Tuberculosis and Bartonella co-infection in people living with human immunodeficiency virus (HIV)

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SUMMARY

Malaysia is classified by the World Health Organization (WHO) as a country with an upper moderate burden of tuberculosis (TB). While TB cases are commonly reported, there is currently limited data on the prevalence of *Bartonella* infections in Malaysia. Here, we present the case of a Malaysian woman living with human immunodeficiency virus (HIV), who initially presented with right cervical lymphadenopathy and was subsequently diagnosed with, and successfully treated for, a TB and *Bartonella* co-infection. This case highlights the diagnostic challenges involved and underscores the importance of maintaining a high index of suspicion for TB and *Bartonella* co-infection, particularly in endemic areas.

INTRODUCTION

It was estimated that 85,283 people were living with HIV in Malaysia at the end of 2023.[1] People living with HIV are 20 times more likely to develop active TB disease than people without HIV.[2] Malaysia is classified by the WHO as a country with an upper moderate burden of tuberculosis, with a notification rate of TB between 50 to 99 per 100,000 populations. The prevalence of TB-HIV co-infection in Malaysia was 12.6% in 2010, and the latest data in 2019 was 5.9%.[3] On the other hand, the global burden of *Bartonella*-associated diseases, although significant, may be underestimated as they often result in undifferentiated febrile illnesses.[4] In people with HIV, bartonellosis is often a chronic illness, lasting for months to more than a year.[5] While TB cases are commonly reported, there is a paucity of data regarding the prevalence of *Bartonella* infections to date. Lina et al. (2010) reported the first suspected case of cat scratch disease in a 29-year-old Malaysian febrile patient with a painful left neck mass and lymphadenopathy. Here, we report a case of cervical lymphadenopathy with tuberculosis and *Bartonella* co-infection in people living with HIV in Malaysia.

CASE PRESENTATION

We encountered a 34-year-old woman who is HIV-positive and on antiretroviral therapy (ART). She was first diagnosed with HIV in year 2010 during premarital screening and was then started on an ART regimen of oral lamivudine 300mg, zidovudine 600mg, and efavirenz 600mg daily. Her disease remained stable until she defaulted on her medications and follow-up in year 2020 due to marital issues. After 2 years of defaulting treatment, she presented to us in year 2022 with progressively enlarging right neck swelling. There was otherwise no history of fever, neurological or ocular symptom. She also denied any constitutional and opportunistic infection symptoms. Upon further questioning, she revealed that she had eight cats at home. She frequently played with them and occasionally sustained scratches. However, she did not seek medical attention for these wounds. On examination, her Glasgow Coma Scale (GCS) was full, and she appeared neither septic nor cachexic. Two right supraclavicular lymph nodes were palpable, measuring 3x4cm and 2x2cm, respectively. No other lymph nodes were palpable. Her lungs were clear on auscultation. There was evidence of a cat scratch wound on her right hand.

Her full blood count, renal profile, and liver function tests were unremarkable, with a CD4 count of 75 and viral load of 521 copies. *Treponema pallidum* serology was non-reactive. Her neck ultrasonography demonstrated multiple enlarged right anterior cervical, right posterior cervical and right supraclavicular lymph nodes with loss of fatty hilum. The largest lymph node was at her right submandibular, measuring approximately 1.8 x 2.7 x 2.9cm. Fine-needle aspirate from the lymph node was sent for fungal culture and sensitivity and was negative. Blood fungal cultures were also negative. She subsequently underwent excisional lymph node biopsy.

Histopathological examination (HPE) of the lymph node sample revealed granulomas with extensive caseous necrosis, composed of epithelioid histiocytes, with surrounding small lymphocytes and few large Langerhans-type multinucleated giant cells. Ziehl-Neelsen staining for acid fast bacilli was positive, suggestive of tuberculous lymphadenitis. Culture of the lymph node confirmed the presence of Mycobacterium tuberculosis complex. The patient was initiated on anti-tuberculous therapy, which she completed over a 9-month course. The finding of granulomas on HPE prompted consideration of a range of differential diagnoses, as listed in Table I. In view of the patient's history of exposure to cat scratches, *Bartonella* infection remained high on our list of differentials. Unfortunately, further specific staining, such as Bartonella staining, could not be performed at our centre and therefore was not included in this case report. Consequently, we proceeded with alternative investigations to confirm Bartonella co-infection in this case.

