

## Lymphoproliferative disorders in paediatric rheumatic diseases. A report of two cases

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### ABSTRACT

*Lymphoproliferative disorders (LPD) are reported with a much lower frequency in children with rheumatic diseases than in their adult counterparts. We describe 2 patients who developed a lymphoma during the course of the disease. The first is a 16-year-old girl diagnosed with systemic juvenile idiopathic arthritis 6 years before who developed a mucosa-associated lymphoid tissue (MALT) lymphoma. The second report involves a boy diagnosed with systemic lupus erythematosus at 9 years of age who developed a Hodgkin's lymphoma 9 years after the disease onset. In spite of the low frequency of LPD in children with rheumatic diseases, these processes do occur.*

### Case 1

A 10-year-old Caucasian female presented in March 1990 with high spiking fevers, evanescent rash, and arthritis of her right knee. Laboratory investigations revealed ESR of 75 mm/h and negative RF and ANA. A diagnosis of systemic onset juvenile idiopathic arthritis (JIA) was made. The disease followed a polyarticular course which required treatment with prednisone during 46 months (cumulative dose 8,670 mg) and methotrexate (MTX) for 6 years (cumulative dose 3,070 mg). No other potential immunosuppressive drugs were used.

In May 1996, while on MTX she developed a painless, firm mass over her right parotid gland. A fine-needle aspiration biopsy revealed reactive lymphadenitis. By March 1997 the mass had increased. A CT showed multiple enlarged nodes in her right parotid area, which led to surgical excision of the parotid. Histopathology revealed a low-grade mucosa-associated lymphoid tissue (MALT) lymphoma. MTX was discontinued at that time. Serology was consistent with a past Epstein-Barr virus (EBV) infection. She had not shown xerophthalmia nor xerostomia, and her anti-Ro/SS-A and anti-La/SS-B antibodies were negative. She received local radiotherapy and her arthritis has been adequately controlled with NSAID and intra-articular steroids.

### Case 2

A 9-year-old Caucasian male presented in November 1991 with vasculitis of the fingertips, butterfly rash, positive ANA 1: 1,250, positive anti-DNA 49 IU/L (reference values 0-30 IU/L), and decreased complement (C3 75 mg/dL; C4 9.1 mg/dL). Lupus anticoagulant (LA) was positive, whereas anticardiolipin antibodies were negative. A diagnosis of SLE was made and he was started on steroids, 0.5 mg/kg/d, and hydroxychloroquine. His mother had a history of SLE.

In July 1993 the patient developed hematuria and proteinuria. Renal biopsy showed focal proliferative glomerulonephritis (Class III, WHO criteria). Prednisone was increased to 1 mg/kg/d and renal function returned to normal. In February 1996 he presented with ulcerative cutaneous vasculitis, malaise, polyarthritis, and anorexia. Laboratory evaluation showed an elevated anti-DNA titer (100 IU/L) with decreased C3 and C4 (60 mg/dL and 5.8 mg/dL respectively). He was started on IV cyclophosphamide for a total of 8 boluses (cumulative dose 8,100 mg), followed by azathioprine for 2 more years. Prednisone was discontinued on December 1999, after the patient had received a total of 17,330 mg.

In November 2000, when his disease was inactive, he presented with a firm, non-tender, enlarged cervical lymph node. A full blood count, biochemistry and complement concentration were normal. Mantoux was non-reactive. Serology disclosed a past EBV infection. A fine-needle aspiration biopsy of the node revealed mixed cellularity Hodgkin's lymphoma (HL) with positive staining for CD30, CD15, and nuclear p53. The disease was classified as stage IIA. He received 6 cycles of chemotherapy (AVBD protocol, combination of adriamycin, vinblastine, bleomycin, and dacarbazine), followed by radiotherapy (mantle supradiaphragmatic; 36 Gy) and complete remission was achieved. Currently his treatment is limited to acetyl salicylic acid 125 mg/d due to LA persistence. He has remained relapse-free from the lymphoma since.

### Discussion

The literature reveals about 100 adults with rheumatoid arthritis (RA) treated with MTX who developed a lymphoma, mainly non-Hodgkin's (NHL). Evidence of EBV infection was observed in approximately 40% of the tested patients, confirming a clonal integration of the viral genome in some of them (1). On the other hand, we have found only 5 reports of children with JIA who presented a lymphoma (2-6), mainly HL (in 4/5) after 1.3 to 2.75 years of therapy with MTX. Two JIA patients with HL had evidence of EBV infection by immunohistochemical analysis. Whether there is a link between the development of lymphomas in patients with inflammatory arthropathies and exposure to MTX, the most widely used second-line treatment in JIA and RA (7) or EBV infection, an extremely common process, is not clear at this time (8). In our patients no EBV status data was obtained from their biopsies, although it should be kept in mind that patients with autoimmune diseases undergoing long-term immunosuppression are at risk for developing lymphoproliferative disorders. According to the Spanish National Register of Paediatric Tumors, which collects about 100 cases of lymphoma per year (R. Peris, personal communication), no other lymphomas have been reported in children with JIA to date in our country. MALT lymphoma has been observed in patients with Sjögren's syndrome, both the primary form and that associated

with RA (9). In addition, MALT lymphomas have occasionally been described in children with HIV or *Helicobacter pylori* infections (10, 11). Therefore, this report represents to the best of our knowledge the first instance of a child with JIA and a MALT lymphoma. With regard to the possible relationship between lymphoproliferative disorders (LPD) and SLE in children, our review only found one adolescent who developed a Hodgkin's lymphoma (12). Some series of adults with SLE have shown an increased incidence of NHL (13), whereas others have observed a higher than expected incidence of HL (14). This report confirms that, although extremely uncommon, patients with paediatric rheumatic diseases are at risk of developing LPD.

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