

Original Article

A case of secondary chondrosarcoma with *TP53* mutation arising from fibrous dysplasia

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Abstract: Malignant transformation in fibrous dysplasia (FD) is a rare event, reported to occur in approximately less than 1% of cases. The most common type of secondary malignant tumor arising from FD is osteosarcoma. We report a case of secondary chondrosarcoma arising in a patient with polyostotic FD. Magnetic resonance imaging (MRI) showed a multilobulated tumor, 12.6 cm in diameter, in the right scapular region. Histologically, the secondary tumor was composed of a proliferation of atypical chondroblasts within chondromatous stroma adjacent to the FD area. Atypical chondroblasts showed pleomorphism and obvious nuclear atypia. Mitotic figures, including atypical ones and focal necrosis were also seen. Based on these findings, we diagnosed chondrosarcoma, Grade 3, arising from FD. Genetic testing revealed a R201H *GNAS* mutation in both components and a *TP53* mutation in the chondrosarcoma area only, suggesting an important role for *TP53* mutation in this malignant transformation. The patient remains alive with no evidence of disease recurrence 6 months after surgery.

Keywords: Chondrosarcoma, malignant transformation, fibrous dysplasia, *GNAS*, *TP53*

Introduction

Fibrous dysplasia (FD) is a dysplastic anomaly of bone-forming mesenchymal tissue that occurs primarily in the ribs, jaw, skull, and long bones. This lesion is composed of dysplastic fibrous stroma and immature, distorted bone without osteoblastic rimming. Numerous studies have documented the relationship between FD and McCune-Albright syndrome (MAS) and Mazabraud syndrome (MS), which are syndromes caused by the continuous activation of the *GNAS* resulting from the gain-of-function mutation [1, 2]. FD has the potential to develop malignant tumors such as osteosarcoma, fibrosarcoma, and chondrosarcoma, which occur in approximately 0.4-1.0% of all FD patients [3, 4], and 10% of those patients develop chondrosarcoma [5, 6].

We report a case of secondary chondrosarcoma with *TP53* mutation arising in a patient with polyostotic FD. The sarcoma-specific *TP53* mutation in this tumor may provide insight into

the effect of p53 during the malignant transformation of FD.

Case report

Clinical course

A 33-year-old woman with polyostotic FD had noticed continuous stiffness and swelling in her right shoulder and was referred to our hospital 8 months after her first symptom appeared. Her long bones had deformed and contracted due to FD, and she was 130 cm tall. She had experienced the pathological fracture of long bones 3 times since the age of 3 years. There was swelling and tenderness in her right shoulder, and it was warm to the touch. Range of motion in her shoulder was extremely limited: flexion was reduced to 20°, abduction to 10°, and external rotation to 10°. Skin pigmentation was not evident. Laboratory examination revealed that serum thyroglobulin was elevated by only 37.1 ng/dl, and endocrine disorder was not evident.

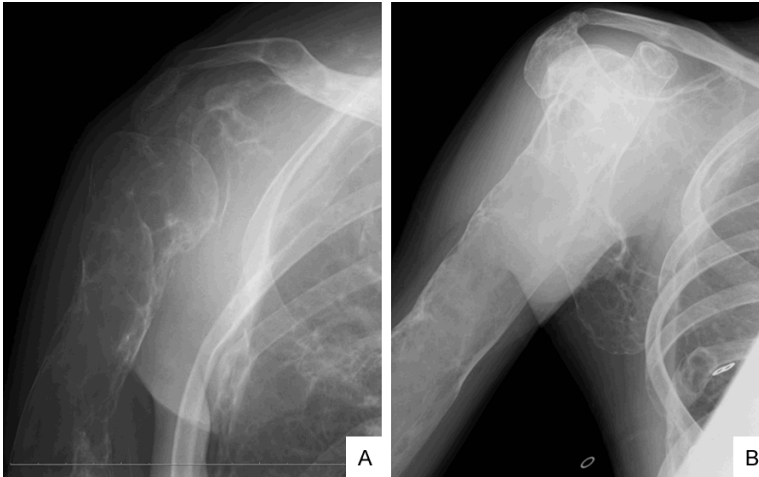


Figure 1. Radiograph of the right scapular region shows osteolytic lesion with cystic changes and swelling of the surrounding soft tissue (A) compared to those radiograph taken 8 years earlier (B).

