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ARTICLE

Primary mammary angiosarcomas harbor frequent mutations in *KDR* and *PIK3CA* and show evidence of distinct pathogenesis

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Abstract

Angiosarcoma (AS) is the most frequent primary sarcoma of the breast but nevertheless remains uncommon, accounting for <0.05% of breast malignancies. Secondary mammary AS arise following radiation therapy for breast cancer, in contrast to primary AS which occur sporadically. Essentially all show aggressive clinical behavior independent of histologic grade and most are treated by mastectomy. *MYC* amplification is frequently identified in radiation-induced AS but only rarely in primary mammary AS (PMAS). As a heterogeneous group, AS from various anatomic sites have been shown to harbor recurrent alterations in *TP53*, MAP kinase pathway genes, and genes involved in angiogenic signaling including *KDR* (VEGFR2) and *PTPRB*. In part due to its rarity, the pathogenesis of PMAS has not been fully characterized. In this study, we examined the clinical, pathologic, and genomic features of ten cases of PMAS, including one patient with bilateral disease. Recurrent genomic alterations were identified in *KDR* (70%), *PIK3CA/PIK3R1* (70%), and *PTPRB* (30%), each at higher frequencies than reported in AS across all sites. Six tumors harbored a *KDR* p.T771R hotspot mutation, and all seven *KDR*-mutant cases showed evidence suggestive of biallelism (four with loss of heterozygosity and three with two aberrations). Of the seven tumors with PI3K alterations, six harbored pathogenic mutations other than in the canonical *PIK3CA* residues which are most frequent in breast cancer. Three AS were hypermutated (≥10 mutations/megabase (Mb)); hypermutation was seen concurrent with *KDR* or *PIK3CA* mutations. The patient with bilateral disease demonstrated shared alterations, indicative of contralateral metastasis. No *MYC* or *TP53* aberrations were detected in this series. Immunohistochemistry for VEGFR2 was unable to discriminate between *KDR*-mutant tumors and benign vascular lesions of the breast. These findings highlight the underrecognized frequency of *KDR* and *PIK3CA* mutation in PMAS, and a significant subset with hypermutation, suggesting a pathogenesis distinct from other AS.

Introduction

Angiosarcomas (AS) represent a heterogeneous group of malignant vascular tumors expressing the morphologic and phenotypic properties of endothelial cells. These tumors represent 1–2% of soft tissue sarcomas and arise within different anatomic sites, among a wide age range, and in a variety of clinical settings, such as prior radiation therapy or chronic lymphedema [1–3]. Surgery and possible radiotherapy are the mainstay of treatment for patients with localized disease [2]. Metastasis is reported in ~50% of cases, often treated with adjuvant chemotherapy [4]. Median overall survival time is ~50 months for local disease and ~10 months for metastatic cases [5]. Treatment with targeted agents, such as tyrosine kinase inhibitors, has shown partial responses in selected patients, but overall prognosis remains poor [6–9].

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AS of the breast is rare, accounting for 0.04% of all breast malignancies, yet remains the most common breast sarcoma [10]. Primary mammary AS (PMAS) arise spontaneously in women with no relevant breast history, typically in their third and fourth decades. Secondary mammary AS (SMAS) occur either in the setting of radiation therapy following breast conservation surgery or lymphedema following mastectomy (Stewart–Treves syndrome); postradiation AS are by far the most frequent contemporaneously [11, 12]. On average, patients with SMAS present at an older age, usually within the sixth or seventh decade and a median postradiation latency of 6–7 years [13, 14]. Primary AS typically involve the mammary parenchyma and may secondarily involve the skin, whereas postradiation AS most often primarily arise in the skin and may invade deeper into the breast [15–18]. AS may be classified into low, intermediate, and high grades based on a combination of histologic features including degree of vasoformative growth, cytologic atypia, mitotic activity, and presence of endothelial multilayering/tufting, solid growth, necrosis, and hemorrhage (blood lakes) [19]. Historically thought to be prognostic, more recent studies have failed to show an association between tumor grade and clinical outcome [20, 21]. Most cases of mammary AS are treated by mastectomy, although the use of breast conserving surgery may be increasing [16, 17, 22, 23]. Frequent sites of metastasis include the lung, liver, contralateral breast, bone, and other skin and soft tissue sites [16, 17, 23].

