



“*PRRX1*-rearranged mesenchymal tumors”: expanding the immunohistochemical profile and molecular spectrum of a recently described entity with the proposed revision of nomenclature

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Abstract

Since the publication of the 2020 World Health Organization classification of soft tissue and bone tumors, the classification of “fibroblastic” tumors has expanded to include a novel subset of tumors characterized by *PRRX1::NCOA1/2* gene fusions. These tumors defy conventional classification and are morphologically distinct, characterized by a multi-nodular growth of bland spindle cells suspended in a myxo-collagenous stroma with mild cytologic atypia, “staghorn-like” vessels, and variable perivascular hyalinization. Mitotic activity is rare, and necrosis is not identified. Herein, we present six additional cases of *PRRX1*-rearranged mesenchymal tumors, including five cases with *PRRX1::NCOA1* fusion and one case with *PRRX1::KMT2D* fusion. Three cases (3/6, 50%) demonstrated focal co-expression of S100 protein and SOX10, thereby expanding the immunohistochemical profile of this emerging entity. Like prior reported cases, there was no evidence of malignant behavior on short-term follow-up. The novel fusion, *PRRX1::KMT2D*, further expands the molecular spectrum of this entity and leads to a proposed revision of the provisional nomenclature to “*PRRX1*-rearranged mesenchymal tumor” to both accommodate non-*NCOA1/2* fusion partners and allow for the possibility of partial neural or neuroectodermal differentiation.

Keywords Mesenchymal tumor · *PRRX1* · *NCOA1* · *KMT2D* · Spindle cell · Soft tissue

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Introduction

Since the publication of the 2020 World Health Organization classification of soft tissue and bone tumors [1], the classification of so-called fibroblastic tumors has expanded to include a novel subset of tumors characterized by *PRRX1::NCOA1/2* gene fusions [2]. These morphologically unique tumors were first formally described in 2019 in a series of four cases by Lacambra et al. [3], who proposed the name “*PRRX1-NCOAx*-rearranged fibroblastic tumor.” These distinct tumors are characteristically multinodular, well-circumscribed, predominantly hypocellular, and composed of bland spindle cells growing in a myxo-collagenous stroma with minimal to mild cytologic atypia. Mitotic activity is rare, and necrosis is not identified. The tumors are most often centered in the subcutis and follow a benign clinical course following marginal excision. Since their initial description, additional studies have further characterized and

expanded the morphologic spectrum of this newly recognized mesenchymal tumor [4–6].

Herein, we present six additional cases of *PRRX1*-rearranged mesenchymal tumors, a subset of which demonstrated variable degrees of expression of S100 protein and *SOX10*, thereby broadening the immunohistochemical profile of this emerging entity. Moreover, one of our cases harbored a novel *PRRX1::KMT2D* fusion, which expands the molecular spectrum of this tumor. Based on these observations, we propose a revision to the provisional nomenclature from “*PRRX1-NCOAx*-rearranged fibroblastic tumor” to “*PRRX1*-rearranged mesenchymal tumor” to both accommodate non-*NCOA1/2* fusion partners and allow for the possibility of partial neural or neuroectodermal differentiation.

Materials and methods

Case selection

This study was approved by the Institutional Review Boards of the participating institutions. All cases were identified either through routine clinical practice or through expert subspecialty consultation by the authors. Clinicopathologic features of all six cases were assessed.

Immunohistochemistry

Immunohistochemical stains were performed on available 4- μ m formalin-fixed paraffin-embedded (FFPE) tissue sections for each case using standard techniques. Due to the consultative nature of the cases, immunohistochemistry techniques and panels varied among contributing institutions. The details of the staining protocols and antibody sources are available upon request.

