

Axillary lymph node morphology in women with in situ breast carcinoma

An autopsy study

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Summary. Axillary lymph nodes in 184 female autopsy cases were studied using morphological criteria. Special attention was paid to the morphology in 34 women with in situ breast carcinoma (in situ BC) compared to the remaining women without malignant breast lesions, who served as controls. Sinus histiocytosis (SH) and diffuse cortical hyperplasia (DCH) were significantly more frequent among women with in situ BC compared to controls. No significant association was found between unilateral in situ BC and these lymph node patterns on the contralateral side. Germinal center and follicular hyperplasia (GCH/FH), lymphocyte depletion (LD), fibrosis, hyalinization, calcifications and lipomatosis were not associated with in situ BC. The results indicate that in situ BC provokes reactive morphological changes of the regional axillary lymph nodes similar to the changes associated with a good prognosis in women with invasive breast cancer (IBC).

Key words: In situ breast carcinoma – Axillary lymph nodes

Introduction

The possible significance of morphological changes other than metastatic involvement of the regional lymph nodes in women operated on for invasive breast cancer (IBC) has been investigated in several studies (Black 1973; Fisher et al. 1976; Hunter et al. 1975; Syrjänen 1979; Tsakraklides et al. 1974). Sinus histiocytosis (SH), germinal center and follicular hyperplasia (GCH/FH), lymphocyte predominance (equivalent to diffuse cortical hyper-

plasia (DCH) in the current study) and lymphocyte depletion (LD) have all been interpreted as local manifestations of tumour-host interactions. However, the exact role and prognostic significance of these morphologic lymph node patterns has been a matter of controversy.

Regional lymph node morphology in women with in situ breast carcinoma (in situ BC) has so far only been examined in two clinically based studies (Black and Chabon 1969; Fisher et al. 1986). The same nodal patterns as in IBC cases were found, although mainly those associated with a good prognosis (Black and Speer 1960; Syrjänen 1979).

The current study was undertaken to investigate bilateral axillary lymph node morphology in women with in situ BC diagnosed at autopsy.

Materials and methods

Two groups of women were studied: the first 83 consecutive female autopsy cases from a general county hospital in Esbjerg during 1976 to 1977 (mainly elderly women, median age 67 years, range 22–89 years) and the second 110 consecutive forensic female autopsy cases from the University Institute of Forensic Medicine in Copenhagen during 1983 to 1984 (young and middle-aged women, median age 39 years, range 20–54 years).

Parity, oral contraceptives, disorders of the reproductive system, height and weight of the women were the clinical variables registered, which did not differ from the general Danish female population (Nielsen et al. 1984; Nielsen et al. 1987). In the medicolegal group of women 45% had abused alcohol and the frequency of alcoholism and of cases with steatosis and/or cirrhosis of the liver was significantly increased among women with breast malignancy ($p < 0.02$ and $p < 0.02$, respectively, Nielsen et al. 1987). Except for a hypothetical alcohol induced increase in the frequency of cases of breast malignancy, there was no reason to suspect any selection of high risk women for IBC in the two groups of women.

At autopsy each woman included in the study was subjected to bilateral total mastectomy with partial axillary dissection as described by Cady (1973). An extensive histopathological examination of all available breast tissue was carried out

