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Short Communication

The Mephitic Vascularity-Bacillary Angiomatosis

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Preface

Bacillary angiomatosis is an uncommon, reactive vascular proliferation additionally denominated as "epithelioid angiomatosis", engendered by miniature, gram- negative bacilli of *Bartonella* genus especially *Bartonella henselae* and *Bartonella quintana*.

Bacillary angiomatosis was initially scripted by Stoler., *et al*. in 1983 as an "atypical, subcutaneous infection associated with autoimmune deficiency syndrome (AIDS)" [1]. The condition commonly appears in subjects infected with human immune deficiency virus (HIV) although immunocompromised, non HIV infected or immune competent individuals are also incriminated.

Disease pathogenesis

Bartonella henselae is a fastidious, aerobic, oxidase- negative, gram-negative, minimally curved bacillus optimally propagating at 37°C. Cauliflower-like bacterial colonies are discerned. The bacterium is approximately 2 microns in magnitude with a circular genome of 1.9 million base pairs. Type 1 *Bartonella henselae* engenders peliosis and type 2 is associated with cutaneous or lymph node lesions [2,3].

Bartonella quintana is a gram- negative, gradually evolving bacillus appearing as abbreviated rods. Bacterial magnitude is around 0.4 millimetres to 1.5 millimetres with a genome of 1.5 million base pairs. *Bartonella quintana* necessitates up to 12 days to 14 days or 45 days for primary isolation. *Bartonella henselae* and *Bartonella quintana* are non-flagellate organisms, in contrast to adjunctive bacteria as *Bartonella* bacilliformis and demonstrate distinctive fimbriae [2,3].

Cats are natural reservoirs of *Bartonella henselae* and depict several episodes of asymptomatic bacteraemia wherein bacteria adapt to a life cycle within the erythrocytes. Cats are infected by cat fleas or *Ctenocephalides felis* which incorporate *Bartonella henselae* or *Bartonella quintana* [2,3].

Human transmission of aforesaid bacteria through ticks is documented although transference through cat fleas is ambiguous and undocumented. *Bartonella henselae* is transmitted to humans through scratch or bite of a cat in around 65% instances. Besides, *Bartonella henselae* generally engenders cat-scratch disease [2,3].

Bartonella henselae may thus be isolated from cat scratch disease and lesions of bacillary angiomatosis.

Humans or Japanese macaques *Macaca fuscata* are reservoirs for *Bartonella quintana* which is implicated in generation of bacillary angiomatosis although is un- associated with cat scratch disease. Also, body louse is incriminated in transmission of *Bartonella quintana* within the impoverished population [2,3].

Human inoculation of *Bartonella* spp by blood sucking arthropods or cutaneous penetration following exposure to cat ensures the adherence of gram negative bacteria to diverse host cells such as erythrocytes, monocytes, macrophages or dendritic cells [2,3].

Endothelial cells are targeted by *Bartonella quintana*, in contrast to *Bartonella henselae* [2].

Several mechanisms pertain to ingress of host-specific *Bartonella* spp within host cells and consequent complex, surface interactions between bacterial and host cell proteins emerge. Bacterial adhesion to host cell membrane permits bacterial uptake within a host cell vacuole [2,3]. Alternatively, bacteria accumulate upon host cell surface and induce self-phagocytosis with subsequent configu-

ration of phagosomes wherein *Bartonella* spp are subjected to the environment created by enzymes of oxidative stress. The bacteria are competent in resisting intracellular oxidative stress and produce heat shock protein [2,3].

Additionally, bacterial ingress into the erythrocytes necessitates secretion of protein designated as deformin. Deformin engenders invaginations within the erythrocyte membrane, thereby facilitating inundation of adherent bacteria with subsequent rearrangement of cellular cytoskeleton [2,3].

Bartonella releases factors which activates endothelial cells with production of angiopoietin-2 and vascular endothelial growth factor (VEGF) engendered from epidermal cells. Cell surface of *Bartonella henselae* depicts BadA protein which ensures cellular adhesion to endothelial cells and fibronectin with stimulation of angiogenesis. BadA protein can activate angiogenesis through configuration of inducible hypoxia factor -1 (IHF-1) [2,3].

Besides, expression of outer membrane protein (Vomp) can promote vascular genesis, especially in infections with *Bartonella quintana*.

The bacilli are protected from host's adaptive and innate immune response due to ingression into erythrocytes [2,3].

