

Methotrexate-associated Lymphoproliferative Disorders

Definition

- A lymphoid proliferation or lymphoma in a patient immunosuppressed with methotrexate, typically for treatment of autoimmune disease (rheumatoid arthritis, psoriasis, dermatomyositis)
- May resemble large B-cell lymphoma, Hodgkin lymphoma, or polymorphous PTLD
- These LPDs are often EBV related, and may regress with cessation of methotrexate therapy

Epidemiology

- Frequency of these disorders is not known
- Slightly over 100 cases have been reported in the literature
- 85% of the cases have been seen in patients with rheumatoid arthritis, 6% in dermatomyositis, and 6% in psoriasis.

Epidemiology

- Patients with RA are estimated to have a 2-20-fold increased risk of lymphoma in the absence of methotrexate therapy. It remains debated whether methotrexate *per se* increases the risk of lymphoma development.
- A case control study of lymphoma developing in patients with and without RA demonstrated no increased frequency of EBV-positivity in the RA patients, suggesting that most lymphomas developing in RA patients are not immunosuppression-related.

Epidemiology

- The interval from the diagnosis of connective tissue disease to the development of lymphoma is approximately 15 years, which is not significantly different from that in patients not treated with methotrexate.
- The mean duration of therapy with methotrexate is 3 years, with a range of 0.5-5.5 years.
- The median cumulative dose of methotrexate in one study was 0.8 g (0.01-2.9g).

Site of Involvement

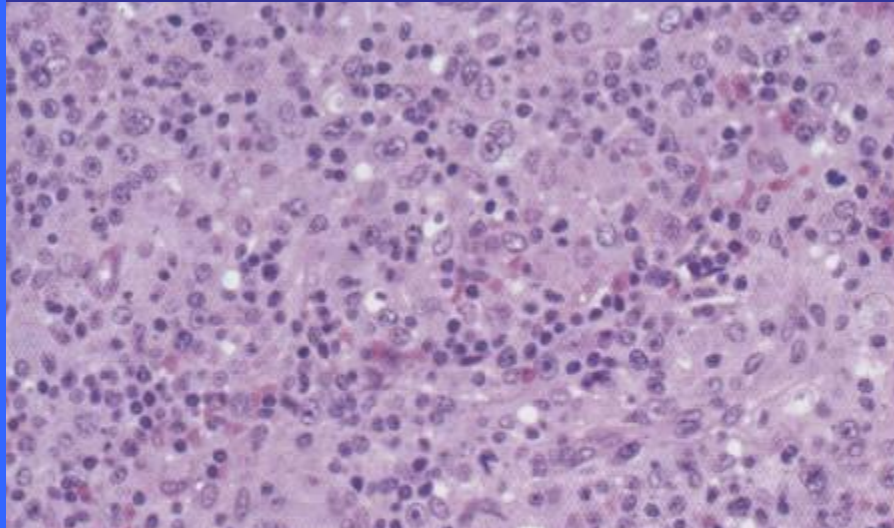
- Overall approximately 40% of reported cases have been extranodal, including the gastrointestinal tract, skin, lung, kidney and soft tissue.
- The frequency of extranodal involvement differs among histological types, with 50% of DLBCL, 20% of HL, 100% of lymphoplasmacytic lymphomas and atypical lymphoplasmacytic infiltrates, and 40% of follicular lymphomas being extranodal.

Clinical Features

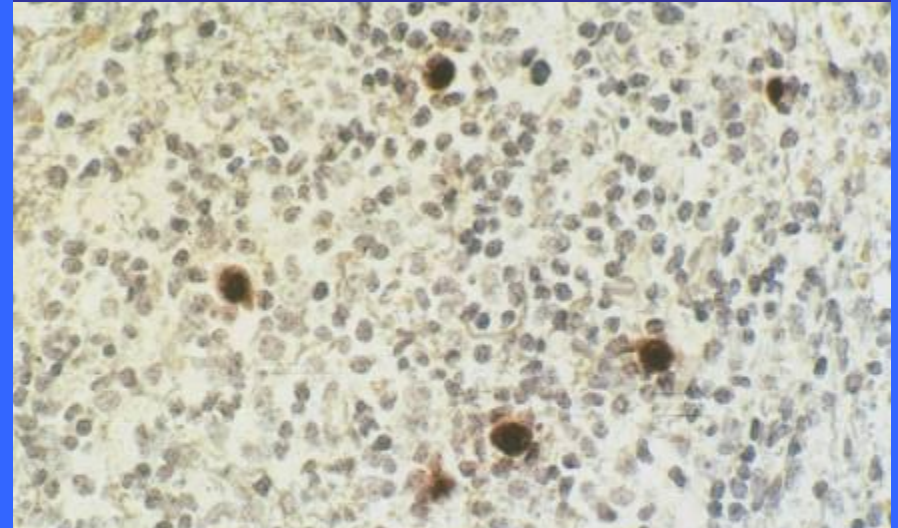
These do not appear to differ from those of non-immunosuppressed patients with lymphomas of similar histological types.

