Case Report

Clinically 'Benign' Breast Lumps: Sarcoma in Hiding? – Case Reports and Literature Review

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Abstract

Breast sarcoma is a very rare entity that accounts for less than 1% of all breast malignancies and less than 5% of all soft tissue tumours. Although uncommon, we highlight 2 recent cases encountered at our centre. The aim is to emphasise their apparent benign appearance on physical examination, so that readers will be alerted in a similar clinical setting. Medline was used to search for relevant articles concerning the pathology, treatment modalities and long-term prognosis of patients with this rare illness. We also reviewed soft tissue sarcomas found elsewhere. Articles relating to phyllodes tumour were excluded or only relevant sections used. We discuss the controversy regarding axillary lymph node clearance and the use of radiotherapy. Despite conflicting reports and lack of clinical studies, we believe that a simple mastectomy will suffice as adequate treatment, hence avoiding the undesirable side effects of chemotherapy or radiotherapy.

Ann Acad Med Singapore 2004;33:270-4

Key words: Fibroadenoma, Immunohistochemistry, Soft tissue sarcoma

Introduction

Sarcoma of the breast was first described by Chelius in 1828.[1] It is an unusual condition accounting for less than 1% of all breast malignancies and less than 5% of all soft tissue sarcomas (STS).[2] This article reviews the current status of various treatment modalities available. Using 2 cases as examples, we hope to emphasise their benign appearance on clinical examination and subsequent treatment. We also hope to shed light on how the aetiology and pathology of this disease affects treatment modalities and long-term prognosis.

A Medline search was conducted for articles pertaining to breast sarcoma, with criteria for pathology, immunohistochemistry and therapy. Information concerning other soft tissue tumours found elsewhere was included. Papers which included phyllodes tumour in their studies were not used or only relevant sections reviewed. Papers reviewed shared the same definition of breast sarcoma as our article.

Case Reports

Patient A is a 46-year-old Chinese lady who presented in July 2000 with a lump in her left breast. No distinct lump was evident on examination, but the site had prominent nodularity. A benign-looking group of microcalcifications was seen on the mammogram. Based on the appearance of an obvious lesion 6 months later, surgical excision was advised. Histology revealed myofibrosarcoma with invasion of surrounding tissues. Further excision achieved only a further margin of 6 mm, subsequent to which a simple mastectomy was performed. Neither residual tumour nor involvement of the axillary tail lymph nodes was found in the mastectomy specimen. As part of her metastatic work-up, a computed tomography scan of the thorax and ultrasound of the liver were done and they were negative for distant disease. She was well on follow-up.

Patient B is a 41-year-old Chinese lady who first presented in February 2001 with a lump in her left breast of 1 week's duration. It was progressively enlarging but non-tender. On examination, there were 3 well-defined lumps: 1 (5 cm) in the left breast and 2 (2.5 cm and 2 cm, respectively) in the right breast. Mammographically, the lumps appeared benign and were classified as Breast Imaging Reporting and Data System (BI-RADS) 2.[3] Ultrasonic features were benign in appearance. Fine-needle aspiration cytology (FNAC) was performed on all 3 lesions. The lumps in the right breast at 1 o'clock and 10 o'clock were reported back as proliferative

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atypical lesion and benign yield, respectively. An inconclusive, non-diagnostic result was obtained from the left-sided lump. Excision biopsy of all 3 lumps was advised and accepted by the patient. The final histology was benign for both lumps in the right breast, with low-grade stromal sarcoma found in the left breast lump. A left simple mastectomy was done and no residual tumour was found. She has remained disease-free on follow-up.

Classification

Berg et al[4] first defined stromal sarcoma of the breast in 1962. It was described as a group of rather homogeneous tumours with "fibrous, myxoid, and fatty patterns" as seen by light microscopy, and were considered as variations of the normal mammary stroma.

