British Journal of Plastic Surgery (2003), **56,** 129–134

doi:10.1016/S0007-1226(03)00025-0

BRITISH JOURNAL OF PLASTIC SURGERY

Angiosarcoma of the breast: a 30 year perspective with an optimistic outlook

S.N. Georgiannos and M. Sheaff*

*Departments of Academic Surgery, and *Histopathology, Royal London Hospital, London, UK*

SUMMARY. The aim of this study was to investigate the incidence and clinicopathological features of angiosarcoma of the breast by focusing on those cases passing through a busy general teaching hospital over a 30 year period. A search was carried out of all cases in the files of the Department of Pathology of the Royal London Hospital from 1970 to 2000. Four cases were identified as primary angiosarcomas involving the breast. The medical and surgical histories, macroscopic and microscopic features and clinical outcome with long-term follow-up are described in each case. Similarities were identified, such as initial presentation with a 'bruise' and a latent period before the diagnosis was established. Half of our cases followed irradiation for breast cancer. In all cases the prognosis after surgery was excellent. The rarity of primary mammary angiosarcoma was confirmed. In younger patients the lesion was not associated with previous radiotherapy, but the older patients presented after radiotherapy for adenocarcinoma of the breast. Although very uncommon, these tumours must be considered in the differential diagnosis, especially with the increasing use of fine-needle-aspiration and core biopsy for preoperative diagnosis. The prognosis after complete surgical excision may be better than generally believed. © 2003 The British Association of Plastic Surgeons. Published by Elsevier Science Ltd. All rights reserved.

Keywords: breast, angiosarcoma, radiotherapy.

Sarcomas of the breast are uncommon and account for less than 1% of primary malignant mammary-gland tumours.[1] Although the type distribution and frequency of sarcomas is similar in the breast to other sites around the body, angiosarcoma arises in the breast more than any other organ.[1] Contemplating a diagnosis of mammary sarcoma rather than carcinoma is important since lymph-node metastases are infrequent in the former, and, therefore, the unwanted morbidity of axillary-node dissection can be avoided.

Following the introduction of limited-sampling methods for the preoperative diagnosis of breast lesions (fine-needle-aspiration or needle-core biopsy), it is becoming increasingly important that clinicians remain aware that non-epithelial tumours may arise in the breast. Early confirmation of non-epithelial tumours, such as angiosarcomas, is crucial for appropriate management and to avoid unnecessary and potentially harmful treatment being offered to these patients. The pathologist may, however, occasionally encounter difficulties when confronted with a possible angiosarcoma because they need to be differentiated from benign vascular proliferations, metaplastic carcinomas and malignant phyllodes tumours.

Historical data regarding the incidence, pathological features and outcome of primary angiosarcomas of the breast provide a useful source of reference for the interpretation of biopsy and cytological material and for guiding management. Many breast angiosarcomas have been described as single case reports. In an attempt to provide more meaningful data on these rare tumours, a search of the surgical material of the Department of Histopathology at the Royal London Hospital was made, which identified four cases between 1970 and 2000.

Materials and methods

The files of the Department of Histopathology at the Royal London Hospital from 1970 to 2000 were reviewed. This is a busy hospital serving the surgical needs of a local and regional population, but it is not a tertiary breast referral centre. Around 10 500 surgical breast specimens were received during the study period, the majority from either benign lesions or primary adenocarcinomas. Four cases of primary angiosarcoma of the breast were identified. The pathological material was briefly reviewed to confirm the diagnosis, and then the case histories, histological sections and follow-up information were reviewed in detail. Tumours were classified as mammary angiosarcomas only if a known primary site outside the breast had been excluded and there was no evidence of systemic disease with coincidental involvement of the breast.

