EFFECTIVENESS OF EMPIRIC ANTITUBERCULAR THERAPY TO TREAT CERVICAL GRANULOMATOUS LYMPHADENOPATHY AMONG PATIENTS NOT CONFIRMED TO HAVE *MYCOBACTERIUM TUBERCULOSIS* INFECTION

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Abstract. In high prevalence areas, tuberculosis is a common cause of cervical lymphadenopathy. We aimed to determine the efficacy of antitubercular therapy (ATT) to treat patients with cervical granulomatous lymphadenitis, in whom there was no evidence of *Mycobacterium tuberculosis* infection, in order to determine if this method is a viable strategy to manage these patients at the study institution. We retrospectively reviewed the medical records of patients who presented to Hatyai Hospital, Thailand, had biopsy proven cervical granulomatous lymphadenitis without evidence of *M. tuberculosis* infection and were treated with empiric ATT during January 2015-December 2019. A total of 69 subjects were included in the study, 71.0% female. The mean (±standard deviation) age of study subjects was 43.1 (±13.7) years. Pathology of the lymph nodes of these 69 subjects showed 38 (55.1%) had caseous necrosis, 23 (33.3%) had nonspecific necrosis and 8 (11.6%) had no necrosis. Sixty-three subjects (91.3%) (100% with caseous necrosis and 80.6% with non-caseous necrosis, p=0.006) had complete resolution of their cervical granulomatous lymphadenopathy with ATT. In summary, the great majority of subjects with cervical granulomatous lymphadenopathy and all those with caseous lymphadenopathy, were treated successfully with ATT. We conclude, patients with cervical granulomatous lymphadenitis at the study institution can be treated with ATT, even if there is no evidence of *M. tuberculosis*. Further studies at other institutions need to be conducted to determine if this finding can be applied to other institutions in Thailand.

Keywords: antitubercular antibiotics, cervical lymphadenopathy, granulomatous inflammation, *Mycobacterium tuberculosis*, tuberculous lymphadenitis

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INTRODUCTION

Tuberculosis (TB) is a major health problem in developing countries (Tatar *et al*, 2011). The lungs are the most common part of the body infected by *Mycobacteria tuberculosis* but extrapulmonary tuberculosis (EPTB) comprises approximately 15-20% of all TB cases (Sharma and Mohan, 2004; Hegde *et al*, 2014). Tuberculous lymphadenopathy is the most common form of EPTB, of which 60-90% of cases occur in the cervical lymph nodes (Artenstein *et al*, 1995; Hegde *et al*, 2014). In high TB prevalence settings, TB is the most common cause of cervical lymphadenopathy (Khajanchi *et al*, 2016; Patel, 2019).

The diagnosis of cervical tuberculous lymphadenopathy (CTL) is a challenge because of the paucibacillary nature of the specimens and smear microscopy has a low sensitivity for detecting *M. tuberculosis* (Prakash and Reiman, 1985; Chakravorty *et al*, 2005). Smear microscopy in TB lymphadenitis is positive for acid-fast bacilli (AFB) in <10% of patients (Chakravorty *et al*, 2005). In developing countries with a high prevalence of tuberculosis, fine-needle aspiration (FNA) has been suggested as the initial diagnostic modality because it has adequate sensitivity and avoids the need for hospitalization and general anesthesia (Artenstein *et al*, 1995). However, the overall diagnostic yield of lymph node FNA (including histology, AFB smear and culture) has been reported to be only 46% (Memish *et al*, 2000).

