Review Article

Primary angiosarcoma of the breast: a literature review

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Background and Objective: Primary angiosarcoma of the breast (PBA) is an extremely rare and heterogeneous disease. PBA is difficult to diagnose and has a poor prognosis. In order to better understand the disease and provide evidence-based treatment for PBA patients, a review of the published literature in the English language was conducted.

Methods: A literature review in agreement with the PRISMA protocol was conducted. Medline and Cochrane databases were searched for English articles on PBA patients in September 2023 with a predetermined strategy. The articles were categorized and assessed based on hierarchical levels of scientific evidence.

Key Content and Findings: A total of 255 articles were identified, among these 137 publications which included 1,888 patients met the criteria for inclusion in the final analysis. No prospective, randomized trials exclusive to PBA have been recognized. This article provides an overview of the most current and comprehensive evidence concerning the epidemiology, etiology, genomic features, clinical presentations, diagnosis, treatment, and prognosis of PBA.

Conclusions: Despite the fact that current evidence is largely derived from retrospective studies, database analyses, and case reports, we utilized this information to tackle important clinical questions concerning optimal patient management practices for PBA. Complete surgical excision continues to be the mainstay treatment for PBA. However, the effectiveness of adjuvant therapies is still unclear. This narrative review highlights the urgent need for more rigorously designed research to enhance the management and treatment strategies for PBA.

Keywords: Primary angiosarcoma of the breast (PBA); complete surgical excision; hierarchal levels of scientific evidence; literature review

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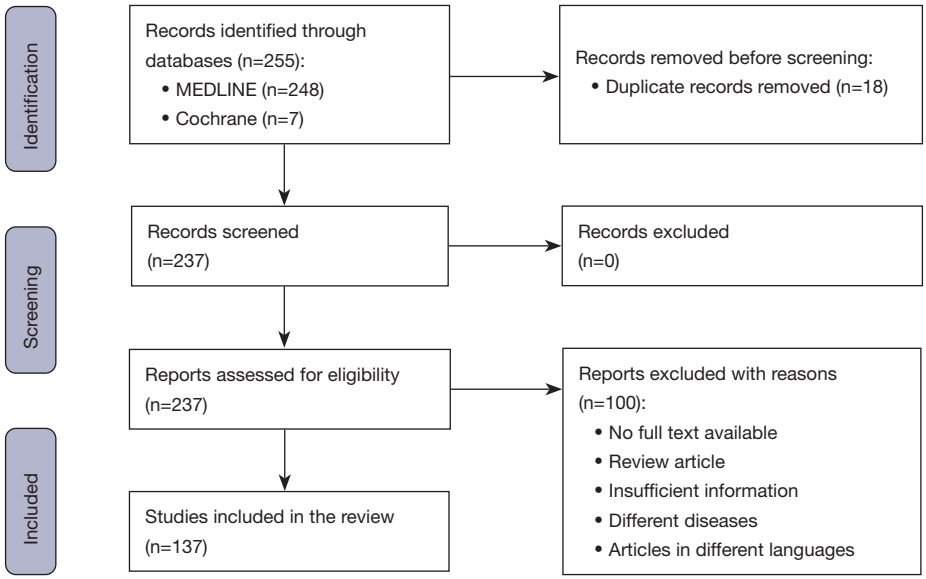

Figure 1 Search diagram.

Introduction

Angiosarcoma of the breast is a high-grade malignant soft tissue tumor, and it can be classified into a primary form with no known precursor and a secondary form, secondary breast angiosarcoma (SBA), with a history of primary breast diseases followed by radiotherapies (1). Primary angiosarcoma of the breast (PBA) is a malignant vascular tumor originating in the breast parenchyma. And it is a very rare disease that accounts for only 0.04% of all malignant breast tumors, with a difficult diagnosis and poor prognosis (2). PBA is difficult to study due to the low disease incidence and geographically dispersed patient populations, which resulted in considerable unmet therapeutic requirements for people with uncommon malignancies. There is little evidence of a comprehensive and systematic approach to the treatment and management of PBA. Also, PBA is easily misdiagnosed due to the rarity of the disease, the similarity of other benign diseases, and the non-specific imaging findings. Accurately diagnosing PBA is essential prior to initiating treatment. Furthermore, the existing evidence to inform clinical practice is predominantly derived from retrospective studies, database reviews, and case reports. Most of the retrospective studies included limited patients and mixed with the other diseases. Moreover, the current reported reviews about PBA are limited and were provided with limited evidence. For a greater comprehension of the disease and to evaluate evidence-based practices for the treatment of PBA, we systematically reviewed the published literature in the English language. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-24-16/rc).

