Tick-borne diseases and viruses in cancer and unexplained syndromes

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PART I: Cancer and infections
What cancers are tick-borne diseases (TBDs) associated with?

Haematologic disorders that can develop into malignancies

- Myelodysplastic syndromes
- Leukaemia
- Monoclonal Gammopathy of Undetermined Significance (MGUS)
- Lymphomas/Non-Hodgkin’s Lymphoma
- ... and others

Source: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/
Question:

Why primarily blood-related disorders/cancers?
Lyme and co-infections find the blood/lymph a welcome host

Babesia: red blood cells

Ehrlichia: leukocytes and granulocytes

Coxiella/ Q fever

Borrelia spirochetes in the blood

..........within white blood cells:

Bartonella
Myelodysplastic Syndromes (MDS) are a group of diverse bone marrow disorders in which the bone marrow does not produce enough healthy blood cells. MDS is often referred to as a “bone marrow failure disorder”.
Myelodysplastic syndromes / Leukemia

Myelodysplastic diseases and Ehrlichia: Consideration of a possible etiologic connection and mechanisms of pathogenesis, in 12th annual symposium on myelodysplastic syndromes (Abstract #238), Berlin, 2013

Could ehrlichial infection cause some of the changes associated with leukemia, myelodysplastic diseases and autoimmune disorders, and offer antibiotic treatment options?, Kallick, C.A.; Friedman, D.A., Nyindo, M.; Medical hypotheses (2015) 891-893, Elsevier Ltd.: “...We reference here 3 leukemia patients with direct or indirect evidence of Ehrlichia/Anaplasma (EA) infection....Though they did not survive, their condition improved dramatically for a time, suggesting Rifampin provided some therapeutic benefit...”
Members of the Ehrlichia genus are gram-negative, rod shaped bacteria that live inside white blood cells.

Ehrlichia chaffeensis primarily infects mononuclear leukocytes (predominantly monocytes and macrophages).

The pathogen that causes human granulocytic ehrlichiosis (HGE) (Anaplasmosis) primarily infects granulocytes (neutrophils and rarely eosinophils).
Ehrlichia associated with myelodysplastic disease and leukaemia

Could ehrlichial infection cause some of the changes associated with leukemia, myelodysplastic diseases and autoimmune disorders, and offer antibiotic treatment options?

Charles A. Kallick, Daniel A. Friedman, Mrama B.A. Nyindo

"Ensconced in the stem cells of the bone marrow, EA may disrupt the normal development and function of many of the cells of immunity, manifesting itself as different syndromes."
Ehrlichia associated with myelodysplastic disease and leukaemia

Medical Hypotheses
Volume 85, Issue 6, December 2015, Pages 891-893

Could ehrlichial infection cause some of the changes associated with leukemia, myelodysplastic diseases and autoimmune disorders, and offer antibiotic treatment options?

Charles A. Kallick, Daniel A. Friedman, Mramba B.A. Nyindo

Abstract

We hypothesize that a large group of medical conditions of unknown etiology including leukemia, multiple myeloma, myelodysplastic and autoimmune disorders, may be associated with or caused by an obscure group of intracellular obligate parasitic bacteria named Ehrlichia/Anaplasma (EA). Ensconced in the stem cells of the bone marrow, EA may disrupt the normal development and function of many of the cells of immunity, manifesting itself as different syndromes. Recent studies of the activity of EA suggest direct effects on the immune system consistent with the manifestations of leukemia. We reference here three leukemia patients with direct or indirect evidence of EA infection. Moreover, EA have been

“Recent studies of the activity of EA [Ehrlichia/Anaplasma] suggest direct effects on the immune system consistent with the manifestations of leukemia”

“It is further hypothesized, moreover, that treatment of leukemia with antibiotics effective against EA would also result in beneficial impact. This has been tried. The results, cited below, hint at proof of EA infection as a cause of leukemia as well as a potentially important course of treatment.”
Ehrlichia and leukaemia

Hypothesis: ehrlichial infection and leukaemia

Diseases of the immune system broadly described by the term leukaemia include acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML), chronic lymphocytic leukaemia (CLL) and chronic myeloid leukaemia (CML). The causes of these leukaemic syndromes are unknown though many genetic changes have been associated with some forms.

In leukaemia we observe the overproduction of cells needed for immune system function, accompanied by large numbers of immature and dysfunctional cells of immunity (termed blasts) that are inappropriately released into the circulation. Something unknown is causing these blasts to fail to function as expected and accumulate in the system of the patient.

The Ehrlichia/Anaplasma (EA) are a family of obligate intracellular parasitic bacteria that infect leukocytes. They have been recognized as human pathogens for a variety of medical conditions [[1], [2]]. EA can alter the DNA of their host cell during its division, as discussed below. Interference with the normal progression of marrow cell development may facilitate the survival of the bacteria in their host leukocytes, by suppressing apoptosis and could also cause a cascade of subsequent immune system failures.

The EA are a Chlamydia, which have different reproductive methods than many other invasive bacterial pathogens. A study of Ehrlichia Chaffeensis infection in a human monocyte cell line demonstrated the ability of EA to alter host genes during transcription (transcriptomic effects) [3]. These effects included suppression of apoptosis, a primary defensive activity of intracellular pathogens regulating cell differentiation, and others essential for survival of the obligatory intracellular parasite. A culture of Anaplasma phagocytophilium was induced to grow in human immune system cells and produced most of the changes seen in leukaemia [4].

“EA can alter the DNA of their host cell during its division .... Interference with the normal progression of marrow cell development may facilitate the survival of the bacteria in their host leukocytes, by suppressing apoptosis and could also cause a cascade of subsequent immune system failures.”

Source: http://dx.doi.org/10.1016/j.mehy.2015.09.015

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Ehrlichia and bone marrow diseases

Ehrlichia and bone marrow cells: could Ehrlichial infection explain the unsuspected etiology of some diseases of the immune system?

