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# Primary Non-Hodgkin's Lymphoma of Breast Masquerading as Inflammatory Breast Cancer Clinically in a Patient on TNF Alpha Inhibitors

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ABSTRACT

**Background**: Primary non-Hodgkin's lymphoma of the breast is an aggressive and rare disease with DLBCL (Diffuse Large B Cell Lymphoma) being the most common variant followed by Marginal zone lymphoma (MZL), follicular lymphoma (FL) and Burkitt's lymphoma. Out of these, MZL and FL are less aggressive variants unless they undergo transformation. Primary breast lymphoma can mimic inflammatory breast cancer clinically due to peau d'orange appearance of the overlying skin. Association of primary breast lymphoma with TNF alpha inhibitors is rare but has been reported in the literature.

**Case presentation**: We present one such case where a 56-year-old lady presented with a breast lump and nipple retraction in her right breast for 6 weeks. The patient had a history of psoriatic arthritis and had been on Disease modifying anti-rheumatic drugs (DMARDS) for six years. TNF alpha inhibitor was started 3.5 years ago. Clinically, the case was highly suspicious for inflammatory breast cancer. Bilateral mammogram revealed 80mm irregular density in the right retro areolar region of breast; however, no discrete mass was identified on ultrasound examination. Core biopsy showed extranodal marginal zone lymphoma with features of impending transformation. The neoplastic cells were positive for CD45, CD20, PAX5 and BCL6. These cells were negative for AE1/AE3, CD5, CD10, MUM1 and cyclin D1. The patient was then started on R-CHOP (rituximab-cyclophosphamide-hydroxydaunorubicin-oncovin-prednisone) chemotherapy regime for six cycles. TNF alpha inhibitor was stopped. The patient tolerated the chemotherapy regime well and no flare ups of psoriasis were noted.

**Conclusion**: There was rapid progression of breast tumour within a span of 6 weeks in a patient with no family history, no systemic lymphadenopathy and in a background of TNF alpha inhibitors. Based on these findings and the published literature, a probable association of primary breast lymphomas with TNF alpha inhibitors is likely. Although this causal association may be minimal, more research should be done to consolidate the findings.



## INTRODUCTION

Non-Hodgkin lymphoma is a type of cancer that develops in the lymphatic system. In the UK, more than 13,000 people are diagnosed with non-Hodgkin lymphoma (NHL) each year. The most common symptom of non-Hodgkin lymphoma is a painless swelling in the lymph node, usually in the neck, armpit or groin.[1] NHL occurring outside the lymph nodes is "Extranodal NHL" and has been reported in

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gastrointestinal tract, Waldeyer's ring, bone, and skin, to name a few.[2]

Extranodal non-Hodgkin's lymphoma (NHL) of the breast is a rare entity. It represents 0.04-1.1% of malignant tumors of the breast, 1.7-2.2% of extranodal lymphomas and 0.7% of all NHL. However, primary NHL (PNHL) is the most frequent hematopoietic tumor of the breast.[3]

The disease occurs almost exclusively in women. Bilateral breast involvement accounts for 11% of all breast lymphomas[4] or 5% according to Ryan *et al.*[5] This rare situation is especially observed during pregnancy or postpartum, suggesting that tumor growth is influenced by hormonal stimulation.

Breast lymphoid cells probably originate in mucosa-associated lymphoid tissue (MALT).[6] Primary breast lymphomas (PBL) may also originate from lymphatic tissue present within the breast adjacent to ducts and lobules, or from intramammary lymph nodes.[7,8]

This study is a report of primary NHL of the breast, a rare breast malignancy, along with the evaluation of its possible association with anti TNF drugs.

The clinical and imaging findings in breast lymphoma can mimic those of breast carcinoma. Sometimes, PBL presentation is suggestive of inflammatory breast cancer. Diagnosis depends on adequate tissue sampling for histology examination and immunophenotyping.[9] Inflammatory breast cancer is also a rare type of breast cancer. The cancer cells block the smallest lymph channels in the breast. The lymph channels cannot drain the lymphatic fluid properly if they are blocked. This blockage causes the skin to become red and inflamed, resulting in peau d' orange appearance. Between 1 and 5 out of 100 breast cancers (1 to 5%) are inflammatory.[10]

## CASE PRESENTATION

A 56-year-old lady presented with a lump on her right breast with nipple retraction for 6 weeks. Clinical examination revealed a palpable lump with peau d'orange appearance of the overlying skin. No family history of breast cancer was present. Past history included psoriatic arthritis, chronic lymphedema of lower limbs likely due to obesity and high Body Mass Index (BMI) of 54, hypertension, diabetes mellitus and hypercholesterolemia. No paraneoplastic symptoms such as neuropathy or dermatomyositis were manifested.

