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Original contribution

Fibro-osseous pseudotumor of digits and myositis ossificans show consistent *COL1A1-USP6* rearrangement: a clinicopathological and genetic study of 27 cases☆,☆☆

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Summary Myositis ossificans (MO) and fibro-osseous pseudotumor of digits (FOPD) are localized, self-limiting bone-producing pseudosarcomatous lesions characterized by nodular fasciitis–like proliferation and osteoid and immature woven bone production, which may eventually develop into more mature lamellar bone. Traditionally, MO and FOPD were thought to be of reactive, non-neoplastic nature. *USP6* gene rearrangement was recently reported as a consistent finding in MO and FOPD, thus expanding the spectrum of transient, *USP6*-rearranged neoplasms. *COL1A1* was described as the fusion partner of *USP6* in a subset of MO cases, but the fusion partners of *USP6*-rearranged FOPD have not been uncovered so far. Initially, we carefully reviewed all 27 cases of MO/FOPD from our archives, documenting the remarkable morphological overlap between both lesions. Sixteen cases were seen in consultation, and our review was requested to rule in or rule out tentative diagnoses by referring pathologists. Malignant diagnosis (osteosarcoma) was suggested by the submitting pathologists in 3 cases, whereas 7 cases were sent by the referring pathologists to "rule out sarcoma." In the following step, using next-generation sequencing, we confirmed the *COL1A1-USP6* rearrangement in 5/7 cases of MO and found the same abnormality in 4/5 of FOPD. Overall, 9 of the 12 analyzable cases (75%) of MO and FOPD harbored this gene fusion. The presence of *COL1A1-*

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USP6 gene rearrangement in MO/FOPD links these lesions to other *USP6*-driven tumors and represents a very useful supportive marker, which may help to avoid overdiagnosis of MO/FOPD as a sarcoma.

1. Introduction

Myositis ossificans (MO) and fibro-osseous pseudotumor of digits (FOPD) are localized, self-limiting bone-producing lesions affecting mainly younger adults, although broad age distribution was reported [1-7]. Both lesions are typified by hypercellular nodular fasciitis (NF)–like fibroblastic proliferation and osteoid and immature woven bone production, which may eventually develop into more mature lamellar bone. From the early descriptions to the present days, zonal maturation was emphasized as the most important feature in differentiating MO from sarcomas [1,2], whereas FOPD was reported to show less well-organized structure without the typical zoning pattern of MO [5]. However, later studies showed that MO and FOPD share both clinical and histological features [4,6,7] and that the subtle differences between MO and FOPD may be related only to the site of occurrence, for example, the musculature in MO and more superficial subcutaneous tissues in FOPD [4,6]. In the current World Health Organization classifications of tumors of soft tissue, MO and FOPD are classified together [8].

Because of the rapid and painful growth, hypercellularity, and high mitotic activity of the myofibroblastic proliferation and because of the presence of osteoid, immature bone and in some cases mildly atypical and hypercellular hyaline cartilage, MO and FOPD often raise clinical and/or histological suspicion of malignancy. Some of these lesions regress spontaneously, and their recurrence is exceedingly rare; nevertheless, many MO/FOPD cases are sent for a second opinion with a diagnosis of sarcoma, most commonly being overdiagnosed as extraskeletal or parosteal osteosarcoma [4-7]. This makes MO/FOPD one of the most eminent examples of pseudosarcoma [9].

Traditionally, MO and FOPD were thought to be of non-neoplastic/reactive origin, with a history of trauma or repetitive minor injury documented in 60%-75% of cases [8]. Recently, however, *USP6* rearrangement was reported as a consistent genetic finding in MO and FOPD, thus expanding the spectrum of clonal "transient" neoplasms harboring *USP6* translocation, which currently also includes aneurysmal bone cyst (ABC) and NF [10,11].

COL1A1 was described as a fusion partner of *USP6* in a subset of MO cases [12], but the fusion partners of *USP6* in the USP6-rearranged FOPDs have not been reported to date. We therefore analyzed a series of MO and FOPD cases using next-generation sequencing (NGS) and the Archer FusionPlex Sarcoma kit "(ArcherDX Inc, Boulder, CO)" to find out whether FOPD cases will show the same genetic change as MO.

2. Materials and methods

Fifteen cases of MO and 12 cases of FOPD were retrieved from Tumor Registry at Bioptical Laboratory Plzen, Czech Republic. Some cases of FOPD have been reported previously [7]. Hematoxylin-eosin slides were reviewed to confirm the diagnosis of MO and FOPD, respectively, and to evaluate the histologic features.

