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# Breast lymphoma

## A clinical and pathological review and 10-year treatment results

**S. Ariad, D. Lewis, R. Cohen, W. R. Bezwoda**

Sixteen patients presenting with lymphoma involving the breast are described. Seven fulfilled the criteria for primary breast lymphoma, while the other 9 had evidence (sometimes only detected after extensive staging procedures) of concurrent lymphomatous involvement outside the breast. Histological diagnoses of the so-called primary breast lymphomas included 1 case of Hodgkin's disease and 6 of non-Hodgkin's lymphoma (including 2 with T-cell phenotypes). The patients with so-called secondary breast involvement included 8 with non-Hodgkin's lymphoma and 1 with a plasmacytoma of the breast with concomitant myelomatous involvement of bone marrow. Among the non-Hodgkin's lymphomas involving the breast the whole range of histological subtypes from low-grade to high-grade lesions were seen. There was no subtype of lymphoma with a specific predilection for breast involvement. Expression of oestrogen receptor protein as determined by immunocytochemical investigation using specific monoclonal antibodies was uniformly negative in lymphoid cells of 11 patients studied. Most of the patients in this series were treated by chemotherapy with uniformly good local control of lymphomatous involvement of the breast and an outcome similar to that of lymphomas presenting at other body sites. It is concluded that the approach to lymphomas of the breast should be similar to that of the equivalent types presenting elsewhere.

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Lymphoma of the breast is a rare tumour constituting an estimated 0,04 - 0,5% of all malignant breast lesions.[1-6] Wiseman and Liao[2] proposed that lymphomatous breast lesions be classified into primary and secondary breast lymphoma. To fulfil the criteria for primary breast lymphoma, the following characteristics were required: (*i*) technically adequate specimens; (*ii*) mammary tissue and lymphomatous infiltrate in close association; (*iii*) no evidence of concurrent widespread disease; and (*iv*) no previous diagnosis of extramammary lymphoma. Cases that did not fulfil these criteria were classified as secondary breast lymphomas.

While this classification has been fairly widely accepted, a number of questions regarding lymphomatous breast involvement remain unanswered. Firstly, is classification into primary or secondary breast lymphomas truly of value from a pathological, a clinical, or a prognostic point of view? It is also not established whether there is any *specific pattern* of lymphoma that shows predilection for breast involvement. In this regard it has been suggested that lymphomatous involvement of the breast is a specific entity, namely mucosa-associated lymphoid tissue (MALT cell) lymphoma.[6,7] Another question that has been raised about breast lymphoma is the possibility that their growth may be influenced by hormones.[7] This has been suggested by the apparent finding of oestrogen binding in two patients with breast lymphomas.

Finally, the approach to treatment of patients with breast lymphomas remains controversial.

In an attempt to clarify some of these issues, the records of patients who attended the Haematology/Oncology Clinic at Johannesburg Hospital between January 1981 and January 1991 with lymphoma involving the breast were reviewed.

## Patients and methods

Criteria for inclusion in this study included: (*i*) breast involvement as the initial presenting clinical feature; (*ii*) availability of adequate pathological material for review; and (*iii*) availability of detailed clinical data, especially staging investigations, on the patients under review. Pathological review utilised 3 μ sections stained with routine haematoxylin and eosin and Masson trichrome stains as well as a variety of immunocytochemical investigations, including leucocyte common antigen, epithelial membrane antigen and cytokeratin tests. Phenotype studies included T- and B-cell analysis using a panel of monoclonal antibodies. Pathological classification was based on the working formulation but included other specific diagnoses where appropriate.

