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BRIEF REPORT

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A novel *IRF2BP2::CDX2* Gene fusion in digital intravascular myoepithelioma of soft tissue: An enigma!

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Abstract

Soft tissue myoepitheliomas (STM) are benign myoepithelial neoplasms (of nonsalivary gland origin) arising, most commonly within subcutaneous and deep soft tissues of the extremities and rarely within bones. To the best of our knowledge, the intravascular location of STM as well as the identification of a novel *IRF2BP2::CDX2* fusion have not been previously reported. Herein, we report a case of spindle cell myoepithelioma arising within the intravascular space of the right index finger in a 52-year-old male of more than 20 years duration. Histopathology demonstrated an intravascular tumefactive lesion composed of predominantly plump banal spindle cells in a fascicular arrangement within a mixed collagenous and chondromyxoid stroma colliding with papillary endothelial hyperplasia (Masson tumor). By immunohistochemistry, the lesional cells were positive for keratin-AE1/3, epithelial membrane antigen, S100, SOX10, glial fibrillary acid protein, calponin and negative for CD34, smooth muscle actin, desmin, p63, and ERG. Fluorescence in situ hybridization for *EWSR1* gene rearrangement was negative. Next-generation sequencing detected a novel *IRF2BP2::CDX2* fusion involving Exon 1 of the *IRF2BP2* gene and Exon 2 of the *CDX2* gene confirmed by reverse transcriptase polymerase chain reaction and Sanger sequencing. Further, clinical evaluation for a salivary gland mass in the head and neck region and magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis was performed with no evidence of tumor elsewhere. Taken together, the overall features were considered diagnostic of STM. Our current case underscores the novelty of the *IRF2BP2::CDX2* gene fusion in STM and its exceptionally rare intravascular location.

KEYWORDS
collision tumor, digital intravascular location, *IRF2BP2::CDX2* gene fusion, Masson tumor, molecular genetics, myoepithelioma of soft tissue

1 | INTRODUCTION

Soft tissue myoepitheliomas (STMs) have gained increasing interest and characterization within recent literature. STMs demonstrate predominantly or exclusively myoepithelial differentiation; the histogenesis of which has not been well elucidated. The majority of STMs occur on the limbs and limb girdles, arising within the subcutaneous and deep soft tissues as well as bone.[1,2] A comprehensive molecular

profiling of STM indicates that ~45% of cases harbor *EWSR1* gene rearrangement with a variety of different partner genes such as *POU5F1*, *PBX1*, *ZNF444*, *ATF1*, and *KLF17*.[3,4] Furthermore, there have been reports of *EWSR1* negative gene fusion STM, including *SRF::E2F1* and those involving *FUS* gene rearrangements.[5] Rearrangements involving *PLAG1*, frequently identified in myoepitheliomas and myoepithelial carcinoma of salivary gland origin, are not observed in STMs, but have been detected in a subset of cutaneous mixed tumors.[6,7] Noteworthy, a rare but distinctive benign cutaneous variant of myoepithelial neoplasm, cutaneous syncytial myoepithelioma, displays a predilection for the distal extremities in adults and exhibits a unique histomorphology and immunophenotypic profile characterized by S100 and epithelial membrane antigen (EMA) reactivity and infrequent keratin expression. Cutaneous syncytial myoepitheliomas harbor recurrent *EWSR1::PBX3* gene fusion in virtually all cases, suggesting that they are phenotypically and molecularly distinct from STM.[3,8]

The histopathological spectrum of STM varies from spindled, ovoid, or epithelioid cells arranged in cords or nests within a hyalinized stroma or arranged in reticular or trabecular pattern within a myxoid stroma.[2] The lesional cells display positive immunohistochemical reactivity to keratins and S100 with variable expression of EMA, glial fibrillary acid protein (GFAP), and SOX10.[1] Herein, we describe a unique case of a spindle cell myoepithelioma harboring a novel *IRF2BP2::CDX2* fusion, arising within the intravascular space of the hand and colliding with papillary endothelial hyperplasia (PEH), and Masson tumor.

