Paper

Non-epithelial malignancies and metastatic tumours of the breast

Mark E O’Donnell1,4, Mark McCavert1, Jim Carson2, Fred J Mullan3, Michael W Whiteside1, W Ian Garstin.1

Accepted 12 December 2008

ABSTRACT

Introduction: Non-epithelial breast malignancies include primary lymphomas, sarcomas, haematological malignancies, melanomas as well as secondary metastases to the breast. They account for less than 1% of all breast tumours. The demographics and clinical features are similar to epithelial breast cancers but the prognosis and management options are often very different. Most reported series are small with limited follow-up. The main aim of this study was to review our experience for these malignancies and to compare this with the published literature.

Methods: A 14-year retrospective review of all breast resection specimens was completed in the Antrim Area Hospital Cancer Unit. Clinical records of patients presented with non-epithelial breast malignancies were then reviewed for data regarding patient demographics, clinical presentation, pre-operative investigations, operative findings and outcome. Pathology reports were examined carefully for tumour type, location and for evidence of lymphovascular spread. This data was compared with the available literature.

Results: Nineteen (F = 16) patients were found to have non-epithelial breast malignancies between April 1994 and August 2007. Mean age was 61.6 years (range 25-86). 17 patients (89.5%) presented with a palpable lump, mastalgia or skin change, while 2 (10.5%) patients’ tumours were detected through screening. The histological types of non-epithelial malignancies were as follows: lymphoma (n = 8; M = 1 and F = 7, mean age: 68.5 range 52-86), sarcoma (n = 5; M = 1 and F = 4, mean age 56.4 range 29-69), malignant melanoma (n = 3; M = 1 and F = 2, mean age 54.3 range 25-70), multiple myeloma (n = 1; F; 71), metastatic renal cell carcinoma (n = 1; F; 63) and metastatic carcinoid tumour (n = 1; F; 52). The mean follow-up was 1541 days (32-4589 days). Nine patients were alive at the end of follow-up. Only 1 of 11 deaths was not directly related to the malignancy. The average time from surgery to death was 798.5 days (range 32-3248 days).

Conclusion: Non-epithelial breast malignancies are rare cancers with significant mortality rates. Correct diagnosis and avoidance of inappropriate therapies requires a comprehensive triple assessment and a multidisciplinary management approach.

Keywords: Breast, lymphoma, melanoma, myeloma, renal, neoplasm, sarcoma.

INTRODUCTION

Breast cancer is one of the most common cancers in Northern Ireland with an annual incidence of approximately 1000 newly diagnosed cases and over 300 deaths. Between 1993 and 2003, the incidence of breast cancer in Northern Ireland increased by an average of 1.1% per year - equivalent to 20 cases. Worldwide, more than a million women are diagnosed with breast cancer every year, accounting for 10% of all new cancers and 23% of all female cancer cases.

Carcinomas such as ductal and lobular carcinoma are responsible for over 95% of all breast cancers. Non-epithelial breast malignancies include haematogenous and non-epithelial tumours such as lymphoma, sarcoma and metastatic breast neoplasms of neuroendocrine, renal or skin origins. Less than 1% of breast tumours are non-epithelial cancers and between 0.5% and 2% are metastatic deposits. Much less is known about these non-epithelial malignancies of the breast compared with epithelial breast cancers. Most reported series are small with limited follow-up data. Young et al investigated 363,801 patients with newly diagnosed malignant breast cancers between 1994 and 1998 and found that 1401 (0.4%) were non-epithelial in origin. The majority of these were sarcomas. A further 613 tumours were classified as haematopoietic cancers and were mostly lymphomas. The presentation, demographics and clinical features of non-epithelial and epithelial breast malignancies are similar. However, the prognosis and management options are often very different. Our objective was to review all patients diagnosed with non-epithelial malignancies of the breast and to compare our clinical experience with the published evidence.
METHODS

A 14-year retrospective histopathological review of all breast resection specimens was completed in the Antrim Area Hospital Cancer Unit. Clinical records of patients diagnosed with non-epithelial breast malignancies were then reviewed for data regarding patient demographics, clinical presentation, pre-operative investigations, operative findings, treatment and outcome. Investigative modalities were graded in a standardised manner where grade 1 corresponded to normal appearance, grade 2 benign disease, grade 3 atypical or indeterminate but probably benign, grade 4 suspicious of malignancy and grade 5 consistent with malignancy. Pathology reports were examined carefully for tumour type, location and for evidence of lymphovascular spread.

