Primary breast lymphoma with cutaneous involvement in a patient with rheumatoid arthritis – a complication of infliximab therapy?

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ABSTRACT

It is well established that rheumatoid arthritis is associated with an increased risk of lymphoma. The use of tumor-necrosis factor-α inhibitors as a therapy in rheumatoid arthritis has been related to higher incidence of lymphoma arising at atypical and/or unusual locations; however, recent data shows their safety. We report the case of a 79 year-old woman with rheumatoid arthritis treated with infliximab, who presented a primary breast lymphoma with cutaneous involvement.

Keywords: Rheumatoid arthritis; Anti-tumor necrosis factor-alpha therapy; Breast lymphoma.

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic and potentially destructive inflammatory arthropathy. Several epidemiological studies have demonstrated that the risk of lung, non-melanoma skin cancer and hematopoietic cancers (such as non-Hodgkin's lymphoma and myeloma) is higher in patients with RA than in the general population, while the incidence of breast and colon cancer incidence is decreased[1-3]. In addition, it is known that disease activity by itself is a risk factor for developing lymphoma[1-3].

Inhibitors of tumor necrosis factor-α (TNF-α), such as infliximab, have had a significant impact on the treatment of RA. However, their immunosuppressive effects have raised safety concerns, including the potential to increase the risk of cancer[4, 5]. Unusual types of lymphoma arising at atypical/unusual locations in patients with RA treated with TNF-α antagonists have been reported[6-8] but their relation with disease activity and/or its treatment is uncertain.

To our knowledge, this is the second reported case of primary breast lymphoma in a patient with long-standing RA undergoing anti-TNF therapy.

CASE REPORT

A 79 year-old Caucasian woman was admitted to our department, due to a one-month history of anorexia, evening fever, profuse nocturnal sweats and chills. She also referred inflammatory polyarticular pain, swelling joints and morning stiffness lasting over 30 minutes. She didn't report other systemic symptoms, such as weight loss, dyspnea, cough or dry symptoms.

This patient had been diagnosed, 14 years before, with erosive and seropositive (rheumatoid factor and anti-cyclic citrullinated peptides (CCP)) RA and she was under biological treatment since 2 years ago, receiving a combination of infliximab (3mg/kg iv every six weeks), methotrexate (15 mg/week) and prednisolone (10 mg once daily) being in remission in the last visit. She also had a prior history of monoclonal gammopathy of uncertain significance (MGUS), not requiring treatment until then, type 2 diabetes mellitus, pinna basal-cell carcinoma (T1N0M0, excised 3 months earlier), dyslipidemia, atrophic gastritis and hepatic steatosis. Family history was negative for RA and breast cancer; she had one sister with gastric adenocarcinoma. Colon and breast cancer screening were updated. She denied any known contact with patients with tuberculosis.

There was no smoking or alcohol abuse history. Her other medication included glargin insulin (18 UI+

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10UI), simvastatin 20mg/day, pregabalin 75mg/day, acetylsalicylic acid 150mg/day, folic acid 5mg/day, omeprazole 20mg/day, calcium and vitamin D supplementation and alendronate 70mg/week. She had no medication allergies.

Musculo-skeletal examination revealed 8 tender joints and 3 swollen joints (in 44 articular count). General examination revealed a stiff node in the inferior inner quadrant of the left breast (4 x 4 cm), which was painless, adherent to deep planes without skin erythema. An enlarged lymph node was identified in the left cervical zone. There were no palpable supraclavicular, axillar or inguinal lymph nodes. A few subcutaneous painless nodes, without skin changes, were noted in the interscapular region.

The laboratory workup showed an erythrocyte sedimentation rate of 120 mm/h, C-reactive protein 15.64 mg/dL, procalcitonin 0.07 ng/mL (reference value < 0.5 ng/mL), hemoglobin 10.3 g/dL, mean corpuscular volume 81.4 fl, leukocytes 10.7 x 10^9/L, neutrophils 6.7 x 10^9/L, lymphocytes 2.7 x 10^9/L, monocytes 1.0 x 10^9/L, LDH 173 U/L, creatinine 0.62 mg/dL, serum calcium 9.9 mg/dL, negative antinuclear antibodies, normal complement levels and β2-microglobulin 3.47 mg/L (reference value 1.09-2.53 mg/L). Serum protein electrophoresis revealed a monoclonal peak elevation in the gamma zone (similar to those previously known) and a negative serum and urinary immunofixation.