Case reports

Case 1

A 45-year-old female phlebotomist presented to her general practitioner in November 1973 with a 2 week history of a lump in the upper outer quadrant of her left breast. Excision by lumpectomy confirmed an infiltrating ductal carcinoma ('scirrhous'). There was no vascular invasion, and the margins appeared clear. She was treated with local external-beam radiotherapy to the breast and axilla as an outpatient. During follow-up in September 1975 a further non-tender lump in the right breast was excised and found to be benign fibroadenosis.

In February 1998 the patient noticed a discrete lump on the left side, measuring about 1.5 cm × 1.5 cm, which seemed to appear after a road-traffic accident. This was associated with overlying bruising and was initially thought to be traumatic in origin. Over the next month the lesion did not resolve and was excised. Histology confirmed a well-differentiated grade 1 angiosarcoma. It was incompletely excised, and wide local excision was performed 1 week later. Excision was still incomplete and, in May 1998, a left simple mastectomy with split-skin grafting was performed. The margins were uninvolved.

Close follow-up has been unremarkable on the left side to date, but, interestingly, a basal cell carcinoma was removed from her back in late 1998 and a basal cell papilloma and lymphomatoid papulosis have both been diagnosed on skin biopsies removed more recently from her right breast. She remains well 28 years after treatment for adenocarcinoma of the left breast and 3 years after removal of an angiosarcoma from the same breast.

Case 2

A 64-year-old retired upholsterer, who had been previously well, was found to have a right breast lesion during routine screening mammography. She was nulliparous and postmenopausal. Examination revealed a 1 cm × 2 cm firm mobile mass but no palpable lymphadenopathy. A right segmental mastectomy with axillary sampling, performed in July 1990, confirmed an invasive lobular adenocarcinoma with associated in situ ductal carcinoma. The lymph nodes and margins were clear. Receptors were not available at the time, but the patient was started on tamoxifen (20 mg daily), and in April 1991 a 32-day course of radiotherapy (4250 Gy) was delivered.

Follow-up examinations and mammograms were unremarkable until August 1996, when the patient noticed a red area just medial to the scar. A biopsy showed radiotherapy changes only. In 1997 the patient developed a 'blood blister' over extensive 'bruising' of the right breast. This enlarged, and an incisional biopsy performed in December 1997 revealed a hemangiosarcoma. Mammography and ultrasound revealed no discrete masses, but MRI showed a 15 cm × 2 cm plaque of tumour. In February 1999 a mastectomy with skin grafting was performed, and histology confirmed an extensive poorly differentiated (grade 3) angiosarcoma. All margins were clear, and follow-up to date has been unremarkable.

Case 3

This woman, who worked as a secretary, presented in February 1984 at the age of 20 years with a 3 month history of a hard mass in the upper outer quadrant of her left breast. She had no children, was taking the oral contraceptive pill and was a non-smoker. She had never received radiotherapy. Clinically, the mass measured 3–4 cm across and was associated with bruising of the overlying skin. The latter appeared to resolve, but the mass increased in size to 5 cm. It remained hard and mobile. It was thought to be a haematoma, but a biopsy was felt necessary. Excision of the haemorrhagic tissue and the cavity wall was performed in early March 1984, and a diagnosis of angiosarcoma was made. She went on to have a mastectomy in April 1984; complete clearance of the tumour, which did, however, extend close to the deep margin, was achieved. Axillary-node sampling revealed six normal lymph nodes. Follow-up has been unremarkable and she has since had two children.

Case 4

A 35-year-old patient identified a lump in her right breast in autumn 1986, which became more noticeable over 6 weeks. She also complained of a creamy nipple discharge. Clinically, the lump was 2 cm in maximum diameter, was not fixed and was situated above the nipple. She had never received radiotherapy. Excision biopsy was performed in September 1986, and a diagnosis of angiosarcoma was made. The tumour extended very close to the excision margins, and, therefore, she underwent a right simple mastectomy later that month; the axilla was left intact. Follow-up has been uneventful.

