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ORIGINAL ARTICLE

Rare non-epithelial primary breast neoplasms: A ten-year experience at a Greek University Hospital

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Summary

Purpose: Non-epithelial breast neoplasms cover a large spectrum of histopathological entities. The demographics and clinical features are similar to epithelial breast lesions but the diagnosis, prognosis and management options are often very different.

Methods: During 2001-2010, 1362 patients were examined at the Pathology Department of the Aretaieion General Hospital for various breast lesions. All specimens were processed routinely and slides stained with hematoxylin-eosin were re-examined. The patient clinical records were examined for demographics, clinical presentation and therapeutic approach.

Results: In 23/1362 cases (1.68%) pathological examination showed non-epithelial lesions: in 12/1362 cases (0.8%) haemangiomas (11 women, one man) , in 4 /1362 cases (0.3%) myofibroblastomas (MFB), in 2/1362 cases (0.1%) primary breast non-Hodgkin's lymphoma (NHL), in 3 /1362 cases (0.2%) granular cell tumor (GCT), and in 2/1362 cases (0.1%) angiosarcomas (one developed after radiotherapy for breast cancer).

Conclusions: Non-epithelial primary breast tumors are rare (1.68%) and present significant difficulty in accurate preoperative diagnosis and in certain cases in pathological diagnosis as well, which is necessary for the selection of the appropriate treatment. Avoidance of inappropriate therapies requires a multidisciplinary management approach.

Key words: angiosarcoma, breast neoplasms, haemangioma, granular cell tumor, lymphoma, myofibroblastoma

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Introduction

Breast neoplasms cover a large spectrum of histopathological entities. Among them the most common are epithelial in nature and breast adenocarcinomas have been extensively studied. Rare non-epithelial forms of breast tumors, benign and malignant, are rarely encountered and the optimal management options for both remain unproven. Less than 1% of breast tumors are non-epithelial neoplasms [1]. We report herein our 10-year experience on rare non-epithelial breast neoplasms diagnosed during that period. Their incidence, clinical and histopathological characteristics are discussed in this article. Our findings are compared with the available relevant reports and a literature review is also attempted.

Methods

All cases of breast lesions diagnosed at the Pathology Department of the Aretaieion Hospital from 2000 to 2010 were retrieved from the surgical pathology files and studied for tumor type, size, location and histological characteristics. All specimens were processed routinely and slides stained with hematoxylin-eosin were re-examined. In certain cases additional sections of paraffin-embedded tissues were investigated by a Ventana automatic immunohistological method and antibodies appropriate for establishing the immunophenotype were used. The patients' clinical records were examined for demographics, clinical presentation and therapeutic approach.

Results

Between January 2001 and November 2010, 1362 patients were treated at our institution with lumpectomy, simple mastectomy or modified radical mastectomy for various primary breasts tumors. Of the 1362 patients examined, 23 (1.8%) presented various primary non-epithelial lesions (Table 1). Their age ranged from 32 to 77 years (mean 59). Tumor sizes ranged from 0.8 to 6 cm (mean 3.1) and the disease was unilateral, equally distributed to the right and left breast (Table 2). It is to be noted that preoperative mammography showed "benign lesions "in 11/ 23 cases (corresponding to haemangiomas with fibrocystic disease, MFBs and GCTs), "suspicious lesions" in 2 cases (NHLs) and was "non-diagnostic" for angiosarcomas. Pathological examination showed (Table 3):

Breast haemangiomas: 12 cases (11 women and one man; 50% of non-epithelial and 0.8% of total breast lesions). Four out of 12 haemangiomas were accidental findings in the breast parenchyma presenting fibrocystic disease (Figure 1). Regarding the male patient, he was 77 years old, and a previous thoracic wall trauma was reported after a traffic accident many years ago. A slow growing, non-tender, bluish breast mass was observed, measuring 6x5 cm (Figure 2) of indeterminate duration, with the typical histological features of a cavernous haemangioma. All patients of this group are tumor-free on follow-up visits, without any evidence of recurrence.