We differentiated primary breast sarcoma from cystosarcoma phyllodes7, therefore, we excluded patients with malignant phyllodes tumours. In the absence of adequate clinical follow-up data in the hospital records, a postal questionnaire was sent to each patient’s General Practitioner. All aspects of adjuvant therapies were documented.

RESULTS

Approximately 3900 patients had a pathological diagnosis of breast cancer between April 1994 and August 2007. Nineteen (F = 16) were found to have non-mammary breast malignancies (Table I). Mean age was 61.6 years (range 25-86). Seventeen patients presented to a symptomatic breast out-patient clinic with either a history of a breast lump, skin change or mastalgia. Two patients were referred to the breast clinic for further follow-up because of a screening detected abnormality on mammography.

The histological types of non-epithelial malignancies were as follows: lymphoma (n = 8, 0.21% of all breast malignancies), sarcoma (n = 5, 0.13%), malignant melanoma (n = 3, 0.07%), multiple myeloma (n = 1, 0.03%), metastatic renal cell carcinoma (n = 1, 0.03%) and metastatic carcinoid tumour (n = 1, 0.03%) (Figures 1 – 5). The mean follow-up was 1541 days (32-4589 days). Nine patients were alive at the end of follow-up. Only 1 of 11 deaths was not disease related. The mean time from surgery to death was 798.5 days (range 32-3248 days).

Lymphoma

Five female patients (patients 1-5 from table I) were diagnosed with a primary breast lymphoma (mean age 70.4 years, range 59-86 years). Four patients presented with a breast lump. An asymptomatic patient was referred from the breast screening unit. All patients had unilateral disease (left = 2, right = 3). The mean duration of symptoms was 37.3 days (range 7-93 days). Three patients had mammography performed (Grade: M3 = 1 from screening, M4 = 2). One patient had an ultrasound scan (Grade: U3). Four patients had FNA cytology performed (Grade: C1 = 1, C3 = 3). The lymphoma diagnosis was made following core biopsy in two cases and excision biopsy in three cases. Pathological analysis identified primary diffuse large B-cell non-Hodgkins lymphoma (NHL) (n = 4) (Figure 1) and a primary MALT-type lymphoma (n = 1). Four patients had chemotherapy with the CHOP regimen (cyclophosphamide, doxorubicin HCl, vincristine (Oncovin), prednisolone). There is no documentation of whether chemotherapy was administered in patients 2 and 4 who both had advanced metastatic disease from their primary breast lymphoma. Patient 3 underwent subsequent radiotherapy for metastatic axillary node disease. Three patients are currently still alive. Patient 5 has had several recurrences and has had further courses of chemotherapy for lung involvement. Patient 1 also required a further course of chemotheraphy for recurrence. Patients 2 and 4 died from metastatic spread of their primary breast lymphoma where the mean time from diagnosis to death was 3248 and 32 days respectively.

![Fig 1](image1.png)

Fig 1. High-grade non-Hodgkin’s breast lymphoma (haemotoxylin and eosin x 200) (Inset CD45 staining). This field shows large blast-like lymphoid cells with conspicuous background apoptosis, features in keeping with a diffuse large B-cell lymphoma.

![Fig 2](image2.png)

Fig 2. Breast sarcoma (H&E x 200). This field shows large spindle shaped cells with nuclear pleomorphism and eosinophilic cytoplasm. There is no differentiation which would indicate the cell of origin.