Methods

The study flow of the search diagram is illustrated in *Figure 1*. For this narrative review, an extensive literature search was conducted in MEDLINE (via PubMed) and Cochrane in September 2023 (*Table 1*). The search strategy and data analysis methods were established prior to commencing the study. Searches were restricted to English-language publications and covered works published from 1975 onward, following the first description of primary angiosarcoma in 1976 (3). The search used the keywords "primary angiosarcoma of the breast", "primary mammary angiosarcoma", "angiosarcoma and breast", and "breast angiosarcoma with no radiation exposure". Identical articles and abstracts were identified to avoid duplication. Publications from the same institution were examined, the results from both searches were merged, and duplicate entries were eliminated. Articles with no available full text or insufficient information, research of different diseases, review articles, comment articles, and articles in different languages were excluded.

Table 1 The search strategy summary

Items	Specification
Date of search	15th September, 2023
Databases and other sources searched	MEDLINE and Cochrane
Search terms used	"Primary angiosarcoma of the breast", "primary mammary angiosarcoma", "angiosarcoma and breast", and "breast angiosarcoma with no radiation exposure"
Timeframe	From 1975 to 2023
Inclusion and exclusion criteria	Inclusion: all research articles relevant to the PBA in English were included
	Exclusion: no full text available, review article, insufficient information, different diseases, articles in different language
Selection process	The search and selection of articles were conducted by primary authors Y.Z., S.N., and X.Z. These were then reviewed by senior authors T.T., Y.T., Y.I., T.I., M.T., and T.S.

PBA, primary angiosarcoma of the breast.

Results

A total of 255 studies or reports were identified through the implementation of the strategy predefined in the study protocol. A total of 137 studies were incorporated into the review, encompassing 1,888 patients. A notable deficiency persists in the current body of literature due to the absence of substantial evidence to inform the management of PBA. We classified and evaluated the 137 original articles in accordance with the hierarchical levels of scientific evidence as described in *Table 2* by Hadorn *et al.* (4). The PBA patients (n=1,888) were separated into subgroups, along with their critical clinical data based on levels: (I) level 1 evidence. We found no prospective, randomized trials exclusive to PBA. Only one randomized controlled trial with mixed diseases which concentrated in all kinds of angiosarcoma (9 PBA patients included) has been conducted so far (2,5). (II) Level 3 evidence (*Table 3*). Thirty-six articles involving 1,759 patients with PBA are included, of which 11 articles are exclusive to PBA, including 395 patients (3). (III) Level 5 evidence (*Table 4*). One hundred articles involving 120 PBA patients were included. No level 2, level 4, level 6, or level 7 evidence was discovered.

Epidemiology and etiology

Angiosarcoma of the breast accounts for 1% of all breast tumors that occur in the soft tissues. It originates from the interconnected breast tissues and may spread to the skin above it (142). PBA is an extremely rare and heterogeneous disease that is not related to radiation exposure. Only around 20% of the mammary angiosarcomas are primary angiosarcomas, accounting for about 0.04% of all breast malignancies and 8% of breast sarcomas (27,143,144). PBA is typical of young age, compared to the SBA, which manifests suddenly and has a median onset age ranging from 30 to 50 years (34). PBA almost exclusively affects female patients, four well-documented male patients which were extremely rare were reported in the literature so far (66,130,145,146). Given the rarity of PBA, risk factors are difficult to elucidate. It is plausible that the alteration of lymphatic drainage of the breast contributes to the development of angiosarcoma in the breast (147). According to the retrospective database research by Friedrich *et al.*, black and Asian/Pacific Islander patients were more likely to have primary angiosarcoma (34). The incidence of certain diseases varied by race and ethnicity due to genetic factors and dietary and lifestyle differences. There still exists uncertainty about other factors contributing to the development of PBA.