Immunocytochemical staining for oestrogen receptor protein was performed where material was available, by means of a modified immunocytochemical technique using paraffin-embedded material partially digested with trypsin and DNAse. The primary antibody utilised was derived from the ABBOT ERICA kit (Abbot Diagnostics). The details of the immunocytochemical method have been published elsewhere.[8] Quantitation of ER was by the H-score method, which includes assessment of both the intensity of staining and the percentage of positive cells.[9]

During the period under review, 19 patients were identified as having lymphoma with breast involvement. Of these, 16 met the criteria set out above for inclusion in the study; the other 3 either had insufficient clinical data or no material for histological review. Of the 16 patients included, 7 met the clinical and pathological criteria proposed by Wiseman and Liao[2] for a diagnosis of primary breast lymphoma, while the other 9 had evidence of concurrent lymphoma at sites other than the breast and regional nodes. All had undergone

**Haematology/Oncology Division, Department of Medicine, Department of Histopathology and School of Pathology, University of the Witwatersrand, Johannesburg**

**S. Ariad**, M.D.

**D. Lewis**, F.F. PATH.

**R. Cohen**, F.F. PATH.

**W. R. Bezwoda**, PH.D.

clinical and pathological staging procedures, including as a minimum a full history and physical examination, chest radiographs, computed tomography of the chest and abdomen, and bone marrow aspiration and trephine biopsy. In addition, all had a full blood count with differential count and automated biochemical analysis, including tests of renal and hepatic function. A number underwent additional staging procedures, depending on specific clinical indications. Four patients underwent staging laparotomy.

# Results

## *Clinical characteristics*

All the patients were female. Their ages ranged from 20 to 77 years, with a mean of 47 ± 15,9 years. In all, breast involvement had been the initial and major clinical manifestation. Eleven of the 16 presented with a localised breast mass, with cutaneous ulceration in 1 case, and 5 with diffuse swelling; 3 of the latter had features similar to 'inflammatory' breast carcinoma, with cutaneous erythema, oedema and increased heat of the entire breast. There were no instances of bilateral breast involvement at presentation. Further clinical details are shown in Table I.

**Table I. Clinical features of 16 patients with breast lymphoma**

| Patient No. | Age (yrs) | Size (cm) | Regional nodes | Other nodes | Visceral |
|---|---|---|---|---|---|
| Localised involvement | | | | | |
| 1 | 44 | 4 x 4 | Yes | No | Neg. |
| 2 | 30 | 5 x 5 skin ulceration | Yes | No | Neg. |
| 3* | 20 | 4 x 4 | Yes | No | Neg. |
| 4 | 51 | Diffuse inflammatory | Yes | No | Neg. |
| 5 | 50 | 5 x 5 | No | No | Neg. |
| 6 | 70 | Diffuse | Yes | No | Neg. |
| 7 | 26 | Diffuse inflammatory | No | No | Neg. |
| Lymphoma of breast + distal sites | | | | | |
| 8 | 77 | 6 x 6 | No | Yes | Neg. |
| 9 | 33 | 4 x 4 | Yes | No | BM+ |
| 10* | 55 | 5 x 5 | No | No | BM+ |
| 11* | 62 | 5 x 6 | No | No | S+, BM+ |
| 12* | 59 | 5 x 5 | No | No | SB+ |
| 13 | 70 | Diffuse | Yes | No | L+ |
| 14† | 52 | Diffuse inflammatory | Yes | No | BM+ |
| 15 | 34 | 5 x 5 | Yes | Yes | Neg. |
| 16 | 39 | 5 x 5 | No | Yes | BM+ |

* Patient underwent staging laparotomy.
† Patient had previous adenocarcinoma of left breast 9 yrs before presentation with lymphoma of right breast.
BM+ = bone marrow involvement; S+ = splenic involvement; L+ = pulmonary involvement; SB+ = small-bowel involvement (histological).

## *Pathological features (Table II)*

The majority of both primary and secondary lymphomas (15 of the 16) were of the non-Hodgkin's type, but there was 1 case of Hodgkin's disease, localised to the breast, that fitted the clinical criteria of primary breast lymphoma. The majority (5) of the 7 so-called primary breast lymphomas were of intermediate or high grade, according to the Working Formulation (including the patient with peripheral T-cell lymphoma — this lesion could best be described as immunoblastic, high-grade lymphoma, according to the Working Formulation).

Among the secondary lymphomas with breast involvement, intermediate and high-grade non-Hodgkin's lymphomas also predominated. This group, however, included 1 patient with an extramedullary plasmacytoma involving the breast, who was found to have bone marrow involvement with multiple myeloma on further investigation. The diagnosis of multiple myeloma was only made after histological diagnosis of plasmacytoma.