For NGS analysis, 2-3 formalin-fixed, paraffin-embedded sections (10 μm thick) were macrodissected to isolate tumor-rich regions. Total nucleic acid was extracted from tumor samples using Agencourt FormaPure Kit (Beckman Coulter, Brea, CA) following the corresponding protocol, with an overnight digestion and an additional 80°C incubation as described in the modification of the protocol required by ArcherDX (ArcherDX Inc, Boulder, CO). RNA component of the total nucleic acid was quantified using the Qubit Broad Range RNA Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA). Input of 250 ng of formalin-fixed, paraffin-embedded RNA was used for library preparation of the FusionPlex Sarcoma kit. PreSeq RNA QC Assay using iTaq Universal SYBR Green Supermix (Biorad, Hercules, CA) was performed on all samples following the Archer Fusion Plex Protocol for Illumina (ArcherDX Inc). Final libraries were quantified using Library Quantification for Illumina Libraries kit assuming a 200-bp fragment length (KAPA, Wilmington, MA). Libraries were sequenced on a NextSeq500 sequencer (Illumina, San Diego, CA). Analysis of sequencing results was performed using the Archer Analysis software (v5; ArcherDX Inc.). Fusion detection parameters were set to a minimum of 5 valid fusion reads with a minimum of 3 unique start sites within the valid fusion reads. Fusion Plex Sarcoma kit contains four 5′ probes in the *USP6* gene in exons 1, 2, and 3.

The study was conducted following the rules set by the Faculty Hospital in Pilsen Ethics Committee. Informed consent was not required.

3. Results

3.1. Clinicopathological findings

The clinical and molecular features of all cases are summarized in the Table.

The study group consisted of 15 MO and 12 FOPD cases. Of these cases, 15 were men and 12 were women, and their

Table Clinicopathological features of 27 MO/FOPD cases

Case #	Sex/age	Site/size (cm)	Clinical history/duration of symptoms (wk)	Radiological diagnosis	Diagnosis	Referral diagnoses	Sequencing	Histology pattern
1	M/44	Left vastus medialis muscle/7.7	Painful mass/4	NP	MO	NA (in-house case)	Negative	Mature
2	F/22	Left thigh/2	Painful mass following trauma/4	NP	MO	MO, Nora lesion	NA	Mature
3	M/28	Left gluteal muscle/4	Painful mass/7	NP	MO	MO	*COL1A1-USP6*	Complete zonal
4	F/35	Right thigh/5	Organized hematoma?/NA	NP	MO	MO, extraskeletal OSa	NA	Complete zonal
5	M/53	Left scapular region/10	Mass lesion/2	Soft tissue lesion, not involving ribs	MO	Rule out sarcoma	*COL1A1-USP6*	Haphazard–no zonal
6	M/10	Neck region/NA	Mass lesion/NA	NP	MO	Rule out sarcoma	*COL1A1-USP6*	Haphazard–no zonal
7	M/35	Left thigh/3.5	Mass lesion/4	NP	MO	NA (in-house case)	*COL1A1-USP6*	Incomplete zonal
8	F/52	Thigh/9	Mass lesion/4	Parosteal osteosarcoma *vs* MO	MO	NA (in-house case)	NA	Haphazard–no zonal
9	F/19	Upper arm/4	Painful mass/4	NA	MO	NA (in-house case)	NA	Haphazard–no zonal
10	M/31	Thigh/NA	Mass lesion/NA	cyst	MO	Giant cell tumor of soft tissue	NA	Incomplete zonal
11	F/46	Thigh/3.4	Mass lesion/several months	NP	MO	OSa	NA	Complete zonal
12	F/37	Biceps brachii muscle/5	Mass lesion/12	Expansile solid lesion, probably malignant	MO	NA (in-house case)	NA	Complete zonal
13	M/60	Vastus medialis muscle, NA	Contusion/several weeks	NA	MO	MO, parosteal OSa	Negative	Mature
14	M/62	Biceps brachii muscle/6	Painful mass following trauma/12	NA	MO	MO	NA	Mature
15	M/6	Abdominal oblique muscle/NA	Mass lesion/NA	NP	MO	Rule out sarcoma	*COL1A1-USP6*	Immature
16	M/53	Palm, wrist/NA	Mass lesion/NA	NP	FOPD	Rule out sarcoma	NA	Complete zonal
17	F/7	3rd metacarpus/NA	Mass lesion/NA	NA	FOPD	Rule out sarcoma	NA	Incomplete zonal
18	F/64	Foot, 4th toe/2.5	Mass lesion/NA	NA	FOPD	NA (in-house case)	NA	Immature
19	M/42	Foot, 1st toe/1.5	Granulation tissue?/NA	NP	FOPD	NA (in-house case)	NA	Incomplete zonal
20	F/30	Hand, metacarpus/1.8	mass lesion/4	NP	FOPD	MO	NA	Haphazard–no zonal
21	M/19	Foot, 1st toe/NA	Osteochondroma?/NA	NP	FOPD	Rule out sarcoma	Negative	Haphazard–no zonal
22	F/34	Hand, thenar/NA	Mass lesion/NA	NP	FOPD	FOPD	*COL1A1-USP6*	Mature
23	F/27	Hand, digit/NA	Mass lesion/NA	NP	FOPD	NA (in-house case)	NA	Haphazard–no zonal
24	M/5	Foot, 5th toe/NA	Mass lesion/32	NP	FOPD	NA (in-house case)	NA	Mature
25	F/38	Hand, 5th digit/1.6	Mass lesion/5	NP	FOPD	NA (in-house case)	*COL1A1-USP6*	Haphazard–no zonal
26	M/55	Hand, hypothenar/15	Mass lesion/8	NP	FOPD	NA (in-house case)	*COL1A1-USP6*	Haphazard–no zonal
27	M/8	Hand, metacarpus, digits/2.4	Painful mass lesion/4	Infiltrative lesion involving soft tissues of the hand, phlegmon?	FOPD	Rule out sarcoma	*COL1A1-USP6*	Haphazard–no zonal