Systemic examination failed to detect soft tissue mass.

Plain radiography of the right scapular region showed an osteolytic lesion and swelling of the surrounding soft tissue compared to radiographs taken 8 years earlier (**Figure 1A, 1B**). Magnetic resonance imaging (MRI) revealed a multilobulated lesion 12.6 cm in diameter, which showed low intensity on T1-weighted images (WI), high intensity on T2-WI, and high intensity on short TI inversion recovery (STIR) (**Figure 2A-C**). Contrast-enhanced computed tomography (CT) showed the osteolytic change of the right scapula with ballooning (**Figure 2D**). These image findings suggested that FD in the right humerus was causing massive cystic changes; in addition, the FD component in the right scapula was obscure, although this may have been because it was present at the tumor's periphery. Systemic examination revealed polyostotic FD that included skull bone, vertebral bone, rib, bones of the upper and lower extremities, and pelvic bone.

Biopsy from the scapular tumor revealed chondromatous tumor without apparent FD area, suggesting a possible secondary chondrosarcoma arising from FD. Wide resection of the tumor including right scapula and clavicle was performed.

Pathological findings

Gross section showed a multilobulated chondromatous tumor (**Figure 3A**). Histologically, most of the tumor was occupied by the chon-

dromatous tumor, and the FD area remained at the periphery of the tumor only (**Figure 3B**). The tumor consisted of multilobulated chondromatous lesions separated by fibrous septa (**Figure 3C and 3D**), and the lobules' cellularity differed such that some lobules had scattered areas with markedly increased cellularity (**Figure 3E**). Tumor cells showed nuclear pleomorphism and obvious nuclear atypia with chromatin-rich nuclei (**Figure 3F and 3G**). Mitotic figures including atypical ones were encountered up to 5/10 high-power fields (HPFs) (**Figure**

3G), as was focal necrosis. Immunohistochemically, tumor cells were diffusely positive for p53 (**Figure 3H**).

Genetic testing

We performed a polymerase chain reaction (PCR) for formalin-fixed, paraffin-embedded (FFPE) tissue followed by direct sequencing to examine the presence of *GNAS* and *TP53* mutations in this tumor. To analyze *GNAS* mutations in exon 8 and exon 9 in the chondrosarcoma and FD areas, respectively, genomic DNA was extracted from each. The corresponding non-tumoral genomic DNA was also extracted. (Primer sequences have been previously described [7]). The PCR product was separated on a 2% agarose gel, and the product of the anticipated size was cut from the gel and analyzed for the sequence. Mutational analysis of the *TP53* followed by direct sequencing with previously described primer pairs [8, 9] was also performed on the tumor, FD area, and corresponding non-tumoral tissue. We used macrodissected FFPE section to analyze the *TP53*, and the rest of the procedure was performed as described above. Sequencing confirmed the presence of a *GNAS* mutation, 201 CGT > CAT (R201H) (**Figure 4A**). Based on these findings, we diagnosed chondrosarcoma, Grade 3, arising from FD. In addition, we detected a *TP53* mutation (R280K) in the chondrosarcoma component only (**Figure 4B**).

Six months after surgery, the patient is alive and well with no evidence of tumor recurrence and without any adjuvant therapy.

