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Case Report

Dedifferentiated Osteosarcoma of the Distal Ulna: A Case Report

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Abstract
Osteosarcoma is the most common malignant primary bone tumor that occurs most frequently in the second decade of life but rarely in patients over 40 years of age. The most common primary sites of osteosarcoma are the distal femur followed by proximal tibia and proximal humerus, and involvement of the wrist is extremely rare. Moreover, dedifferentiated osteosarcoma is also a rare condition that progresses to high-grade osteosarcoma from low-grade osteosarcoma, usually central low-grade osteosarcoma or parosteal osteosarcoma that bears MDM2 and/or CDK4 gene amplifications. We herein report an extremely rare case of dedifferentiated osteosarcoma arising in the distal ulna of an adult over 40 years of age. The patient was a 46-year-old man with a 2-month history of pain in his left swollen wrist. The initial radiological findings suggested a benign bone tumor in the distal ulna, and the lesion was marginally excised at the nearby hospital. Although the pathological diagnosis at the nearby hospital suggested a benign cartilaginous tumor, the tumor recurred in an aggressive manner 8 months after the initial surgery. The patient was referred to our hospital, and an incisional biopsy showed a high-grade osteosarcoma. The primary tumor was retrospectively re-evaluated at our hospital and diagnosed as low-grade osteosarcoma. Since neoadjuvant chemotherapy failed to shrink the tumor, the patient had to undergo below the elbow amputation to cure the disease. Although the tumor was negative for MDM2 nor CDK4, the definitive diagnosis of dedifferentiated osteosarcoma was made according to the clinical course and the histological findings. Lung metastases were found 10 months after the amputation, which were successfully treated by neoadjuvant chemotherapy and surgery. The patient has been doing well with no evidence of disease for 1 year and 6 months. Surprisingly, the literature

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review revealed that many low-grade osteosarcomas of the distal ulna progressed to high-grade dedifferentiated osteosarcomas. One should bear in mind that the diagnosis and treatment for bone-forming tumors of the distal ulna should be made very carefully because, although rare, it is possible that the tumor may initially appear as a benign or low-grade malignant tumor and may progress to high-grade osteosarcoma.

Introduction

Osteosarcoma is the most common malignant primary bone tumor, with an incidence in the general population of 2–3/million/year [1]. Osteosarcoma occurs most frequently in the second decade of life, with approximately 60% of patients affected under the age of 25 years, and 30% of osteosarcomas occur in patients over 40 years of age [2]. The most common primary sites are the distal femur, proximal tibia, and proximal humerus. Involvement of the wrist in osteosarcoma is extremely rare, accounting for <1% of all osteosarcomas [3–9]. Dedifferentiated osteosarcoma is also a rare condition that progresses to high-grade osteosarcoma from low-grade osteosarcoma, usually parosteal osteosarcoma or low-grade central osteosarcoma, which frequently shows immunoactivity for MDM2 or CDK4 [10, 11]. We report an extremely rare case of dedifferentiated osteosarcoma without immunoactivity for MDM2 or CDK4 arising in the distal ulna of an adult.

Report of the Case

The patient was a 46-year-old man with a 2-month history of pain in his left swollen wrist. Radiographs taken at a nearby hospital showed a 2-cm densely ossified lesion with a multilobular surface in the left distal ulna (Fig. 1a). CT revealed a bone-forming lesion in the left distal ulna infiltrating intramedullary cancellous bone and developing into an extracortical mass (Fig. 1b). The lesion was marginally excised at the nearby hospital, and the pathological diagnosis suggested a benign cartilaginous tumor (Fig. 1c). Eight months after the initial surgery, radiographs showed an ossified lesion with a multilobular surface in the distal ulna, with an associated soft tissue mass (Fig. 2a). MRI showed a T1 low-signal (Fig. 2b), T2 high-signal (Fig. 2c), gadolinium contrast-enhanced (Fig. 2d) tumor approximately 8 cm in size with bone destruction and extraskeletal infiltration. He was then referred to our hospital for further evaluation and treatment at the age of 47 years. An incisional biopsy showed spindle cell proliferation in a fascicular pattern with marked nuclear atypia, mitosis, and osteoid formation, suggesting a high-grade osteosarcoma (Fig. 2e). Whole-body CT revealed no clear evidence of metastases, which led to the diagnosis of T2N0M0 stage 2b high-grade osteosarcoma. Because the tumor was so close to the neurovascular bundle, we administered neoadjuvant chemotherapy in anticipation of safe limb salvage; however, after 2 cycles of neoadjuvant chemotherapy with ifosfamide (IFO) and pirarubicin (THP), radiographs showed rapid growth of the tumor and severe bony destruction of the ulna (Fig. 3a). MRI also showed marked enlargement of the tumor and infiltration of the neurovascular bundle (Fig. 3b–d), which led to a decision to perform below the elbow amputation to achieve adequate surgical margins. Postoperative gross findings showed a yellow-white solid tumor approximately 8 cm in size with no obvious involvement of the carpal bones or the radius (Fig. 3e). Postoperative pathology showed a mixture of a well-differentiated low-grade sarcoma with ossification, with nuclear atypia and

