PRIKAZ SLUČAJA

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PRIMARNI ANGIOSARKOM DOJKE: PRIKAZ SLUČAJA

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SAŽETAK

Uvod/Cilj: Angiosarkom dojke je redak tumor porekla vaskularnog endotela, koji čini manje od 0,05% svih malignih tumora dojke. Cilj ovog prikaza slučaja je bio da ukaže na važnost ranog prepoznavanja i multidisciplinarnog pristupa u dijagnostici i lečenju ovog retkog entiteta.
Prikaz bolesnika: Žena životne dobi 44 godine, javila se na klinički pregled zbog tumora u desnoj dojci. Nakon mamografskog pregleda, na kom je verifikovana visoko suspektna lobulirana promena na spoju gornjih kvadranata desne dojke promera 86 × 98 mm, učinjena je biopsija širokom iglom, a potom i radikalna mastektomija. Patohistološki je verifikovan mezenhimalni tumor vaskularnog porekla. Imunohistohemijskom metodom bojenja tumor je pokazao imunoreaktivnost na Vimentin, CD31, CD34, Faktor VIII, dok su AE1/AE3, EMA, estrogen, progesteron i HER2 bili negativni. Postavljena je dijagnoza slabo diferentovanog primarnog angiosarkoma.
Zaključak: Primarni angiosarkom dojke predstavlja pravi dijagnostički izazov. Zbog izuzetne retkosti i agresivnosti tumora, od izuzetne važnosti je multidisciplinaran pristup pri dijagnostici i lečenju. S obzirom na to da su kliničke i radiološke karakteristike primarnog angiosarkoma nespecifične, a diferencijalne dijagnoze podrazumevaju spektar najčešće benignih, ali i malignih promena u dojci, histopatološka analiza je od ključnog značaja za postavljanje dijagnoze.

Ključne reči: angiosarkom dojke, imunohistohemija, mezenhimalni tumor, primarni angiosarkom

Uvod

Angiosarkom dojke je vrlo redak tumor porekla vaskularnog endotela, koji čini manje od 0,05% svih malignih tumora dojke (1,2). Na osnovu etiologije, može se klasifikovati na primarni i sekundarni angiosarkom. Primarni angiosarkom dojke javlja se sporadično, kod mlađih žena, dok su sekundarni najčešće udruženi sa radioterapijom, i javljaju se kod starijih pacijenata (3,4).

Cilj ovog prikaza slučaja je bio da ukaže na važnost ranog prepoznavanja i multidisciplinarnog pristupa u dijagnostici i lečenju ovog retkog entiteta.

Prikaz bolesnika

Pacijentkinja životne dobi 44 godine, javila se na klinički pregled zbog palpabilne mase u desnoj dojci. Dostupna medicinska dokumentacija pacijentkinje i anamnestički podaci ne upućuju na lečenje ili prisustvo maligniteta, niti naslednih oboljenja u porodici. Pre 7 godina bila je podvrgnuta eksciziji tumorske promene u levoj dojci, kada je histopatološki potvrđena dijagnoza fibroadenoma. Kliničkim pregledom nije utvrđeno prisustvo promena na koži, kao ni retrakcija bradavice i limfadenopatija.

Nakon mamografskog pregleda, na kom je na spoju gornjih kvadranata desne dojke verifikovana visoko suspektna tumorska promena lobulirane građe, promera 86 × 98 mm, učinjena je biopsija širokom iglom. Patohistološki izveštaj je na osnovu histomorfologije i imunohistohemijskog bojenja pokazao da se radi o mezenhimalnom tumoru vaskularnog porekla. Primenjena imunohistohemijska metoda pokazala je imunoreaktivnost na CD31,

