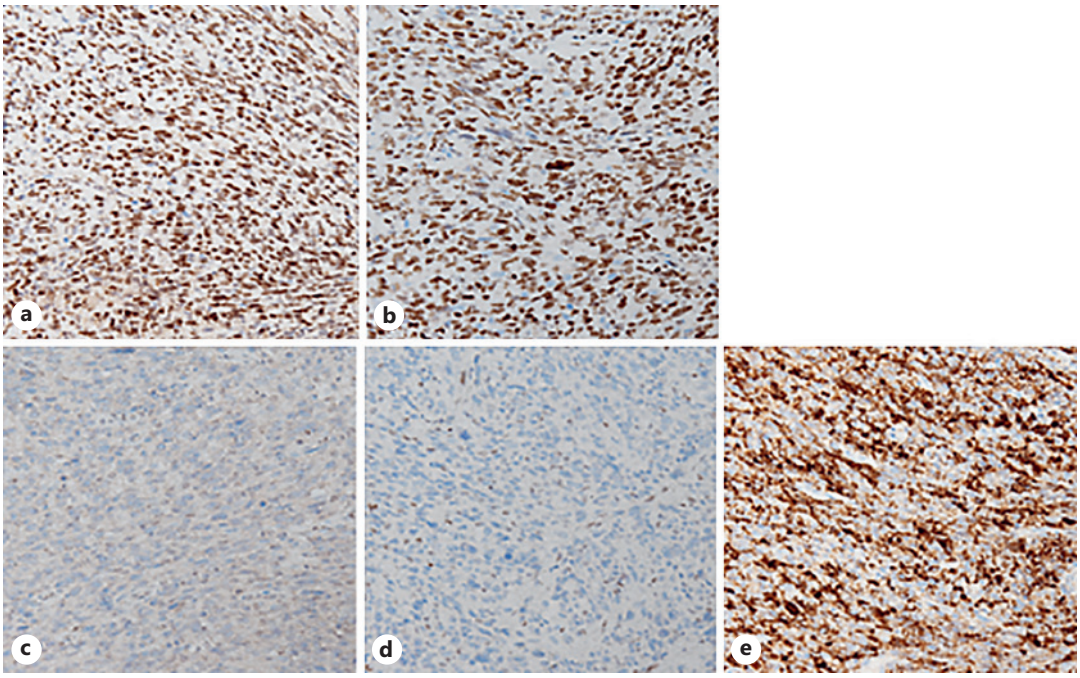

Fig. 3. Immunohistochemistry of MMR proteins and PD-L1 in the tumor. **a** MSH2. **b** MSH6. **c** PMS2. **d** MLH1. **e** PD-L1.

(c.1399G>A) in the general Japanese population is as low as 0.04% [10]. MSI-high, TMB-high, and the decreased immunoreactivity for both PMS2 and MLH1 were confirmed in the IS specimen of this patient. In contrast, no variants of MLH1 have been detected in IS or in her germline. Although the methylation status of the *MLH1* gene in IS was not examined, the loss of MLH1 protein may be attributed to the disorder of the promoter methylation status of *MLH1*. Furthermore, PMS protein may be lost together with MLH1 in IS. It has been reported that the loss of MLH1 occurred prior to the loss of PMS2 [11]. The fragility or the functionality of PMS2 (pV467I) remains unknown, although this variant is the sole variant in 4 MMR detected in her germline, and her family history meets the Revised Amsterdam Criteria II. The pathogenicity of the PMS2 (pV467I) variant remains controversial. It was reported that the onset of carcinogenesis of PMS2-related LS ranged from 24 to 80 years of age (peak at 51.7 ± 11.7 years) [12]. The DNA samples from the other family members of this pedigree were not available. The onsets of carcinogenesis in this pedigree occur rather sooner than the average when they were hypothesized as cases of PMS2-related LS. Especially, the onset of CRC of this provand at the age of 15 years is very early. We could not analyze her CRC as the sample was not available. There were 6 missense variants in her germline, except PMS2 (pV467I), including AXIN1 (pA740T), BARD1 (pS186G), and PALB2 (pE837K), all of which are VUSs. AXIN1 is a tumor suppressor, and point mutations have been reported to contribute to CRCs [13]. BARD1 has a dual function of carcinogenesis, either tumor suppressive or oncogenic [14]. Germline PALB2 variants have been associated with cancer risks, but not with CRCs [15]. They might be responsible for this early onset of CRC. To examine the functions of PMS2 (pV467I), genetic modification might be necessary, using the CRSPR/CAS9 method in embryonic stem (ES) cells so as to substitute the PMS2 (c.1399G) allele to PMS2 (c.1399A), developing homozygous ES cells bearing the PMS2 (c.1399A) allele to enable the evaluation of the fragility and MMR functions of PMS2 (pV467I) in vitro, as described elsewhere [16]. To the best of our knowledge, this is the first report of IS arising in a patient with LS. It remains

