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Commentary

The Aphid Arthritis- Lyme Disease

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Preface

Lyme disease is a common, tick-borne infection engendered by a spirochete designated as *Borrelia burgdorferi* wherein the multisystem disorder demonstrates an essentially universal geographic distribution. Additionally, denominated as Lyme borreliosis, Lyme disease commonly incriminates the cutis, central nervous system, joints, cardiac and ocular tissue and exceptionally the hepatic parenchyma. Lyme disease is commonly discerned in children and adults, especially individuals congregating in areas endemic to ticks such as forests. Lyme disease terminates in diverse complications such as arthritis, carditis, neurological deficits, ocular disease and cutaneous conditions such as acrodermatitis chronica atrophicans. Vaccine for Lyme disease is currently unavailable.

Disease characteristics

Lyme disease is a bacterial disease engendered by spirochete *Borrelia* burgdorferi which is transmitted by tick bite of Ixodes genus, generally *Ixodes scapularis* or *Ixodes dammini*. In additional to *Borrelia burgdorferi*, spirochetes such as *Borrelia afzelii* and *Borrelia garinii* can initiate the disease [1,2].

Lyme disease is subdivided into distinct stages designated as early localized, early disseminated and late stage:

1. Early localized disease delineates a red, ring-like, expansive cutaneous rash, akin to erythema migrans, upon the site of recent tick bite. Associated flu-like clinical symptoms appear such as malaise, headache, pyrexia, myalgia and arthralgia. Majority of subjects delineate clinical symptoms within early, localized disease [1,2].

2. Early disseminated disease emerges within an estimated 20% subjects. Common clinical symptoms are multiple lesions of erythema chronicum migrans, flu-like symptoms, lymphadenopathy, arthralgia, myalgia, cranial nerve palsies with frequent incrimination of facial nerve, ophthalmic disorders and lymphocytic meningitis. Cardiac anomalies such as conduction defects, myocarditis or pericarditis may ensue [1,2].

3. Late stage disease commonly manifests pauci-articular arthritis which involves large joints, especially the knee joint.

Lyme disease demonstrates a disease incidence of nearly 0.0004 individuals per year wherein the condition may be discerned at any age group. A female predominance is observed. Seasonal variation associated with the disorder occurs during late spring, summer and early fall [1,2].

Clinical elucidation

Lyme disease commences with the appearance of rash associated with erythema migrans. In a majority (~80%) of subjects the rash appears as an expansive, erythematous cutaneous lesion of magnitude exceeding > 5 centimetres, observed at site of tick bite. The lesion

may present as homogeneous erythema or display a targetoid appearance. The rash generally emerges one week or two weeks following the initial tick bite [2,3].

Characteristic erythema migrans of localized Lyme disease appears as a pink, purple or reddish, expansive cutaneous patch, papule or macule within 14 days following infection with tick bite. Several centimetres in magnitude, clear surface circumscribes the centric spot with surrounding, expansive, red coloured rash. Erythema migrans may additionally represent as a uniform, erythematous patch with centric induration and blistering [2,3].

Erythema migrans is usually asymptomatic although pruritus, cutaneous sensitivity or warmth can ensue. Pain is exceptional. The patch may be accompanied by reoccurring clinical symptoms such as fatigue, chills, headache, low-grade pyrexia, myalgia or joint pain. Regional lymph nodes may be enlarged. Erythema migrans regresses spontaneously within 4 weeks [3,4].

Untreated localized disease progresses to early disseminated or delayed stage, disseminates to incriminate diverse organs and demonstrates early arthritis (~30%), neurologic manifestations (~15%) or cardiac involvement (~2%) [1,3].

Non specific clinical symptoms may concur with tick bite associated coinfections with Babesia microti and Ehrlichia in around 10% subjects. Tick bites can transmit infections such as tick borne encephalitis, anaplasmosis and babesiosis. Coinfection is indicated with emergence of severe, extensive Lyme disease associated with excessive pyrexia and anomalous haematological or biochemical parameters with leucopenia, thrombocytopenia and elevated liver transaminases.

Early stage Lyme disease with neurologic features depict facial nerve palsy, lymphocytic meningitis or radiculopathy. Cardiac manifestations typically emerge as heart block or myopericarditis [3,4].

Delayed stage of Lyme disease appears months following initial tick bite and manifests as mono-articular or pauci-articular arthritis which implicates large joints, commonly the knee joint [3,4].

