Biphasic sarcomatoid carcinoma or carcinosarcoma of the breast: prognosis and therapy

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Summary

Biphasic sarcomatoid carcinoma of the breast represents only 0.2% of all breast cancer. Due to its rarity and repetitive reclassifications little is known about optimal treatment modalities. These tumours form a diagnostic and therapeutic challenge. The present report describes our experience with a case of biphasic sarcomatoid carcinoma of the breast and a review of the relevant literature is discussed.

Key words: Biphasic sarcomatoid carcinoma; Carcinosarcoma; Breast cancer; Prognosis; Treatment.

Introduction

Biphasic sarcomatoid carcinoma (BSC) is a rare metaplastic neoplasm. The distinct pathological properties, origin and classification of this atypical tumour have long been controversial and much debated. Less is known of its clinical behaviour and optimal treatment. In this article we describe a case with adverse outcome and review the latest literature with particular focus on prognosis and therapy.

Case report

A 56-year-old postmenopausal, nulliparous woman presented with a large ulcerative mass in the left breast at the University Multidisciplinary Breast Clinic Antwerp (UMBA).

Her personal history included neurofibromatosis, feochromocytoma, mental retardation, arterial hypertension, splenectomy, cholecystectomy, adrenalectomy and total thyroidectomy.

On clinical examination a large (6 x 7 cm) solid mass was observed in the outer quadrants of the left breast, with nipple retraction and spontaneous ulceration to the outer lower quadrant. A 3-cm large fixed lymph node was palpated in the ipsilateral axilla. Excisional biopsy revealed biphasic sarcomatoid carcinoma. A minimal increase in tumour marker CA 15.3 (38 U/ml, normal value < 36) was seen. No signs of distant metastatic disease were present. The tumour was clinically staged as T4 N2 M0.

A CT-scan of the chest clearly demonstrated the ulcerative mass in the breast and axillary involvement, but no enlarged mediastinal nodes were seen.

Neo-adjuvant chemotherapy with a doxorubicin-cyclophosphamide regimen (2 cycles) was initiated, and then converted to a docetaxel mono-regimen (6 cycles) due to failing tumour response. Despite initial improvement after changing the regimen, further tumour progression was observed.

A total mastectomy with axillary dissection was performed for local tumour control and hygienic purposes, followed by adjuvant radiation therapy of the chest wall and locoregional lymphatic drainage system.

Histopathology showed a biphasic sarcomatoid carcinoma with maximal diameter of 4 cm, and mitotic activity index (MAI) of 11. All resection margins were clear. Axillary node dissection revealed a 4-cm large infiltrated lymph node. Necrosis was observed as well as desmosomes and inflammatory infiltrate with lymphocytes, plasma cells, histiocytes and neutrophils. The tumour was staged as pT4pN2M0.

Immunohistochemistry indicated positivity for CA 15.3, pancytokeratine and to a lesser extent for calcitonine. No immunoreactivity was detected for oestrogen receptor (ER) or progesterone receptor (PR).

Twelve months after the initial diagnosis liver metastases were detected and the patient succumbed two months later.

Discussion

Biphasic sarcomatoid carcinoma (BSC) or carcinosarcoma (CS) of the breast is a rare tumour composed of both malignant epithelial- and mesenchymal-like tissues.

It is suspected to account for 0.2% to 0.5% of all malignant breast tumours [1, 2].

Peak incidence is in postmenopausal women at a mean age of 56 year [3, 4]. Some authors believe this tumour occurs at a later age than other forms of breast cancer (mean 65 years) [2, 5, 6].

BSC often presents as a large, single, firm, rapidly growing mass in the upper outer quadrant of the breast [3, 7, 8]. Ulceration, skin or nipple retraction, discharge, pain and adherence to the thoracic wall are often associated [3]. No differential diagnostic mammographic features have been described. Still, the presence of matrix calcification or bone associated with a mass may suggest a sarcomatous or metaplastic lesion [9, 10].