Three patients (patients 6-8 from table I, male = 1) were
diagnosed with a metastatic breast lymphoma from a remote primary lesion (mean age 65.3 years, range 52-79 years). All three patients presented with a breast lump while one complained of mastalgia. All patients had unilateral disease (left = 2, right = 1). The mean duration of symptoms was 186.0 days (range 7-365 days). One patient had mammography performed (Grade: M4). One patient had an ultrasound scan (Grade: U4). Two patients had FNA cytology performed (Grade: C2 = 1, C5 = 1). The lymphoma diagnosis was made following core biopsy in one case and excision biopsy in two cases. Pathological analysis identified the presence of metastatic B-cell NHL in all three patients. Two patients had chemotherapy with the CHOP regimen. Patient 6 underwent simple mastectomy without adjuvant therapy. Patient 8 underwent subsequent radiotherapy to treat cerebral metastases. Unfortunately all three patients have died where the mean time from diagnosis to death was 775, 1045 and 133 days for patients 6-8 respectively.

**Sarcoma**

Three patients (patients 9-11 from table I, male = 1) had primary breast sarcomas (fig 2) with an average age of 50.7 years (range 29-65 years). All patients presented to our symptomatic breast clinic with either a lump (n = 2) and/or mastalgia (n = 2) (left = 2, right = 1). The mean duration of symptoms was 192 days (range 31-365 days). Patients 9 and 10 had palpable masses whereas patient 11 had minimal localised thickening only. Patients 9 and 10 had positive mammograms (M4 = 2) while patients 10 (U4) and 11 (U1) had ultrasound assessments. Fine needle aspiration was positive in patient 9 (C5) but insufficient in patient 11 (C1). Patient 9 underwent simple mastectomy and axillary node clearance for a primary rhabdomyosarcoma where immunohistochemical labeling was positive for actin (smooth muscle) and negative for epithelial markers. Despite adjuvant chemo- and radiotherapy, she died 553-days post-surgery. Patient 10 had a simple mastectomy for dermatofibrosarcoma protruberans and remains well 380-days later. Although ultrasound, magnetic resonance imaging (MRI) and FNA cytology investigations were normal patient 11, further investigation was arranged due to a persistent clinical suspicion of a possible lesion. A subsequent ultrasound-guided excisional biopsy demonstrated an angiosarcoma. She proceeded to simple mastectomy with adjuvant radiotherapy followed by delayed breast reconstruction one-year later. She remains well 1415 days following her initial breast surgery.

Two female patients (patients 12-13 from table I), aged 69 and 61, were diagnosed with metastatic sarcomas from distant primary neoplasms. Patient 12 had a previous primary thigh liposarcoma resection while patient 13 had a previous excision of a primary retroperitoneal leiomyosarcoma. Both of these patients presented with painless lumps in the left breast. The mean duration of symptoms was 5 days (range 3-7 days). Patient 12 had a positive mammogram (M4) and FNA (C5) with confirmation of sarcoma following core biopsy with vimentin positive immunohistochemical labeling while other epithelial, neural (S100) and muscle (actin and desmin) markers were negative. She was treated with palliative chemo- and radiotherapy and died 679 days later. Patient 12 had a positive mammogram (M4) and FNA (C5) with confirmation of sarcoma following core biopsy. Patient 12 did not undergo surgery as staging investigations had shown widespread metastatic disease. She was treated with palliative chemo- and radiotherapy and died 679 days later. Patient 13 proceeded directly to lumpectomy. She refused adjuvant therapy and remains well 2980-days following lumpectomy and has had further surgery for abdominal wall recurrences in the interim.

**Malignant melanoma**

Three patients (patients 14-16 from table I, male = 1) had a malignant melanoma with an average age of 54.3 years (25-70 years). These patients presented with an enlarging naevus on the right breast (patient 14), a superficial nodule on the left breast (patient 15) and a right-sided breast lump (patient 16). The mean duration of symptoms was 699 days (range 93-1825 days). Patient 14 had palpable axillary nodes and proceeded directly to excision biopsy with ANC. A mastectomy was subsequently required due to involved breast margins from deeper infiltration of the primary melanoma. Although further adjuvant treatment was declined, the patient remains disease-free. Patient 15 had been treated 3-years earlier for metastatic melanoma with lung involvement from a separate lesion on the left arm but was thought to be in remission. In view of the history she proceeded straight to excisional biopsy of the left breast nodule and pathology showed malignant melanoma. She received adjuvant chemotherapy and immunotherapy but developed lung metastases 3-years later. Following further oncological therapy the patient has been disease-free for the last 9-years. Patient 16 had been treated with chemotherapy 8-years previously for a cutaneous malignant melanoma of her left lower limb and was also thought to be in remission. She had both USS and mammogram investigations (U = 4, M = 4). Subsequent FNA and core biopsy confirmed malignant melanoma (Figure 3). Despite palliative radiotherapy, this patient died 7-weeks later from metastatic disease.
Metastatic multiple myeloma