Localized disease disseminated disease and persistent disease are stages of Lyme disease wherein localized and disseminated disease occur with preliminary infection and persistent disease manifests as the chronic phase usually emerging within one year of infection [3,4]:

- Stage I is constituted of preliminary, localized disease occurring within 28 days of tick bite, extends for one day to one month and represents with flu-like symptoms and erythema migrans. The rash is uniform, expansive with concentric circles, occurs at the site of tick bite, may be asymptomatic or associated with pruritus or burning and untreated rash persists for two weeks to three weeks. Around 20% subjects depict repetitive occurrence of the rash. Multiple foci of rash are accompanied by flu-like symptoms with low grade pyrexia, myalgia, headache, stiffness of neck, conjunctival injection and excessive tears. Disease progression ceases in nearly 30% subjects with rash [3,4].

  Acrodermatitis chronica atrophicans occurs within the extremities or dorsum of hands and feet of elderly female subjects and is associated with an erythematous, oedematous and pruritic phase terminating in sclerosis and atrophy. Cutaneous lymphoid hyperplasia may also be discerned [3,4].

- Stage II commences within three weeks to twelve weeks of initial infection, is configured by early, disseminated disease and represents general malaise, pain, pyrexia, neurological manifestations as dizziness, headache, myalgia and cardiac symptoms as chest pain, palpitations and dyspnoea. Ocular pain and keratitis are documented. The knee, ankle and wrist joints are incriminated. Clinical symptoms of stage II extend to up to 20 weeks although reappearance of symptoms is exceptional [3,4].

  Roughly 20% subjects display involvement of central nervous system with emergence of encephalopathy, meningitis and cranial nerve neuropathies which manifest as diplopia. Bell palsy occurs in around 5% individuals. Spirochetes induces host cells

which generates quinolinic acid with consequent stimulation of NMDA receptors and occurrence of Lyme encephalopathy with accompanying malaise [3,4].

Encephalopathy manifests as lack of concentration, defective cognition, loss of memory and altered personality with depression and excessive irritability. Meningitis appearing in Lyme disease is associated with headache exceeding > 7 days, cerebrospinal fluid imbued with > 70% mononuclear cells and facial nerve or associated cranial nerve palsy. Encephalomyelitis due to *Borrelia* is uncommon and manifests with ataxia, seizures, hemiparesis, autonomic dysfunction and hearing loss. Cardiac disease represents as arrhythmia, transient heart block or infrequently, transient conduction defects [3,4].

- Stage III or delayed phase of Lyme disease develops months or years following initial infection and is comprised of delayed, chronic disease. History of erythema migrans may be absent. Incriminated subjects manifest aseptic meningitis, Bell palsy, arthritis or dysesthesias. Radicular pain or cognitive deficits are frequent. Implication of joints, muscles and nerves is observed along with pathognomonic appearance of Lyme arthritis [3,4].

Typically, stage III Lyme disease demonstrates migratory polyarthritis which commonly implicates the knee joint. Clinical symptoms may simulate fibromyalgia [5,6].

Histological elucidation

Erythema migrans exhibits a nonspecific histology with a perivascular cellular infiltrate of histiocytes, lymphocytes and plasma cells. Mast cells and neutrophils are exceptional. Localized tissue reaction to the tick bite may occur with eosinophilic infiltration. Spirochetes can be identified with silver stains or antibody-labelled techniques. Commonly, a paucity of spirochetes is observed with examination of tissue samples of Lyme disease [5,6].

On microscopy, superficial and deep-seated, perivascular, polymorphic inflammatory infiltrate composed of neutrophils, lymphocytes, plasma cells, eosinophils and mast cells is discerned. Foci of vascular proliferation and dermal necrosis may be observed [5,6].

Antecedent tissue examination of acrodermatitis chronica atrophicans exhibits a predominant infiltration of lymphocytes with a few plasma cells confined to dermal perivascular region. Additionally, vascular lymphedema and telangiectasia is delineated [5,6].

Delayed stage exemplifies attenuation of superimposed epidermis with absence of cutaneous appendages and significant infiltration of plasma cells. Deep seated dermal tissue is infiltrated by nodules of fibrotic tissue along with hyalinization of collagen fascicles. Occasionally, *Borrelia* burgdorferi may be isolated [5,6].

Borrelia lymphocytoma is exceptional in preliminary Lyme disease and manifests as a nodular, painful, reddish-blue nodule usually appearing upon the ear lobe or areola of nipple. *Borrelia* lymphocytoma enunciates a dense infiltrate of lymphocytes confined to the dermis with configuration of lymphoid follicles and pseudo-terminal appearance of germinal centres. B lymphocytes, T lymphocytes, occasional macrophages, plasma cells and eosinophils are observed [5,6].

