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Histopathology of tumour associated sarcoid-like stromal reaction in breast cancer

An analysis of 5 cases with immunohistochemical investigations*

R. Bässler and F. Birke
Institute of Pathology, City and Academic Hospital, Pacelliallee 4, D-6400 Fulda, Federal Republic of Germany

Summary. In 5 cases of invasive ductal and lobular carcinoma of the breast multiple epithelioid and giant cell containing granulomas were detected, localized mainly in circumferential regions, but also in the center of the carcinomas. These granulomas were interpreted as sarcoid-like stromal reactions, occurring as sarcoid-like lesions in uni- and bilateral primaries, in a recurrent tumour, and also in axillary lymph nodes. Histopathologically, these granulomas were not quite uniform, some of them corresponding to typical sarcoidosis, others showing marked proliferations of epithelioid or giant cells or containing fibrinoid exudate or necroses. The granulomas were surrounded by dense infiltrates of mononuclear cells. Tuberculosis and mycosis was excluded. There were no hints of generalized sarcoidosis. Pathogenetically, these are reactions in the tumour stroma of varying intensity, and are not caused by necroses of the tumour tissue nor by microbial infections. Such tumour-associated sarcoid-like stroma reactions are interpreted as a T-cell mediated immune response to an antigen expression of the carcinoma acting as the local trigger; in 2 cases they were connected with sarcoid-like lesions of the axillary lymph nodes. Their occurrence in bilateral carcinoma of the breast points to an immunological disposition for this special kind of host-versus-tumour response. The intensity of these changes in a recurrent tumour reflects an immunological hypersensitivity reaction.

The pathogenetic and differential diagnostic aspects of epithelioid granulomas of the female breast in chronic granulomatous mastitis, panniculitis, foreign body reaction, rare infections, and in therapeutically induced sarcoidosis are described and discussed.

Key words: Breast cancer – Tumour-associated sarcoid-like stromal reaction – Tumour immunology – Host-versus-tumour response – Sarcoid-like lesion of the axillary lymph nodes

Introduction

Cellular stroma reactions of breast cancer are interpreted as an expression of the varying antigenicity of the tumour. They usually present as lymphomonocytic infiltrates which, except for medullary carcinoma with lymphoid stroma, reflect no evident type-dependent differences for the single carcinoma. To date, investigations of invasive breast cancer have indicated an absence of mononuclear stromal reaction in the peripheral zones of invasion in 22.3%, evidence of low-grade to moderate reactions in 62.2%, and of marked reactions in 15% (Schiødt 1966; Fisher et al. 1975; Bässler et al. 1981).

Immunohistochemical differentiations revealed a predominance of T-lymphocytes, with a large proportion of T-helper cells. B-lymphocytes, which occur in follicular infiltrates, have no quantitative importance (Caselitz et al. 1986; Gokel et al. 1986; Müller et al. 1986; Pickartz et al. 1986).

In breast cancer, epithelioid-cell granulomas of "sarcoid-like lesion" (SLL) type were observed in axillary lymph nodes (Nickerson 1937; Symmers 1951; Lennert 1957, 1961; Wuketich 1959; Fischer 1984). Identical or similar epithelioid-cell granulomas in the stroma or marginal zones of primaries have been described as tuberculoid or pseudo-tuberculous reactions in germ cell tumours (Schiller

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Offprint requests to: R. Bässler

Table 1. Histopathology and classification of the investigated cases of breast cancer with sarcoid-like stroma reaction and sarcoid-like lesion (SLL)

No.	Localization	Histol. classification	Grading	Size of tumor (cm)	Axillary lymph nodes		pTNM classification
					Metastases	SLL	
1	Left upp. out. quadr.	Inv. duct. Ca. (NOS)	G 2	2.0 × 1.8 × 1.5	9/22	0	pT1ac pN1bb
2	Right upp. out. quadr.	Inv. duct. Ca. (NOS)	G 2/3	4.5 ∅	0/ 4	0	pT2 pN0
	Left upp. out. quadr.	Inv. duct.-lobul. Ca. Intraduct. component	G 2	2.0 × 1.5 × 1.0	0	3/22	pT1ac pN0
3	Left upp. out. quadr. local recurrence	Intraduct. inv. Ca. Inv. duct. Ca.	G 2 G 2/3	2.0 × 1.8 × 2.0 1.5 ∅	2/ 4	0	pT2a pN1a
	Right upp. out. quadr.	Intraduct. inv. Ca. (Comedo-Ca.)	G 2	4.5 × 3.3 × 3.5	0/ 7	(+)	pT2a pN0
4	Left upp. out. quadr.	Inv. duct. Ca. (NOS)	G 3	5.5 × 5.0 × 2.5	2/10	0	pT4a pN1bb
5	Left lower quadr.	Inv. lobul. Ca.	G 2/3	4.0 × 3.0 × 2.0	0	4/28	pT2a pN0