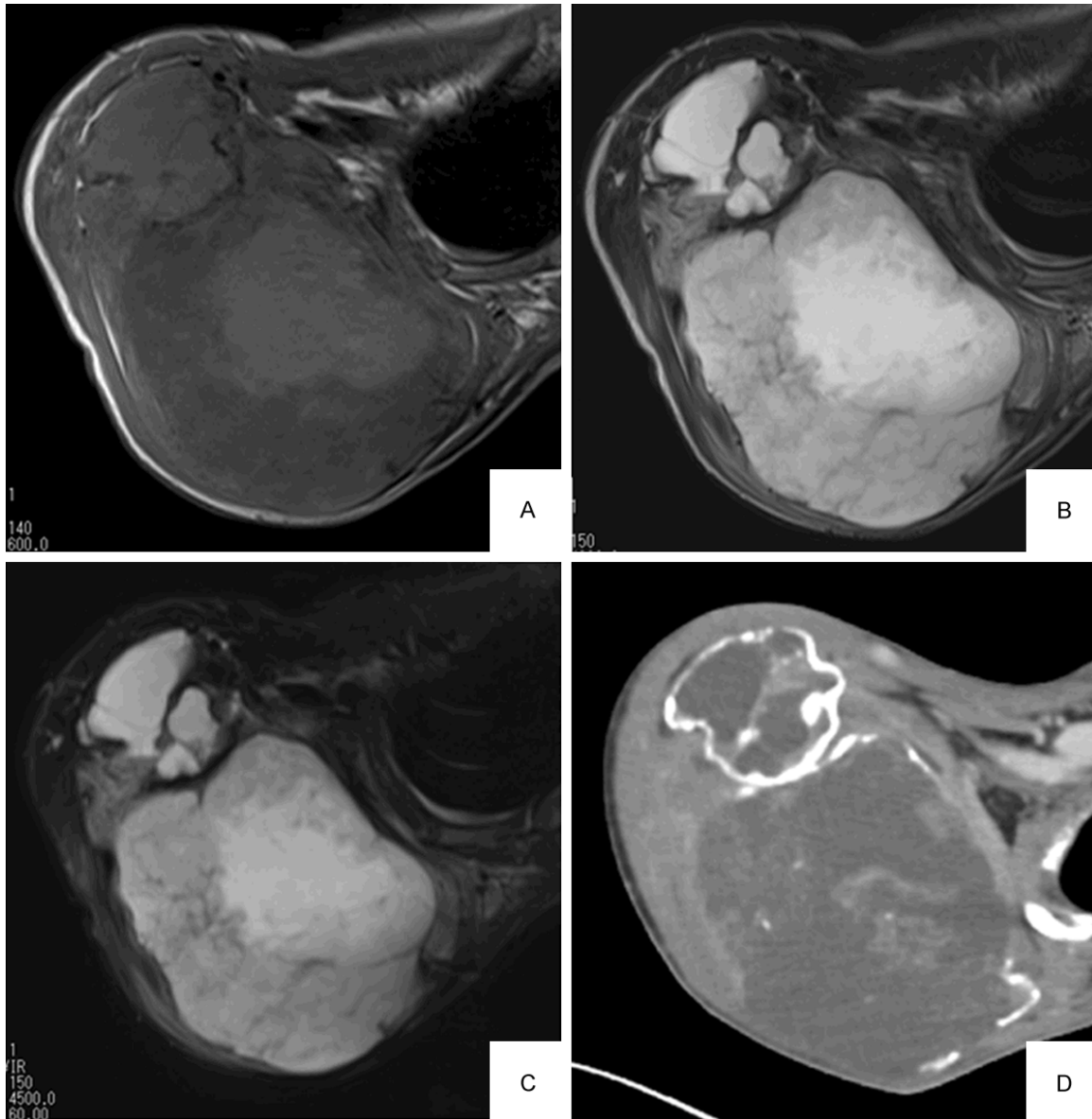


Figure 2. Magnetic resonance images (MRI). The scapular tumor shows low intensity on T1-weighted images (WI) (A) and high intensity on both T2-WI (B) and short T1 inversion recovery (STIR). In the central area, hemorrhage and/or necrosis were considered (B, C). Septal-like structure with low intensity on T2WI and STIR suggest a chondroid tumor. Contrast-enhanced computed-tomography (CT) (D) shows the osteolytic change of the right scapula with ballooning. Note that the humerus was ballooning but that the cystic change was observed within the humerus.

