Carcinoma of breast co-existing with non-Hodgkin's lymphoma of axillary lymph nodes

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ABSTRACT

نادرا ما وصف وجود سرطان الثدي مع الورم اللمفاوي في العقد اللمفاوية في الإبط بغياب تاريخ معالجة كيميائية أو إشعاعية سابقة، يصف هذا البحث حالة امرأة تبلغ من العمر ٥٠ عاما شخصت لديها كتلة في الصدر أثبت الفحص أنها من نوع سرطان الثدي المخاطي، بعد فحص العقد اللمفاوية في الإبط التي أرسلت بعد تجريف الإبط أظهرت ترافق الورم اللمفاوي صغير الخلايا/ابيضاض الدم اللمفاوي المزمن بدون دليل على وجود انتقالات سرطانية ثديية، يصف البحث هذا الترابط غير المألوف وتراجع الأدبيات حول الموضوع.

The co-existence of breast carcinoma and lymphoma in the axillary lymph nodes, without a history of previous chemotherapy or radiotherapy is rarely described. We present a case of a 50-year-old female with right breast mass, proved by pathological examination to be invasive mucinous carcinoma. Examination of the axillary lymph nodes as axillary clearance showed concomitant small lymphocytic lymphoma and chronic lymphocytic leukemia, with no evidence of metastatic mammary carcinoma deposits.

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Multiple primary malignant neoplasms occurring in the same patient are rare. Combined tumors are defined as tumors discovered simultaneously, during the investigation and the treatment course of one tumor. They form a subtype of synchronous tumors defined as tumors diagnosed within a period of 6 months. The association of non-Hodgkin's lymphoma (NHL) and carcinoma is described in several case reports. The co-existence of breast carcinoma and NHL is a well-described finding after chemotherapy and radiotherapy for patients with breast carcinoma. However, the existence of both tumors in the same patient at the initial time of diagnosis, without previous treatment has rarely been described.[1] This report documents the unusual association between mucinous breast carcinoma and small lymphocytic lymphoma and chronic lymphocytic leukemia in our patient, as well as to touch on possible explanation for this association.

Case Report. A 50-year-old female, presented with a right breast lump of 7 years duration. Her mother died of breast carcinoma at the age of 70. On examination a slightly tender, soft, retroareolar right breast mass was palpated. The right axilla contained multiple discrete enlarged lymph nodes. The left breast was unremarkable. On further examination, the left axilla and both inguinal regions contained palpable lymph nodes. Mammography proved the presence of the right breast mass (**Figure 1**) and ipsilateral enlarged axillary lymph nodes. Fine needle aspiration of the breast mass revealed infiltrating ductal carcinoma. Staging workup included complete blood count, liver function tests, cancer antigen (Ca), chest x-ray, liver ultrasound, and bone scan. The lactic dehydrogenase and the tumor marker Ca 15.3 were slightly elevated. The white blood count showed absolute lymphocytosis of mature lymphocytes ($39.2x10^3/mm^3$, normal range: 1.0-4.8 $x10^3/mm^3$), suggesting the diagnosis of chronic lymphocytic leukemia.

Pathological findings. Excisional biopsy for the right breast mass and axillary lymph node dissection were performed. Gross examination of the breast mass revealed a well circumscribed soft tissue mass 40x40x25 mm. Several discrete lymph nodes were dissected from the axillary fat. By microscopy; the mass was infiltrating ductal carcinoma of mucinous type (**Figure 1a**). All axillary lymph nodes examined showed no evidence of metastatic deposits. Instead, there was total effacement of the architecture by small lymphocytes with round nuclei and clumped chromatin (**Figure 2a**). Proliferation

centers; characterized by medium-sized lymphocytes with vesicular nuclei and nucleoli, were also seen. The impression was that of involvement of the lymph nodes by non-Hodgkin's lymphoma of SLL/CLL type.

Further diagnostic and staging work up for SLL/CLL included bone marrow aspirate and trephine biopsy with flowcytometry and CT scan for chest, abdomen and pelvis. The bone marrow smears contained numerous mature looking lymphocytes and the trephine biopsy revealed cellular marrow with diffuse pattern of involvement. The bone marrow aspirate flow cytometric immunophenotypic findings of monoclonal kappa positive B-cells which coexpressed CD19 and CD5 and had weak surface immunoglobulin, was diagnostic of SLL/CLL. An extensive retroperitoneal lymphadenopathy and increase in liver span were found in the CT scan. The patient was categorized as stage II according to Rai-Sawitsky staging system[2] for SLL/CLL. The patient refused further radiotherapy treatment for the breast carcinoma. However; she was started on chemotherapy regimen for CLL due to the extensive lymphadenopathy and lymphocytosis (cyclophosphamide 300 mg and prednisolone 30 mg daily). After 51 months of follow up she had neither breast carcinoma recurrence nor SLL/CLL relapse.