Kallick CA1.

Author information

Abstract

A large group of diseases of unknown etiology, including leukemia, systemic lupus erythematosus, myelodysplastic disease, multiple sclerosis, amyotrophic lateral sclerosis, and rheumatoid arthritis, all present with some elements of immune system disturbance. The Ehrlichia/anaplasma (EA) are an obscure group of obligate parasitic intracellular pathogens that excrete intracellularly a substance called host transcriptional protein, which can alter transcription in cell division. Infection with EA may lead to changes in transcription in proliferating cells, such as those in the marrow, and alter the biology of the products such as T and B cells. Normally 60% of B cells produced in the marrow may be self reactive, but are eliminated before release from the marrow. Changes in transcription could allow self reactive cells to escape into the peripheral circulation and injure normal tissue, creating the dysfunctions which characterize the different immune system diseases and give them their separate identities. A number of studies previously published, and new information presented here, suggest that EA infections may be an underlying, undiagnosed cause for these and other immune system diseases. This hypothesis, long overlooked, has never been subjected to adequate, rigorous study sufficient to prove or disprove its truth. If so, patients may be treated with antibiotics, and marrow transplant manipulations already used in treatment of diseases such as lupus and leukemia may become more effective.

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Myelodysplastic syndrome/Leukemia: Laboratory tests

1. Ehrlichia/Anaplasma IgG/IgM antibodies
2. Ehrlichia/Anaplasma EliSpot
MGUS (Monoclonal Gammopathy of Undetermined Significance)

Monoclonal gammopathy of undetermined significance (MGUS) is a condition in which an abnormal protein — known as monoclonal protein or M protein — is in your blood. ... MGUS can progress over years to other disorders, including some forms of blood cancer.
**MGUS (Monoclonal Gammopathy of Undetermined Significance) associated with infections**

<table>
<thead>
<tr>
<th>Description</th>
<th>Positive MGUS cases</th>
<th>Positive controls</th>
<th>Control rate$^b$</th>
<th>Relative risk (95% CI)</th>
<th>$P$ value$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperlipidemia$^d$</td>
<td>247</td>
<td>2205.1</td>
<td>8653</td>
<td>3321.7</td>
<td>0.7 (0.6-0.8)</td>
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<tr>
<td>Uterus retroversion</td>
<td>6</td>
<td>347.9</td>
<td>36</td>
<td>32.6</td>
<td>10.7 (4.5-25.4)</td>
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<tr>
<td>Chalazion</td>
<td>44</td>
<td>336.9</td>
<td>695</td>
<td>170.7</td>
<td>1.97 (1.5-2.7)</td>
</tr>
<tr>
<td>Clavicle fracture</td>
<td>4</td>
<td>27.8</td>
<td>7</td>
<td>1.7</td>
<td>15.9 (4.6-55.9)</td>
</tr>
<tr>
<td><strong>Upper respiratory bacterial infection</strong></td>
<td>4</td>
<td>30.4</td>
<td>11</td>
<td>2.4</td>
<td>12.6 (3.9-40.5)</td>
</tr>
<tr>
<td>Small intestine diverticulum</td>
<td>4</td>
<td>32.6</td>
<td>3</td>
<td>1.8</td>
<td>18.0 (4.7-68.6)</td>
</tr>
<tr>
<td>Acute depression</td>
<td>13</td>
<td>183.2</td>
<td>172</td>
<td>54.4</td>
<td>3.4 (1.9-5.9)</td>
</tr>
<tr>
<td>Vitreous degeneration</td>
<td>6</td>
<td>47.2</td>
<td>31</td>
<td>7.3</td>
<td>6.5 (2.7-15.7)</td>
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<tr>
<td>Aphakic detachment</td>
<td>3</td>
<td>22.9</td>
<td>3</td>
<td>0.8</td>
<td>29.5 (5.8-150.4)</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>26</td>
<td>301.8</td>
<td>217</td>
<td>130.8</td>
<td>2.3 (1.5-3.5)</td>
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<tr>
<td>Ventricular hypertrophy due to hypertension</td>
<td>9</td>
<td>69.8</td>
<td>54</td>
<td>17.7</td>
<td>3.9 (1.9-8.0)</td>
</tr>
<tr>
<td><strong>Spontaneous bacterial peritonitis</strong></td>
<td>3</td>
<td>20.8</td>
<td>5</td>
<td>1.3</td>
<td>16.7 (3.9-72.3)</td>
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<tr>
<td>Peritoneum cyst</td>
<td>4</td>
<td>28.3</td>
<td>14</td>
<td>3.2</td>
<td>8.8 (2.8-27.2)</td>
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<tr>
<td>Group 1 hypertension</td>
<td>16</td>
<td>119.4</td>
<td>188</td>
<td>44.5</td>
<td>2.7 (1.6-4.5)</td>
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<tr>
<td>Swine pahelititis</td>
<td>4</td>
<td>20.2</td>
<td>13</td>
<td>2.2</td>
<td>8.8 (2.8-27.2)</td>
</tr>
<tr>
<td><strong>Mycobacterium infection</strong></td>
<td>4</td>
<td>29.3</td>
<td>11</td>
<td>3.2</td>
<td>9.1 (2.8-29.0)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>68</td>
<td>501.2</td>
<td>2835</td>
<td>782.4</td>
<td>0.6 (0.5-0.8)</td>
</tr>
<tr>
<td>Sigmoid diverticulum with diverticulitis</td>
<td>10</td>
<td>71.1</td>
<td>80</td>
<td>21.5</td>
<td>3.3 (1.7-6.4)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>48</td>
<td>386.9</td>
<td>1871</td>
<td>647.7</td>
<td>0.6 (0.5-0.8)</td>
</tr>
<tr>
<td>Subconjunctival hematoma</td>
<td>3</td>
<td>21.6</td>
<td>8</td>
<td>1.9</td>
<td>11.2 (2.9-43.0)</td>
</tr>
</tbody>
</table>

$^a$ CI = confidence interval; MGUS = monoclonal gammopathy of undetermined significance.