Results

Clinical details

All our cases occurred in women. Two patients were young women (20 and 35 years of age) with no relevant medical histories, whilst the other two were older women (45 and 64 years of age) and had received local radiotherapy for breast carcinoma 25 years and 7 years previously (Table 1). Radiotherapy is a known cause of secondary neoplasms, including sarcomas. Three of the four cases were associated with 'bruising' of the superficial tissues of the breast. Although limited details are available, there does not appear to be a pattern in the patients' social or occupational histories, with none recorded as smokers and all having different jobs. One of the younger patients was taking exogenous hormones (oral contraceptive pill) and at least one of the older patients was receiving tamoxifen.

Table 1 Clinical and pathological features of four cases of angiosarcoma of the breast

Age at presentation (years)	Time from presentation to diagnosis (weeks)	Side	Previous radiotherapy	Surgery	Histology	Follow-up from initial diagnosis (months)
45	4	left	yes	lumpectomy followed by simple completion mastectomy	grade 1 angiosarcoma	42
64	?58	right	yes	incisional biopsy followed by completion mastectomy (segmental previously for carcinoma)	grade 3 angiosarcoma	30
20	3	left	no	initial biopsy followed by mastectomy and axillary sampling	grade 3 angiosarcoma and fibrocystic change	87
35	1 day	right	no	excision biopsy followed by simple mastectomy	grade 1 angiosarcoma with surrounding fibrocystic change	60

Surgery

In all cases the diagnosis seems to have been delayed. In the majority this was just a matter of weeks, but in one case it may have been as much as 14 months. Once the diagnosis was established there were several operative procedures in each case, all proceeding ultimately to mastectomy. In the single case with axillary sampling the lymph nodes were uninvolved.

Histology

Case 1 showed some similarities with case 2 (both patients had had previous radiotherapy). There were typical radiotherapy-induced changes in the dermal connective tissue and the underlying breast tissue. These comprised stromal fibrosis, vascular ectasia and stellate fibroblasts. In both cases, the bulk of the tumour appeared to be centred on the dermis and the superficial breast parenchyma. Case 1 was well differentiated (grade 1) and composed of vascular channels lined by hobnail-shaped endothelial cells, whilst case 2 was poorly differentiated (grade 3) and composed of pleomorphic spindle-shaped cells (Fig. 1).

Cases 3 and 4 also shared some similarities in that both tumours predominantly replaced the breast parenchyma, with extension into the overlying dermis. Both showed features of surrounding fibrocystic change, but no evidence of radiation-induced alterations. Case 3 was poorly differentiated (grade 3) and extremely pleomorphic with necrosis, whilst case 4 was well differentiated (grade 1) and composed of readily recognisable endothelial-lined channels lying between residual lobules (Fig. 2). All cases were confirmed with CD31 and CD34 staining (Fig. 3). The lymph nodes in case 3 were normal.

Follow-up

All patients are currently alive and clinically free of disease, including those with initial carcinomas (11 and 28 years ago). Treatment of the angiosarcomas was undertaken 3 years and 3 years (the post-radiation cases) and 7 and 5 years (the primary tumours) ago, respectively.

Discussion

Breast cancer is the most common malignancy in women in northern Europe and the USA, accounting for about 30% of all female cancers.[2] Data from the International Union Against Cancer show that, in most populations, the incidence is increasing by about 1.5% per annum.[3] Although carcinoma of the breast has just become the most common mortality-associated malignancy of adult women in Britain above lung cancer,[4] other malignancies occur within the breast with lesser frequencies. Sarcomas make up less than 1% and, of these, 0.04% are angiosarcomas.[5] These figures are based upon reports from several institutions, many of which are tertiary referral centres specialising in breast disease.

Whilst such descriptions can provide detailed information on such tumours, they may also give a distorted impression of the overall incidence of mammary angiosarcomas. We therefore retrieved all of the cases of angiosarcoma that were processed through a single teaching hospital histopathology department during the period 1970–2000. We identified four cases (about 0.13% of all breast malignancies seen locally during this period).

