CASE REPORT

Generalized lymphadenopathy as an atypical initial clinical manifestation in rheumatoid arthritis and a possible hypothetical mechanism

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ABSTRACT

Objective: To describe a 60-year-old male with diffuse generalized lymphadenopathy preceding a diagnosis of rheumatoid arthritis.
Case presentation: The patient was admitted on suspicion of lymphoma. Chest positron emission/computed tomography showed enlarged lymph nodes bilaterally, mediastinum in the perihilar, retroperitoneum, and inguinal regions, with normal hematopoiesis of bone marrow. Lymph node biopsy revealed reactive follicular lymphadenopathy. Polyarthritis was present, and a rheumatoid factor test was positive eight months after the initial medical evaluation. A diagnosis of rheumatoid arthritis associated with generalized lymph node involvement was made. The patient was treated with leflunomide and corticosteroids and showed complete recovery without recurrence at 18 months of follow-up.
Conclusions: Once histological findings of reactive lymph node hyperplasia are established as primarily related to rheumatic disease activity, clinicians should consider a possible diagnosis of rheumatoid arthritis.

Key Words: Lymphadenopathy, Rheumatoid arthritis, Lymphoproliferative disorder, Lymph node hyperplasia

1. INTRODUCTION

Rheumatoid arthritis is a complex autoimmune disorder that primarily targets the synovial membrane. There is growing evidence indicating the potential involvement of additional anatomical compartments such as lymphoid tissues. Lymphadenopathy complicating rheumatoid arthritis [RA] is not unusual and is observed in 41%-82% of patients with RA.[1] Lymphadenopathy in RA might be due either to an overactive immune state, haematologic malignancy, or secondary to treatment-related immunosuppression. In some cases,

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lymphadenopathy may be an early feature of inflammatory polyarthritis. The observation supports this hypothesis that 20% of patients with unexplained reactive lymphadenopathy develop an inflammatory polyarthritis within one year of lymph node biopsy.[2]

In this study, we report the case of a patient who was diagnosed with RA and a lymphoproliferative disorder that was considered to be associated with the rheumatic disease activity, prompting the investigation of a haematological malignancy.

2. CASE PRESENTATION

Until six months before his first visit to a hematology specialist, our patient, a 60-year-old male, had been healthy. Then, he began experiencing systemic symptoms, including weight loss, anemia, malaise, and diffuse lymphadenopathy that gradually developed in the neck, axillae, and inguinal regions. This man was healthy with no history of smoking or alcohol abuse and no family history of hematologic malignancies. However, on physical examination, the patient was emaciated with palpable, enlarged, and bilateral tender lymph nodes between 1 and 2 cm in diameter in the anterior cervical, axillary, and inguinal regions. The patient had hepatomegaly but no splenomegaly. The remainder of the physical examination was ordinary. The laboratory tests are shown in Table 1.

Table 1. Laboratory findings at initial visit and follow-up

	Patient values (Initial)	Patient values (follow-up,18 months)	Reference values
Hemoglobin (g/dl)	11	13.7	13-18
Hematocrit (%)	33	41.8	40-50
White blood cells (per/mm^3)	12,000	7,900	4,000-11,000
Neutrophils (%)	86	76	40-70
Lymphocytes (%)	8	16	25-45
Platelet count (per/mm^3)	599,000	304,000	150-450,000
Erythrocyte sedimentation rate (mm/hr)	45	16	0-20
Protein C reactive (mg/dl)	17	0.3	0-1.0
Lactate dehydrogenase (UI/L)	485	143	105-333

Laboratory tests for human immunodeficiency virus (HIV) antibodies and quantitative polymerase chain reaction in lymph nodes for Mycobacterium tuberculosis were negative. A bone marrow biopsy showed normal hematopoiesis without morphologic evidence of lymphoma, and a lymph node (LN) biopsy was performed. LN biopsy specimens taken from the cervical and inguinal areas and stained with hematoxylin and eosin showed follicular hyperplasia with irregular follicles but the normal follicular architecture of the LN, large germinal centers and LNs with numerous macrophages (histiocytes) within enlarged sinuses (see Figure 1).

A chest positron emission/computed tomography maximum standardized uptake value [PET/CT SUV max] was 3.2 and showed enlarged LNs bilaterally at cervical, axillary, mediastinum, and perihilar, retroperitoneum, and inguinal regions (see Figure 2).

3. DISCUSSION

When a patient develops lymphadenopathy before the onset of joint symptoms, diagnostic procedures usually can be complicated. This is because malignant hematologic neoplasms such as lymphoma or leukemia and other diseases, like M. tuberculosis or HIV, must first be ruled out in these patients.