$^b$ Rates per 100,000 person-years; age and sex adjusted.

$^c$ Unadjusted $P$ values are reported.

$^d$ $P$ value was significant after Bonferroni correction for 16,062 comparisons.

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MGUS - Bartonella

Transient monoclonal gammopathy in a patient with Bartonella quintana endocarditis.

Seve P¹, Turner R, Stankovic K, Perard L, Brousolle C.

Abstract

Monoclonal gammopathy has been reported rarely in association with infectious diseases. Viral infection has been the most frequently reported. We report a case of Bartonella quintana endocarditis in a 45-year-old homeless male associated with a monoclonal IgG kappa gammopathy. The gammopathy disappeared after 8 months of antibiotics while the Bartonella antibody titre was decreasing. This correlation suggests a causative role for B. quintana for the monoclonal gammopathy. To the best of our knowledge, this the first report of monoclonal gammopathy in the course of B. quintana infection.

2006 Wiley-Liss, Inc.

PMID: 16432857 DOI: 10.1002/ajh.20499

Source: Am J Hematol. 2006 Feb;81(2):115-7
MGUS and axonal neuropathy

"There is considerable pathological evidence suggesting that the neuropathy associated with MGUS is primarily demyelinating."

It is known that Lyme borreliosis and multiple sclerosis are associated with primary effusion lymphoma.


Lyme borreliosis and multiple sclerosis are associated with primary effusion lymphoma.
Monoclonal gammopathy of unknown significance (MGUS): Laboratory tests

1. Borrelia EliSpot + Borrelia SeraSpot + CD57 cells
2. Bartonella IgG/IgM antibodies

... and consider the tests recommended for MS-type syndromes in cases accompanied by axonal neuropathy:

1. Borrelia SeraSpot + Borrelia EliSpot + CD57-cells
2. Chlamydia pneumonia IgG/IgA antibodies + Chlamydia pneumoniae EliSpot
3. Mycoplasma pneumoniae IgG/IgA antibodies
4. Bartonella IgG/IgM antibodies
5. Coxsackie Virus IgG/IgA antibodies
6. EBV EliSpot
7. CMV EliSpot
8. HHV6 IgG/IgM antibodies
Ehrlichiosis can also mimic T-cell lymphoma.

Ehrlichiosis Mimicking T-Cell Lymphoma/Leukemia.
Ashok Malani, Robert Weigand, Vicram Gupta, Lawrence Hertzberg and Gautam Rangineni
Blood 2005 106:4348;

Abstract

Immunophenotyping by flow cytometry has revolutionized the diagnosis of blood cell disorders such as leukemias and lymphomas and is now commonly used in diagnosis and prognosis of such patients. We describe a case of human ehrlichiosis mimicking T-cell lymphoma/leukemia based on flow cytometry of bone marrow cells and confirmed by T-cell receptor gene rearrangement (TCR) by polymerase chain reaction (PCR). Treatment with doxycycline reversed these findings. A 20-year-old, Amish female presented with fatigue, fever, chills, sweating, low back pain, and lower abdominal pain for 2 days. She admitted to multiple bites from ticks 2 weeks prior to presentation and also reported having numerous animals such as cats, dogs, cows, goats, horses at her farm where she lived. Clinical exam was significant for fever of 101.4 F, heart rate of 118/min, BP of 80/60 mm Hg and a distended urinary bladder which was treated by catheter drainage. Relevant laboratory tests are shown in table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>9.7 12-16 gm/dl</td>
</tr>
<tr>
<td>WBC</td>
<td>0.8 4-10.8</td>
</tr>
</tbody>
</table>
Babesia and red blood cells

Babesia is a parasite that infects red blood cells causing a disease known as babesiosis.

Erythrocytes carry oxygen throughout the body. Damage to a large number of these cells can decrease the level of oxygen in the blood.

Babesiosis, according to the CDC, can cause low and unstable blood pressure, severe hemolytic anemia (hemolysis), a very low platelet count (thrombocytopenia), disseminated intravascular coagulation (DIC, or consumptive coagulopathy), which can lead to the above-mentioned blood clots and bleeding.

"Very high D-Dimer and thrombin-antithrombin complex formation (TAT) blood levels were found in our Babesia patients"
Lymphomas are "blood cancers" in the lymph nodes.

Non-Hodgkin lymphoma (NHL) is a group of blood cancers that includes all types of lymphoma except Hodgkin’s lymphomas.

It comes in the form of
B-cell lymphoma and T-cell lymphoma.
Babesia and B-cell lymphoma

Human Babesiosis

Edouard Vannier, PhD,¹ Benjamin E. Gewurz, MD, PhD,² and Peter J. Krause, MD³,⁴

Introduction

Human babesiosis is an emerging tick-borne infectious disease caused by protozoa of the genus Babesia that are obligate parasites of red blood cells. Long recognized as pathogens imposing a significant health burden on domesticated animals, Babesia spp. increasingly have been identified over the last 50 years as a cause of infection in people throughout the world.