1934; Mostofi and Price 1973), in their metastases (Richter and Leder 1979), and also in lympho-epithelial carcinomas (Schmincke-Regaud) by Rennke and Lennert (1973) and Wöckel and Wernert (1981). As far as breast cancer is concerned, localized and juxtaposed sarcoid lesions in the stroma of primary carcinomas have not been observed previously, but there are a few cases of sarcoidosis with breast involvement and concomitant occurrence of breast cancer and other malignancies.

Materials and methods

Five cases of invasive carcinoma of the breast were collected from diagnostic and consultative material. Histopathological data and tumour classification, as well as grading and status of the axillary lymph nodes of the investigated cases are presented in Table 1. The microscopic sections were stained by haematoxylin and eosin, van Gieson-resorcine and PAS. Bacterioscopic and mycoscopic investigations were performed by Ziehl-Neelson- and Grocott staining; the immunohistochemical examinations with histiocytic markers were performed using polyclonal antibodies against alpha-1-antitrypsin, lysozyme (Ortho Diagnostics, Heidelberg, FRG), alpha-anti-chymotrypsin (Dakopatts, Hamburg, FRG) and by the immunoglobulins A, M, G (Ortho Diagnostics, Heidelberg, FRG).

In case no. 1 (P.E.; * 1942) a cherry-sized tumour in the left breast was detected in 1984, with enlarged axillary lymph nodes. The tumour biopsy, mastectomy and axillary dissection specimen showed invasive ductal carcinoma of the breast with axillary lymph node metastases. Multiple, variously differentiated sarcoid-like granulomas formed a stromal reaction in the periphery of the carcinoma in early and late phases of development (Fig. 1a). Sarcoid-type granulomas surrounded by collagenous tissue were found on the surface of the carcinoma, partly compressed by the growing tumour (Fig. 1b). On X-ray no signs of sarcoidosis of the lung or of the hilar lymph nodes were seen.

Case no. 2 (K.E.; * 1913) (Fig. 2) was a carcinoma of the right breast in the upper outer quadrant. Surgical biopsy and mastectomy with axillary dissection was followed by radiotherapy. There was no chemotherapy and no recurrence. A diagnosis of invasive ductal carcinoma with spread into the surrounding tissue was made. Small epithelioid-cell granuloma were seen at the margin of the primary. In 1985, development of a cherry-sized tumour in the upper outer quadrant of the left breast occurred. Axillary lymph nodes were inconspicuous. A diagnosis of invasive ductulo-lobular carcinoma was made. In the periphery of the carcinoma and in adjacent fat tissue, 10 epithelioid-cell granulomas were seen on the gross section (Fig. 2), partly surrounded by tumour cells. Only low-grade lymphocytic infiltrates in the vicinity of these granulomas were observed. The round granulomas contained large, uniform epithelioid and multinucleated giant cells of Langhans type, some with scattered birefringent Schaumann bodies. No foreign body reactions were seen.

Mastectomy and axillary dissection followed by chemotherapy and telecobalt therapy apparently prevented recurrence. X-ray of the lungs showed low-grade radiation fibrosis of the left. The right was inconspicuous. There were no signs of sarcoidosis of the lungs or of the hilar lymph nodes.

In case no. 3 (M.J.; * 1923) (Fig. 3a) in June 1979 a surgical biopsy of the left breast showed plurifocal, partly invasive and intraductal carcinoma. Mastectomy was carried out with axillary dissection. In the primary, a large epithelioid-cell granuloma with Langhans giant cells and central fibrinoid necrosis was found. In October 1980, a nodular tumour recurrence in the scar occurred measuring 1.5 cm in diameter; excision of the scar was performed. The axilla and lung were free of metastases. The local recurrence contained multiple epithelioid-cell granulomas with numerous giant cells. Some of the granulomas were located in the marginal zones, the others in the center of the tumour in an irregular arrangement. In the right breast in October 1980 there was detection of a tumour in the upper