Bartonella henselae DNA was detected in the same lymph node sample by Polymerase Chain Reaction (PCR). Serological testing for *Bartonella* was also performed, showing

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Table I: Differential diagnosis for infectious granulomatous inflammation[9]

Necrotizing granulomatous inflammation	Non-necrotizing granulomatous inflammation
Tularemia	*Mycobacterium tuberculosis*
Cat scratch disease	Nontuberculous mycobacterium (including Hansen disease)
Yersinia lymphadenitis	*Salmonella typhi*
Lymphogranuloma venereum	*Rickettsia* spp.
Dematiaceous fungal infection	*Coxiella*
Brucellosis	*Candida albicans*
Actinomyces	*Candida immitis*
Syphilis	Viral (cytomegalovirus, herpes, hepatitides)
Fungal infection *(Cryptococcus, Histoplasma, Coccidiomycosis, Pneumocystis, Aspergillus, Blastomyces*, Mucorales)	Parasitic (toxoplasmosis, schistosomiasis)
Mycobacterium tuberculosis	
Nontuberculous mycobacteria	
Nocardia	

Table II: Reported cases of Bartonella and TB co-infection

Author	Age, sex	CD4 count	Clinical features	Clinical features	Treatment	Outcome
Bernit E et al. (2003)	32, female	416	Supraclavicular inflammatory lymphadenitis	Cultures onto Columbia agar with sheep blood and onto human endothelial cells in shell vial: *B. quintana* and *M. tuberculosis* hominis	Anti-TB, doxycycline	Remains well, no relapse
Eleftheriotis et al. (2014)	23, male	67	Fever, malaise, worsening neck pain, painful swallowing, bilateral cervical lymphadenopathy, axillary and inguinal lymphadenopathy	FNAC of lymph node: positive Ziehl - Neelsen stain for acid fast bacilli Aspirate for culture and PCR: pan-susceptible *Mycobacterium tuberculosis* strain Positive *Bartonella henselae* and *Bartonella quintana* IgM antibodies on a titer of 1:24 and IgG antibodies on a titer of 1:256	Anti-TB, methylprednisolone, doxycycline	Lymph node tenderness resolved after one month of tuberculosis treatment and lymph node size decreased. One month after ART initiation, he presented with fever and bilateral painful cervical lymphadenopathy. Symptoms resolved after treating with doxycycline and methylprednisolone
Our patient (Malaysia)	34, female	75	Cervical lymphadenopathy	HPE of lymph node: tuberculous lymphadenitis, positive Ziehl-Neelsen staining for acid fast bacilli Lymph node TB C+S: Mycobacterium tuberculosis complex Lymph node for Bartonella PCR: Bartonella henselae DNA detected Bartonella henselae Ig M positive, Ig G > 1:512 Bartonella quintana Ig M positive, Ig G > 1:512	Anti-TB, doxycycline	Lymphadenopathy resolved after completed treatment

positive IgM results for both *Bartonella henselae* and *Bartonella quintana*, with an IgG titre >1:512. The patient denied any skin rashes or lesions, and there were no signs or symptoms suggestive of central nervous system or endocardial involvement. Abdominal ultrasonography revealed no evidence of intra-abdominal involvement or disease dissemination.

She was commenced on oral doxycycline, in addition to the existing rifampicin-based anti-tuberculous therapy. A repeat *Bartonella* serology done six months later revealed a significant response to treatment, showing positive *Bartonella henselae* Ig M and negative Bartonella henselae Ig G, with both *Bartonella quintana* IgM and IgG remaining negative. By the end of treatment, there was no palpable lymph node, and she remained well under our care with no new complaints.

DISCUSSION

We describe the case of a Malaysian woman living with HIV who initially presented with right cervical lymphadenopathy and was treated for both tuberculosis and *Bartonella* infection. Her lymphadenopathy resolved after completing treatment for both infections.

Several case reports and studies have discussed co-infections of Mycobacterium tuberculosis (MTB) and *Bartonella* species, particularly *Bartonella henselae* and B*artonella quintana*, in individuals with HIV. These co-infections pose a diagnostic challenge due to overlapping clinical symptoms such as fever and lymphadenopathy, which are common in both diseases.