Distinct differences have emerged among AS subgroups, and prognosis has been shown to vary depending on primary site [2]. Among breast tumors, some reports suggest that SMAS has a worse prognosis than PMAS, while others find no difference [16, 22, 24]. Genomic studies of AS across anatomic sites have shown a heterogeneous mutational spectrum. Activating alterations in mitogen-activated protein kinase (MAPK) pathway genes, such as *KRAS*, *HRAS*, *NRAS*, *BRAF*, and *MAPK1*, were detected in over half of AS cases in one series [25]. Reports of *TP53* mutation vary from 4 to 35% [25–27]. In the breast and other sites, amplification of *MYC* is the hallmark of most postradiation secondary AS (54–100% of cases), while only sparingly reported in primary AS [28–34]. Amplification of *FLT4* (VEGFR3, vascular endothelial growth factor receptor 3) has also been identified in SMAS (18–25% of cases), typically coamplified with *MYC* [28, 31]. Additional recurrently mutated genes in SMAS include *PTPRB* (45%), a tyrosine phosphatase specific to endothelial cells that inhibits angiogenesis, and *PLCG1* (9%), which encodes phospholipase C gamma 1 [27, 35]. In one series of AS from various sites, Antonescu et al. identified mutations in *KDR*, the gene that encodes VEGFR2, in 10% of cases (4/44); all *KDR*-mutant tumors originated in the breast/chest wall (4/17) and included both PMAS and SMAS (two cases each) [36].

As a specific subgroup, the molecular landscape of PMAS has not been fully characterized. Rare cases of PMAS have been analyzed in the aforementioned case series among larger numbers of SMAS or nonmammary AS. Italiano et al. included nine PMAS in their study reporting the absence of both deleterious *TP53* mutations and activating *PIK3CA* mutations (using hotspot analysis on a subset of cases) [26]. To our knowledge, the largest series to date with genomic analysis included 22 PMAS, of which five (23%) harbored *KDR* mutations and four (18%) demonstrated *PLCG1* mutations [35].

In this study, we comprehensively characterize a cohort of PMAS by capture-based next-generation sequencing of 479 cancer-related genes. We sought to define their molecular drivers and determine whether these rare tumors have a pathogenesis distinct from other AS. Although limited in number of cases, our work highlights a high frequency of *KDR*, *PIK3CA*, and *PTPRB* mutations in PMAS, as well as a subset demonstrating hypermutation. Such novel genomic findings may have much-needed therapeutic implications for these aggressive tumors.

Materials and methods

Study population

With institutional review board approval, the pathology archives of Stanford University and the University of California San Francisco were searched for cases of PMAS. Tumors were selected from patients with no known prior breast cancer or radiation treatment. Cases were reviewed to confirm that the tumors were centered in the mammary parenchyma; AS appearing to originate in the dermis were excluded. The series is comprised of ten cases total, including one with bilateral tumors. Clinical information was obtained from online electronic medical records when available.