Next-generation sequencing (NGS)

Cases were sent for testing with the Sarcoma Targeted Gene Fusion/Rearrangement (SARCP) panel, performed at Mayo Clinic Laboratories. The SARCP panel is a custom-designed, PCR-based panel developed in collaboration with Qiagen. The panel is designed to detect 138 gene fusions (>280 gene variants) in 39 sarcoma types. Next-generation sequencing (NGS) is performed on an Illumina MiSeq instrument, and the NGS data is analyzed using an in-house developed bioinformatic pipeline called SeekFusion. Case 3 underwent additional testing at Cleveland Clinic using an anchored multiplex polymerase chain reaction and at the University of Washington using FusionPlex analysis, neither of which identified any gene fusion. Finally, at Bioptical Laboratory, Ltd. (Plzen, Czech Republic), RNA libraries were prepared using the TruSight Oncology 500 Kit (Illumina) according

to the manufacturer’s protocol. The original set of probes for fusion detection was replaced with TruSight RNA Pan-Cancer Panel (Illumina) targeting 1385 genes. Data analysis for fusion detection was performed using Dragen RNA app version 4.0.4 (Illumina). Case 4 was analyzed using TruSight RNA Fusion panel (Illumina, Inc., San Diego, CA, USA) at the Institute of Pathology, Friedrich-Alexander University Erlangen-Nürnberg in Germany as previously described in detail [7]. Cases 5 and 6 were analyzed using the TruSeq RNA Access Library Prep Kit (Illumina, San Diego, CA, USA) as previously described [8].

Results

Clinically, the tumors frequently presented as slow-growing nodules centered in the subcutaneous tissue of middle-aged patients (median, 41 years; range, 29–65 years) with a female predominance (4 female, 2 male). The duration of the clinical history varied from weeks to years with one patient reporting a 4–5-year history of a slow-growing mass prior to presenting for excision. While most of the tumors were centered in the superficial subcutaneous tissue, two were intramuscular and involved deeper soft tissue. Half of the cases involved the head and neck region (neck, $n=2$; forehead, $n=1$), and half involved the trunk (chest wall, $n=1$; flank, $n=1$; back, $n=1$). Most tumors were relatively small in size (median, 3.2 cm; range, 2.2–9.5 cm) with only one case being larger than 4.0 cm.

Each patient underwent a marginal to complete excision, which grossly showed a circumscribed, multi-nodular, solid and firm, white-tan mass (Fig. 1) involving the subcutaneous tissue. Microscopically, the characteristic multi-nodularity was further appreciated from low-power (Fig. 2 A, B). The



Fig. 1 Resection specimens typically showed a circumscribed, multi-nodular, solid and firm, white-tan mass