Patient 17 (F, 71) presented with a 28-day history of a rightsided breast lump. She had a history of multiple myeloma and left mastectomy 4-years earlier for a metastatic myelomatous deposit. Although mammography was indeterminate (M = 3), ultrasound imaging was suspicious of malignancy (U = 4). Subsequent FNA and core biopsy investigations were indeterminate. Excisional biopsy confirmed metastatic multiple myeloma which was treated with adjuvant chemotherapy (melphalan in combination with prednisolone and allopurinol) (Figure 4). The patient died from metastatic disease 342 days later.

DISCUSSION

We will discuss the various types of non-epithelial breast malignancies, with particular emphasis on epidemiology, symptomatology, investigation, pathology, and current management strategies for each particular type, with reference to our own experience over the last 14-years.

Metastatic carcinoid tumour

Patient 18 (F, 52) was referred from the breast-screening department with an abnormality in the right breast. USS and FNA investigations were equivocal and suggested fibroadenosis. Core biopsy suggested invasive ductal carcinoma and she proceeded to WLE and ANC. Histopathology analysis confirmed a grade-1 carcinoid tumour without nodal involvement. She proceeded to a simple mastectomy and was subsequently referred to the regional neuroendocrine department. Although she had no clinical evidence of carcinoid syndrome, she was commenced on the somatostatin analogue lanreotide. She was subsequently referred for gastrointestinal screening where a primary carcinoid tumour was detected in the distal small bowel 9-months following her initial breast surgery. A small bowel resection was then performed and she remains well on lanreotide with no evidence of carcinoid syndrome.

Metastatic renal cell carcinoma

Patient 19 (F, 63) presented with a seven-day history of a rightsided breast lump. Past medical history included left nephrectomy for renal cell carcinoma 4-years previously and she had known bony metastases. Mammogram and USS were suspicious of malignancy (M = 4, U = 4). FNA showed malignant cells and core biopsy confirmed metastatic renal cell carcinoma (Figure 5). Wide local excision and ANC was performed and the patient received chemotherapy. A subsequent CT scan revealed widespread metastases. She died 1128 days later.

Lymphoma

Epidemiology: The reported incidence of primary breast lymphoma (PBL) in the literature ranges from 0.04% to 0.5% for all breast malignancies. It is estimated that the breast is involved in less than 1% of all patients with non-Hodgkin’s lymphoma and approximately 1.7% of extra-nodal non-Hodgkin lymphomas. Secondary spread of lymphomas to the breast is reported to account for just 0.07% of all breast malignancies. However, these secondary lymphomas comprise the largest group (17%) of tumours that metastasise to the breast. Our experience was similar with an incidence of 0.13% for PBL and 0.08% for secondary breast lymphomas.

Symptomatology: Wiseman and Liao defined the clinical criteria for the diagnosis of PBL where; the breast is the clinical site of the first major manifestation of the lymphoma, there is no history of previous lymphoma or widespread lymphomatous disease elsewhere and that the lymphoma is demonstrated with close association to breast tissue in the pathologic specimen. They also state that ipsilateral lymph nodes may be involved if they develop simultaneously with the primary breast tumour.

The reported median age for primary and secondary breast lymphoma ranges from 51 to 61 years. The patients in our study were slightly older (mean 70.4 and 65.3 years for primary and secondary lymphomas respectively).