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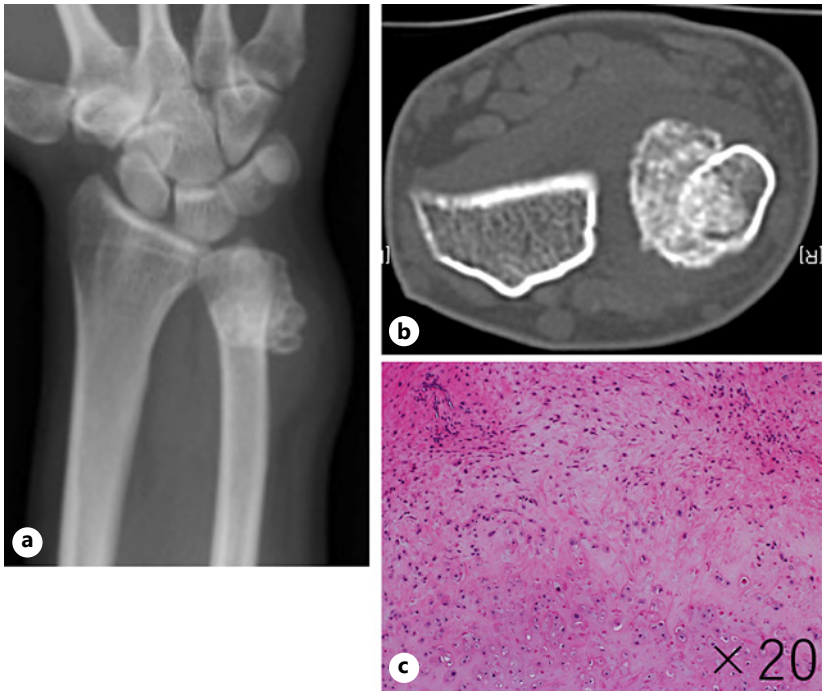

Fig. 1. Radiological findings at initial presentation. **a** X-ray showed a 2-cm densely ossified lesion with a multilobular surface in the distal ulna. **b** CT showed a bone-forming lesion in the left distal ulna infiltrating intramedullary cancellous bone and developing to an extracortical mass. **c** Excisional biopsy showed proliferated woven bone and small numbers of atypical tumor cells.