CD4+ T helper lymphocytes configure interferon gamma (IFN-ɣ) and tumour necrosis factor alpha (TNF-α) which are adequate for bacterial elimination. Thus, *Bartonella* spp are competent in attenuating host immune response with articulation of a chronic, asymptomatic carrier state, especially perceived in impoverished, homeless subjects infected with *Bartonella quintana* [2,3].

Disease characteristics

Bacillary angiomatosis was initially discerned in individuals infected with human immune deficiency virus (HIV) with reduced quantification of CD4+ T helper lymphocytes and an incidence of 1.2/1000 subjects prior to institution of antiretroviral therapy. The condition may arise on account of delayed discernment of HIV or non-compliance with antiretroviral therapy. It is exceptional following commencement of antiretroviral therapy although can occur within natural disease settings [4,5].

Bacillary angiomatosis is an infectious disorder with proliferation of miniature, cutaneous and visceral blood vessels appearing predominantly in immunocompromised hosts or subjects with human immune deficiency virus (HIV) infection. Bacillary angiomatosis can emerge within transplant recipients with concurrent chronic hepatitis B, subjects with leukaemia or individuals on systemic steroid therapy or chemotherapy with decimated CD4+ T helper lymphocytes [4].

Immunocompetent individuals demonstrating bacillary angiomatosis is concomitant to burn sites or cat scratch disease. The condition can manifest as pyogenic granuloma [4,5].

Bacillary angiomatosis is commonly discerned in California, New York and Florida, United states. The disorder is also documented in Europe, Africa, Southeast Asia, Middle East, Australia and South America. Although of obscure incidence, an estimated 40% Caucasians, 40% Hispanics and 20% Africans in the Unites States are incriminated with bacillary angiomatosis. Paediatric subjects are rarely implicated although no age of disease emergence is exempt and the condition appears within infancy to elderly candidates [4,5].

Infectivity with *Bartonella henselae* and *Bartonella quintana* is almost equivalent. The disorder is associated with an identical gender predilection [5].

Clinical elucidation

Common clinical manifestation is a vascular, reddish-purple papule or nodule. Alternatively, disseminated crops of multiple, reddish, smooth papules or nodules are discerned. Frequently discerned cutaneous lesions of bacillary angiomatosis manifest as multiple, reddish papules, subcutaneous nodules or plaques with accompanying cellulitis [5,6].

Centric ulceration and haemorrhage appear in enlarged nodules which vary from miniature, pinhead lesions to up to 10 centimetres in magnitude. Systemic symptoms such as fever, chills, weight loss and anorexia are discerned [5,6].

Generally, lesions are congregant upon upper extremities. Additionally, nodular lesions can occur within the oral mucosa, tongue, nose, penis and anus. Nodules arising within gastrointestinal mucosa may engender haemorrhage [5,6].

Bacillary angiomatosis appears at diverse mucosal or visceral sites as the lymph node, hepatic parenchyma, (bacillary peliosis hepatitis), spleen, soft tissue, bone, heart, central nervous system, oropharynx, larynx, endobronchus, duodenum and circulating blood [5,6].

Bacillary angiomatosis is associated with a characteristic vascular and neo-vascular proliferation confined to the cutaneous

surfaces, organs or internal viscera. Tumour-like masses are configured on account of infection with *Bartonella henselae* or *Bartonella quintana*. Typical neo-vascular, proliferative lesions emerging within the internal organs such as spleen or hepatic parenchyma are denominated as peliosis [5,6].

Clinical symptoms of bacillary angiomatosis engendered by diverse species of *Bartonella* are variable. Subcutaneous and osseous lesions are frequently discerned with *Bartonella quintana* whereas *Bartonella henselae* engenders peliosis of spleen and hepatic parenchyma [5,6]. Cutaneous lesions are observed with dual pathogenic species [6].

Neuropsychiatric symptoms, endocarditis, abdominal pain and weight loss are observed in visceral bacillary angiomatosis. Hepatic and splenic bacillary peliosis are frequently asymptomatic although may demonstrate systemic symptoms such as fever, lymphadenopathy, organomegaly, anaemia, elevated alkaline phosphatase or initially manifest as spontaneous haemorrhage and hemoperitoneum [5,6].

Bacillary angiomatosis can manifest as pyrexia of unknown origin (PUO) [5].

Exceptional neurological symptoms are denominated by intracerebral bacillary angiomatosis commonly preceding cutaneous lesions. Bacillary angiomatosis can emerge as invasive disease wherein *Bartonella henselae* or *Bartonella quintana* infect the heart, brain, spleen, larynx, lymph nodes, hepatic parenchyma and gastrointestinal tract. History of exposure to cats may be absent [5,6].