The macroscopic appearance of BSC is highly variable. It may present both with a well-circumscribed nodular contour or irregular shape. Tumour size varies between 1 to 20 cm with a mean diameter of 5.3 cm [1, 3, 7, 11]. These neoplasms are often described as soft and fleshy, with patchy areas of hard gritty tissue [3, 4, 7]. They have a tan to greyish or pinkish cut surface, often with a mottled aspect due to necrosis and haemorrhage [3]. Histologically, both infiltrative as in situ carcinoma may be present, alone or admixed. Infiltrative carcinoma is mostly moderately to

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poorly differentiated. Any type of carcinoma may be present, though the infiltrating duct, squamous or adenosquamous appear to be most common.

The sarcomatous component is often characterised by high cellularity with a mean MAI of 29 [3] and can morphologically present as a fibrosarcoma, malignant fibrous histiocytoma, pleomorphic sarcoma, osteogenic or chondrosarcoma, rhabdomyosarcoma or as a combination of these.

Inflammatory infiltrate predominantly composed of lymphocytes and plasma cells is often present. Oestrogen- and progesterone-receptor status are predominantly negative [1,3,12]. Vascular permeation may be associated whereas neural invasion has not been described [3].

Since their first description by Pasternak and Wirth in 1936 as sarcomatous adenoacanthoma, these admixed breast tumours have been crowned with a plethora of names and have long been referred to as CS of the breast [13]. They are classically considered as a tumour admixture of malignant epithelial and mesenchymal components. In an attempt to clearly distinguish them from metaplastic carcinomas, ground rules for classification as CS were set. These require exclusion of zones of transition between the carcinomatous and mesenchymal components on histological, ultrastructural and immunohistochemical grounds [7, 14-16]. A classification based on such a strict concept of true collision of both tumours (collision tumour: independent and separate occurrence of carcinoma and sarcoma) would make this an entity of extreme rarity [5, 14].

However, light microscopic examination of these biphasic tumours often, although inconstantly, reveals forms of transition between the carcinomatous and sarcomatous elements which is consolidated by ultrastructural electomicroscopic findings of desmosomes and tight junctions [2, 3]. Immunohistochemical findings also demonstrate occasional anti-epithelial positivity on the mesenchymal component and vice versa [2-4, 8, 17].

All this suggests a metaplastic origin of CS rather than the occurrence of a true collision of tumours. Wargotz and Norris consider CS to be a distinct form of metaplastic carcinoma, describing it as a biphasic neoplasm with at least half of the tumour composed of a cellular malignant appearing spindle cell component and carcinoma, which is contiguous or admixed with the sarcomatous component [3, 18]. They differentiated it from matrix-producing carcinoma, spindle cell carcinoma, and pure squamous cell carcinoma of ductal origin and metaplastic carcinoma with osteoclastic giant cells. The question remains whether the very rare cases where no histological or immunohistochemic signs of epithelial differentiation can be demonstrated, should be considered as only true CS.

Genetic studies evaluating clonality and loss of heterozygosity strongly indicate a monoclonal origin of both components of these tumours [19-21]. This supports the hypothesis that both components stem from a same totipotent cell. The myoepithelial cell exhibits characteristics of biphasic differentiation on immunohistochemical and ultrastructural levels and has thus been suggested as a stem cell [3]. Although animal models add some evidence to this hypothesis, CS also occurs in organs lacking myoepithelial cells. To this day evidence only indicates that CS is truly a biphasic tumour of unicellular origin, derived from a yet unconfirmed totipotent stem cell [2, 21, 22].

With regards to these recent understandings, a consensus has progressively been established that CS (carcinoma + sarcoma) does not exist, but corresponds to a metaplastic epithelial tumour doted with the more appropriate general name of biphasic sarcomatoid carcinoma (BSC) with high grade of malignancy [2, 8]. BSC appears to be a composite tumour capable of arising in merely any organ. Sarcomatoid carcinomas are divided when occurring in breast tissue in a biphasic and monophasic subclass [8]. The former is being suggested as a new designation for the outmoded CS, the latter for purely sarcoma-like carcinomas.