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CASE REPORT

PRIMARY ANGIOSARCOMA OF THE BREAST: A CASE REPORT

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SUMMARY

Background/Aim: Breast angiosarcoma is a rare tumour of vascular endothelium origin, accounting for less than 0.05% of all breast malignancies. The aim of this case report was to point out the importance of early recognition and a multidisciplinary approach in the diagnosis and treatment of this rare entity.
Case report: A 44-year-old woman presented for a clinical examination due to a tumour in her right breast. After a mammographic examination, which verified a highly suspicious lobular change at the junction of the upper quadrant of the right breast with a diameter of 86 × 98 mm, a biopsy with a core needle was performed, followed by a radical mastectomy. Pathohistologically, a vascular mesenchymal tumor was verified. Using the immunohistochemical staining method, the tumor showed immunoreactivity to Vimentin, CD31, CD34, and Factor VIII, while AE1/AE3, EMA, estrogen, progesterone, and HER2 were negative, and the diagnosis of poorly differentiated primary angiosarcoma was made.
Conclusion: Primary breast angiosarcoma represents a real diagnostic challenge. Due to the tumor's rarity and aggressiveness, a multidisciplinary approach to diagnosis and treatment is essential. Because of the nonspecific clinical and radiographic features of primary angiosarcoma, differential diagnoses encompass both benign and malignant breast conditions. Therefore, histopathological analysis is crucial for accurate diagnosis.

Keywords: Breast angiosarcoma, Immunohistochemistry, Mesenchymal tumours, Primary angiosarcoma

Introduction

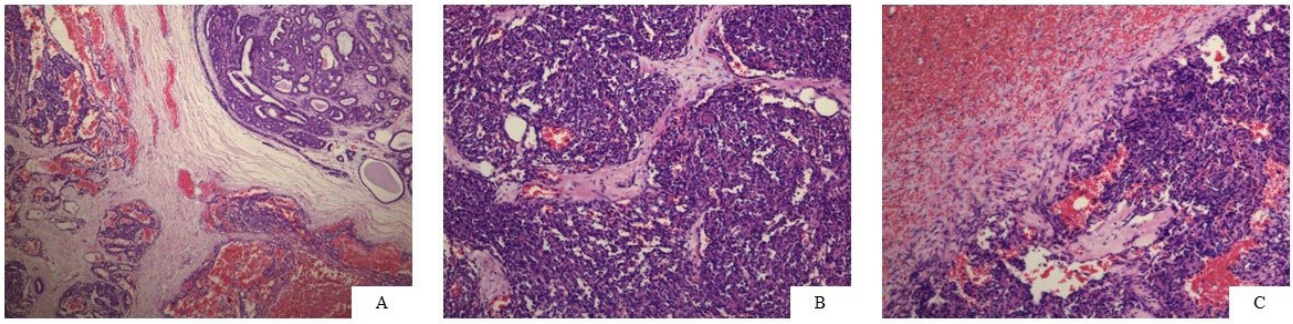
Breast angiosarcoma is a very rare tumor of vascular endothelium accounting for less than 0.05% of all breast malignancies (1,2). Based on its etiology, it can be classified into primary and secondary angiosarcoma. Primary breast angiosarcoma occurs sporadically, in younger women, while secondary is most often associated with radiation therapy, and it occurs in older patients (3,4).

The aim of this case report was to point out the importance of early recognition and a multidisciplinary approach in the diagnosis and treatment of this rare entity.

Case report

A 44-year-old female patient presented for a clinical examination due to a palpable mass in the right breast. The available medical documentation of the patient and anamnestic data did not indicate the treatment or presence of malignancies and hereditary diseases in the family. She underwent the excision of a tumor change in the left breast seven years ago, when the diagnosis of fibroadenoma was confirmed histopathologically. The clinical examination did not reveal the presence of skin changes or nipple retraction and lymphadenopathy.

After a mammographic examination, which verified a highly suspicious lobular tumor change with a diameter of 86 x 98 mm at the junction of upper quadrants of the right breast, a core needle biopsy was performed. The pathohistological report, based on histomorphology and immunohistochemical staining, showed that it was a vascular mesenchymal tumor. The



Slika 1. Mikrofotografije angiosarcoma u uklonjenom tkivu dojke:
A) U gorenjem desnom uglu slike prisutno tkivo dojke benignih karakteristika, dok se u preostalim delovima slike uočava tumorsko tkivo koga čine prošireni vaskularni kanali (bojenje hematoksilinom i eozinom, x40);
B) Prisutni solidni delovi tumora sa papilarnim formacijama endotelnih ćelija i izraženom atipijom (bojenje hematoksilinom i eozinom, x100);
C) Fokalno prisustvo solidnih delovi sa poljem krvarenja (bojenje hematoksilinom i eozinom, x400)