The first reference to babesiosis is probably in Exodus 9:3, which describes the plague visited upon the cattle of Pharaoh Rameses II. Viktor Babes, a Hungarian pathologist who discovered hemoglobinuria in cattle grazing in the Danube region of Romania, was the first to identify a microorganism residing in red blood cells.[1] Shortly thereafter, Smith recognized Babesia bigemina as the vector for transmission of Texas cattle fever. By making this seminal observation, Smith and Kilborne established the concept that hematophagous arthropods can transmit an infectious agent to vertebrate hosts. More than 100 species of babesia subsequently have been identified in wild and domestic animals.[3]"
Borrelia and non-Hodgkin lymphoma

"Reports of the presence of Borrelia burgdorferi DNA in malignant lymphomas have raised the hypothesis that infection with B burgdorferi may be causally related to non-Hodgkin lymphoma (NHL) development"

"Moreover, regression of lymphomas upon treatment of the Borrelia infection has also been reported"

Bartonella and lymphoma

"The spleen is a vital organ in clearing erythrocytes .... The role of the spleen can be illustrated by the mechanism of sequestration, since the parasitized erythrocytes lack the deformability needed to transit the splenic sinusoids and are therefore sequestered within the spleen by resident macrophages"

Source: https://ann-Clinmicrob.biomedcentral.com/articles/10.1186/s12941-017-0179-z
B-Cell Non-Hodgkin’s Lymphoma: *Coxiella burnetii*


  “*Coxiella burnetii* is associated with an increased risk of lymphoma, its presence in the tumor microenvironment may favor lymphomagenesis.”

  “Lymphoma has to be considered in patients with Qfever and lymphoid disorders, especially those with persistent focalized infections.”
B-Cell Non Hodgkin’s Lymphoma: Coxiella burnetii

Q fever is a worldwide disease with acute and chronic stages caused by the bacteria Coxiella burnetii. Cattle, sheep, and goats are the primary reservoirs. Coxiella burnetii are excreted in milk, urine, and feces of infected animals.

Infection of humans usually occurs by inhalation of Coxiella burnetii from air that contains airborne barnyard dust contaminated by dried placental material, birth fluids, and excreta of infected animals.

Other modes of transmission to humans, including tick bites, and ingestion of unpasteurized milk or dairy products.
Coxiella/Q fever and B-cell lymphoma

Identifying risk factors for B-cell lymphoma

Christopher R. Flowers and Christine F. Skibola

This is one of the first studies to focus on *Coxiella burnetii* (the infectious agent associated with Q fever) as an inciting factor for lymphomas. Building on the identification of an incident case, the authors examined the incidence of lymphoma among individuals within a cohort of patients with Q fever. These analyses provide clinically meaningful insights that may aid in the identification of a novel risk factor for diffuse large B-cell lymphoma (DLBCL) and other B-cell NHLs and support the development of a comprehensive understanding of factors associated with lymphoma incidence. Utilizing a French National Referral Center for Q fever database of 1468 consecutive patients diagnosed from 2004 to 2014, and accounting for differences in age and sex distribution between the Q fever cohort and the general French population, the authors identified an increase in the incidence of DLBCL and follicular lymphoma (FL) in individuals who had Q fever compared with the general population, with standardized incidence rates of 25.4 (95% confidence interval [CI], 11.4-56.4) and 6.7 (95% CI, 0.9-47.9), respectively. Moreover, a diagnosis of Q fever with a persistent focal infection was noted to have a greater risk of lymphoma with a hazard ratio of 9 over the period of observation. For these analyses, acute Q fever was defined by the association of clinical symptoms (fever, hepatitis, and/or pneumonia) with the serological criteria of a phase 2 immunoglobulin G (IgG) titer ≥200 and a phase 2 IgM titer ≥50, seroconversion or a positive polymerase chain reaction (PCR), and no endocarditis. Supporting these epidemiological data were findings that interleukin-10 production was significantly increased in patients with lymphoma, particularly those with Q fever.
Link between Coxiella/Q fever and leukaemia/lymphoma

3 February 2016

Revisiting the Link between Coxiella Infection and Leukemic/Lymphoma Transformation

Han Sang Kim, Medical Oncologist Department of Pharmacology, Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Korea

Other Contributors:

Won Young Lee, Professor Emeritus

We have read with great interest the recent article published by Melenotte et al.1 In 1993, we reported that Coxiella burnetti infection causes hairy cell transformation.2 In our research, all three strains of Coxiella induced hairy cell transformation in vitro in average of 20 days after inoculation, and the half (6 of 12) of newly established hairy cells from the blood samples of patients with hematologic disorders (hairy cell leukemia and polymorphic reticulosis) were parasitized with Coxiella burnetti.2

An obligate intracellular pathogen Coxiella replicates within acidic, highly proteolytic, and oxidative lysosome–like vacuole known as Coxiella–containing vacuole (CCV). More than 120 Coxiella effector proteins, secreted by Dot/Icm (defect in organelle trafficking/intracellular multiplication) system from CCV into the host cell, (i) contribute to anti-apoptotic effects by inhibition of cytochrome c release from mitochondria, (ii) activate pro-survival kinases (e.g., AKT and ERK1/2) and mitogen–activated protein (MAP) kinase signaling, (iii) induce filamentous–actin cytoskeleton reorganization by Src–related kinase activation, and (iv) evade immune surveillance through lipopolysaccharide, demonstrating a potential role for tumorigenesis.3 Although Coxiella invades both phagocytic cells (monocytes and macrophages) and non–phagocytic cells (epithelial and endothelial cells) and Coxiella can bind to macrophages via αvβ3 integrin as the specific receptor, it rem...
B-cell Non Hodgkin Lymphoma: Laboratory tests

1. EBV-antibodies
2. EBV-EliSpot
3. CMV-antibodies
4. CMV-EliSpot
5. Coxiella burnetii IgG/IgM antibodies
6. Ehrlichia/Anplasma IgG/IgM antibodies
7. Ehrlichia/Anplasma EliSpot
8. Borrelia-EliSpot
9. CD57 cells + Borrelia-SeraSpot + CD57 cells
Involvement of viral co-infections in cancer is well documented, too

E.g., Herpes viruses EBV and CMV and a number of haematological cancers, e.g., Non-Hodgkin’s B-cell lymphoma
Epstein-Barr virus (EBV) is a tumorigenic herpes virus, which is associated with several human hematologic neoplasias such as Burkitt lymphoma, Hodgkin disease, and posttransplantation lymphoproliferative disease (PTLD).
B-Cell Non-Hodgkin’s Lymphoma: EBV/CMV

- EBV-Associated Lymphoproliferative Disorders: Classification and Treatment, Carbone A, Annunziata G, Dotti, G. The oncologist 1083-7159/2008
History of the discovery of EBV points to its tumorigenic origin

“The fact that the geographical distribution of Burkitt’s lymphoma (BL) overlapped that of several mosquito-borne diseases suggested the possibility that the disease was transmittable. Burkitt gave several talks about his findings on a visit to London, and Anthony Epstein, a virologist interested in tumor viruses, was present. He had Burkitt send him samples of the tumors and was able to detect a herpes-like virus by electron microscopy.”

