Mantle cell lymphoma presenting as a breast mass

P Windrum, T C M Morris, M A Catherwood, H D Alexander, D T McManus, G M Markey

Abstract

Breast lymphoma accounts for less than 1% of all non-Hodgkin's lymphomas (NHLs) and approximately 0.1% of all breast neoplasms. Most breast lymphomas are classified as diffuse large B cell or mucosa associated lymphoid tissue (MALT) lymphomas. The case of a 53 year old woman presenting with a breast mass and found to have mantle cell lymphoma is described. Core biopsy of the breast lesion showed a B cell NHL, probably of large cell type and of high grade. Morphological and immunophenotypic analysis of peripheral blood and bone marrow samples suggested a mantle cell lymphoma (MCL). This was confirmed by the detection of a t(11;14) in the bone marrow aspirate and breast tissue by polymerase chain reaction analysis. There have been no previous reports of an MCL presenting as a breast lump. Because a diagnosis of MCL has prognostic and therapeutic implications, this case highlights the need for an awareness of MCL presenting in this way, and the requirement for specialised investigations in its detection.

(*J Clin Pathol* 2001;**54**:883–886)

Keywords: mantle cell lymphoma; breast lymphoma; cyclin D1; t(11;14)

Department of Haematology, Belfast City Hospital, Lisburn Road, Belfast BT9 7AD, Northern Ireland
P Windrum
T C M Morris
M A Catherwood
H D Alexander
G M Markey

Department of Histopathology, Belfast City Hospital
D T McManus

Correspondence to:
Dr Morris
curly.morris@bll.n-i.nhs.uk

Accepted for publication
1 May 2001

Breast lymphoma is rare. Akbari *et al* at the University of Connecticut school of medicine found only three cases in 4491 consecutive breast malignancies,[1] whereas a similar study in Ljubljana[2] revealed eight cases in 5711 malignant breast tumours examined. It accounts for approximately 2% of extranodal non-Hodgkin's lymphomas (NHLs) and less than 1% of total NHL.[3] However, it remains the second most common breast malignancy after breast carcinoma. Interestingly, it has been noted that breast lymphomas are more likely to develop in the right breast.[2 4–8] The reason for this phenomenon is unknown.

Breast lymphoma has been separated into primary and secondary types based on criteria described by Wiseman and Liao.[5] Primary breast lymphoma is defined as involvement of the breast and ipsilateral nodes only, whereas secondary breast lymphoma refers to more widespread disease. Primary and secondary breast lymphomas have roughly equal incidences.[4] The most frequent subtype of lymphoma diagnosed in the breast is diffuse large B cell NHL.[2 5–8] Mucosa associated lymphoid tissue (MALT) lymphomas are also relatively common. Although many other types have been reported—for example, follicle centre cell NHL, lymphoplasmacytoid lymphoma, anaplastic large cell lymphoma,[8] and Hodgkin's lymphoma[9]—mantle cell lymphoma (MCL) has not been described.

Case report

A 53 year old woman presented to a symptomatic breast clinic with a one month history of a painless right breast lump noted on self examination. No nipple bleeding or discharge was present and there was no family history of breast carcinoma. She had a hysterectomy without oophorectomy 20 years previously, but no other relevant history.

On examination she had a hard 3 cm diameter mass above the right nipple. No lymphadenopathy or organomegaly was detected. Full blood count revealed a mild lymphocytosis for her age (total leucocyte count, 11.83×10^9/litre; lymphocyte count, 4.81×10^9/litre; neutrophil count, 6.04×10^9/litre). The erythrocyte sedimentation rate was 19 mm/hour and biochemical screening tests (including urea and electrolytes, liver function tests, lactate dehydrogenase, and immunoglobulins) were within normal limits. Mammography showed an asymmetric density above the right nipple, with distortion of the surrounding breast tissue, but no evidence of calcification. Fine needle aspiration cytology was suspicious of malignancy and a core biopsy was then taken. This showed a large B cell NHL and the patient was referred for haematology assessment.

A computed tomography scan of chest, abdomen, and pelvis did not reveal further evidence of disease. Peripheral blood (PB) and bone marrow (BM) examinations were carried out and a diagnosis of MCL was made. The patient received six cycles of CHOP chemotherapy. Her breast mass was impalpable after two courses. Mammography after three courses confirmed a reduction in the hyperdense area above the right nipple. However, BM biopsy did not indicate an appreciable response. After six cycles, there was no evidence of a lesion on mammography, but residual disease remained in the BM trephine biopsy. In view of this, the patient proceeded to high dose chemotherapy with autologous peripheral blood stem cell transplantation. Subsequent BM trephine biopsy examination has also shown evidence of residual disease.