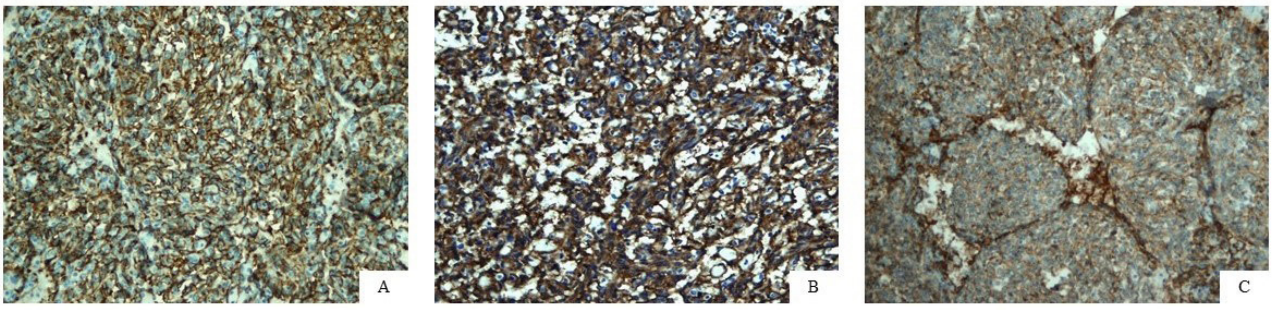
CD34, Faktor VIII, Vimentin, i fokalno Aktin, dok su CKAE/AE3, CK7, CK5/6, LCA, EMA, S100, p63, Calponin, CD10, estrogen, progesteron i HER2 bili negativni.

Urađena je radikalna mastektomija desne dojke. Na serijskim presecima, makroskopski, uočen je jasno ograničen tumor promera 120 × 70 × 45 mm, braonkaste boje, delom hemoragičan, mekše konzistencije. Patohistološki je verifikovan mezenhimalni tumor, koga čine prošireni vaskularni kanali, papilarne formacije endotelnih ćelija, sa izraženom atipijom i brojnim mitozama, uz fokalno prisustvo solidnih delova sa poljima nekroze i krvarenja (slika 1). Imunohistohemijskom metodom bojenja tumor je pokazao imunoreaktivnost na CD31, CD34, Faktor VIII i Vimentin, dok su AE1/AE3, EMA, estrogen, progesteron i HER2 bili negativni (slika 2). C-myc je pokazao nespecifično bojenje. Ekspresija ćelijskog proliferativnog indeksa, Ki67, je bila oko 25 %. Postavljena je dijagnoza umereno diferentovanog primarnog angiosarkoma visokog gradusa. Zahvaćenost limfnih čvorova nije bila prisutna.

Pacijentkinji je indikovana sistemska mono hemoterapija sa adriamicinom.

Diskusija

Angiosarkom je redak tumor, karakterističan po svom agresivnom ponašanju, lošoj prognozi i visokom malignom potencijalu (2). Može se javiti u svim organima, i čini oko 8% svih sarkoma koji nastaju u tkivu dojke (5). Dojka predstavlja jednu od češćih lokalizacija za primarni angiosarkom, koji se najčešće dijagnostikuje kod žena životne dobi od 30 do 40 godina (5,6). Dok se sekundarni angiosarkom češće javlja kod starijih pacijentkinja životne dobi preko 60 godina, koje su prethodno bile podvrgnute konzervativnoj terapiji praćenoj radioterapijom (7). *Yin* i saradnici su pokazali da se primarni angiosarkom dojke visokog gradusa znatno češće javlja u mlađem uzrastu, u odnosu na primarni angiosarkom srednjeg i niskog gradusa (3).



Slika 2. Mikrofotografije imunohistohemijske metode bojenje. Tumorske ćelije pokazuju:
A) CD31 pozitivnost (imunohistohemijsko bojenje, x200);
B) CD34 pozitivnost (imunohistohemijsko bojenje, x200);
C) Pozitivnost na FVIII, (imunohistohemijsko bojenje, x200).