Source: Epstein-Barr Virus and Cytomegalovirus Infections Alex Tselis
EBV/CMV and tumours

“The role of EBV was then established in a number of tumors”
EBV: Latency antigens and types associated with various cancers

Table 1. Latency antigens and types

<table>
<thead>
<tr>
<th>Latency type</th>
<th>Latency antigens</th>
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<tbody>
<tr>
<td></td>
<td>EBER</td>
</tr>
<tr>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
</tr>
<tr>
<td>Other</td>
<td>+</td>
</tr>
</tbody>
</table>

Latency types

- Latency 1: Burkitt’s lymphoma
- Latency 2: Nasopharyngeal carcinoma, Hodgkin’s disease
- Latency 3: Infectious mononucleosis, lymphoproliferative disease
- Other: Peripheral blood B lymphocytes

EBER Epstein–Barr virus-encoded RNA, EBNA Epstein–Barr nuclear antigen, LMP Latent membrane protein, BART BamHI A rightward transcripts

The pathogenesis of encephalitis (or meningitis or hepatitis or other focal visceral involvement) is not completely clear and there are several possibilities, which are not mutually exclusive. First, EBV may affect neurons (or other neural cells or endothelium) directly (Jones et al. 1995). There have been a few scattered reports of neurons and glial cells staining with EBV antigens, although there is not much detail (Biebl et al. 2009). In some patients with EBV encephalitis, as well as some with primary CNS lymphoma, lytic EBV mRNA was detected in the CSF, suggesting lytic replication of EBV in the brain in addition to latent replication (Weinberg et al. 2002a). Secondly, EBV-infected B cells are in an activated state and elaborate several proinflammatory cytokines, which can cause injury of the surrounding parenchyma (Foss et al. 1994). This injury is not necessarily irreversible. Third, EBV-infected B cells are actively attacked by EBV-specific cytotoxic T cells, and this can also injure the surrounding parenchyma. Finally, an acute disseminated encephalomyelitis can be triggered as in other viral infections.

Normally, EBV-infected B cells are suppressed (though not eliminated) by the immune system and lymphoproliferation can result during immunosuppression. In tissue culture in which T cells have been eliminated, B cells are immortalized and proliferate. In vivo, the B cell lymphoproliferation proceeds sequentially from polyclonal to oligoclonal to monoclonal, and evolves into a lymphoma. This can occur under circumstances of immunosuppression in transplant, chemotherapy, and AIDS patients as mentioned above. The lymphoproliferation can be accompanied by the elaboration of various cytokines, and a severe systemic illness resembling
“How EBV causes blood cancer”, study, University of Sussex - report November 2016

Scientists reveal how a common virus triggers blood cancer

Scientists at the University of Sussex, trying to uncover how the common Epstein-Barr virus causes blood cancer in adults and children, have discovered how the virus takes control of two genes involved in cancer development so it can switch them on or off.

The research team, led by Professor Michelle West, set out to determine how the Epstein-Barr virus controls two genes: MYC, a gene known to drive cancer development when it is altered or switched on at high level and BCL2L11, a gene which normally triggers cell death to prevent cancer, but can be turned off by the virus.

With thanks to funding from the blood cancer charity Bloodwise, the scientists discovered that the virus controls the MYC and BCL2L11 genes by hijacking ‘enhancer’ DNA regions which are situated far away from the genes. These enhancers act as ‘control centres’ and are able to contact and control genes from long distances by the looping out of the intervening stretches of DNA.

Professor West’s team found that Epstein-Barr virus turns on the MYC gene by increasing contacts between a specific set of enhancers and the gene. The scientists believe this may explain how the virus causes the changes to the MYC gene that are found in Burkitt’s lymphoma.

The team also discovered new enhancers which control the BCL2L11 gene. In this case, they found that Epstein-Barr virus stops these control centres from contacting the gene. Encouragingly the team have discovered that this blocking effect can be reversed by using a specific drug - paving the way for new treatments.

Professor West said: “This is a key step towards uncovering how this common virus which, affects thousands of people every year, causes blood cancer.

“It is now important to carry out further studies to discover what genes the virus is controlling and how they tell us more about how the virus drives lymphoma development. This could lead to new ways of targeting and stopping the disease, but we still need to understand exactly how the virus controls the behaviour of genes that control cancer growth.

“By mapping out the complex genetic interactions that help lymphoma cells grow and survive, this research can guide the design of new treatments to target the disease. It may also help to identify those drugs currently used to treat other diseases that could be effective in treating these types of lymphoma.”
Herpes viruses and blood cancers: Laboratory tests

1. EBV antibodies
2. EBV EliSpot
3. CMV antibodies
4. CMV EliSpot
5. Coxiella burnetii IgG/IgM antibodies
6. Ehrlichia/Anplasma IgG/IgM antibodies
7. Ehrlichia/Anplasma EliSpot
8. Borrelia EliSpot
9. CD57 cells + Borrelia SeraSpot + CD57 cells
PART III: Lyme and infections in other syndromes
Case report: “Mixed dementia”

65-year old patient with ataxia in walking, fatigue, loss of memory and concentration, depressions, increasing disorientation, hypertension, panic attacks, helplessness, change of character since 2011. Patient remembers several tick bites before the start of the illness.