Capture-based next-generation DNA sequencing

Matched normal and tumor tissue was selected from nine cases for capture-based next-generation DNA sequencing. The bilateral case consisted of separate tumor-only specimens. Sequencing libraries were prepared from genomic DNA extracted from punch biopsies or macrodissected unstained sections from formalin fixed paraffin embedded tissue. Target enrichment was performed by hybrid capture using a custom oligonucleotide library. Capture-based next-generation sequencing was performed at the UCSF Clinical Cancer Genomics Laboratory, using an assay (UCSF500 panel) that targets the coding regions of 479 cancer-related genes, select introns from ~40 genes, and the *TERT*

promoter with a total sequencing footprint of 2.8 Mb (Supplementary Table S1). Sequencing was performed on a HiSeq 2500 (Illumina, San Diego, CA). Duplicate sequencing reads were removed computationally to allow for accurate allele frequency determination and copy number calling. The analysis was based on the human reference sequence UCSC build hg19 (NCBI build 37), using the following software packages: BWA: 0.7.10-r789, Samtools: 1.1 (using htslib 1.1), Picard tools: 1.97 (1504), GATK: 2014.4–3.3.0–0-ga3711, CNVkit: 0.3.3, Pindel: 0.2.5a7, SATK: 2013.1–10- gd6fa6c3, Annovar: v2015Mar22, Freebayes: 0.9.20, and Delly: 0.5.9 [37–47]. Only insertions/deletions (indels) up to 100 bp in length were included in the mutational analysis. Somatic single nucleotide variants and indels were visualized and verified using Integrated Genome Viewer. Genome-wide copy number analysis based on on-target and off-target reads was performed by CNVkit and Nexus Copy Number (Biodiscovery, Hawthorne, CA, USA). Lollipop plots were modified from MutationMapper [48, 49]. Tumor mutational burden was quantified for matched tumor-normal cases. For hypermutated tumors, signatures were delineated by deconstructSigs using nonsynonymous mutations; only alterations with ≥5 mutant reads were reported [50]. Microsatellite instability analysis was performed with MSIsensor and interpreted using revised Bethesda guidelines [51, 52].

Immunohistochemistry

Immunohistochemistry for VEGFR2 was performed on whole slide sections of PMAS and benign vascular lesions using the rabbit monoclonal 55B11 antibody (Cell Signaling Technology, Beverly, MA) at 1:200 with Tris–EDTA antigen retrieval (pH 9).

Results

Clinicopathologic features of primary mammary angiosarcomas

Clinicopathologic features of PMAS included in this study are shown in Table 1 and Fig. 1. All patients were female, with ages ranging from 31 to 64 years (mean 45 years). Nine of 11 tumors were right sided. The majority presented as palpable masses (8/11, 73%). Tumor size at initial excision ranged from 2 to 13.6 cm (mean 5.2 cm). Histologic grades ranged from low to high. All patients ultimately underwent mastectomy; 6 of 11 (55%) mastectomies followed an earlier excision or lumpectomy. Six of 10 (60%) patients were treated with adjuvant chemotherapy and radiation. One woman had germline testing which

Table 1 Clinicopathologic features of PMAS.

Case No.	Laterality	Age	Size (cm)	Presentation	Histologic grade	Surgery	Adjuvant therapy	Sites of metastasis	Follow-up (months)
1	Right	59	2.1	Palpable mass	Low	Excision, mastectomy			NED (38)
2	Right	31	5.6	Mass on imaging	Intermediate	Excision, mastectomy, excision to metastasis	Radiation, chemotherapy	Liver	AWD (24)
3	Right	64	2.8	Palpable mass	Low	Excision, mastectomy			NED (6)
4	Right	32	7.9	Mass on imaging	High	Excision, mastectomy	Radiation, chemotherapy		NED (10)
5	Right	49	3	Palpable mass	Intermediate	Excision, mastectomy	Radiation, chemotherapy		NED (9)
6	Left	33	7	Palpable mass	High	Mastectomy	Radiation, chemotherapy, radiation to metastases	Lung, brain, tonsil, right breast	DOD (11)
7	Right	35	2.1	Palpable mass	Low	Mastectomy, re-excision x3	Radiation, chemotherapy, radiation to metastases	Lung, liver, bone, spleen	DOD (27)
8	Right	49	7.4	Palpable mass	Low	Mastectomy	Radiation, chemotherapy		NED (32)
9	Right	54	6	Palpable mass	Low	Mastectomy		a	NED (44)[a]
9	Left	56	2	Mass on imaging	Low	Mastectomy			NED (17)
10	Right	38	13.6	Palpable mass	High	Lumpectomy, mastectomy			LFU (9)

NED no evidence of disease, *AWD* alive with disease, *DOD* died of disease, *LFU* lost to follow-up.
[a]Excluding occurrence of contralateral tumor at 27 months.

