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Diffuse Large B-Cell Lymphoma in a Patient with Rheumatoid Arthritis Receiving Methotrexate and Adalimumab: A Diagnostic and Therapeutic Challenge

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Abstract

Immunosuppressive therapy with methotrexate and tumour necrosis factor-α inhibitors is a recognised risk factor for lymphoproliferative disorders in patients with rheumatoid arthritis (RA) [1-3]. We present the case of a 58-year-old woman with longstanding seropositive RA treated with methotrexate 20 mg weekly and adalimumab 40 mg fortnightly who developed a six-week history of dry cough, fatigue, night sweats, and weight loss. Examination revealed a right supraclavicular lymph node and bilateral axillary lymphadenopathy. Core biopsy confirmed diffuse large B-cell lymphoma (DLBCL), activated B-cell subtype with double-expressor (BCL-2$^+$, c-MYC >30%) phenotype. Immunosuppression was ceased immediately. Staging PET-CT demonstrated Ann Arbor stage III disease. She received six cycles of R-CHOP chemo-immunotherapy, resulting in complete metabolic remission. At nine-month follow-up, she remains in remission with rheumatoid arthritis controlled on hydroxychloroquine. This case highlights the importance of early recognition and biopsy of lymphadenopathy in immunosuppressed RA patients and demonstrates that excellent outcomes are achievable with prompt multidisciplinary management.

Keywords: Rheumatoid arthritis; Methotrexate-associated lymphoproliferative disorder; Diffuse large B-cell lymphoma; Adalimumab; Double-expressor lymphoma; R-CHOP

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease frequently requiring long-term immunosuppressive therapy. Methotrexate remains the anchor disease-modifying antirheumatic drug (DMARD), and tumour necrosis factor-α (TNF-α) inhibitors such as adalimumab are commonly added for inadequate responders [2]. Both agents have been implicated in the development of lymphoproliferative disorders, including methotrexate-associated lymphoproliferative disorder (MTX-LPD) and aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) [1-3]. Although some MTX-LPDs regress after stopping methotrexate, monomorphic DLBCL rarely regresses and typically requires immediate chemo-immunotherapy [4-5]. The contribution of TNF-α inhibitors to lymphoma risk remains debated, with conflicting evidence from observational studies and meta-analyses [6-7]. Diagnosing lymphoma in RA patients on immunosuppression is challenging because symptoms often overlap with infection, RA flare, or drug-induced lung disease. This case illustrates such diagnostic complexity and demonstrates excellent therapeutic response following standard treatment.

Case Presentation

A 58-year-old woman with a 15-year history of seropositive, erosive RA presented with a six-week history of persistent dry cough, rhinorrhoea, post-nasal drip, progressive fatigue, reduced exercise tolerance, drenching night sweats, and 4 kg unintentional weight loss. She denied fever, haemoptysis, or infectious contact.

Her RA had been well controlled (DAS28 <2.6 for the previous four years) on methotrexate 20 mg weekly and adalimumab 40 mg fortnightly. Other medications included folic acid 5 mg weekly and paracetamol as needed. She was a lifelong non-smoker with no occupational exposures. On examination, the patient was afebrile and haemodynamically stable. A firm, non-tender 1 cm right supraclavicular lymph node and bilateral axillary lymphadenopathy were palpable. Respiratory examination showed mild expiratory wheeze with no crackles. There was no hepatosplenomegaly. Laboratory studies showed normocytic anaemia (haemoglobin 99 g/L, later 89 g/L), mild thrombocytopenia (135 × 10^9/L), elevated C-reactive protein (45 mg/L), and a mild cholestatic pattern on liver function tests. Contrast-enhanced CT of the chest, abdomen, and pelvis demonstrated bilateral axillary lymphadenopathy (largest node 19 mm), right hilar lymphadenopathy (12 mm), and borderline splenomegaly without pulmonary parenchymal disease.

Ultrasound-guided core biopsy of a right axillary lymph node demonstrated complete architectural effacement by intermediate-to-large atypical lymphoid cells. Immunohistochemistry was positive for CD20, BCL-2, MUM1, and c-MYC (>30% of cells), with a Ki-67 proliferation index of approximately 50%. CD10, CD5, CD23, and cyclin D1 were negative. Flow cytometry confirmed kappa light-chain restriction. Fluorescence in situ hybridisation (FISH) for MYC, BCL2, and BCL6 rearrangements was negative. EBER in situ hybridisation was negative. These findings established a diagnosis of DLBCL, activated B-cell (non-germinal centre) subtype, double-expressor phenotype. Methotrexate and adalimumab were discontinued immediately. A staging ^{18}F-FDG PET-CT scan demonstrated avid bilateral axillary, mediastinal, and hilar lymphadenopathy with low-grade splenic uptake, consistent with Ann Arbor stage IIIA disease. Bone marrow biopsy revealed minor paratrabecular CD20-positive lymphoid aggregates without overt marrow involvement. Following multidisciplinary discussion, the patient received six cycles of R-CHOP-21 (rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², vincristine 1.4 mg/m² capped at 2 mg, and prednisone 100 mg daily on days 1–5). Pegfilgrastim was administered for primary prophylaxis. She experienced grade 2 fatigue, transient grade 1 neutropenia, and a single episode of febrile neutropenia after cycle 3, which responded promptly to oral and intravenous antibiotics. Vincristine dose was reduced by 25% from cycle 4 due to mild sensory neuropathy. Interim PET-CT after cycle 3 demonstrated partial metabolic response (Deauville score 4). End-of-treatment PET-CT performed six weeks after cycle 6 showed complete metabolic remission (Deauville score 2). Nine months after completing therapy, she remains in clinical and radiological remission. Her rheumatoid arthritis is currently managed with hydroxychloroquine 200 mg twice daily and low-dose prednisolone 5 mg daily.

Discussion

This case highlights the diagnostic and therapeutic complexities of lymphoma arising in the context of long-term immunosuppression for rheumatoid arthritis. The patient had received methotrexate for over a decade and adalimumab for five years, durations consistent with reported latency periods for MTX-LPD and biologic-associated lymphoma [1,7]. Although 40–50% of MTX-LPDs regress after methotrexate withdrawal [5], monomorphic DLBCL almost never regresses and requires prompt chemo-immunotherapy [4-5]. The double-expressor phenotype, characterised by co-expression of BCL-2 and MYC proteins, is associated with inferior event-free survival, yet patients still respond well to R-CHOP when treated early [8]. The presenting respiratory symptoms in this case could easily have been attributed to infection, RA-associated airway disease, or methotrexate pneumonitis. The presence of B symptoms, supraclavicular and axillary lymphadenopathy, and cytopenias should always raise suspicion for lymphoma in immunosuppressed RA patients. Early biopsy remains essential to avoid delays in diagnosis and treatment.

Conclusion

Lymphoma should be considered early in rheumatoid arthritis patients receiving immunosuppressive therapy who present with constitutional symptoms or lymphadenopathy. Prompt lymph node biopsy, cessation of immunosuppression, accurate staging with PET-CT, and timely treatment with R-CHOP can achieve excellent outcomes, even in high-risk subtypes such as double-expressor DLBCL.

Patient Consent

Written informed consent was obtained from the patient for publication of this case report.

Declaration of Conflicting Interests

The authors declare no conflicts of interest.

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