Feb. 3\textsuperscript{rd}, 2013: University Hospital Munich: “Mixed dementia” with no findings in spinal fluid - “Exclusion of Neuroborreliosis”

Nov. 11\textsuperscript{th}, 2014: Appointment in my office:
- Borrelia IgG-/IgM-specific antibodies detectable
- Borrelia EliSpot positive (Borrelia full antigen: SI 3)

Case report: “Mixed dementia”

April 2$^{nd}$, 2016 ) Increasing autonomy, significant improvement in ataxia und movement disorders, no panic attacks anymore

June 6$^{th}$, 2016 Condition remains stable, following treatment for 12 weeks with oral Donta treatment scheme (Clarythromycin und Hydroxychloroquin)

Nov. 11$^{th}$, 2016: Next consultation in my office:
- Borrelia antibodies IgG/IgM antibodies unchanged
- Borrelia EliSpot negative (SI <2)!

Patient is symptom-free!

Correct diagnosis: Chronic Neuroborreliosis with dementia-like symptoms
Acrodermatitis Chronica Atrophicans ACA and Alopecia

Acute Diffuse and Total Alopecia of the Female Scalp Associated with Borrelia-Infection

Ekta K Bhardwaj and Ralph Michel Trueb

Renovia Medical Aesthetics and Hair Center, Manchester, England, UK
Center for Dermatology and Hair Diseases, Zurich-Wallisellen, Switzerland

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Abstract

A case of acute diffuse and total alopecia of the female scalp associated with Borrelia-infection (acrodermatitis chronica atrophicans) is presented. Today, acute diffuse and total alopecia of the female scalp is recognized as a distinct variant of alopecia areata (AA) predominantly observed in women. Cases of AA have formerly been reported in association with infections. AA is understood to represent an organ-specific autoimmune disease of the hair follicle. It is conceivable that the antigenic stimulus provided by the infection may act as a trigger for alopecia. Vice versa, alopecia may act as a marker for detection of undiagnosed infection. Treatment of the patient with intravenous ceftriaxone led to the resolution of cutaneous borreliosis, and in addition to topical clobetasol foam to complete recovery of hair.

Keywords: Borrelia-infection, co-morbidity, diffuse alopecia areata
Researchers find that ancient Iceman's infection helps Lyme disease bone loss discovery

- Mitochondrial DNA analysis has shown that the bacteria responsible for Lyme disease resided deep in Ötzi’s bones. Though he didn’t die from complications of the disease, work from a team of scientists at the University of Toronto’s Faculty of Dentistry now suggests that the 5,000-year-old man might have suffered from bone loss as a result of his infection.

- While scientists have long established a link between advanced Lyme disease and the development of osteoarthritis, until now no one has systematically studied the effects of this disease on bones.

- The bacteria were not only detectable in the bones of mice, they were seen to cause significant bone loss in the longer bones, mere weeks after infection.

- In fact, the bone loss developed at a rapid rate, taking just four weeks to advance to osteopenia, a forerunner to the more severe form of bone loss disease, osteoporosis. The study found that the amount of bone loss directly correlated to the bacterial load found in the bones. The more bacteria present, the greater the rate of bone loss.

- The findings suggest that monitoring bone loss in human Lyme disease patients may be warranted, especially because bone loss is a significant risk factor for fractures later in life.

- “One of our main focuses right now is on the mechanism that induces the bone loss,” said Tian Cornelia Tang, Faculty of Dentistry.

- Cellular studies are currently underway to determine just how the bacteria interact with the bone building cells of the body, osteoblasts, with the hope of finding new drug targets to combat not just the bacteria, but the newly discovered associated bone loss.

- “We need to know how long the osteopenia lasts after bacterial infection, and whether it progresses to osteoporosis,” added Moriarty.
Borrelia is associated with multiple autoimmune conditions

► Rheumatic fever, reactive arthritis, rheumatoid arthritis

► Molecular mimicry in neuroborreliosis

► Neuropathy

► Vasculitis

► Autoimmune thyroid disease/Hashimoto’s

► Multiple sclerosis

► .....
Lyme arthritis: the first link between Borreliosis and autoimmune disease

The first indication that treatment-resistant Lyme borreliosis might be an autoimmune disease came from a study analysing MHC (major histocompatibility complex) II alleles (HLA-DR4) in patients with Lyme arthritis. MHC class II molecules play a critical role in activation of the immune system.

PX with chronic treatment-resistant Lyme arthritis have been found to have MHC II alleles associated with rheumatoid arthritis, partic. HLA-DRB1* 0401 and 0101 alleles.

These PX also develop anti-OspA antibodies correlating with the duration of their arthritis [138], suggesting that OspA may be involved in the autoimmune process.

Gross et al. suggested that LFA-1 (human leucocyte function-associated antigen 1) can serve as a cross-reactive autoantigen for OspA-reactive Th1 cells, leading to treatment-resistant Lyme arthritis. One potential explanation for antibiotic-resistant Lyme disease is thus generation of A/I directly or indirectly mediated by the pathogen and based on molecular mimicry.