Drug history included Hyrimoz (TNF alpha inhibitors) injections for 3.5 years. The switch from Humira to Hyrimoz was done on April 2019. Prior to this, the patient was on disease modifying anti-rheumatic drugs (DMARDs) which included methotrexate and sulphasalazine. The patient was also on antidiabetic and antihypertensive medications.

Radiological examinations of breast were done three times from 2015-2022. The earlier two results (done in 2015 and 2021) were unremarkable; however, the mammogram done in 2022 showed an 80mm irregular density in the retro areolar region of the right breast. There was rapid growth of tumor in a span of 6 weeks.

No discrete underlying mass was identified on ultrasound breast. Both of the axillae were normal. Ultrasound abdomen showed fatty liver and no evidence of systemic lymphadenopathy while ultrasound pelvis showed the left ovary with polycystic appearance and the right ovary with a small dominant follicle. Thickened endometrium was also noted which showed complex hyperplasia without atypia on biopsy.

FDG PET scan of the breast showed a metabolically active mass in the upper aspect of the right breast with associated cutaneous thickening. A small right axillary lymph node with no significant activity was also noted. No FDG avid lymph nodes were identified above or below the diaphragm. FDG distribution elsewhere was unremarkable and the spleen was also normal.

A core biopsy was carried out for the breast lesion with clinical suspicion of inflammatory breast cancer. Histological examination revealed dense lymphocytic infiltrate (Figure 1) highlighted by CD45 and negative for AE1/AE3.

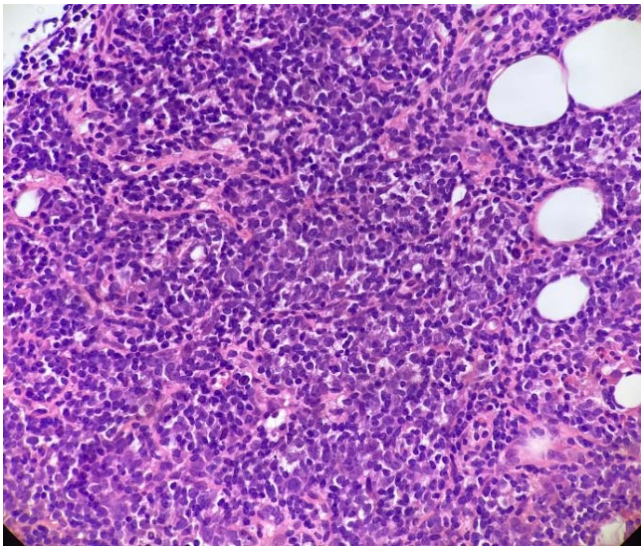

**Figure 1.** Dense lymphoid infiltrate with small to medium sized monomorphic cells (H/E, x40).

Further immunohistochemistry showed atypical lymphoid blasts staining for CD20, PAX 5 (Figure 2) and BCL6 (Figure 3).