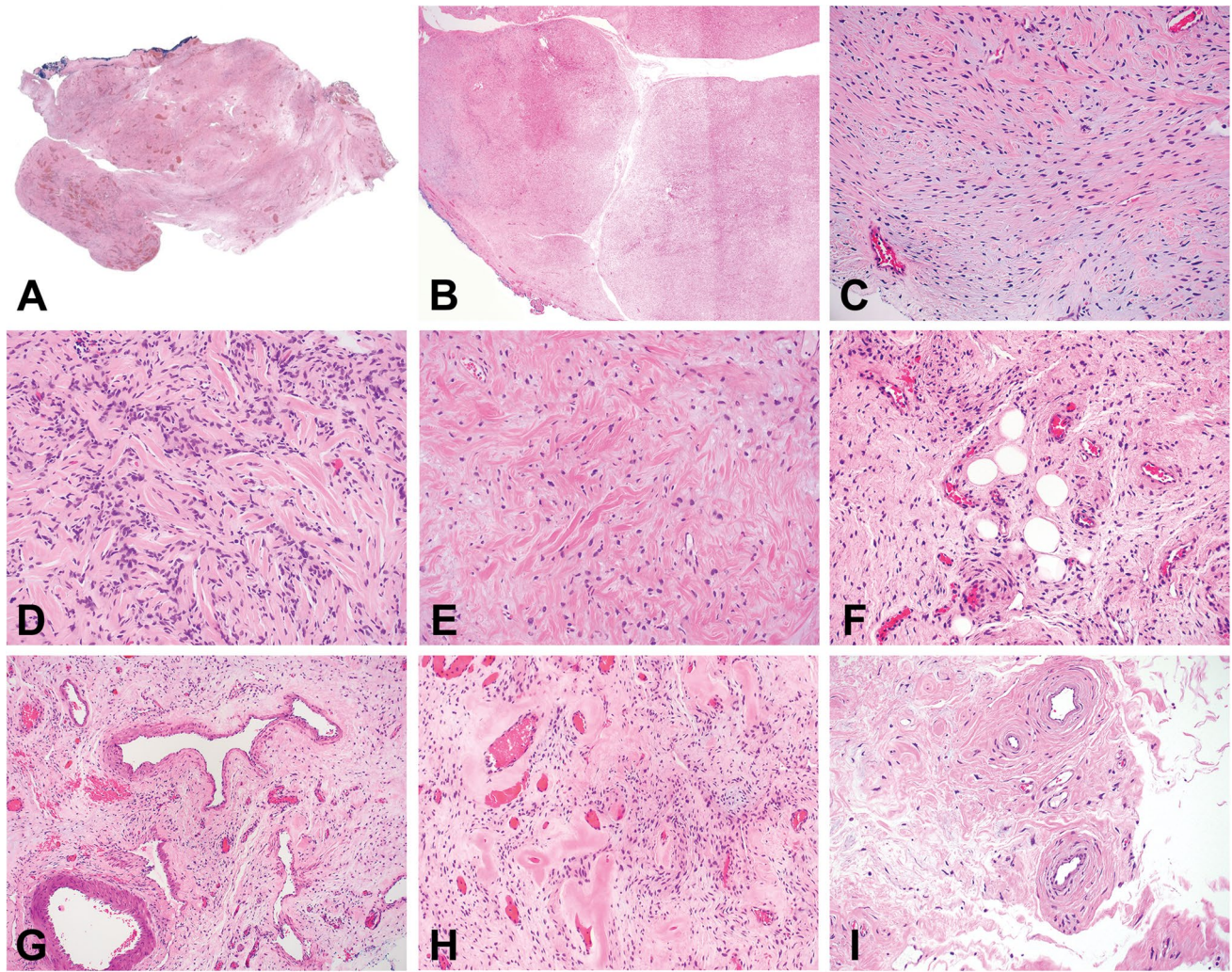


Fig. 2 *PRRX1*-rearranged mesenchymal tumors are usually treated with conservative excision, which often shows a circumscribed and multinodular bland spindle cell neoplasm (**A**, **B**). These spindle cell neoplasms are predominantly hypocellular (**C**) with focal areas with increased cellularity (**D**). The spindle cells grow in a myxo-

collagenous stroma with ropey collagen bundles (**E**). One case also had a focal area with entrapped benign adipose tissue (**F**). Along the periphery of the lesion, scattered “staghorn-like” vessels with prominent perivascular hyalinization are present (**G–I**)

tumors were composed of bland, predominantly hypocellular spindle cells (Fig. 2C) with focal areas with increased cellularity (Fig. 2D). The tumors had, at most, mild cytologic atypia and were embedded in a myxo-collagenous stroma with ropey collagen bundles (Fig. 2E) and rare mast cells. No melanin pigment was identified. One case had a focal area with entrapped benign adipose tissue (Fig. 2F). Along the periphery of the lesion, scattered “staghorn-like” vessels with prominent perivascular hyalinization were variably present (Fig. 2 G–I). Mitotic figures were inconspicuous, and no areas of necrosis were identified.

Immunohistochemical stains showed that scattered cells were positive for S100 protein (Fig. 3) in four cases (4/6, 67%) and SOX10 (Fig. 3) in three cases (3/6, 50%), while all tested cases were negative for CK cocktail, EMA, SMA,

desmin, CD34, STAT6, MUC4, CD117, MDM2, and CDK4. One case (Case 6) was also diffusely positive for pan-TRK, raising the possibility of a TRK-rearranged neoplasm. All control slides are stained appropriately.

In five of the cases, next-generation sequencing (NGS) revealed a gene rearrangement between *PRRX1* exon 1 at genomic position Chr1:g.170633600 and *NCOA1* exon 13 at genomic position Chr2:g.24949458. Case 3 underwent additional testing with several sarcoma-targeted gene panels, including the SARCP panel at Mayo Clinic Laboratories, the Sarcoma Fusion NGS panel at Cleveland Clinic, and FusionPlex analysis at the University of Washington. All three targeted panels screened for alterations in the *NCOA1* gene; however, they did not specifically search for gene rearrangements involving either *PRRX1* or *KMT2D* and failed to