The tuberculin skin test was negative. Urine and blood cultures were negative. Chest radiography revealed no recent abnormalities, namely signs of tuberculosis or lung nodes. Mammography and breast ultrasound demonstrated various nodes on both breasts and bilateral axillary lymphadenopathies. Thoraco-abdominal and pelvic Computed Tomography (CT) revealed multiple bilateral breast nodes, bilateral axillary lymphadenopathies and subcutaneous dorsal nodes with imaging characteristics similar to the breast nodes (Figure 1-2). There was no hepatosplenomegaly.

A biopsy of cutaneous and breast nodes was performed. Histology and immunohistochemistry demonstrated bilateral involvement by small B-cell lymphoma (marginal zone lymphoma) – strongly positive for CD20, CD138 and bcl-2 in plasmocyte population, with lambda light-chain restriction (Figure 3). Cutaneous biopsy identified a secondary infiltration of small B-cell lymphoma (marginal zone lymphoma) with the same immunohistochemistry characteristics (Figure 4). The bone marrow aspirate revealed normocellular bone marrow with 5% of plasmocytes, without infiltration of other cells. These findings were consistent with a B cell non-Hodgkin lymphoma

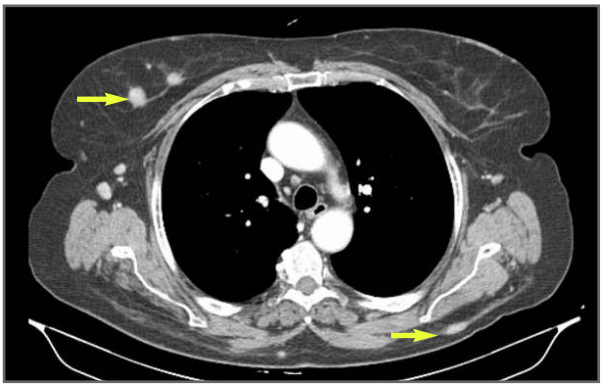

FIGURE 1. Bilateral breast and subcutaneous nodes

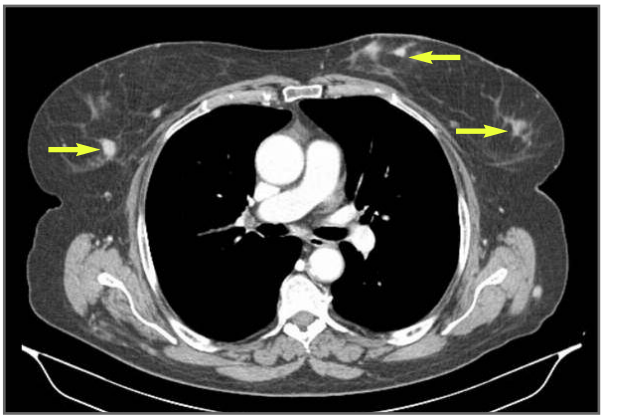

FIGURE 2. Multiple bilateral breast nodes

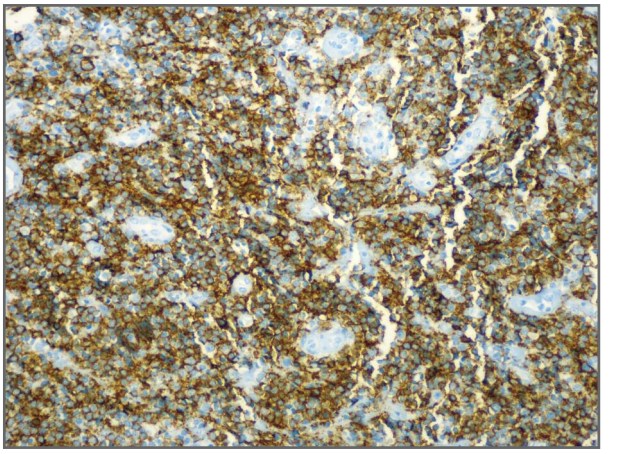

FIGURE 3. Breast biopsy (200x): small B-cell lymphoma strongly positive for CD20 (golden capture)

