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Abstract

Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) are associated with various infectious pathogens. We analyzed the presence of Chlamydia psittaci, Chlamydia pneumoniae, and Chlamydia trachomatis DNA in 47 nongastrointestinal and 14 gastrointestinal MALT lymphomas, 37 nonmalignant control samples, and 27 autoimmune precursor lesions by polymerase chain reaction amplification and direct sequencing. In 47 nongastrointestinal MALT lymphomas, 13 (28%) were positive for C psittaci DNA compared with 4 (11%) of 37 nonmalignant control samples (P = .09). C psittaci was detected at variable frequencies in MALT lymphomas of different sites: lung, 100% (5/5; P < .01); thyroid gland, 30% (3/10; P > .05); salivary gland, 13% (2/15; P > .05); ocular adnexa, 15% (2/13); and skin, 25% (1/4). Of 27 autoimmune precursor lesions (11 Hashimoto thyroiditis and 16 Sjögren syndrome), 11 (41%) contained C psittaci DNA. Only 1 (7%) of 14 gastrointestinal MALT lymphomas was positive for C psittaci. All specimens were negative for C trachomatis and C pneumoniae. Besides ocular adnexal lymphomas, C psittaci infection is associated with nongastrointestinal MALT lymphomas and autoimmune precursor lesions, suggesting possible involvement of C psittaci-induced antigenic-driven MALT lymphomagenesis.
Hematopathology / CHLAMYDIA psittaci IN MALT lymphomas

Chlamydia psittaci Infection in Nongastrointestinal Extranodal MALT Lymphomas and Their Precursor Lesions

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Key Words: MALT lymphoma; Chlamydia psittaci; Infection

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Abstract

Extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue (MALT) are associated with various infectious pathogens. We analyzed the presence of Chlamydia psittaci, Chlamydia pneumoniae, and Chlamydia trachomatis DNA in 47 nongastrointestinal and 14 gastrointestinal MALT lymphomas, 37 nonmalignant control samples, and 27 autoimmune precursor lesions by polymerase chain reaction amplification and direct sequencing.

In 47 nongastrointestinal MALT lymphomas, 13 (28%) were positive for C psittaci DNA compared with 4 (11%) of 37 nonmalignant control samples ($P = .09$). C psittaci was detected at variable frequencies in MALT lymphomas of different sites: lung, 100% (5/5; $P < .01$); thyroid gland, 30% (3/10; $P > .05$); salivary gland, 13% (2/15; $P > .05$); ocular adnexa, 15% (2/13); and skin, 25% (1/4). Of 27 autoimmune precursor lesions (11 Hashimoto thyroiditis and 16 Sjögren syndrome), 11 (41%) contained C psittaci DNA. Only 1 (7%) of 14 gastrointestinal MALT lymphomas was positive for C psittaci. All specimens were negative for C trachomatis and C pneumoniae.

Besides ocular adenexal lymphomas, C psittaci infection is associated with nongastrointestinal MALT lymphomas and autoimmune precursor lesions, suggesting possible involvement of C psittaci–induced antigenic-driven MALT lymphomagenesis.

Extranodal marginal zone (MZ) B-cell lymphomas of mucosa-associated lymphoid tissue (MALT lymphomas) are the second most common indolent lymphomas among all non-Hodgkin lymphomas, originating from B cells of the MZ of MALT.1,2 There is clear evidence that MZ lymphomagenesis is closely associated with chronic antigenic stimulation by microbial pathogens or autoantigens.3

The list of pathogens associated with MZ lymphoproliferations has grown longer and currently includes at least 5 members: Helicobacter pylori, Campylobacter jejuni, Borrelia burgdorferi, Chlamydia psittaci, and hepatitis C virus. These pathogens have been associated with MZ-derived gastric lymphoma, immunoproliferative small intestinal disease, cutaneous lymphoma, ocular adenexal lymphoma, and spleen lymphoma.3