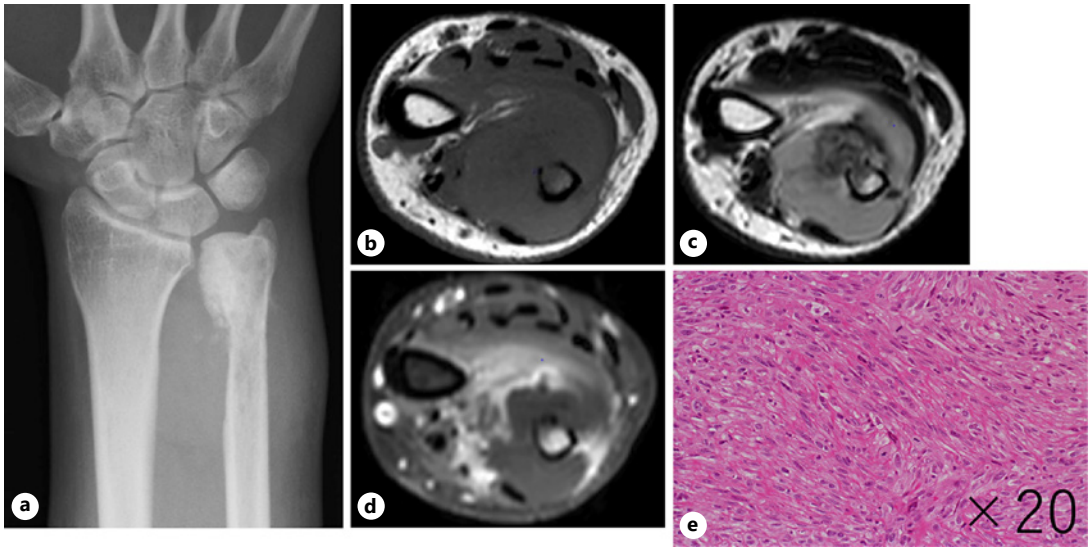

Fig. 2. Image findings 8 months after the initial surgery. **a** Radiograph showed an ossified lesion with a multilobular surface in the distal ulna, with an associated soft tissue mass. **b–d** MRI showed a T1 low-signal (**b**), T2 high-signal (**c**), gadolinium contrast-enhanced (**d**) tumor approximately 8 cm in size with bony destruction and extraskeletal infiltration. **e** Incisional biopsy showed spindle cell proliferation in a fascicular pattern with marked nuclear atypia, mitosis, and osteoid formation, suggesting a high-grade osteosarcoma.

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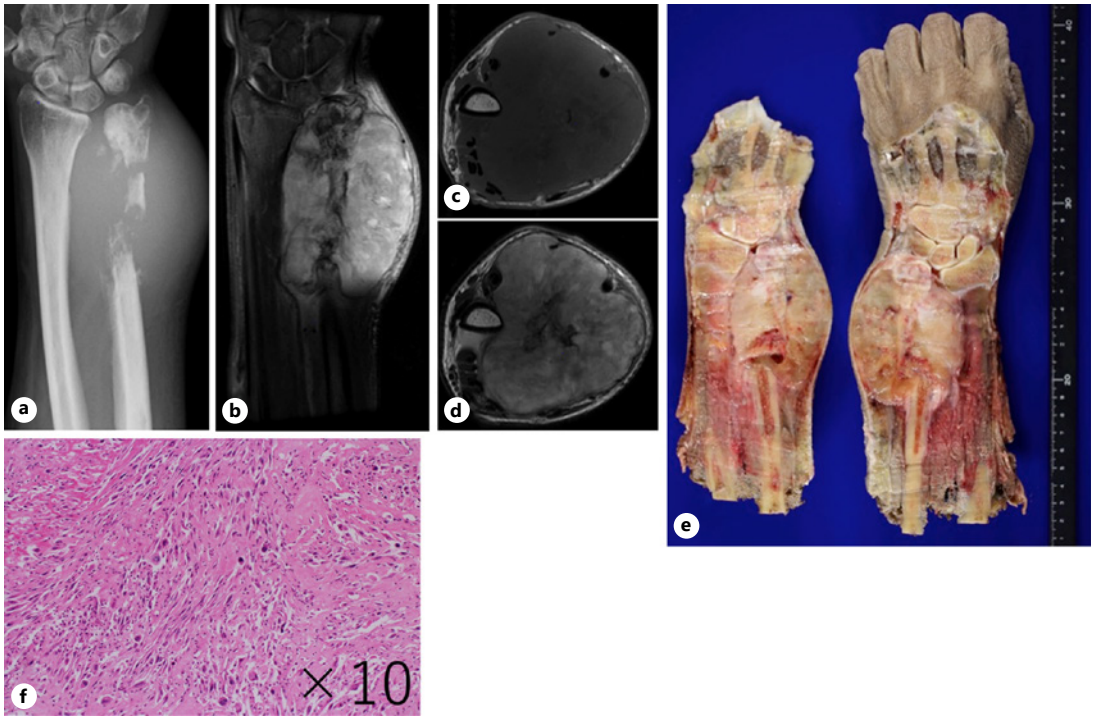