Accurate diagnosis of angiosarcoma, and, in particular, differentiation from primary breast carcinoma, is important for optimal therapy and the avoidance of unnecessary radical surgery. Clinically, angiosarcomas

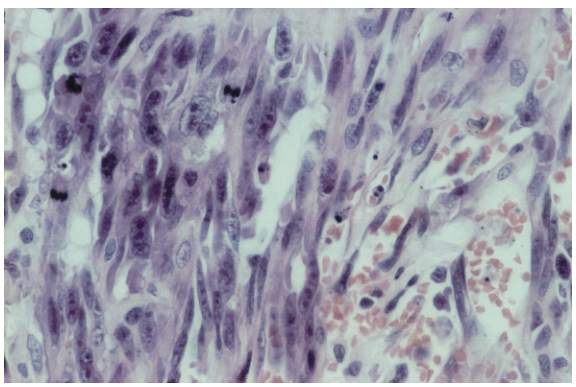

Figure 1—*Case 2.* Post-radiotherapy grade 3 angiosarcoma with marked pleomorphism of the spindle-cell neoplasm, vascular lumen formation and mitotic figures (H&E × 200).

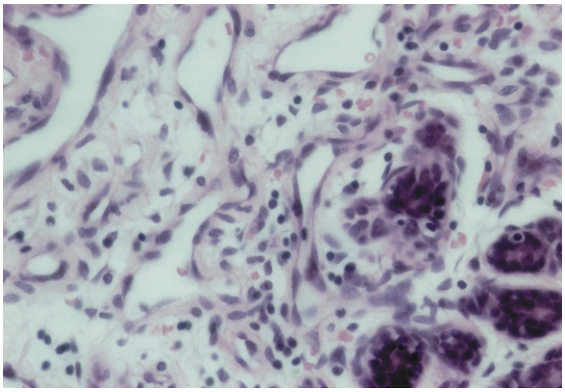

Figure 2—*Case 4.* Well-differentiated angiosarcoma infiltrating between residual breast acini, which are themselves normal (H&E × 200).

are not usually readily distinguishable from other neoplasms of the breast,[6] in which case radiology may have a role in establishing the true diagnosis.[7,8]

Clinical features

All of our cases, and the vast majority of cases reported in the literature, occurred in women. There are very rare reports of primary mammary angiosarcomas occurring in men[9] but the reasons for this discrepancy are unclear. Possibly, the difference in the mass of breast tissue between the sexes is important. Alternatively, hormone status or receptor expression may be relevant.

The majority of angiosarcomas recorded have occurred in young adult women (reported average ages vary from 38 to 60 years). The wide age range with a more recent bias towards older women may, in part, reflect the fact that most of those reported recently have followed radiotherapy for breast carcinomas and the latter tend to occur in later life. Both our post-radiation tumours presented at an older age than our two *de novo* cases, again raising the possibility of premenopausal hormone levels influencing tumour development in some way.

Two of our cases presented in the left breast and two in the right, one of each in both groups. As expected, the post-radiotherapy tumours both developed in the breasts that were in the field of external-beam irradiation.

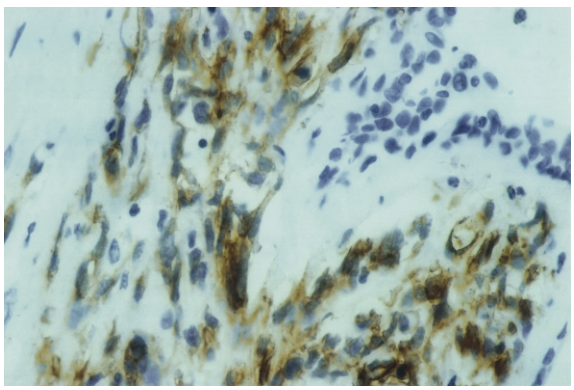

Figure 3—*Case 3.* Immunohistochemistry for CD31 (PECAM). Note the positive labelling of neoplastic cells and the negative staining of residual breast epithelial components (top right) (ABC method × 200).