The most common site of MALT lymphomas is the gastrointestinal tract, especially the stomach, where they are closely linked to H pylori–induced chronic gastritis, but virtually every organ can be affected.2,4 Because most of the organs in which MALT lymphomas develop lack lymphoid tissue, MALT acquisition following chronic antigenic stimulation is a prerequisite for lymphomagenesis.5 The best characterized model of “indirect lymphomagenesis” involving sustained stimulation of the immune system leading to lymphoid transformation is the H pylori–associated MALT lymphoma of the stomach.1,5 H pylori eradication leads to complete regression of MALT lymphoma in early stages of disease, demonstrating a continuous dependency on chronic antigen stimulation.

Similar to chronic infection with H pylori, other pathogens have been reported to be associated with the development of MALT lymphomas at nongastrointestinal sites, although the causative role is less well established.3,6,7 C psittaci...
was identified as the causative infectious agent of ocular adnexal MALT lymphomas. C psittaci was detected in up to 87% of ocular adnexal MALT lymphoma specimens, and a significant proportion of patients responded to doxycycline treatment.8,13,14 The strong association of C psittaci with ocular adnexal lymphomas, observed by Ferreri et al,5 could not be confirmed by other groups,15-17 suggesting evidence for geographic heterogeneity.18 There is also serologic evidence of an association between chronic chlamydial infection and non-Hodgkin lymphomas.19 Recently, C psittaci was detected in nodal and extranodal lymphomas, including different lymphoma entities and affecting localizations other than ocular adnexa.20 However, in that study, only a small number of non-gastrointestinal MALT lymphomas other than ocular adnexal cases were included.

The aim of our study was, therefore, to investigate the presence of C psittaci, Chlamydia pneumoniae, and Chlamydia trachomatis DNA in a larger cohort of nongastrointestinal MALT lymphomas, nonmalignant control samples of the respective organs, and specimens from patients with Sjögren syndrome and with Hashimoto thyroiditis. As control samples from the gastrointestinal tract, gastric and intestinal MALT lymphomas and H pylori–positive gastritis were included. To determine the serum prevalence of C psittaci, serum samples of patients with nongastrointestinal MALT lymphomas and control serum samples from a standard hospital population were analyzed.

Materials and Methods

Clinical Samples

A total of 47 MALT lymphomas were studied. Specimens were obtained from nongastrointestinal sites (lung, 5; thyroid gland, 10; salivary gland, 15; ocular adnexa, 13; and skin, 4). Normal lung tissue (n = 10), normal thyroid tissue (n = 13), normal salivary gland tissue (n = 7), and specimens obtained from patients with Sjögren syndrome (n = 16) and patients with Hashimoto thyroiditis (n = 11) were included as nonmalignant control samples. From the gastrointestinal tract, gastric MALT (n = 6), intestinal MALT (n = 8) lymphomas and H pylori–positive gastritis (n = 7) samples were included.

Lymphoma entities were classified according to the World Health Organization classification of lymphoid neoplasms.21 Macrodissected tissue containing more than 80% lymphoma cells from formalin-fixed, paraffin-embedded tissue was processed for DNA isolation.

For the study, 14 serum samples from patients with nongastrointestinal MALT lymphomas were obtained from the serum collection of the Medical University of Vienna, Vienna, Austria. As control samples, 100 serum samples obtained from 100 patients visiting the outpatient department of the Medical University of Graz, Graz, Austria, were analyzed.

All samples were analyzed in triplicate by C psittaci polymerase chain reaction (PCR) and positive cases directly sequenced as published previously.22 Real-time PCR was used for C trachomatis and C pneumoniae.

