Cystosarcoma Phylloides: 20 years experience

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Abstract

Cystosarcoma phylloides (CSP) is a rare tumour of the breast whose clinical behaviour does not correlate well with its histological findings. The optimal treatment of this tumour remains controversial. A retrospective study on the treatment and outcome of women diagnosed with CSP in Brunei between 1986 and 2005 was undertaken. Sixty-one women were diagnosed over the 20-year study period. Follow-up was complete in 59 cases. The mean age at diagnosis was 35 years. There were 38 (65%) histologically benign lesions, 12 (20%) borderline lesions and 9 (15%) malignant lesions. The mean follow-up period was 72 months. Eight patients (14%) had recurrences after initial operative treatment (in 5 benign, 1 borderline and 2 malignant lesions). Mean time to recurrence was 6 months. Breast-conserving surgery with adequate resection margin is advocated in benign and borderline lesions. For malignant lesions, simple mastectomy without routine axillary dissection is recommended. More research is required to determine the role of adjuvant chemotherapy and radiotherapy in the management of malignant CSP.

Introduction

Cystosarcoma phylloides (CSP) was first named and described by Johannes Muller in 1838, based on the gross pathological description of a 'bulky, cystic, fleshy and leafy tumour of the breast' [1]. Classically, the name CSP was applied because of the tumour's fleshy appearance and tendency to contain macroscopic cysts. Phyllodes tumor is another proposed nomenclature. The term CSP however, is a misnomer as these tumours are usually benign. Cystosarcoma phylloides is characterised by the presence of both stromal and epithelial components. It is rare with an incidence estimated to be 0.3% to 0.5% of all breast tumours [2-3]

Several classifications of CSP have been proposed based on certain histopathological criteria (Treves and Sunderland [4], Pietruszka and Barnes [5], Azzopardi [6] and World Health Organization classifications [7]. These criteria consist of cellular atypia, stromal cellularity, sarcomatous differentiation and mitotic index. The WHO classification was proposed in 1982 in order to promote uniformity in the recording and reporting of breast diseases and to facilitate international comparisons. Numerous reports have attempted to correlate the histological features with clinical outcome. These reports generally showed a poor correlation between the two and histopathology does not necessarily predict the clinical course [8-9]. As a result, the incidence of malignant CSP has been variably quoted to be between 3% and 54% [3].

CSP has presented a diagnostic and treatment dilemma for surgeons since its original description. Over the years, there has been debate regarding the optimal management of this tumour and clinical management still remains controversial. This report was undertaken to review our experience with CSP and to attempt to provide a practical approach to these rare and unpredictable breast tumours.

Materials and methods

Cases indexed CSP or phyllodes tumours between 1986 and 2005 (20 years) inclusive were obtained from the Department of Pathology. Cases diagnosed as pure sarcomas

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or giant fibroadenomas of the breast were excluded from the study. The records were retrieved and the cases were reviewed retrospectively. Histopathological material from each case was reviewed by one of the authors (Telesinghe). The WHO Classification of CSP was used and the lesions were categorised as benign, borderline or malignant based on the frequency of mitoses, infiltrative margins, cellular atypia and cellularity [7]. Data was obtained with regard to age, presentation, histological diagnosis, treatment, recurrence and follow-up.

Results

There were 61 patients diagnosed with CSP in Brunei during the 20-year study period. Clinical details and follow-up were complete for 59 cases; one benign CSP case was lost to follow-up and another malignant case sought further management overseas. All of the patients were female. There were 38 (65%) histologically benign lesions, 12 (20%) borderline lesions and 9 (15%) malignant lesions. The mean follow-up period was 72 months (range 1-240 months).

The mean age at the time of diagnosis was 35 years (range 11-64 years). The mean ages of patients with histologically benign, borderline and malignant lesions were 30, 37 and 47 years respectively. All patients presented with a palpable breast lump and 11 cases (19%) also had associated pain. The mean duration of symptoms was 6 months (range 1-36 months). There appeared to be a predominance of left-sided lesions. There were 37 (63%) left-sided lesions and 22 (37%) right-sided lesions. The mean size of the presenting breast lump was 6cm (range 1-25cm). The mean size of malignant lesions was larger (9cm) than benign and borderline lesions (both 5cm). Postmenopausal women consisted of only 4 cases (7%).