Most angiosarcomas present as painless lumps with no defining characteristics to indicate their nature. Superficial or large tumours may also show purple discoloration of the overlying skin with apparent bruising. In fact, three of our patients did have evidence of bruising on clinical examination. In one case this led to a delay in diagnosis since the bruising was first noticed after a road-traffic accident and was attributed to local trauma to the breast. This delay in diagnosis was only a matter of a few weeks, but it is common for the diagnosis of angiosarcoma to be delayed and initial misdiagnosis is also common.[6]

Radiological features may lead to a correct diagnosis initially, but in most cases (as in ours) mammography is non-specific and heterogeneous.[7] The use of Doppler and MRI can be helpful in characterising breast masses more accurately.[8]

Aetiology and pathogenesis

It would seem logical to seek a role for hormones and/or receptors in the development of angiosarcoma, but no such evidence emerges from our results.

After radiation, a range of effects may be seen in the breast parenchyma and overlying skin. These include epithelial atrophy, stromal fibrosis, stellate fibroblasts, fat necrosis, inflammation, vascular changes and a range of vascular proliferations.[10,11] The latter include both benign and malignant neoplastic lesions as well as lesions that are difficult to categorise.[11] Numerous cases of angiosarcoma developing after radiation for breast carcinoma have now been described.[11–14] These characteristically occur after a latent period of several years and may occur in the breast or the ipsilateral arm.[13] In the majority of cases there is evidence of radiation-induced tissue injury and lymphoedema. It is frequently assumed that radiation is the most important aetiological factor,[15,16] but occasional cases of mammary angiosarcoma after segmental mastectomy for ductal carcinoma have been described in which there was local breast lymphoedema but no radiation treatment.[17] This suggests that the lymphoedema may play the most important role. However, Bolin and Lukas[18] and Moskaluk et al[19] have described cases of angiosarcoma developing after radiotherapy without evidence of lymphoedema. There is also considerable confusion as to whether angiosarcomas of the breast described in the literature arise from the overlying dermis (cutaneous) or from the parenchymal vascular endothelial cells (true mammary), and these may, in fact, be two different tumours with different aetiologies.

Pathological features

Angiosarcomas of the breast are usually composed of easily recognisable vascular structures, and their nature is frequently immediately obvious. It is possible to diagnose angiosarcoma by fine-needle aspiration

cytology.[20,21] Tumours range in morphology from well-differentiated (low grade, grade 1) tumours composed of neoplastic vessels lined by bland endothelial cells, through an intermediate grade, to poorly differentiated (high grade, grade 3) tumours that are generally composed of pleomorphic spindle-shaped cells with necrosis and numerous mitotic figures. It is important to grade these tumours, as this is usually a useful means of predicting behaviour.

From our few cases it seems likely that the grade of the tumour does not reveal whether or not it is radiation induced, as both grade extremes were observed in each group. Of note, however, was the location of the bulk of the tumour, with radiation associated with superficial tumours centred on the dermis, and the non-radiation tumours apparently arising deeper in the parenchymal tissue. This also suggests that these may be two different types of tumour.

Pathologically, it is valuable to differentiate angiosarcomas from other lesions in the breast in order to institute the correct therapy. The other lesions include benign vascular proliferations,[22] benign lymphangioendothelioma,[23] hamartomas,[24] stromal hyperplasias, phyllodes tumours, other sarcomas and sarcomatoid (metaplastic) carcinomas. The presence of in situ epithelial components together with immunohistochemical studies, including cytokeratin antibodies and endothelial markers (factor VIII related antigen, CD34 and CD31), should aid with the differentiation.

Treatment and prognosis

It has become clear that complete surgical excision of mammary angiosarcomas is the treatment of choice, without the need for primary axillary dissection. Hyperthermia, chemotherapy and radiotherapy may have roles to play in cases of unsuccessful surgical clearance, and chemotherapy may be more effective with high-grade tumours.[25,26] It may be difficult to be confident of complete removal at the time of surgery owing to the infiltrative nature of sarcomas, and, indeed, all four of our cases required at least two attempts at clearance. All cases ultimately proceeded to mastectomy.

