Detection of M. paratuberculosis Bacteremia in a Child With Lupus Erythematosus and Sjögren’s Syndrome

Coad Thomas Dow*

Mc Pherson Eye Research Institute University of Wisconsin-Madison and Chippewa Valley Eye Clinic Eau Claire Wisconsin, USA

*Corresponding author: Coad Thomas Dow, Mc Pherson Eye Research Institute University of Wisconsin-Madison, and Chippewa Valley Eye Clinic 2715 Damon Street, Eau Claire Wisconsin, USA, Tel: 7158348471; E-mail: ctdow@me.com

Abstract

*Mycobacterium avium ss. paratuberculosis* (MAP) is the cause of Johne’s disease, an enteric inflammatory disease mostly studied in ruminant animals. MAP is also the putative cause of the very similar human malady, Crohn’s disease. Recently, MAP has been associated with additional human inflammatory/autoimmune diseases: autoimmune thyroiditis, autoimmune diabetes, Blau syndrome and multiple sclerosis. The etiology of autoimmunity is multi-factorial for both genetically determined risk factors and environmental triggers. Systemic lupus erythematosus (SLE) and Sjögren’s syndrome (SS) are autoimmune diseases that are related both clinically and immunologically which may simultaneously occur in the same individual. Both diseases are associated with systemic autoimmunity frequently presenting with antinuclear antibodies (ANA). Two of these autoantigens, common immune targets in both SLE and SS, are the Ro (or SSA) and La (or SSB) ribonucleoproteins. Auto-antibodies to these proteins are frequently found in the sera of individuals with SLE and SS. It has been suggested that MAP triggers autoantibodies via mimicry between protein elements of its immunodominant heat shock protein, HSP65, and host tissue proteins. Animal studies support a role for mycobacterial HSP65 in SLE. This article presents the case of a child with SLE and SS. She has both the anti-Ro and anti-La antibodies and MAP was cultured from her blood. BLAST analysis of MAP HSP65 showed homology with the anti-Ro and anti-La proteins. Further investigation of a link between MAP and SLE/SS is warranted.

Background

Lupus and Sjögren's

Systemic lupus erythematosus (SLE) and Sjögren’s syndrome (SS) are autoimmune diseases that are related both clinically and immunologically. SLE is a clinically diverse chronic inflammatory disease resulting from the interplay of genetic, hormonal, and environmental factors. [1] SS is a chronic inflammatory and autoimmune disorder that is characterized by diminished lacrimal and salivary gland secretion resulting in keratoconjunctivitis sicca (dry eye) and xerostomia (dry mouth) [2,3]. The two diseases can occur together in the same person. Where this occurs, SS is usually considered secondary to the occurrence of SLE, as it is with other autoimmune diseases such as rheumatoid arthritis. There is no known cause for either SLE or SS.

SLE and SS are associated with systemic autoimmunity frequently in the form of antinuclear antibodies (ANA) [3]. The individual self proteins targeted by ANA have been elucidated and characterized. One of these auto-antigens, a common target of autoimmunity in both SLE and SS, is the Ro (aka SSA) ribonucleoprotein [5].

Anti-Ro is found in the sera of up to 50% of SLE patients and a higher percentage of patients with SS [5]. Originally identified by double immunodiffusion in the sera of SLE patients with no ANA [6], and later identified as SSA-A in the sera of SS patients [7], anti-Ro is associated with several clinical aspects of both diseases including lymphopenia, leukopenia, and hypergammaglobulinemia [8]. Anti-La (aka SSB) autoantibodies are found in sera from patients with SLE or SS, but are invariably found in sera that also contain anti Ro. Anti-Ro without anti-La is more commonly found in patients with SLE, while anti-Ro along with anti-La is more common in SS [9].

MAP

*Mycobacterium avium ss. paratuberculosis* (MAP) is a Gram-positive, acid-fast staining small rod-shaped bacterium. MAP causes a chronic granulomatous inflammation of the intestines in ruminant animals called Johne's disease; mostly studied in dairy cattle, goats, and sheep. MAP also causes a chronic inflammation of the intestines in beef cattle and in a wide variety of other domestic and wild ruminants. A majority of the dairy herds in the United States and Europe have MAP infected animals within the herd [10].

MAP and human exposure

Infected cows shed up to 1.6×10^7 organisms per 2 grams of manure (0.07 oz) – a dose large enough to infect a calf. A single high-shedding animal can excrete up to 15 gallons of such contaminated manure per day – a staggering 25,000 infective doses per day [11]. MAP is present in pasteurized milk [12,13], infant formula made from pasteurized milk [14], surface water [15,16], soil [15], cow manure “lagoons” that leach into surface water, cow manure in both solid and liquid forms that is applied as fertilizer to agricultural land [17,18], and municipal tap water [18,19]. This provides multiple routes of transmission to humans.