MFBs: 4 cases (25% of non-epithelial , 0.3% of total

Table 1. Patients treated for breast neoplasms in 10 years

Pathological type	*Lumpectomy*	*Simple mastectomy*	*Modified radical*	*Total*
	N (%)	*N (%)*	*N (%)*	*N (%)*
Epithelial	785 (57.6)	68 (5)	486 (35.7)	1339 (98.3)
Non-epithelial	10 (0.7)	4 (0.3)	9 (0.7)	23 (1.7)
Total	795 (58.3)	72 (5.3)	495 (36.4)	1362

Table 2. Pathological type and right/left localization of breast neoplasms

Pathological type	*Right*	*Left*	*Total*
	N (%)	*N (%)*	*N (%)*
Epithelial	615 (45.1)	724 (53.1)	1339 (100)
Non-epithelial	10 (0.7)	13 (1)	23 (100)

Table 3. Pathological types of non-epithelial breast neoplasms

Pathological type	*Male*	*Female*	*Total*
	N	*N*	*N (%)*
Haemangiomas	1	11	12 (50)
Myofibroblastomas	2	2	4 (17.4)
Granular cell tumor	0	3	3 (13)
Primary non-Hodgkin's lymphoma	0	2	2 (8.7)
Angiosarcoma	0	2	2 (8.7)

breast lesions) in 2 male and 2 female patients. Tumor diameter ranged from 1-3 cm. All patients are disease free after surgical excision of the tumor.

GCTs: 3 cases, all in female patients (14% of non-epithelial and 0.2% of total breast lesions). Mean tumor diameter ranged from 0.8-2 cm with typical features of this lesion (Figure 3). All patients are also tumor-free after surgical excision of the neoplasm.

Breast NHLs: 2 cases of non-Hodgkin's lymphoma (8.7% of non epithelial neoplasms and 0.14% of total breast lesions), without any concominant lymph node involvement. The diagnosis of primary breast lymphoma (Figure 4) was made after extensive clinical and imaging studies of the patients and exclusion of other primary sites. Patients were referred to specialized Hematology and Lymphoma Units.

Angiosarcomas: 2 patients (8.7% of non epithelial neoplasms and 0.14% of total breast lesions). In the first case a 33-year-old woman underwent lumpectomy for a tumor measuring 3 cm in greatest diameter, which was soft and grossly hemorrhagic. Pathological examination revealed an angiosarcoma with diffuse infiltration of the surrounding breast parenchyma. After lumpectomy, tumor relapse occurred one year later in the original bed of the neoplasm. The patient underwent total mastectomy and adjuvant chemotherapy but was lost to follow up. In the second case, a 55-year-old woman developed a diffuse angiosarcoma, mainly affecting the subcutaneous tissue (Figures 5, 6) with minimal invasion of the breast parenchyma. The tu-

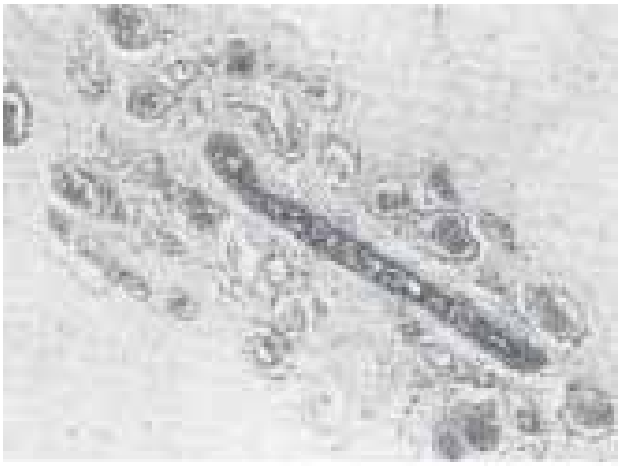

Figure 1. Histological section of a breast haemangioma, perilobular type (H&E, x120).