2 | MATERIAL AND METHODS

2.1 | Immunohistochemistry

Immunohistochemical stains using the following commercially available antibodies were performed using the Leica Bond III autostainers (Leica Biosystems): CD34 (Cell Marque, QBEnd/10, 1:400), smooth muscle actin (SMA; Dako, 1A4, 1:600), desmin (Dako, D33, 1:200), ERG (BioCare M, 9FY, 1:50), S100 (Dako, R poly, 1:2000), AE1/E3 (Dako, AE1&AE3, 1:1200), Ki-67 (Dako, MIB-1, 1:400), EMA (Dako, E29, 1:700), BCL-2 (Dako, 124, 1:1200), MUC4 (Cell Marque, 8G-7, 1:25), SOX-10 (BioCare, BC34, 1:200), GFAP (Dako, R poly, 1:10000), calponin (Dako, CALP, 1:600), p63 (Biocare, 4A4, 1:300), CD163 (Leica, 10D6, 1:900), and CDX2 (BioGeneX, M mono, 1:300). All protocols were developed by and performed at the OSU Wexner Medical Center Clinical Laboratory, 410 West 10th Avenue, Doan Hall 310, Columbus, OH 43210. All positive and negative controls showed appropriate staining.

2.2 | Fluorescence in situ hybridization

Translocation involving the *EWSR1* gene at 22q12 was evaluated with interphase fluorescent in situ hybridization (FISH) on formalin-fixed and paraffin-embedded (FFPE) tissue sections using a commercially available LSI break-apart probe set (Vysis). The LSI *EWSR1* dual color, break-apart rearrangement probe consisted of a mixture of two FISH DNA probes. The first probe, a ~500 kb probe labeled in SpectrumOrange, flanked the 5′ side of the *EWSR1* gene and extended inward into Intron 4. The second probe, a ~1100 kb probe labeled in SpectrumGreen, flanked the 3′ side of the *EWSR1* gene. Using a panel of normal tissues and well-defined sarcomas not expected to harbor an *EWSR1* translocation, split signals were identified in fewer than 15% of cells.

2.3 | Next-generation sequencing and reverse transcriptase polymerase chain reaction validation

Microscopic examination of an hematoxylin and eosin (H&E) stained slide was performed by a pathologist to identify areas of tumor for macrodissection and subsequent RNA extraction. Areas of tumor consisting of ≥10% neoplastic cells were required for testing. RNA was extracted from 5-μm thick FFPE unstained slides using Qiagen miRNeasy FFPE kits. The SARCP gene fusion panel was used which consists of a targeted, custom-designed, polymerase chain reaction (PCR)-based panel designed in collaboration with QIAGEN. The panel assesses 138 genes for fusions (>280 fusion variants) in 39 sarcoma types. For a list of the genes and the specific targeted regions of each gene see www.mayocliniclabs.com (Test ID SARCP).

In brief, the QIAseq-Targeted RNAscan Panel utilizes a single primer extension target enrichment and unique molecular identifier technology to identify gene fusions. RNA samples were converted to double-stranded cDNA, end repaired, and A-tailed. The cDNA was ligated with a UMI and separate sample index. Adapter-ligated cDNA molecules were subject to limited target enrichment using single primer extension. Universal PCR was carried out to amplify the library and add a second sample index. The final library was then sequenced on a MiSeq sequencer (Illumina). SARCP next-generation sequencing (NGS) data were bioinformatically analyzed using SeekFusion an internal pipeline that uses a combination of traditional alignment and de novo assembly-based approaches. Fusion/rearrangement nomenclature was based on build GRCh37 (hg19) and RefSeq reference transcripts (RefSeq accession numbers) for the genomic coordinates (chr1:g234744193) for *IRF2BP2* and (chr13:g28539152) for *CDX2* corresponding to transcripts NM_182972 and NM_001265, respectively.

2.3.1 | Reverse transcriptase-PCR and sanger sequencing

Reverse transcriptase-PCR (RT-PCR) and Sanger sequencing were performed at the Mayo Clinical Laboratories (Rochester, Minnesota) to confirm the NGS assay-positive results. RNA was extracted from FFPE unstained slides of the tumor using Qiagen miRNeasy FFPE kits. RNA was converted to cDNA using the SuperScript III VILO cDNA synthesis kit. The cDNA was used as the genomic template to specifically amplify the fusion of interest using the following primers designed for the *IRF2BP2::CDX2* fusion (Exons 1–2) developed based on the IGV breakpoint sequence (SARCP NGS results): forward Primer: *IRF2BP2* Exon 1– CAGGCAGGTTGTTGGGTTTC and reverse Primer: *CDX2* Exon

2– TTTCCTCCGGATGGTGATGTAG. Primers were checked for specificity with BLAT and SNP checks. The PCR product was purified using the AMPure XP purification system (Beckman Coulter). Sanger sequencing was performed using universal primers that bind to the UPS tags. The Sanger sequencing product was purified using the Agencourt CleanSEQ Dye-Terminator removal system (Beckman Coulter) and then loaded onto the ABI 3730xl DNA Analyzer (ThermoFisher) for capillary electrophoresis. Sequencing electropherograms were viewed using the Mutation Surveyor v4.09 software (SoftGenetics).

