Nasal type extranodal NK/T cell lymphoma diagnosed in a patient with rheumatoid arthritis under methotrexate

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ABSTRACT

Rheumatoid arthritis (RA) patients have increased risk of lymphoma which seems associated mainly with high inflammatory state and disease activity, but also with immunosuppressive agents or Epstein-Barr virus (EBV) infection. Many case reports describe lymphoproliferative lesions arising during methotrexate therapy, often EBV positive with possible regression after methotrexate withdrawal.

The authors report the case of an 85-year-old patient with erosive and seronegative RA, in remission under methotrexate who developed a midfacial destructive lesion with epistaxis and local inflammatory signs.

The magnetic resonance imaging showed a large nasal septum defect. Anti-neutrophil cytoplasmic antibodies titres and angiotensin converting enzyme were normal.

Biopsies of the lesion identified a NK/ T nasal type lymphoma. EBV latent membrane protein research on the lesion was negative.

Polymerase chain reaction analysis of the bone marrow aspirate showed EBV DNA positivity. Withdrawal of methotrexate was performed without tumour regression.

The authors described the single case of a patient with RA in stable remission under methotrexate who presented a rare type of lymphoma, a nasal type NK/T. EBV active replication was found in the bone marrow.

Keywords: Nasal type extranodal NK/T lymphoma; Rheumatoid arthritis; Epstein-Barr virus; Methotrexate.

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder characterised by a chronic polyarticular synovial inflammation eventually leading to irreversible joint damage with disability and deformity[1].

Studies have shown that, on average, rheumatoid arthritis patients have a doubled increased risk of lymphoma in comparison with the general population[1-5] both for Hodgkin lymphoma (HL) and non-Hodgkin's lymphoma (NHL)[6]. The risk seems greater for HL than for NHL[1-5].

Although the pathogenesis of RA-associated lymphoma is still unclear, it is speculated that the increased risk is related mainly to the high inflammatory state and disease activity levels[1], but also to immunosuppressive agents or Epstein-Barr virus (EBV) infection[2,3,5,7].

EBV is an oncogenic virus engaged in lymphomagenesis. An immunodeficient state is considered to provide a basis for the development of lymphomas, probably through EBV activation.

NHLs associated with states of immunossupression, such as HIV/ AIDS and organ transplantation, display an increased proportion of EBV positive lymphomas. In RA-associated lymphomas, the knowledge of the role of EBV infection is limited.4 Most of the information on EBV in RA-related lymphomas derives from case reports and case series, but the frequency of EBV in lymphomas reported from population-based studies seems to be low[4,8].

It has been suspected that latent EBV infection may participate in the development of lymphoma in RA patients, like EBV-associated B-cell lymphoproliferative disorders (LPD) occuring in immunossupressed patients[5].

EBV-positivity is associated with the virus' latent cycle and three different types of EBV latency have been

characterized. Latency Type III EBV infection is usually expressed in LPD arising in an immunocompromised host with impaired T-cell immunosurveillance[5].

Methotrexate, an inhibitor of the metabolism of folic acid, is a disease-modifying antirheumatic drug (DMARD) recommended as a first-line agent for RA management by the European League Against Rheumatism and the American College of Rheumatology[1].

A relationship between methotrexate treatment and the occurrence of LPD in RA has been extensively discussed[1].

Lymphoma has been reported as a complication of long-term, low-dose methotrexate treatment[5].

A study by Wolfe *et al.* compared the incidence rates of lymphoma in patients with RA with and without methotrexate. In the methotrexate group, this rate was higher than in the "no methotrexate, no biological agent" group. Unfortunately, no adjustment on RA severity was performed and the higher incidence could be related to a higher severity of RA in the methotrexate group and not to the drug effect itself[12].

A study has shown that methotrexate may induce EBV replication while producing immunossupression and that methotrexate could be associated with EBV--related NHL[9]. Spontaneous regression of LPD after methotrexate withdrawal has been described[1,4,5]. In patients who were treated with methotrexate for RA and developed NHL, remission was observed following methotrexate withdrawal especially in NHL with latency Type III EBV infection[9].