**Table II. Pathological features of 16 patients with breast lymphomas**

| Patient No. | Pathologic classification | Phenotype | Vascular and/or lymphatic invasion | Sclerosis | Infiltration of duct/ acinar epithelial layer |
|---|---|---|---|---|---|
| Localised involvement | | | | | |
| 1 | DL | T cell | Vascular +++ | +++ | Pos. |
| 2 | PTL | T cell | Dermal lymphatics | Neg. | Neg. |
| 3 | HD | – | Neg. | Neg. | Neg. |
| 4 | DL | – | Vascular + angiocentric | ++++ | Neg. |
| 5 | BL | B cell | Vascular ++ | ++ | Pos. |
| 6 | DS | B cell | Venous +++ | Neg. | Neg. |
| 7 | DL | B cell | Neg. | Neg. | Pos. |
| Lymphoma of breast + distal sites | | | | | |
| 8 | DS (plasmacytoid) | – | Neg. | ++++ | Neg. |
| 9 | Plasmacytoma | B cell | Neg. | Neg. | Neg. |
| 10 | DS | B cell | | Neg. | Pos. |
| 11 | DM | B cell | Vascular ++ | Neg. | Pos. |
| 12 | DL | B cell | Vascular ++ | +++ | Pos. |
| 13 | HGU | B cell | Neg. | Neg. | Neg. |
| 14 | DL | B cell | Venous ++ | ++ | – |
| 15 | DL | B cell | Neg. | ++ | Neg. |
| 16 | HGU | B cell | Vascular ++ | ++ | Pos. |

DL = diffuse large-cell lymphoma; PTL = peripheral T-cell lymphoma; HD = Hodgkin's disease; BL = Burkitt's lymphoma; DS = diffuse small-cell lymphocytic lymphoma; DM = diffuse mixed small- and large-cell lymphoma; HGU = high-grade unclassifiable lymphoma.

In both primary and secondary breast lymphoma, the pattern of involvement at the edge of the tissue was infiltrative even when the breast mass appeared clinically to be discrete. Invasion of the mammary parenchyma and of mammary adipose tissue occurred frequently, both in so-called primary lesions and in cases with involvement of tissues other than the breast. In addition, vascular and/or lymphatic invasion occurred in 9 cases (56%). Other notable histological features were the presence of sclerosis and involvement of ductules and acini by lymphoma cells. Sclerosis was present in approximately half (8) of the cases, and in most instances consisted of a fairly dense fibrous stroma surrounding areas of lymphoma involvement. Invasion of the duct epithelial layer, giving rise to a so-called lympho-epithelial lesion, occurred in 7 cases (44%). Both sclerosis and invasion of the epithelial layer occurred with approximately equal frequency in primary and secondary breast lymphomas. Background reactive lymphoid infiltration of the normal breast tissue, when present, was generally sparse and germinal centres were not found.

Immunophenotyping (available for 12 patients) showed 10 cases to be B-cell and 2 T-cell lymphomas. Both the lymphomas, specifically typed as T-cell lymphomas, were in the so-called primary group.

In 11 cases in which immunocytochemical investigation for oestrogen receptor protein was performed, the result was uniformly negative in tumour cells. The adequacy of the immunocytochemical technique was confirmed by positive findings in the adjacent and entrapped breast ducts and lobules.

## Treatment and prognosis

Details and results of treatment are shown in Table III. The majority of patients received chemotherapy only, those with diffuse large-cell or other high-grade lymphomas mostly receiving primary therapy with CHOP (cyclophosphamide + adriamycin + vincristine + prednisolone), while patients with low-gade lymphomas were treated either with single-agent chlorambucil or with COPP (cyclophosphamide + vincristine + prednisolone + procarbazine). The patient with plasmacytoma of the breast and evidence of bone marrow infiltration with multiple myeloma was initially treated with VAD (vincristine + adriamycin + dexamethasone), while the patient with Hodgkin's disease involving the breast was treated with MOPP/ABVD (nitrogen mustard + vincristine + prednisolone + procarbazine, alternating with adriamycin + DTIC + vinblastine + bleomycin).