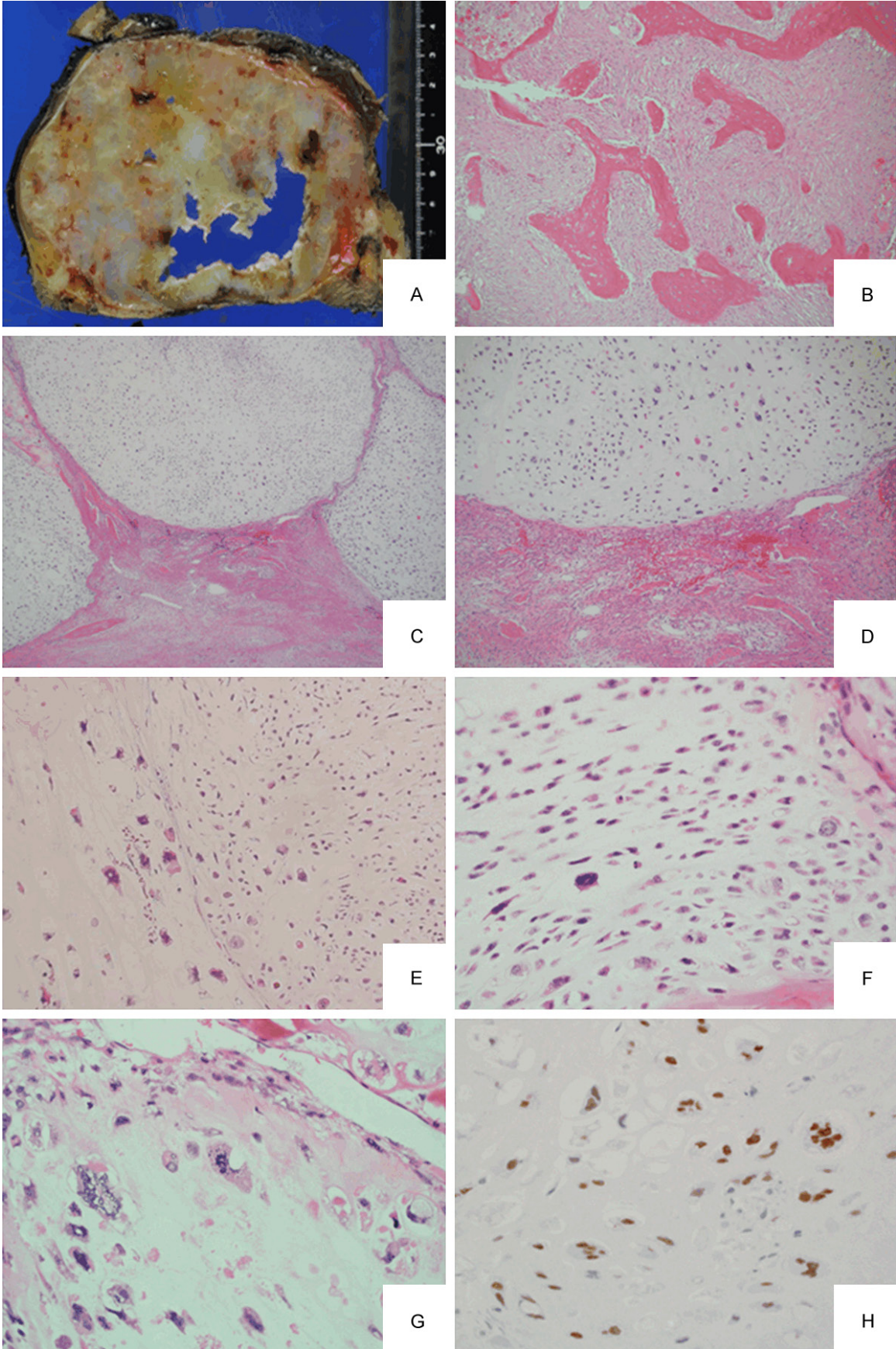
Discussion

Malignant transformation from FD, especially malignant transformation to chondrosarcoma, is very rare. To the best of our knowledge, only 15 cases of secondary chondrosarcoma arising from FD have been reported so far in the literature (**Table 1**). A cartilaginous component has been seen as a rare variant within FD. However, in these cases, the cartilaginous cells show neither obvious nuclear atypia nor mitotic