Intracellular persistence of Bb in synovial cells - molecular mimicry in Lyme arthritis

Antigen-presenting cells (monocytes, macrophages, dendritic cells and synovial fibroblasts) present peptides generated from borrelial OspA and host LFA-1a (human leucocyte function-associated antigen 1), which induce a cross-reactive T-cell response

Source: Singh SK, Girschick HJ. Lyme borreliosis: from infection to autoimmunity. 2004. Clinical Microbiology and Infection (CMI), 10, 598–614
Infection-induced autoimmunity in rheumatic diseases
Important to consider Borrelia in the differential diagnosis of rheumatoid arthritis
Molecular mimicry in chronic neuroborreliosis

Hemmer et al. demonstrated that several T-cell clones responded to Borrelia peptides and endogenous host peptides.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Potency</th>
<th>PB</th>
<th>Definition</th>
<th>Notes</th>
<th>Reference or submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>(23) YSICKSGCFY</td>
<td>0.1-1</td>
<td>nt</td>
<td>nt</td>
<td>Myelin-associated oligoden drocyte basic protein (MOBP)</td>
<td>Third-most-abundant protein in CNS compact myelin</td>
</tr>
<tr>
<td>(61) LHIISKRVEA</td>
<td>0.1-1</td>
<td>70.0</td>
<td>0</td>
<td>Titin</td>
<td>Giant protein involved in muscle ultrastructure and elasticity</td>
</tr>
<tr>
<td>(62) SFIYSVCLV</td>
<td>0.1-1</td>
<td>75.7</td>
<td>9</td>
<td>Somatostatin receptor isoform 1</td>
<td>Somatostatinergic neurotransmission modulates cognitive function and may be defective in Alzheimer disease</td>
</tr>
<tr>
<td>(63) GHIKKKRVEA</td>
<td>1-10</td>
<td>56.5</td>
<td>0</td>
<td>Transforming growth factor (TGF-β3)</td>
<td>Potent immunosuppressive cytokine; TGF-β3 is mainly expressed in cells of mesenchymal origin</td>
</tr>
<tr>
<td>(64) FNITSSTCEL</td>
<td>0.1-1</td>
<td>66.3</td>
<td>1</td>
<td>Human C-C chemokine receptor type 7 precursor</td>
<td>Lymphoid-specific EBV-induced G protein-coupled receptor; upregulated during dendritic cell maturation</td>
</tr>
<tr>
<td>(66) ENVKKSRLI</td>
<td>0.1-1</td>
<td>64.1</td>
<td>0</td>
<td>Interleukin (IL)-1 receptor type 1, precursor</td>
<td>Receptor for IL-1α and IL-1β; type I membrane protein; binding to agonist leads to activation of NFκB</td>
</tr>
<tr>
<td>(71) DNIITSSVLFN</td>
<td>0.1-1</td>
<td>60.6</td>
<td>5</td>
<td>Aminopeptidase A</td>
<td>Cleaves acidic amino acids off N-terminus of polypeptides (angiotensin II, IL-8, CCK-8); may cleave both IL-7 and IL-7R (N-terminal E); EC 3.4.11.7; genomic structure similar to CD10, CD26; marker of immature B cells, upregulated by IL-7, viral transformation, type I interferons</td>
</tr>
</tbody>
</table>

Anti-axonal IgM antibodies have been found in the serum of patients with neurological Lyme disease

“Previous studies have demonstrated that patients with LD-associated neuropathy have serum and cerebrospinal fluid antibodies to B. burgdorferi flagellin, often binding to the H9724-defined epitope”

The H9724-defined epitope cross-reacts with human peripheral nerve axons*

Vasculitis in affected nerves has been reported as part of the neuropathological process.

Perivasculitis of epineurial vasa nervorum in sural nerve biopsies from patients with PNS complications of Lyme Borreliosis.

Borrelia burgdorferi can cross-react with thyroid tissue, triggering Hashimoto’s

“... in some genetically predisposed subjects, Borrelia infection can be the trigger of Hashimoto’s thyroiditis and/or lichen sclerosus”
IgG antibodies that cross-react with myelin basic protein discovered in sera from LD patients

Sera from Lyme disease patients contain antibodies to Bb that crossreact with nervous tissue antigens. Sigal and Tatum found IgM antibodies that cross-reacted with axonal antigens, and Garcia-Monco et al. found IgG antibodies that cross-reacted with myelin basic protein

“...A statistically significant (p=0.0422) relationship was found between the clinically confirmed diagnosis of multiple sclerosis and the positive serologic reaction with Borrelia antigen...”

Borrelia burgdorferi as well as viruses associated with neurological disease

► Clear role in neurodegenerative and neurobehavioural conditions

► Alzheimer’s

► Parkinson’s/Parkinsonism

► ALS/motor neurone disease

► ...
"Evidence of *Mycoplasma* species, *Chlamydia pneumoniae*, *Borrelia burgdorferi*, human herpesvirus-1, -6 and -7 and other bacterial and viral infections revealed high infection rates in the above illnesses that were not found in controls."
Alzheimer Plaques can be Borrelia biofilms
Amyloid plaques in Alzheimer’s Disease: Protection against microbial infection?

“When you look in the plaques, each one had a single bacterium in it,” says Tanzi. “A single bacterium can induce an entire plaque overnight.”

“Our findings raise the intriguing possibility that Alzheimer's pathology may arise when the brain perceives itself to be under attack from invading pathogens.”
Numerous studies have found connections with Parkinson’s/Parkinsonism

The association between infectious burden and Parkinson’s disease: A case-control study.
Bu XL¹, Wang X¹, Xiang Y¹, Shen LL¹, Wang QH¹, Liu YH¹, Jiao SS¹, Wang YR¹, Cao HY¹, Yi X¹, Liu CH¹, Deng B¹, Yao XQ¹, Xu ZQ¹, Zhou HD¹, Wang YJ².

Abstract
INTRODUCTION: The etiology of Parkinson’s disease involves common pathogenic infections and PD.
METHODS: Antibody titers to common infectious pathogens (CMV, EBV, HSV-1, B. burgdorferi, C. pneumoniae, H. pylori) were measured by ELISA in serum of 131 PD patients and compared to 131 age- and sex-matched controls. Seropositivity was defined as the presence of antibodies to a pathogen. The infectious burden was quantified as the number of seropositive results.
RESULTS: Seropositivity to CMV, EBV, HSV-1, B. burgdorferi, C. pneumoniae, H. pylori was found in 11.2%, 44.1%, 7%, 15.6%, 3.8%, 15.6% of PD patients, respectively, compared to 6.7%, 28.2%, 6%, 10%, 0%, 9.2% in controls. The infectious burden correlated positively with the duration of PD and the severity of disability.