3 | RESULTS

3.1 | Case report

The present case features a 52-year-old male who presented with a right index finger mass (Figure 1A,B). The mass had been present since adolescence (more than 20 years ago) remaining constant in size without associated pain or numbness. An x-ray was performed to reveal a focal, ovoid, soft tissue swelling along the radial aspect of the second digit at the level of the proximal interphalangeal joint without evidence of dislocation or underlying osseous changes (Figure 1C,D). An excisional biopsy was performed with negative margins and sent for pathological examination.

Gross examination revealed a cystic, tan, soft tissue lesion measuring 1.6 × 1.2 × 0.8 cm. The cyst wall was 0.1 cm in maximum thickness with a smooth tan lining. Histopathological evaluation revealed a well-circumscribed tumefactive lesion, composed predominantly banal spindle cell proliferation with cells arranged in tight fascicles, colliding with areas of PEH in association with an organizing thrombus. The less dominant areas consisted of spindled cells within a prominent myxoid stroma arranged in a fine reticular growth pattern as well as cords of banal cells within a hyalinized stroma with minimal pleomorphism and no appreciable increased mitotic rate or necrosis

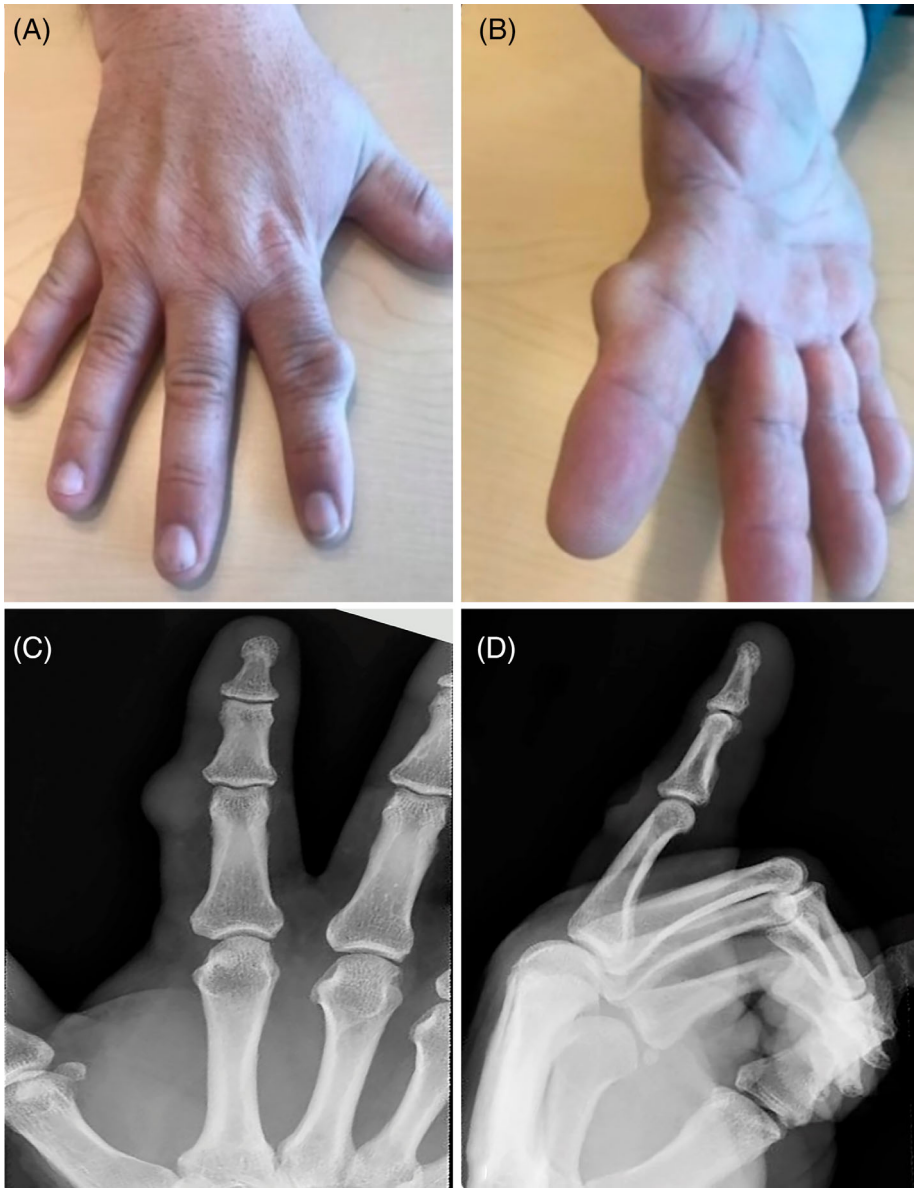

FIGURE 1 Right index finger mass. Dorsal and lateral views of superficial mass located on the radial aspect of the right index finger at the level of the proximal interphalangeal joint (A,B). X-ray (AP and lateral) radiographs demonstrating a focal, ovoid, soft tissue swelling along the radial aspect of the second digit at the level of the proximal interphalangeal joint without evidence of underlying osseous changes (C,D).