Abbreviations: F, female; M, male; NA, not available; NP, not performed; OSa, osteosarcoma.

median age was 35 years (range 5-64 years). For MO cases, the median age was 35 years (range 6-62 years), and the median age of FOPTD cases was 32 years (range 5-64 years).

Sixteen cases were seen in consultation, and the tentative diagnosis or differential diagnosis was provided by the submitting pathologist for 10 cases. In 7 cases, the correct diagnosis of MO or FOPTD was suggested (including 1 case of FOPD diagnosed as MO). Besides the correct diagnosis, second preferred diagnosis was proposed in 3 of the 7 cases and included the following: Nora lesion, extraskeletal osteosarcoma, and parosteal osteosarcoma. Two incorrect diagnoses comprised giant cell tumor of soft tissue and osteosarcoma. Seven cases were sent without a submitting diagnosis to "rule out sarcoma."

Microscopically, both MO and FOPD lesions were composed of loosely textured or myxoid, richly vascular fibroblastic proliferation indistinguishable from NF, with extravasated erythrocytes, scattered osteoclast-like giant cells, and varying amounts of collagen fibers. Osteoid merging with trabeculae of variably mineralized woven bone could be seen interspersed between the fibroblasts, always being rimmed by prominent osteoblasts. In MO, injured and regenerating myocytes were randomly scattered throughout the lesions. Three MO cases showed blood-filled aneurysmal bone cyst-like pseudocystic spaces. In 6 MO and 3 FOPD cases, islands of mildly atypical and cellular hyaline cartilage with enchondral ossification were present. Eventually, some cases contained well-formed trabeculae of mature mineralized lamellar bone, which were predominantly localized at the periphery of the lesions. Generally, MO lesions were more circumscribed than FOPD but almost invariably showed microscopic foci of infiltrative growth between the muscle fibers.

The well-developed complete or incomplete zonal pattern, as defined by de Silva et al [4], with centralized immature NF-like proliferation and peripheral bony maturation with or without nodules of hyaline cartilage (the incomplete pattern further

