Bone marrow granulomas in infiltrating lobular breast cancer

P Kettle, D C Allen

Abstract
A 50 year old woman with a history of infiltrating lobular breast carcinoma presented with back pain. Bone scan and magnetic resonance imaging were not conclusive. A bone marrow aspirate appeared normal. A routine trephine biopsy specimen showed granulomas but no obvious infiltration by carcinoma. Immunohistochemical staining with epithelial markers demonstrated carcinoma cells in the trephine specimen. This case illustrates the difficulty of detecting infiltrating lobular carcinoma in bone marrow and the value of immunological techniques in this context. It also describes the development of bone marrow granulomas as a response to infiltration by carcinoma.

Keywords: bone marrow granulomas; lobular breast cancer; immunohistochemistry.

Granuloma formation is well recognised in lymph nodes draining an area of carcinoma. Granuloma formation in bone marrow has a wide differential diagnosis, including granulomatous infections, sarcoid, drug hypersensitivity, lymphoid, and haemopoietic malignancy. Metastatic carcinoma does not seem to be a widely recognised cause.

**Case report**

A 45 year old woman, with a long psychiatric history, presented in 1991 with a mass in the right breast. Histological examination showed infiltrating lobular carcinoma. A simple mastectomy was performed. She declined further intervention at that stage. In 1993, biopsy of a mass in the left breast showed lobular carcinoma which also involved four axillary nodes. She then had a mastectomy with local radiotherapy followed by five courses of chemotherapy (5-fluorouracil, epirubicin and cyclophosphamide).

In 1995, the patient developed back pain. A bone scan was inconclusive. Magnetic resonance imaging of the pelvis was reported as abnormal but not typical of metastatic disease. Bone marrow was sampled from the posterior superior iliac crest—the findings are given in detail later. The patient was subsequently started on tamoxifen but has not attended regularly for follow up. There was no evidence of tuberculosis or sarcoidosis, and the patient was not on any regular medication.

**Pathology**

The bone marrow aspirate was stained routinely with Giemsa. The aspirate was of normal cellularity with no abnormality detected. Immunostaining with epithelial markers by the APAAP technique was negative. The bone marrow trephine specimen was fixed in Bouin’s solution, decalcified for 24 hours by adding concentrated formic acid to a dilution of 10%, embedded in paraffin wax, and processed using standard techniques. The haematoxylin and eosin stained section revealed a normocellular marrow. The most striking feature was the presence of non-caseating granulomas (fig 1). These granulomas were composed of epithelioid cells and Langhans giant cells. No tumour cells were evident. A Ziehl-Neelsen stain did not show any acid fast bacilli. However, streptavidin-biotin immunoperoxidase staining showed cells which were positive for cytokeratins AE1/AE3 and Cam 5.2 (acidic keratins 40–56.5 kD, basic keratins 52–67 kD), and EMA. These positive cells occurred singly throughout the section, in keeping with micrometastases (fig 2). The granulomas were adjacent to the carcinoma cells.

**Discussion**

Infiltrating lobular carcinoma of breast is difficult to detect in standard haematoxylin and eosin stained sections of bone marrow. Bitter et al distributed 50 core biopsy specimens to three surgical pathologists. Infiltrating lobular carcinoma of breast was correctly identified in only 39% of positive specimens compared with 88% for ductal carcinoma. The low detection rate was explained by the difficulty in distinguishing infiltrating lobular carcinoma cells from haemopoietic cells of similar size, and by their bland cytological features and infiltration as single cells with little tissue reaction. The findings in this case would concur and support the suggestion that trephine specimens from patients with infiltrating lobular carcinoma be immunostained routinely with cytokeratin.

Granuloma formation in regional lymph nodes draining carcinoma, especially breast and cervix, is well recognised. The simultaneous occurrence of granulomas and metastatic carcinoma within the bone marrow is unusual and, to our knowledge, has not been documented previously. No other cause of granuloma formation could be detected in this patient. Quite often, no cause can be established for granuloma formation in the bone.
marrow despite extensive investigation. It is possible that a cell-mediated immune response to soluble tumour-related antigens is the pathogenetic mechanism for granuloma formation in this case.