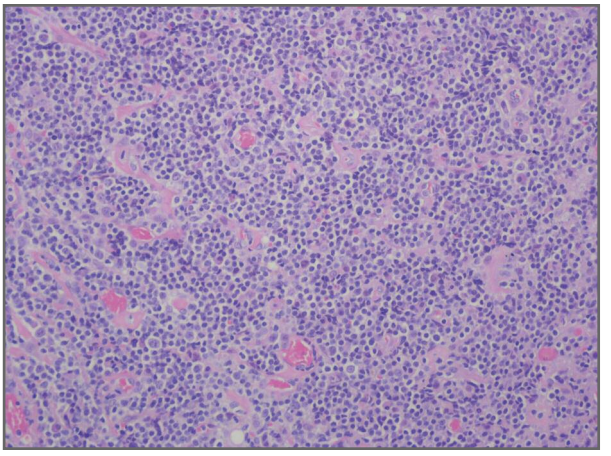

FIGURE 4. Skin biopsy (HE, 200x): infiltration of small B-cell lymphoma

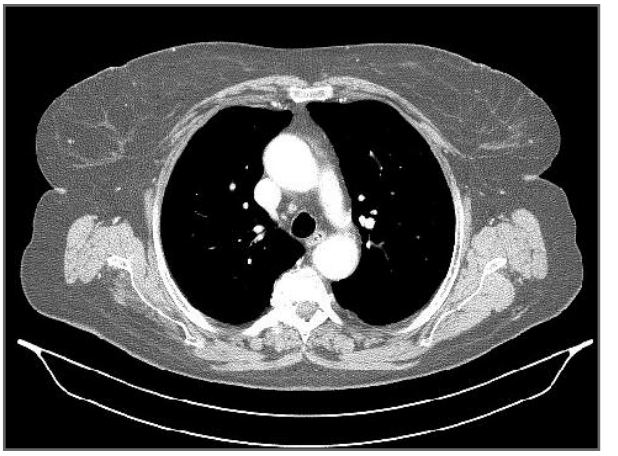

FIGURE 5. Toraco-abdominal and pelvic CT after treatment (resolution of breast and subcutaneous nodes)

(NHL) – marginal zone lymphoma with lymphoplasmocytic differentiation.

Our patient was referred to the Hematology Department. Infliximab and methotrexate were discontinued and she started treatment with cyclophosphamide, vincristine and prednisolone (CVP).

At a 6 month follow up (after 8 cycles of CVP without complications), the patient is asymptomatic from both the lymphoma and rheumatoid arthritis, with normalization of inflammatory markers, no full blood count abnormalities and a second toraco-abdominal and pelvic CT showed resolution of breast and subcutaneous nodes (Figure 5). She is also medicated with prednisolone 5mg/day and hydroxychloroquine 400mg/day.

DISCUSSION

To our knowledge, this is the second report of a case of primary breast lymphoma developing in a patient with RA under anti-TNF-α therapy. Diagnosis of breast lymphoma with cutaneous involvement was particularly challenging in this patient, as the differential diagnosis included RA flare, paraneoplastic arthritis, infection, tuberculosis, multiple myeloma, hematological lymphoma (associated or not to a secondary Sjögren's syndrome) and other malignancies. In this patient, age, longstanding RA and the chronic use of immunosuppressive agents (methotrexate and TNF-α antagonist - infliximab) could be considered as an additional risk factor for infections but also for malignancies.

It is recognized that RA increases, by itself, the risk of developing lymphoma, which is closely related to disease activity and extra-articular manifestations[2,3]. Long-lasting inflammatory activity of RA is considered a main risk factor for lymphoma[2,9-11].

Inflammation is believed to play a key role in the risk of lymphoma development and epidemiologic studies have suggested that higher inflammatory activity is a major risk for lymphoma[3,10-12]. This has been attributed to the continuous stimulation of B-cells.

In a 2008 meta-analysis, the risk of lymphoma in RA patients was two-fold increased compared with general population (standardized incidence ratio (SIR) 2.08 (95% CI 1.80-2.39), regardless lymphoma type. A higher risk was observed for Hodgkin lymphoma than for non-Hodgkin lymphoma: SIR 3.29 (95% 2.56--4.22) and 1.95 (95% CI 1.70-2.24), respectively. The included studies did not show a statistically elevated risk associated with anti-TNF use[12].