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Table 1. Results of cancer gene panel test

1. MSI	(+)	
2. TMB	69.00 mutations/Mb	
3. somatic variants (IS)	Gene function	Annotation
NF1: pP678fs*10	Tumor suppressor	Pathogenic
TP53: pR273C	Tumor suppressor	Pathogenic
CREBBD: pI1084fs*15	Transcriptional activation	No evidence
MEN1: pR521fs*43	Tumor suppressor	Pathogenic
MSH6: pF1088fs*5	Mismatch repair	No evidence
ARID2: pL97P	DNA binding protein	VUS
CDK4: pN41S	Cell cycle regulation	VUS
ERBB3: pH584N	Growth factor	VUS
ERBB4: pH1118R	Growth factor	No evidence
FBXW7: pG9C	Ubiquitination	VUS
KDM6A: pA482T, pA371V	DNA methylation	VUS
MAP3K1: pN382I	Signal transducer	VUS
NOTCH1: pT1897M	Signal transducer	No evidence
NRG1: pR220H	Signal transducer	No evidence
NTRK2: pL346F	Signal transducer	VUS
PALB2: pV1036I	Tumor suppressor	VUS
POLD1: pV751L	DNA polymerization	VUS
TSC2: pQ1665R	Tumor suppressor	VUS
NFE2L2: pH416R	Transcriptional factor	VUS
4. Germline variation (allele frequency)	Gene function	Annotation
PMS2: pV467I (0.50)		VUS
AXIN1: pA740T (0.48)	Mismatch repair negative growth regulation	VUS
BARD1: pS186G (0.48)	Tumor suppressor	VUS
CD274: pR260C (0.49)	Immunosuppression	VUS
JAK2: pQ955R (0.40)	Cytokine signaling	VUS
MAP3KI: pR1238K (0.46)	Signal transducer	VUS
PALB2: pE837K (0.46)	Tumor suppressor	VUS

Gene function and annotation are referred from the results of cancer gene panel test.
MSI, microsatellite instability; TMB, tumor mutational burden; VUS, variant of unknown significance.

unclear whether IS can be controlled with an ICI. However, in this case there was MSI-high and TMB-high. As pembrolizumab, an anti-PD-1 antibody, has been approved for use in tumors bearing these features, this drug was used to treat multiple metastatic lesions. Responses to this drug differed for different lesion sites. For instance, the lung and intrapelvic metastases shrank, but the liver and abdominal wall metastases did not.

Overall, the lesions were judged to be progressive disease after 3 months of treatment. The response rate of the TMB-high subgroup in the study by Marabelle et al. [17] was 28%, whereas that of the non-TMB-high subgroup was 6% in the trial of advanced solid tumors treated with pembrolizumab. The response rates of MMR-D tumors to ICIs varied from 31% to 53% in a study by Adam et al. [18]. Le reported that the overall response rate of LS-related