Materials and methods

Immunohistochemistry was carried out on 5 μm (breast core) or 3 μm (bone marrow biopsy) sections cut on to 3-aminoproplytriethoxysilane (APES) coated slides. All antigen retrieval except for cyclin D1 was carried out using citrate buffer (pH 6.0) and pressure cooking. Antigen retrieval for cyclin D1

used a high pH (pH 9.9) buffer at 95°C for 40 minutes. Detection was carried out using the Dako StreptABComplex Duet kit. All antibodies were supplied by Dako (Glostrup, Denmark).

DNA was extracted from formaldehyde fixed paraffin wax embedded tissue and polymerase chain reaction (PCR) detection of t(11;14) was carried out using a seminested procedure, owing to the small amount of starting material, as described previously.[10 11] Briefly, PCR was performed in 50 µl of PCR buffer containing 3mM $MgCl_2$, 50µM of each deoxynucleotide, 10pmol of each primer, and 1 unit of Taq polymerase. The amplification products were separated on a 2% agarose gel and visualised by ethidium bromide staining under UV illumination.

Immunophenotypic analysis was carried out on whole blood using two colour direct labelling, followed by red cell lysis, and analysed on a FACScan flow cytometer using Cell Quest software (BD Biosciences, Oxford, UK). Light chain restriction studies (PB and BM aspirate) and immunophenotyping (BM aspirate) were