C psittaci PCR and DNA Sequencing

For detection of C psittaci, a PCR according to Madico et al22 was performed using identical primer sequences in single PCR reactions. The total volume of 40 μL of Master mixture contained 100 pmol of each primer, 0.25 mmol/L deoxynucleoside triphosphates (dNTPs), PCR buffer containing 15 mmol/L magnesium chloride, and 2 U of HotStarTaq DNA polymerase (Qiagen, Hilden, Germany). A touchdown method for thermal cycling was used according to Madico et al.22

PCR products were separated by electrophoresis in 2% agarose gels at 95 V for 30 minutes with 1× tris(hydroxymethyl) aminomethane-acetate EDTA buffer and visualized with ethidium bromide (0.5 mg/mL). DNA fragments with the appropriate size of 111 base pairs were excised from the agarose gel with a clean, sharp scalpel, and DNA was extracted with the QIAquick Gel Extraction Kit (Qiagen). In addition, a control PCR was performed using 100 pmol of the primers Pim1-1fw and Pim1/1-rev-a, 0.25 mmol/L dNTPs, PCR buffer containing 15 mmol/L magnesium chloride, and 0.75 U of HotStarTaq DNA polymerase (Qiagen). To prove the origin of C psittaci, sequencing of 100 ng of the extracted samples was performed, according to the BigDye Terminator v1.1 Cycle Sequencing Kit protocol (Applied Biosystems, Foster City, CA) with primers CPS100 and CPS101. Products were purified by using ethanol precipitation, and samples were diluted in Hi-Di Formamide (Applied Biosystems). Sequencing was done with the ABI Prism 310 Genetic Analyzer (Applied Biosystems), and the results were evaluated by BLAST search.

Real-Time PCR for Detection of C trachomatis and C pneumoniae DNA

As described by Aigelsreiter et al,9 a real-time PCR protocol was used for the detection of C pneumoniae DNA. The real-time PCR assay on the LightCycler 2.0 instrument (Roche Applied Science, Mannheim, Germany) was used as recently described.23 For the detection of C trachomatis DNA, a commercially available assay, the AMPICOR Chlamydia trachomatis test (Roche Molecular Systems, Branchburg, NJ), was used according to the manufacturer’s instructions.

Immunohistochemical Studies for Detection of Chlamydial Antigen

If a sufficient amount of tissue (n = 24) was available, immunohistochemical analysis for C psittaci was performed.
Paraffin sections were prepared for the presence of chlamydial antigen using a Chlamydiaceae family–specific mouse monoclonal antibody (Ab) directed against chlamydial lipopolysaccharide (clone ACI-P, Progen, Heidelberg, Germany). Detection was performed with the ChemMate Detection Kit (DAKO, Glostrup, Denmark) according to the manufacturer’s instructions. Briefly, paraffin sections were deparaffinized in xylene and rehydrated through graded ethanol to water. Antigen retrieval was performed by 10 minutes of enzyme digestion (Promase, DAKO). To inhibit the endogenous peroxidase activity, the slides were immersed in peroxidase-blocking solution for 5 minutes at room temperature (RT) and incubated with the primary Ab diluted in Ab diluent with background-reducing components for 60 minutes at RT. The sections were incubated for 30 minutes at RT with the link Ab; developed in 3-amino, 9 ethyl-carbazole substrate solution for 10 minutes at RT; and counterstained with hematoxylin. A negative control experiment of each section was performed using the Ab diluent instead of the primary Ab. Intestinal tissue from gnotobiotic piglets experimentally infected with avian C psittaci strain T49/90 was used as a positive control sample.

**Serum Assay**

For analysis of the serum samples, the recomLine Testkit Chlamydia (Mikrogen), a qualitative in vitro test for the detection of IgG and IgA-Ab against protein antigens of C trachomatis, C pneumoniae, and C psittaci, was used according to the manufacturer’s instructions.

**Statistical Analyses**

The distribution of C psittaci infection among nongastrointestinal and gastrointestinal MALT lymphomas, autoimmune precursor lesions, and nonneoplastic control samples was analyzed by using the χ² or Fisher exact test for categorical variables. Analyses were carried out using SPSS software, version 15.0 (SPSS, Chicago, IL). All of the probability values were 2-sided, with an overall significance level of .05.