Lattes divided primary sarcoma of the breast into 4 categories, namely, cystosarcoma phyllodes, lymphoma, angiosarcoma and pure sarcoma (that is, without epithelial elements).[5] Malignant phyllodes tumour has epithelial elements within a cellular stroma that had undergone malignant change.[6] Stromal sarcomas, in contrast, lack the epithelial component and are, by definition, formed entirely from within the breast tissue. Extensions to the breast tissue originating from overlying tissues (such as dermis) or underlying tissues (such as striated muscle) are to be excluded.[7] In addition, breast sarcoma should be distinguished from carcinoma that had undergone sarcomatoid metaplasia.[8]

Pathology

Stromal sarcoma of the breast is used as a collective term to describe a group of sarcomas that is actually made up of several histologic types, all of which behave in a manner similar to tumours of equivalent histologic type found in extra-mammary tissues. Pollard et al,[9] in their review of 25 patients, found the histological types to be malignant fibrous histiocytoma (MFH) (44%), liposarcoma (24%), fibrosarcoma (16%), clear cell sarcoma (4%), neurogenic sarcoma (4%), leiomyosarcoma (4%) and alveolar soft part sarcoma (4%).

Four subtypes of MFH have been recognised, namely, giant cell, fibrous, myxoid and inflammatory types. The cell of origin is probably a tissue histiocyte or primitive mesenchymal cell with the ability for dual differentiation into a fibroblast or histiocyte. Liposarcoma is derived from adipocytes while fibrosarcoma arises from a mature fibroblast. Clear cell sarcoma is considered to be a soft tissue form of melanoma[10] and was only described as recently as 1965. Neurogenic sarcoma and leiomyosarcoma arise from the neural and myo-epithelial elements, respectively. Alveolar soft part sarcomas are of uncertain histogenesis and carry a poorer prognosis due to its propensity for early metastasis.[11]

Stromal sarcomas should be reported in a similar manner as STS in terms of size, histogenesis and degree of differentiation.[2] Some authors advocate reporting histological grade in terms of tumour differentiation, tumour necrosis and mitotic activity.[7] This is because histologic grade is an important contributor to prognosis.[6]

Aetiology

The cause of breast sarcoma is unknown.[2] Killick and McCann[12] reported a case of mammary osteosarcoma associated with fibroadenoma. They suggested that the latter may be a precursor of the sarcoma.[13] However, fibroadenomas have traditionally been regarded as benign tumours of the breast. Indeed, most available evidence suggests that fibroadenomas are actually hyperplastic, rather than neoplastic, lesions. Because they are composed of 3 different cell types – secretory epithelial, myo-epithelial and stromal connective tissue cells – it is difficult to reconcile with the clonal theory of neoplasia.[14] Noguchi et al,[15] using restriction fragment length polymorphism of the X-chromosome-linked phosphoglycerokinase gene, showed that fibroadenomas are composed of polyclonal epithelial and stromal cells. This finding is in keeping with a hyperplastic, rather than a neoplastic, process. Augmentation mammoplasty with silicone prosthesis as a foreign body was postulated to increase the risk of breast sarcoma, but this was not supported by the SEER data.[16] Post-surgical radiotherapy has been shown to increase the risk of angiosarcoma, which is often discussed separately from stromal sarcoma in view of its highly aggressive nature.

Immunohistochemistry

Several immunohistochemistry markers have been used in stromal sarcoma. The most important reason for using these markers is to aid in differentiating pure sarcomas from sarcomatoid metaplasia in carcinoma. This differentiation is important for therapeutic modality and prognosis. However, it is worth noting that interpretation of immunohistochemistry results is dependent on proper technique, strict use and interpretation of well-characterised positive and negative controls, and detailed knowledge of the performance reagents.[17] Several markers are used by our centre and their roles are shown in Table 1.

Although immunohistochemistry can help the pathologist to differentiate carcinoma from sarcoma, it does not aid in subtyping.[7] However, because of the relatively low incidence of breast sarcoma, the lack of subtyping does not change its therapeutic modality or prognosis. This is probably due to the small numbers, rather than an actual lack of differences, between the subtypes. Immunoreactivity with antibodies to epithelial surface antigens or the presence of oestrogen receptors has given rise to the possibility that an