Initial local control of the breast tumour, whether of the primary or the secondary type, was achieved in all 16 patients. The breast involvement responded completely in all patients, irrespective of the chemotherapeutic regimen employed. The 2 patients classified as having a partial response had evidence of persistent disease at other sites.

Local breast disease recurred in 5 patients (1 with primary lymphoma and 4 with secondary breast lymphomas). All 3 of the patients with low-grade lymphoma treated with either chlorambucil alone or chlorambucil plus radiation therapy showed evidence of local recurrence. The other 2 relapses in the breast included the patient with plasmacytoma of the breast treated with VAD (patient 9), and the patient with Burkitt's lymphoma treated with an acute leukaemia induction and maintenance regimen (patient 5). The patient with plasmacytoma/multiple myeloma had complete clinical regression of the breast plasmacytoma and partial response of the myeloma (as determined biochemically by protein immuno-electrophoresis of blood and urine). Regrowth of the breast plasmacytoma was again the first evidence of progression of her disease, followed by a later rise of the serum paraprotein concentration. The patient with Burkitt's lymphoma relapsed with bilateral breast involvement, together with bone marrow infiltration. In only 1 instance (patient 6 with primary breast lymphoma) was the breast the sole site of recurrence. In 3 patients who relapsed (including 1 patient with primary breast lymphoma), sites other than the breast were involved.

**Table III. Therapy in primary breast lymphoma**

| Patient No. | Initial therapy | Response | Duration of first response (mo.) | Sites of relapse | Further therapy | Alive/dead |
|---|---|---|---|---|---|---|
| 1 | CHOP | CR | 24+ | | – | A |
| 2 | CHOP | CR | 60+ | | – | A |
| 3 | MOPP/ABVD | CR | 60+ | | – | A |
| 4 | CHOP | CR | 48 | LN | MACOP-B* | D |
| 5 | L2 protocol | CR | 12 | Breast, BM | CHOP | D |
| 6 | Chlor. | CR | 36 | Breast | Chlor. | A |
| 7 | CHOP | CR | 38+ | | — | A |
| 8 | DXT + Chlor. | PR† | 7 | Breast, BM | COPP | D |
| 9 | VAD | PR | 9 | Breast, BM | Melph. + Pred. | D |
| 10 | Chlor. | CR | 24 | Breast, LN | Cyt. + Pred. | A |
| 11 | CHOP | CR | 4 | CNS | CNS DXT | D |
| 12 | CHOP | CR | 120+ | | — | A |
| 13 | CHOP | CR | 12 | LN, CNS | NOPE | D |
| 14 | CHOP | CR | 16+ | | MACOP-B | A |
| 15 | CHOP | CR | 10 | LN, BM | NOPE | D |
| 16 | CHOP | CR | 14+ | | — | A |

* Achieved 2nd remission with MACOP-B. Died of disseminated fungal infection.
† Local control of breast tumour. Persistent marrow infiltration.
CHOP = cyclophosphamide + adriamycin + vincristine + prednisolone; MOPP = nitrogen mustard + vincristine + prednisolone + procarbazine; ABVD = adriamycin + bleomycin + vinblastine + DTIC; L2 protocol = 6-week induction cycle of vincristine + prednisolone + adriamycin (weeks 2 and 4) + L-asparaginase consolidation; Chlor. = chlorambucil; DXT = deep X-ray therapy; VAD = vincristine + adriamycin + dexamethasone; COPP = cyclophosphamide + vincristine + prednisolone + procarbazine; Melph. + Pred. = melphalan + prednisolone; Cyt.+ Pred. = cyclophosphamide + prednisolone; MACOP-B = methotrexate + adriamycin + vincristine + prednisolone + bleomycin; NOPE = mitoxantrone + vincristine + prednisolone + etoposide; CR = complete response; PR = partial response; LN = lymph node; BM = bone marrow; CNS = central nervous system; A = alive; D = dead.