Such phenomena are well recognised in post-transplant immunossupression, which may be complicated by EBV-lymphoproliferative disorders that regress after withdrawal of the immunossupressive treatment[4].

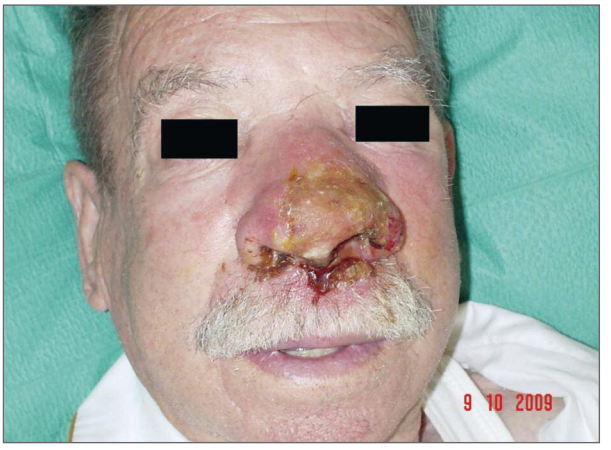

FIGURE 1. Nasal lesions

Many case reports describe lymphoproliferative lesions arising during methotrexate therapy. These lymphoproliferations are often EBV positive (about 30-50%)[7,10] and may regress with methotrexate withdrawal[10,11]. However, there is little evidence that methotrexate per se (as used to treat inflammatory disorders) increases lymphoma risk[7,12,13].

In a case-control study, only 4 of 378 RA-associated lymphomas displayed spontaneous regression, and only 1 of these 4 occurred in a patient exposed to methotrexate[13].

CLINICAL CASE

An 85-year-old caucasian male patient was diagnosed with erosive rheumatoid arthritis seronegative for rheumatoid factor and anti-cyclic citrullinated peptide and achieved remission (disease activity score 28 <2.6) under oral methotrexate (17.5 mg/weekly). His RA was not associated with secondary Sjögren syndrome or other extra-articular features.

Six years afterwards, he complained of epistaxis, nasal obstruction and presented a painful rapid growing midfacial destructive lesion showing local inflammatory signs and ulceration (Figure 1).

He did not have systemic symptoms such as fever, malaise or weight loss. There was also no evidence of other symptoms or signs, such as articular inflammation, lower respiratory symptoms, hepatosplenomegaly or lymphadenopathies.

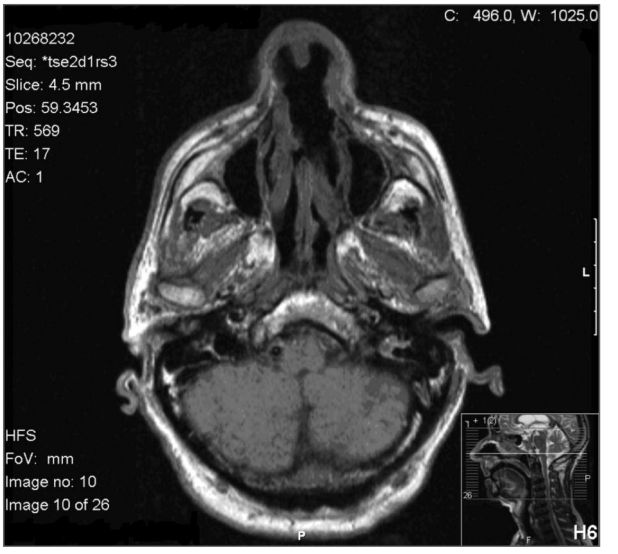

FIGURE 2. MRI showing large septal defect

A paranasal sinuses magnetic resonance imaging showed a large nasal septum defect measuring 36 x 34 mm suggestive of Wegener's granulomatosis (Figure 2).