Six patients had breast ultrasonography as a pre-operative diagnostic modality; 3 were misdiagnosed as fibroadenomas, 1 was reported as ‘a complex mass’ and only 2 were correctly diagnosed as CSP. Nine patients underwent mammography with only 1 case correctly diagnosed as CSP and others misdiagnosed as fibroadenomas. Fine needle aspiration (FNA) of the breast lump was performed in 19 cases. The results were diagnostic in only 10 cases; 6 cases were misdiagnosed as fibroadenomas, 1 fibrocystic disease, 1 was reported as ‘a malignant lesion ‘ and 1 had no cellular yield. One patient underwent a core biopsy of the breast lump which was correctly diagnosed as a malignant CSP.

Primary treatment in this series included excisional biopsy in 31 cases, wide local excision (WLE) in 19 cases and mastectomy in 9 cases. All the 38 patients with benign CSP underwent either excisional biopsy or WLE only. WLE was used in 11 borderline lesions and in 1of the 9 malignant lesions. Two patients in the borderline group had an intra-operative frozen section examination of the excised lump and subsequently had WLE under the same anaesthesia when the diagnoses revealed borderline lesions. One borderline lesion and 8 malignant lesions had mastectomy as the primary treatment (Table. 1).

	Excisional biopsy	Wide local excision	Mastectomy
Benign	31	7	
Borderline		11	1
Malignant		1	8

Table 1. Primary operations in the treatment of Cystosarcoma phylloides

Eight (14%) tumour recurrences were noted in the present study. Tumours recurred in 5 benign (17%), 1 borderline (8%) and 2 malignant (22%) cases. The time to recurrence ranged from 2 to 24 months (with a mean of 6 months); with recurrences occurring within 3 months in malignant lesions. In contrast, the time to tumour recurrence in benign lesions ranged from 6 to 24 months after the initial surgery. One benign lesion that recurred was initially treated by excisional biopsy and the original histopathology revealed involved resection margins. This patient subsequently underwent WLE. Recurrence occurred in 1 borderline lesion 14 months after the initial WLE. Mastectomy was performed for the recurrent tumour and the patient remained disease free at 91-month follow-up. One malignant lesion initially treated by mastectomy developed local recurrence after 2 months. Histopathology of the lesion showed a necrotic tumour with hypercellular stroma and marked mitotic activity. Despite excision of the recurrent tumour followed by chemotherapy, the patient died 10 months later with liver and brain metastases. The other malignant lesion had a WLE as the primary treatment in another country; she developed local recurrence 3 months later. This patient subsequently underwent a mastectomy. She remained disease-free 95 months later and had received no chemotherapy.

Axillary lymph nodes were sampled in 5 of the 8 patients in whom mastectomy was performed, as part of the primary treatment. None showed evidence of metastases. Similarly, no lymph node involvement was seen in the patient who underwent mastectomy for recurrent disease. Two of the patients with malignant CSP received adjuvant radiotherapy and chemotherapy after mastectomy because one histopathology of the lesion showed a highly cellular and vascular stroma and another showed marked mitotic activity. Both patients remained disease-free at 100 and 114 months follow-up respectively.

Discussion

Cystosarcoma phylloides is an unusual neoplasm of the breast that demonstrates all the extremes of biological activity. It continues to present problems to both histopathologists and surgeons alike because of its atypical and unpredictable behaviour. 'Benign' lesions have been noted to metastasise, and can recur locally [10]. In one study, local recurrence was seen to occur in 5% of benign tumours, 45% of borderline tumours and 37% of malignant tumours [11]. Another study noted more recurrence with benign lesions [12], whereas others noted no difference in recurrence rates between benign and malignant lesions [13]. Overall recurrence in the current series was 14% and this was compatible to that reported by Bennett *et al* (16.5%) [13] and Holthouse *et al* (15.4%) [14]. Metastasis in this series was 1.7%, which was much lower than the reported frequency of metastases in the literature (10% - 30%) [12, 15].