Fig. 3. a–d Radiographs and MRI after 2 cycles of neoadjuvant chemotherapy with ifosfamide and pirarubicin. **a** Radiograph showed rapid growth of the tumor and severe bony destruction of the ulna. **b–d** MRI showed marked enlargement of the tumor and infiltration of the neurovascular bundle. **e** Postoperative gross findings showed a yellow-white solid tumor approximately 8 cm in size with no obvious involvement of the carpal bones or the radius. **f** Postoperative pathology showed spindle cell proliferation in a fascicular pattern with marked nuclear atypia, mitosis, and osteoid formation.

low cell density, and spindle cell proliferation in a fascicular pattern with marked nuclear atypia, mitosis, and osteoid formation, suggesting a high-grade osteosarcoma (Fig. 3f). Although immunohistochemical analysis did not show clear positive staining for MDM2 or CDK4, and fluorescence in situ hybridization (FISH) did not show MDM2 gene amplification (data not shown), the definitive diagnosis of dedifferentiated osteosarcoma was made according to the morphological findings on hematoxylin and eosin staining. CT performed 10 months after the amputation showed multiple lung metastases (Fig. 4a), and 6 cycles of adjuvant chemotherapy with ifosfamide (9 g/m^2) and etoposide (500 mg/m^2) were administered. The patient responded well to chemotherapy, and the multiple lung metastases observed 10 months after the amputation either decreased in size or disappeared (Fig. 4b). Two months after the chemotherapy, one of the lung metastases had gradually increased in size on chest CT (Fig. 4c), and the mass was resected; the patient was 50 years old at the time of this surgery (Fig. 4d). The pathology of the resected specimen was consistent with high-grade sarcoma (Fig. 4e, f). One year and 6 months after the resection of the lung metastasis, the patient was doing well with no evidence of disease.

Discussion

There were 2 reasons for the difficulty in diagnosing this case. First, osteosarcoma arising in the distal ulna is extremely rare. The most common primary sites of conventional osteosarcoma are the distal femur, proximal tibia, and proximal humerus; wrist involvement in

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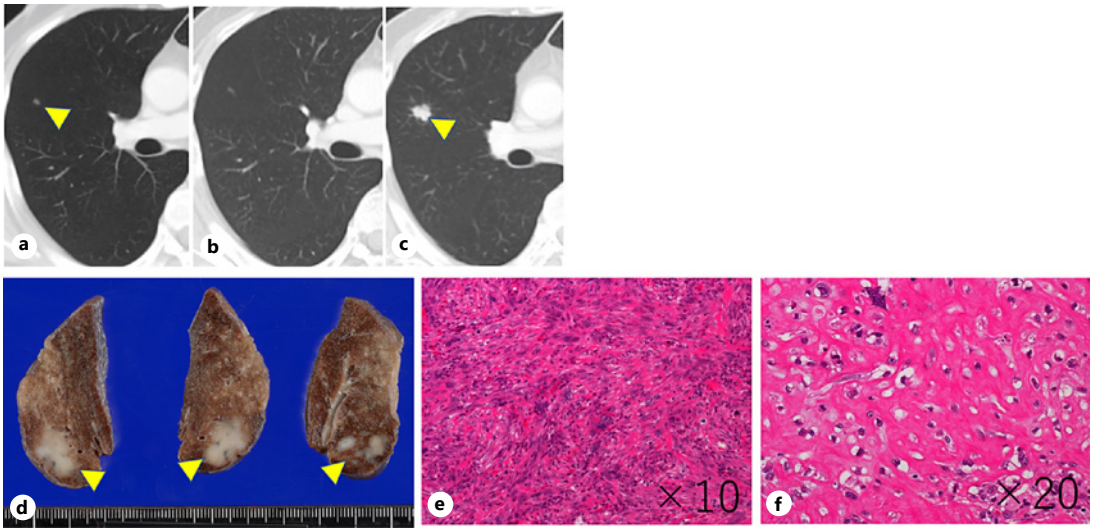

Fig. 4. Image findings after the amputation. **a** CT performed 10 months after the amputation showing multiple lung metastases (arrow). **b** CT performed after 6 cycles of adjuvant chemotherapy. Nearly complete response of the multiple lung metastases was observed. **c** Two months after the chemotherapy, one of the lung metastases had gradually increased in size on chest CT (arrow). **d** Postoperative gross findings of the lung metastasis measuring approximately 1.5 cm in size (arrow). **e**, **f** Pathology of the resected specimen showing spindle cell proliferation in a fascicular pattern with marked nuclear atypia, mitosis, osteoid formation, and osteogenesis and chondrocytes, suggesting a high-grade osteosarcoma.