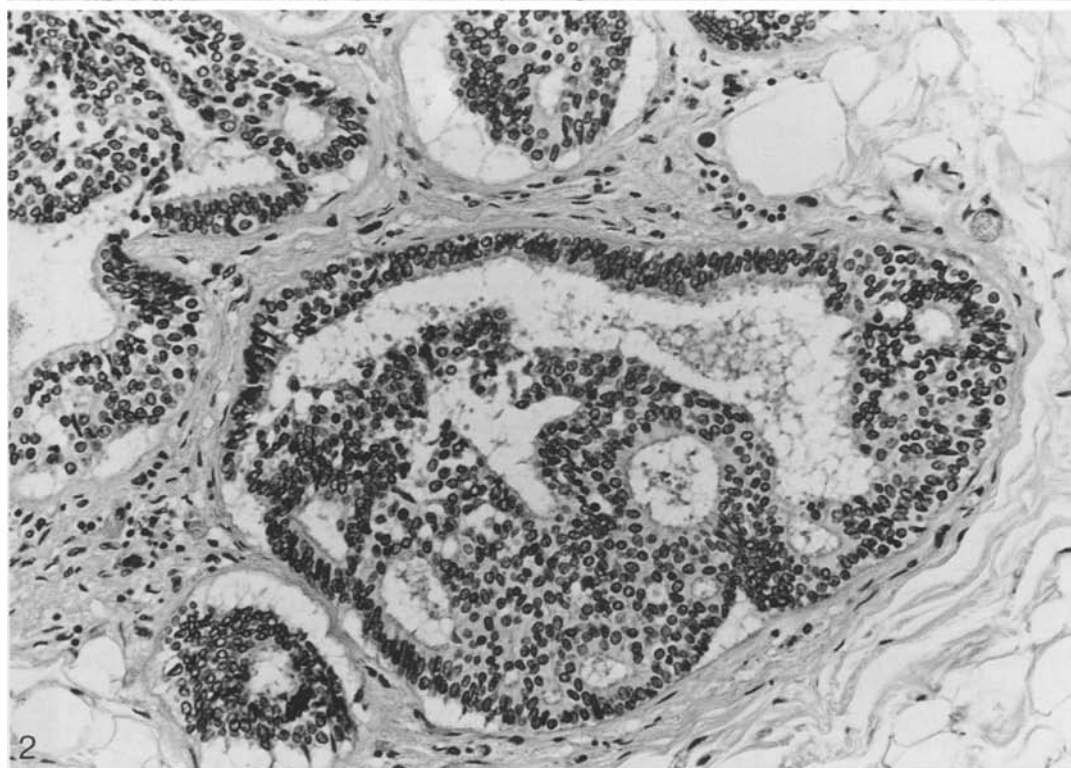
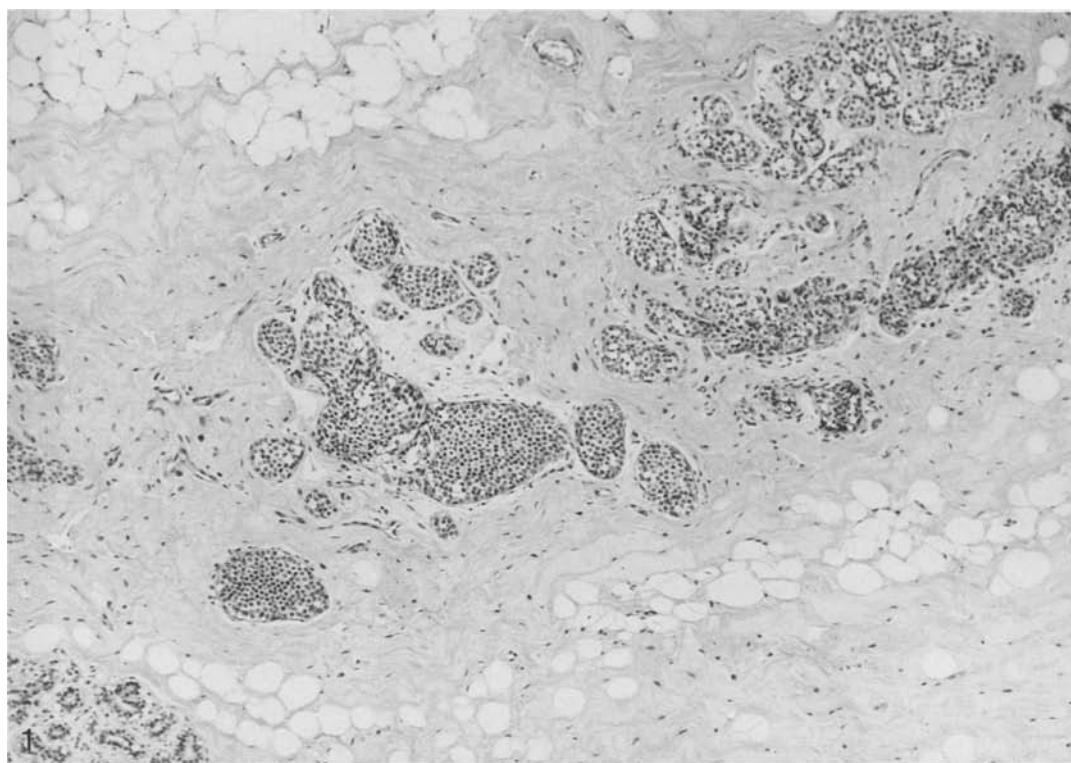


Fig. 1. Lobular carcinoma in situ. Haematoxylin and eosin ($\times 96$)

Fig. 2. Intraductal carcinoma of cribriform type. Haematoxylin and eosin ($\times 240$)