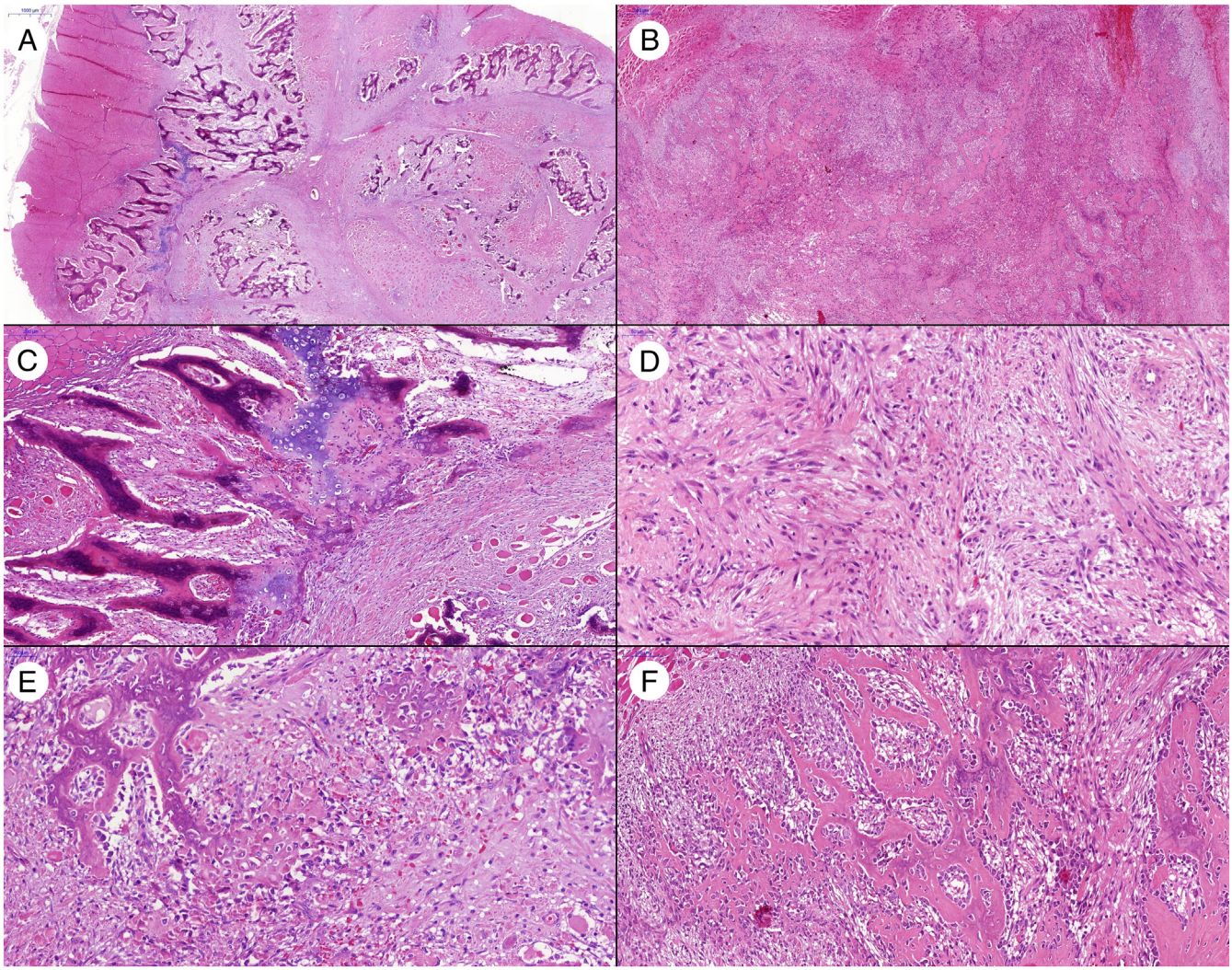

Fig. 1 Histological features of MO (shown) overlap with FOPD (left column—A, C, E: case 2; right column—B, D, F: case 6). A, C, and E, In the first case, there were randomly distributed foci of maturing lamellar bone, islands of hyaline cartilage, and only few foci with osteoid and immature woven bone production. The bony outer shell is incomplete. B, D, and F, The second case showed haphazard intermingling of fibroblastic proliferation with abundant osteoid deposits merging with trabeculae of immature woven bone, and no definite zonal pattern.

characterized by gaps in the outer shell of mature bone), was present in 6 MO cases and 3 FOPD cases. The mature pattern [4], comprising mostly of mature woven or lamellar bone and islands of cartilage with small areas of sparsely cellular collagenous tissue, was seen in 4 MO cases and 2 FOPD cases. One lesion of MO and 1 lesion of FOPD showed immature pattern [4], typified by NF-like proliferation, with only sparse osteoid and no definite zonal pattern. Finally, 4 MO cases and 6 FOPD cases showed haphazard intermingling of fibroblastic proliferation with abundant osteoid deposits merging with trabeculae of immature woven bone, and randomly scattered sheets of mature lamellar bone, without any zonal pattern (termed by us as *haphazard–no zonal pattern*). Examples of MO and FOPD are presented in Figs. 1 and 2. Unusual and "alarming" features of MO/FOPD, such as the presence of "atypical" cartilage, "atypical" fibroblasts, and ABC-like pseudocysts, are presented in Fig. 3.

3.2. Molecular genetic findings

The sequencing results are summarized in the Table. Using the Archer FusionPlex Sarcoma kit NGS panel, 5 of 7 (71.4%) MO cases and 4 of 5 (80%) FOPD cases, which could be analyzed, showed *COL1A1-USP6* fusion. In 8 MO and 7 FOPD cases, the analysis failed due to the suboptimal quality of RNA of the archival tissue, possibly aggravated by the prolonged decalcification. Thus, considering MO and FOPD together as a single entity, 75% of the analyzed cases were positive for *COL1A1-USP6* rearrangement, which provides confidence limits CI_{95} = 47%-91% for population estimate of *COL1A1-USP6* positivity.