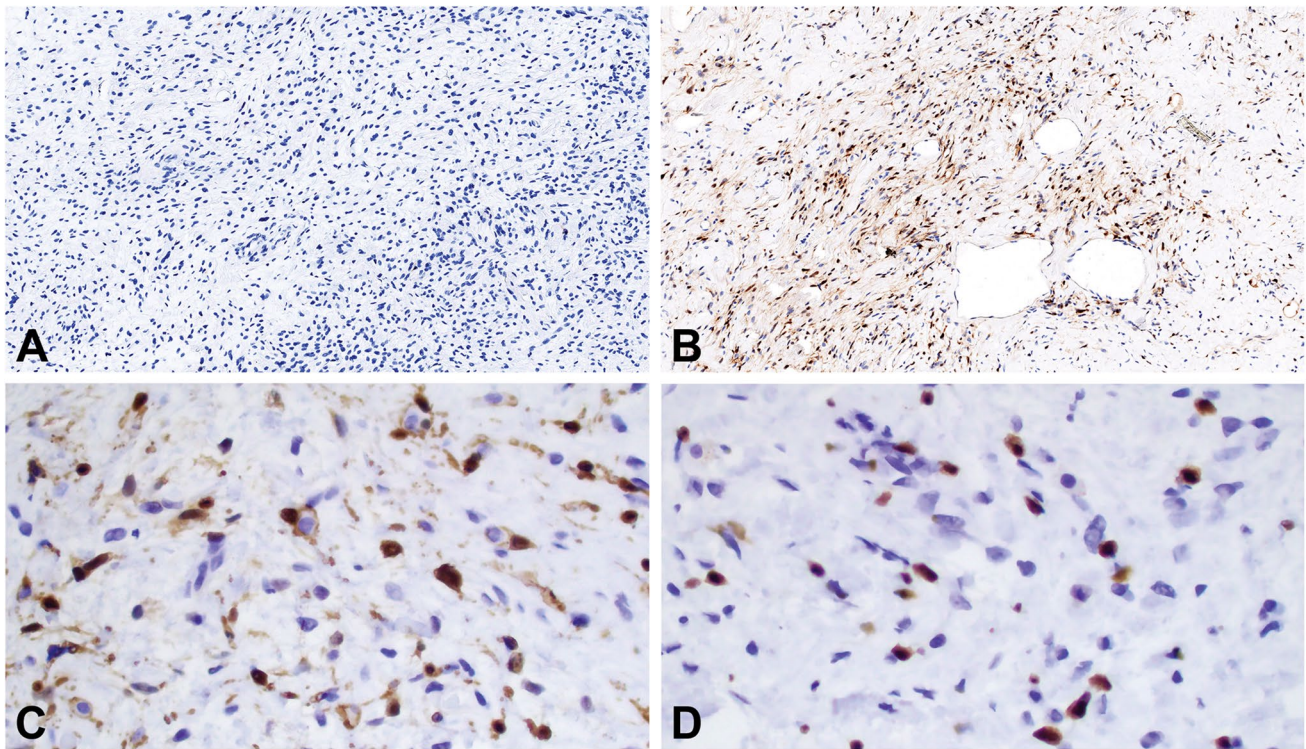


Fig. 3 Immunohistochemical stains showed that while several cases were negative for both S100 protein and SOX10 (A, Case 5), a subset of cases (4/6, 67%) demonstrated focal expression of S100 protein (B,

Case 6). Three cases showed focal positivity for both S100 protein (C, Case 1) and SOX10 (D, Case 1)

identify any gene fusions. Further molecular testing using a TruSight RNA Pan-Cancer Panel (Illumina) eventually revealed a reciprocal fusion of *KMT2D* and *PRRX1*. The sample showed 3 co-existing breakpoint-defined subclones affecting adjacent exons 25, 26, and 27 of *KMT2D*. The morphologic features and immunohistochemical profile of the mesenchymal tumor with *PRRX1::KMT2D* fusion were the same as the mesenchymal tumors with *PRRX1::NCOA1* fusion (Fig. 4).

All patients with clinical follow-up (range, 4–16 months; median 9 months) were alive with no evidence of disease at last follow-up.