Warthin-Starry silver stain can be employed for isolation of *Borrelia* spirochetes along with immunocytochemistry with monoclonal antibodies, manoeuvers which are diagnostic in highlighting *Borrelia* species [5,6].

Differential diagnosis

Preliminary stage of Lyme disease with erythema migrans requires segregation from diverse cutaneous conditions such as tinea and nummular eczema.

Erythema migrans associated Lyme disease can be established with pertinent history and physical examination. However, instances where erythema migrans is absent, disguised or incorrectly determined Lyme disease may be challenging to discern [7,8].

Bacterial infection with non-spirochete, curved or wavy bacilli such as *Vibrio, Campylobacter* and *Helicobacter* or spirochetes such as Treponema and Leptospira requires distinction from Lyme disease. Additionally, segregation is required from acute memory disorders, ankylosing spondylitis, rheumatoid arthritis, atrioventricular nodal block, cellulitis, contact dermatitis, gout, pseudo-gout, granuloma annulare and prion-related diseases [7,8].

Investigative assay

Therapy can be preliminarily initiated in endemic zones with recent history of tick bite and occurrence of classic rash. Majority of subjects depict non specific symptoms and require additional evaluation [7,8].

Preliminary diagnosis of Lyme disease is imperative. Lyme disease can be discerned with history or evidence of tick bite, appearance of erythema migrans or additional clinical symptoms [7,8].

Morphological evidence of erythema migrans is usually non-specific. Appropriate discernment of *Borrelia* lymphocytoma and acrodermatitis chronica atrophicans is required. A polymerase chain reaction (PCR) may isolate the organism from cutaneous tissue samples or synovial fluid [7,8].

Serological assay is insensitive during antecedent disease or recent infection. Quantitative screening for serum IgG antibodies or IgM antibodies to *Borrelia burgdorferi* can be achieved with enzyme immunoassay (EIA) or immunofluorescent antibody assay (IFA) and depicts a sensitivity of ~80%. Western blot examination is recommended for confirmation or equivocal results. Antibody titres against *Borrelia* burgdorferi remain elevated for a significant duration and can be discerned several years following cessation of pertinent therapy [7,8].

Additionally, elevated erythrocyte sedimentation rate (ESR), leukopenia or thrombocytopenia may be observed. *Borrelia* spirochetes are elongated, spiral bacilli with regular undulations and a magnitude varying from 5 microns to 20 microns. The spirochetes are usually non discernible on peripheral blood films. Possible septic arthritis can be evaluated with cogent joint aspiration. Electrocardiogram (ECG) reveals an atrioventricular (AV) block appearing in Lyme carditis [7,8].

Brain imaging of central nervous system disease depicts an anomaly in 20% subjects, usually punctate lesions of periventricular white matter. Lumbar puncture and examination of cerebrospinal fluid is warranted in order to evaluate meningeal involvement [7,8].

The spirochetes can be appropriately discerned by dark-field microscopy. Culture of *Borrelia* species is challenging and not recommended [9,10].

Therapeutic options

Cogent therapy may be commenced in subjects depicting typical rash in the absence of history of tick bite or diagnostic serology [9,10].

Pertinent therapy of Lyme disease is contingent to age of incriminated subject and stage of disease. Early, localized disease in children above >8 years can be aptly managed with doxycycline for 10 days. Children < 8 years are treated with amoxicillin or cefuroxime for 14 days. Extensive oral or parenteral antibiotics are necessitated for treating severe disease manifestations such as arthritis, atrioventricular heart block, carditis, meningitis or encephalitis. Pregnant women usually respond to ceftriaxone [9,10].

Additionally, macrolides, azithromycin and erythromycin can be employed. Intravenous penicillin and ceftriaxone are adopted for managing advanced stage Lyme disease. Route of administration and duration of antibiotic delivery is contingent to disease stage and incriminated organ [9,10].

Lyme disease with carditis requires hospitalization and monitoring until atrioventricular block subsides [9,10].

Central nervous system disease or neuroborreliosis is aptly treated with intravenous antibiotics. Lyme arthritis subjected to cogent therapy resolves within 6 weeks to 8 weeks. Ocular Lyme disease is treated with topical steroids and intravenous ceftriaxone or penicillin [9,10].

Approximately 5% individuals depict persistent fatigue, pain and joint or muscle ache for a period of > 6 months, a phenomenon labelled as "post-treatment Lyme disease syndrome" [9,10].

Occasionally, "post-treatment Lyme borreliosis syndrome" occurs as a component of autoimmune response, demonstrates nonspecific symptoms and is unamenable to antibiotic therapy [9,10].