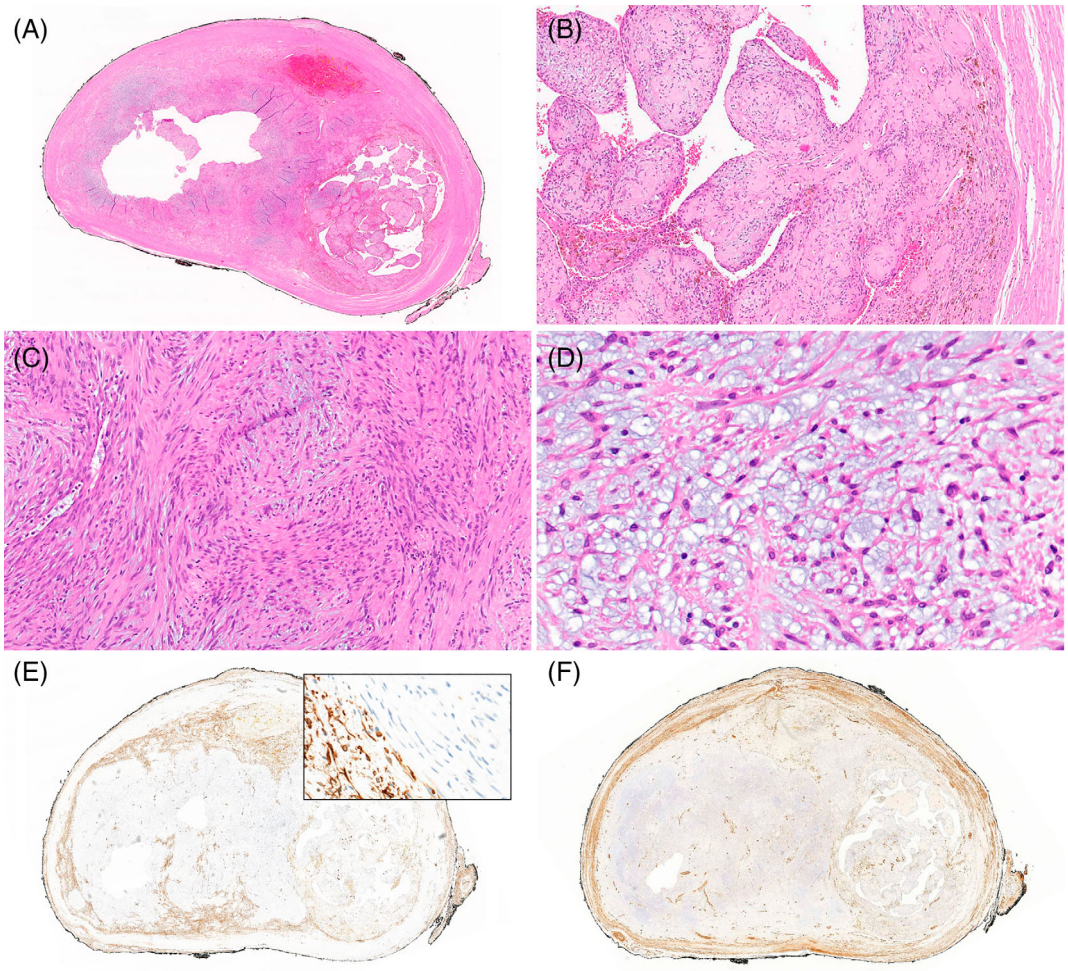

FIGURE 2 Histomorphology by H&E and Immunohistochemistry of the right index finger mass. Low magnification view highlighting the intravascular lesion (A). Papillary endothelial hyperplasia extending from the vascular wall (B). High power view (Magnification ×400) of plump spindle cells arranged in a fascicular pattern within a mixed collagenous and myxoid stroma (C,D). Endothelial cells are highlighted by CD34 staining at low power (E) and high power, magnification ×400 (E insert). Smooth muscle actin highlights smooth muscle cells of vascular wall at low power (F). Endothelial cells lining the surrounding vessel are highlighted by ERG immunostaining at magnification ×400 (G). Lesional cells are strong and diffusely positive for glial fibrillary acid protein, keratin (AE1/E3), epithelial membrane antigen, S100, SOX10, calponin, and CK7 at magnification ×400 (H–N).

(Figure 2A–D). By immunohistochemistry, the lesional cells were positive for keratin-AE1/AE3, EMA, S100, and glial fibrillary acid protein (GFAP) as well as CK7, SOX10, calponin, and BCL-2 and negative for negative for SMA, desmin, p63, CD163 (positive expression identified in intralesional histiocytes), MUC4, CD34, and ERG (positive endothelial lining of the vessel) (Figure 2E–L). The Ki-67 proliferative index was estimated at ~1% by manual quantitation. Taken together, the overall