Discussion

Since the first description of *PRRX1*-rearranged mesenchymal tumors in 2019 by Lacambra et al. [3], 20 cases, including the six cases presented in this series, have been reported in the literature (Table 1). The most common fusion partner for *PRRX1* is *NCOA1* ($n=17$), followed by *KMT2D* ($n=2$) and *NCOA2* ($n=1$). Clinically, the tumors most often present as slow-growing nodules centered in the subcutaneous tissue of middle-aged patients (median, 40 years; range, 20–76 years) with an equal gender distribution (10 male, 10

female). The most common anatomic locations are the neck ($n=4$), abdominal wall ($n=3$), shoulder ($n=2$), and groin ($n=2$). The lesions are well-circumscribed, multi-nodular, and composed of bland spindle cells growing in a myxo-collagenous stroma with rope-like collagen bundles and inconspicuous mitotic activity. Cellularity is generally low but often focally increased; cytologic atypia is, at most, mild; and necrosis has not been reported. Furthermore, “staghorn-like” vessels, often present at the periphery of the tumor, have also been a frequent finding. A subset of cases demonstrates focal immunohistochemical expression of S100 protein (6/20, 30%) and SOX10 (at least 3/11, 27%). Since S100 and SOX10 co-expression is present in a significant subset of cases, it may be utilized as a useful diagnostic hint, while at the same time representing a potential diagnostic pitfall. Co-expression of these two markers also raises the possibility of partial neural or neuroectodermal differentiation, which may be explored further in subsequent studies. Of the fourteen cases with clinical follow-up, all patients treated with simple, conservative excision are alive with no evidence of disease, suggesting benign behavior; however, long-term follow-up is still warranted to fully understand the full biologic potential of this emerging entity.

PRRX1 (paired related homeobox 1) is a gene that encodes a DNA-binding protein that acts as a transcription