The clinical presentation of our patient is similar to that reported by Bernit E et al. (2003).[6] However, in that case, the serological tests were negative. Diagnosis was confirmed by isolation of *B. quintana* and *M. tuberculosis hominis* from cultures onto Columbia agar with sheep blood and onto human endothelial cells in a shell vial. This case emphasized the difficulty of diagnosing *Bartonella* in HIV-positive patients, as its symptoms often mimic other diseases, especially TB.

Eleftheriotis et al. (2014) discussed an HIV-infected patient who developed both TB lymphadenopathy and *Bartonella* lymphadenopathy, along with immune reconstitution inflammatory syndrome (IRIS).[7] The patient was treated with anti-TB therapy and doxycycline, leading to subsequent resolution of symptoms. This case illustrates the complexity of diagnosing and treating co-infections in HIV-infected individuals, especially in the presence of IRIS.

Bartonella infection is a major cause of unexplained fever in patients with advanced HIV and should be considered in the differential diagnosis of patients with CD4 counts <100 cells/mm^3 and fever. *Bartonella* species can cause infections that include cat scratch disease (CSD), retinitis, trench fever, relapsing bacteremia, culture-negative endocarditis, bacillary angiomatosis (BA), and bacillary peliosis hepatis. The latter two manifestations occur almost exclusively in individuals who are immunocompromised. BA most often occurs late in HIV infection in patients with median CD4 T lymphocyte (CD4) cell counts <50 cells/mm^3. The development of BA lesions caused by *B. henselae* is statistically linked to cat exposure in people with HIV.[5] In contrast, BA caused by *B. quintana* is associated with body louse infestation and homelessness.[5]

Lymphadenopathy was one of the initial presentations of *Bartonella* and TB co-infection in most of case reports. In a review of 1200 patients with CSD by Carithers, all patients in the series had lymphadenopathy; 85% had single-node involvement and the remainder had regional lymph node involvement, usually with only two, occasionally three, and rarely four or more nodes enlarged. None of the patients in this series had generalized lymphadenopathy.[8]

Co-infection with TB and *Bartonella* can lead to a range of similar symptoms, such as fever, weight loss, fatigue, and lymphadenopathy, which can obscure the diagnosis. The overlapping clinical signs necessitate the use of multiple diagnostic approaches (cultures, PCR, serological tests) to accurately identify both pathogens.

Serological testing is the most accessible, and when positive, is helpful both for diagnosis and subsequent monitoring of treatment response. However, as many as 25% of *Bartonella* culture-positive patients never develop antibodies in the setting of advanced HIV infection.[5] Monitoring of antibody levels can be useful for tracking treatment response, reflecting resolution or recrudescence.[5] Due to interlaboratory variability, longitudinal testing should be conducted at the same laboratory to enable direct comparison of titres over time.[5]

This case report highlights an important yet underrecognized issue. *Bartonella* infection should be considered in the differential diagnosis of lymphadenopathy in people living with HIV, alongside TB. *Bartonella* infection should be ruled out in patients with risk factors, even when a TB diagnosis is confirmed, as co-infection can occur, as shown in our case. Early recognition of TB and Bartonella co-infection is crucial for the initiation of prompt and effective treatment. A high index of suspicion should be maintained, with careful screening for risk factors for TB and *Bartonella* infection in patients presenting with lymphadenopathy, and investigations should be tailored accordingly. Routine *Bartonella* PCR testing may not be necessary in all cases and can be considered based on clinical context and individual risk assessment. This report advocates for increased awareness and further research into the immune interactions between these pathogens and the development of tailored treatment regimens for TB and *Bartonella* co-infection in HIV patients.

CONCLUSION

Co-infection with TB and *Bartonella* in HIV-infected patients remains an important clinical consideration. Awareness of the possibility of both infections, especially in endemic areas, is crucial for timely diagnosis and effective treatment. While TB is a well-known complication in HIV, *Bartonella* should also be considered, particularly in patients with a history of exposure to cats or fleas. Further studies and case reports are needed to better understand the epidemiology and management of TB and *Bartonella* co-infection in HIV-positive individuals.

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DECLARATIONS

The authors declare no conflicts of interest related to this publication.

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