features were those of a benign intravascular spindle cell myoepithelioma of soft tissue in collision with PEH (Masson tumor). In view of the strikingly unique location of this tumor and the histopathologic mimicry with the salivary gland counterpart, we considered the possibility of a vascular tumor emboli from an otherwise pleomorphic adenoma (metastasizing pleomorphic adenoma) but examination of the head and neck region and MRI of the chest, abdomen, and pelvis, were negative for any masses.

FISH for *EWSR1* gene rearrangement was performed due to the identification of *EWSR1* gene rearrangements arising in approximately half of STMs. Translocation involving the *EWSR1* gene at 22q12 was evaluated with interphase FISH and no break-apart signals for the *EWSR1* gene were detected above background. NGS performed at the Mayo Clinic Laboratories identified the *IRF2BP2*::*CDX2* fusion (Figure 3) involving the rearrangement of the *IRF2BP2* gene at Exon 1 (chr1:g234744193) and the *CDX2* gene at Exon 2 (chr13:g28539152). This novel gene fusion was confirmed by RT-PCR and Sanger sequencing. Immunohistochemistry for CDX2 was negative.

Taken together, the pathological diagnosis was intravascular spindle cell myoepithelioma of soft tissue with associated PEH, completely excised with negative margins. The patient has remained free from clinical recurrence, 3 years after complete surgical excision.

