

Systemic lupus erythematosus following acute lymphocytic leukemia

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Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder of autoimmune origin, characterized by a wide variety of associations and an unpredictable course. The association of SLE and myeloproliferative and lymphoproliferative malignancies is widely reported in the adult literature.¹⁻⁴ Most of the data show that the malignancy is detected after the diagnosis and treatment of SLE.⁴ However, the development of SLE has been described following treatment of different types of malignancies.⁵⁻⁸ There is only scarce information available as to the association of both disease conditions in children. We report here a girl with SLE diagnosed 4 years after acute lymphocytic leukemia (ALL) was successfully treated.

Case

A 12-year-old girl who presented at the age of 3 years with fever, lymphadenopathy, hepatosplenomegaly and pancytopenia was diagnosed with ALL based on the clinical, bone marrow aspirate and biopsy findings. She was started on the CCG 1891 chemotherapy protocol, comprising cycles of prednisone, L-asparaginase, vincristine, methotrexate, 6-mercaptopurine and cyclophosphamide. She completed her chemotherapy over 3 years and subsequently remained in full remission. Four years later she presented with multiple cervical lymphadenopathy associated with malaise and intermittent fever. Her work up, including bone marrow aspirate and lymph node biopsy, was normal. However, a few days later, she presented with shortness of breath and respiratory distress. She was treated with broad-spectrum antibiotics but her condition deteriorated and she required admission to the intensive care unit where she received ventilator support. She was found to have pulmonary hemorrhage and she developed generalized tonic clonic convulsions. Computed tomography (CT) of the brain showed no intracranial bleeding and septic screening was negative. She was started empirically on intravenous methylprednisolone 1 gram for 3 consecutive days, and there was marked improvement. She was sent home on tapering doses of oral prednisone and phenobarbitone. A few weeks after stopping prednisone she presented with a facial erythematosus rash and active synovitis in multiple joints. Investigations at a local hospital showed a normal complete blood count (CBC), and normal renal and liver function. However, the antinuclear antibody (ANA) titer was very high (1:1280) and complement (C3, C4) levels were low; she also had significant proteinuria. Further evaluation in our hospital revealed a normal CBC with mild lymphopenia ($1.34 \times 10^9/L$) and a high erythrocyte sedimentation rate (ESR) (97 mm/h). She had normal renal and liver function, but the serum albumin level was low (15 g/L). Urinalysis found blood +3, protein +3 and granular casts and proteinuria of 0.74 g/day in a 24-hour urine collection. Repeat serology showed ANA 1:2560, anti-double stranded DNA (ds DNA) 1785 μ/mL (normal,

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Table 1. Clinical and laboratory features in three children with systemic lupus erythematosus following acute lymphocytic leukemia.

| | Sheehan, 2002 ⁹ | Steinbach and Sandborg, 2001 ¹⁰ | Our patient |
|------------------------------|-------------------------------------|---|---|
| Age at onset of ALL | 2 years | 4 years | 3 years |
| Gender | Female | Male | Female |
| Treatment of ALL | Chemotherapy/radiotherapy | Chemotherapy/ autologous BMT | Chemotherapy |
| Interval of remission | 10 years | 3 ½ years | 6 years |
| SLE clinical features | Arthritis, Raynoud's syndrome, rash | Arthritis, malar rash | Arthritis, malar rash, pulmonary hemorrhage, seizure, nephritis |
| SLE lab features | ANA+, low WBC, anti-Smith | Low plat, ANA+, high ds-DNA, anti-Smith, low C3, C4 | Low C3, C4, ANA+, high ds-DNA, APL+, Stage-V nephritis |
| Work-up for relapse | N/A | BMA (negative) | BMA/ lymph node biopsy (negative) |
| Treatment for SLE | N/A | Steroids, IV cyclophosphamide | Steroids, cyclosporine, hydroxychloroquine |

0-20 µ/mL), anti-Sjögren's syndrome A antibodies (SS-A) 892 µ/mL (normal, 0-4 µ/mL), SS-B 10.2 µ/mL (normal, 0-4 µ/mL), anticardiolipin IgG 25.5 GPL/mL (normal, 0-15 GPL/mL), anticardiolipin IgM 11 MPL/mL (normal, 0-7 MPL/mL), anti-β₂ glycoprotein IgG 14.9 SGH/mL (normal, 0-10 SGH/mL), anti-phosphatidylserine IgG 25.5 GPL/mL (normal, 0-10 GPL/mL), C3 0.24 g/L (normal, 0.9-1.8 g/L) and C4 <0.05 g/L (normal, 0.1-0.4 g/L). Repeat bone marrow aspirate and biopsy revealed normocellular marrow with no evidence of leukemia. Lymph node biopsy and floctometry showed reactive cells with no phenotypic evidence of recurrent lymphoma or leukemia. The morphology of renal biopsy on the light microscopy examination showed lupus nephritis class V, however, the electron microscopy examination revealed evidence of class III according to the WHO classification. Based on these findings, she was diagnosed with SLE and treated accordingly with prednisone, hydroxychloroquine and cyclosporine.

Discussion

SLE has been reported to precede or follow the diagnosis of malignant disorders¹⁻⁴ suggesting a link

between the two diseases, which cannot be explained by coincidence alone. However, various hypothesis such as the role of chemotherapy in disturbing the immunoregulatory mechanisms or a common etiologic agent and/or a similar genetic susceptibility for SLE and malignancy, have failed to explain the exact mechanism of association between SLE and malignancy.^{1,7,9}

We report a girl with SLE in whom ALL preceded the onset of SLE by four years. The diagnosis of SLE was made based on major multi-organ involvement (seizure, pulmonary hemorrhage and membranous nephritis) in addition to arthritis and mucocutaenous manifestations and the presence of a high ANA and ds-DNA titer and low C3 and C4 levels. A review of the English literature (1966-2004) through *Medline* (Ovid) for the development of SLE following ALL in children revealed only two cases^{9,10} (Table 1). All of these cases satisfied the revised American College of Rheumatology (ACR) Criteria for SLE.¹¹ All cases, including ours, developed SLE within several years after completion of successful treatment of ALL.

Although some of the clinical features of SLE, namely arthritis, lymphadenopathy and leukopenia,

may mimic those of ALL, the described patients had features typically associated with SLE such as malar rash, Raynaud's syndrome and nephritis. The presence of ANA has been reported in patients with malignancy, but none had positive autoantibodies such as ds-DNA and anti-Smith antibodies or low complement levels.

Although the association of SLE and ALL is very rare, the possibility of the development of autoimmunity in patients with malignancy after chemotherapy and/or bone marrow transplant must be considered after excluding the recurrence of leukemia or other malignancy.

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