All fusion-positive cases, with the exception of a single case, showed the presence of the following 2 types of *COL1A1-USP6* fusions. The first type was characterized by breakpoints in exon 1 of *COL1A1* gene (chr17:48278772) and exon 1 of

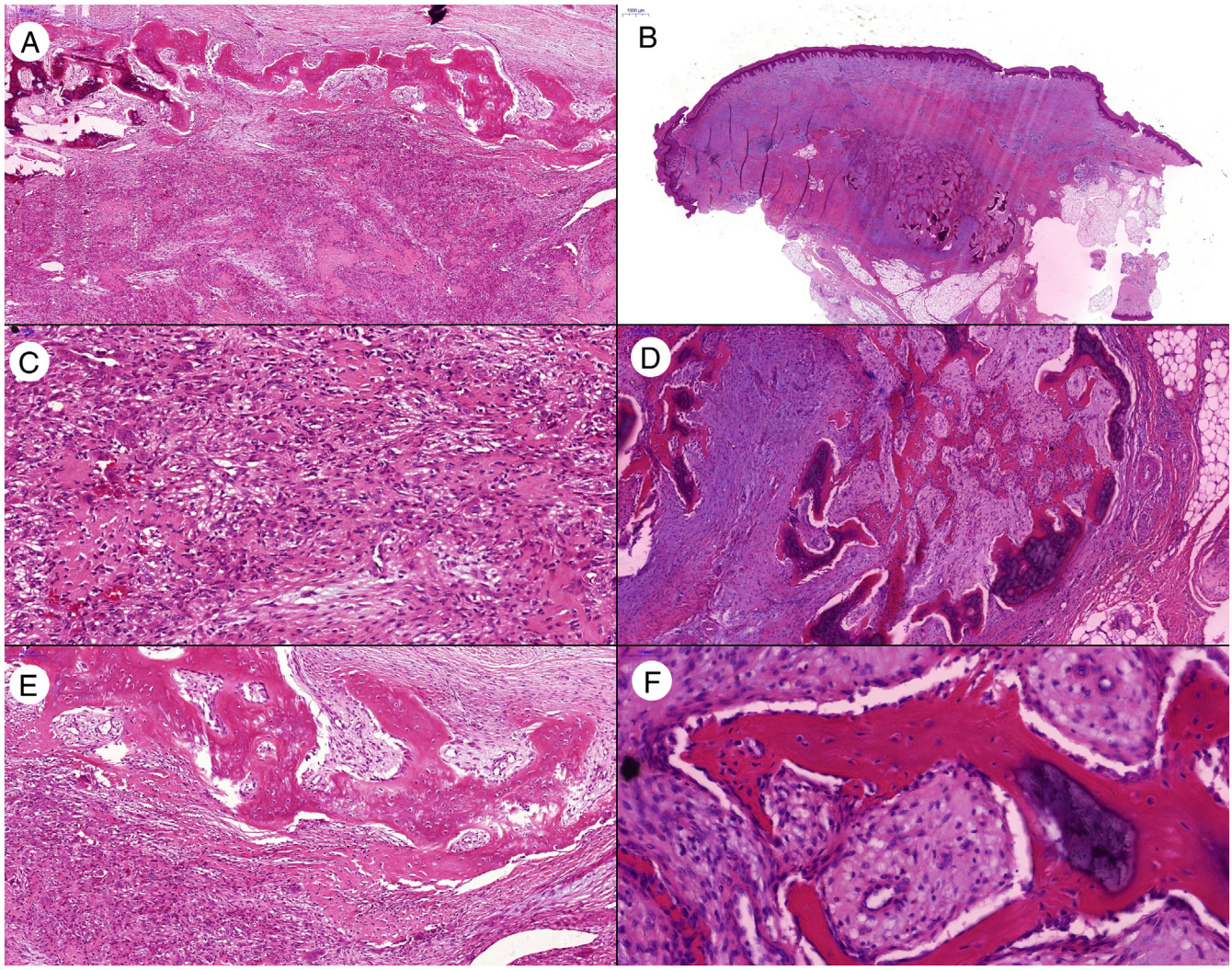

Fig. 2 Histological features of FOPD (shown) overlap with MO (left column—A, C, E: case 17; right column—B, D, F: case 23). A, C, and E, The first case showed complete zonal pattern, with continuous shell of lamellar bone at the periphery of the lesion (A). NF-like proliferation with some osteoid was found in the center (C) and maturing bone at the periphery (E). B, D, and F, The second case was almost entirely composed of mature lamellar bone and hypocellular fibrous tissue, without any zonal configuration.