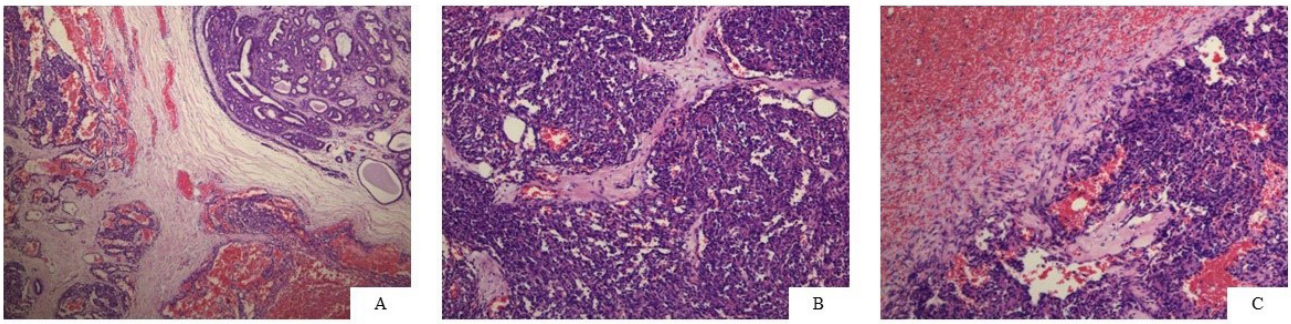


Figure 1. Microphotographs showing angiosarcoma in excised breast tissue.
A) Breast tissue with benign features is present in the top right corner of the picture. In contrast, cancer tissue consisting of dilated vascular channels is seen in the rest of the image (hematoxylin and eosin staining, x40);
B) Solid tumour portions with endothelial cell papillary forms and atypia (haematoxylin and eosin staining, x100);
C) Solid tumour parts with a lake of haemorrhage (haematoxylin and eosin staining, x400).

applied immunohistochemical method showed immunoreactivity to CD31, CD34, Factor VIII, Vimentin and focally Actin, while CKAE/AE3, CK7, CK 5/6, LCA, EMA, S100, p63, Calponin, CD10, estrogen, progesterone and HER2 were negative.

A radical mastectomy of the right breast was performed. In serial sections, macroscopically, a clearly demarcated tumor with a diameter of 120 x 70 x 45 mm, brownish in color, partly hemorrhagic, with softer consistency, was observed. Pathohistologically, a mesenchymal tumor was verified, consisting of dilated vascular channels, endothelial cell papillary forms, with pronounced atypia and numerous mitoses, with the focal presence of solid parts with a lake of necrosis and hemorrhage (Figure 1). Using the immunohistochemical staining method, the tumor showed immunoreactivity to CD31, CD34, Factor VIII and Vimentin, while AE1/AE3, estrogen, progesterone and HER2 were negative (Figure 2). C-myc showed non-specific staining. The expression of the cell proliferative index, Ki67, was around 25%. The diagnosis of poorly differentiated high-grade primary angiosarcoma was made. Lymph nodes were not involved.

Systemic mono chemotherapy with adriamycin was indicated for the patient.

Discussion

Angiosarcoma is a rare tumor, which is characterized by its aggressive behavior, poor prognosis and high malignant potential (2). It can occur in all organs, and it represents about 8% of all sarcomas that develop in the breast tissue (5). The breast is one of common localizations for primary angiosarcoma, which is most often diagnosed in women aged 30 to 40 years (5,6). However, secondary angiosarcoma occurs more often in patients older than 60 years, who were previously treated using conservative therapy followed by radiation therapy (7). Yin et al. showed that high-grade primary breast angiosarcoma

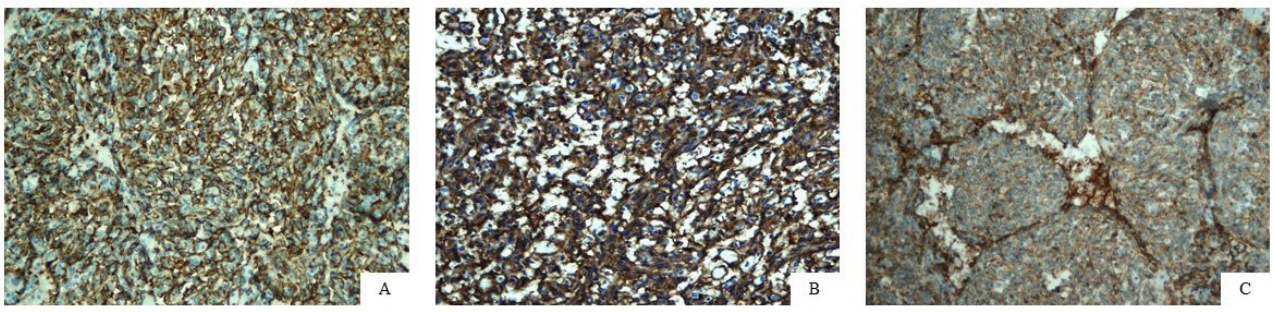


Figure 2. Microphotographs of immunohistochemical staining. Tumour cells show:
A) CD31 positivity (immunohistochemical staining, x200);
B) CD34 positivity (immunohistochemical staining, x200);
C) FVIII positivity, (immunohistochemical staining, x200).