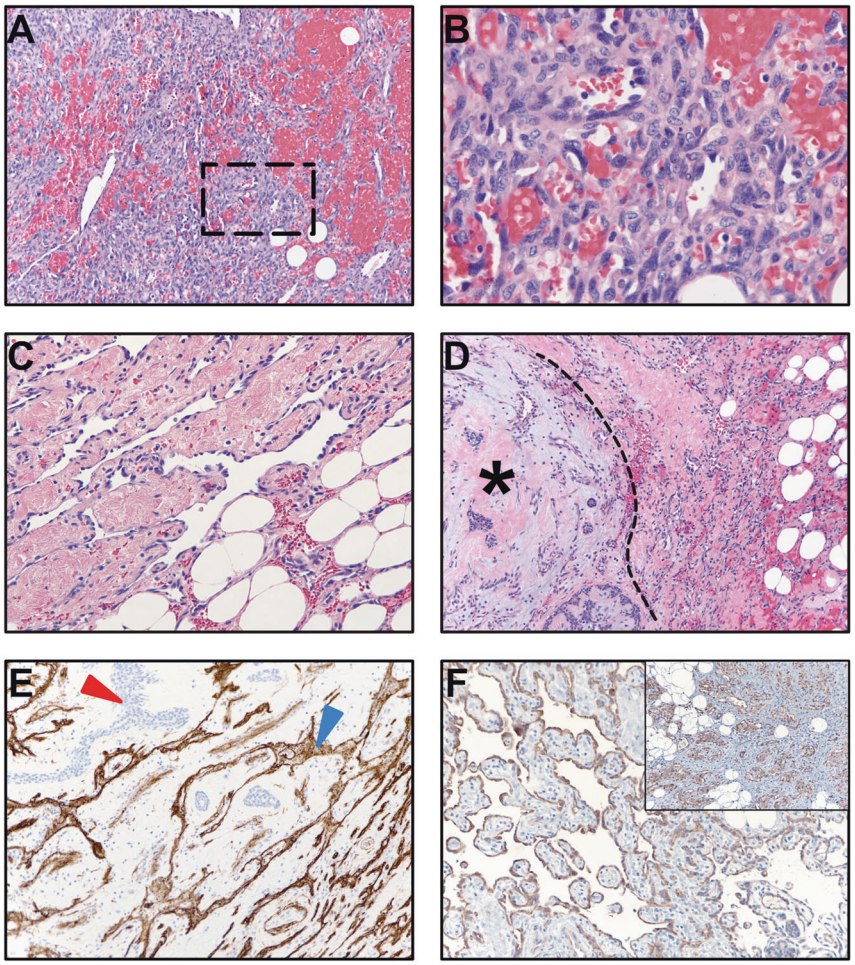

Fig. 1 Morphologic and immunohistochemical features of primary mammary angiosarcomas. Representative photomicrographs of hematoxylin and eosin (H&E)-stained PMAS: (**a**) complex anastomosing channels and "blood lakes" of high grade tumor, (**b**) inset at higher power showing cellular pleomorphism, (**c**) papillary tufts and invasion into adjuvant adipose tissue, (**d**) angiosarcoma involving fibroadenoma (*). **e** Immunohistochemistry for CD34 showing strong and diffuse expression in AS (blue arrowhead) with negative staining in adjacent breast epithelium (red arrowhead). **f** Immunohistochemistry for VEFGR2 was diffusely positive in all PMAS ($n = 8$) and benign vascular lesions ($n = 4$, inset with angiolipoma) tested. Magnification, ×100 (**a**, **d**–**f**), ×200 (**c**), ×400 (**b**).