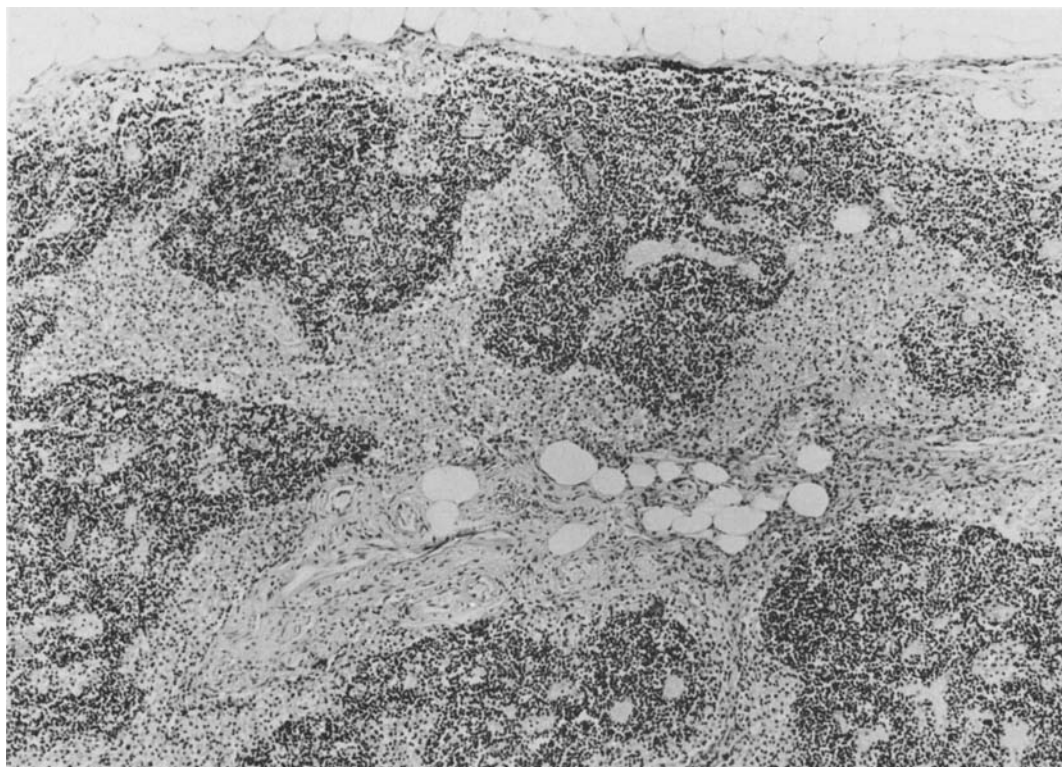


Fig. 3. Sinus histiocytosis of axillary lymph node in a woman with in situ breast carcinoma. Haematoxylin and eosin ($\times 96$)

(Nielsen et al. 1984; Nielsen et al. 1987). With the nipple as the center point each fresh breast specimen was divided into the four quadrants. Each quadrant was cut into 3–5 mm thick slices before or after fixation. The tissue sampling resulted in a total of 76,027 tissue blocks (range 57–638 per breast specimen) which were processed for paraffin embedding. At least one section for microscopic examination was cut from each paraffin block and stained with haematoxylin and eosin. The microscopic changes were evaluated according to the guidelines of World Health Organization (WHO, Sobin 1981) and Azzopardi (1979).

A total of 34 women had a diagnosis of in situ BC (Figs. 1 and 2) at autopsy examination, nine with bilateral involvement. Only one of these women had had a previous breast biopsy, showing only benign changes, whereas the other women had had no breast symptoms. Excluded from the study were nine women with a diagnosis of IBC made during life-time (seven cases) or at autopsy (two cases). The remaining 150 women without any breast malignancy served as controls.

A total of 5695 axillary lymph nodes were examined. The number of nodes per woman varied from four to 98 with an average of 31. They were all fixed in formaldehyde and routinely embedded in paraffin. Lymph nodes larger than one cm were cut transversely before fixation. Sections from each lymph node were prepared and stained by haematoxylin and eosin, Giemsa stain, Gordon and Sweets reticulum stain and the Una Pappenheim stain.

The axillary lymph node morphology was evaluated for each node according to the guidelines of other authors (Black and Chabon 1969; Fisher et al. 1976; Hunter et al. 1975; Tsakraklides et al. 1974); Sinus histiocytosis (SH) was present when most medullary and cortical sinuses were dilated by a syncytium

of histiocytes and hyperplastic medullary cords (active SH, Black's grade 3–6 (Black and Chabon 1969)). Degenerative SH with vacuolated histiocytes was included because the available evidence suggests that it is derived from the active form of SH (Black 1973; Hunter et al. 1975).