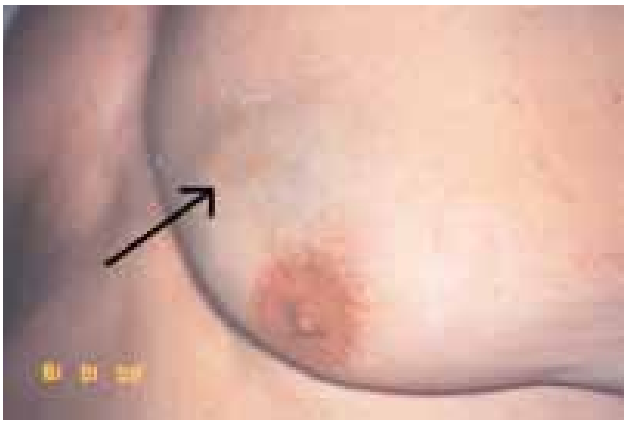

Figure 2. Gross view of breast haemangioma of a 77-year-old male patient (arrow).

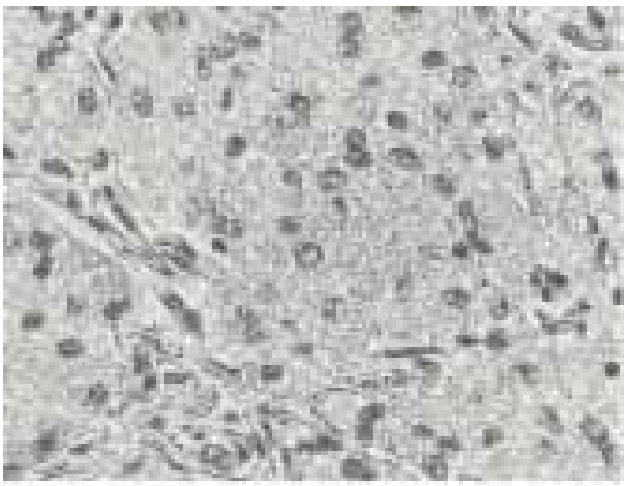

Figure 3. Histological section of a breast granular cell tumor (H&E, x250).

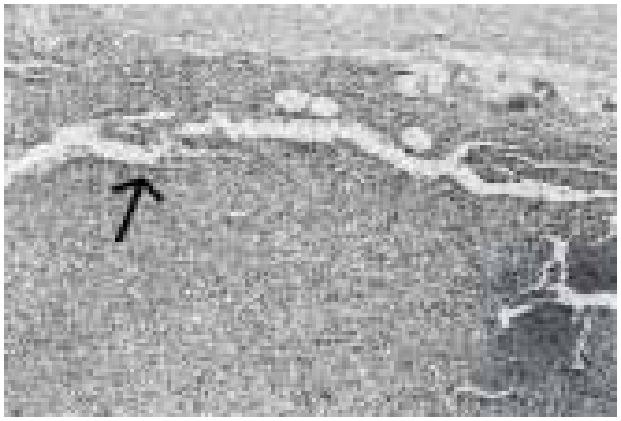

Figure 4. Histological section of breast extensively infiltrated by a non-Hodgkin's lymphoma. Remnants of a compressed mammary duct are observed (arrow) (H&E, x25).

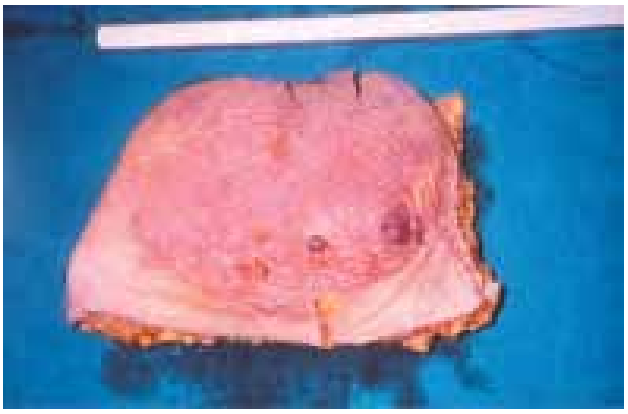

Figure 5. Gross view of breast angiosarcoma which developed after radiotherapy for breast cancer in a 55-year-old patient.