A first nasal biopsy was performed: it showed extensive necrosis but was otherwise inconclusive.

Methotrexate was stopped and the patient was admitted to the hospital for further investigation.

Laboratory blood tests revealed a normocytic normochromic anemia (Hb 8.7 g/dL), an erythrocyte sedimentation rate of 34 mm/h, and a C-reactive protein of 101.6 mg/L. Serum creatinine, calcium and transaminases were within the normal range. The anti-neutrophil cytoplasmic antibodies titres were negative. Angiotensin converting enzyme was within the normal limits. There was no monoclonal immunoglobulin on serum and urine immunoelectrophoresis. The chest computed tomography (CT) scan didn t show any abnormalities.

He presented a subfebrile temperature and the nasal lesion showed a purulent exsudate. Secondary infection was suspected and there was isolation of *Pseudomonas aeruginosa*, *Proteus mirabilis* and Meticilin-resistant *Staphylococcus aureus* on the nasal exsudate s microbiological examination. Gentamicine was started according to in vitro antibiotic sensibility tests.

Another biopsy of the nasal lesion was performed, yielding a small quantity of viable material. Extensive fibronecrotic tissue was found. The immunocytochemistry study was performed using CD45, CD20, CD3, CD56/NK1 and granzime. Positivity for CD45 and a predominance of CD3 positive T lymphocytes were found. Few cells were granzyme positive.

The histhopathologic aspects raised the diagnosis of lymphoma. Given the lack of viable material yielded, another biopsy was required.

Finally, the third nasal biopsy identified aspects of a lymphoproliferative disorder suggestive of NK/ T nasal type lymphoma (Figure 3a). The immunocytochemical study showed positivity to CD45, CD3 (Figure 3b) and granzyme (Figure 3c). CD56/ NK expression, although tested several times, was not conclusive and unequivocal CD56 positivity was not demonstrated (Figure 3d). EBV latent membrane protein research on the lesion specimen was negative. EBV serologies were not performed.

A bone marrow aspirate was performed and polymerase chain reaction (PCR) analysis demonstrated EBV DNA positivity (1.2 x 10^3 copies/mL).

Cervical, thoracic, abdominal and pelvic CT scans were performed and no sign of metastasis was found. Regression of the nasal lesion was not observed after cessation of methotrexate. Radiotherapy was started with reduction of the tumoral mass and remission was achieved.

DISCUSSION

Nasal type extranodal NK/ T-cell lymphoma is characterized by vascular damage and destruction, prominent necrosis, cytotoxic phenotype and an association with EBV.

These lymphomas almost always show an extranodal presentation, mostly in the upper aerodigestive tract

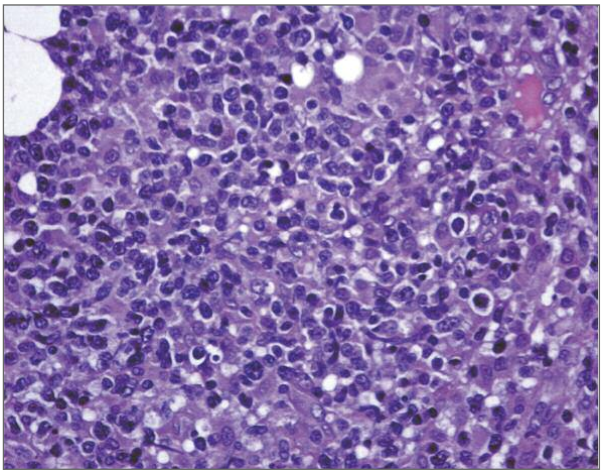

FIGURE 3a. Hematoxylin and eosin colouration showing lymphoproliferative disorder suggestive of NK/T nasal type lymphoma