showed a pathogenic *FANCA* c.987_990delTCAC (p.T329fs) mutation. This patient initially presented with AS of the right breast (Case 9R), and 2 years later subsequently presented with AS of the left breast (Case 9L). She underwent mastectomy for each diagnosis with no adjuvant chemotherapy; the left breast tumor was clinically considered a separate primary AS. Three women demonstrated definite metastasis (Cases 2, 6, and 7); metastatic sites included liver and lung. In patients with available follow-up clinical data (9/10 women, average 22 months), two women died of disease (at 11 and 27 months following excision), one woman is alive with disease, and the remainder have no evidence of residual disease. Although limited in number, no associations were evident between patient age, tumor size, histologic grade, initial surgery, adjuvant therapy, metastasis, and outcome.

Genomic features and immunohistochemistry of primary mammary angiosarcomas

Genomic data are depicted in Fig. 2 and Supplementary Table S2. The mean target sequencing coverage was 548 (± 279) unique reads per target interval (Supplementary Table S3). The number of identified nonsynonymous coding mutations across the 2.8 Mb footprint of the panel ranged from 1 to 74 per Mb (median 3, mean 16 ± 24).

KDR was the most frequently altered gene in the series, detected in seven PMAS (of ten, 70%). Six of these tumors harbored a *KDR* p.T771R hotspot mutation. All seven *KDR*-mutant AS showed evidence suggestive of biallelism: four with loss of heterozygosity (LOH) and three with two separate aberrations (*cis* vs. *trans* orientation could not be definitively determined). Pathogenic alterations in PI3K were also common (7/10, 70%), including six cases with *PIK3CA* mutations (specifically p.P104L, p.P539R, p.E545A, p.M1004V in two cases, and p.M1043I) and one case with two *PIK3R1* mutations. Among the *PIK3CA* alterations, only one mutation (p.E545A of Case 2) was in the most common canonical residue in exon 9 (E542 and E545) and none were in the common canonical residue in exon 20 (H1047) [53]. In addition, inactivating mutations in *PTPRB* were identified (3/10, 30%), with no association with *KDR* or *PIK3CA*. No alterations in *MYC, FLT4*, or *TP53* were identified.