© The Ulster Medical Society, 2009.
TABLE I:

Clinical data for all 19 patients

| NO | Age | Sex | Symptom | Investigations | Diagnostic (+/- therapeutic) procedure | Pathological Diagnosis | Treatment | Current Status | Length of follow-up (days) |
|----|-----|-----|---------|---------------|----------------------------------------|------------------------|-----------|---------------|---------------------------|
| 1  | 59  | F   | L       | Mam USS       | EB                                     | PBL                    | C         | Alive (recurrence 2003) | 2741                      |
| 2  | 83  | F   | L, P    | n/a n/a      | WLE                                    | PBL                    | Palliative | Dead          | 3248                      |
| 3  | 63  | F   | L       | n/a n/a      | EB                                     | PBL                    | Dx, C      | Alive          | 4589                      |
| 4  | 86  | F   | L       | n/a n/a      | EB                                     | PBL                    | Palliative | Dead          | 32                        |
| 5  | 61  | F   | SC      | + n/a        | WLE                                    | PBL                    | C         | Alive; several recurrences | 3150                      |
| 6  | 79  | F   | L       | n/a n/a      | CB                                     | SBL                    | SM        | Dead          | 775                       |
| 7  | 52  | M   | L       | n/a n/a      | EB                                     | SBL                    | C         | Dead          | 1045                      |
| 8  | 65  | F   | L, P    | + +          | FNA/CB                                 | SBL                    | Dx, C      | Dead          | 133                       |
| 9  | 58  | F   | L, P    | + n/a        | FNA                                    | PBS (rhabdomyosarcoma) | SM+ANC, Dx, C | Dead          | 553                       |
| 10 | 65  | M   | L       | + +          | SM                                     | PBS (dermatofibrosarcoma) | SM        | Alive          | 380                       |
| 11 | 29  | F   | P       | n/a -        | FNA / US-guided EB                     | PBS (angiosarcoma)     | SM, Dx     | Alive          | 1415                      |
| 12 | 69  | F   | L       | + n/a        | FNA/CB                                 | Metastatic liposarcoma from primary thigh lesion | Palliative C, Dx | Dead          | 679                       |
| 13 | 61  | F   | L       | n/a n/a      | L                                      | Metastatic leiomyosarcoma from primary retroperitoneal lesion | L- | Alive; several recurrences | 2980                      |
| 14 | 59  | M   | S       | n/a n/a      | EB                                     | Malignant Melanoma     | EB+ANC; SM later | Alive          | 373                       |
| 15 | 25  | F   | L       | n/a n/a      | EB                                     | Metastatic melanoma    | EB, C, I   | Alive          | 4470                      |
| 16 | 70  | F   | L       | + +          | FNA/CB                                 | Metastatic melanoma    | Palliative | Dead          | 50                        |
| 17 | 71  | F   | L       | + +          | EB                                     | Metastatic multiple myeloma | EB, C     | Dead          | 342                       |
| 18 | 52  | F   | SC      | + -          | WLE                                    | Metastatic Carcinoid   | WLE+ANC - | Alive          | 1210                      |
| 19 | 63  | F   | L       | + n/a        | FNA/CB                                 | Metastatic renal cell carcinoma | WLE+ANC, Dx | Dead          | 1128                      |

(symptom: L = lump, P = pain, S = skin change, SC = screening detected abnormality; investigations: Mam = mammography, US = Ultrasound, n/a = not performed or result not available, + = abnormality detected, - = abnormality not detected; diagnostic (+/- therapeutic) procedure: WLE = wide local excision, SM = simple mastectomy; ANC = axillary node clearance, EB = excisional biopsy, L = lumpectomy, CB = core biopsy; Pathological diagnosis: PBL = primary breast lymphoma, SBL = secondary breast lymphoma, PBS = primary breast sarcoma; Treatment: Dx = radiotherapy, C = chemotherapy, I = immunotherapy).

a benign or less suspicious lesion on clinical assessment even though some reports state that lymphomas are larger at diagnosis than carcinomas. Skin changes or nipple discharge are uncommon. Previous reports document a right-sided predominance. However, recent studies have not supported this and in our series there was equal involvement bilaterally. Axillary lymph nodes are involved in 30-40% of cases. Only one patient in this series had palpable nodes (patient 8). The presence of B symptoms (fever, night sweats and weight loss) is uncommon.