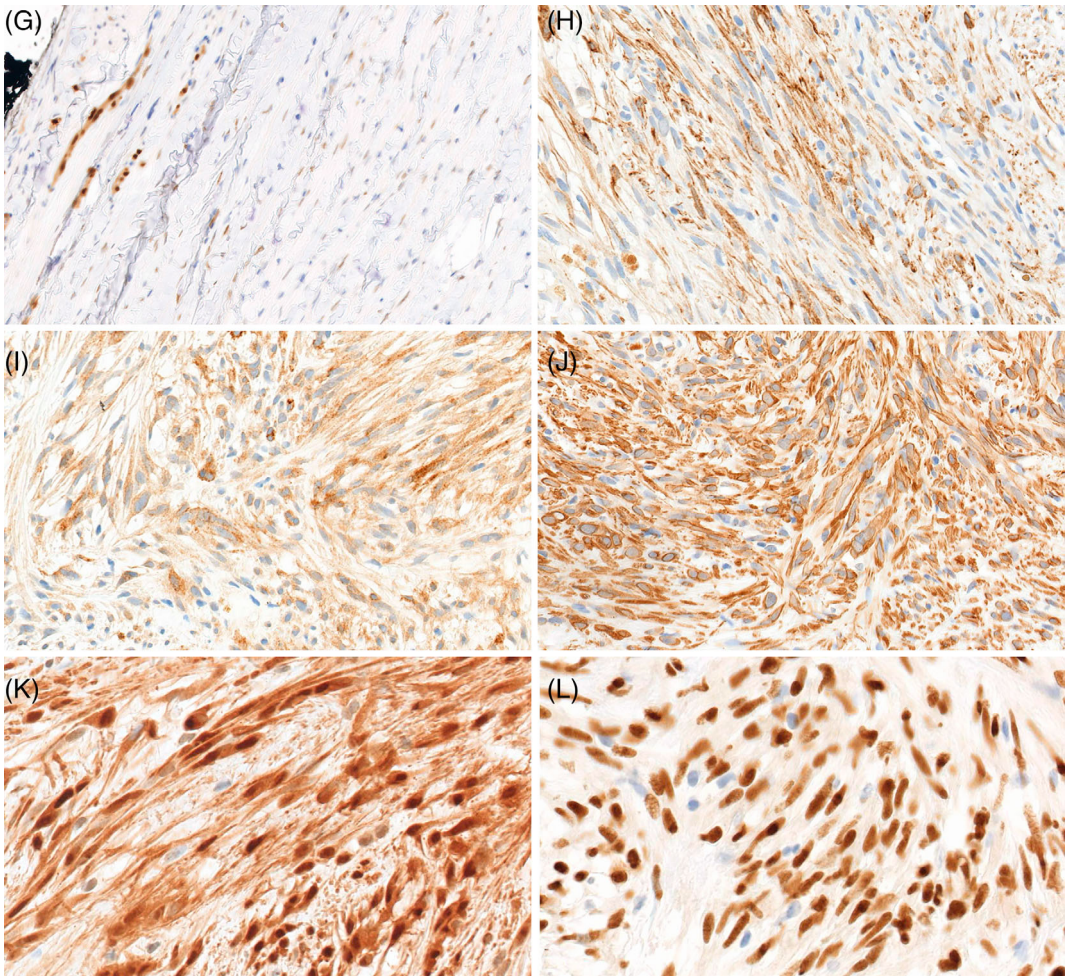

FIGURE 2 (Continued)

4 | DISCUSSION

Soft tissue neoplasms involving the hand and digits are relatively common and comprise a heterogeneous group of entities with distinct histogenesis involving the skin, subcutaneous tissue, tendons, vasculature, and nerves with differing implications for treatment of prognosis.[9]

STM is a relatively rare entity arising as a painless mass within the subcutaneous and deep soft tissue.[10–15] Although diverse in location, STM share morphologic and immunophenotypic characteristics with myoepitheliomas of the salivary gland. The histopathological features display great heterogeneity with a predominantly reticular growth pattern consisting of ovoid, eosinophilic, or spindled cells within a collagenous or chondromyxoid matrix.[1,2,10,16,17] Heterologous differentiation including squamous, adipocytic, osseous, and cartilaginous elements may occur in a minority of myoepitheliomas.[1,12] Lesional cells display frequent expression of broad-spectrum keratins, S100, EMA, and GFAP.[1,2,12] The histopathological features consisting of spindle and epithelioid cells in a reticular pattern within a myxoid stroma and hyalinized stroma, in concert with prototypic immunophenotypic profile (of co-expression for S100 and keratins) were consistent with STM.

Unique to this case, however, is the complete encapsulation of the mass by a vascular structure indicating that the mass arose within the vessel. PEH or Masson tumor is a reactive lesion arising from the organization and recanalization of a thrombus.[18] Located within the vessel of the index case was a focal area of papillary fronds covered by a single layer of endothelial cells consistent with a secondary component of PEH.

Approximately half of the reported cases of myoepithelioma, myoepithelial carcinoma, and mixed tumor of soft tissue harbor recurrent *EWSR1* gene rearrangements.[4] Cases of *EWSR1* rearrangement-negative STMs have been reported. The *SRF::E2F1* gene fusion was identified in a case of a spindle cell myoepithelioma of the iliac region and a mixed type tumor of soft tissue of the foot also found to harbor a second gene fusion, *FUS::KLF17*.[5] Furthermore, the novel *OGT::FOXO3* fusion was reported in two cases characterized as a myoepithelioma-like hyalinizing epithelioid tumor involving the subcutis of the palmar region of the hand.[19]

To date, the *IRF2BP2::CDX2* fusion has not been reported in any of the precedent cases of STM. Moreover, to the best of our knowledge, recurrent fusions involving the *IRF2BP2* and *CDX2* genes have not been described in human neoplasia. Interferon regulatory factor