Genomic features

Numerous studies demonstrated that c-MYC amplification was a recurrent genetic alteration in SBA but not in PBA or atypical vascular lesions (AVL), indicating that PBA and SBA have genetically distinct pathogenetic mechanisms (7,12,148,149). Wei *et al.* compared the differentially

Table 2 Hierarchal levels of evidence

Level	Definition
Level 1 evidence	Supportive evidence from well-conducted randomized controlled trials with ≥100 patients
Level 2 evidence	Supportive evidence from well-conducted randomized controlled trials with <100 patients
Level 3 evidence	Supportive evidence from well-conducted cohort studies
Level 4 evidence	Supportive evidence from well-conducted case-control studies
Level 5 evidence	Supportive evidence from poorly conducted or uncontrolled studies
Level 6 evidence	Conflicting evidence with the weight of evidence supporting the recommendation
Level 7 evidence	Expert opinion

Table 3 Level 3 evidence (n=1,759)

Study	Type of study (n of patients diagnosed with PBA)	Primary endpoint
Yan *et al.* 2021 (6)	Single center retrospective review (n=3)	Clinicopathological and immunohistochemical characterization of primary and secondary breast angiosarcoma
Ginter *et al.* 2014 (7)	Single center retrospective review (n=17)	Diagnostic utility of MYC amplification and anti-MYC immunohistochemistry staining among PBA, atypical vascular lesions, radiation-induced mammary angiosarcomas, and primary angiosarcomas of other sites
Li *et al.* 2023 (8)	Review of database patients (n=264)	Prognostic factors, overall survival, and disease-specific survival of primary and secondary breast angiosarcoma
Bentley *et al.* 2023 (9)	Multi-center retrospective review (n=13)	The role of imaging in the diagnosis of primary and secondary breast angiosarcoma
Bae *et al.* 2011* (10)	Single center retrospective review (n=9)	Overall survival, time from diagnosis to death
Beca *et al.* 2020* (11)	2 facilities retrospective review (n=10)	Genomic features and distinct pathogenesis
Fraga-Guedes *et al.* 2015 (12)	2 facilities retrospective review (n=12)	Diagnostic and prognostic role of *MYC* gene amplification and protein expression among angiosarcoma and vascular lesions of the breast
Laé *et al.* 2015 (13)	Single center retrospective review (n=15)	Pathogenetic differences between primary and secondary breast angiosarcoma
Kim *et al.* 2022* (14)	Single center retrospective review (n=15)	Disease free survival and overall survival
Wang *et al.* 2017* (15)	Single center retrospective review (n=36)	Clinicopathologic and radiologic correlations
Wang *et al.* 2009 (16)	2 facilities retrospective review (n=3)	Characterization of the clinicopathologic features of primary and secondary breast angiosarcoma
Teng *et al.* 2023 (17)	Review of database patients (n=100)	Overall survival and prognostic factors of primary and secondary breast angiosarcoma
Yin *et al.* 2017 (18)	Review of database patients (n=218)	Clinicopathological characteristics and their associations with overall survival among non-metastatic primary and secondary breast angiosarcoma
Nascimento *et al.* 2008* (19)	Single center retrospective review (n=49)	Prognostic factors, recurrence-free survival, and overall survival
Darre *et al.* 2022* (20)	Single center retrospective review (n=8)	Clinicopathologic and imaging features

Table 3 (*continued*)