Appropriate treatment of preliminary instances is curative. However, therapy may be non efficacious due to delayed diagnosis, antibiotic resistance and concurrent infection with tick-borne diseases such as ehrlichiosis or babesiosis. Immune suppression engenders lack of therapeutic response [9,10].

Chronic Lyme disease mandates therapy akin to fibromyalgia or chronic fatigue syndrome. Occurrence of chronic disease or post treatment Lyme disease syndrome is debatable. Majority of subjects recover in the absence of residual sequelae [9,10].

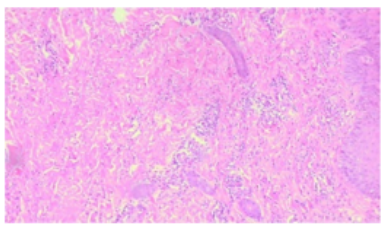

Figure 1: *Lyme disease exhibiting perivascular aggregates of inflammatory cells as lymphocytes, plasma cells, histiocytes, mast cells, few neutrophils and eosinophils surrounded by foci of sclerosis [11].*

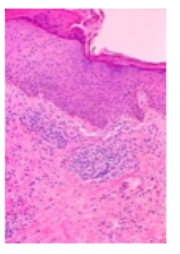

Figure 2: *Lyme disease exhibiting a dermal accumulation of lymphocytes, histiocytes, plasma cells, eosinophils and neutrophils interspersed within a fibrotic stroma and a superimposed stratified squamous epithelium [12].*

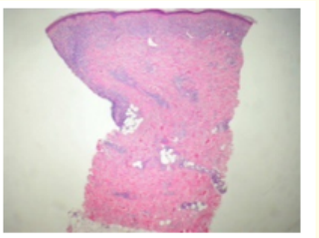

Figure 3: *Lyme disease delineating perivascular accumulation of lymphocytes, plasma cells, histiocytes, mast cells, eosinophils and few neutrophils enmeshed within a fibrotic stroma and a superficial layer of stratified squamous epithelium [13].*

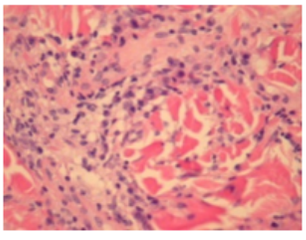

Figure 4: *Lyme disease exhibiting whorls of inflammatory cells such as lymphocytes, macrophages, plasma cells, mast cells, eosinophils and occasional neutrophils intermixed with congested blood vessels and a fibrotic stroma [13].*

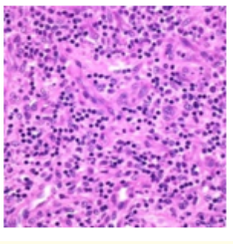

Figure 5: *Lyme disease exhibiting a perivascular inflammatory infiltrate composed on lymphocytes, histiocytes, plasma cells, few neutrophils, eosinophils and mast cells encompassed in a fibrotic stroma [14].*

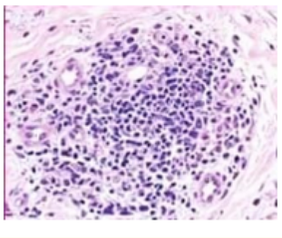

Figure 6: *Lyme disease delineating aggregates of inflammatory cells chiefly lymphocytes, plasma cells, mast cells, neutrophils and eosinophils intermingled within fibro-sclerotic tissue [15].*

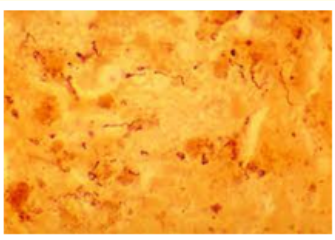

Figure 7: *Lyme disease demonstrating bacilli with regular undulations of Borrelia species as highlighted with silver stain [16].*

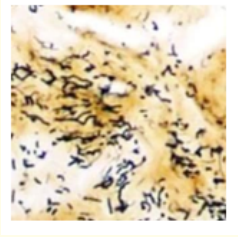

Figure 8: *Lyme disease depicting Warthin starry with undulating Borrelia spirochetes disseminated within incriminated tissue [17].*

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11. Image 1 Courtesy: Springer link.

12. Image 2 Courtesy: JAAD.

13. Image 3 and 4 Courtesy: Dermnet NZ.

14. Image 5 Courtesy: Webpathology.com.

15. Image 6 Courtesy: Plastic surgery key.

16. Image 7 Courtesy: Pathology outlines.

17. Image 8 Courtesy: Cell path.org.

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