Concurrent cutaneous lesions may hinder the diagnosis of invasive bacillary angiomatosis. Immunocompetent individuals infected with *Bartonella henselae* depict visceral inflammatory nodules in the absence of concurrent angiomatosis, lesions which are intermediary to bacillary angiomatosis and cat scratch disease. Cutaneous, subcutaneous and bony bacillary angiomatosis in the absence of hepatic and splenic peliosis is observed with *Bartonella quintana* [5,6].

Majority of incriminated subjects are immunosuppressed. However, a nodule in an immunocompetent individual is exceptionally due to bacillary angiomatosis and requires competent discernment [5,6].

Histological elucidation

Bacillary angiomatosis is a vaso-proliferative, pseudo-neoplastic lesion which morphologically resembles pyogenic granuloma and segregation solely on histological features is unattainable. Nodules are composed of endothelium coated vascular or peliosis spaces [5,6].

The lobular lesion is composed of proliferating capillaries and ectatic vascular articulations layered with prominent endothelial cells. Vascular configurations are encompassed by an oedematous stroma. An inflammatory infiltrate of neutrophils, lymphocytes and histiocytes is frequently admixed with purplish- grey colonies and aggregates of bacteria especially abutting neutrophils, thereby configuring a "peripheral collarette" [6,7].

Characteristically, bacillary angiomatosis demonstrates proliferation of miniature, spherical vascular articulations layered with plump, histiocytoid or epithelioid endothelial cells. The circumscribing stroma is oedematous and admixed with an inflammatory cell infiltrate composed of lymphocytes, histiocytes and neutrophils. Deep-seated lesions are accompanied by an extensive neutrophilic infiltrate [6,7].

Hepatic parenchyma and spleen demonstrate peliosis with randomly distributed, haemorrhagic cavities [7].

Gram negative organisms or dense aggregates of bacilli appear as clumps of amphophilic, granular substance adjacent to neutrophils. Warthin- Starry or Grocott-Gomori's methanamine silver stain is optimal for discerning the bacilli. Special stains such as Warthin-Starry highlight aggregates of miniature bacilli upon examining cogent tissue sections. Lymphadenopathy is infrequently discerned in bacillary angiomatosis although the occurrence of multiple lymph nodes may be observed with incriminated upper extremity, akin to sporotrichosis [6,7].

Differential diagnosis

Clinically, cutaneous lesions of bacillary angimatosis are indistinguishable and require demarcation from Kaposi's sarcoma, pyogenic granuloma or benign epithelioid haemangioma. Nodules of bacillary angiomatosis necessitate distinction from Kaposi's sarcoma in individuals infected with HIV and pyogenic granuloma in immunocompetent subjects [2,3].

Lesions of *Bartonella* bacilliformis may resemble verruga peruana. Bacillary angiomatosis mandates segregation from various reactive and neoplastic vascular proliferations [2,3].

Kaposi's sarcoma occurs in immunocompromised individuals or subjects infected with HIV and can morphologically recapitu-

late bacillary angiomatosis. The vascular proliferation with slit-like vascular spaces is composed of spindle-shaped cells. Cleft-like vascular articulations are layered with spindle- shaped endothelial cells. Admixed plasma cells are discerned. Tumour cells are immune reactive to human herpes virus 8 (HHV8). Purplish- grey bacterial colonies or aggregates are absent [2,4].

Pyogenic granuloma is an ulcerated, lobulated lesion devoid of bacterial organisms with neutrophils confined to the surface. Lobular proliferation of capillary- sized vascular arrangement may be accompanied by minimal foci of non- ulcerated inflammation. Purplish -grey bacterial colonies are absent [2,4].

Verruga Peruana is a vascular, proliferative condition engendered by *Bartonella* bacilliformis. Specific Rocha-Lima or enlarged cytoplasmic inclusions are discerned within the endothelial cells. Bacillary angiomatosis can be differentiated from neo-vascular neoplasms with cogent histology [2,4].

Investigative assay

Cogent tissue sampling of a cutaneous nodule is an optimal manoeuver to diagnose bacillary angiomatosis. Hepatic and splenic peliosis require exclusion. Associated clinical symptoms mandate precise evaluation and physical examination.

Bacterial serological values are a sensitive assay when evaluated at initial clinical representation and depict an estimated four-fold elevation during the convalescent phase [7,8].

Immunofluorescence assay (IFA) is adopted for detecting immunoglobulin G (IgG). Pertinent enzyme immunoassay (EIA) can be additionally employed [7,8].