In diffuse cortical hyperplasia (DCH) there was increased cortical thickness compared with normal lymph nodes, with no or few, small germinal centers and hyperplastic lymphoid tissue of the paracortical area (T-zones).

Hyperplastic follicles with and without hyperplastic germinal centers (>3 per field of vision at $50\times$ magnification) and an increased number of plasma cells (>10 cells per field of vision at $500\times$ magnification) in the follicles and the medullary cords, were noted germinal center and follicular hyperplasia (GCH/FH).

Hypocellular lymphoid tissue of cortical and paracortical areas when compared with normal nodes and with more than three fourths replaced by fibrous tissue and/or hyaline deposits was termed lymphocyte depletion (LD).

Fibrosis and hyalinization was noted where one to three fourths of the normocellular lymphoid tissue were replaced by fibrous bands and/or hyaline deposits.

Calcification was registered if visible in the haematoxylin and eosin staining, and in lipomatosis more than one third of the lymphoid tissue was replaced by fat.

The occurrence of metastases or malignant infiltrates from extramammary malignancies was recorded.

A case was considered positive for these morphological features if typical changes were found in any one lymph node on one or both sides.

No attempts were made to identify the exact levels of the axillary lymph nodes specifically.

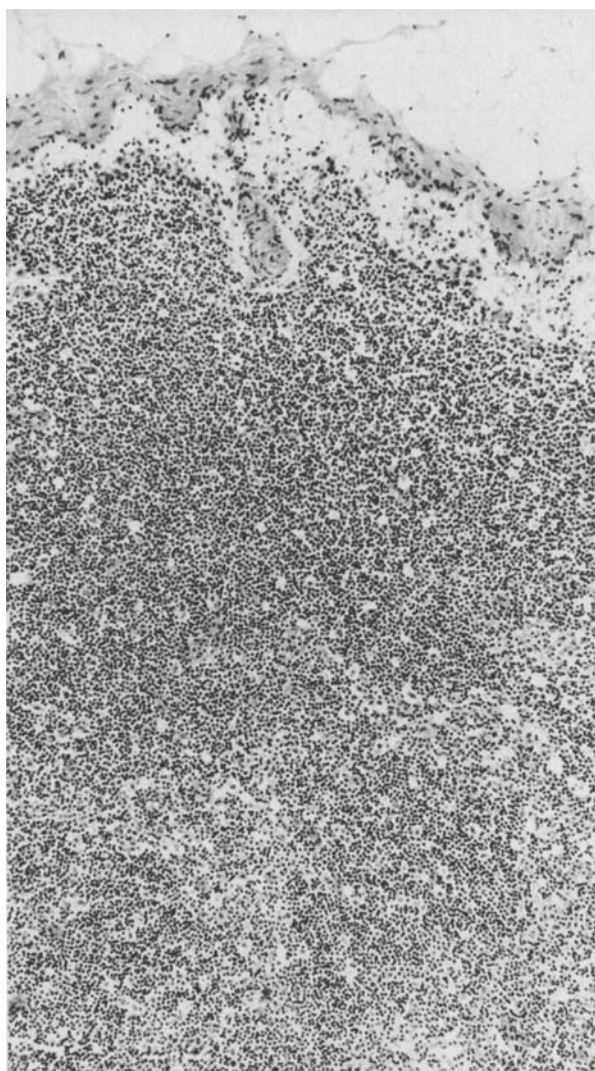


Fig. 4. Diffuse cortical hyperplasia of axillary lymph node in a woman with in situ breast carcinoma. Haematoxylin and eosin ($\times 96$)

Available information was obtained from police reports, death certificates, autopsy reports, hospital records and general practitioners.

Statistical analysis was carried out by the chi-square test.