Klinički se ispoljava kao bezbolna masa, koju karakteriše brz rast i retka povezanost sa plavičastom promenom boje kože (8). Retrakcija bradavice, kao i iscedak iz bradavice, obično izostaju (1). *Zellek* i saradnici pokazali su da je veličina tumora u korelaciji sa desetogodišnjom stopom preživljavanja bez recidiva, a da je prognoza posebno nepovoljna kada je dijametar tumora veći od 10 cm(6). Trombocitopenija i hemoragijske manifestacije, kao što je *Kazbah-Merit* sindrom, mogu se javiti kod velikih tumora (9). U studiji *Tian* i saradnika, pokazano je da se primarni angiosarkom dojke češće javlja u levoj dojci (10). Mamografski tumor pokazuje najčešće masu bez kalcifikacija ili fokalnu asimetriju, a sonografski može biti varijabilnih ehogenosti (5). Uprkos visokom malignitetu, zahvaćenost limfnih čvorova je veoma retka (11).

Prema histološkoj slici može se podeliti u tri tipa: angiosarkom niskog gradusa, sa definisanim vaskularnim kanalima, kod koga su papilarne endotelne ćelije i mitoze retke, srednjeg gradusa, sa papilarnim formacijama endotelnih ćelija i solidnim delovima, i visokog gradusa sa vretenastim ćelijama, fokusima nekroze i krvarenja i izraženim mitozama (12). Imunohistohemijska metoda bojenja igra važnu ulogu u postavljanju dijagnoze angiosarkoma dojke. Odsustvo imunoreaktivnosti citokeratinskih markera i pozitivna imunoreaktivnost endotelnih markera, kao što su CD31, CD34 i Faktor VIII, koji ukazuju na endotelno poreklo tumora, karakteristično je kod angiosarkoma, što je potvrđeno i kod naše pacijentkinje (13). CD34 predstavlja specifični marker endotelne diferencijacije, dok je CD31 senzitivniji, međutim oba markera takođe pokazuju pozitivnu imunoreaktivnost i u drugim lezijama (6). Angiosarkomi pokazuju invazivne karakteristike, sa visokom stopom mitoza i visokim indeksom ćelijskog proliferativnog indeksa, Ki67 (14). Prognostički faktori kao što su veličina tumora, stepen diferencijacije i stadijum bolesti od ključnog su značaja za određivanje ishoda (9).

Uprkos činjenici da je biopsija širokom iglom postala zlatni standard u dijagnostici tumora dojke, u slučajevima u kojima preko 90% tumora čine fokusi nekroze i krvarenja, ova metoda je ograničavajuća u dobijanju reprezentativnih uzoraka (3). Preoperativna dijagnoza angiosarkoma širokom iglom, takođe je otežana i nedovoljnom količinom adekvatnog uzorka. I pored toga dijagnoza primarnog angiosarkoma predstavlja izazov, s obzirom da diferencijalne dijagnoze podrazumevaju spektar najčešće benignih vaskularnih lezija, poput atipične vaskularne proliferacije, angiomatoze, angiolipoma ili hemangioma, ali i malignih promena u dojci (1).

Terapiju izbora predstavlja totalna mastektomija (2,4). Mnogi smatraju da konzervativna terapija nije dobar izbor za primarni angiosarkom dojke, jer je stopa recidiva nakon mastektomije 8%, a nakon široke ekscizije 23% (1). Iako je pronađena korelacija hemoterapije sa ukupnim preživljavanjem i preživljavanjem bez recidiva za slabodiferentovane angiosarkome, uloga radioterapije i hemoterapije i dalje ostaje kontroverzna (1,15). Imajući u vidu njegovu lošu prognozu, primarni angiosarkom dojke zahteva ranu dijagnozu i brzo lečenje. Stoga su preventivni pregledi u dijagnostici oboljenja dojki od izuzetnog značaja za njihovo rano otkrivanje, pravovremeno i efikasno lečenje.