Investigation: Radiologically, You et al described lymphomas as oval-shaped and high-density masses on mammography and as single and hypoechoic masses with circumscribed or microlobulated margins on ultrasonography. The detection...
of PBL by screening mammography, as occurred in the case of patient 5, is rare. The reported sensitivity of FNA cytology in breast lymphoma is approximately 90% and is most sensitive when combined with immunohistocytochemistry (IHC) or flow cytometry. In addition to histological analysis, further radiological staging is recommended with CT imaging of the chest, abdomen and pelvis to detect any evidence of visceral or nodal dissemination.

**Pathology:** The most common histological type reported in the literature when primary and secondary cases are grouped together is diffuse large B-cell lymphoma which represents 45% to 90% of all cases. Burkitt-type lymphoma, and mucosa-associated lymphoid tissue–type lymphoma have also been documented.

**Treatment:** In our series, surgical biopsy was required for diagnosis in the majority of patients and excision was part of treatment in several patients treated in the earlier part of the study period. In contrast to epithelial breast neoplasms, it is now accepted that surgical resection is usually only indicated for diagnostic purposes in PBS. Jennings et al. reported that mastectomy conferred no improvement in survival or recurrence risk. They also reported that combined chemoradiotherapy improved survival and recurrence rates in both stage I (node negative) and stage II (node positive) patients. CHOP is the standard chemotherapy regimen. The addition of the monoclonal antibody rituximab is occasionally indicated and had been used in the treatment of recurrent disease in Patient 5.

**Prognosis:** Histological tumour grading and stage can be used to predict patient outcomes. The use of the International Prognostic Index which evaluates risk factors such as Ann Arbor stage, extranodal disease, elevated LDH levels and performance status on echocardiography is limited in PBL. The prognosis for PBL is generally poor with improved survival in patients with low-grade disease. Reported five-year survival rates in PBL are 78-89% for stage I patients and 50% for stage II. Three of the five patients (60%; 2 low-grade, 1 high-grade) with PBL in this series survived beyond five years.

**Sarcoma**

**Epidemiology:** Primary breast sarcomas (PBS) are reported to account for less than 0.1% of all breast malignancies. The incidence of PBS in our series was 0.08%. Although PBS typically affects women in their Forties or Fifties, a wide age range has been reported (24-81 years). The average age of patients in this series was similar (mean age 50.7 years). PBS occurs very rarely in men. Radiotherapy has been implicated in the aetiology of some sarcoma types especially angiosarcoma. No cause was identified for any of the patients in our series. Angiosarcoma of the breast accounted for 0.3% of all breast malignancies in this series, which compares with the 0.04% reported in the literature. Angiosarcomas also occur in younger patients with an age range between 20 and 40 years (patient 11). Symptomatology: PBS most commonly presents as a painless breast lump. Sarcomas tend to spread locally or haematogenously and do not usually spread to regional lymph nodes. Each of the five patients included in this series had palpable breast lumps with no evidence of axillary lymphadenopathy.

**Investigation:** Radiologically, PBS are generally ill-defined lesions without calcification and may be mistaken for fibroadenomas. A combination of ultrasound and MRI has been recommended for investigation of angiosarcoma. However, both modalities failed to detect an angiosarcoma in patient 11 from our series. Therefore, if clinical suspicion persists, the authors recommend further pathological assessment even if these modalities appear normal. Although FNA cytology permits the diagnosis of sarcomatous lesions, it does not facilitate subtyping or tumour grade. Core-needle or excisional biopsies are therefore invariably required.

**Pathology:** Malignant fibrous histiocytoma, fibrosarcoma, angiosarcoma, stromal sarcoma, leiomyosarcoma and liposarcoma comprise the major subtypes of breast sarcomas. Proportional figures of each subtype vary between case series because of differences in classification.

**Treatment:** Excluding angiosarcomas, current evidence suggests that PBS have a similar course to sarcomas arising at any other site. Surgical resection remains the most important treatment factor influencing outcome. All patients in our series underwent surgical resection apart from patient 12 who was known to have widespread metastatic disease which was treated with palliative chemoradiotherapy. Patient 9 had ANC in addition to resection as FNA and core biopsy respectively had suggested an epithelial malignancy. McGowan et al. showed no statistically significant cause-specific survival difference between breast-conserving surgery and mastectomy if negative margins were achieved. Wide local excision should be adequate in most cases as tumour multicentricity and axillary spread is rare. There is no conclusive evidence that radiotherapy is beneficial in PBS. However, as radiotherapy has been shown to be beneficial in the treatment of other sarcomas, adjuvant radiotherapy may be indicated for PBS patients with questionable or positive margins, high-grade features and those that are larger in size. The role of chemotherapy in the treatment of PBS is also unclear.