**Results**

*C psittaci* PCR, DNA Sequencing, and Immunohistochemical Studies

Of 47 nongastrointestinal MALT lymphomas 13 (28%) were positive for *C psittaci* DNA. *C psittaci* was detected at variable frequencies in MALT lymphomas of different sites: 5 (100%) of 5 lung lymphomas (*P* < .01 compared with nonmalignant lung tissue); 3 (30%) of 10 thyroid gland lymphomas (*P* > .05 compared with nonmalignant thyroid gland); 2 (13%) of 15 salivary gland lymphomas (*P* > .05 compared with nonmalignant salivary gland); 2 (15%) of 13 ocular adnexal lymphomas; and 1 (25%) of 4 skin lymphomas. Together, nongastrointestinal MALT lymphomas were more frequently infected by *C psittaci* than their respective nonmalignant control specimens (lung, salivary, and thyroid gland, 4/30 [13%]; *P* = .139). Furthermore, 9 (56%) of 16 specimens from patients with Sjögren syndrome and 2 (18%) of 11 specimens from patients with Hashimoto thyroiditis were positive for *C psittaci* DNA. In contrast, almost all 21 gastrointestinal MALT lymphoma and control samples (including 14 MALT lymphomas of the gastrointestinal tract and 7 *H pylori*-positive gastritis samples) lacked detectable *C psittaci* DNA (Table 1). Comparing *C psittaci* infections of all nongastrointestinal MALT lymphomas to gastrointestinal MALT lymphomas revealed a detectable trend without reaching statistical significance (*P* = .155). None of the MALT lymphoma specimens carried DNA for *C trachomatis* or *C pneumoniae*.

Positive results for 9 patients (8 with MALT lymphoma and 1 with Hashimoto thyroiditis) were confirmed by sequencing analysis of PCR products and confirmed the specificity of the amplified fragments. Moreover, these specimens displayed a marginal degree of sequence heterogeneity among different lymphoma cases, indicating infections by unrelated *C psittaci* variants and consequently ruling out possible contamination from other sources. By using immunohistochemical analysis, only 1 positive PCR result could be confirmed. A positive reaction was

**Table 1**

*Frequency of Chlamydia psittaci DNA Positivity by PCR in MALT Lymphomas, Nonmalignant Control Specimens, and Autoimmune Precursor Lesions*

<table>
<thead>
<tr>
<th>Diagnosis/Organ</th>
<th>No. of Cases</th>
<th>No. (%) PCR+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nongastrointestinal MALT lymphomas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
<td>5 (100)</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>10</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>15</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Ocular adnexa</td>
<td>13</td>
<td>2 (16)</td>
</tr>
<tr>
<td>Skin</td>
<td>4</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>13 (28)</td>
</tr>
<tr>
<td><strong>Gastrointestinal MALT lymphomas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>6</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intestine</td>
<td>8</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>1 (7)</td>
</tr>
<tr>
<td><strong>Nonmalignant control specimens</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thyroid gland</td>
<td>13</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>7</td>
<td>3 (43)</td>
</tr>
<tr>
<td>Helicobacter pylori-positive gastritis</td>
<td>7</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>4 (11)</td>
</tr>
<tr>
<td><strong>Autoimmune precursors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hashimoto thyroiditis</td>
<td>11</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>16</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>11 (41)</td>
</tr>
</tbody>
</table>

MALT, mucosa-associated lymphoid tissue; PCR, polymerase chain reaction.
found mainly in macrophages surrounding the salivary duct system Image 1.

**Serum Assay**

With the recomLine *Chlamydia* IgG test, 4 (29%) of 14 serum samples from patients with nongastrointestinal MALT lymphomas analyzed tested positive for *C. trachomatis* compared with 18 (18%) of 100 control serum samples. For *C. pneumoniae*, also 4 (29%) of 14 serum samples from patients with nongastrointestinal MALT lymphomas tested positive, in contrast with 60 (60%) of 100 control serum samples. For *C. psittaci*, none of 14 serum samples from patients with nongastrointestinal MALT lymphomas were positive compared with 1 (1%) of 100 in the control serum sample group.