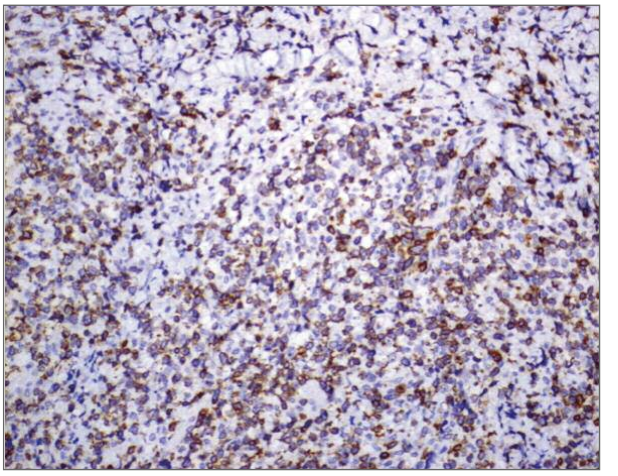

FIGURE 3b. Immunocytochemical study with positivity to CD3

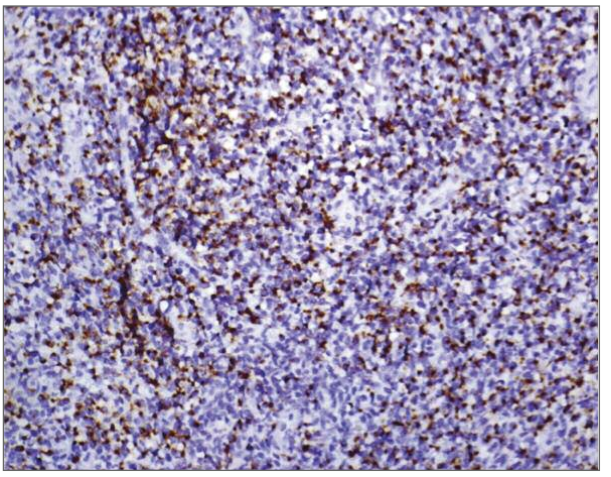

FIGURE 3c. Immunocytochemical study with positivity to granzime

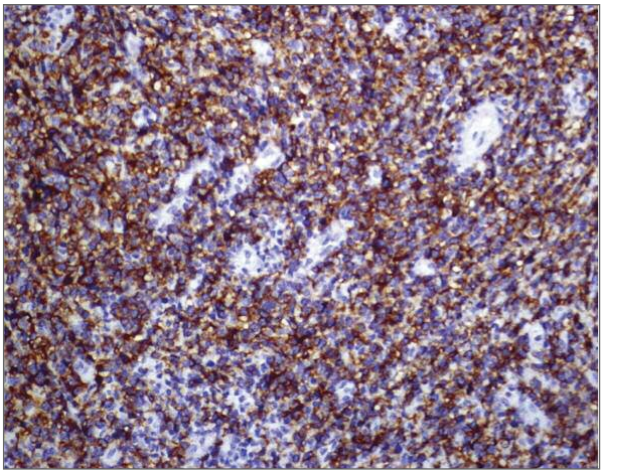

FIGURE 3d. Immunocytochemical study without unequivocal CD56 (NCAM) demonstration

(nasal cavity, nasopharynx, paranasal sinuses) with the nasal cavity being the most common site of involvement.

There is a very strong association with EBV, suggesting a probable pathogenic role of the virus. NK lymphoma cells are almost invariably infected with EBV[14].

Apoptosis of proliferating EBV-related tumour cells releases EBV DNA into the circulation. Quantification of circulating plasma EBV DNA level by quantitative PCR is used as a surrogate marker of tumour burden and is associated with disease status in patients with NK/T cell lymphomas. A high level of circulating plasma EBV DNA is correlated with a high tumour load, extensive disease, poorer response to treatment and inferior survival[14].

A high index of suspicion is essential for early diagnosis. The diagnosis relies on morphologic, immunophenotypic and molecular approaches[15].

Interestingly, it should be pointed out that the specimen for the biopsy of the involved organ should be as sizeable as possible, as zonal necrosis is typically found and a small biopsy may yield only necrotic tissue[15]. Multiple biopsies are usually required before a definitive diagnosis can be made.