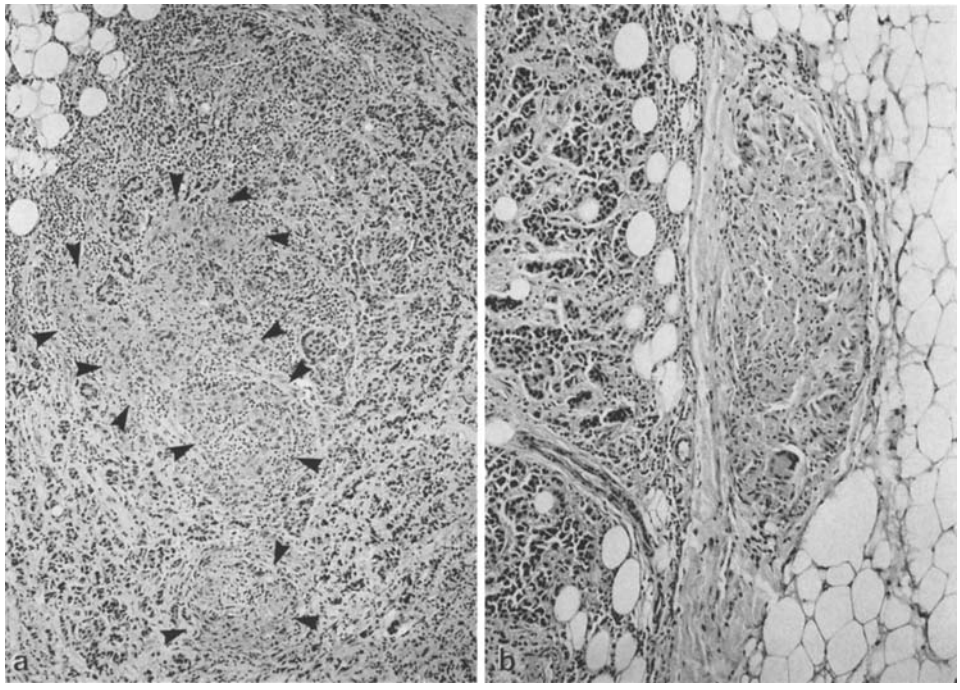

Fig. 1. a Tumour-associated sarcoid-like reaction. A cluster of growing epithelioid-cell granulomas of the stroma within the carcinoma (*arrows*). In the area of the granulomas the tumour cells have disappeared. (*Case 1*) Form., Paraff., HE, Magnification 96×; **b** Sarcoid-like granuloma on the borderline of the invasive duct carcinoma, separated and surrounded by small layers of connective tissue. Form., Paraff., HE, Magnification 96×

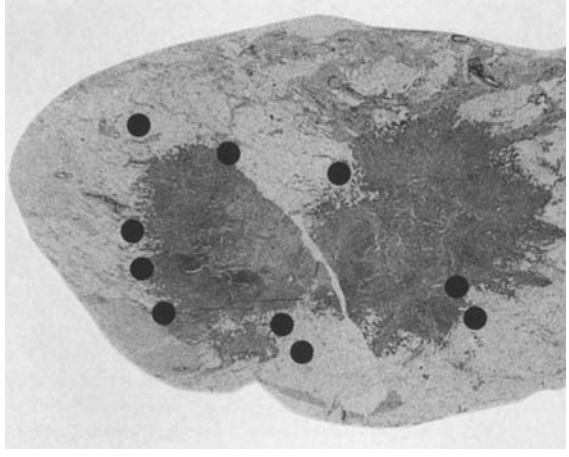

Fig. 2. Gross section of the carcinoma of the left breast with the localization of the tumour-associated granulomas at the borderline areas of the carcinoma as indicated by black dots (*Case 2*). Magnification 2.7×

outer quadrant. Surgical biopsy showed an invasive comedo carcinoma. In the center of the tumour, there was a small epithelioid-cell granuloma with giant cells and marginal lymphocytic infiltration (Fig. 3b). A diagnosis of bilateral carcinoma of the breast with single epithelioid-cell granulomas in both primaries was made, numerous epithelioid and giant cell containing granulomas of varying differentiation were found in the left-side tumour recurrence (Fig. 3c). There were focal epithelioid-cell reactions in the right axillary lymph nodes. No typical sarcoid-like lesion was seen and X-rays showed no signs of sarcoidosis of the lungs or of the hilar lymph nodes.

