CASE OF THE MONTH

Lymphoma in Rheumatoid Arthritis – Catastrophic Sequela of a Common Disease

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Abstract

Rheumatoid arthritis (RA) is a common rheumatological condition affecting the joints and has a wide range of extra-articular manifestations. A 69 year old male, known case of rheumatoid arthritis presented to our OPD with right lower limb redness and swelling, and left axillary lymph node swelling. Lymph node biopsy revealed a high grade diffuse large B-cell lymphoma with co-expression of c-myc and bcl-2 (double expressor). RA increases the risk of both Hodgkin's lymphoma (HL) and non-Hodgkin's Lymphoma (NHL). The association with diffuse large B-cell lymphoma (DLBCL) has been found to be particularly strong, however double expressor DLBCL is an extremely uncommon occurrence. High disease activity of rheumatoid arthritis is a major determinant in development of lymphomas.

Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated, polygenic disease that causes chronic joint inflammation and deformity, with many extra articular manifestations.[1] Incidence of malignancy in patients with RA has been studied in detail and it has been shown that patients with RA have an overall 10 % more risk of developing malignancies as compared to the general population, particularly lung malignancies and lymphomas.[2]

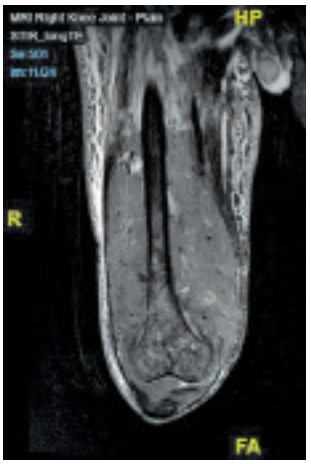

Fig. 1: Magnetic resonance imaging of the right lower limb showing a mass involving the marrow, with evidence of cortical destruction, periosteal reaction and marked circumferential extra-osseous soft tissue component

We report and discuss a case of rheumatoid arthritis who presented to OPD with lymphadenopathy and was diagnosed with high grade diffuse large B-cell lymphoma with co-expression of c-myc and bcl-2.

Case Summary

A 69 year old gentleman presented to our OPD with complaints of redness and swelling in the right lower limb, and swelling in the left axilla for the last 1 month. The patient was a known case of rheumatoid arthritis for the last 20 years. However he was not following up with any physician for his disease. He had however started consuming allopathic medicines, namely methotrexate and hydroxychloroquine only 2 months ago. Before that, he had been on medications of alternative medicine. Examination revealed typical deformities of the hands (swan neck, boutonniere and Z deformity). The right lower limb was red and swollen, the swelling extending from the mid-thigh up to the mid-leg and involving the knee. The right calf was tender. There was a large fixed swelling measuring 6 X 3 cm in the left axilla and multiple enlarged and matted right inguinal lymph nodes. The patient had normal vital signs barring an irregular pulse. ECG revealed occasional premature ventricular complexes. 2D echocardiography was normal. Blood investigations revealed high ESR (60), anaemia (Haemoglobin 9.8 g/dl), normal kidney and liver functions. A colour Doppler ultrasound of the bilateral lower limbs was done with showed thrombosis of the right superficial and deep veins and compression of the external iliac vein by multiple enlarged inguinal lymph nodes. An ultrasound of the left axilla confirmed the mass as a lymph node and also reported presence of multiple other enlarged axillary nodes. An excisional biopsy of the left axillary node was done. The patient was started on enoxaparin. An orthopaedic consultation was sought for the right lower limb swelling. Roentgenogram and MRI of the limb showed a mass involving the marrow, with evidence of cortical destruction, periosteal reaction and marked circumferential extra-osseous soft tissue component (Figure 1). Lymph node biopsy revealed diffuse effacement of nodal architecture by large lymphoid cells and a Non-Hodgkin's Lymphoma was suspected. Immunohistochemistry (IHC) was performed which showed large cells to be diffusely positive for CD20, CD10, Bcl-6 and negative for CD3 and MUM-1 (Figure 2). Further, IHC showed large cells to be positive for c-myc and Bcl-2 (in 75% and 95% of cells respectively) (Figure 3). Thus, a diagnosis of a diffuse large B cell lymphoma; germinal centre subtype with co-expression of c-myc and Bcl-2 (Double expressor phenotype) was made. Bone marrow biopsy also showed infiltration by high grade NHL.