osteosarcoma is extremely rare. In a previous study analyzing 1,649 cases of osteosarcoma [3], involvement of the distal ulna was found in only 2 cases. In another study analyzing 33 patients with high-grade osteosarcoma in the distal forearm [7], the distal ulna was involved in only 6 cases. Several case reports of distal ulnar osteosarcoma have been published [4–6, 8, 9]; however, even with these cases, our case is considered an extremely rare osteosarcoma arising in the distal ulna. In contrast, a wide variety of tumors and tumor mimics may arise in the distal ulna, including giant cell tumors, epithelial tumors, hemangiogenic tumors, subacute osteomyelitis, adamantinomas, desmoid tumors, and primary bone lymphomas [5]. No specific tumor types have been reported to arise in the particular location in our case, the distal ulna, and caution is necessary regarding differentiating neoplastic lesions occurring in this location. Second, the pathology in this case was very complex. Although radiological findings of the tumor showed some features of bony invasion on CT at the nearby hospital, the majority of the tumor was a well-circumscribed bony lesion, which was consistent with the histological diagnosis made at the nearby hospital suggesting a benign cartilaginous lesion. Our retrospective interpretation of the radiological and histological findings in the primary tumor was low-grade osteosarcoma. In contrast, the image findings after referral to our hospital showed a clear high-grade tumor with significant bony destruction and an extraskeletal mass. Additionally, pathology showed a mixture of low-grade and high-grade sarcoma, which led to the diagnosis of high-grade dedifferentiated osteosarcoma. The great majority of low-grade osteosarcomas that progress to high-grade dedifferentiated osteosarcomas bear genomic amplification of the MDM2 and CDK4 genes. There have been 2 studies demonstrating the utility of immunoactivity for MDM2 or CDK4 in the diagnosis of low-grade osteosarcoma, demonstrating 89–100% sensitivity and 97.5–100% specificity [10, 11]. Although we failed to show positive staining for MDM2 or CDK4 by immunohistochemistry and MDM2 gene amplification by FISH, the definitive diagnosis was made according to the morphological changes in histology over time in our patient.

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Table 1. Surgical cases of osteosarcoma arising in the distal ulna

Case	Author	Age/sex	Subtype	Surgery	Surgical margin	Chemotherapy	Follow-up, months	Outcome	Local recurrence	Metastasis
1	Spinelli et al. [9]	51/M	Parosteal	Excision	Wide	n/a	41	CDF	No	No
2	Joo et al. [8]	37/F	Fibroblastic	Excision	Wide	Postop	n/a	n/a	n/a	n/a
3	Spinelli et al. [9]	41/M	Parosteal	Excision	Wide	None	27	CDF	No	No
4	Pradhan et al. [14]	22/F	Telangiectatic	Excision	Marginal	Preop	27	NED	No	No
5		90/F	Fibroblastic	Amputation	Wide	None	6	CDF	No	No
6		52/M	n/a	Excision	Marginal	Preop	53	DOD	Yes	Yes (n/s)
7		9/F	n/a	Amputation	Wide	Preop	31	DOD	No	Yes (n/s)
8	Mulligan et al. [4]	63/M	Small cell	Excision	Wide	Preop	26	DOD	Yes	Lung
9	Exner et al. [5]	20/F	Osteoblastic	Excision	n/a	Preop/Postop	84	CDF	No	No
10	Chowdhury et al. [12]	15/F	Telangiectatic	Excision	Marginal	Postop	111	AWD	Yes	No
11	Ferracini et al. [13]	29/M	Parosteal	Excision	Wide	n/a	n/a	n/a	n/a	n/a
	Present case	46/M	Chondroblastic	Amputation	Wide	Preop	66	NED	No	Lung

CDF, continuous disease free; DOD, dead of disease; AWD, alive with disease; NED, no evidence of disease; LR, local recurrence; n/a, not available; n/s, not specified.