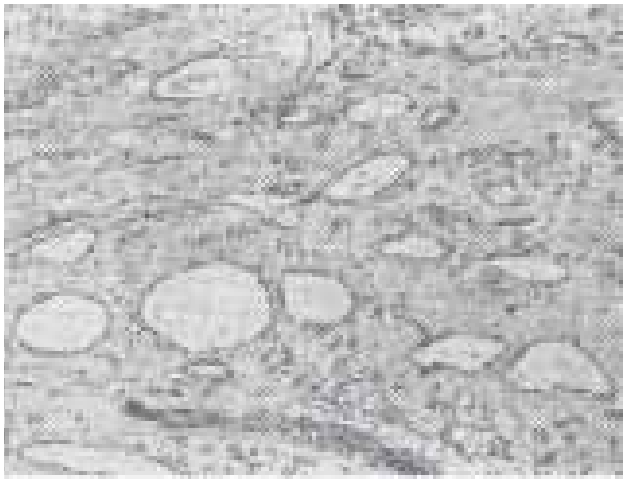

Figure 6. Histological section of angiosarcoma showing vascular spaces of various sizes infiltrating diffusely the breast parenchyma (section of a duct) (H&E, x120).

mor developed 5 years after lumpectomy for an infiltrating ductal adenocarcinoma, followed by radio-and chemotherapy. The patient underwent mastectomy and chemotherapy. No recurrence of the breast cancer was detected at the mastectomy specimen. This patient remains free of metastatic disease or local recurrence 7 months after diagnosis.

Discussion

The most common non-epithelial breast tumors encountered in this study were haemangiomas. Haemangiomas are common soft tissue benign vascular tumors that rarely develop in the breast, and usually are identified incidentally during histological examination of specimens obtained during lumpectomy or mastectomy [2] as in our case. These neoplasms occur in patients aged from 18 months to 82 years and there is no predilection for any particular location in the breast. This lesion is typically described as a dark red or brown circumscribed mass that may grossly appear spongy. On mammography the findings of a breast haemangioma are nonspecific and include a normal mammogram with or without microcalcifications or a well-circumscribed hypoechoic or hyperechoic mass on breast ultrasonography [3,4]. Fine needle aspiration cytology is inconclusive in most cases and complete excision and histopathological examination is generally required for diagnosis. Grossly, it is well circumscribed, however microscopically it may appear to merge with the surrounding tissue, although it never invades or destroys lobules. Histologically, there are two common types: the capillary haemangioma composed of proliferating capillary-sized blood vessels and the cavernous haemangioma having large cavernous vascular channels; cavernous haemangiomas are more common [5,6]. Haemangiomas are subdivided into 4 types: the perilobular, parenchymal, nonparenchymal or subcutaneous, and the venous type [7]. Perilobular haemangioma, a relatively common lesion, is generally small and not palpable and occurs in the extra lobular stroma in the form of microscopic lesions. Parenchymal haemangiomas are microscopically composed of dilated channels filled with red blood cells that may be divided into lobes by internal fibrous septa, with individual vessels varying

in size from capillary to cavernous. Venous haemangiomas are composed largely of venous channels with disorderly vascular proliferation and thick smooth muscle walls [7,8]. Nonparenchymal or subcutaneous haemangiomas are located superficial to the anterior pectoral fascia in the subcutaneous fat. Atypical haemangiomas are benign breast lesions having histological features as above but with broadly anatomizing vascular channels, endothelial hyperplasia, and/or cytological atypia. In the management of haemangiomas, imaging follow up is sufficient as these are not likely precursors of angiosarcomas, however a complete excision is recommended to exclude the possibility of an underlying malignant lesion [9].