Twenty percent of patients with symmetrical polyarthritis or RA initially show LN enlargement without clinical symptoms of arthritis.[3]

It is currently thought that systemic autoimmunity seems to precede synovial tissue inflammation. Other, as yet unidentified immune processes, possibly outside synovial tissues, are altered and contribute to disease development. Recently, Hahnlein et al. developed an experimental model to facilitate research on the role of LN stromal cells during the earliest phases of RA and showed for the first time that the LN stromal environment is changed during the earliest stages.[4]

Individuals positive for arthralgia and anti-citrullinated protein antibodies (ACPA) have an approximately 50% chance of developing RA within 3–4 years.[5,6] During this at-risk phase, as determined by immunohistochemistry, synovial inflammation seems absent, suggesting that infiltration of the synovial tissue by inflammatory cells occurs later.[7]

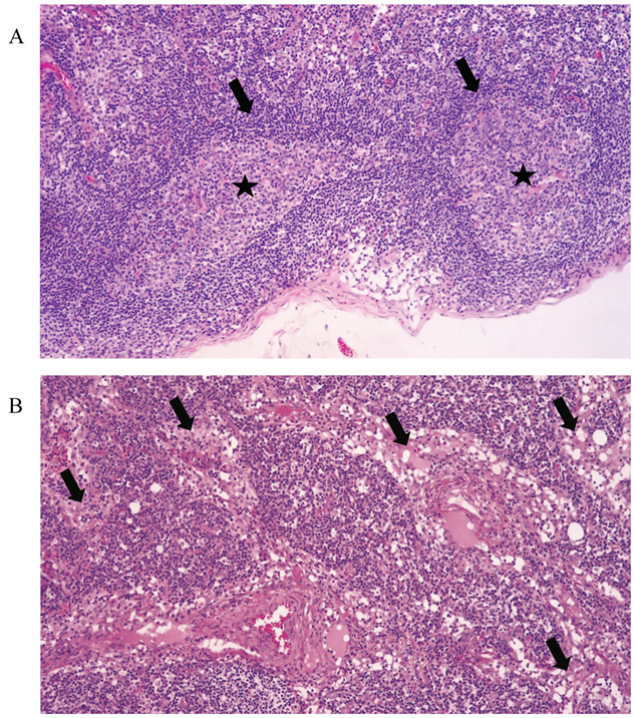

Figure 1. Histological tissue 100× hematoxylin/eosin
(A). Lymph node with two irregular and hyperplastic lymphoid follicles (arrows) surrounding large germinal centers (stars). (B). Lymph node with numerous macrophages (histiocytes) inside dilated sinuses.

This clinical case perfectly exemplifies systemic autoimmunity, initially translated as lymphadenopathy before the diagnosis of RA. The patient showed diffuse lymphadenopathy that predated symmetrical inflammatory polyarthritis by eight months. The histopathological findings of reactive LN hyperplasia (RLNH) are mostly related to rheumatic disease activity in patients with RA.[1] Histologically, LN samples associated with RA demonstrate RLNH, described as follicular hyperplasia, preserving the normal lymph node follicular architecture while having large germinal centers.[8,9] The pathologist's findings in our patient's case were in line with this pattern. Takada et al. in 2021 described clinic pathological characteristics of lymphoproliferative disorders (LPDs) in patients with RA and found that 6.2% of patients with RA had reactive lymphoid hyperplasia associated with high disease activity.[10]

In 2018, Hasegawa reported the first evaluation of axillary lymphadenopathy (AL) using CT imaging and demonstrated that the frequency of AL observed in the chest was 43%, with 22.2% bilaterally and 20.7% unilaterally, concluding that in RA patients, AL was associated with local arthritis as well as with systemic disease activity.[11] In 2021, Filippi et al. reported a case of RA with pleuropulmonary opacities and supra/infra diaphragmatic LN enlargement. PET/CT showed increased tracer uptake in thoracic, iliac, and inguinal nodes.[12]