Results

The most frequent nodal patterns were SH (Fig. 3) and DCH (Figs. 4 and 5), occurring in 33 women (18%) or 58 axillae (16%) and 35 women (19%) or 58 axillae (16%), respectively. Both of these patterns were more common in the regional lymph nodes of breasts with in situ BC when compared with breasts from controls with benign changes only ($p < 0.001$, Table 1). Bilateral SH occurred in 76% of the women and bilateral DCH in 66%, but bilaterality was not significantly more frequent

Table 1. Axillary lymph node morphology in relation to in situ breast carcinoma (43 breasts from 34 women), contralateral breasts without malignancy (25 breasts from 25 women), and controls (300 breasts from 150 women)

Lymph node morphology	In situ BC (<i>n</i> = 43)	Contralateral (<i>n</i> = 25)	Controls (<i>n</i> = 300)
SH	*15 (35%)	6 (24%)	37 (12%)
DCH	*15 (35%)	5 (20%)	38 (13%)
GCH/FH	4 (9%)	2 (8%)	20 (7%)
LD	0	0	9 (3%)
Fibrosis and hyalinization	14 (33%)	5 (20%)	93 (31%)
Lipomatosis	19 (44%)	9 (36%)	122 (40%)

* Significantly different from controls, $p < 0.001$

SH: sinus histiocytosis; DCH: diffuse cortical hyperplasia; GCH/FH: germinal center and follicular hyperplasia; LD: lymphocyte depletion

in women with unilateral in situ BC compared with controls (24% versus 11% for SH, $p = 0.09$, and 20% versus 10% for DCH, $p = 0.06$). The frequency of SH and DCH was comparable for breasts with lobular carcinoma in situ and intraductal carcinoma. Seven women with in situ BC and 10 controls had degenerative SH of variable degree. An increased number of pyroninophilic cells were often present in lymph nodes with SH and DCH.

A much lower frequency of GCH/FH (Fig. 6) was found (15 women or 8% and 26 axillae or 7%), and these lymph node patterns were not related to in situ BC (Table 1). GCH/FH was bilateral in 73 of the women.

LD which was often associated with an increased number of pyroninophilic cells was registered in seven women (4%) two of whom had bilateral changes. All of these women belonged to the control group (Table 1).

Involutionary changes with fibrosis and hyalinization (63 women or 34% and 112 axillae or 30%) and lipomatosis (98 women or 53% and 150 axillae or 41%) occurred frequently. Such changes were bilateral in 78% and 53% of the women, respectively, but were found with comparable frequency among women with in situ BC and controls (Table 1). Fibrosis and hyaline deposits occurred together in two thirds of the nodes, and in 80% of the nodes with hyalinization, calcifications were present as well.

Combinations of the various lymph node patterns were common, especially for the involutionary changes, except for LD which was only seen