MFB is the most commonly used term for a benign stromal neoplasm first described by Toker et al. [10] as a benign spindle cell tumor, also known as myogenic stromal tumor. Originally thought to involve primarily the male breast, it is now known to occur in the female breast with a higher frequency. MFB occurs between 40 and 80 years of age, referring to a solitary slowly growing nodule. There are no reported cases indicating relation to gender, race, medical conditions or use of medication. MFB is most often described in women, who usually present with an asymptomatic and slowly enlarging breast tumor. Mammography typically shows a heterogeneous well-defined encapsulated tumor without microcalcifications. Ultrasonography usually demonstrates a well demarcated tumor, although a variable and mixed echo pattern can be expected. Doppler examination may show a slight peripheral hypervascularization of the tumor. Tru-cut biopsy is a reliable procedure in order to obtain histological diagnosis before planning complete surgical excision of the lesion. Macroscopically, MFB is a well-circumscribed encapsulated tumor ranging in size from 1.0 to 10 cm. Histologically, MFB is an expansile tumor with pushing borders, composed of spindle to oval cells arranged in short, intersecting fascicles, and interrupted by thick bands of collagen. The cells have relatively abundant, ill-defined, eosinophilic cytoplasm with a round to oval nucleus. Necrosis is usually absent. Mitotic index is low, and entrapment of mammary ducts or lobules within the tumor is uncommon. Scattered mast cells may be seen in the stroma. The neoplastic cells are usually immunopositive for vimentin, desmin, CD34, and alpha-smooth muscle actin. There is variable immunostaining for bcl-2 protein, CD99, and estrogen and progesterone receptors. Some cases can show lipomatous, smooth muscle, or cartilaginous components [11]. Surgery is the recommended treatment and, as long as the resection margins are free, relapse is unlikely.

Primary lymphoma of the breast is defined as the tumor localized to the breast with or without ipsilateral axillary lymph node metastases, which occur in 50% of cases [12]. The most common presentation of patients with primary NHL of the breast is with a painless mass located in the upper outer quandrant of the breast. Skin retraction, erythema, peau d' orange appearance, and nipple discharge are uncommon in NHL [13]. Diagnosis of the disease is difficult, because there are no specific imaging characteristics. Most of the times, mammography reports a high-density tumor opacity which often displays similar findings such as diffuse microcalcifications or shape with breast cancer lesions. On ultrasound the lesion is referred to as a heterogeneous mass, with lobulated margins [14]. Core biopsy leads to the definitive histopathological diagnosis and the treatment of choice for primary lesions is systemic chemotherapy, while the role of surgery is very limited since these tumors are particularly sensitive to radiotherapy and chemotherapy [15].

GCT is a rare benign neoplasm of uncertain origin. The first report of GCT is attributed to Abrikossoff in 1926 who described a lesion localized in the tongue; he proposed that its origin was from striated muscle cells and he termed this lesion as myoblastoma. Subsequently, accumulated evidence has cast doubt on this theory. Some authors showed evidence of a histiocytic origin, while others proposed a possible origin from smooth muscle cells. The most widely accepted theory has been that of a Schwann cell origin, apparently because of the positivity of the tumor for the S-100 protein and the similarities exhibited in the ultrastructural features of the tumor cells and those of Schwann cells [17]. GCTs arise throughout the body while these lesions in the breast account for 5% of all cases [18]. These tumors most commonly occur in women between 30 and 50 years of age with a frequency approximately 1 in 1000 breast tumors [19] . The tumor arises from the intralobular stroma in any part of the

breast, but more commonly in the upper inner quadrant, which differs from carcinomas that arise more commonly in the upper outer quadrant, and this distribution appears to correspond to the area of innervations of the skin of the breast by the supraclavicular nerve. Usually the tumor appears as a solitary unilateral lesion, but rarely multiple lesions in the breast and other parts of the body are seen. On mammography GCT of the breast is difficult to distinguish from carcinoma [20], forming typical stellate mass lacking calcifications with a dense core [21]. Ultrasound usually reveals a solid mass with posterior shadowing suggestive of carcinoma . Rarely the ultrasound pattern is hypoechoic with or without attenuation of the sound beam. GCT usually presents as a firm or hard mass. Most of the tumors appear to be well circumscribed. Other examples have ill-defined infiltrative borders. The cut surface is white or gray, or it may have a yellow-two-tan color. Lesions measuring up to 6 cm have been reported, but the tumors generally are 3 cm or smaller. The tumor is indistinguishable from those of GCTs arising at other sites. The lesion is composed of compact nests or sheets of cells that contain eosinophilic cytoplasmic granules. The granules usually are prominent and fill the cytoplasm with a tendency of cytoplasmic vacuolization and clearing. The cytoplasmic granules are diastase-resistant and PAS-positive. Cell borders typically are well defined, and the cells vary in shape from polygonal to spindle. Variable amounts of collagenous stroma are present. Nuclei are round to slightly oval with an open chromatin pattern, and nucleoli tend to be prominent. In some cases a modest amount of nuclear polymorphism and occasional multinucleated cells may be found but these features should not be interpreted as evidence of malignancy. Small nerve bundles sometimes are seen in the tumor or in close association in the periphery of the lesion. As the main striking histological element is the presence of granular cytoplasm, these tumors should be distinguished from carcinomas with oncocytic appearance, histiocytic lesions and metastatic carcinomas.