A recent Japanese cohort composed by 66.953 patients followed by 10 years showed that the overall incidence of malignancies in RA patients was slightly lower than general population (SIR 0.89 95% CI 0.82--0.97), however lymphoma risk was significantly higher (SIR 3.43 95% CI 2.59-4.28). The onset of lymphoma in the next year was significantly associated with higher age (OR 1.04 per an additional year of age), use of methotrexate (OR 3.5 95% CI 2.0-6.3) and the use of tacrolimus (OR 3.9 95% CI 1.9-7.4). However no correlation was observed with methotrexate doses and lymphoma onset. The patients who developed lym-

phoma had longer RA disease duration[13]. The most frequently reported subtype of non-Hodgkin lymphoma in RA patients is diffuse large B cell lymphoma[9,10,12].

The association between TNF-α antagonists and lymphoma remained unclear for some years. Oldest studies suggest that treatment with TNF-α antagonists may be associated with an increased risk for lymphoma[14,15]. A prospective study demonstrated that RA patients treated with TNF-α antagonists had a tripled lymphoma risk (RR= 2.9) compared with the general population. However, after adjustment for sex, age and disease duration, this risk was not higher than in other RA cohorts[13]. In a Swedish cohort study, among 6604 anti-TNF treated RA patients, 26 malignant lymphomas were observed during the 26981 person-years of follow-up, which corresponded to a relative risk of 1.35 (95% CI 0.82 to 2.11) versus RA patients not treated with anti-TNF and 2.72 (95% CI 1.82 to 4.08) versus the general population[16]. A prospective French study demonstrated that the overall risk of lymphoma in RA patients did not differ greatly from patients with other inflammatory diseases. It also revealed that the risk differed depending on which TNF-α antagonist had been used, with a higher risk being reported for infliximab or adalimumab than for etanercept (odds ratio=4.7 and 4.1, respectively)[17]. A recent systematic literature review of observational studies shown that patients on TNF-α antagonist did not have an increased risk for malignancies in general neither lymphoma. When comparing RA patients with TNF-α antagonist with those without TNF-α antagonist there is no increased risk of lymphoma[18]. The recent results from British Society for Rheumatology Biologicals Register for RA showed no difference in the risk of lymphoma for the TNF-α antagonist group versus the biological-naïve RA patients group: HR 1.00 (95% CI 0.56 to 1.80) after adjusting for differences in baseline characteristics[19].

Rare sites of lymphoma have been described in patients receiving anti-TNF-α therapies - colon/rectum (n=2), palate and jaw (n=2), bone marrow (n=1), skin (n= 1), stomach (n=1) or ovary (n=1)[2,11]. We could only find another report of case of breast lymphoma in RA patient receiving TNF-α antagonist, although without cutaneous involvement[20].

A Sjögren's syndrome (primary or secondary) was rule out, because there were not any clinical or immunological features. Despite she had a MGUS, the risk to develop a lymphoma is lower than 1%[21].Our patient had also been treated with methotrexate. A 2008 Australian observational cohort for a 4145 person-years demonstrated a five-fold increased of non-Hodgkin's lymphoma in a RA cohort treated with methotrexate relative to the general population (SIR 5.1, 95% CI 2.2-10.0). However this could be explained by the fact that patients with more severe disease would have higher inflammatory activity and would therefore be more likely treated with methotrexate[22]. There was no association between increased lymphoma risk and any specific drug therapy[2]. Current evidence indicates that there is no increased risk of developing non-cutaneous malignancies with the use of methotrexate in RA[22].

Currently, the effect of anti-TNF therapy or methotrexate discontinuation on tumor regression is unknown, but some reports describe the spontaneous regression of lymphoma after anti-TNF[23,24] or methotrexate discontinuation[25]. We considered it prudent to discontinue both methotrexate and infliximab.

In summary, to our knowledge this is the second case report of a primary breast lymphoma, and the first one with cutaneous involvement, occurring in a patient with RA treated with a TNF-α antagonist. This case report should raise awareness to the more likelihood occurrence of lymphoma, especially in unusual and atypical locations, in patients with RA, particularly in the case of longstanding disease. Assessment and management of these patients is challenging and should incorporate a multidisciplinary team, including rheumatologists, hematologists, gynecologists and pathologists. It is necessary to staying vigilant in RA patients on any therapy and be cautious in patients prescribed biologic therapy.

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