In case no. 4 (L.E.; * 1895) (Fig. 4) a palm-sized tumour in both upper quadrants of the left breast occurred. Peau d'orange and exanthema were present. A modified radical mastectomy and axillary dissection were performed, X-ray of the lung showed no sign of sarcoidosis. Death occurred on the fifth day after operation. The diagnosis was of large carcinoma of invasive ductal type with extensive growth into the subcutis. There was a marked epithelioid-cell and granulomatous stromal reaction, preferentially located at the border of tumour and fat of the subcutis, with formation of florid, fresh and older granulomas of varying differentiation (Figs. 3d, 4a, b).

In case no. 5 (L.L.; * 1916) there had been in 1981, detection of a nodular tumour in the lower outer quadrant of the left breast. Surgical excision was carried out with mastectomy and axillary dissection. X-ray of the lung showed no sign of sarcoidosis. A diagnosis of invasive lobular carcinoma with focally fibrotic granulomas of sarcoid-like reaction within the tumour stroma was made, and typical sarcoid-like lesions were found in several axillary lymph nodes.

A retrospective examination of axillary lymph nodes was also performed, on 1000 histopathologically examined carcinomas of the breast following biopsy, mastectomy and axillary dissection, in the period between 1981 and 1986.

With the exception of case 1, all our patients are women of post-menopausal age. The clinical data and course of the disease were mostly uneventful. Clinical and radiological symptoms of tuberculosis or sarcoidosis were observed in none of the cases, nor were any signs of mastitis or mycosis detected. Prior to biopsy and histopathologic examination, the primaries had not been treated.