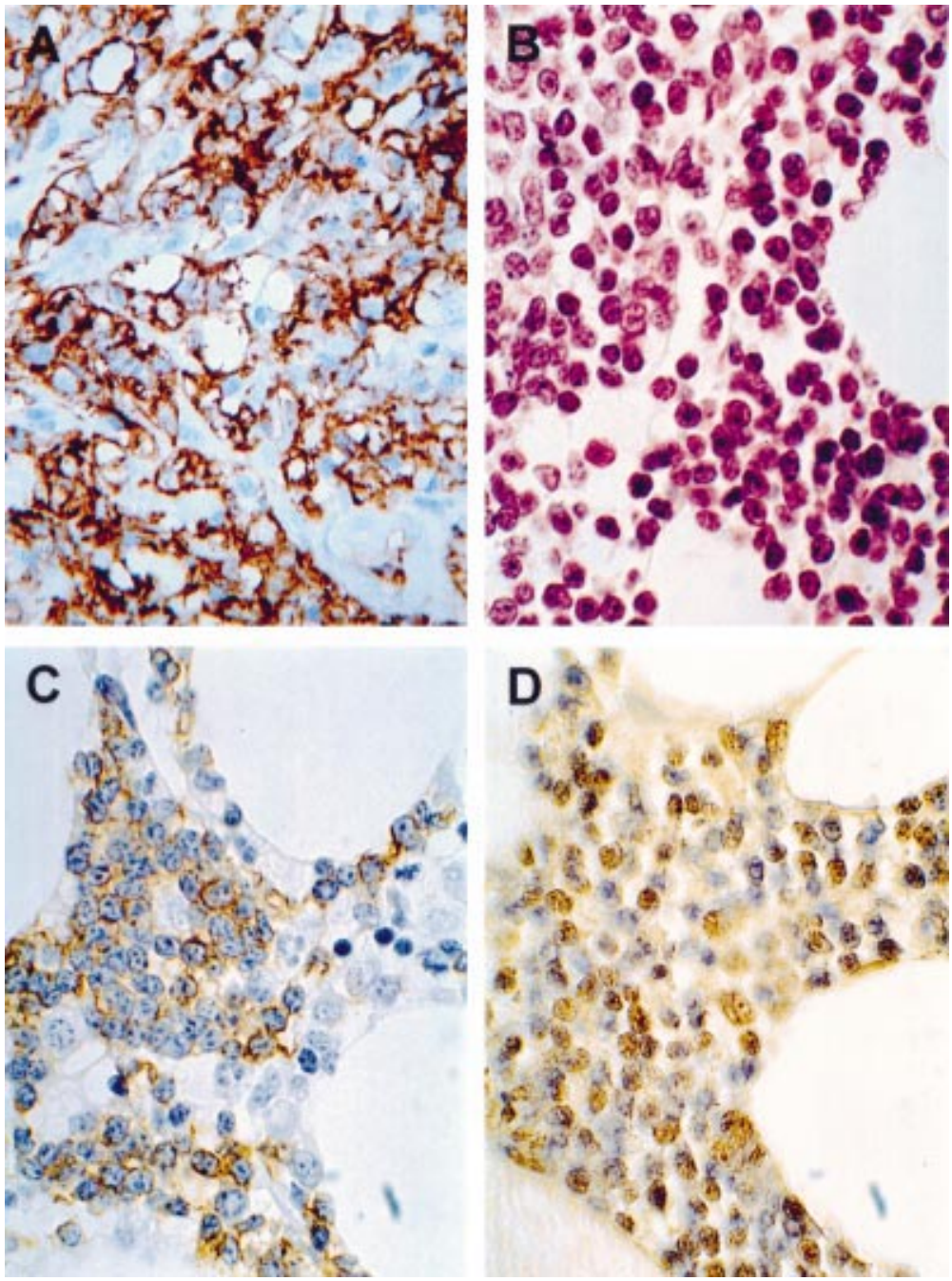

Figure 1 (A) Breast core biopsy. Lymphoma cells showing membrane staining for CD20. Immunoperoxidase, haematoxylin counterstain; original magnification, ×400. (B) Bone marrow trephine. Infiltrate of intermediate sized centrocyte-like malignant lymphoid cells. Haematoxylin and eosin; original magnification, ×630. (C) Bone marrow trephine. Membrane staining of neoplastic lymphoid cells for CD5. Immunoperoxidase, haematoxylin counterstain; original magnification, ×630. (D) Bone marrow trephine. Nuclear staining in neoplastic lymphoid cells for cyclin D1. Immunoperoxidase, haematoxylin counterstain; original magnification, ×630.

carried out using the alkaline phosphatase anti-alkaline phosphatase (APAAP) technique.

Results

MORPHOLOGICAL FEATURES AND IMMUNOHISTOCHEMISTRY

Core biopsy of the breast mass showed extensive infiltration by sheets of malignant cells with mature reactive lymphocytes at the edge of the lesion. There was a degree of crush artifact in the sample. There was no gland formation. Cytokeratin and epithelial membrane antigen staining was negative and the tumour cells stained strongly positively for CD45 and CD20 (fig 1A). Cyclin D1 staining was equivocal. There were scattered small mature CD5+ lymphocytes throughout the biopsy, especially around the ductal epithelium, although CD5 staining of the tumour cells was equivocal. Ki-67 immunoreactivity was noted in more than 50% of the neoplastic cell nuclei. It was reported as a B cell NHL, probably of large cell type and of high grade.

PB examination using FACS analysis showed a 35% population of CD5+, CD19+, CD20+ lymphocytes. These cells showed a considerable degree of pleomorphism, with irregular nuclear outline and occasionally cleaved or convoluted nuclei. Similar cells were seen in the BM aspirate and accounted for 20% of all nucleated cells seen. These cells were CD5+ and CD19+. Staining was negative for CD2, CD4, CD8, and CD10. Only 3% of the cells were Ki-67+ and they were also terminal deoxynucleotidyl phosphatase (TDT) negative. Light chain restriction was noted, with a $\kappa : \lambda$ ratio of 10 : 1. The findings were of a monoclonal (type κ) B cell population in both PB and BM, representing a CD5+ B cell lymphoproliferative disease, most likely an MCL, although pleomorphic B cell chronic lymphocytic leukaemia (B-CLL) was not ruled out at this stage.

Several irregularly shaped lymphoid aggregates (the largest measuring ~ 0.016 mm^2), consisting of monomorphic intermediate sized cells, were detected in the BM trephine (fig 1B). These cells were CD5+ (fig 1C), CD20+, and cyclin D1+ (fig 1D). They were CD3− and Ki-67 positivity was < 1%.

Repeat samples were taken for reassessment after the third course of chemotherapy. No monoclonal population was detected in the PB or BM aspirate samples. One irregularly shaped aggregate (~ 0.016 mm^2) of monomorphic intermediate size lymphoid cells, CD5+ and CD20+, was present in the BM trephine. A similar pattern to this second sample was noted in the biopsy taken after the sixth chemotherapy cycle, and evidence of residual disease was also found in the post autologous peripheral blood stem cell transplant trephine biopsy specimens when sections cut at levels through the biopsy were examined.