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To understand the clinicopathological features, we reviewed reports of osteosarcoma occurring in the distal ulna. To the best of our knowledge, there were 39 surgically treated cases of osteosarcoma occurring in the distal forearm, of which 13 were osteosarcomas in the distal ulna (Table 1) [4, 5, 8, 9, 12–14]. Subtypes of osteosarcoma in the distal ulna were well documented in 11 of 13 cases, and among them, the most common was parosteal osteosarcoma (36%, 4/11 cases). Given the rarity of parosteal osteosarcoma (4% of all osteosarcomas), the incidence of this osteosarcoma in the distal ulna was relatively high. Only one of 4 parosteal osteosarcomas expressed CDK4 immunohistochemistry [10]. The other 3 tumors had no MDM2 or CDK4 immunohistochemical expression, nor amplification of the MDM2 genes by FISH, and the definitive diagnoses were made according to the morphological findings of low-grade osteogenic sarcoma [9, 13]. None of the 4 tumors progressed to high-grade dedifferentiated osteosarcoma. Other reports of osteosarcoma in the forearm inadequately described the patients' prognosis, and the treatment outcomes were unclear. According to these findings, the present case was considered an extremely rare dedifferentiated osteosarcoma from a low-grade osteogenic tumor of the distal ulna that was not confirmed to be the parosteal subtype.

In this case of rapid progression after recurrence, complete resection with perioperative chemotherapy was planned. Regarding the chemotherapy regimen, several studies showed that patients over 40 years of age with osteosarcoma in the extremities did not respond well to chemotherapy using the standard treatment, namely, high-dose methotrexate (MTX), anthracycline, and cisplatin (CDDP). Side effects, such as hematologic toxicity, often prevented patients from completing the full course of treatment, and eventually the prognosis was worse than in younger patients [15]. In contrast, adjuvant chemotherapy with anthracycline and ifosfamide for high-grade soft tissue sarcoma in the extremities was effective and can be administered safely in patients over 40 years of age [16]. Given our patient's age and the fact that both anthracycline and ifosfamide are key drugs for high-grade osteosarcoma, we chose this drug combination for the neoadjuvant chemotherapy instead of including methotrexate and cisplatin, with careful consideration not to damage the patient's renal function. As a result of progression after neoadjuvant chemotherapy, limb-sparing surgery was not considered feasible, and the patient underwent amputation without adjuvant chemotherapy. Although there were discussions regarding ifosfamide, which was part of the neoadjuvant chemotherapy resulting in disease progression, the patient received the ifosfamide and etoposide (IE) regimen after developing lung metastases and responded extremely well. This drug combination in metastatic osteosarcoma has been reported to have a synergistic effect, with a better response than with ifosfamide alone [17]. One study of 294 pediatric patients who received IE as the second-line therapy demonstrated its efficacy, showing that 31 (10%) achieved a complete response (CR), and 57 (20%) achieved a partial response (PR), resulting in a combined CR/PR rate of 30% [18]. Although careful follow-up will be necessary for a certain period of time, the present case adds evidence that IE can be an effective regimen as the second-line therapy in advanced high-grade osteosarcoma.

Conclusion

We reported an extremely rare case of a high-grade osteosarcoma arising in the distal ulna in a man older than 40 years of age. Although the tumor was negative for MDM2 and CDK4, the clinical course and the histological findings suggested dedifferentiation from low-grade osteosarcoma. There have been several reports of tumors arising in the distal ulna, but few reports of osteosarcoma. The diagnosis and treatment for bone-forming tumors of the distal ulna should be made very carefully because, although extremely rare, it is possible that

the tumor may initially appear as a benign or low-grade malignant tumor and may progress to high-grade osteosarcoma.

Acknowledgment

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Statement of Ethics

This study was approved by the Ethics Committee of Keio University School of Medicine (No. 20160298). The patient was informed that the data from the case would be submitted for publication, and he provided his written consent.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

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Author Contributions

R.T. performed the data analysis and initial draft of the manuscript. S.O. was responsible for radiological evaluation. A.S. and H.O. were responsible for histological review. R.T., R.N., T.S., N.A., K.K., and K.T. performed the collection and assembly of data and contributed to writing of the manuscript. R.N., M.N., and M.M. provided final approval of the manuscript. All authors read and approved the final manuscript.

Data Availability Statement

All relevant data are provided in the manuscript. Further inquiries can be directed to the corresponding author.

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