Concerning the lymphomas associated with RA, it is known that the majority are of B-cell origin. Although the pathogenesis of RA-associated lymphoma is still unclear, high disease activity and high inflammation levels are associated with the increased risk of lymphoma in RA patients. Other factors, such as immunossupressive agents or EBV infection could also be implicated.

The authors reported the single case of a patient with RA in stable and long lasting remission under methotrexate who presented a rare type of lymphoma, a nasal type NK/T lymphoma. EBV active replication was found on the bone marrow.

Withdrawal of methotrexate was performed soon after the appearance of the lesion without visible tumour regression.

EBV positive lymphoproliferative lesions have been reported in patients under methotrexate therapy. These lesions may regress with methotrexate cessation, which did not happen in the case reported. There is little evidence that methotrexate increases lymphoma risk but further studies are required to clarify the exact mechanism for increased risk of lymphoma in RA.

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REFERENCES

1. Salliot C, van der Heijde D. Long-term safety of methotrexate monotherapy in patients with rheumatoid arthritis: a systematic literature research. Ann Rheum Dis 2009;68(7):1100-1104.
2. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: The effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum 2004;50(6):1740-1751.
3. Callan MFC. Epstein-Barr virus, arthritis, and the development of lymphoma in arthritis patients. Curr Opin Rheumatol 2004;16(4):399-405.
4. Baecklund E, Askling J, Rosenquist R, Ekbom A, Klareskog L. Rheumatoid arthritis and malignant lymphomas. Curr Opin Rheumatol 2004;16(3):254-261.
5. Miyazaki T, Fujimaki K, Shirasugi Y, et al. Remission of lymp-

homa after withdrawal of methotrexate in rheumatoid arthritis: relationship with type of latent Epstein-Barr virus infection. Am J Hematol 2007;82(12):1106-1109.
6. Smedby KE, Baecklund E, and Askling J. Malignant Lymphomas in Autoimmunity and Inflammation: A Review of Risks, Risk Factors, and Lymphoma Characteristics. Cancer Epidemiol Biomarkers Prev 2006;15:2069-2077.
7. Mariette X, Cazals-Hatem D, Warszawki J, et al. Lymphomas in rheumatoid arthritis patients treated with methotrexate: a 3--year prospective study in France. Blood. 2002;99(11):3909--3915.
8. Baecklund E, Sundstorm C, Ekbom A, et al. Lymphoma subtypes in patients with rheumatoid arthritis: increased proportion of diffuse large B cell lymphoma. Arthritis Rheum 2003, 48:1543- 1550.
9. Feng W, Cohen JI, Fischer S, et al. Reactivation of latent Epstein-Barr virus by methotrexate: A potential contributor to methotrexate-associated lymphomas. J Natl Cancer Inst 2004; 96:1691-1702.
10. Salloum E, Cooper DL, Howe G, et al. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. J Clin Oncol 1996;14(6):1943-1949.
11. Kamel OW, van de Rijn M, Weiss LM, et al. Brief report: reversible lymphomas associated with Epstein-Barr virus occurring during methotrexate therapy for rheumatoid arthritis and dermatomyositis. N Engl J Med 1993;328(18):1317-1321.
12. Wolfe F, Michaud K. Lymphoma in rheumatoid arthritis: the effect of methotrexate and anti-tumor necrosis factor therapy in 18,572 patients. Arthritis Rheum 2004;50(6):1740-1751.
13. Baecklund E, Iliadou A, Askling J, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum 2006;54(3):692-701.
14. Gill H, Liang RH, Tse E. Extranodal natural-killer/t-cell lymphoma, nasal type. Adv Hematol. 2010;2010:627401. doi: 10.1155/2010/627401.
15. Kwong YL. The Diagnosis and management of extranodal NK/T cell lymphoma, nasal type and aggressive NK-cell leukemia. J Clin Exp Hematopathol 2011; 51:21-28.

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