**Discussion**

The concept that chronic inflammation due to infection by a pathogen such as *H. pylori*, *C. jejuni*, *B. burgdorferi*, hepatitis C virus, or *C. psittaci* or autoimmune disorders such as Sjögren syndrome and Hashimoto thyroiditis provides a staging ground for lymphocyte transformation and MALT lymphomagenesis has emerged in recent years. It has been suggested that the MZ B lymphocyte is the cell of origin that proliferates induced by a persisting antigen. Several antigens have been found responsible for chronic infection at various sites of MALT lymphoma origin. The outstanding response rate observed after microbial eradication therapy and the possibility of treating patients without antineoplastic therapy are promising.

![Figure 1](Image 1) Sequence alignment of polymerase chain reaction products from patients with mucosa-associated lymphoid tissue lymphomas (n = 8) and Hashimoto thyroiditis (n = 1). A dashed line indicates sequence identity of the patient with *Chlamydia psittaci* sequence; a letter indicates a different base; the prefix denotes the usual patient number. A, adenosine; C, cytosine; G, guanine; T, thymine.

![Image 1](Image 1) A, Mucosa-associated lymphoid tissue (MALT) lymphoma of salivary gland. Immunohistochemical staining of *Chlamydia psittaci*. Overview of remnant of salivary duct with positive reaction in surrounding macrophages (Chlamydiaceae family–specific antibody, ×25). B, MALT lymphoma of salivary gland. Immunohistochemical staining of *Chlamydia psittaci*. Note positive reaction in macrophage (arrow) (Chlamydiaceae family–specific antibody, ×60).
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chemotherapy in a number of MALT lymphomas raises the need to further elucidate the as yet unrecognized microbial agents of MALT lymphomas at different sites of origin.\(^{8,13}\)

In our study of 47 nongastrointestinal MALT lymphomas, 13 (28%) were positive for \(C\) psittaci DNA as opposed to 4 (11%) of 37 nonmalignant control specimens \((P = .09;\) Table 1). These results are in accordance with a recent study by Ponzoni et al.\(^{20}\) demonstrating an association between \(Chlamydia\) infection and lymphomas other than those arising from the ocular adnexa. By multiple detection methods, they elegantly identified the monocytic/macrophage system as a carrier of viable \(C\) psittaci. However, there were clear differences with our study regarding prevalence rates within the extranodal B-cell lymphoma subgroup: In contrast with Ponzoni et al.,\(^{20}\) we found a 100% (5/5) positivity in MALT lymphomas of the lung and 2 of 15 (13%) of salivary gland lymphomas; \(C\) psittaci is an obligate intracellular bacterium that in humans causes pulmonary infections called pneumonitis. None of our normal lung specimens in our series (10/10) tested positive, indicating that \(C\) psittaci is not normally encountered at this localization.

A recent study of \(Chlamydia\) and \(Mycoplasma\) infections in pulmonary MALT lymphoma from 3 countries was also able to detect \(C\) psittaci in lung biopsy specimens, albeit at lower frequencies.\(^{25}\) Although we used identical PCR amplification methods, a further discrepancy with the findings of Ponzoni et al.\(^{20}\) was a higher prevalence among ocular adnexal MALT lymphomas, with nearly 70% of cases testing positive compared with 2 (15%) of 13 in the present study. Furthermore, we demonstrated 3 (30%) of 10 positive cases in thyroid gland MALT lymphomas, an entity that was not included in the study by Ponzoni et al.\(^{20}\) Methodological biases or geographic variation might account for these differences.\(^{26}\)

Although it has been suggested that \(C\) pneumoniae and \(C\) trachomatis seropositivity may be associated with lymphomas,\(^{19}\) no evidence of infection with \(C\) pneumoniae and \(C\) trachomatis was found in our MALT lymphoma specimens. Therefore, an association of MALT lymphomas and \(Chlamydia\) species other than \(C\) psittaci appears unlikely.