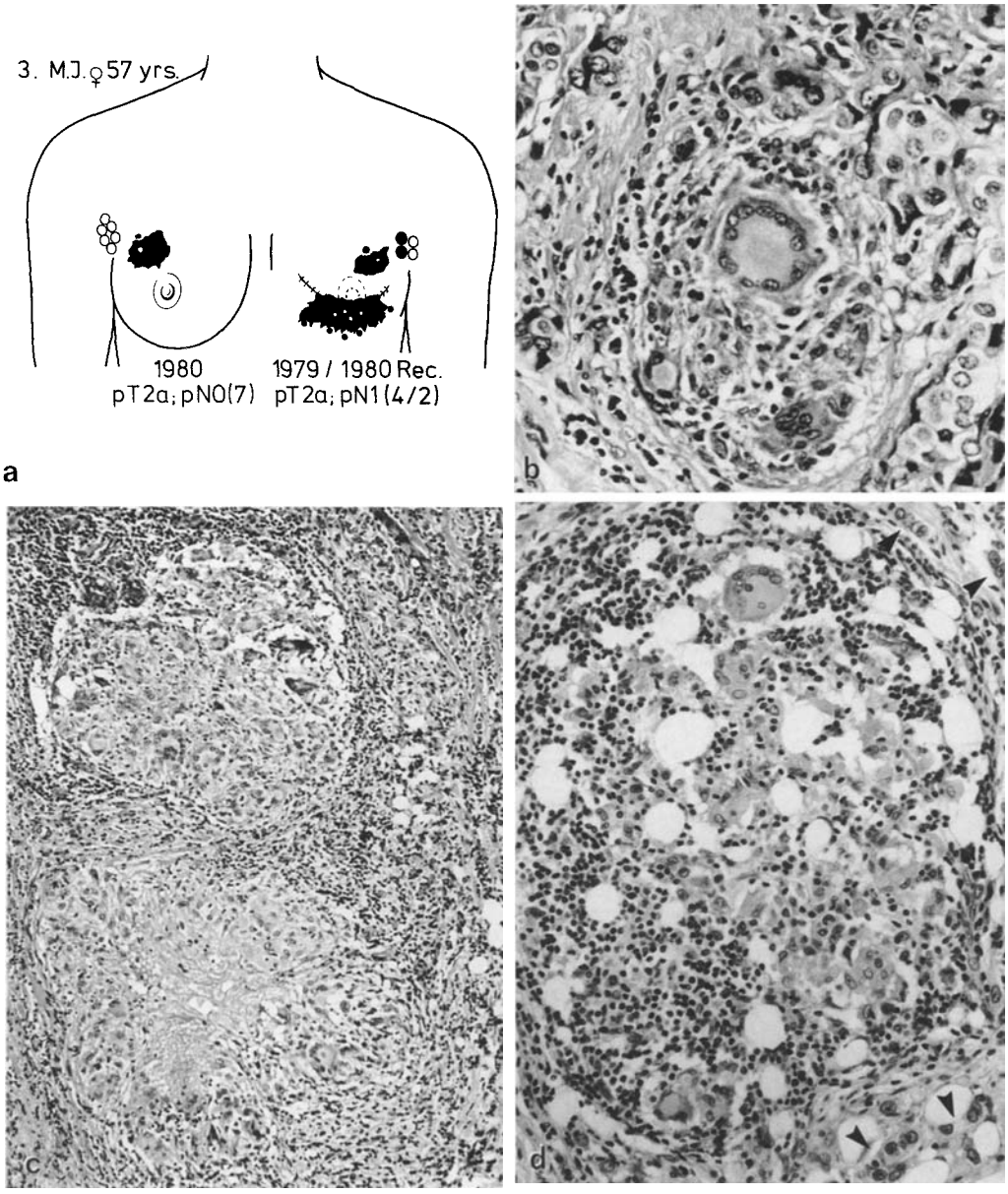

Fig. 3. **a** *Case 3*. Schematical drawing of the bilateral breast cancer and of the recurrence of the left side. The black and white dots display the localization of the tumour-associated granulomas; **b** Epithelioid granuloma with giant cells of Langhans type of the primary tumour of the right breast. Form., Paraff., HE, Magnification 240×; **c** Two granulomas of a central cluster of the recurrent carcinoma with a distinctive cellular activity producing many epithelioid and giant cells. In the granuloma below, fibrinoid exudation is seen in the center. Form., Paraff., HE, Magnification 96×; **d** Early phase with proliferation and differentiation of epithelioid cells and giant cells. Cells of the carcinoma are only seen outside the granulomatous reaction (*arrows*) (*Case 4*). Form., Paraff., HE, Magnification 240×

Although there was no typical pattern in the arrangement of epithelioid-cell granulomas, the majority of granulomas were localized at the tumour periphery (Fig. 2). In this area, granulomas were partly surrounded by tumour cells, embedded in the borderline between tumour and fat tissue, or isolated in the fat tissue, but always within the vicinity of the tumour. In case 4, numerous granulomas are found on the border between the subcutis and the carcinoma. The recurrent carcinoma in case 3 was characterized by a prevalence of florid granulomas in the tumour stroma with a tendency to confluence (Fig. 3b). The granulomas proper are free of tumour cells. Where granulomas develop, the stroma is free of tumour cells (Fig. 3d).

Granulomatous stromal reactions generally consisted of three components; a proliferation of epithelioid cells in dense or nodular formations, or an unstructured infiltrate. In circumscribed granulomas, epithelioid cells were largely similar in appearance at the margin of scattered fibrinoid necroses, "succulent" forms with proliferation and transformation into giant cells were observed (Fig. 3c). Epithelioid-cell proliferations in the tumour stroma and fat tissue mostly contained many lym-