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Study	Type of study (n of patients diagnosed with PBA)	Primary endpoint
Abdou *et al.* 2019 (21)	Single center retrospective review (n=9)	The association between survival outcomes, overall survival, and recurrence-free survival of primary and secondary breast angiosarcoma
Biswas *et al.* 2009 (22)	Single center retrospective review (n=1)	Overall survival and relapse-free survival of primary and secondary breast angiosarcoma
Masai *et al.* 2016 (23)	Single center retrospective review (n=6)	Clinicopathological features and prognostic factors of primary and secondary breast angiosarcoma
McClelland *et al.* 2019 (24)	Review of database patients (n=220)	Extent of resection, treatment plans and their association with overall survival in localized breast angiosarcoma
Lokanatha *et al.* 2018* (25)	Single center retrospective review (n=4)	Overall survival
Aljohani *et al.* 2017 (26)	Single center retrospective review (n=4)	Disease free survival and overall survival of primary and secondary breast angiosarcoma
Hui *et al.* 2012 (27)	Single center retrospective review (n=6)	Loco-regional recurrence free survival of primary and secondary breast angiosarcoma
Kronenfeld *et al.* 2021 (28)	Single center retrospective review (n=11)	Local recurrence, distant recurrence, and median overall survival of primary and secondary breast angiosarcoma
Merino *et al.* 1983* (29)	Single center retrospective review (n=15)	Prognostic factors
Banks *et al.* 2021 (30)	Multiple center retrospective review (n=34)	Overall survival, disease-specific survival, number of recurrences, 5-year recurrences, cause of death of primary and secondary breast angiosarcoma
Kondi-Pafiti *et al.* 2013 (31)	Single center retrospective review (n=1)	Incidence, clinical and histopathological characteristics among non-epithelial primary breast neoplasms
Pandey *et al.* 2015* (32)	Review of database patients (n=226)	Overall survival and influence of radiotherapy
Gennaro *et al.* 2010 (33)	Single center retrospective review (n=10)	Disease-free survival, overall survival and VEGFR expression of non-metastatic breast angiosarcoma
Friendrich *et al.* 2021 (34)	Review of database patients (n=313)	Prognostic factors of all breast angiosarcoma in primary and secondary breast angiosarcoma
Shet *et al.* 2006* (35)	Single center retrospective review (n=12)	Histological prognostic factors and c-kit expression
Gutkin *et al.* 2020 (36)	Single center retrospective review (n=24)	Overall survival and recurrence-free survival in primary and secondary breast angiosarcoma
Cannella *et al.* 2023 (37)	Single center retrospective review (n=12)	Recurrence-free survival and overall survival in primary and secondary breast angiosarcoma
Scow *et al.* 2010 (38)	Single center retrospective review (n=27)	Prognostic factors and overall survival of primary and secondary breast angiosarcoma
Vorburger *et al.* 2005 (39)	Single center retrospective review (n=32)	Prognostic factors, overall survival, and disease-free survival in primary and secondary breast angiosarcoma
Kunkiel *et al.* 2018* (40)	Single center retrospective review (n=11)	Clinicopathological profile, treatment, recurrence
Luini *et al.* 2007 (41)	Single center retrospective review (n=9)	Overall survival and disease-free survival in primary and secondary breast angiosarcoma

*, articles exclusive to primary angiosarcoma of the breast. MYC, myelocytomatosis oncogene; PBA, primary angiosarcoma of the breast; VEGFR, vascular endothelial growth factor receptor.

Table 4 Level 5 evidence (n=120)

Study	Type of study (n of patients diagnosed with PBA)	Primary endpoint
Tang *et al.* 2018 (42)	Case report (n=1)	Case report
Takenaka *et al.* 2009 (43)	Case report (n=1)	Case report
Malolan *et al.* 2016 (44)	Case report (n=1)	Case report and literature review
Abdelhady *et al.* 2020 (45)	Case report (n=1)	Case report
Qiu *et al.* 2022 (46)	Case report (n=1)	Case report
Philip *et al.* 2018 (47)	Case report (n=1)	Case report
Babarović *et al.* 2011 (48)	Case report (n=1)	Case report
Al-salam *et al.* 2012 (49)	Case report (n=1)	Case report and literature review
Rincón-Riveros *et al.* 2022 (50)	Case report (n=1)	Case report and literature review
Silverman *et al.* 1994 (51)	Case report (n=1)	Case report and literature review
Muzumder *et al.* 2010 (52)	Case report (n=1)	Case report and literature review
Teruyama *et al.* 2022 (53)	Case report (n=1)	Case report
Mumin *et al.* 2021 (54)	Case report (n=1)	Case report and literature review
Baum *et al.* 1990 (55)	Case report (n=3)	Case report
Alshaar *et al.* 2021 (56)	Case report (n=1)	Case report
O'Donnell *et al.* 2020 (57)	Case report (n=1)	Case report
Souza *et al.* 2009 (58)	Case report (n=1)	Case report
Yagi *et al.* 2021 (59)	Case report (n=1)	Case report
Wang *et al.* 2013 (60)	Case report (n=1)	Case report
Yang *et al.* 2024 (61)	Case report (n=1)	Case report and literature review
Ooe *et al.* 2023 (62)	Case report (n=1)	Case report
Mahdi *et al.* 2018 (63)	Case report (n=1)	Case report
Alexandroba *et al.* 2014 (64)	Case report (n=1)	Case report and literature review
Yang *et al.* 2021 (65)	Case report (n=1)	Case report
da Silva *et al.* 2018 (66)	Case report (n=1)	Case report
Sasahara *et al.* 2019 (67)	Case report (n=1)	Case report
Mendoza *et al.* 2019 (68)	Case report (n=1)	Case report
Bennani *et al.* 2013 (69)	Case report (n=1)	Case report
Meng *et al.* 2022 (70)	Case report (n=1)	Case report
Issar *et al.* 2022 (71)	Case report (n=1)	Case report
Burusaoat *et al.* 2019 (72)	Case report (n=1)	Case report
Im *et al.* 2019 (73)	Case report (n=1)	Case report
Lee *et al.* 2023 (74)	Case report (n=1)	Case report
Huang *et al.* 2023 (75)	Case report (n=1)	Case report
Kagawa *et al.* 1997 (76)	Case report (n=1)	Case report