Although angiosarcoma of the breast has a reputation for having a poor outcome, the prognosis depends on the histological grade of the primary angiosarcoma,[26–28] its stage and the status of the margins at operation. In general, angiosarcomas of all grades have a 5 year disease-free survival of 33%.[28] Patients with low-grade (grade 1, well-differentiated) tumours usually do well, with most living for more than 15 years[26] and 24 years[27] after treatment. Patients with high-grade (grade 3, poorly differentiated) tumours fare very badly, with a median disease-free survival of only 15 months in one series.[26]

It was unexpected, therefore, that our four cases, which included both ends of the differentiation spectrum, have all had good outcomes and long-term survival. This may have been due to aggressive surgical intervention once the diagnosis was established, but it has been noted previously that the prognosis for angiosarcoma of the breast may be improving.[28] Whatever the reason for this apparent discrepancy, it serves as a reminder that it is possible for angiosarcomas of the breast to be treated effectively, with excellent prospects for the patient. It should not be assumed that all mammary angiosarcomas, including the high-grade lesions, have a poor outlook. There are occasional reports in the literature of similar outcomes,[29,30] and perhaps the pessimistic view of these tumours ought to be revised.

In conclusion, primary angiosarcoma of the breast is rare, comprising only 0.13% of cases presenting to the Royal London Hospital between 1970 and 2000. In our series, the patients who presented young had no known predisposing factors, whilst those presenting at a later age had previously received radiotherapy for breast adenocarcinomas. With adequate surgery, the outlook may not be as poor as generally anticipated. It is crucial that these tumours are recognised, particularly with the widespread use of fine-needle aspiration cytology and needle-core biopsies for the primary diagnosis of breast neoplasms, in order that the patient is managed appropriately and unnecessary treatment is avoided.

References

1. Rosen PP, Oberman HA. *Tumors of the mammary gland*. Atlas of Tumor Pathology, third series, fascicle 7, Washington, DC: Armed Forces Institute of Pathology; 1993.
2. Georgiannos SN, Chin Aleong J, Goode AW, Sheaff M. Secondary neoplasms of the breast: a survey of the 20th century. Cancer 2001;92:2259–66.
3. Parkin DM, Laara E, Muir CS. Estimates of the worldwide frequency of sixteen major cancers in 1980. Int J Cancer 1988;41:184–97.
4. Department of Health, *Number of female deaths from cancer by site and age, England and Wales, 1999*. Cancer trends in England and Wales 1950–1999, London: Department of Health; 2001.
5. Aydogdu M, Trams G. Angiosarcoma of the breast after conservatively operated breast carcinoma—a sequela of adjuvant radiotherapy? Geburtshilfe Frauenheilkd 1996;56:60–2.
6. Britt LD, Lambert P, Sharma R, Ladaga LE. Angiosarcoma of the breast. Initial misdiagnosis is still common. Arch Surg 1995;130:221–3.
7. Zincone GE, Perego P, Rossi GM, Bovo G. A case of breast angiosarcoma: diagnostic imaging and review of the literature. Tumori 1995;81:387–96.
8. Elwady N, Ousehal A, Alibon F, Tazi Z, Boukind H, Kadiri R. Angiosarcoma of the breast. Radiological aspects. About one case. J Radiol 2000;81:50–3.
9. Mansouri H, Jalil A, Chouhou L, et al. A rare case of angiosarcoma of the breast in a man: case report. Eur J Gynaecol Oncol 2000;21:603–4.
10. Sheaff M, Baithun S. Pathological effects of ionizing radiation. Curr Diagn Pathol 1997;4:106–15.
11. Fineberg S, Rosen PP. Cutaneous angiosarcoma and atypical vascular lesions of the skin and breast after radiation therapy for breast carcinoma. Am J Clin Pathol 1994;102:757–63.
12. Parham DM, Fisher C. Angiosarcomas of the breast developing post radiotherapy. Histopathology 1997;31:189–95.
13. Autio P, Kariniemi AL. Angiosarcoma. A rare secondary malignancy after breast cancer treatment. Eur J Dermatol 1999;9:118–21.
14. Majeski J, Austin RM, Fitzgerald RH. Cutaneous angiosarcoma in an irradiated breast after breast conservation therapy for cancer: association with chronic breast lymphedema. J Surg Oncol 2000;74:208–12.
15. Cozen W, Bernstein L, Wang F, et al. The risk of angiosarcoma following primary breast cancer. Br J Cancer 1999;81:532–6.