Duration of both response and survival were variable, as would be expected from a group of patients with lymphoma with heterogeneous histological type and staging. Disease-free survival of patients with high-grade lymphomas with breast involvement, treated with CHOP, varied from 14 to over 120 months (median 48 months). Although 4 patients with involvement of breast plus other extranodal sites showed evidence of early relapse (between 4 and 10 months), this would be expected in view of the more widespread nature of their disease. There was, however, no statistically significant difference in overall survival of patients with so-called primary lymphoma of the breast, and those with secondary breast lymphomas with involvement outside the breast (Fig. 1).

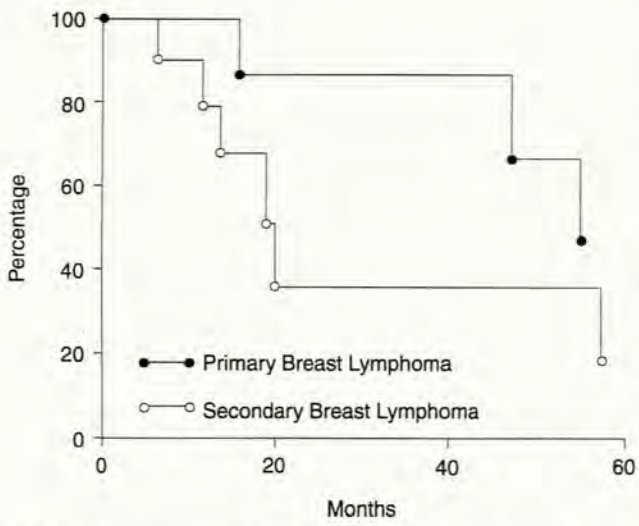


**Fig. 1. Cumulative survival of patients with breast lymphoma.**

## Discussion

Lymphoma of the breast is a rare diagnosis.[10-16] During the period under review, the 16 patients with breast masses documented to be lymphomatous at histological examination represented 1,8% (16 of 870) of all patients and 3,4% (16 of 463) of all females with a diagnosis of lymphoma. The distribution between so-called primary and secondary lymphomas was found to be roughly equal. Of female patients with extranodal presentation, 8,6% (16 of 187) had breast lymphoma. During the same period there were 1 252 patients with breast carcinoma. In addition, there were 7 patients with sarcomas involving the breast (2 malignant fibrous histocytoma, 3 cytosarcoma phalloides, 1 fibrosarcoma and 1 neuroblastoma), and 2 cases of leukaemic involvement of the breast (2 M4 AML, 1 T-ALL). While lymphoma of the breast represented only a small proportion of malignant breast lesions (16 of 1 281; 1,25%), it represented 62% (16 of 26) of all non-carcinomatous malignant lesions of the breast. These figures are somewhat higher than those reported in the literature, a difference which may be related to referral patterns at this institution, patients with unusual lesions such as breast lymphoma being more likely to be referred to a specialist centre than patients with breast carcinoma.

In this review we have attempted to address a number of issues raised in the literature regarding breast lymphoma. From the clinical point of view, while the presentation of breast lymphoma is often similar to that of breast carcinoma (including the occurrence of 'inflammatory' features), this issue is usually readily resolved by histological examination.

More important is the question of whether the classification into so-called primary and secondary breast lymphoma has any value, over and above that of distinguishing between localised and widespread lymphoma (staging). In this regard it should be pointed out that, as is evident with lymphomas presenting at other sites, a proportion of patients will be found to have more widespread involvement as a result of clinical or more comprehensive radiological and pathological investigations. This was certainly the case in the current series, where clinical involvement of distal nodes was evident in only 3 of 9 patients eventually classified as having so-called secondary breast lymphoma. Other sites of involvement, including visceral involvement, were detected only as a result of systematic staging procedures.