Table 4 (*continued*)

Table 4 (*continued*)

Study	Type of study (n of patients diagnosed with PBA)	Primary endpoint
Ferre *et al.* 2022 (77)	Case report (n=1)	Case report
Darré *et al.* 2020 (78)	Case report (n=1)	Case report
Vailas *et al.* 2015 (79)	Case report (n=1)	Case report
Killoran *et al.* 2023 (80)	Case report (n=1)	Case report
Dashevsky *et al.* 2013 (81)	Case report (n=1)	Case report
Combemale *et al.* 2016 (82)	Case report (n=2)	Case report
Kilic *et al.* 2015 (83)	Case report (n=1)	Case report
Tang *et al.* 2023 (84)	Case report (n=2)	Case report and literature review
Keshav *et al.* 2013 (85)	Case report (n=1)	Case report
Bender *et al.* 2020 (86)	Case report (n=1)	Case report
Palanisamy *et al.* 2020 (87)	Case report (n=1)	Case report
Varghese *et al.* 2019 (88)	Case report (n=1)	Case report
Luczynska *et al.* 2021 (89)	Case report (n=1)	Case report
Vimugdha *et al.* 2020 (90)	Case report (n=1)	Case report
Jagtap *et al.* 2015 (91)	Case report (n=1)	Case report
Rohan *et al.* 2010 (92)	Case report (n=1)	Case report
Russo *et al.* 2020 (93)	Case report (n=1)	Case report and literature review
Mouhoub *et al.* 2019 (94)	Case report (n=1)	Case report
Christodoulakis *et al.* 1998 (95)	Case report (n=1)	Case report
Cassou-Mounat *et al.* 2019 (96)	Case report (n=6)	Case report
Kader *et al.* 1987 (97)	Case report (n=1)	Case report
Azizun-Nisa *et al.* 2013 (98)	Case report (n=5)	Case report
Qin *et al.* 2021 (99)	Case report (n=1)	Case report
Marana *et al.* 2000 (100)	Case report (n=1)	Case report
Zincone *et al.* 1995 (101)	Case report (n=1)	Case report
Rosner *et al.* 1988 (102)	Case report (n=3)	Case report
Ronzen *et al.* 2007 (103)	Case report (n=1)	Case report
Georgiannos *et al.* 2003 (104)	Case report (n=4)	Case report
Akrami *et al.* 2016 (105)	Case report (n=1)	Case report
Pramanik *et al.* 2017 (106)	Case report (n=1)	Case report
Pandey *et al.* 2014 (107)	Case report (n=1)	Case report
O'Neill *et al.* 2014 (108)	Case report (n=1)	Case report
Wang *et al.* 2015 (109)	Case report (n=1)	Case report
Maehara *et al.* 2017 (110)	Case report (n=1)	Case report
Hu *et al.* 2019 (111)	Case report (n=1)	Case report

Table 4 (*continued*)

Table 4 (*continued*)