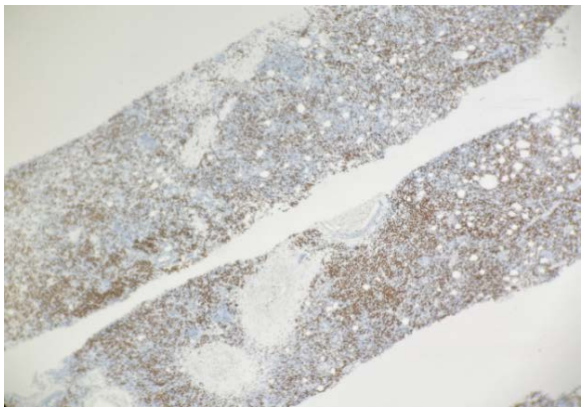

**Figure 2.** Atypical lymphoid cells stained by PAX 5 (x10).

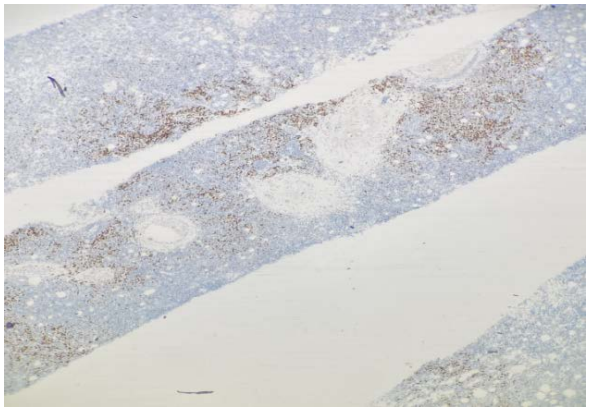

**Figure 3.** Atypical lymphoid cells stained by BCl6 (x10).

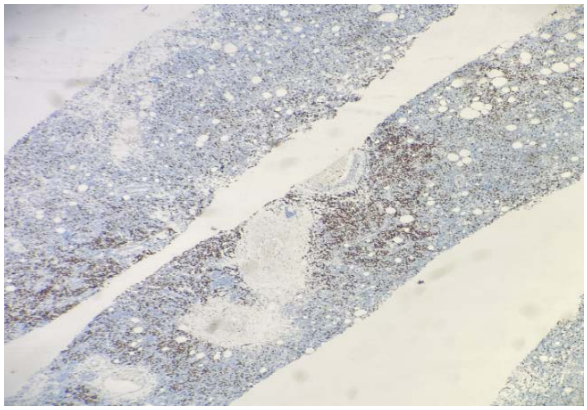

**Figure 4.** Ki67 mitotic index of 40-60% in tumor cells (x10)

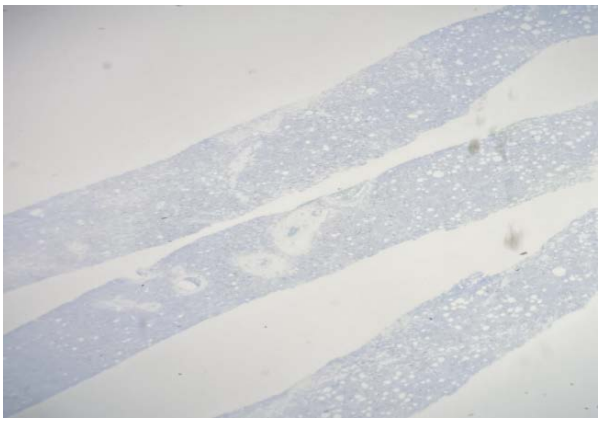

**Figure 5.** Atypical lymphoid cells negative for MUM1 (x4).

Ki67 index ranged between 40-60% (Figure 4). There was variable expression of CD23 and cells were negative for CD5, CD10, MUM 1 (Figure 5) and cyclin D1.

No follicular dendritic cell (FDC) meshwork was identified with CD21 or CD23. Reactive T cells highlighted by CD5 (Figure 6) outnumbered the tumour cells, which were however >10% of the overall cell population. No overexpression of MYC protein was seen. Lymphoepithelial lesions were not identified by AE1/AE3. Overall, the features were those of CD5 (-) CD10 (-) B- cell non-Hodgkin lymphoma, most likely Extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma) with features of impending transformation. Pseudolymphoma was excluded from the differential diagnosis on the basis of lack of germinal centres and follicular dendritic cell meshwork (FDC) with CD21/ CD23. The infiltrate mainly consisted of atypical lymphoid cells highlighted by CD20, PAX5 and BCL6, which were arranged as vague nodules. There was no significant increase in plasma cells. Ki67 index was also moderately high (40-60%).

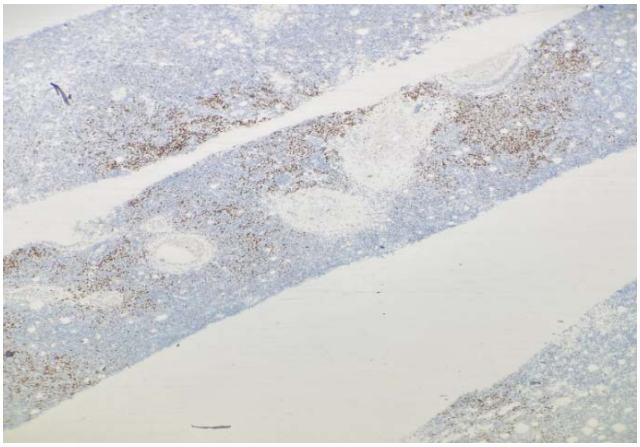

**Figure 6.** Dense reactive T cells stained by CD5 (x4).

The patient was referred to the Haematology team and was started on R-CHOP treatment, six cycles on a three weekly basis. Dose attenuation was done in the first cycle due to underlying co-morbidities. The patient tolerated the first two cycles of chemotherapy well with only mild diarrhoea noted. No radiation therapy was given and no surgery was done.