Immunohistochemical findings. Immunostains on the breast mass and the lymph nodes were performed as routinely described and **Table 1** lists all the antibodies used and their sources. Four µm sections were cut and mounted onto coated slides. Antigen retrieval by heat-induced epitope retrieval is carried out, except for CD20 primary antibody. All slides were then washed with PBS for 5 minutes and visualized using a 0.05% solution of DAB for 5-10 minutes. Positive and negative controls were used. The breast mucinous carcinoma stained positive with ER, PgR and scored 0 with Her-2/neu. CD20, CD5 (**Figure 2b**) and CD23 were positive in the lymph node, while CD3 and CD10 were negative, confirming the SLL/CLL diagnosis in the lymph node. The proliferative marker Ki67 showed low proliferative index apart from the proliferative centers in which the labeling index was increased. The findings were in keeping with concomitant breast invasive mucinous carcinoma and SLL/CLL. Retrospectively, and based on the literature review, CD5 was performed on the breast invasive mucinous carcinoma and there was strong cytoplasmic positivity in the tumor islands within the mucin pools (**Figure 1b**).

Table 1 - List of the primary antibodies used in the study.

Specificity	Antibody	Source
ER	Clone 1D5	Dako. Denmark
PR	Clone PgR-636	Dako, Denmark
Her-2/neu	Clone CB-11	Biogenex, USA
CD20	L-26	Biogenex, USA
CD3	Clone PS1	Biogenex, USA
CD5	Clone 4C7	Biogenex, USA
CD10	Clone CD-10-270	Novocastra, UK
CD23	Clone 1B12	Novocastra, UK
Ki-67	Clone Ki-88	Biogenex, USA

Discussion. Synchronicity of malignant tumors, defined as the occurrence of two tumors within a six-month period in the same patient, is rare. In an autopsy study; 68 out of 1870 cancer cases had multiple tumors (3.6%) 3. Synchronous and combined tumors were seen in 19/68 (27.9%) cases. For breast carcinoma patients, 8% were shown to develop multiple primary malignant tumors.[4] Genetic predisposition, immunological

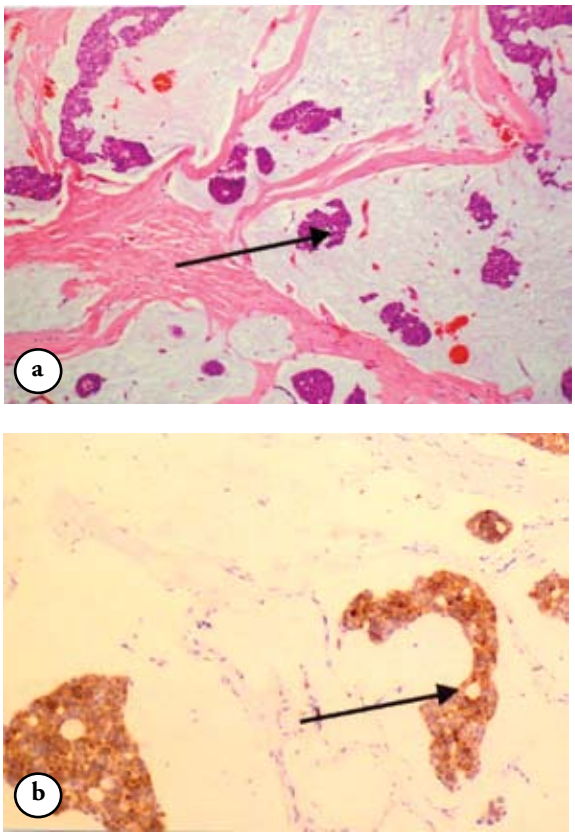

Figure-1 - Histopathological findings showing **a)** epithelial clusters within mucin lakes in breast mucinous carcinoma H&E and **b)** CD5 positivity in mucinous carcinoma of the breast.