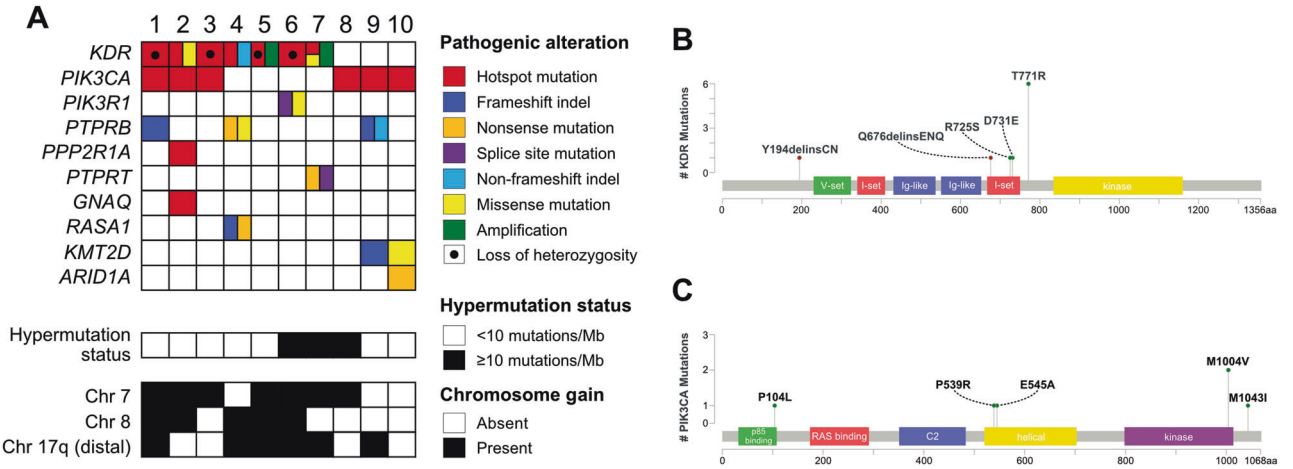

Fig. 2 Genomic features of primary mammary angiosarcomas. **a** Pathogenic alterations and recurrent copy number alterations. Amplification of *KDR* also included coamplification of *PDGFRA* and *KIT* in Case 5 and *KIT* in Case 7. **b** Lollipop plot of all *KDR* mutations. **c** Lollipop plot of all *PIK3CA* mutations.

PLCG1 is not included on the UCSF500 panel and could not be evaluated.

For the patient with bilateral but asynchronous disease, differential tumor sequencing indicated shared mutations in *PTPRB* (two alterations) and *KMT2D*, at mutant allele frequencies not compatible with germline findings (Supplementary Table S4). These results are virtually confirmative of metastasis to the contralateral breast. Interestingly, a *PIK3CA* p.M1004V mutation was identified in the primary AS of the right breast, but this was not detected in the subsequent left breast tumor. As expected, this patient's previously identified germline *FANCA* inactivating mutation was also identified in both specimens (at appropriately ~50% mutant allele frequency). Treated with consecutive mastectomies and no adjuvant therapy, she remains with no evidence of disease nearly 4 years after initial diagnosis. No pathogenic germline alterations were identified in the remaining patients.

Copy number analysis revealed two cases with concomitant amplification of the *KDR* locus, both in mutant-positive tumors. Case 5 demonstrated mutant allele-specific amplification (10×) of 4q11-q13.1 including *KDR*, *KIT*, and *PDGFRA* genes, and Case 7 harbored 4q12 amplification with *KDR* (5×) and *KIT* (2×). Recurrent copy number gains included chromosome 7 (7/10, 70%), distal 17q (6/10, 60%), and the majority of chromosome 8 (5/10, 50%). The bilateral case showed identical copy number changes, with gains in distal 15q and distal 17q in both specimens. Overall, no associations between chromosomal gain and other genomic aberrations were seen.

Hypermutation was detected in three tumors (Cases 6–8), defined as ≥10 mutations/Mb, each with a prevalence of C > T transitions (Supplementary Fig. 1) [54]. Signature analysis of hypermutated cases was inconclusive, with dominant COSMIC Signatures 1 and 6 identified; these are typically ascribed to age and DNA mismatch repair deficiency, respectively. However, there was no association between patient age and hypermutation status, and all tumors tested were microsatellite stable by MSIsensor (cutoff = 10). In addition, hypermutation was seen concurrent with *KDR* or *PIK3CA* alterations.

Based on the high frequency of *KDR* mutations in PMAS, immunohistochemistry for VEGFR2 was performed on the majority of cases ($n = 9$), supplemented with a limited number of benign vascular lesions of the breast including hemangiomas and angiolipomas ($n = 4$). Prior works have published conflicting data, with both VEGFR2 protein overexpression by immunohistochemistry reported in *KDR*-mutant AS, and paradoxically others reporting AS were negative for VEGFR2 expression [36, 55, 56]. Here, we found that VEGFR2 was positive in all vascular lesions tested, with no discrimination between *KDR*-positive and -negative AS, as well as benign entities (Fig. 1f).