figures. The cartilaginous cells in this case showed marked atypia and pleomorphism as well as mitotic figures. Thus, both the pathological findings at biopsy and the image findings preclude the possibility of FD with a cartilaginous component.

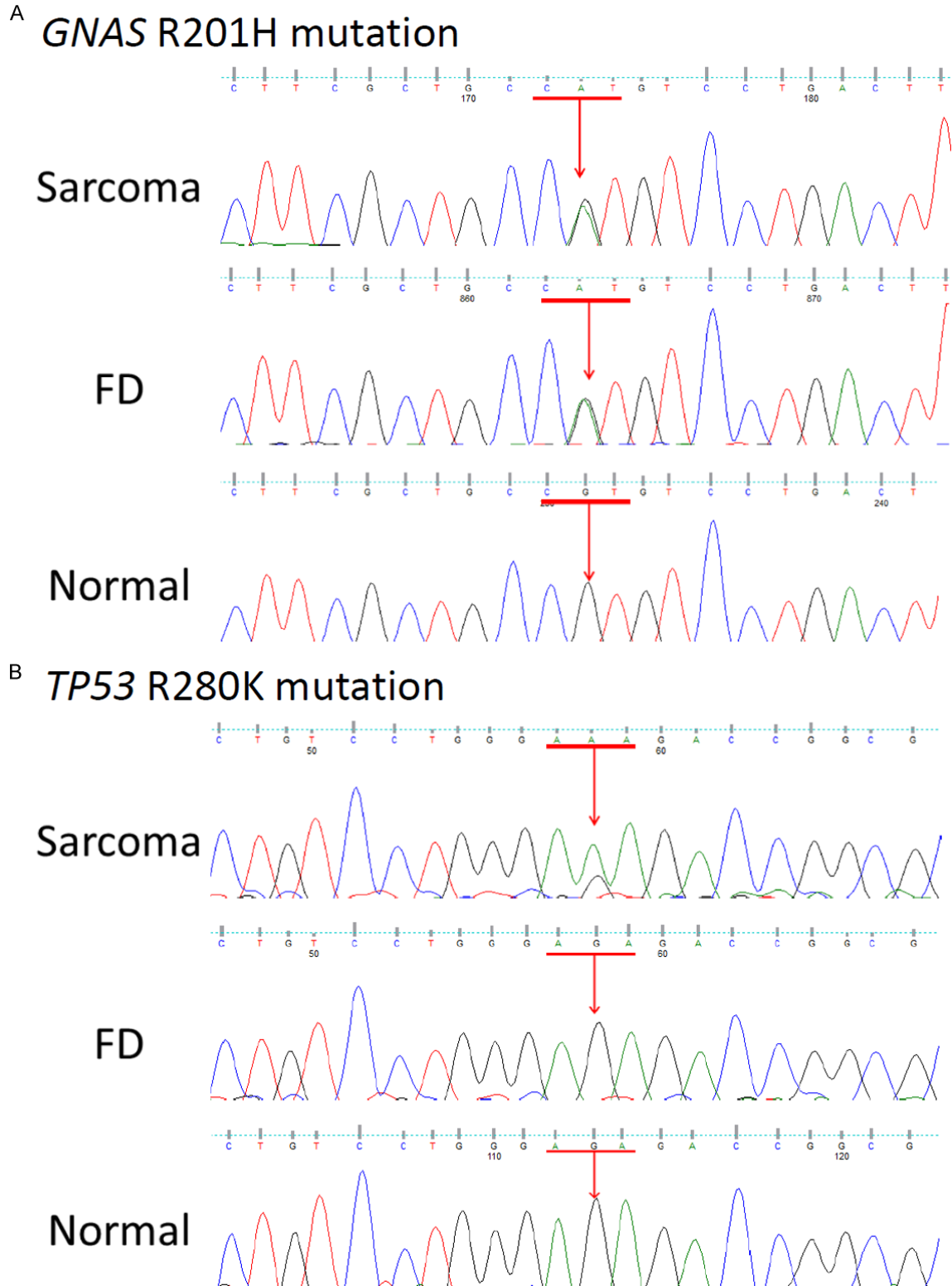
In addition to emerging in this monostotic type, FD is also known to emerge as one of the symptoms of MAS and MS. FD is caused by the activation of the *GNAS* mutation that leads to the