The difficulty of predicting the clinical behaviour of CSP is well known. Norris and Taylor [9] were among the first to use histopathological features in an attempt to predict prognosis, but highlighted the fact that no single feature was reliable. Further studies have found certain pathological criteria to be useful in predicting the tumours that are likely to behave in a malignant fashion. These include stromal overgrowth, nuclear pleomorphism, high mitotic rate and infiltrating margins [16]. Other studies have also reported the significance of the presence of necrosis and increased vascularity within the tumour [17]. In general, malignant lesions tend to be larger than benign ones, as noted in the present series; it is however, well recognised that even small lesions may behave in an aggressive manner and conversely large lesions may be benign.

Cystosarcoma phylloides has been described as occurring in patients with a wide range of ages from prepubertal to elderly [18]. The youngest patient in our series was 11 years old. The mean age of patients in this series is 35 years, which is younger than that noted in most series (in their 40's) [11, 13, 15]. This observation was also reported by Chua *et al* [19] and Iau *et al* [20] whose patients consisted of non-caucasian populations similar to ours. The mean age of patients with malignant lesions is generally reported to be greater than that for those with benign lesions and this was observed in this study. Malignant lesions also exhibited a tendency to recur early; both malignant recurrences in the present series recurred within 3 months of the initial surgery.

Classically, patients with CSP present with a firm, mobile, well-defined, round, lobulated and painless mass. The tumor can be extremely difficult to differentiate from fibroadenoma on physical clinical examination. In the series reported by Chua *et al.*, 71% of patients with a postoperative diagnosis of CSP had a presumptive pre-operative diagnosis of fibroadenoma [19]. Another series showed a preoperative diagnosis of CSP in only 10-20% of patients [21].

A variety of techniques have been utilized to improve the pre-operative diagnosis of CSP. Cole-Beuglet *et al.* [22] performed a retrospective study on 8 cases of histologically proven CSP that were evaluated by mammography and ultrasound scan. They showed that while ultrasound findings (low-level internal echoes, smooth walls and smooth-margined fluid-filled clefts in a predominantly solid mass) may suggest a CSP, there is no consistent and reliable way to distinguish between CSP and other benign appearing tumors on ultrasound scan [22]. Mammographic diagnosis was unreliable since many of the lesions do not have typical mammographic malignant characteristics [14, 23]. Fine needle aspiration (FNA) cytology has not been shown to be of value, as seen in this and other studies [14, 21], primarily because of the difficulty in obtaining adequate numbers of stromal cells for cytogenic analysis [24]. Salvadori *et al.* found the FNA to be diagnostic in only 4 of 30 cases [11]. Core tissue biopsy is an attractive alternative to FNA, and several authors have suggested its use as a preliminary procedure [25-26]. Core tissue biopsy may represent a preferred means of preoperative diagnosis for giant breast tumors, and the histological information gained is important in guiding surgical treatment.

Certain guidelines on the surgical treatment of CPS have been proposed [27] but the optimal management of patients with CSP remains controversial. A high index of suspicion is therefore, required for the initial diagnosis of CSP. In general, these tumours are large, palpable and painless on presentation. Skin fixation, ulceration and nipple changes are rare. A rapid growth is often noted. It tends to present in younger patients than carcinoma of the breast [4-5].

Surgery remains the primary treatment. The aim is to excise the lesion with adequate margins to prevent local recurrence, including mastectomy if required. This is advocated for benign lesions. It is felt that local recurrence is due to inadequate local excision; as seen in one of the recurrences in benign lesion in the present series. If the lesion is found to be malignant, a simple mastectomy is recommended at that time. Malignant CSP, unlike carcinoma, is generally not responsive to radiotherapy or chemotherapy and simple mastectomy is the best procedure to prevent local recurrence. Routine axillary lymph node dissection is not generally performed because of low yield, as this disease rarely spreads by lymphatics [9, 15]. No positive nodes were seen in this series in which axillary dissections were performed. For borderline lesions, the optimal primary treatment is more controversial. Breast-conserving surgery with WLE was employed as the primary treatment in the present series. As seen in other series [14-16], this primary treatment for borderline lesions seemed to be adequate. However, when a borderline lesion recurs after primary surgery, a simple mastectomy may be required. This more radical treatment may be justifiable as most reports have shown that recurrent tumours tend to be more aggressive with a higher mitotic count and greater degree of nuclear pleomorphism than the original lesions [13, 28].