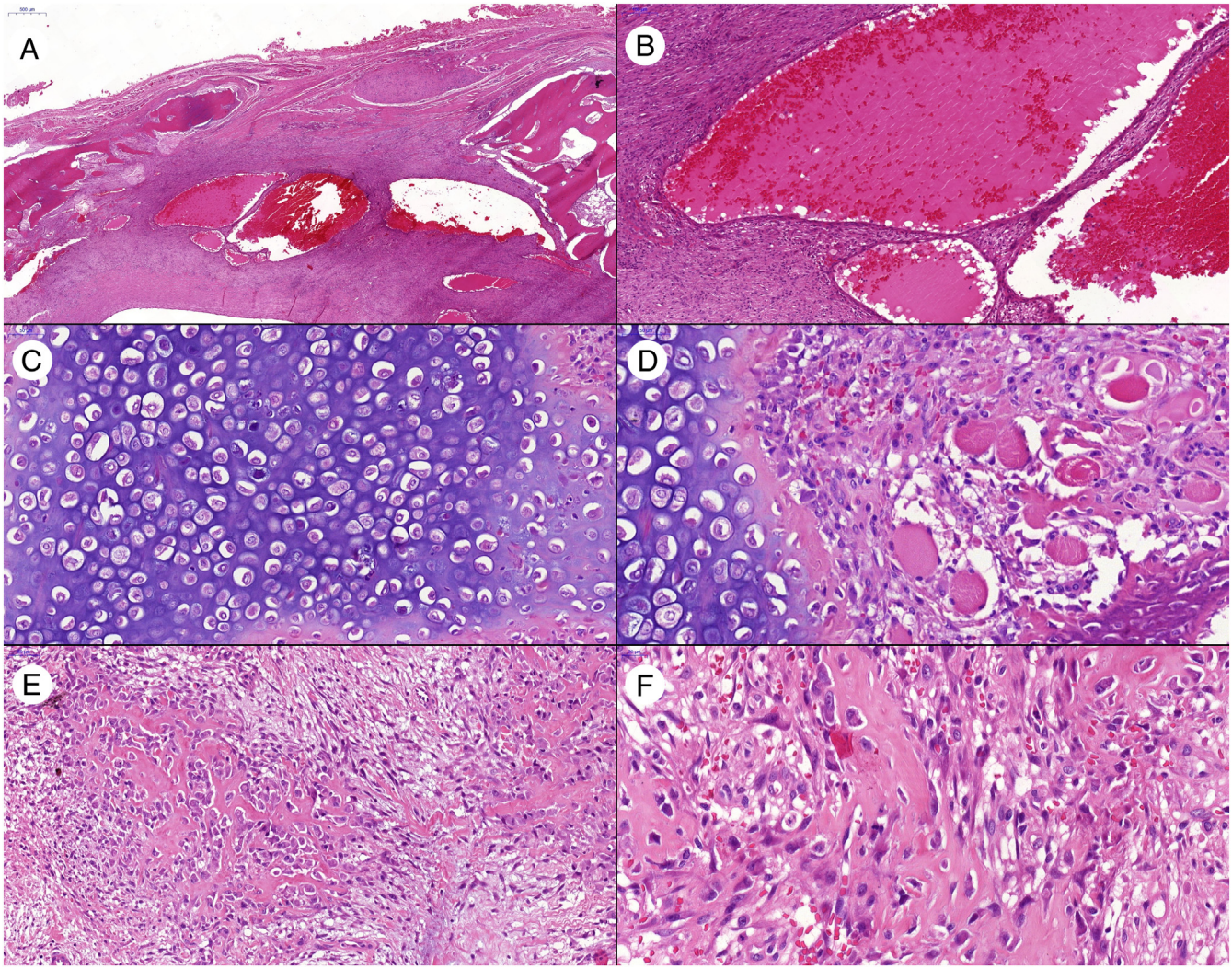

Fig. 3 Unusual and "alarming" features of MO and FOPD. A and B, Aneurysmal bone cyst-like pseudocystic spaces infrequently occur in MO. C and D, Islands of hypercellular and mildly atypical cartilage, contiguous with plump fibroblasts at the periphery, may raise concern for chondrosarcoma or chondroblastic osteosarcoma. E and F, "Atypical" plump and mitotically active fibroblastic proliferation with immature bone production may lead to the diagnosis of osteosarcoma.

USP6 gene (chr17:5033231), and the second type had exon 1 of *COL1A1* gene (chr17:48278772) rearranged with exon 2 of *USP6* gene (chr17:5033662) (Fig. 4A). The third fusion type, which was detected in a single case (#25), involved exon 1 of *COL1A1* (chr17:48278772) and exon 3 of *USP6* (chr17:5033897) (Fig. 4B). The reference transcript sequences used for describing *COL1A1* and *USP6* have accession numbers NM_000088.3 and NM_004505.2, respectively. Chromosomal position is described using reference genome GRCh37.p13.

4. Discussion

Initially identified in ABC [13-15] and later in NF [16], *USP6* gene rearrangement is a common finding in a group of so-called *USP6*-induced neoplasms [17]. Extraosseal soft tissue ABC [18,19], giant cell reparative granuloma of the hands and feet (best regarded as a solid variant of ABC of small bones) [20], and cellular fibroma of tendon sheath (best viewed as tenosynovial variant of NF) [21] are other *USP6*-induced tumor family members. The nature of these lesions was long considered to be reactive, but the discovery of recurrent *USP6* gene rearrangement supports their neoplastic character. In addition to this shared molecular background, all of these lesions share some clinical and morphological features, such as the tendency for self-limited growth, low recurrence rate even when incompletely excised, the presence of plump (myo)fibroblasts, and variable bone production.