Chondrosarcoma with *TP53* mutation arising from FD



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Figure 3. Tumor histology of resected tumor. Grossly, the tumor shows a multilobulated chondromatous appearance (A). Histologically, the FD area was observed only at the periphery of the tumor (B). The tumor shows multilobular formation with fibrous septa (C, D). The lobules' cellularity differed such that some lobules had scattered areas with markedly increased cellularity (E). Tumor cells show obvious nuclear atypia (F, G), and mitotic figures including atypical ones are detected (G). Immunohistochemically, tumor cells were diffusely positive for p53 (H).



Chondrosarcoma with *TP53* mutation arising from FD

Figure 4. *GNAS* R201H mutation (red underline) was detected both in the FD and chondrosarcoma components, but not in non-tumoral tissue (A). *TP53* R280K mutation (red underline) was detected only in the chondrosarcoma component and not in non-tumoral tissue or the FD area (B).

Table 1. Secondary chondrosarcoma arising from FD

Case (REF#)	Sex	Onset of FD	Onset of Chondro sa.	MAS	Poly or Mono	Irradation	Treatment	Grade	Follow up (months)	Prog-nosis	<i>GNAS</i> mut.	<i>TP53</i> mut.
1 [5]	F	7	40	N.A.	P	(+)	Disarticulation	2	60	DOD	N.A.	N.A.
2 [5]	M	6	45	N.A.	P	(-)	Hip disarticulation	clear cell	19	DOD	N.A.	N.A.
3 [5]	F	52	52	N.A.	P	(-)	Amputation	2	36	DOD	N.A.	N.A.
4 [10]	F	Infant	40	N.A.	P	(+)	Disarticulation	2	N.A.	N.A.	N.A.	N.A.
5 [16]	M	8	11	N.A.	M	N.A.	Curettage	1	24	NED	N.A.	N.A.
6 [16]	F	19	19	N.A.	P	N.A.	Hemipelvectomy	N.A.	12	NED	N.A.	N.A.
7 [17]	F	29	30	N.A.	M	N.A.	Exarticulation	N.A.	84	NED	N.A.	N.A.
8 [18]	F	N.A.	52	N.A.	P	N.A.	N.A.	2	N.A.	N.A.	N.A.	N.A.
9 [19]	M	9	36	N.A.	P	(-)	Hemipelvectomy	N.A.	18	DOD	N.A.	N.A.
10 [20]	F	23	48	N.A.	N.A.	(+)	Mandibulectomy	N.A.	120	NED	N.A.	N.A.
11 [21]	M	28	28	N.A.	N.A.	N.A.	N.A.	Mesenchymal	N.A.	N.A.	N.A.	N.A.
12 [22]	M	Infant	52	(+)	P	(-)	Amputation	Dedifferentiated	15	NED	N.A.	N.A.
13 [23]	F	23	27	(+)	P	N.A.	Amputation	2	few	DOD	(-)	N.A.
14 [24]	M	5	27	(+)	P	(-)	Endoscopic drill-out	3	48	NED	N.A.	N.A.
15 [25]	M	59	66	N.A.	M	(-)	Radical resection	Dedifferentiated	24	NED	N.A.	N.A.
This case	F	4	33	N.A.	P	(-)	Disarticulation	3	6	NED	(+)	(+)