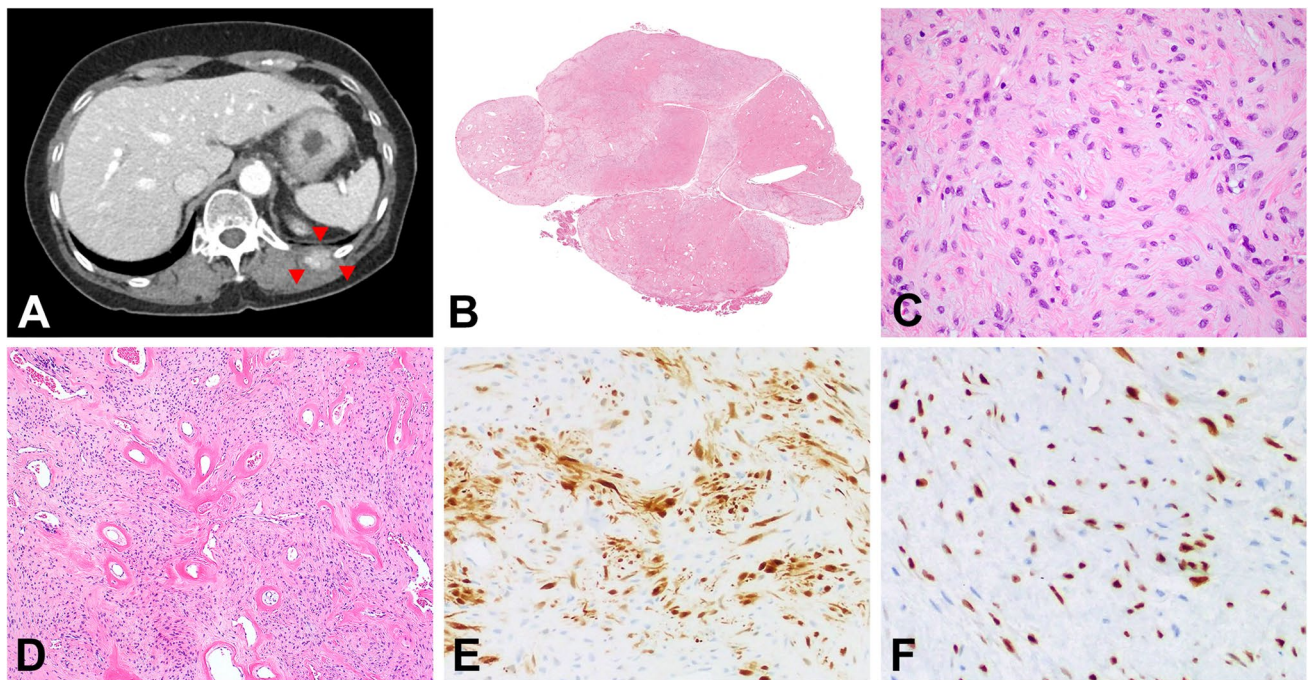


Fig. 4 Mesenchymal tumor with *PRRX1::KMT2D* fusion (Case 3). A 65-year-old female presented with a soft tissue mass involving her left posterior chest wall. Axial CT scan (A) showed that the mass (arrowheads) arose within the skeletal musculature near the uninvolved rib. Excision of the mass showed a multinodular bland spindle

cell neoplasm growing in a myxo-collagenous stroma (B, C). Scattered vessels with prominent perivascular hyalinization were present (D). Immunohistochemical stains showed that the tumor cells were focally positive for both S100 protein (E) and SOX10 (F)

co-activator that is important in development. Fusions involving *PRRX1* have previously been reported in acute myelogenous leukemia [9]. In *PRRX1*-rearranged mesenchymal tumors, the most common fusion partner is nuclear receptor coactivator 1 (*NCOA1*), also known as steroid receptor coactivator-1 (*SRC-1*), which is a transcriptional coregulatory protein that contains nuclear receptor-interacting domains [10]. *NCOA1* mediates transcriptional up-regulation by acetylating histones [11]. When *PRRX1* is fused to *NCOA1*, the nuclear receptor binding protein of *NCOA1* is lost, being replaced by exon 1 of *PRRX1*, whereas the transcriptional activation domains of *NCOA1* remain intact. While less common than *NCOA1*, one tumor with *PRRX1::NCOA2* has been reported [3]. *NCOA2* fusions have also been described in other soft tissue tumors including mesenchymal chondrosarcoma [12], spindle cell rhabdomyosarcoma [13], uterine adenocarcinoma [14], and biphenotypic sinonasal sarcoma [15], among others.

PRRX1-rearranged mesenchymal tumors can mimic both benign and malignant lesions. The bland spindle cells with rope-like collagen bundles and rare mast cells can resemble the *RBI*-deficient family of tumors, including spindle cell lipomas when rare areas with entrapped benign adipose tissue are present. The finding of CD34 positivity and loss of Rb1 expression, however, contrasts with the immunohistochemical profile of *PRRX1*-rearranged

mesenchymal tumor. The focal staining for both S100 protein and SOX10 in a subset of *PRRX1*-rearranged mesenchymal tumors, along with the prominent perivascular hyalinization, could be mistaken for a schwannoma on limited sampling with core needle biopsy. However, the lack of Verocay bodies, lack of distinct Antoni A and B areas, and lack of strong, diffuse staining for both S100 protein and SOX10, could help to exclude schwannoma. The focal staining for S100 protein could further raise consideration for an unusual, non-ossifying variant of ossifying fibromyxoid tumor (OFMT); however, the lack of expression of desmin as well as the absence of *PHF1* gene rearrangements eliminates this possibility. Nevertheless, the expression of SOX10 is not a feature of OFMT and helped exclude OFMT as a diagnostic consideration. The focal staining for S100 protein, along with diffuse expression of pan-TRK in one case, also raises the possibility of kinase-fused tumors, which can also have hyalinized blood vessels and myxoid stroma. In contrast to *PRRX1*-rearranged mesenchymal tumors, kinase-fused tumors often have an infiltrative growth pattern, rarely have ropey collagen bundles, often express CD34, and are not known to express SOX10. The presence of “staghorn-like” vessels at the periphery of the lesion can further mimic solitary fibrous tumor (and, interestingly, unsupervised hierarchical clustering of RNA-Seq data has shown that *PRRX1*-rearranged

Table 1 Summary of clinical and molecular pathologic findings in reported cases of *PRRX1*-rearranged mesenchymal tumors