Study	Type of study (n of patients diagnosed with PBA)	Primary endpoint
Tomich *et al.* 2017 (112)	Case report (n=1)	Case report and literature review
Lvoff *et al.* 2007 (113)	Case report (n=1)	Case report
Lacoponi *et al.* 2016 (114)	Case report (n=1)	Case report
Tiwary *et al.* 2007 (115)	Case report (n=1)	Case report
Taib *et al.* 2006 (116)	Case report (n=1)	Case report
Britt *et al.* 1995 (117)	Case report (n=1)	Case report
Alvarado *et al.* 2013 (118)	Case report (n=1)	Case report
Costa *et al.* 2012 (119)	Case report (n=1)	Case report
Bhosale *et al.* 2013 (120)	Case report (n=1)	Case report
Cantile *et al.* 2018 (121)	Case report (n=3)	Case report
Marchant *et al.* 1997 (122)	Case report (n=1)	Case report
Khoshim *et al.* 1991 (123)	Case report (n=1)	Case report
Cao *et al.* 2012 (124)	Case report (n=1)	Case report
Brown *et al.* 2020 (125)	Case report (n=1)	Case report
Lin *et al.* 2016 (126)	Case report (n=1)	Case report
Ohta *et al.* 1997 (127)	Case report (n=1)	Case report
Bernathova *et al.* 2006 (128)	Case report (n=1)	Case report
Farrokh *et al.* 2016 (129)	Case report (n=1)	Case report
Kamat *et al.* 2015 (130)	Case report (n=1)	Case report
van Geel *et al.* 2009 (131)	Case report (n=1)	Case report
Myerowitz *et al.* 1978 (132)	Case report (n=1)	Case report
Carter *et al.* 2005 (133)	Case report (n=1)	Case report
Zhou *et al.* 2009 (134)	Case report (n=1)	Case report
Gatcombe *et al.* 2010 (135)	Case report (n=1)	Case report
Losanoff *et al.* 2006 (136)	Case report (n=1)	Case report
Johnson *et al.* 2002 (137)	Case report (n=1)	Case report and literature review
Kiluk *et al.* 2005 (138)	Case report (n=1)	Case report
Hsiao *et al.* 2013 (139)	Case report (n=1)	Case report
Mulder *et al.* 2017 (140)	Case report (n=1)	Case report
Altan *et al.* 2010 (141)	Case report (n=1)	Case report

PBA, primary angiosarcoma of the breast.

expressed genes (DEGs) between PBA and SBA. Out of these instances, 13 were downregulated (*PGM5*, *IQCA1*, *CETP*, *WASF3*, *GCOM1*, *CTLA4*, *SLR2*, *MYC*, *RELN*, *UNC5A*, *CMBL*, *ICOS*, *CDCA7L*) and five were upregulated (*SERPINE1*, *TGM2*, *BNC2*, *LXN*, and *BAMBI*) in PBA and the related protein-protein interaction networks of these DEGs identified the most outstanding genes including *MYC*, *FOXP3* and *SERPINE1*, suggesting the potential

to serve as therapeutic targets as well new biomarkers for the diagnosis and prognosis between PBA and SBA (150). Gennaro *et al.* found that vascular endothelial growth factor receptor (VEGFR) expression is significantly correlated with low- and intermediate-grade breast angiosarcoma, and VEGFR was also significantly more frequent in patients with PBA and younger patients, therefore suggesting anti-angiogenic treatment may represent a novel therapeutic approach in VEGFR-positive cases of this rare and aggressive disease (33,151). Teruyama *et al.* reported a PBA case with repeated resection and recurrence over 15 years. Germline mutations linked to malignancy were identified through a comprehensive genetic mutation analysis conducted throughout the progression of the disease. Notable mutations identified included single nucleotide polymorphisms in the tumor protein p53 (TP53), kinase insert domain receptor (KDR), and fibroblast growth factor receptor 4 (FGFR4). PBA is an aggressive disease and has a high chance of local recurrence and metastasis. Although many metastasized tumors had been reported to inherit driver gene mutations from the primary tumor, this particular case did not exhibit any driver gene mutations associated with angiosarcoma that had been previously documented (53). There was clear evidence of genetic heterogeneity among PBA; therefore, additional research is required to determine the oncogenic trigger events that are distinct to this subset of tumors.