Although less common than in other metaplastic carcinomas of the same size, axillary node invasion frequently occurs in BSC [1, 3, 10, 23, 24]. However, the number of invaded lymph nodes is often limited [3]. It may consist of carcinomatous or sarcomatous components or an admixture of both. Distant metastasis is rare at primary presentation despite the large tumour size [11, 16]. It may both be sarcomatous or carcinomatous and is to be found primarily in pleura, lungs, bone, liver, brains and other viscera [3, 24].

BSC has a less favourable outcome than invasive breast carcinoma or other forms of metaplastic breast carcinoma [1-3, 18]. Several attempts have been made to correlate histological features with outcome. Nodal involvement only indicates an unfavourable trend but cannot be retained as an independent prognostic factor [1].

Tumour size at time of diagnosis appears to be indicative of progression and death from disease as well as for recurrence [3]. Complete microscopic circumscription and presence of admixed inflammatory infiltrate are also of prognostic significance for recurrence [3]. The recurrence rate is around 60% and tends to be locoregional in approximately 1/3 of the cases [1, 3].

Expertise and evidence-based information on optimal treatment is very limited due to the low incidence and inconsistent classification. Excisional surgery with axillary dissection is indicated. No sufficient data is present to give any advantage to radical surgery over breast conserving procedures [1-3, 8]. Adjuvant chemotherapy and/or radiation therapy improves survival over surgery alone, especially in Stage II disease, and reduces recurrence rate [1]. Little information is available concerning optimal chemotherapeutic regimens. Attention has to be paid to both the carcinomatous and sarcomatoid characteristics of these neoplasms. In this regard, cyclophosohamide-doxorubicine containing chemotherapy has been suggested, as well as other combinations [1, 3, 23]. Hormonal therapy is of low significance considering the low incidence of hormonal receptors in these tumours (around 10%) [1, 3, 7, 25]. Responsiveness to chemotherapy, radiotherapy and hormone therapy is low in recurrent disease [8,18]. If possible it should then be treated by surgery followed by adjuvant therapy as for primary disease. Remarkably, long disease-free survival has been reported after surgical treat-

ment for a case of inflammatory CS, refractory to neo-adjuvant chemotherapy [24]. This questions the unknown prognostic significance and therapeutic value of neo-adjuvant chemotherapy in inflammatory breast cancer of this subtype.

Conclusion

BSC of the breast is a rare tumour with a worse prognosis than other forms of breast carcinoma. Its recent redefinition from CS to BSC reflects our better understanding of this neoplasm. Still many questions remain about its origin and optimal treatment modalities.

References

[1] Gutman H., Pollock R.E., Janjan N.A., Johnston D.A.: "Biologic distinctions and therapeutic implications of sarcomatoid metaplasia of epithelial carcinoma of the breast". *J. Am. Coll. Surg.,* 1995, *180,* 193.

[2] Diebold-Berger S., de Roquancourt A.: "Carcinome sarcomatoïde du sein". *Arch. Anat. Cytol. Pathol.,* 1995, *43,* 51.

[3] Wargotz E.S., Norris H.J.: "Metaplastic carcinomas of the breast. III. Carcinosarcoma". *Cancer,* 1989, *64,* 1490.

[4] Mainguene C., Laporte J.L., Zakhama A., Destable M.D., Amouroux J.: "Carcinosarcoma of the breast. Anatomic-clinical study of a case". *Arch. Anat. Cytol. Pathol.*, 1993, *41*, 25.

[5] Gersell D.J., Katzenstein A.L.: "Spidle cell carcinoma of the breast. A clinopathologic and ultrastructural study". *Hum. Pathol.,* 1981, *12,* 550.

[6] Ellis I.O., Bell J., Ronpan J.E., Elston G.W., Blamey R.W.: "Immunohistochemical investigations of intermediate filament proteins and epithelial membrane antigen in spidle cell tumours of the breast". *J. Pathol.,* 1988, *154*, 157.