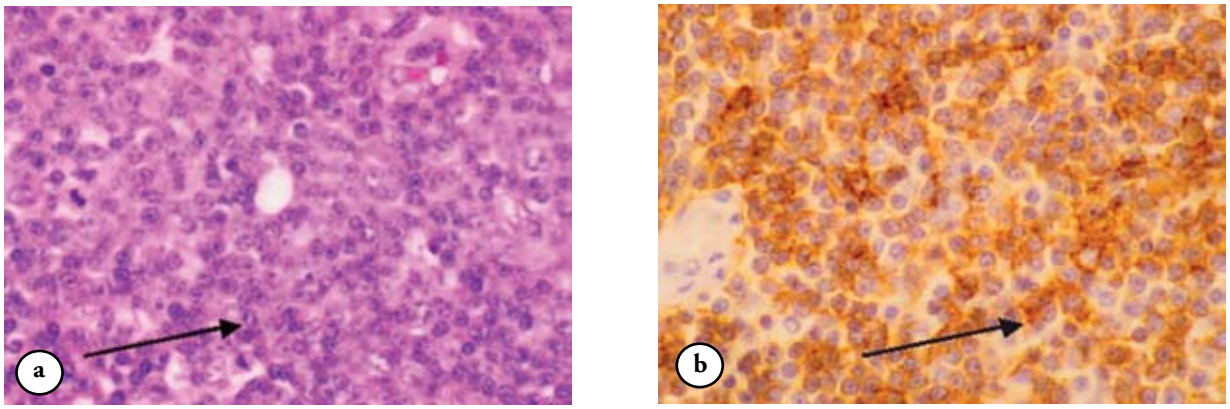

Figure 2 - Histopathological findings showing **a)** Sheets of small neoplastic lymphocytes from the axillary lymph nodes with small lymphocytic lymphoma/chronic lymphocytic leukemia hematoxylin and eosin and **b)** CD5 positivity A in the lymph node.

disturbances or common environmental influences may play a role in the predisposition to concomitant tumors, although multiple tumors may coincide by chance.[1,3] Cancer therapy predisposes individuals to the development of a second cancer. However; this possibility can be excluded in cases of combined or synchronous tumors. According to Lee et al, the most common primary malignant tumor occurs in the hematopoietic system and the cervix, while the second tumor occurs mostly in the lungs and the hematopoietic system. Small lymphocytic lymphoma/chronic lymphocytic leukemia is one of the most common types of lymphoma accounting for 6.7% of non-Hodgkin's lymphomas.[5] It occurs in old patients with a male: female ratio of 2:1. Most patients are asymptomatic. Pathologically it is characterized by total effacement of the lymph node architecture by a "sea of small round mature looking lymphocytes", interposed by less mature looking, larger lymphocytes with vesicular nuclei and prominent nucleoli, or prolymphocytes, arranged in proliferative centers. The leukemic picture is confirmed by the presence of peripheral blood lymphocytosis. The association of SLL/CLL with another primary malignancy has been noted several times, which could be explained partially by the impairment of the immune system caused by SLL/CLL.[3,6] Breast carcinoma is the most common type of malignancy in females. It is the most frequent cancer in females in Jordan according to the Jordanian National Cancer Registry.[7] Lymph node metastasis remains one of the most powerful prognostic factors, and axillary lymph node clearance for the assessment of lymph node metastasis is performed routinely in cases of invasive mammary carcinoma. The occurrence of breast carcinoma and non-Hodgkin's lymphoma in the same patient is rarely described in the literature. This association is well documented following chemotherapy and/or radiotherapy in the context of the carcinoma treatment.[8,9] It is postulated that the lymphoma represents a complication of the previous treatment. However; their association in the absence of previous history of treatment is described only in few case reports.[1,9,10] CD5 is a pan T-cell marker that can be expressed by the B-cells in SLL/CLL.[5] It can be detected in few examples of carcinoma of various location,[11] especially thymic carcinoma. In one previous report,[10] CD5 positivity was detected in both the SLL/CLL and the breast carcinoma, a finding similar to the current case. Deletion in the band 13q14 is the most common genetic abnormality in SLL/CLL and is detected in >50% of cases,[13] where a tumor suppressor gene is found. The BRCA-2 is a tumor suppressor gene involved in breast familial carcinoma and is located at 13q12-13.[14] This patient has a family history of breast carcinoma, which raises the possibility of the presence of genetic predisposition. The close location of BRCA-2 gene and SLL/CLL gene might offer an explanation for the association between the two tumors in this patient. Although the lymph nodes harboring the lymphoma may contain foci of metastatic carcinoma,[15,16] many cases reported, including our case, showed no evidence of metastatic deposits in the lymph nodes.[10,11] This might be related to the infrequent lymph node metastasis in mucinous carcinoma. However; other suggested mechanisms are the occlusion of the lymph node sinuses by the lymphoma cells, as well as interference with the immunological interaction between the tumor cells and the surrounding lymphocytes, which hinder the metastatic process. One important point to emphasize is that regional lymph node enlargement in cases of carcinoma, detected during clinical examination

and imaging, does not mandate metastatic deposits. Excision and examination of the nodes pathologically to establish the underlying cause of the nodal enlargement and to exclude, though rare, the occurrence of a second malignancy is needed. Treatment options should be offered for the patient. Small lymphocytic lymphoma/chronic lymphocytic leukemia is known to be an indolent lymphoma, but is not usually considered curable with available treatment, although purine nucleoside analogues may result in sustained remissions.[5]

In summary, we hereby present a case of an unusual association between invasive mucinous carcinoma of the breast and lymphoma in a patient, without a previous history of treatment.

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