This case illustrates the difficulty of demonstrating infiltrating lobular breast carcinoma in bone marrow using routine haematoxylin and eosin stains. It shows the value of immunohistological techniques. Demonstration of infiltration can have implications for prognosis and patient management. It also describes the formation of epithelioid granulomas in the bone marrow in response to micrometastases of lobular breast carcinoma.

We thank Dr McAleer for permission to report this case.


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**Leu-M1 immunoreactivity and phaeochromocytoma**

L Masmique, M Castro-Forns, I de Torres, A Garcia, M T Vidal, R Simó

**Abstract**

The aim was to evaluate Leu-M1 immunoreactivity as a prognostic factor in phaeochromocytoma. Anti-Leu-M1 monoclonal antibodies were used to determine the Leu-M1 immunoreactivity in 17 histologically confirmed phaeochromocytomas from 15 patients, using an avidin-biotin technique. Ten patients had a sporadic phaeochromocytoma, and five had multiple endocrine neoplasia type 2A (MEN 2A). Malignancy was diagnosed in three patients by the presence of metastases. Leu-M1 immunoreactivity was identified in 12 (70.5%) phaeochromocytomas. Three patterns of arrangement were observed: isolated (scattered positive cells) (n = 3); focal (aggregates of positive cells) (n = 5), and diffuse patterns (dispersed positive cells) (n = 4). Two cases of malignant phaeochromocytoma were positive (one focal and one isolated pattern). All cases of MEN 2A showed immunoreactivity, although no characteristic pattern was prevalent. A diffuse pattern was observed in all phaeochromocytomas longer than 7 cm. In conclusion, Leu-M1 expression is frequent in phaeochromocytoma. However, Leu-M1 immunoreactivity seems to be useless in predicting malignant behaviour and to be influenced mainly by tumour size.

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**Keywords:** Leu-M1 antigen; phaeochromocytoma; multiple endocrine neoplasia.

Phaeochromocytoma is an infrequent tumour derived from chromaffin tissue. It occurs sporadically but in 10% of cases it is associated

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**Table 1** Clinopathological characteristics of patients studied

<table>
<thead>
<tr>
<th>Clinicopathological characteristic</th>
<th>Case number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>38 33 67 41 48 34 47 33 39 54 28 25 19 58 23</td>
</tr>
<tr>
<td>Sex</td>
<td>M M M F F F F M M M M M M M F F F F F F</td>
</tr>
<tr>
<td>Type</td>
<td>S S S S S S S S S S S S S S S S</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>+ + + + + + + + + + + + + +</td>
</tr>
<tr>
<td>Size (cm)</td>
<td>3.5 2.7 4.5 7.8 5 6.3 8 6 5.5 3.5 5.4 2.5/4 9.5/3</td>
</tr>
<tr>
<td>CM (μmol/24 hours)</td>
<td>3.4 4.9 5.9 1.4 8.4</td>
</tr>
<tr>
<td>VMA (μmol/24 hours)</td>
<td>62.6 58.9 79 272 110 55.7 129 34 56 85 340</td>
</tr>
<tr>
<td>Leu-M1 pattern (intensity)</td>
<td>F (+) D (+++) F (+) D (+) F (+)</td>
</tr>
<tr>
<td>Inflammatory component (Leu-M1 intensity)</td>
<td></td>
</tr>
</tbody>
</table>

*Malignant phaeochromocytomas.
B = bilateral; S = solitary; I = isolated; F = focal; D = diffuse; CM = urinary catecholamines (fluorometric assay, normal range 0.1–0.5 μmol/24 hours); VMA = urinary vanillylmandelic acid (colorimetric assay, normal range 3.6–52 μmol/24 hours).*
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