Clinical presentation and diagnosis

Patient with PBA usually presents a rapidly growing painless and palpable mass in a relatively larger size. PBA usually manifests with bluish, reddish, violaceous, or black skin discoloration, yet the discoloration may be mistaken for bruising, leading to a delayed diagnosis (143,152-155). Angiosarcoma is characterized by its highly aggressive nature, frequent multicentric presentation, which may indicate localized metastasis or locoregional dissemination, and its propensity for distant metastasis. Mammography and ultrasound often lead to misdiagnosis since the image findings are non-specific and because of the dense breast parenchyma (92). In comparison, magnetic resonance imaging (MRI) with dynamic contrast enhancement is more informative. PBA typically exhibits moderate intensity on T1-weighted images and high intensity on T2-weighted images on MRI. Angiosarcomas of low-grade exhibit progressive enlargement. High-grade angiosarcomas are characterized by frequent visualization of large draining vessels and rapid enhancement and discharge. In conjunction with numerous unenhanced regions within the tumor, these results may be indicative of angiosarcoma (108,142,156,157). Three grades of angiosarcoma were described (2). Multiple grades may exist in the same tumor; therefore, a complete excision and careful histologic evaluation are needed to accurately determine the tumor grade (152). Histologically, the PBA is often composed of well-formed vascular spaces and appears deceptively benign. Consequently, the accurate diagnosis of breast angiosarcoma poses a frequent challenge in clinical practice. The lesions were misdiagnosed as hemangioma, lymphangioma, hematoma, or dysplasia. Percutaneous biopsy frequently yields a false negative conclusion (92,158). Immunohistochemical staining for CD31, CD34, vascular markers factor VIII, and Fli-1 is a valuable technique in the identification and localization of specific proteins or antigens within tissue samples (69,159,160). A clear clinical history in conjunction with clinical, radiological and pathological findings is essential for establishing an early and accurate diagnosis.

Treatment

Complete surgical excision is the gold standard treatment for patients with PBA. However, there is no compelling evidence for us to make a conclusive recommendation on the total mastectomy or breast-conserving treatment. Patients with smaller tumors may benefit from wide local excision surgery (10,11,67). Only isolated cases are reported to have lymphatic spread and the PBA is thought to be hematogenous metastasis (136). Presently, the necessity of axillary nodal dissection is unknown, and the node dissection is controversial unless clinically positive nodes are identified (14,161). Regardless of the rarity of PBA, there is no international consensus on the role of neoadjuvant, adjuvant chemotherapy, and radiotherapy. McClelland *et al.* conducted a database review and concluded adjuvant therapies are not associated with improved survival, except for the possible role of adjuvant chemotherapy in large primary tumors (24). A meta-analysis of patients treated with doxorubicin and a randomized trial of epirubicin plus ifosfamide exhibited longer disease-free survival and overall survival (OS) (162). Survival may be enhanced and locoregional control could benefit from hyperfractionated radiotherapy (161,163,164). Also, as was mentioned in the above paragraph on 'genomic features', several genes provide the potential to serve as therapeutic targets to

improve the prognosis. Further investigations, preferably prospective clinical studies are needed.

Prognosis

The median OS was 38 months and the 1-, 3- and 5-year OS with PBA was 80%, 39%, and 25%, respectively (17). The incidence of distant metastasis was considerable, affecting around 60% of the patients. Skin, lungs, liver, and bones emerged as the most frequent sites of metastasis (19). The prognosis of PBA, like the other types of sarcomas, is proposed to be related to the tumor size, the tumor grade, and the resection margin status (69). The most frequently discussed and controversial prognostic factor is grade. It was believed that the histologic grade of the tumor in PBA played a pivotal role in predicting (10,67) patients' prognosis (35,152,153). Regardless of grade, PBA demonstrated a high propensity for metastasis and a high risk of tumor-related mortality. Nascimento *et al.* proposed that there was no correlation between the histologic grade of the tumors and the probability of distal metastasis, local recurrence, or mortality in their series, which contradicts previous findings (19).

Conclusions

PBA is a rare breast neoplasm that impacts the younger females, and it is characterized by its challenging diagnostic criteria and unfavorable prognosis. This review of PBA evaluated the epidemiology, etiology, genomic features, clinical presentations, diagnosis, treatment, and prognosis for this rare disease. No published articles presented evidence exclusive to PBA at levels 1 or 2. Thus, no adequate evidence is available to guide clinicians. Complete surgical excision continues to be the principal approach in managing PBA. Regrettably, the exact role of adjuvant and neoadjuvant chemotherapy and radiotherapy is still unknown. Adjuvant therapies could be offered for residual microscopic diseases after surgery. This review emphasizes the necessity for additional meticulously designed studies to educate the management and efficiently direct the treatment of PBA.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-24-16/rc

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