MOLECULAR STUDIES

A t(11;14) clonal product was identified in the breast tissue (fig 2). Individual PCR products varied in size owing to the length of the respective N-region and the location of the break point on chromosomes 11 and 14. A β globin control verified that DNA was suitable for PCR amplification. DNA extracted from BM at diagnosis, after chemotherapy, and after transplantation was also analysed and in all cases a similar t(11;14) PCR product was detected.

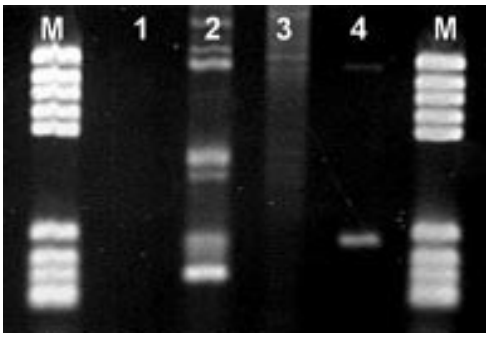

Figure 2 PCR amplified products from bcl-1/JH consensus primers visualised with ethidium bromide in a UV illuminated agarose gel. Lane 1, negative control without DNA; lane 2, positive t(11;14) control; lane 3, negative control with DNA; lane 4, amplified DNA from patient; lane M, molecular weight markers.

Discussion

MCL has recently been defined as a distinct disease entity, with specific immunohistochemical and cytogenetic features, and is included in the Revised European American Lymphoma (REAL) and World Health Organisation (WHO) classifications.[12 13] Before this, MCL would have been included as diffuse centrocytic lymphoma (DCL) in the Kiel classification, or as intermediate grade diffuse small cleaved cell lymphoma in the Working Formulation.

MCL carries a poor prognosis. Although morphologically it appears to be of low to intermediate grade and exhibits a survival curve similar to other low grade lymphomas with no survival plateau,[14] the gradient of this curve is steep and an approximate median survival of three years, with a five year survival of approximately 20%, has been reported.[15] At present, this is the worst outlook for any type of lymphoma. Therefore, its accurate diagnosis has implications for patients and for their treatment.

In this case, the core biopsy of the breast lump was reported as a malignant NHL of B cell lineage, possibly of large cell type and high grade. There was a degree of crush artefact in the biopsy and limited tissue was available for immunohistochemical staining. Although the tumour cells were clearly CD20 positive and had a high Ki-67 labelling index, staining with antibodies to CD5 and cyclin D1 was equivocal. Examination of PB, the BM aspirate, and the trephine biopsy showed morphology and immunophenotypic staining patterns consistent with MCL. PCR detection of the t(11;14) translocation in both the breast biopsy and the BM aspirate confirmed a clonal origin for both lesions and demonstrated a chromosomal translocation consistent with a diagnosis of MCL. Discordant morphology between sites occurs in lymphomas and lymphoproliferative diseases and has specifically been described in

breast lymphomas.[8] The only alternative explanation in our case is that the breast lesion represented a Richter transformation of B-CLL. However the morphology of the PB and BM aspirate cells and the trephine infiltrate favoured MCL and the occurrence of t(11;14) in unequivocal B-CLL is debatable.

Extranodal presentation of MCL is common.[16] It is seen most frequently in the digestive tract, but other sites including the thyroid gland and central nervous system have been reported. However, an extensive search of the literature using both the National Library of Medicine's Internet GratefulMed and Pubmed systems failed to reveal any matches between MCL and breast lymphoma. Because MCL may have been recognised previously as DCL or intermediate lymphocytic lymphoma (ILL), further searches were carried out. A search for DCL and breast lymphoma detected no relevant matches, whereas a search for ILL and breast lymphoma revealed one paper in which a patient presented with a breast mass.[17] Although this case may represent MCL, it was reported before knowledge of the association between t(11;14) and upregulated cyclin D1 expression in MCL, and these important confirmatory tests were therefore not carried out.