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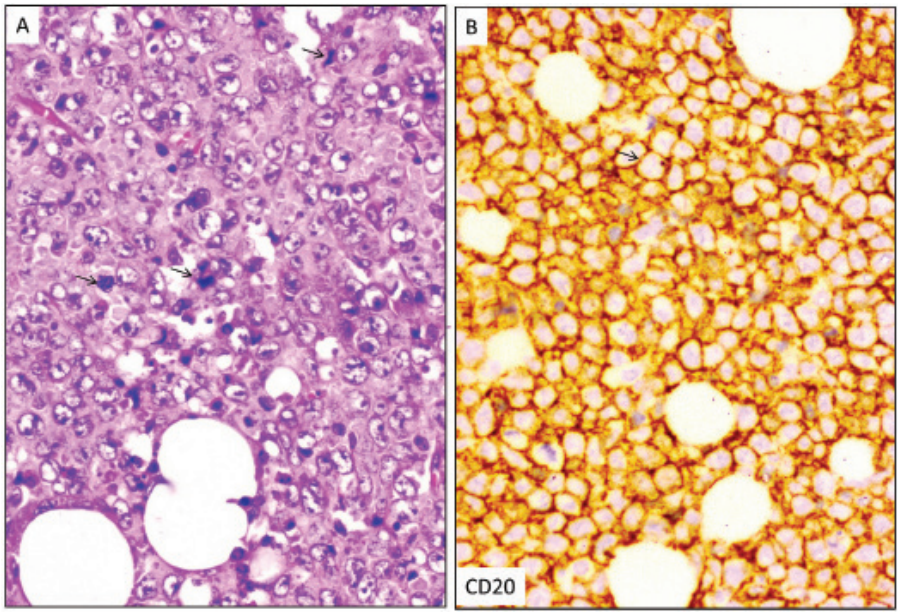

Fig. 2: A: HE section (400x) shows sheets of large pleomorphic lymphoid cells with prominent nucleoli and mitotic figures (arrow mark →). B: CD20 IHC showing strong membranous uniform staining (arrow mark →) around large lymphoid cells (400x)

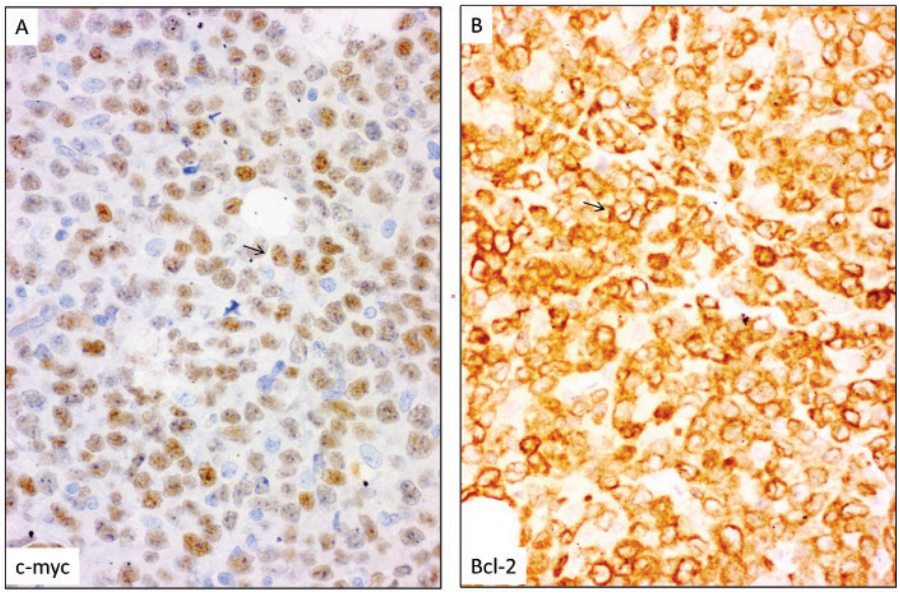

Fig. 3: A: Immunohistochemistry for c-myc shows nuclear positivity in majority of lymphoid cells (arrow mark →) (400x). B: Bcl-2 immunostaining showing diffuse cytoplasmic positivity (arrow mark →)among all tumor cells

The patient was transferred under the department of haematology and started on chemotherapy - rituximab plus cyclophosphamide, vincristine and prednisolone. The patient showed marked clinical improvement, including the decrease in size of swellings in the left axilla and right lower limb, after the initiation of chemotherapy.

Discussion

The WHO in 2001 classified lymphomas into three main types – B-cell, T-cell and Hodgkin's lymphoma; which were further subdivided into over 40 categories.[3] The classification was updated in 2008 and then in 2016; and many new categories were created.