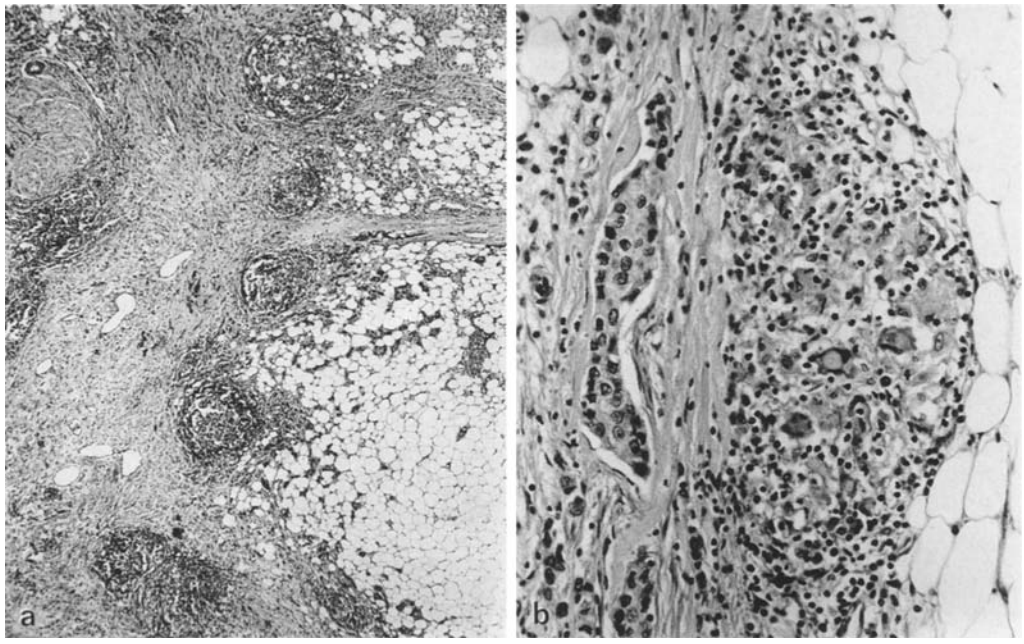

Fig. 4. a Border of the invasive duct carcinoma and fat tissue with multiple tumour-associated granulomas in a row with strong lymphomononuclear stromal reaction. (*Case 4*). Form., Paraff., HE, Magnification 38.4 × ; **b** Detail from this area of the carcinoma with a cellular-active granuloma of epithelioid cells, small giant cells and a scattered lymphomononuclear stromal infiltrate. Form., Paraff., HE, Magnification 240 ×

phocytes (Figs. 3d, 4). Neither these granulomas nor the fibrinoid necroses contained acid-fast bacilli or fungi. Multinucleated giant cells were mostly of the Langhans type, but others, less typical, show features of foreign-body giant cells. The latter are found in small granulomas with few epithelioid cells; in, for example, the recurrent carcinoma in cases 3 and 4. Polarization microscopy revealed no foreign body inclusions, but birefringent Schaumann bodies and vacuoles were seen. Asteroid bodies were not detected.

When compared with sarcoidosis, these granulomas contained little collagen. Only in places where nodular and circumscribed granulomas occur at the tumour margin was circular fibrosis seen. The lymphocyte content of the granulomas varied: circumscribed forms with dense epithelioid and giant cells usually contained few or no lymphocytes; granulomas with fibrinoid necroses and proliferating epithelioid cells (Figs. 3d, 4) were permeated and surrounded by lymphocytic infiltrates.

Our results showed that epithelioid and giant cells react positively with the histiocyte markers alpha-1-antitrypsin, alpha-1-antichymotrypsin and lysozyme, giant cells generally reacting more strongly than epithelioid cells. This is particularly evident in granulomas with a high cell turnover (case 3). Immunoglobulins, however, were not observed. Ziehl-Neelsen staining revealed no acid-fast bacilli, mycosis was excluded by Grocott and PAS staining.

Discussion

These invasive ductal and lobular carcinomas of the breast were characterized by the development of multiple epithelioid and giant cell containing granulomas, localized at the borders and in the surrounding fat of the carcinomas, as well as in the stroma of the tumours. As these reactions can be compared with sarcoid-like lesions of the lymph nodes, they were termed "tumour-associated sarcoid-like stromal reaction". However, it must be emphasized that these carcinomas show no special kind of differentiation, necroses or any other kind of unusual growth. Bilateral carcinomas occurred in two cases. The unilateral carcinomas, and the recurrent tumour in case 3 were localized in the left breast. Following chemo- and radiotherapy, the course of the disease was uneventful in our cases and, above all, there were no signs of generalized sarcoidosis or tuberculosis.

Tumour-associated epithelioid-cell granulomas do not show an entirely uniform pattern. Some correspond to typical sarcoidosis, whereas others are characterized by a marked cell turnover with intense proliferation of epithelioid and multinucleated giant cells, partly in connection with lymphomonocytic infiltration and fibrinoid necrosis. In parallel to the increase and enlargement of epithelioid and giant cells, the number of lymphocytes is bound to decrease. Mature granulomas of sarcoidosis type were more frequently localized on the surface and in circumferential regions, whereas the cell-rich forms occur in the marginal zones and in the stroma of the carcinomas. Nevertheless, we are convinced that both are pathogenetically similar reactions of the tumour stroma, which are not