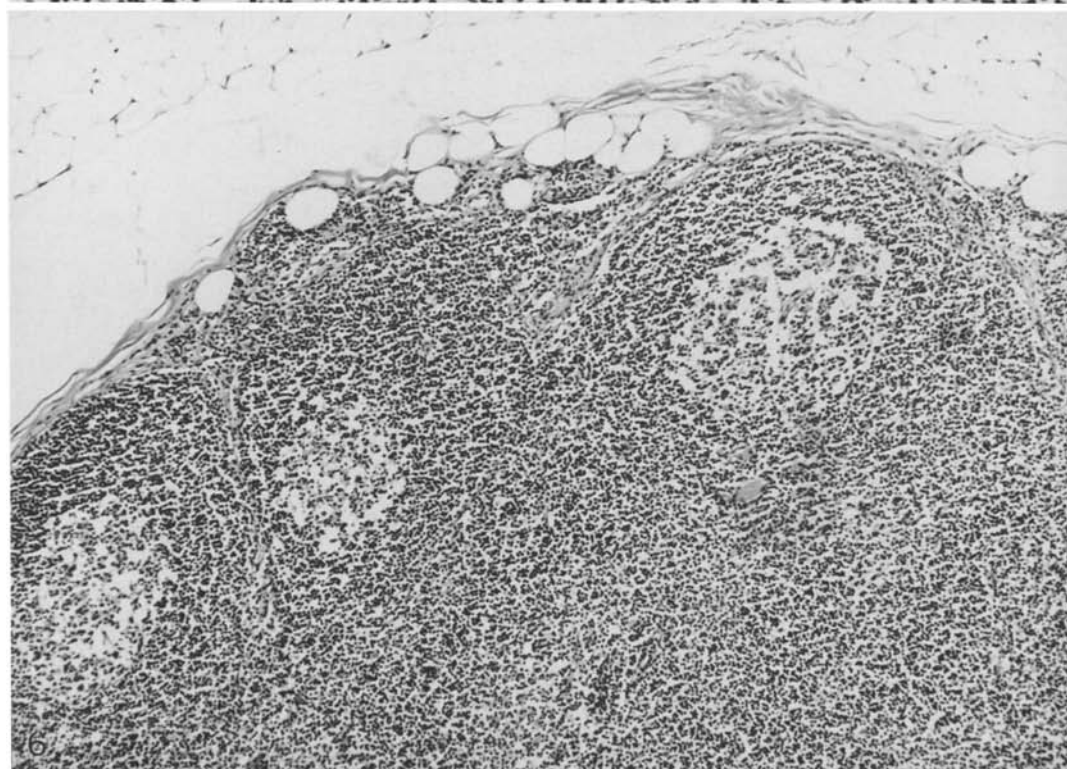
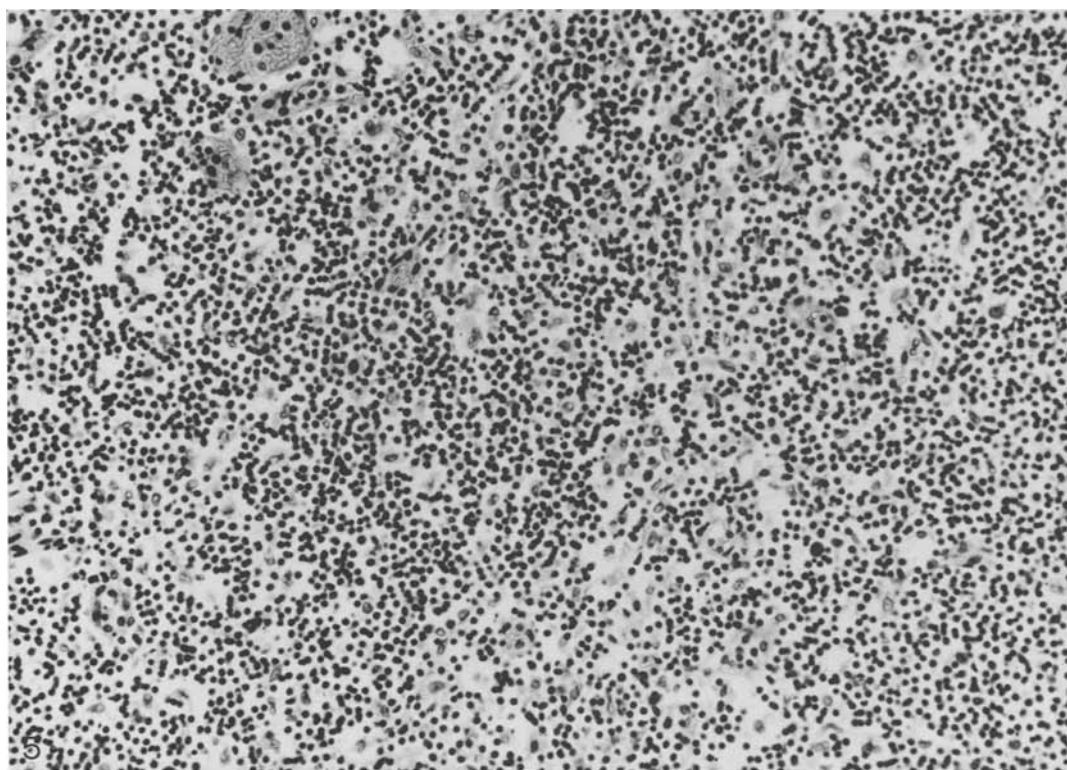


Fig. 5. Higher magnification of same lymph node as in Fig. 4 showing hyperplastic lymphoid tissue of paracortical area. Haematoxylin and eosin ($\times 240$)

Fig. 6. Germinal center hyperplasia of axillary lymph node. Haematoxylin and eosin ($\times 96$)

Table 2. Axillary lymph node morphology in relation to age in 184 female autopsy cases with and without in situ breast carcinoma

Age	+/- in situ BC	SH	DCH	GCH/FH	LD	Fibrosis and hyalinization	Lipomatosis
20-39	+ (n=5)	1 (20%)	3 (60%)	0	0	1 (20%)	0
	- (n=59)	8 (14%)	15 (25%)	11 (19%)	0	4 (7%)	20 (34%)
40-59	+ (n=18)	9 (50%)	8 (44%)	3 (25%)	0	4 (22%)	5 (28%)
	- (n=50)	6 (12%)	7 (14%)	1 (2%)	1 (2%)	15 (30%)	30 (60%)
≥ 60	+ (n=11)	3 (27%)	1 (9%)	0	0	7 (64%)	10 (91%)
	- (n=41)	6 (13%)	1 (2%)	0	6 (15%)	32 (78%)	33 (80%)