Table 1. Common Markers in the Immunohistochemistry of Breast Sarcoma

Histogenesis	Markers	Role of antigen
Mesenchymal	Vimentin	Class III mesenchymal intermediate filament
Neuronal, nerve sheath	S-100 protein	Ionic regulation, widely distributed in peripheral and central nervous systems
	HMB45	Located in premelanosomal vesicles, helpful in melanocytic lesions
Endothelial/vascular	CD31	Cellular adhesion molecular, sensitivity and specificity of 100% for endothelial lesions
	CD34	Transmembrane glycoprotein, very sensitive marker for endothelial cells
Muscle	Desmin	Intermediate filament, expressed in 95% of rhadomyosarcoma
	Actin	Contractile proteins
Epithelial	Epithelial membrane antigen (EMA)	Complex of high-molecular weight cytokeratins isolated from the human milk fat globule membrane
	Cytokeratins	Group of 19 polypeptides expressed in the vast majority of epithelial-like sarcomas

apparently pure sarcoma may be, in reality, a carcinoma with extensive mesenchymal differentiation. Nonetheless, the demonstration of 1 epithelial antigen or a positive oestrogen receptor assay in an apparently pure sarcoma should not change the diagnosis. This is because positivity for each of these determinants has been reported in sarcomas in many different sites.[8]

Clinical Presentation

Breast sarcoma usually presents as a painless, mobile and large breast mass. Features consistent with breast carcinoma of a similar size are often absent. For example, there is no nipple discharge, skin or nipple involvement, or axillary adenopathy. In fact, clinical features tend to be those of a typical fibroadenoma. However, a history of rapid growth in a previous long standing case of an indolent lump should raise the suspicion of a sarcoma.[2,9] Although the age of presentation is variable, the peak incidence is in the fourth and fifth decades of life, which is 1 to 2 decades older than the typical patient with a fibroadenoma. Hence, sarcoma should be considered in older patients.[2]

Investigations

The investigations used to diagnose breast sarcoma are similar to that in any breast lump. A trucut biopsy or FNAC allows a preoperative diagnosis to be made reliably.[9] Mammography is useful in demonstrating the lesion, but it is not particularly so in differentiating it from other benign or malignant lesions. In addition, the lesion may be obscured in dense breast, depending on the nature of the subtype. A sarcoma would be seen as a dense mass with indistinct margins and is rarely associated with tumour calcifications. Hence, it is often mistaken for a benign lesion, such as a fibroadenoma.[2] Ultrasonography would typically show a solid lesion with benign features, making it indistinguishable from a fibroadenoma.[2]

Treatment

In the treatment of breast sarcoma, understanding its biological behaviour and its likely pathway of metastasis is important. This is because the low incidence of this tumour precludes the possibility of any meaningful prospective trial.[9]

Most authors agree that the main treatment of breast sarcoma is surgical extirpation.[1,2,6,9,18,19] The aim is for excellent local control. However, controversy exists with regards to whether wide local excision (WLE) with negative margins is adequate or if adequate local control should be a simple mastectomy (SM). Older series suggest a higher rate of local recurrence with WLE compared to SM,[4] although Gutman et al[1] suggest that WLE is acceptable with a 2- to 3-cm tumour-free cuff of normal tissue. However, the key issue in adequate local control is that of tumour-to-breast size ration, and a large sarcoma in a small Asian breast often means that a mastectomy may be mandatory to guarantee complete excision.[2]

Regional lymph node metastases are very rare. In a review of 32 patients by Callery et al,[18] no regional lymph node was involved. Another review of 25 patients revealed 7 patients with regional lymphadenopathy, of which there was only 1 with metastatic involvement.[9] Gutman et al[1] observed that axillary lymph node tumour involvement represented systemic dissemination rather than an isolated locoregional extension typical of primary epithelial breast tumours. Indeed, once metastasis occurs, the tumours tended to progress rapidly.[15] In contradistinction to breast carcinoma, metastases usually occur via haematogenous spread to the lungs and bones, with local lymph node spread being the exception rather than the rule.[4,19] Hence, a carcinoma with sarcomatoid metaplasia should be considered if the lymph nodes are involved.[8]

The role for adjuvant radiotherapy or chemotherapy is

unclear and controversial. McGowen et al[20] advocate conservative surgery with adjuvant radiotherapy if negative margins can be achieved. The rarity of this disease may mean that the impact of radiotherapy in decreasing local recurrence after breast conservation may never be known. Based on the compartmental concept of sarcoma management elsewhere in the body, it might be reasonable to accept that compartmental extirpation is only achievable with a mastectomy. Johnstone et al[6] reported excellent local-regional control with postoperative radiotherapy to the chest wall following either simple, modified radical or radical mastectomy in 10 patients. Tochika et al[21] reported a case of local recurrence and pulmonary metastasis after adjuvant radiotherapy and chemotherapy which in reality represents the course of the sarcoma when residual disease is left behind as margins were involved even after initial lumpectomy. It might even suggest the limited role of radiotherapy and chemotherapy in disease control in the background of residual disease, highlighting the dominant role of adequate surgical extirpation in this condition. An additional area of concern is the emergence of radiation-induced breast sarcomas after breast conservation therapy, with angiosarcoma being the most common and more aggressive than the primary tumour.[2]