Although no conclusive evidence supports adjuvant radiotherapy or chemotherapy for malignant CSP, encouraging results using radiotherapy and chemotherapy for soft tissue sarcomas suggest consideration be given for its use with malignant CSP [29]. Effective radiotherapy and chemotherapy have also been reported in isolated cases. Radiotherapy was shown to lead to a slow regression of CSP [2, 30] and Chaney *et al* [31] had found adjuvant radiotherapy to be beneficial in 8 patients whose CSP showed adverse features (bulky tumours, positive margins, recurrence and malignant histology). Effective chemotherapy in 4 patients using ifosfamide alone or in combination with doxorubicin was reported by Hawkin *et al* [32]. We have also used ifosfamide in combination with doxorubicin in 2 of our malignant CSP who had poor prognostic histopathological features. Both patients were alive and disease-free at 100 and 114 months follow-up.

Others have also reported effective chemotherapy with cisplatin and etoposide [33]. The use of tamoxifen in CSP has not been fully investigated. However, oestrogen and progesterone receptors were found to be present in these tumours [34] and future studies with hormonal manipulation in CSP may be warranted.

Local recurrence rates for CSP are 15-20% and are correlated with positive excision margins, rather than with tumor grade or size [19, 21, 27]. Other studies have shown a higher risk of local recurrence in borderline and malignant tumors. In a series by Salvadori *et al*., 51 patients were treated with breast conserving surgery (enucleations, wide local excisions), and 14 of the tumors reccurred locally. In contrast the 20 patients treated with mastectomy (subcutaneous, modified radical, or radical) showed no evidence of local recurrence [11].

Cystosarcoma phylloides do not typically metastasize via the lymphatics. About 20% of patients have palpable axillary lymph nodes on presentation, but only 5% of these show histological evidence of metastasis on pathological examination. Of the CSP with a malignant histology, up to 15% will metastasize to the axilla [2]. Kessinger *et al.* found that all metastatic lesions described in the literature contained only the stromal elements [2]. No malignant epithelial elements were observed. Since most sarcomas metastasise haematogenously, this finding may explain why axillary metastasis is so rare. Palpable lymphadenopathy is typically attributed to the patient's immune response to tumor necrosis. The rare patient who does have lymph node metastases tends to have a poor prognosis [35]. Because of the rarity of lymph node involvement, most authors advocate that the removal of axillary lymph nodes is not warranted unless there are palpable nodes [17, 27, 31]. Metastasis is reportedly seen only in 4% of all CSP [11]. The most common sites for metastasis include the lungs, bone, liver and distant lymph nodes, and skin involvement does not appear to be a predictor of metastasis [36].

Reinfuss *et al.*, using the histopathological criteria developed by Azzoperdi and Salvalori *et al,* reported a 5-year survival of 95.7% for benign tumors, 73.7% for borderline tumors, and 66.1% for malignant tumors [37]. A study by Chaney *et al,* which combined the benign and borderline tumors into a single category, found 5-year survival rates of 91 % for benign tumors and 82% for malignant tumors [31]. Ten-year survival rates, however, dropped to 79% and 42%, respectively [31].

Conclusions

Cystosarcoma phylloides is a rare breast tumour that often shows behaviour that is different and unpredictable from histopathological findings. Its management presents the surgeon with unique challenges. Surgery remains the main primary treatment and an adequate resection margin must be obtained in all cases. In benign and borderline lesions, breast-conserving surgery should be employed, except when tumour size prohibits. For malignant lesions, simple mastectomy without routine axillary dissection is recommended. Anecdotal cases have shown that adjuvant radiotherapy and chemotherapy may be beneficial in CSP with poor prognostic histological features (hypercellular stroma, high nuclear pleomorphism, high mitotic rate, infiltrating margins, the presence of necrosis and increased vascularity within the tumour). However, further research is required to determine the role of radiotherapy and chemotherapy in the management of CSP. In all cases of CSP careful long-term follow-up is recommended.

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