GCT of the breast is treated by wide excision. Local recurrence may occur after incomplete excision, but sometimes it is difficult to distinguish between recurrence and asynchronous multifocal lesions. Less than 1% of all GCTs, including mammary lesions are malignant.

Angiosarcoma of the breast is a very rare malignant tumor, with few patients surviving in the long-term [22]. True primary angiosarcomas (PA) account for <0.04% of malignant breast neoplasms [23]. In our series, PAs were 0.14% of the total number of breast lesions. The first documented case of breast angiosarcoma was described by Borrman in 1907. Different from breast carcinomas, PA of the breast occurs sporadically in young women, usually during the third and fourth decades of life. The probability of developing angiosarcoma of the breast has been attributed to multiple risk factors, including trauma, radiation, lymphedema, and breast implants. In a retrospective study of almost 200,000 women with breast cancer, those who received adjuvant radiotherapy were at a 16-fold increased risk for development of angiosarcoma [24]. Patients with PA normally present with a palpable mass. Bluish skin discoloration occurs in up to a third of patients and is thought to be attributable to the vascular nature of the tumor [22]. Mammographic findings of angiosarcoma tend to be nonspecific, while with ultrasound, angiosarcoma typically presents as a heterogeneous, hyperechoic, hypervascular mass [22]. MRI is more likely to image the lesion, ascertaining the extent of tumor and helps in planning surgery. Positron emission tomography (PET) with 18-fluorodeoxyglucose (FDG) may be used for staging of angiosarcoma [25]. A definitive preoperative diagnosis may be achieved with fine-needle aspiration cytology or a core needle biopsy. Histologically, the tumor consists of nodules of vascular proliferation with atypical spindle cells in a cuff-like appearance. Neoplastic cells show moderate to focally marked pleomorphic nuclei, a high mitotic index, and an overall infiltrative pattern. Immunohistochemical stains for epithelial markers (pancytokeratin), endothelial markers (CD34 and CD31), and other sarcoma markers are helpful in making the correct diagnosis [26]. The treatment of choice for this rare clinical entity is lumpectomy with tumor-free margins or simple mastectomy for larger lesions without axillary lymphadenectomy. Survival rates are poor and prognosis is indicated by size and grade of the tumor, which is based on the overall pattern, cellular atypia and mitotic rate, like with other soft tissue sarcomas [27].

In conclusion non-epithelial primary breast tumors are rarely encountered (1.6% of all breast lesions diag-

nosed at our institution) and present significant difficulty in accurate preoperative diagnosis. A thorough history, clinical examination and especially a detailed pathological examination with immunohistochemical studies and finally a multidisciplinary management approach are required to deliver appropriate therapy to these patients.