M: male, F: female, MAS: McCune-Albright syndrome, P: polyostotic FD, M: monostotic FD, NED: no evidence of disease, DOD: dead of disease, N.A.: Information not available, N.E.: Not examined, sa.: sarcoma, mut.: mutation.

hyperproliferation of marrow stromal cells and immature differentiation to woven bone [4, 7, 10]. This *GNAS* mutation, 201 CGT > CAT, was found in the FD and chondrosarcoma areas, however, clinical information did not support the presence of MAS/MS in the subject of the present study.

Previous literature has pointed to the capacity for malignant transformation to arise in post-radiation-therapy patients with polyostotic FD [10]. The patient in our study had polyostotic and polymelic FD but had never received radiation therapy. Thus, the radiation effect was not associated with this transformation.

Notably, the *TP53* mutation was detected in the chondrosarcomatous area only and not in either the FD or non-tumoral area. Our best efforts revealed no past literature referring to a pathogenetic pathway of malignant transformation in FD. The mutation we detected in this patient is one of the most common sites for the single amino acid substitution in *TP53*. Previous literature has pointed out that this missense mutation induces transactivation of target genes by a specific cellular transcript-

ion factor [11] that has a strong tendency to tether itself to chromatin [12]. The effect of *TP53* mutations on malignant transformation has been reported in various bone and soft tissue tumors [13, 14]. Previous research on the *TP53* mutation in chondrosarcoma has revealed that the *TP53* mutation is rare in this tumor type but that when it does occur it is of a high grade and in dedifferentiated chondrosarcoma, especially in the spindle component of the latter [15]. The histological grade of chondrosarcoma in this case was high, consistent with these previous findings.

In conclusion, we investigated a rare case of secondary chondrosarcoma arising in a polyostotic FD patient. The sarcoma-specific *TP53* mutation identified in this tumor may affect the process of malignant transformation in FD.

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Disclosure of conflict of interest

None.