Adjuvant chemotherapy in disease control has also been disappointing. However, in a retrospective study, Gutman et al[1] suggested a disease-free survival benefit (a median of 110 months compared to 12 months without adjuvant therapy; $P = 0.007$), but no overall survival benefit (a median of 133 months to 57 months; $P = 0.063$). However, any form of chemotherapy should only be administered within the context of a clinical trial.[2] Callery et al[18] went as far as to conclude that because excellent local control is possible with mastectomy alone, use of any lesser form of surgery and multimodal adjuvant therapy should be considered as investigational.

Adjuvant therapy with oestrogen antagonists and other hormonal manipulations currently has no place in treatment as, unlike breast carcinoma, sarcomas do not express any hormonal receptors.[9]

Prognosis

Norris and Taylor[22] first proposed 3 prognostic factors, namely, the nature of the microscopic contour of the tumour (pushing, infiltrating or indeterminate), the degree of cellular atypia (+ for mild atypia and histologically benign to +++ for maximal atypia and histologically malignant) and the mitotic count for every 10 high-power fields. Hence, a poor prognosis would be associated with an infiltrating contour rather than pushing or indeterminate, a high mitotic rate and the presence of giant cells.[9]

Size and histologic grade of the breast sarcoma are also highly predictive of outcome.[2] Indeed, 5 cm has been suggested as a cut-off size below which there is a better prognosis, irrespective of any other factors mentioned above.[1] Grade was found to be an important factor predictive of local and distance recurrence, while the histologic subtype has no prognostic significance. This appears to be consistent with the behaviour of sarcomas found elsewhere.[15]

Gutman et al[1] found that local recurrence and metastasis to the lungs are the most common sites of breast sarcoma recurrences. Other organs that may be involved include peritoneal visceral covering and retroperitoneal areas, lymph nodes, bones, skin, rib cage, brain, liver and pleura in decreasing incidence. They also identified 4 distinct subgroups with different patterns of first failure: patients with unresectable primary tumour and/or distant metastases; patients whose treatment fails with synchronous local and distance disease; patients whose treatment fails locally only; and patients whose treatment fails distant only. As would be expected, the prognoses of the first 2 groups were more dismal than the latter 2 groups in terms of disease-free survival and overall survival.

Conclusion

A problem that we often encountered was the way the term "breast sarcoma" was loosely used. Because of its low incidence, many authors analysed data without classifying breast sarcoma into its 4 subgroups. As we have seen, this is of paramount importance as their biological behaviours are different. Hence, data pertaining to stromal sarcoma should be analysed apart from phyllodes tumour, lymphoma and angiosarcoma.

Although rare, a breast lump that is clinically benign but has undergone recent rapid growth or outside the age range of a fibroadenoma should alert the clinician to the possibility of an underlying sarcoma. Once diagnosed using the usual methods of mammography, ultrasound and FNAC/trucut biopsy, we need to exclude sarcomatoid metaplasia of carcinoma using immunohistochemistry.

In most cases, a small sarcoma of less than 5 cm can be treated with wide excision if tumour-free margins can be achieved, provided an aesthetically acceptable breast is left behind. Hence, consideration of the tumour-to-breast size ratio remains paramount in deciding the optimal extent of the surgery. Because of the relatively small size of the Asian breast, a SM leaving the axillary lymph nodes intact is often the more, or even the only, acceptable surgical option. There is currently no role for adjuvant radiotherapy, chemotherapy or hormonal therapy.

Stromal sarcoma of the breast is a rare tumour. Its low incidence and varied subtypes do not allow previous trials to shed light on its optimal treatment and prevention. Nevertheless, using the limited information available,

together with extrapolation from our experience with sarcomas found elsewhere in the body, it is still possible to offer effective therapy for patients with breast sarcoma.

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