**Prognosis:** PBS is an aggressive tumour. Prognosis is based on tumour size and histological grade. Other reported prognostic indicators include the age of the patient, tumour subtype and the presence of positive margins. Zelek et al. reported overall survival rates of 82%, 62% and 36% for patients with grades one, two, and three breast sarcomas respectively. Angiosarcomas have been linked with a poorer prognosis.

**Metastatic Spread to the Breast**

**Epidemiology:** Metastatic spread to the breast from primary tumours at other sites in the body is rare. A retrospective review over a 16-year period showed that non-haematological metastases accounted for 0.2% of all breast malignancies treated. There was a female predominance and the most frequent types of non-haematological tumours spreading to the breast were malignant melanoma and neuroendocrine tumours such as carcinoid. Malignant melanoma of the breast skin, as shown in patient 14, accounts for less than 5% of all malignant melanomas whereas melanoma metastases to the breast, as demonstrated in patients 15 and 16, accounts for 1.2% of all malignant melanomas. Carcinoid tumours...
in the breast may occur as metastases from a known carcinoid primary tumour, as the first presentation of a carcinoid tumour (patient 18), or as a primary carcinoid breast malignancy. Following a review of all documented cases in the literature, Upalakalin et al estimated that 41% of all carcinoid tumours in the breast were metastases from elsewhere. There are only isolated case reports documenting renal cell carcinoma metastasising to the breast. Although metastases were present in approximately 30% of patients with renal cell carcinoma, the breast was rarely involved. As overall survival from metastatic disease improves, the incidence of secondary breast malignancies is likely to increase in number.

Symptomatology: The majority of patients have a known primary tumour. However, some patients will present with occult primary disease where the breast metastases are the first manifestation of the disease. Patient 18 in this series presented with metastatic carcinoid of the breast and subsequent investigations identified a small bowel carcinoid. In the review of metastases from a variety of different primary sites, Vaughan et al reported an average time between the diagnosis of the initial primary malignancy and development of a metastasis to the breast of 60.9 months. We identified a similar time interval for patients with non-haematological breast metastases (Patients 12, 13, 15, 16, 18, 19) of 49.7 months (0-102 months). Metastases to the breast are usually mobile, well-demarcated and firm. Skin changes or mastalgia are unusual but axillary lymphadenopathy is often seen. Clinical differentiation between metastases to the breast and primary cancers is difficult. In melanoma, the patient will usually be menopausal and have had a primary lesion on the upper body. The presence of clinically significant extrasosseous features in myelomatous metastases occur in less than 5% of cases and usually signifies aggressive disease. Carcinoid syndrome is usually not a feature of carcinoid tumours of the breast. If a patient with a breast lump also has symptoms of carcinoid syndrome then the lump should be biopsied to exclude metastatic carcinoid from a primary elsewhere.

Investigation: These malignancies show a wide range of mammographic and ultrasonic appearances. They often appear as round, well-circumscribed lesions without the microcalcifications of primary epithelial malignancies and may be misinterpreted as benign lesions. Ultrasound commonly shows hypoechoic masses. FNA or ultrasound guided core biopsy is advisable to diagnose breast lumps that either clinically or radiographically are not typical of primary breast tumours.

Pathology: Vergier et al reported that histological characteristics of metastases included the presence of well-circumscribed tumours with multiple satellite foci, an absence of an intraductal component or the presence of lymphatic emboli. Histologically, carcinoid tumours of the breast may be misdiagnosed as epithelial malignancies even when the patient has a known history of a carcinoid tumour elsewhere. An accurate diagnosis of a breast metastasis is important to avoid unnecessary mastectomy and to implement appropriate investigations for the primary lesion and to commence systemic chemotherapy if indicated.