Table 2. Histologically documented cases of sarcoidosis with breast involvement

Reference	Age years	Localization	Lesion of the breast	Involvement of other organs and remarks
Scott (1938) Stallard and Tait (1939)	38 (44)	r	Hard mass, 4 × 5 cm	Cerv. lymph nodes, skin and eyes
Prior (1952)	59	l	Mass, 3 cm ∅	Inguin. lymph nodes, spleen, metacarpal bone (?) and breast cancer
Scadding (1967)	43	–	Nodule	Lungs with fibrosis
Haagensen (1971)	53	–	Nodules	Lymph nodes, lung, spleen, liver and breast cancer
Rigden (1978)	22	r	Nodule	Right lung
Gansler and Wheeler (1984)	31	r	Nodule 1.5 cm ∅	Lymph nodes, lung, eyes
Gansler and Wheeler (1984)	28	r	Nodule, 1.0 cm ∅	Lymph nodes, lungs and breast cancer
Gupta and Chatterjee (1984)	42	l	Lump, 2.5 cm ∅	Hilar, bilateral lymph nodes, granulomas in a scar of the breast, Mantoux-test positive
Raju and McShine (1984)	60	l	Lump	Lungs
Fitz-Gibbons et al. (1985)	65	l	Mass, 1.8 cm ∅	Scalene lymph node
Ross and Merino (1985)	29	l	Mass, 3.5 × 3.5 × 1.5 cm	Hilar lymph nodes, Kveim-test positive
Reitz et al. (1985)	39	l	Nodule	Lymph nodes, liver
Banik et al. (1986)	28	r	Nodule	Bilat. hilar lymph nodes, Kveim-test positive

induced by focal necroses in the tumour, by coexistent microbial infections, or by side-effects of therapy.

According to previous investigations on the pathogenesis and histopathology of epithelioid cell granulomas by Gusek (1969), Heymer (1980), Müller-Hermelink and Kaiserling (1980), Spector (1980), and Meyer and Grundmann (1982), tumour-associated – or rather tumour-induced – granulomas in breast cancer are interpreted as an immunological response of the tumour stroma to an antigenic expression by the carcinoma. As can be seen from the lymphocytic infiltrates in fresh granulomas of the tumour stroma, it is manifested as a local T-cell-mediated immune response. By analogy, soluble tumour antigens reaching the axillary lymph nodes via the lymphatic vessels will trigger a sarcoid-like lesion in the axillary lymph nodes. Our cases no. 2 and 5 produced an immunological effect in the primary and in the axillary lymph nodes with a sarcoid-like reaction. It is worth mentioning that lymph nodes with sarcoid-like lesions in these cases contain no metastases, and that the epithelioid-cell granulomas proper and the cellular zones of infiltration in their surroundings, are always free of tumour cells. This suggests that the host-versus-tumour response in the region of the granulomas inhibits tumour growth locally (Fig. 3d).

Sarcoid-like lesions in malignant tumours occur in the regional lymph nodes at a rate of 4–8% of cases (Heymer 1980) and in pelvic lymph nodes of previously irradiated cervix carcinomas in 7.9% of cases (Gorton and Linell 1957). In our investigation, a typical sarcoid-like lesion of the lymph nodes was observed in 7 cases out of 1000 carcinomas of the breast (0.7%), whereas a sarcoid-like reaction of the tumour stroma was detected in 3 cases out of 1000 carcinomas (0.3%).

The presence of epithelioid-cell granulomas in the primary was detected only in follow-up examination of cases with sarcoid-like lesions in the axillary lymph nodes (cases no. 2 and 5). It can therefore be assumed that careful examination, especially in cases of concurrent sarcoid-like lesions of the lymph nodes, will not only reveal these reactions at a higher frequency, but also allow their detection in carcinomas of other sites.

Bilateral breast carcinomas (cases 2 and 3) suggest that the development of sarcoid-like reactions in carcinomas, axillary lymph nodes and in the recurrent tumour, is no accidental process. The stromal reaction occurred within an interval of four years (case 2), or one year (case 3) after diagnosis of the primary. In the local recurrent carcinoma (case 3) the reaction is characterized by an increased cellular activity, greater extension and an increased development of fibrinoid necroses than

is found in the primaries or in the lymph nodes (Fig. 3c). These cellular-exudative forms of granulomas with a large turn-over are interpreted as an expression of an immunologically induced hypersensitivity reaction following recurrent antigen expression. The results from bilateral carcinomas of the breast indicate that every carcinoma developes antigen properties which induce a cell-mediated granulomatous immune reaction locally of varying intensity.