Serological assays depict an estimated sensitivity between 85% - 94%. Cross reactivity between *Bartonella henselae*, *Bartonella quintana*, *Coxiella* and *Chlamydia* is discerned [7,8].

Polymerase chain reaction (PCR) and immunohistochemistry can be beneficially adopted to identify the organisms. Polymerase chain reaction (PCR) can be applied to whole blood, serum or plasma and is an efficacious technique which differentiates between diverse species of *Bartonella* [7,8].

Culture methods are essentially insensitive. Culture of samples from endocarditis display a sensitivity of 28% and culture upon agar plates delineate a sensitivity of 5% [7,8].

Therapeutic options

Majority of cutaneous bacillary angiomatosis can be managed with optimal treatment strategies. However, incrimination of internal organs can be fatal and engender disease related mortality.

Optimal therapeutic agent is the macrolide antibiotic erythromycin or doxycycline. Alternatively, azithromycin or clarithromycin may be employed. Mild lesions of cutaneous bacillary angiomatosis respond within three weeks to four weeks of therapy and may be treated for twelve weeks. Magnitude and quantity of nodules can be estimated in order to assess therapeutic response and duration of therapy is contingent to the response [7,8].

Cutaneous or peliosis lesions respond to and are alleviated by cogent antibiotic therapy. Duration of therapy is generally extended while treating invasive disease [7,8].

Immunosuppressed individuals or subjects with HIV infection require additional, precise therapy to normalize the CD4+ helper T lymphocyte count or emerge in excess of 200 cells/microliter beyond six months. Although occasionally associated with immune reconstitution inflammatory syndrome, individuals with HIV necessitate concurrent antiretroviral therapy [7,8].

Following pertinent antibiotic therapy, adjunctive treatment strategies include cryotherapy, electrodessication with curettage or surgical extermination of solitary, cutaneous lesions can be adopted with antibiotic addenda in order to circumvent occult, procedure-related bacteraemia [7,8].

Declawing or extermination of the cat is not recommended as period of bacterial accumulation is minimal and proportionate transmission is unaffected. Intense manoeuvers of flea-control are recommended, efficacious and are to be applied regularly [7,8].

With appropriate, antecedent antimicrobial therapy, lesions of bacillary angiomatosis resolve rapidly. Immunocompromised subjects depict disease relapse following cessation of therapy. Nevertheless, inadequate treatment of infection is associated with disease related mortality. As bacillary angiomatosis incriminates the brain, heart, spleen, larynx, lymph nodes, hepatic parenchyma or gastrointestinal tract, it may induce gastrointestinal haemorrhage, encephalopathy, endocarditis, laryngeal obstruction or site-specific anatomical disfigurement secondary to extensive lesions [7,8].

Figure 1: Bacillary angiomatosis enunciating vascular spaces coated with plump endothelium, neutrophilic exudate, aggregates of bacteria and an encompassing oedematous stroma [9].

Figure 2: Bacillary angiomatosis exhibiting clusters of bacteria abutting neutrophils, vascular articulations with epithelioid endothelial cells and an enveloping oedematous stroma [10].

Figure 3: Bacillary angiomatosis exemplifying a lobular, vascular lesion with endothelium layered vascular arrangements, aggregates of bacteria and a neutrophilic exudate confined to the stroma [11].

Figure 4: Bacillary angiomatosis demonstrating blood vessels layered with plump endothelial cells, surrounding oedematous stroma, clumps of bacteria and a neutrophilic exudate [12].

Figure 5: Bacillary angiomatosis delineating vascular articulations coated with plump endothelium, neutrophilic exudate, clusters of bacteria and oedematous stroma [13].

Figure 6: Bacillary angiomatosis depicting vascular configurations with plump endothelium, oedematous stroma, neutrophilic exudate and bacillary clusters [14].

Figure 7: BA Warthin-Starry stain highlighting bacillary aggregates adjacent to neutrophils and blood vessels [13].

Figure 8: Bacillary angiomatosis composed of vascular arrangements coated with plump endothelial cells, neutrophilic exudate in an oedematous stroma and bacterial aggregates [15].

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9. Image 1 Courtesy: Pathology outlines.
10. Image 2 Courtesy: Dermatology advisor.
11. Image 3 Courtesy: Dermnet NZ.
12. Image 4 Courtesy: Twitter.
13. Image 5 and 7 Courtesy: Plastic Surgery Key.
14. Image 6 Courtesy: Indian J Dermatol.
15. Image 8 Courtesy: Basic medical key.