References

1. Young JL Jr, Ward KC, Wingo PA, Howe HL. The incidence of malignant non-carcinomas of the female breast. Cancer Causes Control 2004; 15: 313-319.
2. Mesurolle B, Wexler M, Halwani F et al. Cavernous hemangioma of the breast: mammographic and sonographic findings and follow-up in a patient receiving hormone-replacement therapy. J Clin Ultrasound 2003; 31: 430-436.
3. Dener C, Sengul N, Tez S, Caydere M. Haemangiomas of the breast. Eur J Surg 2000; 166: 977-979.
4. Webb LA, Young JR. Case report: haemangioma of the breast--appearances on mammography and ultrasound. Clin Radiol 1996; 51: 523-524.
5. Shi AA, Georgian-Smith D, Cornell LD et al. Radiological reasoning: male breast mass with calcifications. AJR Am J Roentgenol 2005; 185: S205-210.
6. Kim SM, Kim HH, Shin HJ et al. Cavernous haemangioma of the breast. Br J Radiol 2006; 79: e177-180.
7. Rosen PP, Jozefczyk MA, Boram LH. Vascular tumors of the breast. IV. The venous hemangioma. Am J Surg Pathol 1985; 9: 659-665.
8. Bocker W. WHO classification of breast tumors and tumors of the female genital organs: pathology and genetics. Verh Dtsch Ges Pathol 2002; 86: 116-119.
9. Mariscal A, Casas JD, Balliu E, Castella E. Breast hemangioma mimicking carcinoma. Breast 2002; 11: 357-358.
10. Toker C, Tang CK, Whitely JF et al. Benign spindle cell breast tumor. Cancer 1981; 48: 1615-1622.
11. McMenamin ME, Fletcher CD. Mammary-type myofibroblastoma of soft tissue: a tumor closely related to spindle cell lipoma. Am J Surg Pathol 2001; 25: 1022-1029.
12. Garg NK, Bagul NB, Rubin G, Shah EF. Primary lymphoma of the breast involving both axillae with bilateral breast carcinoma. World J Surg Oncol 2008; 6: 5.
13. Brustein S, Filippa DA, Kimmel M et al. Malignant lymphoma of the breast. A study of 53 patients. Ann Surg 1987; 205: 144-150.
14. Takemura A, Mizukami Y, Takayama T et al. Primary malignant lymphoma of the breast. Jpn J Radiol 2009; 27: 221-224.
15. Domchek SM, Hecht JL, Fleming MD et al. Lymphomas of the breast: primary and secondary involvement. Cancer 2002; 94: 6-13.
16. Rosso R, Scelsi M, Carnevali L. Granular cell traumatic neuroma: a lesion occurring in mastectomy scars. Arch Pathol Lab Med 2000; 124: 709-711.
17. Kommoss F, Mercer L, Schmidt RA, Talerman A. Granular cell tumor of the breast mimicking carcinoma in pregnancy. Obstet Gynecol 1989; 73: 898-900.
18. Gogas J, Markopoulos C, Kouskos E et al. Granular cell tumor of the breast: a rare lesion resembling breast cancer. Eur J Gynaecol Oncol 2002; 23: 333-334.
19. Kragel PJ, Fiorella RM, Kremer H. Tumoral fibrosis and lack of circumscription in granular cell tumor of the breast. South Med J 1995; 88: 1146-1148.
20. Willen R, Willen H, Balldin G, Albrechtsson U. Granular cell tumour of the mammary gland simulating malignancy. A report on two cases with light microscopy, transmission electron microscopy and immunohistochemical investigation. Virchows Arch A Pathol Anat Histopathol 1984; 403: 391-400.
21. Vos LD, Tjon ATRT, Vroegindeweij D, Vrints LW. Granular cell tumor of the breast: mammographic and histologic correlation. Eur J Radiol 1994; 19: 56-59.
22. Chen KT, Kirkegaard DD, Bocian JJ. Angiosarcoma of the breast. Cancer 1980; 46: 368-371.
23. Yang WT, Hennessy BT, Dryden MJ et al. Mammary angiosarcomas: imaging findings in 24 patients. Radiology 2007; 242: 725-734.
24. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast carcinoma. Cancer 2001; 92: 172-180.
25. Glazebrook KN, Magut MJ, Reynolds C. Angiosarcoma of the breast. AJR Am J Roentgenol 2008; 190: 533-538.
26. Wang XY, Jakowski J, Tawfik OW et al. Angiosarcoma of the breast: a clinicopathologic analysis of cases from the last 10 years. Ann Diagn Pathol 2009; 13: 147-150.
27. Kaklamanos IG, Birbas K, Syrigos KN et al. Breast angiosarcoma that is not related to radiation exposure: a comprehensive review of the literature. Surg Today 2011; 41: 163-168.