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Bartonella henselae Infection Associated with Autoimmune Thyroiditis in a Child

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Established Facts

- The pathogenesis of autoimmune thyroiditis is multifactorial. Genetic and environmental factors are implicated, including bacterial and viral infections. Recently, *Bartonella henselae* infection is associated with autoimmune conditions.

Novel Insights

- We describe the first case of autoimmune thyroiditis associated with cat-scratch disease in a child.

Key Words
Autoimmune thyroiditis · Infections · *Bartonella henselae*

Abstract

Background: *Bartonella henselae* was discovered a quarter of a century ago as the causative agent of cat-scratch disease. More recently, *Bartonella* has been found to be responsible for a broad range of clinical syndromes (prolonged fever, hepatosplenic disease, encephalopathies, ocular disease) and associated with autoimmune conditions. ***Case:*** This is the first report of autoimmune thyroiditis related to *B. henselae* infection. We describe an 11-year-old boy who presented with goiter and weight loss. At the time of admission a 2 × 1 cm mildly tender right supraclavicular lymph node was noted in association with an erythematous papule at the same side of the neck. We describe an association of autoimmune hyperthyroidism (Hashitoxicosis) with *B. henselae* infection (cat-scratch disease) in a pediatric patient. ***Conclusion:*** Different types of infections are implicated in the pathogenesis of autoimmune thyroid disease through molecular mimicry or other mechanisms, despite their role is disputed. We speculated that autoimmune thyroiditis should be added to the spectrum of clinical syndromes that can be triggered by *B. henselae*.

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Introduction

Bartonella henselae was discovered a quarter of a century ago as the causative agent of cat-scratch disease.

Typical cat-scratch disease starts with an erythematous papule that appears 3–10 days after inoculation at the same site. The lesion persists for 1–3 weeks associated with regional lynphadenopathy. The response to *B. henselae* infection depends on the immune status of the infected host. In immunocompetent individuals, *Bartonella* causes an interferon-γ-mediated T helper 1 cell response, achieving macrophage recruitment and stimulation with a granulomatous and suppurative disease. However, only limited knowledge exists about pathogenetic mechanisms occurring during *Bartonella* infections [1].

In recent decades, more different presentations of *Bartonella* infections have been described [1]. *Bartonella* has been found to be responsible for an extensive range of clinical syndromes. More common clinical manifestations other than typical cat-scratch disease include prolonged fever, hepatosplenic disease in particular hepatosplenomegaly, microabscesses and granulomatous lesion in the liver and/or spleen. The spectrum of various less common recognizable clinical forms of *Bartonella* infection takes account of Parinaud oculoglandular syndrome, neuroretinitis, panuveitis, encephalopathy, radiculopathy, cerebral arteritis, transverse myelitis, pneumonia, pleural effusion, osteomyelitis, arthritis, and endocarditis [1].

Bartonella infection is also associated with autoimmune conditions, particularly, hemolytic anemia [2], thrombocytopenic purpura, systemic juvenile rheumatoid arthritis [3], vasculitis [4], glomerulonephritis [5], Schonlein-Henoch purpura [6], Guillain-Barrè syndrome [7]. The pathogenesis of autoimmune diseases is multifactorial, including both genetic and environmental factors.

In the literature at least 20% of autoimmune thyroid diseases are due to environmental factors [8]. Data from human and animal studies suggest that infection may promote or accelerate autoimmune thyroid disease development in genetically susceptible individuals [9]. In these subjects, autoimmunity develops in response to eradication of an infection agent [8]. Many viruses and bacteria have been suspected to play a role in the pathogenesis of autoimmune thyroid disease, such as *Yersinia enterocolitica*, *Helicobacter pylori*, staphylococci and streptococci, *Enterovirus*, *Rubella*, mumps virus, HSV, EBV, HCV, parvovirus B19, and Coxsackie virus [8–10].

Case

A previously healthy 11-year-old boy was referred to our hospital because of weight loss, diarrhea and occasional finding of swelling of the neck for a few days.

On admission, the patient presented a mild tachycardia without murmurs or gallop. No fever. Chest was clear. Abdomen exam was normal without hepatosplenomegaly. Neurological exam was normal (mental status, gait, strength, and reflexes) except for a mild tremor and agitation. He was found to have a smooth goiter.

A 2 × 1 cm mildly tender, mobile, nonerythematous right supraclavicular lymph node was noted, in association with a 3-mm erythematous papule with a small central crust at the same side of the neck. No lymphadenopathy was found in other locations explored.

His past medical history was unremarkable. Personal history was negative for recent intake of drugs or allergies. When questioned, the parents reported that they have a domestic cat (9 months old) but have no memory of scratches or bites. Family history was negative for autoimmune conditions or thyroid disease.

Laboratory tests showed an increase in thyroid hormones (T4 and T3) with undetectable thyroid-stimulating hormone. Antithyroid immunoglobulin assay showed a considerable increase in antithyroglobulin, antithyroperoxidase antibody titers in combination with a mild raise in anti-thyroid-stimulating hormone receptor antibodies titers (table 1).

Serological data showed a high titer of *B. henselae* IgG (1:100, with indirect fluorescent antibody assay). No serological evidence of other viral or bacterial acute infection was found. Chest radiography and abdominal ultrasonography were normal.

Thyroid ultrasonography showed an increase in glandular size, mainly in the right lobe, hypoechoic echogenicity, and increase in glandular vascularity.

Supraclavicular lymph node ultrasonography revealed inflammatory lymph nodes, markedly hypoechoic with oval shape, maximum diameter of 1.5 cm, richly vascularized.

Peripheral blood smear showed normal red and white cells morphology and no presence of abnormal cells.