Discussion

This work revealed an unexpectedly high frequency of *KDR* and PI3K activating mutations in PMAS, each occurring at ~70%. In fact, every tumor was found to have an alteration in *KDR* and/or *PIK3CA*; the mutations were not mutually exclusive. Here, we confirm the previously reported association between *KDR* mutation and AS of the breast and chest wall, but determination of this high occurrence is made possible by exclusively focusing on PMAS in our series [35, 36]. The hotspot mutation *KDR* p.T771R in exon 16 is particularly prevalent, occurring in the transmembrane domain of VEGFR2. To our knowledge, this alteration has only been reported in vascular lesions: overwhelmingly

cases of AS, with a lone exception of a sporadic angioma arising in a patient on anti-VEGFR2 therapy (ramucirumab) for metastatic rectal cancer [48, 49, 57, 58]. Of note, the *KDR* mutation in this angioma case report was a single copy with no other alteration or evidence of LOH [58]. In contrast, biallelism was present in each of the *KDR*-mutant tumors in our series, a novel finding which suggests it may be necessary for PMAS pathogenesis.

Activating PI3K mutations are common in breast carcinomas but relatively rare in sarcomas. Specific to the breast, *PIK3CA* alterations have been reported in higher grade phyllodes tumors and in one case each of undifferentiated pleomorphic sarcoma and osteosarcoma [59–62]. Yet *PI3KCA* mutations were not identified in AS of the breast or other sites in a prior study despite evidence of PI3K/AKT/mTOR pathway activation [26]. In contrast, *PIK3CA* (and one case of *PIK3R1*) alterations were frequent in our series. Prior work focused on selected exons with canonical *PIK3CA* hotspot mutations, whereas our study more comprehensively assessed the entire coding sequence [26]. Specifically, alterations were detected at P104, P539, M1004 (two cases), and M1043, occurring in exons 2 (adaptor binding domain), 10 (helical domain), and 21 (kinase domain), respectively. Each of these mutations have reported in vitro oncogenic properties and recurrent alteration in breast and other cancers [48, 49, 63–65]. The identification of *PIK3CA* mutations in PMAS may have significant clinical importance, especially with the recent approval of PI3K inhibition for the treatment of *PIK3CA*-mutant advanced breast carcinoma [66].

Other recurrently altered genes in this study include *PTPRB* ($n = 3$) and *KMT2D* ($n = 2$). Mutations in *KMT2D*, a histone methyltransferase, have been previously identified in breast AS among various cancers [59]. Inactivating mutations in *PTPRB* are rare in other tumor types yet frequent in AS, although heretofore had not been reported in PMAS [27]. Each *PTPRB*-mutant PMAS demonstrated at least one truncating alteration, predicted to disrupt the coding sequence before the tyrosine phosphatase domain. Two of three tumors showed a second nontruncating alteration, suggestive of possible biallelism; no features of LOH were observed in the third case with a single frameshift mutation. This pattern of mutation, suggestive but not definitive for a recessive driver mechanism of pathogenesis, is similar to a prior report [27]. Moreover, alterations in other protein phosphatases, such as *PTPRT* and *PPP2R1A*, have been reported in human and canine AS [67]. Although no *KRAS*, *HRAS*, or *NRAS* aberrations were detected in this series, one PMAS showed inactivating somatic alterations in *RASA1*, a negative regulator of the RAS and MAPK pathways, and similarly reported in human and canine AS [67]. Notably, no *TP53*, *MYC*, or *FLT4* aberrations were identified.

Regarding Case 9, the genomic data of bilateral disease is essentially confirmatory of metastasis, despite the 2-year time interval between tumors, absence of adjuvant therapy, and no evidence of additional disease following surgery alone for the past 1.5 years. Clinical germline testing of this patient had shown a pathogenic *FANCA* mutation, and she was managed under the assumption of bilateral primary AS. However, identical somatic nonrecurrent indels in *PTPRB* and *KMT2D* were identified in each tumor, a finding incompatible with two independent malignancies. Mutations in *FANCA* are the most common cause of Fanconi's anemia and have been implicated in increased risk of various cancers, but a specific association with AS is unclear and no evidence of LOH at this locus is identified in either of the patient's tumors. Notably, a *PIK3CA* mutation was detected in the initial right-sided PMAS but not the left-sided tumor; discordance in *PIK3CA* status between primary and metastatic breast cancer is a known phenomenon and may be applicable in this context [68]. Such a case may illustrate the importance of the endogenous microenvironment of the breast that contains niche-promoting elements conducive to contralateral metastasis. The relatively indolent behavior of this case of PMAS is remarkable; in contrast sequencing studies that have positively identified metastasis among metachronous contralateral breast carcinomas have shown poor outcomes [69, 70].