Morphology

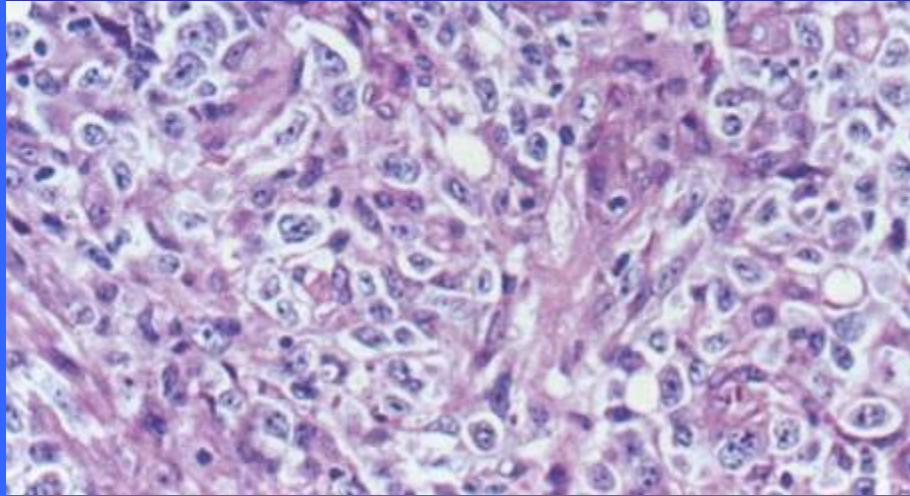
- The reported cases are most commonly DLBL (35%) and HL (25%) or HL-like lesions (8%).
- Less frequent cases of follicular lymphoma (10%), Burkitt lymphoma (4%), and peripheral T-cell lymphomas (4%).
- Polymorphous, small lymphocytic or lymphoplasmacytic infiltrates have been described in approximately 14% of the cases.



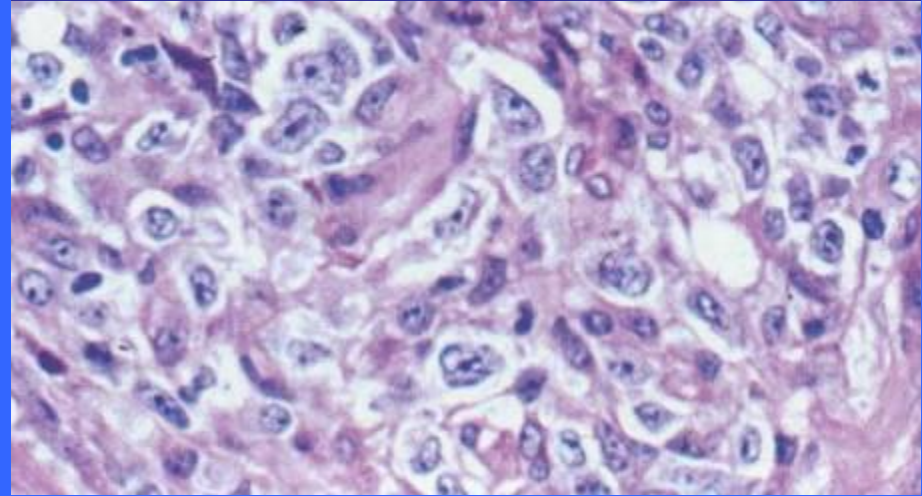
Methotrexate-induced Hodgkin-like lesion



EBER



**Polymorphous EBV-pos
Lymphoproliferative disorder**



EBV-pos DLBCL

Etiology

- Approximately 50% of the lymphoproliferative disorders are EBV+.
- The frequency of EBV infection differs among the histological types, with EBV detected in approximately 50% of DLBCL, 75% of Hodgkin lymphoma and Hodgkin-like lesions, 50% of lymphoplasmacytic infiltrates, and 40% of cases reported as follicular lymphoma.

Immunophenotype

- The immunophenotypes of the lymphomas do not appear to differ from those of similar histological types not associated with methotrexate therapy.
- In cases classified as Hodgkin-like, the large cells were CD20+ and CD30+ but CD15-, while in cases classified as Hodgkin lymphoma, the large cells were CD15+.

Genetic Features

- The genetic features of these cases do not appear to differ from those of similar histological types not associated with methotrexate therapy.
- Only a few cases of follicular lymphoma have been reported; however, these have not been studied for the BCL2 translocation t(14;18).

Prognosis and Predictive Factors

- Overall, approximately 60% of the reported cases have shown at least partial regression in response to withdrawal of methotrexate; the majority of responses have occurred in EBV-positive cases.
- In DLBCL, approximately 40% have regressed, while 60% require cytotoxic therapy; overall survival is approximately 50%.

Prognosis and Predictive Factors

- In HL about 30% regress, while of the HL-like lesions, 100% regressed; the overall survival for HL cases is about 75%.
- Cases classified as lymphoplasmacytic infiltrates or lymphoplasmacytic lymphoma typically regress with withdrawal of methotrexate therapy and survival is about 75%.