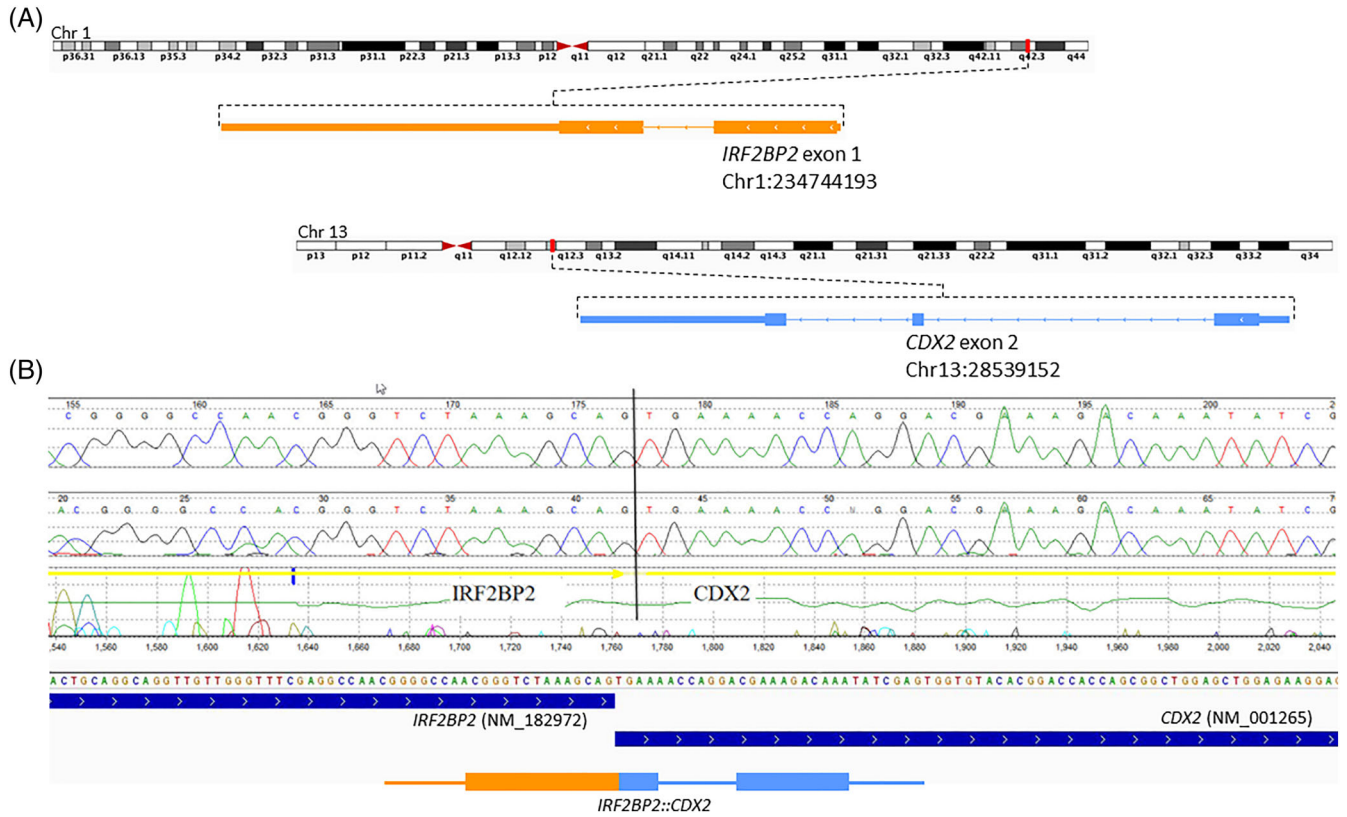

FIGURE 3 Novel *IRF2BP2::CDX2* fusion identified by next-generation sequencing. Schematic showing the *IRF2BP2::CDX2* gene fusion with breakpoints in Exon 1 of *IRF2BP2* (chr1:234744193) and Exon 2 of *CDX2* (chr13:28539152) corresponding to transcript variants NM_182972 and NM_001265, respectively identified by next-generation sequencing and confirmed by Sanger sequencing (B).

2-binding protein 2 (IRF2BP2) encodes a member of the IRF2BP family of transcription factors which function to regulate different cell signaling pathways. Dysregulation of *IRFBP2* signaling is thought to be a key player in tumorigenesis.[20,21] Caudal type homeobax 2 (*CDX2*), at locus 13q12.2, is a member of the caudal-related homeobox transcription factor gene family, that plays an important role in the embryogenesis of the intestinal tract as well as regulation of intestinal-specific genes in cellular growth and differentiation.[22] Dysregulation of the *CDX2* gene has been implicated in various malignancies including acute myeloid leukemia, colorectal carcinoma, pancreatic carcinoma, paranasal carcinoma, cervical carcinoma, and uveal neoplasms.[22] Translocations involving the fusion partner *IRF2BP2* have been described in literature. The *IRF2BP2::NTRK1* fusion has been identified in various cancers including non-small cell lung cancer and *NTRK*-rearranged thyroid carcinomas.[21] In a sarcoma panel validation study, the *IRF2BP2::CDX1* fusion was detected in one case of soft tissue myoepithelioma that was negative for *EWSR1* rearrangements by FISH.[23] The t(1;5) *IRF2BP2::CDX1* fusion has also been identified in one case of mesenchymal chondrosarcoma which display histomorphology similar to classic mesenchymal chondrosarcoma, consisting of hyperchromatic small round to spindled cells arranged in clusters or fascicles with variably formed hyaline cartilage and staghorn vessels, a morphology distinctly different from the present case.[20]