Recently, the spectrum of *USP6*-induced neoplasms has been expanded by the discovery of *USP6* rearrangement in both MO as well as FOPD [10,11]. In 2 studies, the Dutch authors detected *USP6* rearrangement in 4/5 (80%) FOPD and 8/9 (88.8%) analyzed MO cases [10,11]. Subsequently,

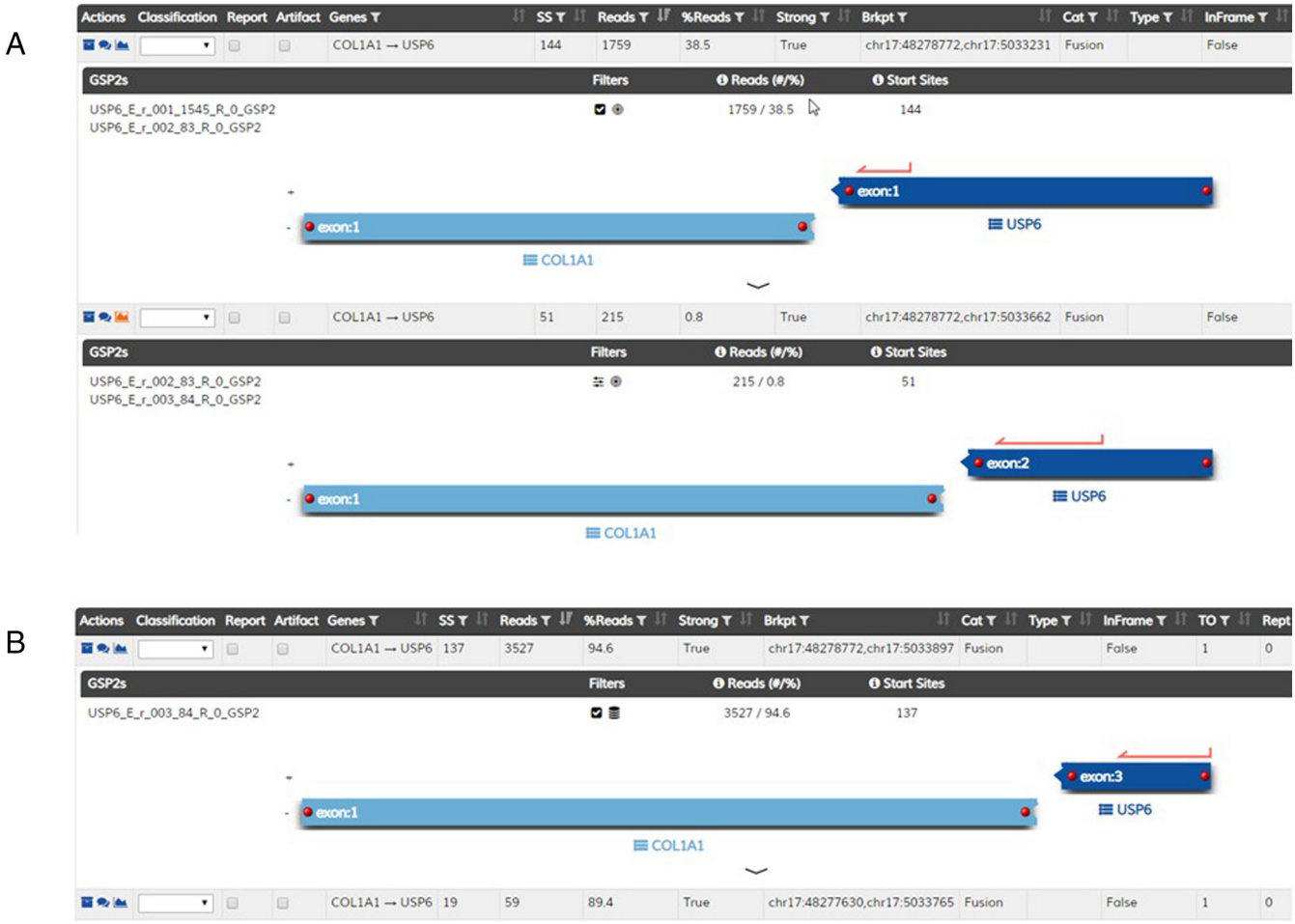

Fig. 4 Details of detected fusion transcripts in *COL1A1-USP6*. A, Types 1 and 2. B, Type 3.SS (start sites)—number of unique starts of reads involving the fusion; Reads (#)—number of reads involving the fusion; %Reads—percentage of reads involving the fusion of all reads in the locus (from Archer Analysis software).