If the distinction between primary and secondary breast lymphomas and the related concept that primary breast lymphomas represent a specific instance of MALT cell[6] malignancy are to have any validity, they must be based on specific pathological, immunohistological or biological (including prognosis and response to treatment) features. In this regard, however, there were no specific pathological features that distinguished breast lymphomas from lymphomas arising at other sites, or indeed that distinguished between patients with lymphomatous involvement confined to the breast, and those with more widespread involvement. In both the patients with localised lymphomas and those with breast involvement as part of disseminated lymphoma, the predominant histological subtype was diffuse large cell (type G, Working Formulation). While this finding is in keeping with the results of other series,[1,2,5,8,16-21] it should be pointed out that other types of non-Hodgkin's lymphoma as well as other lymphoproliferative disorders were also observed in both clinical groups. Infiltration of the epithelial layer of ducts and of acini occurred in a number of cases, but this pattern was not specific and occurred in a number of different histological subtypes of lymphoma in both secondary and so-called primary cases. Furthermore, the presence or absence of infiltration of the ductal or acinar epithelial layer appeared to have no influence on prognosis. Stromal sclerosis or infiltration of the breast parenchyma was also of no prognostic significance,[22] when examined in a multivariate analysis.

Immunophenotyping results were also of limited value in distinguishing between localised and disseminated lymphomas with breast involvement. While a predominance of B-cell lymphomas was demonstrated, this is not unexpected among patients with non-Hodgkin's lymphoma. There were 2 cases of T-cell lymphoma (both in patients with 'primary' breast lymphoma). While the striking angiocentricity demonstrated in case 6 might suggest (in the absence of immunophenotyping) that this patient also had a T-cell lymphoma, it should be pointed out that significant vascular invasion was also seen in a number of other lymphomas typed as being of B-cell origin. T-cell

lymphomatous involvement of the breast has also been described by Cohen and Brooks,[23] who found 1 case of primary T-cell lymphoma of the breast. We were unable to distinguish between B- and T-cell lymphomas on purely histological criteria, since vascular invasion was also found with B-cell immunophenotypes.

The occurrence of both Hodgkin's disease and 2 cases of T-cell lymphoma among the 'primary' breast lymphomas also argues against the concept that breast lymphomas specifically represent MALT cell lymphomas and suggests that, while the relative rarity of breast involvement may well be related to the paucity of lymphoid tissue in the breast, the full spectrum of malignant lymphomas may on occasion be encountered at this site.

Immunohistochemical investigation did not reveal specific oestrogen receptor protein in either lymphoid cells or surrounding stroma in any of the cases. Since immunohistochemical detection of oestrogen receptor protein has, in our hands, been positive in 95% of breast cancers with oestrogen receptor binding of > 30 fmol/mg protein as detected by ligand binding assays, it is unlikely that oestrogen receptor protein is present in any of these tumours at clinically significant concentrations.

Reported treatment regimens for patients with lymphoma of the breast have varied. While a number of series have suggested that these tumours should be treated as localised primary extranodal lymphomas with surgery and local radiation therapy,[18,20,21] the risk of recurrence, even in stage 1E non-Hodgkin's lymphoma of the breast, appears significant.[21,22,24] Both the histological type and the extent of the disease need to be taken into consideration. In the present series, 7 of 11 patients with non-Hodgkin's lymphoma of the breast had diffuse large-cell or other high-grade lesions, and in only 1 of these was the lymphoma staged as IE. This, together with the frequent finding of vascular invasion, suggested to us that chemotherapy was the most appropriate treatment modality. In the event none of the patients who received CHOP therapy for diffuse large-cell lymphoma had local recurrence in the breast. While the small size of this and other series makes it difficult to make firm recommendations with regard to treatment, the results of the present series tend to indicate that the prognosis and treatment of breast lymphomas are and should be similar to those of equivalent types of lymphomas occurring at other sites.

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# Dokter en digter

## *Tussen jou en my*

Kyk!
Die wynglas skommel rooi —
in die helder vog
ons onvas oë

Onthou jy?
Ek aan hiérdie kant
jy aan die ander —
tussen óns,
die wyn;
rooi soos die najaar
beleë soos verlange . . .

Maar die glas —
voor ons dit in sy volheid
kon fynproe . . .
kristalglas
is breekbaar soos die liefde
en die rooiwyn vlek
en herinneringe is rooibruin blare;

Maar, voor die winter wit
is dit eers herfs
en die glas skommel rooi skadu's
voor dit breek

***Lieb Sauermann***

Hierdie gedig het in *Tandem*, 'n versameling verse deur Lieb Sauermann en Johann de Jager (1992), verskyn.