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References

- [1] Turan S, Bastepe M. GNAS Spectrum of Disorders. *Curr Osteoporos Rep* 2015; 13: 146-58.
- [2] Boyce AM, Collins MT. Fibrous Dysplasia/McCune-Albright Syndrome. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors. *SourceGene-Reviews*® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016.
- [3] Adetayo OA, Salcedo SE, Borad V, Richards SS, Workman AD, Ray AO. Fibrous Dysplasia: An Overview of Disease Process, indications for Surgical Management, and a Case report. *Eplasty* 2015; 15: e6.
- [4] Riddle ND, Bui MM. Fibrous Dysplasia. *Arch Pathol Lab Med* 2013; 137: 134-8.
- [5] Ruggieri P, Sim FH, Bond JR, Unni KK. Malignancies in Fibrous Dysplasia. *Cancer* 1994; 73: 1411-24.
- [6] Hoshi M, Matsumoto S, Manabe J, Tanizawa T, Shigemitsu T, Izawa N, Takeuchi K, Kawaguchi N. Malignant change secondary to fibrous dysplasia. *Int J Clin Oncol* 2006; 11: 229-35.
- [7] Riminucci M, Liu B, Corsi A, Shenker A, Spiegel AM, Robey PG, Bianco P. The histopathology of fibrous dysplasia of bone in patients with activating mutations of the Gsa gene: site-specific patterns and recurrent histological hallmarks. *J Pathol* 1999; 187: 249-258.
- [8] Schirosi L, Lantuejoul S, Cavazza A, Murer B, YvesBrichon P, Migaldi M, Sartori G, Sgambato A, Rossi G. Pleuro-pulmonary solitary fibrous tumors: a clinicopathologic, immunohistochemical, and molecular study of 88 cases confirming the prognostic value of de Perrot staging system and p53 expression, and evaluating the role of c-kit, BRAF, PDGFRs (alpha/beta), c-met, and EGFR. *Am J Surg Pathol* 2008; 1627-1642.
- [9] Saito T, Mitomi H, Suehara Y, Okubo T, Torigoe T, Takagi T, Sato K, Matsumoto T, Yao T. A case of secondary malignant giant-cell tumor of bone with p53 mutation after long-term follow-up. *Hum Pathol* 2011; 42: 727-733.
- [10] Feintuch TA. Chondrosarcoma arising in a cartilaginous area of previously irradiated fibrous dysplasia. *Cancer* 1973; 31: 877-881.
- [11] Polotskaia A, Xiao G, Reynoso K, Martin C, Qiu WG, Hendrickson RC. Proteome-wide analysis of mutant p53 targets in breast cancer identifies new levels of gain-of-function that influence PARP, PCNA, and MCM4. *Proc Natl Acad Sci USA* 2015; 112: 1220-1229.
- [12] Freed-Pastor WA, Prives C. Mutant p53: one name, many proteins. *Genes Dev* 2012; 26: 1268-1286.
- [13] Akaike K, Kurisaki-Arakawa A, Hara K, Suehara Y, Takagi T, Mitani K, Kaneko K, Yao T, Saito T. Distinct clinicopathological features of NAB2-STAT6 fusion gene variants in solitary fibrous tumor with emphasis on the acquisition of highly malignant potential. *Hum Pathol* 2015; 46: 347-356.
- [14] Okubo T, Saito T, Mitomi H, Takagi T, Torigoe T, Suehara Y, Kaneko K, Yao T. p53 mutations may be involved in malignant transformation of giant cell tumor of bone through interaction with GPX1. *Virchows Arch* 2013; 463: 67-77.
- [15] Terek RM, Healey JH, Garin-Chesa P, Mak S, Huvos A, Albino AP. p53 Mutations in Chondrosarcoma. *Diagn Mol Pathol* 1998; 7: 51-56.
- [16] Huvos AG, Higinbotham NL, Miller R. Bone sarcomas arising in fibrous dysplasia. *J Bone Joint Surg Am* 1972; 54: 1047-1056.
- [17] Dabska M, Buraczewski J. On malignant transformation in fibrous dysplasia of bone. *Oncol* 1972; 26: 369-383.
- [18] Unni KK, Dahlin DC. Premalignant tumors and conditions of bone. *Am J Surg Pathol* 1979; 3: 47-60.
- [19] DeSmet AA, Travers H, Neff JR. Chondrosarcoma occurring in a patient with polyostotic fibrous dysplasia. *Skeletal Radiol* 1981; 7: 197-201.
- [20] Ebata K, Usami T, Tohna I, Kaneda T. Chondrosarcoma and osteosarcoma arising in polyostotic fibrous dysplasia. *J Oral Maxillofac Surg* 1992; 50: 761-764.
- [21] Blackwell JB. Mesenchymal chondrosarcoma arising in fibrous dysplasia of the femur. *J Clin Pathol* 1993; 46: 961-962.
- [22] Ozaki T, Lindner N, Blasius S. Dedifferentiated chondrosarcoma in Albright syndrome. *J Bone Joint Surg Am* 1997; 79: 1545-1551.
- [23] Blanco P, Schaefferbeke T, Baillet L, Lequen L, Bannwarth B, Dehais J. Chondrosarcoma in a patient with McCune-Albright syndrome. *Rev Rhum* 1999; 66: 177-179.
- [24] Heller AJ, DiNardo LJ, Massey D. Fibrous dysplasia, chondrosarcoma, and McCune-Albright syndrome. *Am J Otolaryngol* 2001; 22: 297-301.
- [25] Riddle ND, Yamauchi H, Caracciolo JT, Johnson D, Letson GD, Hakam A, Smith PV, Bui MM. Dedifferentiated chondrosarcoma arising in fibrous dysplasia: A case report and review of the current literature. *Pathol Lab Med Int* 2009; 1: 1-6.