16. Huang J, Mackillop WJ. Increased risk of soft tissue sarcoma after radiotherapy in women with breast cancer. Cancer 2001;92: 172–80.
17. Benda JA, Al-Jurf AS, Benson III AB. Angiosarcoma of the breast following segmental mastectomy complicated by lymphedema. Am J Clin Pathol 1987;87:651–5.
18. Bolin DJ, Lukas GM. Low-grade angiosarcoma of the breast following radiotherapy. Am Surg 1996;62:668–72.
19. Moskaluk CA, Merino MJ, Danforth DN, Medeiros LJ. Low-grade angiosarcoma of the skin of the breast: a complication of lumpectomy and radiation therapy for breast carcinoma. Hum Pathol 1992;23:710–4.
20. Vesoulis Z, Cunliffe C. Fine-needle aspiration biopsy of postradiation epithelioid angiosarcoma of breast. Diagn Cytopathol 2000; 22:172–5.
21. Gupta RK, Naran S, Dowle C. Needle aspiration cytology and immunocytochemical study in a case of angiosarcoma of the breast. Diagn Cytopathol 1991;7:363–5.
22. Rosen PP. Vascular tumors of the breast: III. Angiomatosis. Am J Surg Pathol 1985;9:652–8.
23. Guillou L, Fletcher CD. Benign lymphangioendothelioma (acquired progressive lymphangioma): a lesion not to be confused with well-differentiated angiosarcoma and patch stage Kaposi's sarcoma: clinicopathologic analysis of a series. Am J Surg Pathol 2000;24:1047–57.
24. Fisher CJ, Hanby AM, Robinson L, Millis RR. Mammary hamartoma—a review of 35 cases. Histopathology 1992;20:99–106.
25. Silverman LR, Deligdisch L, Mandeli J, Greenspan EM. Chemotherapy for angiosarcoma of the breast: case report of 30-year survival and analysis of the literature. Cancer Invest 1994;12: 145–55.
26. Rosen PP, Kimmel M, Ernsberger D. Mammary angiosarcoma. The prognostic significance of tumor differentiation. Cancer 1988;62:2145–51.
27. Merino MJ, Carter D, Berman M. Angiosarcoma of the breast. Am J Surg Pathol 1983;7:53–60.
28. Donnell RM, Rosen PP, Lieberman PH, et al. Angiosarcoma and other vascular tumors of the breast. Am J Surg Pathol 1981;5: 629–42.
29. Azzopardi JG. *Problems in breast pathology*. Major problems in pathology, 11. London: WB Saunders; 1979.
30. Bundred NJ, O'Reilly K, Smart JG. Long term survival following bilateral breast angiosarcoma. Eur J Surg Oncol 1989;15:263–4.

The Authors

Stavros N. Georgiannos FRCS, Visiting Consultant Surgeon

Department of Academic Surgery,

Michael Sheaff MRCPath, Consultant Histopathologist

Department of Histopathology,

Barts and the London NHS Trust, Royal London Hospital, Whitechapel, London E1 1BB, UK

Correspondence to Dr Michael Sheaff

Accepted 19 July 2002.