Intriguingly, 3 of 10 PMAS (30%) demonstrated somatic hypermutation. Hypermutation has been recently reported in a subset of sarcomas, primarily with high levels of ultraviolet (UV)-associated mutations and categorized as Signature 7 (or cluster C6) in the hypermutant tumor classification [54, 71]. In fact, in a large series interrogating the tumor mutational burden of 100,000 diverse cancer genomes, hypermutation was detected in ~13% of soft tissue AS, although anatomic site and radiation history were not provided [72]. To our knowledge, the finding of somatic hypermutation specifically in PMAS is novel. Cases were too few to identify any associations between hypermutation and other clinicopathologic features, but it is noted that the two patients who died of disease demonstrated hypermutant tumors.

Although limited in number, our series nonetheless clearly suggests a number of therapeutic options for PMAS. The outcome data show that some tumors may require no more treatment beyond surgery, even curiously including Case 9. On the other hand, aggressive or recurrent tumors may benefit from targeted therapies implicated by the high frequency of *KDR* (VEGFR2) and *PIK3CA* mutations in PMAS, as well as a subset showing hypermutation. Our findings coincide with recently reported therapeutic efforts. For AS, data on targeting the PI3K pathway are limited to in vitro work in cell lines, but this potential treatment avenue may indirectly benefit from the rapidly expanding

targeting of *PIK3CA*-mutant breast carcinomas [73]. A number of agents targeting the VEGFR pathway have been reported, including the anti-VEGF monoclonal antibody bevacizumab and tyrosine kinase inhibitors pazopanib, sorafenib, sunitinib, and axitinib [74]. Results in AS patients have been underwhelming, but such trials have been primarily comprised of tumors of heterogeneous origin and unknown *KDR* status. Limited individual case reports of therapeutic responses to VEGFR inhibition in which the tumor had been first shown to harbor *KDR* amplification/overexpression have been described [75, 76]. How PMAS with pathogenic *KDR* mutations specifically respond to such inhibitors has not been fully characterized, and is an avenue for further clinical investigation. For the subset of hypermutated tumors, immune checkpoint inhibitors may show promise. A small series of heterogeneous AS without mutational burden testing demonstrated mixed responses to immune checkpoint blockade [77]. Yet a recent case report of a hypermutated AS with a UV-induced signature treated with pembrolizumab showed a dramatic clinical response [78].

In conclusion, by exclusively focusing on a series of PMASs, our work expands on the earlier work of Antonescu et al. by identifying a high frequency of recurrent *KDR* and *PIK3CA* mutations in these rare tumors [26, 35, 36]. Comprehensive genomic sequencing of PMAS also revealed alterations in *PTPRB* and a subset of tumors with somatic hypermutation. Importantly, we note an ongoing patient-partnered research platform termed the Angiosarcoma Project as part of the Count Me In initiative, which is accumulating genetic data on a series of AS including PMAS. Ad hoc review of this publicly available data on cBioPortal reveals a similar prevalence of *KDR* alterations (9/14 cases, 64%) in PMAS, as well as frequent *PIK3CA* mutations (5/14 cases, 36%), providing additional support of our findings [48, 49]. Large-scale endeavors such as this have an incredible potential for unraveling the genomic underpinnings of especially rare tumors. Together, our findings provide evidence that PMAS demonstrate a pathogenesis distinct from AS of other sites, with the hope of guiding future therapies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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