Case	Age (y)/Sex	Location (depth)	Size (cm)	S100 protein	SOX10	Gene fusion	Follow-up (months)	Reference
1	55/F	Thigh (subcutis)	4.0	Positive (patchy, weak) in one of four cases	Negative in individual cases tested	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (24)	Lacambra et al. [3]
2	33/M	Neck (subcutis)	14.0			<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (6–18)	Lacambra et al. [3]
3	43/F	Neck (subcutis)	3.0			<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (6–18)	Lacambra et al. [3]
4	21/F	Groin (subcutis)	2.0			<i>PRRX1</i> (exon 1):: <i>NCOA2</i> (exon 15)	ANED (6–18)	Lacambra et al. [3]
5	40/M	Knee (deep)	13.0	Negative	N/A	<i>PRRX1</i> (exon 1):: <i>KMT2D</i> (exon 22)	N/A	Puls et al. [22]
6	49/M	Abdominal wall (subcutis)	4.0	Negative	N/A	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (2)	Dermawan et al. [4]
7	43/M	Axilla (subcutis)	5.5	Negative	N/A	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (3)	Dermawan et al. [4]
8	34/F	Shoulder (subcutis)	N/A	Negative	N/A	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	N/A	Dermawan et al. [4]
9	41/F	Abdominal wall (subcutis)	4.0	Negative	Negative	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	N/A	Dermawan et al. [4]
10	76/F	Abdominal wall (subcutis)	2.6	Negative	Negative	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (1)	Dermawan et al. [4]
11	20/M	Hip (subcutis)	5.0	Negative	N/A	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (1.5)	Dermawan et al. [4]
12	23/M	Scalp (subcutis)	2.9	Negative	Negative	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (26)	Chen et al. [5]
13	46/M	Groin (subcutis)	5.0	Negative	Negative	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (7)	Chen et al. [5]
14	23/M	Shoulder (subcutis)	2.5	Positive (focal)	Negative*	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	N/A	Cloutier et al. [6]
15	46/F	Neck (subcutis)	2.2	Positive (focal)	Positive (focal)	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (4)	Current series (Case 1)
16	36/M	Neck (subcutis)	3.4	Positive (focal)	Positive (focal)	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (5)	Current series (Case 2)
17	65/F	Chest wall (intramuscular)	4.0	Positive (focal)	Positive (focal)	<i>PRRX1</i> (exon 1):: <i>KMT2D</i> (exons 25–27)	ANED (12)	Current series (Case 3)
18	37/F	Flank (subcutis)	9.5	Negative	Negative	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	N/A	Current series (Case 4)
19	29/M	Forehead (frontal muscle)	2.5	Negative	Negative	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	N/A	Current series (Case 5)
20	56/F	Back (subcutis)	3.0	Positive (focal)	Negative	<i>PRRX1</i> (exon 1):: <i>NCOA1</i> (exon 13)	ANED (16)	Current series (Case 6)

*Lesional cells are considered to be the non-pigmented tumor cells (not including pigmented melanocytes) [6]

Abbreviations: ANED, alive with no evidence of disease; F, female; M, male; N/A, not available; y, years

mesenchymal tumors cluster closely with solitary fibrous tumor [3]). Fortunately, the lack of nuclear staining with STAT6 excludes this possibility. The rare presence of fusions involving the *NCOA2* gene raises the possibility of soft tissue angiofibroma, which has been described to have fusions involving *AHRR::NCOA2* [16] and *GTF2I::NCOA2* [17]. The lack of staining with EMA, which is frequently positive in soft tissue angiofibroma, and careful attention to morphologic features, particularly the different pattern of tumor vasculature, can help to distinguish these two entities. *PRRX1*-rearranged mesenchymal tumors can also resemble sarcomas, including low-grade fibromyxoid sarcoma (LGFMS), sclerosing epithelioid fibrosarcoma (SEF), and the recently described *KMT2A*-rearranged sarcomas. The lack of immunohistochemical expression of MUC4 could exclude both LGFMS and SEF, while the lack of usually more high-grade morphological features combined with NGS studies could help exclude a rare *KMT2A*-rearranged sarcoma.