Case Report

An 11-year old female with cutaneous lupus erythematosus (biopsy proven) and Sjögren’s syndrome was seen. She had a history of facial malar rash, several bouts of parotitis as well as leukopenia. She had no sign of renal involvement. Significant laboratory tests included positive ANA and antibodies to Ro and La. Peripheral blood was sent for culture for *Mycobacterium avium ss. paratuberculosis* (Figure 1), the culture was positive after six months as identified by IS900, indicative of MAP*. Blast analysis of both Ro and La antibodies showed positively with epitopes of MAP HSP65 (Figure 2).

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Discussion

Molecular mimicry

The concept of molecular mimicry is based on a structural similarity between a pathogen and self. The similarity could be expressed as shared amino acid sequences or similar conformational structure between a pathogen and self antigens. Molecular mimicry has become a very popular explanation for the frequent association of infection with autoimmune disease [20].

Heat shock proteins are found in virtually all life forms and are closely linked to the immune response. HSP65 of mycobacteria is an immunodominant antigen. In human mycobacterial infection it has been estimated that up to 40% of the T-cell response is directed against this single protein [21,22]. The HSP65 of MAP was compared to amino acid sequences of the Ro and La proteins. It is postulated that the similarity manifest between HSP65 and Ro and La is the trigger of anti-Ro and anti-La antibodies (Figure 2). The HSP65 of M. leprae significantly accelerates the progression of SLE in a standard murine model of SLE [23].

MAP and human granulomatous disease: Crohn’s and Sarcoidosis

In addition to John’s disease of animals, MAP is the putative cause of the very similar Crohn’s disease of humans. The DNA of MAP can be identified within the granulomas of Crohn’s biopsies [24] and, with extreme care and patience, MAP can be grown from the gut and blood

![Figure 1: Nested IS900 PCR products. Lane 1, molecular weight standards ladder; Lane 2, M. a. paratuberculosis positive control; Lane 3, patient sample; Lane 4, sample negative control; Lane 5, PCR reagent negative control; Lane 6, molecular weight standards ladder](image1)

![Figure 1a: BLAST analysis HSP65 and Ro (SSA)](image2a)

![Figure 1b: BLAST analysis HSP65 and La (SSB)](image2b)
of Crohn's patients [25-27]. In limited series, anti-mycobacterial therapy directed at MAP has been shown to have a favorable effect on patients with Crohn's disease [28]. Moreover, MAP has been historically linked to sarcoidosis; a multisystem inflammatory disease in which DNA evidence of MAP has been found (sporadically) in sarcoid granulomas [29]. Juvenile sarcoidosis (Blau syndrome) is an inherited granulomatous disease of children. The DNA of MAP was detected from every sample in a small series of archived tissues [30].

MAP and type 1 diabetes, autoimmune thyroiditis, and Multiple sclerosis

While it is not difficult to envision a role for MAP in human disease where there is a granuloma, it is more difficult to assign a role to MAP in diseases that feature autoantibodies. This divide is bridged by the concept that MAP HSP65 mimics host protein elements. An example is that of MAP as a proposed infectious trigger of autoimmune diabetes. T1DM is an autoimmune disease manifest by progressive T cell-mediated autoimmune destruction of insulin-producing beta cells in the pancreatic islets of Langerhans [31]. In 2005, Dow postulated a causative role for MAP in the T1DM [32].

Sechi et al. in 2007 found the DNA of MAP in the blood of autoimmune (type 1) patients but not nonautoimmune (type 2) diabetics [33-35]. (Sechi also found an association of polymorphisms of the SLC11A1 gene and MAP in T1DM patients [36].) The link connecting MAP and T1DM: MAP HSP65 mimic the host pancreatic glutamic acid decarboxylase (GAD) [37]. Similar mechanisms are proposed for the role of MAP in autoimmune (Hashimoto's) thyroiditis [38, 39] and multiple sclerosis [40].

Summary

MAP is associated with an increasing number of human diseases. In this case report MAP bacteremia was found in a child with lupus and Sjögren's syndrome. MAP bacteremia may trigger SLE and SS via molecular mimicry: the persistent presence of MAP results in its production of mycobacterial HSP65, the response to HSP65 results in the production of antibodies to Ro and La which produce inflammation characteristic of lupus erythematosus and Sjögren's syndrome.

Acknowledgements

The author acknowledges, with gratitude, the expertise of Dr. Mike Collins and his laboratory at the University of Wisconsin-Madison for his testing of the sample from this patient.

References