Serological HLA typing for class II (HLA-DR, DQ) showed the presence of both HLA-DR3 and HLA-DR4. Interestingly, these haplotypes were demonstrated to be associated with a susceptibility to Hashimoto's thyroiditis in Caucasians [11].

Therapy with tapazole (10 mg/day) and clarithromycin (15 mg/kg/day) was started. We have documented a gradual normalization of thyroid function (data shown in table 1). Clinically, there was resolution of tachycardia, weight gain and a decrease in goiter size. In association, we documented a regression of lymphadenopathy and the erythematous lesion of the neck within 2 weeks.

Laboratory serological control data showed an increase in IgG titer for *B. henselae* (1:320) after 20 days. We made a diagnosis of cat-scratch disease following the diagnostic criteria updated by Margileth [12] in 2000: presence of cat contact and inoculation site, negative serology for other causes of adenopathies, positive indirect fluorescent antibody assay with a titer ratio of >1:64.

The patient's thyroid function was monitored routinely and the dose of tapazole adjusted as indicated to maintain a euthyroid state. He needed treatment with tapazole for about 3 months. The patient remained euthyroid for 5 months after stopping tapazole.

Table 1. Laboratory findings

Laboratory findings	On admission	After 20 days	Normal values
WBC ($\times 10^3/\mu l$)	8.01	6.22	4.00–10.00
C-reactive protein, mg/dl	<0.290	<0.290	<0.290
Erythrocyte sedimentation rate, mm/h	6	4	<12
B. henselae titer	positive (IgG 1/100)	positive (IgG 1/320)	negative
EBV titer	negative	negative	negative
CMV titer	negative	negative	negative
Toxoplasma titer	negative	negative	negative
TSH, μIU/ml	<0.001	<0.001	0.250–4.500
T3, pg/ml	7.70	4.83	2.00–4.90
T4, ng/dl	2.31	1.21	0.07–1.70
Ab-HTG, IU/ml	5,103.67	4,350.13	<28.7
Ab-TPO, IU/ml	1,442.31	1,656.94	<10.1
Ab-TSH receptor, IU/ml	7.9	6.6	<1.5

Hashimoto's thyroiditis was diagnosed on the basis of antithyroid antibodies and ultrasonography. In addition, a presumptive diagnosis of hashitoxicosis was made on the basis of biochemical and clinical hyperthyroidism presentation and subsequent resolution.

Discussion

To our knowledge, this appears to be the first association of cat scratch disease and autoimmune thyroiditis reported in the literature.

It is well known that in many autoimmune diseases, genes are not the only contributing factor and environmental agents are secondary but important aspects.

Different environmental precipitating factors were associated with the development of autoimmune thyroiditis. These include irradiation, drugs, smoking, allergy, stress and several types of viruses and bacteria. Pathogenetic mechanisms have not yet been clarified. However, some possible mechanisms by which infections may stimulate the development of autoimmune thyroiditis involve molecular mimicry, polyclonal T cell activation by bacteria superantigens and increased thyroid expression of human leukocyte antigen [8, 9].

Hashitoxicosis is a rare complication of autoimmune thyroiditis. It is considered that this condition will achieve an unregulated discharge of thyroid hormones during inflammatory-mediated destruction of the thyroid gland. Sometimes the concomitant presence of thyroid-stimulating immunoglobulins could be found with no clear reason for their presence. Maybe it could be the result of nonspecific immune dysregulation, characteristic of autoimmune thyroid disease [13].

Bartonella infection has been associated with the development of systemic juvenile rheumatoid arthritis in a 4-year-old girl [3], severe Coomb's-negative autoimmune hemolytic anemia in an adult man [2], IgA nephritis in a 13-year-old boy [5], and transverse myelitis in an adolescent and adult [14]. In all these patients, clinical and serological evidence of *B. henselae* infection was found at the time of diagnosis of autoimmune disease.

In our case, given the patient's clinical signs, symptoms and history (recent exposure to a cat), the high antibody titers specific for *B. henselae* at the time of autoimmune thyroiditis in the presence of a genetic susceptibility to Hashimoto's thyroiditis, the association between thyroiditis and *Bartonella* as a trigger factor is likely. The pathophysiological mechanisms of immune response to this bacterial infection have not been defined exactly. The available information is insufficient to describe how the initial insult of cat-scratch disease triggers the development of autoimmune disease. Our findings suggest this possible association.

Different types of infection are implicated in the pathogenesis of autoimmune thyroid diseases through molecular mimicry or other mechanisms, although their role is disputed.

Our findings suggest that *Bartonella* may in part be responsible for the development of thyroiditis by a direct inflammatory process or a 'molecular mimicry' that triggers the host's altered immune response to this organism [3]. The available information is insufficient to

delineate the mechanism by which the initial insult of cat-scratch disease triggered the development of thyroiditis in our patient. Only a limited knowledge exists about the pathomechanisms operating in the course of a *B. henselae* infection. It has been hypothesized that in immunodeficient patients *Bartonella* causes an interferon-mediated T helper 1 cell response, modulates host or target cell cytokines and growth factors to cause angiogenesis and granulomatous disease [1]. *B. henselae* may also have a strong action on the immune system of the normal host and promote the development of autoimmune diseases.

The immune response to *B. henselae* infection seems to be associated with the development of autoimmune disorders. We speculate that autoimmune thyroiditis should be added to the spectrum of clinical syndromes that can be triggered by *B. henselae*.

Unfortunately, the description of a single case does not allow one to clarify the mechanisms responsible for a causal association between thyroiditis and cat-scratch disease.

Definitely, further research is necessary to determine the role of *Bartonella* in the pathogenesis of autoimmune thyroiditis and other disorders.

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