Immunohistochemically, only 1 positive PCR result could be confirmed. This might be due to different sensitivities of the applied methods or to imperfect antigen retrieval on the formalin-fixed, paraffin-embedded material. It is interesting that the positive reaction was exclusively found in macrophages, which have been shown by multiple detection methods to harbor viable and infectious \(C\) psittaci.\(^{8}\)

Furthermore, no anti–\(C\) psittaci Abs were detected in 14 serum samples from patients with nongastrointestinal MALT lymphomas. However, owing to a shortage of material, the intratumoral \(C\) psittaci status of these patients is not known. In 100 control serum samples, 1 tested positive for \(C\) psittaci, reflecting the normal seroprevalence among the general population of the region not being exposed to chlamydial infections through work conditions. However, owing to the limited sensitivity and specificity of serologic test systems together with a high cross-reactivity for other chlamydial species, serologic testing is considered an unreliable method to predict associations of \(C\) psittaci infections and lymphomagenesis.

Among normal control tissue samples, 1 (8%) of 13 thyroid gland tissue specimens and 3 (43%) of 7 normal salivary gland tissue specimens also tested positive. Remarkably, in patients with Hashimoto thyroiditis (2/11 cases positive [18%]) and Sjögren syndrome (9/16 [56%]), 2 characteristic autoimmune precursor lesions of MALT lymphomas, an even higher infection rate of \(C\) psittaci was detected. Because salivary and thyroid gland MALT lymphomas start as nonmalignant antigen-selected expansion of polyclonal lymphoid cells with ongoing immunoglobulin gene hypermutation representing continuous antigen dependency, a potential role for \(C\) psittaci as an initiating pathogenic event leading to chronic persistent inflammation may be hypothesized. By triggering a chronic antigen selection process, the bacterial infection may initiate an autoimmune response and finally promote lymphomagenesis.

Virtually no gastrointestinal MALT lymphoma or \(H\) pylori–positive gastritis specimens tested positive for \(C\) psittaci DNA, corroborating findings of \(H\) pylori and \(C\) jejuni being the dominant causative microorganisms of MALT lymphoma development in these anatomic regions.

These findings suggest a possible role for \(C\) psittaci in MALT lymphomagenesis at nongastrointestinal sites beyond the ocular adnexa with potential clinical implications for antibiotic treatment: Recent reports provide encouraging data about long-lasting clinical remissions of \(C\) psittaci–positive ocular adnexal MALT lymphomas induced by doxycycline used as first-line treatment, even in patients with multiple failures with previous chemotherapy or radiotherapy.\(^{13,14}\)

There is also sporadic evidence of therapeutic success in a case of \(C\) psittaci–positive diffuse large B-cell lymphoma of the bronchus\(^{27}\) and of transformed high-grade gastric MALT lymphomas treated with antibiotics alone.\(^{28}\) In marked contrast, ex juvantibus doxycycline treatment in patients with MALT lymphoma of the ocular adnexa without prior testing for \(C\) psittaci DNA did not result in any significant response and was considered ineffective.\(^{29}\) Hence, exclusive antibiotic treatment in \(C\) psittaci–positive patients remains an investigational approach and must be carefully evaluated in prospective randomized trials.

This study demonstrated the presence of \(C\) psittaci DNA in a larger cohort of nongastrointestinal MALT lymphomas other than ocular adnexa. Furthermore, a high prevalence of \(C\) psittaci infection in patients with Sjögren syndrome and Hashimoto thyroiditis, 2 frequent precursor
lesions for MALT lymphomas, suggests possible involvement of C. psittaci–induced antigenic-driven MALT lymphomagenesis. However, the pathophysiologic and clinical implications deserve further investigation.

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References