The majority of epithelioid and multinucleated giant cell granulomas in the stroma of carcinomas of the breast and in their immediate surroundings were of the sarcoidosis type, even though their cellular components varied. In the female breast, giant cell containing, histiocytic and epithelioid-cell granulomas can be observed in various diseases. The most frequent types of granulomatous inflammation of the breast, chronic granulomatous mastitis, panniculitis, and foreign-body reactions were not present in the cases described here. Other rare forms like tuberculosis, Hodgkin's disease, mycosis, syphilis, leprosy and Wegener's disease were excluded. The granulomas of our five cases of breast cancer correspond to the sarcoidosis type. Granulomatous inflammation of the breast, especially epithelioid-cell reactions, cover a broad differential diagnostic spectrum. Therefore, it must be considered whether tumour-associated granulomas in breast cancer can be interpreted as latent sarcoidosis or tuberculosis. The non-caseating granulomas, the absence of acid-fast bacilli, the lack of corresponding granulomas in regional lymph nodes and of specific lesions of the lung all exclude tuberculosis.

According to the literature (Table 2), latent sarcoidosis presenting with epithelioid-cell reactions in the stroma of the carcinomas is unknown, although some solid granulomas resemble sarcoidosis without fibrosis.

Using clinical criteria, sarcoidosis of the skin, of the eyes and of other lymph nodes was not found in our five patients. There was no hypercalcaemia, and there was no radiographic proof of hilar lymphadenopathy or specific changes of the lung. Kveim testing was not performed. Therefore, the tumour-associated granulomas are considered to be local reactions of the tumour stroma and its circumference. No other sections from the mammary glands contained these granulomas.

The number of cases with sarcoidosis of the breast in generalized forms is small (Table 2). These case reports, without clinical data, are supplemented by 8 cases from the literature, namely Nickerson (1937): 1 of 6 cases; Reisner (1944): 2 of 35 cases with generalized sarcoidosis; Geschickter (1949): 4 cases; and Azzopardi (1979): 1 case.

Solitary and localized forms have been described by Dalmark (1942), Bodo et al. (1978), Shinoda et al. (1979), Bonnecchi et al. (1981), Fitzgibbons et al. (1985, case 2), and Riefkohl et al. (1985) who reported on two cases after augmentation. In these cases no further manifestations of sarcoidosis were present and so it cannot be safely concluded that all the observations can be classified as sarcoidosis.

Breast involvement by sarcoidosis and combination of sarcoidosis with breast cancer was reported by Prior (1952, case 3), Haagensen (1971) and Gansler and Wheeler (1982, case 2) (Table 2). A similar observation concerning metastasizing bronchial carcinoma with sarcoidosis of the lungs and lymph nodes was described by Ellman and Hanson (1958) and by Shoenfeld et al. (1978). In comparison with the SLL in axillary lymph nodes without metastases Prior (1952) and Murata et al. (1974) observed metastatic adenocarcinoma of the stomach with both metastases and sarcoid-like lesions in the draining lymph nodes. In cases of lymphoepithelial carcinomas (Wöckel and Wernert 1986) and in lymph node metastases from seminomas (Richter and Leder 1979), the epithelial cells were arranged around the enclosed and well preserved tumour cells indicating an immunologial response (cell-mediated immunity). This type of epithelioid-cell reaction differs from the granulomatous sarcoid-like stroma reaction of the primary tumours in the breast. In this connection, an unusual epithelioid-granulomatous myositis of the pectoral muscle in an ipsilateral carcinoma of the breast is worth mentioning (Bohrer 1985).

The role of cytostatic therapy in the induction of pulmonary sarcoidosis is discussed in a report on two cases of breast cancer by Wittington and Lazarus (1986). Israel (1978) reports an identical reaction following chemotherapy of osteosarcomas and testicular tumours. Abdi et al. (1987) found pulmonary sarcoidosis after interferon treatment of a renal cell carcinoma. Here, too, an immune modulatory effect on T-cell activity was assumed.

In conclusion although the literature on both breast cancer and sarcoidosis is abundant, few coincidental lesions have been recorded. The five cases reported here are unusual; they are characterized by a local sarcoid-like stromal reaction and not by generalized sarcoidosis. The instances in which both carcinoma and sarcoid-like lesion were present are of particular interest because they dis-

play the broad aetiological spectrum of the different types of sarcoid-like lesions and sarcoidosis.

The sarcoid-like stromal reactions in breast cancer and the literature confirm that disturbances of the cellular immune system occur in local as well as in generalized sarcoidosis. Local reactions in the stroma of breast carcinomas are induced by tumour-inherent antigenic substances.

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