The differential diagnosis of intravascular spindle cell neoplasms is broad and often context dependent. Intravascular fasciitis (considered a variant of nodular fasciitis) is far more common and shows a variable cellular spindled proliferation with associated interstitial collagen, mucous cysts, and inflammation; the degree of which depends on the stage in the temporal evolution of the tumor. However, these lesions are frequently positive for SMA but negative for S100 and keratin. Molecularly, they tend to harbor *USP6* gene rearrangements, a profile that distinguishes them from STM.[24]

Extraskeletal myxoid chondrosarcoma (EMC) shares common morphology with myoepitheliomas. Rearrangements in the NR4A3 gene are commonly encountered in EMC with the majority of cases harboring the *EWSR1::NR4A3* variant fusion.[25] Clinically, EMC tends to occur in deep-seated soft tissues and rarely in superficial locations or digits. Notwithstanding, both entities display eosinophilic spindled to ovoid cells distributed in cords within a myxoid matrix. Moreover, diffuse immunohistochemical reactivity to S100 and keratins are observed in myoepitheliomas and rarely in EMC.[25]

A variant of myoepithelial neoplasms known to occur in the skin, cutaneous syncytial myoepitheliomas, shares overlap features with STM. They comprise a group of mesenchymal neoplasms with myoepithelial differentiation and dermal involvement. They do exhibit characteristic histopathological features, consisting of syncytial growth of ovoid, eosinophilic, or spindled cells. The lesional cells share a similar

immunophenotype to STM with expression of S100 and EMA. However, unlike STM, keratin expression is rare and GFAP expression is variable in cases of cutaneous myoepithelioma.[10] Importantly, virtually all cutaneous syncytial myoepitheliomas are known to harbor *EWSR1*::*PBX3* gene fusion while only about 45% of STM will manifest rearrangement of *EWSR1* gene with multiple partner genes.[3] Rearrangements of *FUS* and *PLAG1*, seen in mixed tumor/chondroid syringoma, have also been detected in a subset of myoepitholiomas.[7,8]

STMs behave largely in a benign fashion.[2] However, despite their low-grade histopathology, local recurrence can occur in up to 20% of cases and in exceptionally rare instances, may behave aggressively with metastasis.[1] The malignant counterpart, myoepithelial carcinoma of soft tissue, is characterized by increased cytological atypia and mitotic activity compared with myoepithelioma. Our index case did not manifest any features of cellular anaplasia to the degree that would be concerning for myoepithelial carcinoma of soft tissue. Second, the long clinical history of >20 years duration of stable size without evidence of metastasis was doubly reassuring of the benign behavior of this entity.

The prognostic implications including local recurrence of STM located within a vessel are not well known. It is conceivable that the index case would parallel a benign course suggesting a prognosis akin to STM occurring in other soft tissue locations reported in precedent literature, given the low-grade histomorphology. Further, the implications of the novel *IRF2BP2*::*CDX2* gene fusion in this entity remain to be seen. Surgical excision remains the treatment of choice for this lesion.

In summary, we present a unique description of an intravascular soft tissue myoepithelioma harboring a novel *IRF2BP2*::*CDX2* gene fusion. This case expands the differential diagnosis of intravascular lesions to now include STM. It is unlikely, though unclear, if the unique location of this entity and novel gene fusion will affect the clinical course and prognosis of the patient.

AUTHOR CONTRIBUTIONS

O. Hans Iwenofu, conceived the project. Ashley Patton, Xiaoyan Cui, Amy Speeckaert, Micayla Zeltman, Steve Oghumu, and O. Hans Iwenofu provided essential tools/data. Ashley Patton and O. Hans Iwenofu wrote the article. All authors approved the final article.

CONFLICT OF INTEREST

The authors declare that they do not have any conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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