COL1A1 was identified by fluorescence in situ hybridization as a fusion partner of *USP6* in 4/6 MO cases [12]. Interestingly, *USP6* rearrangement was previously identified in 2 patients with radiologic and histologic features consistent with

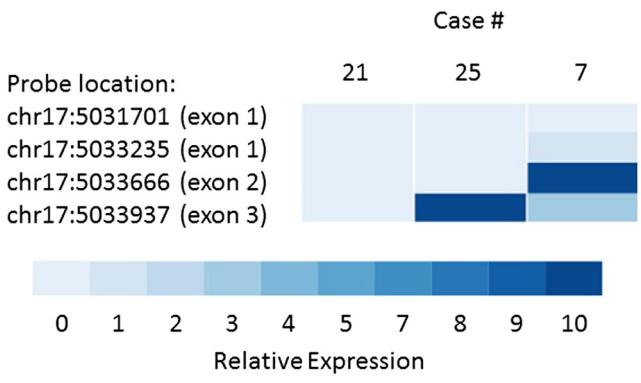

Fig. 5 Heatmap of relative expression of *USP6*. Relative expression was determined using reference genes *CHMP2A, GPI, RAB7A*, and *VCP*. Case 21 is negative for USP6 fusion; case 25 shows overexpression only in exon 3; and in case 7, overexpression is in exons 2 and 3.

MO, but the authors considered these lesions to be soft tissue ABC rather than MO [22]. In ABC, *CDH11* (cadherin 11 gene) was originally identified as the fusion partner for *USP6*, but several alternate partners were soon discovered, including *TRAP150*, *ZNF9*, *OMD*, *COL1A1*, *SEC31A*, *E1F1*, *FOSL2*, *RUNX2*, *PAFAH1B1*, *STAT3*, and *CTNNB1* [15,17,19,23,24]. In contrast to ABC, the most common fusion partner of *USP6* in NF is *MYH9* (a member of the nonmuscle myosin class II family), with alternate fusion partners represented by *RRBP1*, *CALU*, *CTNNB1*, *MIR22HG*, *SPARC*, *THBS2*, and *COL6A2* [16,17,25,26]. In the current study, we found *COL1A1-USP6* fusion in 75% of analyzed MO/FOPD cases, which reaffirms that MO and FOPD represent a morphological spectrum of the same entity, related to and sometimes indistinguishable from other *USP6*-driven lesions, especially extraosseal ABC [18,22].

With the exception of 1 case (case # 25) with breakpoints in *COL1A1* exon 1 and *USP6* exon 3, all fusion transcripts detected in this study were represented by *COL1A1* exon 1 fused to a of *USP6* exon 1 or 2 (with majority fused to USP6 exon 2). Identical finding was previously described in ABC [15] and in

a case of an unclassified benign bone lesion, for which no histologic details were provided [27]. The mechanism of *USP6* protein activation in the cases described herein is uncertain. The overexpression of USP6 transcripts with exons located beyond the breakpoints is likely driven by strong promoter from the fused *COL1A1* gene (Fig. 5). This explanation is plausible because overexpression of an oncogene driven by a strong promotor of *COL1A1* is known to operate in another neoplasm, dermatofibrosarcoma protuberans, in which case the role of oncogenic fusion partner is played by *PDGFB* [28]. The use of *COL1A1* translation start would produce a truncated USP6 protein. However, USP6 protein functionality can be preserved if *USP6* translation starts (type 1 and 2 fusions) [15] or an alternative translation start that preserves functional domains of *USP6* protein is used (type 3 fusion). As a result, upregulation of functional oncoprotein USP6 can be driven by *COL1A1* promoter, which is likely responsible for the neoplastic transformation. Indeed, oncogenic function of USP6 was previously shown to be associated with its overexpression, which was followed by activation of Wnt/β-catenin pathway [29].

The Archer FusionPlex Sarcoma kit only covers exons 1-3 of *USP6*, so there is a theoretical possibility of missing the fusions occurring at different exons of *USP6.* However, to the best of our knowledge, no fusion breakpoints of *USP6* outside the regions covered in this study were described in the Fusion Hub [30] or elsewhere in the literature. On the other hand, NGS technique allows to detect different fusion partners of *USP6* in the covered exons; however, no other potential fusion partners, apart from *COL1A1,* were found in MO so far [12]. Thus, *COL1A1* rearrangement seems to be quite characteristic for MO/FOPD, whereas *MYH9* and *CDH11* rearrangements are hallmarks of NF and ABC, respectively [15-17,19,23-26].

In conclusion, we identified *COL1A1-USP6* fusions in a majority of MO and FOPD cases, which now may be included in the *USP6*-related family of neoplasms. These lesions are notorious for mimicking various low-grade and high-grade soft tissue sarcomas [4-7,9,31]. The presence of *USP6* gene rearrangement in the majority of NF, ABC, and MO/FOPD cases represents a very useful ancillary test, particularly in limited biopsies and in cases when clinical history and/or imaging studies are not available to the pathologist (which is a common scenario in our experience) [25,31,32].

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