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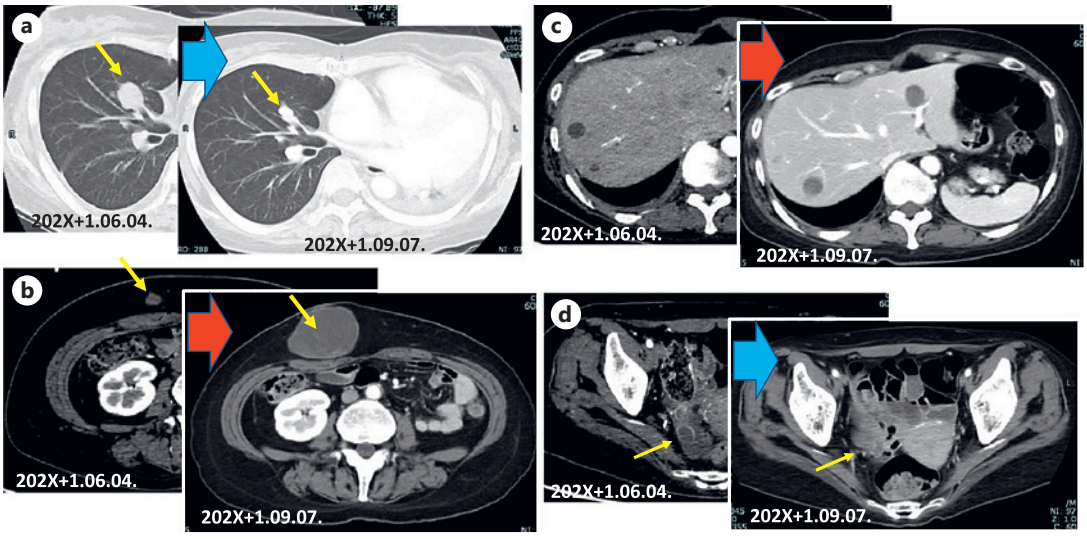

Fig. 4. CT images pre- and posttreatment with pembrolizumab. **a** Lung metastasis. **b** Abdominal wall metastasis. **c** Liver metastasis. **d** Disseminated tumor in the pelvic cavity. The blue arrow indicates the shrunken tumors. The red arrow indicates the enlarged tumors.

cancers with ICIs was 27%, whereas that of sporadic MSI tumors was 100% [19]. In a systemic review of 77 cases of the LS-related cancers, the overall response rates of LS-related CRC with ICIs and LS-related non-CRC were 63% and 29%, respectively [20]. Some LS-related cancers may not respond to ICIs. The underlying mechanism of ICI resistance remains to be fully understood. However, while speculation about this resistance includes defects in antigen presentation and additional inhibitory checkpoints, approximately ~25% of the causes remain unknown [18]. These pathways include genetic alterations of the immune evasion mechanisms in HLA genes, B2M. JAK1/2, PTEN, and Wnt signaling pathway genes and TAP1 genes [21]. The heterogeneity of the responses to ICI noted in this case indicates that MMR-D tumors are sensitive to ICIs, although this may easily change to resistance to ICI monotherapy due to their hypermutable nature. We could not obtain any metastatic tumor samples from the resistant metastatic lesions for ICI as well as sensitive lesions. In addition, we could not approach the underlying biological mechanisms of heterogeneous responses.

In a systemic review of LS-related non-CRC studies, the progression-free survival was reported to be 15.2 months [20]. In our LS-related IS, progression-free survival was only 3 months. IS arising in an LS patient bearing a *PMS2* (c.1399G>A, pV467I) missense variant, representing MMR-D, heterogeneously responded to an ICI. However, some of the metastases showed the development of resistance. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

Acknowledgment

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Statement of Ethics

Study approval was approved by the Ethical Committee of Akita University (Examination of responsible and related genes involving familial cancers, #1191) and a written informed

consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images. This study was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Mounai Y, Yoshida T, Ito S, Fukuda K, Shimazu K, Taguchi D, Shinozaki H, Takagi D, Imai K, Yamamoto H, and Minamiya Y treated the patients. Nanjyo H. performed histopathological analysis. Mounai Y mainly described this manuscript. Shibata H. overviewed this study.

Data Availability Statement

All data in this study are included in this article. Further inquiries can be directed to the corresponding author.

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