The TNF-alpha inhibitors which the patient had been receiving were also stopped. Since the patient was on TNF-alpha inhibitors for 3.5years, no flare ups were noted after stopping the medications. This indicated that the patient was responding to TNF alpha inhibitors.

## DISCUSSION

Primary breast lymphoma (PBL) is defined pathologically as the presence of lymphomatous

infiltrate in normal breast tissue in a patient with neither previous nor concurrent non-Hodgkin's lymphoma at another site, although the involvement of ipsilateral axillary lymph node enlargement may be present.[11]

PBL is a rare tumor and is often present as an innocuous lump.[12] However, it can also present with mammary asymmetry and inflammatory signs such as orange-peel skin, thereby raising the clinical suspicion of inflammatory breast cancer[9] as in this case.

There are no current established guidelines for the treatment of PBL. Treatment options include surgery, chemotherapy and radiotherapy.[13] In general, treatment of PBL is similar to that used for other lymphomas and depends on the histological type.[14] At present, the treatment of breast lymphoma, whether primary or secondary, should be with systemic chemotherapy. The choice of chemotherapy regimen should be based on histologic subtype, disease extent, and individual patient.[15]

Whether long term TNF blockers are associated with primary breast lymphomas is a matter of debate. In a nested case control study with retrospective cohort of adults with rheumatologic conditions carried out at the University of Illinois, Chicago in between 2009 and 2015, it was found that TNFI ever-use was associated with nearly two-fold increased risk of NHL (OR=1.93; 95% CI: 1.16-3.20) suggesting increasing risk with duration (P-trend=0.05) as compared to controls.[16]

In another controlled study of clinical trials of all the TNF-blockers in adults, more cases of lymphoma have been observed among TNF-blocker-treated patients compared to control-treated patients. In a controlled study of 34 global adalimumab clinical trials in adult patients with RA (Rheumatoid arthritis), PsA (Psoriatic arthritis), AS (Ankylosing spondylitis), CD (Crohn’s disease), UC (Ulcerative colitis) and Ps (Psoriasis), 3 lymphomas occurred among 7304 adalimumab-treated patients versus 1 among 4232 control-treated patients.

In 47 global controlled and uncontrolled clinical trials of adalimumab in adult patients with RA, PsA, AS, CD, UC and Ps with a median duration of approximately 0.6 years, including 23,036 patients and over 34,000 patient-years of adalimumab, the observed rate of lymphomas was approximately 0.11 per 100 patient-years.

This is approximately 3-fold higher than expected in the general U.S. population according to the SEER database (adjusted for age, gender, and race). Post-marketing cases of acute and chronic leukaemia have also been reported in association with TNF-blocker use in RA and other indications.

Having said that, it is seen that patients with RA and other chronic inflammatory diseases, particularly those with highly active disease and/or chronic exposure to immunosuppressant therapies, may be at a higher risk (up to several fold) than the general population for the development of lymphoma, even in the absence of TNF- blockers.[17]

## CONCLUSION

In conclusion, it was found that there was a rapid development of breast mass in the absence of family history and in the background of TNF alpha inhibitor treatment. The patient responded well to chemotherapy regime after the cessation of TNF alpha inhibitors. Also, no other lymphoma deposit was noted on systemic FDG PET scan, and the likelihood of lymphomatous spread from outside the breast is questionable, thus making TNF alpha inhibitors the likely etiologic factor for primary breast lymphoma in this patient.

Primary breast lymphomas should always be considered in the differential diagnosis of inflammatory breast cancer in the absence of discrete mass.

And patients with a history of arthritis on DMARDs/ TNF inhibitors should be closely monitored for evidence of any underlying malignancy.

## ETHICAL CONSIDERATIONS

Written consent was obtained from the patient for the presentation of her medical record and history.

## FUNDING

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## CONFLICT OF INTEREST

The authors have no financial or non-financial interests to disclose.

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