Treatment: Deciding which treatment is most appropriate can be challenging in these cases as it is often difficult to predict if and when a patient will develop complications of metastatic disease. There is little information in the literature regarding best practice. In the study by Vaughan et al, 61% of patients underwent some form of resection but only 22% of these patients had their resection for a curative intent. Surgical debulking or excision for palliative purposes may be appropriate in widely metastatic disease. In cases of melanoma of the breast without multiple deposits, WLE or quadrantectomy is acceptable. For solitary multiple myeloma of the breast, a localised biopsy with radiotherapy has been recommended, with chemotherapy reserved for disseminated disease. With regards to primary carcinoid tumours of the breast, modified radical mastectomy or breast conserving surgery with ANC and radiotherapy has been advised. Patients with metastatic carcinoid tumours should undergo lumpectomy alone.

Prognosis: There is limited data in the literature regarding the prognosis of these patients but breast metastases usually indicate disseminated metastatic disease and a poor prognosis. As new systemic treatments emerge however survival rates may improve. Vaughan et al reported a mean survival time of 17.8 months following the diagnosis of a breast metastasis of non-haematological origin. Survival was similar regardless of primary site apart from patients with medullary thyroid cancer who survived for longer. In this study, three patients with non-haematological metastases to the breast died (patients 12, 16 and 19) with a mean survival time of 619 days (approximately 20 months). Median survival in a review of 27 cases of melanoma metastases to the breast was 12.9 months.

CONCLUSION

Non-epithelial malignancies of the breast include primary breast tumours such as lymphoma and sarcoma and metastatic deposits from primary tumours elsewhere in the body. They are rare cancers with a female predominance. Nineteen patients were identified in this 14-year retrospective review accounting for 0.49% of all breast malignancies treated. A thorough history and triple assessment is required to correctly identify these cancers as clinical and radiological differentiation from the more common epithelial cancers is often challenging. Primary breast sarcomas require surgical excision and adjuvant therapy whereas lymphomas can be predominantly managed with oncological therapies alone. Management of metastases to the breast depends on a number of factors including tumour type and extent of metastatic disease.

Conflict of interest - the authors have no conflict of interest.

REFERENCES

1. Department of Epidemiology and Public Health, Queen’s University of Belfast. Northern Ireland Cancer Registry. Online statistics. Belfast, Northern Ireland: NICR; 2007. Available online from: http://www.qub.ac.uk/research-centres/nicr/Data/OnlineStatistics/Breast#breast_mort. Last accessed January 2009

2. Fitzpatrick D, Gavin A, Donnelly D. Department of Epidemiology and Public Health, Queen’s University of Belfast. Cancer trends in Northern Ireland 1993-2003. Northern Ireland Cancer Registry. Belfast, Northern Ireland: NICR; 2006. Available online from: http://www.qub.ac.uk/research-centres/nicr/FileStore/PDF/FileUpload/32872_en.pdf . Last accessed January 2009.
8. Duncan VE, Reddy VV, Jhala NC, Chhieng DC, Jhala DN. Non-Hodgkin's Lymphoma. Cancer Causes Control 2004;15(2):313-9.

5. You JL Jr, Ward KC, Wingo PA, Howe HL. The incidence of malignant non-carcinomas of the female breast. Cancer Causes Control 2004;15(2):313-9.

4. Berg JW, Hutter RV, Percy C, Young JL Jr, Muir C. Histology of cancer incidence and prognosis: SEER Population-Based Data, 1973-1987. Cancer 1995;75(Suppl 1):139-421.

3. Ferlay J, Bray F, Pisani P, Parkin DM. Globocan 2002: Cancer incidence, mortality and prevalence worldwide, IARC CancerBase No.5, Version 2.0. Lyon: IARCPress; 2004. Available online from: http://info.cancerresearchuk.org/cancerstats/geographic/world/incidence/. Last accessed January 2009.

2. Berg JW, Hutter RV, Percy C, Young JL Jr, Muir C. Histology of cancer incidence and prognosis: SEER Population-Based Data, 1973-1987. Cancer 1995;75(Suppl 1):139-421.

1. Berg JW, Hutter RV, Percy C, Young JL Jr, Muir C. Histology of cancer incidence and prognosis: SEER Population-Based Data, 1973-1987. Cancer 1995;75(Suppl 1):139-421.