Similar to *PRRX1*-rearranged mesenchymal tumors, NGS has identified another new subset of clinically significant fibroblastic tumors characterized by gene rearrangements involving *KMT2A*. In 2019, Yoshida et al. first described two sarcomas with *KMT2A* (*MLL*) fusions, one each having *YAP1* and *VIM* partners [18]. Prior to being described in soft tissue tumors, lysine methyltransferase 2A (*KMT2A*) was known as a frequent fusion partner in ~10% of acute leukemias [19, 20], while fusions have also been reported in type B2 and B3 thymomas [21]. Within soft tissue pathology, *KMT2A*-rearranged sarcomas usually have infiltrative growth, distinct morphologic features resembling SEF when fused to *YAP1*, and aggressive behavior. In a subsequent study, Puls et al. described seven additional tumors with *YAP1::KMT2A* fusions, as well as one case with *PRRX1::KMT2D* fusion, which was notably distinct from the other tumors with *KMT2A* alterations [22]. Their case with *PRRX1::KMT2D* fusion morphologically resembled our Case 3, was multi-nodular, well-circumscribed without infiltrative borders, relatively hypocellular, had no areas resembling SEF, and lacked both mitotic activity and necrosis. Puls et al. conceded that the tumor was morphologically similar to those described by Lacambra et al. and noted prominent perivascular hyalinization as described in our cases. Furthermore, the patient with the previously described case of *PRRX1::KMT2D*-rearranged tumor was confirmed to be well and without disease at last clinical follow-up over 2 years after the publication of their article (personal communication with Drs. Puls and Flucke). Based on the morphologic similarities and seemingly benign clinical behavior, we think that these lesions with *PRRX1::KMT2D* fusions are best classified with the *PRRX1*-rearranged mesenchymal tumors as opposed to the aggressive *KMT2A*-rearranged sarcoma family.

KMT2D (also known as *MLL2*) encodes histone-lysine methyltransferase 2D belonging to the same family as *KMT2A* [23]. *KMT2D* predominantly monomethylates H3K4 whereas *KMT2A* shows mono and dimethyltransferase activity [24]. Somatic *KMT2D* loss-of-function mutations are frequently found in a variety of human cancers, including prostatic adenocarcinoma and lung squamous cell carcinoma [25, 26]. In sarcomas, a *KMT2D::BCOR* gene fusion has been identified in a large pelvic undifferentiated round cell sarcoma in a 10-year-old girl [27], and point mutations in *KMT2D* have been identified in approximately 25% of adamantinoma tumors [28]. While the characterization of soft tissue tumors with *KMT2D* rearrangements continues to evolve, it is important to note that both *KMT2A* and *KMT2D* are frequently not included in solid tumor or sarcoma-targeted gene panels due to the low prevalence of structured alterations in these tumors [29]. Fortunately, sarcoma-targeted gene panels continue to expand as new entities are described, and both *KMT2A* and *KMT2D* alterations can often be identified within sequencing panels for hematolymphoid neoplasms.

In summary, we present six additional cases of *PRRX1*-rearranged mesenchymal tumors, expanding the immunohistochemical profile with co-expression of S100 protein and SOX10. We also expand the molecular spectrum with a relatively novel *PRRX1::KMT2D* fusion, which appears to fit best within the family of *PRRX1*-rearranged mesenchymal tumors, and propose a revision of the provisional nomenclature from “*PRRX1-NCOAx*-rearranged fibroblastic tumor” to “*PRRX1*-rearranged mesenchymal tumor” to both accommodate non-*NCOA1/2* fusion partners and allow for the possibility of partial neural or neuroectodermal differentiation. Due to the tumor’s ability to mimic other benign and malignant lesions, molecular support, including coverage of *KMT2A* and *KMT2D*, is essential to avoid misclassification and advance our understanding of this emerging entity.

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Author contribution Laura Warmke contributed a case, interpreted the results, collected data, and prepared the manuscript draft. Michael Michal and Petr Martinek analyzed and interpreted the results and performed molecular analysis. Nasir Ud Din contributed a case and collected imaging findings. Abbas Agaimy helped with study conception and design and data collection. Raul Perret, François Le Loarer, and Isabelle Hostein contributed a case and helped with the analysis and interpretation of results. Lysandra Voltaggio contributed a case and helped with data collection. John Gross contributed a case, helped with study conception and design, and performed analysis and interpretation of results. All authors reviewed the results and approved the final version of the manuscript.

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Declarations

Ethics approval This study was performed in accordance with the ethical standards of the participating institutions. No animals were involved in this research.

Conflict of interest The authors declare no competing interests.

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