Chlamydia psittacci-eradicating antibiotic therapy in patients with advanced-stage ocular adnexal MALT lymphoma

Twenty-five percent of ocular adnexal mucosa-associated lymphoid tissue (MALT) lymphoma (OAML) patients have disseminated disease (distant nodal and/or extranodal lesions) [1]. These patients are usually treated with chemotherapy, which is active though, sometimes, too toxic, or with rituximab, which is better tolerated but has only transient activity. Generally, these patients experience multiple relapses, requiring more lines of treatment, but exhibit an excellent cause-specific survival. Accordingly, lack of side-effects is critical in designing new treatments for disseminated OAML.

OAML is variably associated with Chlamydia psittacci (Cp) infection [1, 2]. In a phase II trial [3], Cp-eradicating therapy with doxycycline has been associated with lymphoma regression in 64% of Cp-positive OAML, even in patients with regional lymphadenopathies. This finding contrasts with the experience gained in gastric MALT lymphoma, where nodal involvement predicts a poor response to antibiotics [4], and indicates a role for Cp-eradicating therapy in the management of disseminated OAML.

Although patients with disseminated OAML were excluded from the above-mentioned trial [3], preliminary results prompted us to propose doxycycline treatment also to these patients. To date, six patients with relapsed or newly diagnosed Cp-positive, disseminated OAML (Figure 1) were treated according to the same protocol [3].

Cp DNA was detected by Touchdown enzyme time release-PCR [1] in preantibiotic samples from both ocular adnexae and peripheral blood mononuclear cells (PBMCs) in all six patients. Conversely, Cp DNA was not detected in biopsies of systemic lesions (subcutaneous nodules) from patients 1, 3 and 4.

After doxycycline treatment, Cp DNA was no longer detectable in PBMC of the six patients, and after a median follow-up of 31 months (7–56 months), three patients achieved an objective response (Figure 1): patient 1 achieved a durable complete response complete disappearance of all evidence of lymphoma of the orbit lesion, with stable systemic disease but demanded immediate salvage therapy; patients 2 and 4 experienced progressive disease requiring additional therapy. All patients but one are alive, with a median overall survival of 81 months (7–128 months); the remaining patient died of cardiovascular complications when she was 91 years old. The study conformed to the tenets of the Declaration of Helsinki and written informed consent was obtained from each patient.
disease; patient 3 (Figure 1A and B) achieved a durable complete regression of systemic lesions, with stable orbit disease; patient 5 (Figure 1C and D) achieved a partial regression of both primary and systemic lesions. Interphase FISH (Figure 1) showed trisomy/polysomy 3–18 in four patients, but this was not associated with response.

In conclusion, systemic Cp infection is common in advanced stage OAML and could favor dissemination in these malignancies. This is in line with our unpublished experience on 40 consecutive Cp-positive OAML patients, where Cp infection of PBMC was detected in 11% of patients with stage I lymphoma and in 62% of disseminated cases ($P = 0.001$). Doxycycline is a valid therapeutic alternative in disseminated OAML, mostly in elderly patients (Figure 1), but response degree can vary among the lesions, indicating that tumor clones dependent on antigenic stimulation may be heterogeneously distributed. The obscure effect of a disseminated infection like that caused by Cp cannot be easily compared with the effect of the local Helicobacter pylori infection on gastric MALT lymphoma. Moreover, other interfering factors that could explain the heterogeneous response observed in our patients, like prolonged contact with infected household animals resulting in continuous re-infections [5] or concomitant infections, cannot be excluded; for instance, four patients had chronic conjunctivitis and prolonged contact with household cats, while patients 1 and 3 had hepatitis C virus infection. Additional studies are needed to address molecular evidence explaining this heterogeneity and pathogenic implications of the absence of Cp DNA in systemic lesions.

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