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Chlamydia psittaci and ocular adnexal lymphomas

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Infectious agents, including bacteria, have been variously associated with lymphomagenesis and, in some cases, regarded as targets for new therapeutic approaches. Several lines of evidence indicates that ocular adnexal lymphomas (OAL) may be antigen-driven disorders, although the source of the putative antigen(s) is still unknown. *Chlamydiae* infection is responsible for inflammatory ocular diseases including chronic follicular conjunctivitis, which could provide persistent antigenic stimulation. On these grounds, we have carried out a study aimed to assess whether infection by *Chlamydiae* is associated with the development of OAL. To these ends, the presence of *Chlamydia (Chl.) psittaci, trachomatis, and pneumoniae* DNA was investigated by multiplex PCR in 40 OAL samples and in 20 non-neoplastic orbital biopsies and 26 reactive lymphadenopathy samples used as controls. The same analysis was performed in peripheral blood mononuclear cells (PBMCs) from 21 OAL patients and 38 healthy individuals. PCR products were sequenced to confirm the specificity of the fragment amplified. The location of the microorganisms within lymphomatous lesions was carried out by immunohistochemical detection of *Chlamydia* lipopolysaccharide. The analysis disclosed that 32 (80%) of the 40 OAL investigated carried *Chl. psittaci* DNA, whereas all lymphoma samples were negative for Chl. trachomatis and pneumoniae. In contrast, none (0%) of the non-neoplastic orbital biopsies was positive for *Chl. psittaci* DNA (0% vs. 80%; p<0.00001) and only three of 26 (12%) reactive lymphadenopathies (12% vs. 80%; p<0.00001) carried *Chl. psittaci* DNA. Nine (43%) of 21 patients with Chlamydia-positive OAL carried *Chl. psittaci* DNA also in PBMCs, whereas none (0%) of the PBMCs from healthy donors was positive for *Chl. psittaci* DNA (43% vs. 0%; *p<0.00001*). A variable degree of sequence heterogeneity was found, indicating that OAL probably carry unrelated variants of *Chl. psittaci*. Immunocytochemical analysis localized the immunoreactivity for *Chlamydia* lipopolysaccharide in tumor infiltrating cells characterized by macrophage-like morphology.

These findings provide the rationale to verify whether, similarly to what adopted for *Helicobacter pylori*–associated gastric lymphomas, eradication of *Chl. psittaci* infection with a specific antibiotic therapy may constitute a novel therapeutic approach for OAL. Seven patients with *Chl. psittaci*-positive marginal zone B-cell lymphoma of the ocular adnexa, at diagnosis or relapse, were treated with doxycycline 100 mg, bid orally, for three weeks. The presence of *Chl. psittaci* DNA in PBMC was assessed before and after treatment in six patients. Objective lymphoma regression was assessed one, three and six months after therapy conclusion and every six months during follow-up. All patients completed antibiotic therapy, with excellent tolerability. At one month from doxycycline assumption, chlamydial DNA was no longer detectable in PBMC of all four positive patients. Objective response was complete in two cases and partial in three. Duration of response was 28+, 26+, 9+, 5+, and 3+ months, respectively.

The results of the present study demonstrate that patients with OAL have a high prevalence of *Chl. psittaci* infection in both tumor tissue and PBMCs. This association appears highly specific and does not reflect the occurrence of a subclinical infection widespread among the general population. Non-neoplastic milieu elements, i.e. macrophages, may constitute a reservoir for *Chl. psittaci* infection potentially able to provide local growth-promoting stimuli for lymphoma cells. *Chl. psittaci*-eradicating antibiotic therapy with doxycycline is followed by objective response in OAL patients, even after multiple relapses of the disease. A confirmatory large phase II trial is warranted to confirm whether this fast, cheap and well-tolerated therapy could replace other more aggressive strategies as first-line treatment for these lymphomas.

References

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