A detailed meta-analysis noted that the increased risk of lymphoma varies with various rheumatological conditions and concluded it being highest in sjogren's syndrome, rheumatoid arthritis and SLE – in that order.[4] Other disorders like dermatomyositis, polymyositis and psoriasis also confer higher risk of developing lymphomas, but the rates vary in various studies.[4]

Rheumatoid arthritis is a chronic immune mediated disease that involves the joints and has many extra articular manifestations.[1] RA has been associated with many malignancies in individual case reports, however a meta-analysis concluded that true association existed only in lung malignancies and lymphomas.[1] Both Hodgkin's and non-Hodgkin's lymphomas occur more frequently in patients with rheumatoid arthritis;[4] the association being strongest with diffuse large B-cell lymphoma.[5] Overall the risk of developing lymphoma in a patient with RA is two to three times the general population.[5]

Many factors may contribute to the development of lymphoma in a patient with rheumatoid arthritis. These include genetic factors, environmental factors, high inflammatory activity and treatment related factors.[5] Genetic factors were not found to be of no major importance in a study involving first degree relatives of patients with RA.[6] Smoking is the only major identified environmental factor[5] but the evidence for the same is weak and may even be conflicting.[7] High disease activity has been found to have strong association with development of lymphoma in patients with RA[8] in an elegant study. Disease activity in this study was measured using ESR, number of inflamed joints and the doctor's global assessment. Another group found felty's syndrome as marker of high disease activity and thus a risk factor for development of lymphoma in patients with RA.[9] There is controversy regarding role of immunosuppressive therapy including methotrexate in the causation of lymphomas. In a study involving 1767 RA patients, spanning over two decades, it was showed that high inflammatory activity (elevated ESR) instead of therapy with methotrexate or prednisone, determined the risk of developing lymphoma.[10] Hence, it is speculated that DMARD therapy may, conversely, lower the lymphoma risk.[5]

Many studies have proposed various mechanisms involved in lymphomagenesis. It is believed that clonal proliferation of B-cells

may be a major pathogenic event.[5] The role of B-cell in development of RA-DLBCL was shown in a study that detected higher expression of APRIL (A Proliferation-Inducing TNF Ligand, also called TNFSF13) in RA-DLBCL patients with high disease activity.[11]

Diffuse Large B-cell lymphomas with over-expression of c-myc and bcl-2 at a protein level (detected by immunohistochemistry) are referred to as "double-expressor" phenotype of DLBCL [12]. Over-expression is defined as greater than 40% c-myc expressing cells and greater than 50% bcl-2 expressing cells.[12] At a genetic level (detected by fluorescence in-situ hybridization), if dual re-arrangement of c-myc and bcl-2 is detected, it is called "double-hit" phenotype of DLBCL.[13] This double-hit DLBCL has been reclassified as "high grade B-cell lymphoma (HGBL)" by WHO in 2016.[13] Double-expressor and double-hit phenotypes may be related but the terms cannot be used interchangeably, as all double-expressor phenotypes may not have dual re-arrangement at the genetic level. The DLBCL in our patient had an over expression of c-myc and bcl-2, and is thus a double expressor phenotype. The recognition of double expressor is important for risk stratification and prognostication of the lymphoma. The poor prognostic effect was proved in an independent cohort of 140 double expressor lymphomas.[14]

The double-hit and double-expressor phenoytes have a bearing on the treatment too. It has been shown that standard treatment with R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisone) may be suboptimal and R-EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin plus rituximab) regimen might have more favourable outcomes.[12,15] Large prospective studies are, however, required to find the optimum treatment for such lymphomas.

Conclusions

Rheumatoid arthritis is a common connective tissue disorder, in which the risk of developing lymphomas is much more as compared to the general population. The most common lymphoma associated with RA is diffuse large B-cell lymphoma. High disease activity rather than therapy contributes significantly to the risk of developing lymphoma in RA. A physician must treat his patients with rheumatoid arthritis adequately; and strive to reduce the disease activity; thus reducing the risk of lymphomas. Lymph nodal swelling in patients with RA must alert the physician to look for an underlying lymphoma. When recognised as a diffuse large B-cell lymphoma, it is imperative to quantify c-myc and bcl-2 expression by IHC; which will in turn help to stratify risk, choose the appropriate therapy and prognosticate.

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Informed Consent

A written informed consent was obtained from the patient.

Abbreviations

RA – Rheumatoid arthritis; ECG – Electrocardiogram; ESR – Erythrocyte sedimentation rate; MRI – Magnetic Resonance Imaging; IHC – Immunohistochemistry; HL – Hodgkin's Lymphoma; NHL – Non-Hodgkin's lymphoma; SLE – Systemic lupus erythematosus; DLBCL – Diffuse large B-cell lymphoma; DMARD – Disease-modifying anti-rheumatic drugs; APRIL - A Proliferation-Inducing TNF Ligand; TNF – Tumor necrosis factor.

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