Zaključak

Primarni angiosarkom dojke predstavlja pravi dijagnostički izazov. Zbog izuzetne retkosti i agresivnosti tumora od izuzetne važnosti je multidisciplinaran pristup dijagnostici i lečenju. S obzirom da su kliničke i radiološke karakteristike primarnog angiosarkoma nespecifične, histopatološka analiza je od ključnog značaja za postavljanje dijagnoze ovog retkog entiteta. Edukacija i podizanje svesti jedni su od ključnih događaja u ranijem otkrivanju bolesti i boljem ishodu lečenja.

Konflikt interesa

Autori su izjavili da nema konflikta interesa.

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occurs significantly more often at a younger age, in comparison to intermediate- and low-grade primary angiosarcoma (3).

Clinically, it manifests itself as a painless mass, characterized by rapid growth and rare association with bluish skin discoloration (8). Nipple retraction and nipple discharge are usually absent (1). Zellek et al. showed that the size of the tumor is correlated with the ten-year survival rate without recurrence, and that the prognosis is particularly unfavorable when the diameter of the tumor is greater than 10 cm (6). Thrombocytopenia and hemorrhagic manifestations, such as Kasabach-Merritt syndrome, can occur in large tumors (9). In a study by Tian et al, it was shown that primary breast angiosarcoma occurs more frequently in the left breast (10). Mammography usually shows a tumor mass without calcifications or focal asymmetry, while on ultrasonography it can have mixed echogenicity (5). Despite its high malignancy, the involvement of lymph nodes is very rare (11).

According to the histological picture, it can be divided into three types: low-grade angiosarcoma, with defined vascular channels, in which papillary endothelial cells and mitoses are rare, intermediate-grade angiosarcoma, with endothelial cell papillary forms and solid parts, and high-grade angiosarcoma, with spindle cells, foci of necrosis and hemorrhage and readily identifiable mitoses (12). The immunohistochemical staining method plays an important role in the diagnosis of breast angiosarcoma. The absence of immunoreactivity of cytokeratin markers and positive immunoreactivity of endothelial markers, such as CD31, CD34, Factor VIII, which indicate the endothelial origin of the tumor, is characteristic of angiosarcoma, which was also confirmed in our patient (13). CD34 is a specific marker of endothelial differentiation, while CD31 is more sensitive; however, both markers also show positive immunoreactivity in other lesions (6). Angiosarcomas show invasive characteristics, with a high mitotic rate and a high cell proliferative index, Ki67 (14). Prognostic factors such as the size of the tumor, degree of differentiation, and stage of the disease are of key importance in determining the outcome (9).

Despite the fact that a core needle biopsy has become the gold standard in the diagnosis of breast cancer, in cases where over 90% of the tumor consists of foci of necrosis and hemorrhage, this method has limitations in obtaining representative samples (3). The preoperative diagnosis of angiosarcoma with a wide needle is also difficult due to the insufficient amount of adequate sample. Besides this, the diagnosis of angiosarcoma represents a challenge because differential diagnoses most frequently include the spectrum of benign vascular lesions, such as atypical vascular proliferation, angiomatosis, angiolipoma or hemangioma, as well as malignant changes in the breast (1).

The radical mastectomy is the mainstay of treatment (2,4). Many believe that conservative therapy is not a good choice for primary breast angiosarcoma, because the recurrence rate after mastectomy is 8%, and after wide excision 23% (1). Although the correlation between chemotherapy and overall survival without recurrence has been found for poorly differentiated angiosarcomas, the role of radiation therapy and chemotherapy still remains controversial (1,15). Having in mind its poor prognosis, primary angiosarcoma requires early detection and prompt treatment. Therefore, preventive examinations in the diagnosis of breast diseases are extremely important for their early detection, timely and effective treatment.

Conclusion

Primary breast angiosarcoma represents a real diagnostic challenge. Due to its extreme rarity and aggressiveness, a multidisciplinary approach to diagnosis and treatment is extremely important. Considering that the clinical and radiological characteristics of primary angiosarcoma are non-specific, the histopathological analysis is of key importance for the diagnosis of this rare entity. Education and raising awareness are crucial for early disease detection and better treatment outcomes.

Competing interests

The author declared no competing interests.

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