[7] Tavassoli F.A.: "Classification of metaplastic carcinomas of the breast". *Pathol. Annu.,* 1992, *27,* 89.

[8] Foschini M.P, Dina R.E, Eusebi V.: "Sarcomatoid neoplasms of the breast: proposed definitions for biphasic and monophasic sarcomatoid mammary carcinomas". *Semin. Diagn. Pathol.,* 1993, *10,* 128.

[9] Pope T.L., Fechner R.E., Brenbridge A.N.: "Carcinosarcoma of the breast: radiologic, ultrasonographic, and pathologic correlation". *Can. Assoc. Radiol. J.,* 1987, *38,* 50.

[10] Taylor D.B., Adamson R., Minchin D.E., Reading L.: "Carcinoma of the breast with sarcomatous metaplasia". *Australas. Radiol.,* 1994, *38,* 262.

[11] Kurian K.M., Al-Nafussi A.: "Sarcomatoid/metaplastic carcinoma of the breast: a clinicopathological study of 12 cases". *Histopathology*, 2002, *40,* 58.

[12] Bolton B., Sieunarine K.: "Carcinosarcoma: a rare tumour of the breast". *Aust. NZ. J. Surg.,* 1990, *6,* 917.

[13] Pasternak J.G., Wirth J.E.: "Adeno-acanthoma Sarcomatodes of the mammary gland". *Am. J. Pathol.*, 1936, *12,* 423.

[14] Azzopardi J.G.: "Problems in Breast Pathology". Philadelphia, Saunders, 1979, 297.

[15] Flint A., Oberman H.A., Davenport R.D.: "Cytophotometric measurements of metaplastic carcinoma of the breast:correlation with pathologic features and clinical behavior". *Mod. Pathol.,* 1988, *1,* 193.

[16] Oberman H.A.: "Metaplastic carcinoma of the breast. A Clinopathology study of 29 patients". *Am. J. Surg. Pathol.,* 1987, *11,* 918.

[17] Alexiev B., Popov A.: "Carcinosarcoma of the breast. Immunohistochemical and ultrastructural studies". *Zentralbl. Pathol.,* 1992, *138,* 71.

[18] Wargotz E.S, Norris H.J.: "Metaplastic carcinomas of the breast: V. Metaplastic carcinoma with osteoclastic giant cells". *Hum. Pathol.,* 1990, *21,* 1142.

[19] Wada H., Enomoto T., Tsujimoto M., Nomura T, Murata Y, Shroyer KR.: "Carcinosarcoma of the breast: molecular-biological study for analysis of histogenesis". *Hum. Pathol.,* 1998, *29,* 324.

[20] Zhuang Z., Lininger R.A, Man Y.G., Albuquerque A., Merino M.J., Tavassoli F.A.: "Identical clonality of both components of mammary carcinosarcoma with differential loss of heterozygosity". *Mod. Pathol.,* 1997, *10,* 354.

[21] Teixeira M.R., Qvist H., Bohler P.J., Pandis N., Heim S.: "Cytogenetic analysis shows that carcinosarcomas of the breast are of monoclonal origin". *Genes Chromo. Cancer,* 1998, *22,* 145.

[22] Thompson L., Chang B., Barsky S.H.: "Monoclonal origins of malignant mixed tumors (carcinosarcomas). Evidence for a divergent histogenesis". *Am. J. Surg. Pathol.,* 1996, *20,* 277.

[23] Baker R.R.: "Unusual lesions and their management". *Surg. Clin. North. Am.,* 1990, *70,* 963.

[24] Kuo S.H., Chen C.L., Huang C.S., Cheng A.L.: "Metaplastic carcinoma of the breast: analysis of eight Asian patients with special emphasis on two unusual cases presenting with inflammatory-type breast cancer". *Anticancer Res.*, 2000, *20,* 2219.

[25] Harris M., Persaud V.: "Carcinoma of the breast". *J. Pathol.,* 1974, *112*, 99.

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