SH: sinus histiocytosis; DCH: diffuse cortical hyperplasia; GCH/FH: germinal center and follicular hyperplasia; LD: lymphocyte depletion

Table 3. Axillary lymph node morphology in relation to modes of death among 184 female autopsy cases with and without in situ breast carcinoma

Mode of death	+/- in situ BC	SH	DCH	GCH/FH	LD	Fibrosis and hyalinization	Lipomatosis
Natural							
Malignant disease	+ (n=4)	2 (50%)	1 (25%)	0	0	3 (75%)	2 (50%)
	- (n=23)	3 (13%)	1 (4%)	0	5 (22%)	15 (65%)	14 (61%)
Cardiovascular disease	+ (n=12)	4 (33%)	1 (8%)	0	0	5 (42%)	9 (75%)
	- (n=46)	6 (13%)	3 (7%)	1 (2%)	2 (4%)	27 (59%)	34 (74%)
Infectious disease	+ (n=2)	2 (100%)	0	0	0	1 (50%)	1 (50%)
	- (n=13)	5 (38%)	2 (15%)	0	0	7 (54%)	7 (54%)
Unknown	+ (n=1)	0	0	1 (100%)	0	0	0
	- (n=1)	0	0	0	0	0	0
Unnatural	+ (n=15)	5 (33%)	10 (67%)	2 (13%)	0	3 (20%)	3 (20%)
	- (n=62)	5 (8%)	17 (27%)	11 (18%)	0	2 (32%)	27 (44%)
Unknown	+ (n=0)	0	0	0	0	0	0
	- (n=5)	1 (20%)	0	0	0	0	1 (20%)

SH: sinus histiocytosis; DCH: diffuse cortical hyperplasia; GCH/FH: germinal center and follicular hyperplasia; LD: lymphocyte depletion

together with fibrosis, hyalinization and lipomatosis.

Seven women had malignant deposits in the axillary lymph nodes from extramammary malignancies, and all these women belonged to the control group (lung cancer two, cancer of the thyroid one, cancer of the ovary one, cancer of the gall bladder one, lymphomas two). With the exception of one woman who had lymph nodes with both SH and metastases, lymph nodes with malignant involvement were unstimulated or characterized by fibrosis and hyalinization.

The axillary lymph node morphology in relation to age is shown in Table 2, and in relation to different modes of death in Table 3. The median age and the modes of death of the women with in situ BC did not differ from those of the controls. SH was independent of age but significantly more

frequent in women dying from infectious diseases compared to other causes of death ($p < 0.005$). Active and degenerative SH showed no preponderance in any group. In contrast, DCH was most frequent among young and middle-aged women ($p < 0.001$), and also among women with an unnatural mode of death ($p < 0.001$), but this is probably due to an overrepresentation of younger women in this group. GCH/FH was significantly associated with youth ($p < 0.005$) and thus also with an unnatural mode of death ($p < 0.001$), the majority being users of intravenous narcotics (10 out of 12). The median age of the drug addicts was 27 years, and the majority died from accidents or suicide, but only one had in situ BC. Alcohol abuse was frequent, but lymph node changes in alcoholics did not differ in type and frequency from other women. The majority of women with LD were old

and died from metastasizing malignant diseases. The occurrence of involutionary changes with fibrosis, hyalinization and lipomatosis were most frequent in old women compared to the young age group ($p < 0.001$). These changes were also associated with a natural mode of death ($p < 0.001$ and $p < 0.05$, respectively), but this correlation may well be accidental as a natural mode of death was more frequent among the elderly women.

Discussion

The current study shows that in situ BC is associated with reactive changes in the ipsilateral axillary lymph nodes in the form of SH and DCH. Although bilaterality of these lymph node patterns was frequent, no significant association was found between unilateral in situ BC and changes in the contralateral axillary lymph nodes. Thus our study does not indicate that in situ BC induces systemic lymph node changes.

The higher frequency of SH and DCH in cases of in situ BC may be coincidental. However, as the same axillary lymph node changes are induced by IBC, the association is probably causal. This conclusion is based on the assumption that women with in situ BC and controls are indeed comparable. Except for abuse of intravenous narcotics, the two groups of women in the current study did not differ with respect to the clinical data available.