CONCLUSIONS: The infectious burden consisting of CMV, EBV, HSV-1, B. burgdorferi, C. pneumoniae, and H. pylori is associated with PD. This study supports the role of infection in the etiology of PD.

Drosophila-like 4 gene, which is associated with inflammation and neuronal death and is up-regulated in Parkinson’s disease, was up-regulated in spirochete-stimulated tissues by 9.98-fold*


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MND may be associated with Borrelia and coinfections: Patient recovered when treated accordingly

“... positive testing for Borrelia burgdorferi ..... The patient has continued to be free of MND signs and symptoms for 15 months, although some symptoms consistent with disseminated Borreliosis remain.”
Viral involvement in autoimmunity is well documented

- Examples:
  - SLE (Lupus)
  - Ulcerative colitis
  - Sarcoidosis
  - Grave’s disease
EBV and SLE

Arthritis Research & Therapy

Patients with systemic lupus erythematosus have abnormally elevated Epstein–Barr virus load in blood

Uk Yeol Moon†, Su Jin Park†, Sang Taek Oh, Wan-Uk Kim, Sung-Hwan Park, Sang-Heon Lee, Chul-Soo Cho, Ho-Youn Kim, Won-Keun Lee and Suk Kyeong Lee

†Contributed equally

Received: 4 November 2003 | Accepted: 1 April 2004 | Published: 7 May 2004

Abstract

Various genetic and environmental factors appear to be involved in systemic lupus erythematosus (SLE). Epstein–Barr virus (EBV) is among the environmental factors that are suspected of predisposing to SLE, based...


“The most common viral infections in patients with SLE are parvovirus B19 (predominantly mimicking SLE presentation) and CMV (predominantly presenting in severely immunosuppressed patients).”
EBV / CMV and SLE: Practical example

<table>
<thead>
<tr>
<th>Autoantikörper</th>
<th>Ergebnis Einheit</th>
<th>Normbereich</th>
<th>Grafik</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA-Fluoreszenzmuster-</td>
<td>1:3200</td>
<td>&lt; 1:100</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

EBV EliSpot (lytisch+latent)

<table>
<thead>
<tr>
<th>1</th>
<th>EBV-lytischer Peptidmix</th>
<th>SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>negativ</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>grenzwertig</td>
<td></td>
</tr>
<tr>
<td>ab 4</td>
<td>positiv</td>
<td></td>
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</tbody>
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<td></td>
</tr>
<tr>
<td>ab 4</td>
<td>positiv</td>
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</tr>
</tbody>
</table>

Mittels EliSpot finden sich aktuell positive T-Zell-Reaktionen gegen Epstein Barr Virus (EBV).

Erläuterung EBV-Antigene:
EBV lytisches Antigen: Hinweis auf EBV-Replikation
EBV latentes Antigen: Hinweis auf EBV-Latenz

Achtung: Ab 01.08.2016 geänderte Nachweisgrenze!

CMV EliSpot

<table>
<thead>
<tr>
<th>1</th>
<th>CMV Peptidmix</th>
<th>SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>negativ</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
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<td></td>
</tr>
<tr>
<td>ab 4</td>
<td>positiv</td>
<td></td>
</tr>
</tbody>
</table>
Ulcerative colitis: CMV, HSV and EBV

Cytomegalovirus and ulcerative colitis: Place of antiviral therapy

Sylvie Pillet, Bruno Pozzetto, and Xavier Roblin

Abstract

The link between cytomegalovirus (CMV) infection and inflammatory bowel diseases remains an important subject of debate. CMV infection is frequent in ulcerative colitis (UC) and has been shown to be potentially harmful. CMV reactivation needs to be diagnosed using methods that include in situ detection of viral markers by immunolabeling. The density of infection using particularly important. Althoherpes virus, as an exacerbating factor of UC, has been neglected by many clinicians.
## Sarcoidosis: EBV, CMV, HSV ...

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Noninfectious</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacteria</td>
<td>Dusts</td>
</tr>
<tr>
<td>Tuberculous</td>
<td>Clay</td>
</tr>
<tr>
<td>Nontuberculous</td>
<td>Pine</td>
</tr>
<tr>
<td>Cell-wall deficient (L-forms)</td>
<td>Pollen</td>
</tr>
<tr>
<td>Bacteria</td>
<td>Talc</td>
</tr>
<tr>
<td><em>Corynebacterium</em> spp.</td>
<td>Mixed</td>
</tr>
<tr>
<td><em>Propionibacterium acnes</em></td>
<td>Metals</td>
</tr>
<tr>
<td><em>Tropheryma whippelii</em></td>
<td>Aluminum</td>
</tr>
<tr>
<td>Others</td>
<td>Beryllium</td>
</tr>
<tr>
<td>Fungi</td>
<td>Zirconium</td>
</tr>
<tr>
<td><em>Cryptococcus</em> spp.</td>
<td></td>
</tr>
<tr>
<td>Endotoxins</td>
<td></td>
</tr>
<tr>
<td>Viruses</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td></td>
</tr>
<tr>
<td>Herpes simplex virus</td>
<td></td>
</tr>
</tbody>
</table>

*These organisms have been the focus of most recent studies, but no single agent is confirmed. It is very possible that several disparate agents induce similar reactions leading to sarcoidosis.*

Graves’ Disease and EBV

“In Graves' disease patients with TSH receptor antibodies (TRAb) levels ≥ 10%, EA antibody levels, which indicate EBV reactivation, were moderately but significantly correlated with the levels of TRAb”
„Peeling the onion“
Thank you very much for your attention!

Armin Schwarzbach Ph.D.

Medical Doctor and
Specialist for laboratory medicine