We believe that our patient represents a rare presentation of MCL, a phenomenon that has not been described previously. Although MCL presenting with a breast lump may be very rare, MCL is a fairly recently described entity and so it is possible that cases presenting before the use of the REAL classification may have been given other diagnoses. Breast lymphoma is also rare and few centres treat many cases. Many breast lymphomas present initially to breast surgeons and, as a result, subsequent biopsies may be examined by pathologists without a specialist interest in lymphoma. The relevant immunostaining or PCR analysis may not be done or indeed may not be available. Cyclin D1 immunohistochemistry is available in many centres but is recognised as technically difficult.[18 19] We feel that in our case the most important factor in making the diagnosis was the PCR analysis and suggest that this technique has an important role in the investigation of lymphoproliferative diseases, supplementing morphological/histological examination and immunophenotyping of the tumour.

In summary, a case of MCL presenting as a breast mass is reported. The classic features of MCL existing in the PB and BM and the demonstration of the t(11;14) translocation simultaneously in the breast tissue have not been described previously. Because the diagnosis of MCL has prognostic and therapeutic implications, its accurate identification using a test repertoire including PCR analysis is important, and pathologists should be aware that MCL may present in this way.

Our thanks to Mr W Odling-Smee for his permission to report this case.

1 Akbari CM, Welch JP, Pastuszak W. Primary lymphoproliferative disorders of the breast. *Conn Med* 1995;**59**:651–5.
2 Lamovec J, Jancar J. Primary malignant lymphoma of the breast. Lymphoma of the mucosa-associated lymphoid tissue. *Cancer* 1987;**60**:3033–41.
3 Misra A, Kapur BM, Rath GK. Primary breast lymphoma. *J Surg Oncol* 1991;**47**:265–70.
4 Cohen PL, Brooks JJ. Lymphomas of the breast: a clinicopathologic and immunohistochemical study of primary and secondary cases. *Cancer* 1991;**67**:1359–69.
5 Wiseman C, Liao KT. Primary lymphoma of the breast. *Cancer* 1972;**29**:1705–12.
6 Brogi E, Harris NL. Lymphomas of the breast: pathology and clinical behaviour. *Semin Oncol* 1999;**26**:357–64.
7 Brustein S, Filippa DA, Kimmel M, *et al.* Malignant lymphoma of the breast. A study of 53 patients. *Ann Surg* 1987;**205**:144–50.
8 Topalovski M, Crisan D, Mattson JC. Lymphoma of the breast: a clinicopathologic study of primary and secondary cases. *Arch Pathol Lab Med* 1999;**123**:1208–18.
9 Lin Y, Govindan R, Hess JL. Malignant hematopoietic breast tumors. *Am J Clin Pathol* 1997;**107**:177–86.
10 Jackson DP, Lewis FA, Taylor GR, *et al.* Tissue extraction of DNA and RNA and analysis by the polymerase chain reaction. *J Clin Pathol* 1990;**43**:499–504.
11 Pott C, Tiemann M, Linke B, *et al*. Structure of Bcl-1 and IgH-CDR3 rearrangements as clonal markers in mantle cell lymphomas. *Leukaemia* 1998;**12**:1630–7.
12 Harris NL, Jaffe ES, Stein H, *et al*. A revised European-American classification of lymphoid neoplasms: a proposal from the international lymphoma study group. *Blood* 1994; **84**:1361–92.
13 Jaffe ES, Harris NL, Diebold J, *et al*. World Health Organisation classification of lymphomas: a work in progress. *Ann Oncol* 1998;**9**(suppl 5):S25–30.
14 The Non-Hodgkin's Lymphoma Classification Project. A clinical evaluation of the international lymphoma study group classification of non-Hodgkin's lymphoma. *Blood* 1997;**89**:3909–18.
15 Weisenburger DD, Vose JM, Greiner TC, *et al*. Mantle cell lymphoma. A clinicopathologic study of 68 cases from the Nebraska lymphoma study group. *Am J Hematol* 2000;**64**: 190–6.
16 Bertini M, Rus C, Freilone R, *et al*. Mantle cell lymphoma: a retrospective study on 27 patients. Clinical features and natural history. *Haematologica* 1998;**83**:312–16.
17 Carbone A, Poletti A, Manconi R, *et al*. Intermediate lymphocytic lymphoma encompassing diffuse and mantle zone pattern variants. A distinct entity among low-grade lymphomas? *Eur J Cancer Clin Oncol* 1989;**25**:113–21.
18 Chan JKC. Reliable immunostaining of cyclin D1 is difficult, but the problems can be overcome. *Histopathology* 1999;**34**:266–8.
19 Miller KD, Munson P, Isaacson PG. Optimizing cyclin D1 immunostaining of mantle cell lymphoma. *Histopathology* 1999;**34**:268–70.