Many studies indicate systemic impairment of the immune function of women with IBC, as determined by measures of cell-mediated immunity (Adler et al. 1980; Ludwig et al. 1985; Mandeville et al. 1982). In contrast, an increased reactivity of regional lymph nodes is suggested both by the morphological changes and by in vitro studies of the immunological capacity of lymphocytes from axillary lymph nodes (Barna and Deodhar 1978; Fisher et al. 1974; Heidenreich et al. 1979; Nakajima et al. 1986a, b). However, whether the altered lymph node morphology and function signify immunological changes of importance for the course and the prognosis of women with IBC remains a matter of controversy (Berg 1956; Fisher 1986; Fisher et al. 1975; Fisher et al. 1984; Schiødt 1966; Silverberg et al. 1970; Tsakraklides et al. 1974). The occurrence of SH and DCH (reported frequency: 20–50% and 50–70%, respectively) possibly indicating that cell-mediated immune mechanisms may be involved, has been associated with a reduced frequency of axillary metastases and an improved prognosis (Black 1973; Hunter et al. 1975; Silverberg et al. 1970; Syrjänen 1979; Tsakraklides et al. 1974; Wartman 1959). Morphologi-

cal signs of activation of the humoral system with GCH (reported frequency: 10–30%) have been found to influence adversely the disease-free survival of women without regional lymph node metastases (Fisher et al. 1984). The occurrence of LD (reported frequency: zero to a few per cent), which may reflect immunological exhaustion or inhibition of the immune response, has been found to be an ominous prognostic sign (Tsakraklides et al. 1974).

Little information is available concerning altered immunocompetence of women with in situ BC. However, the reactive morphological changes of ipsilateral axillary lymph nodes in women with in situ BC suggests a local immunological response, mainly of the cell-mediated type.

Moderate and marked SH was found in about 70% of 33 women having surgery for in situ BC in the study of Black and Chabon (1969). They found SH associated with moderately prominent germinal centers in 45% of the cases with in situ BC, and SH was more frequent among women with in situ BC compared to women with IBC. Among 78 women operated for intraductal carcinoma, Fisher et al. (1986) found that 48% had marked SH, 62% DCH, 29% GCH and three per cent LD, figures comparable to the frequencies in women with IBC cited above.

There are no autopsy studies of axillary lymph node morphology with which our results can be directly compared. However, in series of random autopsy cases the frequencies of the different changes were comparable to those of the controls in the current study, except for a lower frequency of SH (Black and Speer 1960; Tsakraklides et al. 1975). Our higher frequency may at least partly be due to the fact that we included degenerative SH among the cases with SH. The well-known high frequency of reactive lymph node patterns with GCH/FH in users of intravenous narcotics (Kringsholm and Christoffersen 1987; Siegel et al. 1966; Toccanier and Kapanci 1985) was confirmed in our study.

The decreased lymph node reactivity in our series of women with in situ BC compared to those of the clinically based studies (Black and Chabon 1969; Fisher et al. 1986) might be explained by differences in the selection of the material. In agreement with other authors we found that involutionary changes increased with age (Denz 1947; Tsakraklides et al. 1975). However, the age difference is probably of minor importance for the discrepancy regarding the frequency of lymph node reactivity. It has been demonstrated that women dying from debilitating diseases which during life-

time are often associated with increased lymph node reactivity, frequently show involutionary changes at autopsy (Black and Speer 1960). The decreased reactivity in the current study is thus in keeping with this finding as several of the women with in situ BC had severe chronic disease in contrast with the otherwise healthy women having surgery for in situ BC in clinical studies.

The growth pattern of in situ BC is another factor which may be of importance in relation to lymph node reactivity. All the in situ BC in the current study were microfocal, i.e. 5 mm or less in diameter (Andersen et al. 1985; Nielsen et al. 1987) compared to the probably larger tumour-forming lesions in the clinically based studies (Black and Chabon 1969; Fisher et al. 1986). However, tumour multicentricity did not increase lymph node reactivity compared with single lesions. The significance of the occurrence of a local stromal inflammatory response to in situ BC for the reactivity could not be evaluated due to the small number examined. Our findings do not support the results of Black and Chabon (1969) that SH was more frequent in the cases of lobular carcinoma in situ.

It is estimated, from the literature, that about 30% of women with biopsy-treated in situ BC develop subsequent IBC (Betsill et al. 1978; Page et al. 1982). Twenty-six per cent of the women with in situ BC in the current study had no reactive nodal patterns, i.e. unstimulated or lymph nodes with only involutionary changes. It would be of importance for future investigations to clarify whether women with in situ BC who develop subsequent IBC are prone to have these nonreactive or other specific morphological patterns in the regional axillary lymph nodes.

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