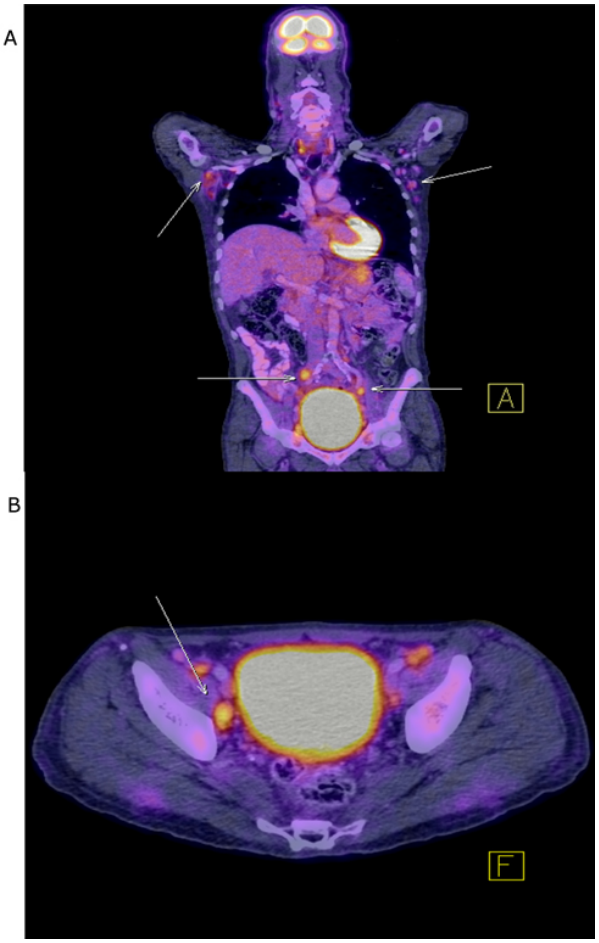

Figure 2. Positron emission tomography
(A).18-FGD PET/CT coronal section showing axillary, mediastinal, and retroperitoneal lymphadenopathy. (B). 18-FGD PET/CT axial section with bilateral external iliac chain lymphadenopathy.

Despite generalized autoantigen expression, the autoimmune response started specifically in the LN draining target joints, spreading thereafter to other lymphoid stations, including the spleen, which may explain the pathological LNs seen in the mediastinum.[13]

Because LNs are essential for immune system function, lymphatic dysfunction may contribute to the pathophysiology of rheumatic autoimmune diseases.

Lymph nodes have a homeostatic structure capable of integrating cell trafficking from the bloodstream, drainage of cells and soluble factors from peripheral tissues through the afferent lymphatic system, and effector cell/molecule output from the efferent lymph.[14] When immune-inflammatory challenges modify the homeostatic architecture of lymph

nodes, lymphocytic and stromal components suffer specific changes referred to as LN reactivity. The clinical sign of this LN reactivity is lymph node hypertrophy. This process involves an induction and resolution phase focused on eradicating the triggering antigen and returning to homeostasis.[14]

We hypothesize that in RA, a systemic autoimmune disease, lymph nodes strategically distributed through the human body initially display pre-arthritic synovial inflammation. The lymphatic system then goes through two processes. First, the lymphatics undergo an "expansion phase" to drain excess cellular debris and inflammatory cells from the site of inflammation either by lymphangiogenesis or by increased frequency of lymphatic vessel contraction.[15, 16] This inflammatory process resolves itself, but if the lymphatic system fails, the LNs progress to the second phase (called the "collapsed phase"), where inflammation cannot be resolved. In this phase, joint inflammation becomes more severe, and clinical synovitis develops.[17] This damage to the lymphatic system contributes to increased joint inflammation, synovial hyperplasia, and, eventually, joint destruction.[18] These immunological events occur in draining lymph nodes in the development of arthritis and have been documented in rats.[9–11] This mechanism may explain why lymphadenopathy occurs before synovitis in patients with RA and may also explain the spread to other lymphoid sites.

Benaglio et al. conclude that a better understanding of immunopathological responses of systemic and local LN will provide answers about the clinical behavior of chronic arthritis. Nevertheless, an important question remains unanswered, "Does the LN compartment represent a primary site of the generation of initial autoimmune responses leading to RA?"[14]

This is the first individual clinical case of initial generalized lymphadenopathy preceding the development of arthritis occurring in a healthy subject demonstrated using PET/CT and with histological confirmation of RLNH, reflecting a high RA disease activity.

Clinicians and pathologists must learn about the benign nature of reactive lymphoid hyperplasia in RA and understand that histological findings commonly encountered at nodes with follicular hyperplasia include large and irregular follicles with the typical architecture of lymph nodes. In addition, clinicians should consider that inflammatory LN activity may be associated with the diagnosis of RA.

ETHICAL STATEMENT

For the development of this study, the authors declare that they have followed the World Medical Association Declaration of Helsinki, and a signed consent form was obtained from the patient.

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CONFLICTS OF INTEREST DISCLOSURE

The authors declare they have no conflicts of interest.

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