Excisional biopsy of cervical lymph nodes has been the main method used to diagnose CTL (Memish *et al*, 2000; Deveci *et al*, 2016). The definitive diagnosis of CTL involves demonstration of *M. tuberculosis* in the specimen using histopathological or bacteriological methods (AFB smear, TB culture) (Sharma and Mohan, 2004). The pathological findings may only show granulomatous inflammation (Sharma and Mohan, 2004). Granulomatous inflammation without identifiable evidence of *M. tuberculosis* infection is a dilemma for clinicians, especially in TB endemic areas. This histological pattern can occur following chronic inflammation and is not pathognomonic for *M. tuberculosis* infection (Asano, 2012). There are no consensus guidelines regarding the management of this condition. In Thailand, physicians usually use empiric antitubercular treatment (ATT) in patients with

cervical granulomatous lymphadenitis without evidence of *M. tuberculosis* infection. We were not able to find any studies of the efficacy of ATT for treating cervical granulomatous lymphadenitis.

In this study, we aimed to determine the efficacy of antitubercular therapy (ATT) to treat patients with cervical granulomatous lymphadenitis, in whom there was no evidence of *M. tuberculosis* infection, in order to determine if this method is a viable strategy to manage these patients at the study institution.

MATERIALS AND METHODS

Study design and patient population

The inclusion criteria for study subjects were: patients aged >18 years diagnosed with excisional biopsy proven cervical granulomatous lymphadenopathy who were treated with empiric anti-tuberculous treatment at the study institution during the study period. The exclusion criteria for study subjects were: having proven evidence of *M. tuberculosis* infection confirmed by histopathology, acid fast bacillus stain or culture, having a previous history of cervical tuberculosis, having inadequate or missing data or who were lost to follow up.

The study institution was Hatyai Hospital, an 800-bed university-affiliated tertiary care center in southern Thailand. The records were retrospectively reviewed for patients meeting inclusion criteria presenting to the study institution during January 2015-December 2019.

Study subjects with cervical granulomatous lymphadenitis were subdivided into three groups based on the histopathology results: granulomatous inflammation with caseous necrosis, granulomatous inflammation with nonspecific necrosis and granulomatous inflammation without necrosis. At our center, patients diagnosed with cervical granulomatous lymphadenitis without evidence of *M. tuberculosis* infection, are treated empirically for CTL using the regimen of the World Health Organization (WHO, 2003). The regimen consists of isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and rifampicin for an additional 4 months.

Treatment responses were assessed based on the change in the size of the lymph node. Patients who had a decrease in lymph node size were classified as responders and those without a decrease were classified as non-responders. Patients who did not respond to treatment after 2 months underwent a repeat excisional biopsy and mycobacterial culture to confirm the diagnosis and test for evidence of multidrug-resistant tuberculosis (MDR-TB); an infectious disease specialist was consulted in these cases.

The hospital information system was used to obtain patient data: age, sex, clinical presentation, findings on physical examination, laboratory results, chest radiography, histopathology reports, treatment and outcome.

This study was approved by the Hatyai Hospital Ethics Committee on Human Subjects (protocol number 59/2563) and was performed in accordance with the Declaration of Helsinki.

Statistical analysis

Categorical variables were summarized using frequency statistics and the Fisher's Exact test was used to determine significant differences between those with and without caseous necrosis on histopathology. Descriptive statistics were used for continuous variables. Analyses were performed using Stata software, version 15.1 (StataCorp LLC, College Station, TX). A *p*-value <0.05 were considered statistically significant.

RESULTS

A total of 69 subject were included in the study, 71.0% female. The mean (±standard deviation) patient age was 43.1 (±13.7) years (Table 1). Twenty-seven subjects (39.1%) had the lymphadenopathy for <4 weeks, 13 (18.8%) for 4-8 weeks and 29 (40.6%) for >8 weeks. Thirteen subjects (18.8%) had constitutional symptoms, 4 (5.8%) had underlying human immunodeficiency virus infection and 10 (14.5%) had an abnormal chest x-ray. Fifty-seven subjects (82.6%) had solid lymph nodes and 12 (17.4%) had abscessed lymph nodes. None of the patients had a fistula or sinus formation. Fifty-four subjects (78.3%) had unilateral cervical lymphadenopathy and 36 (52.2%) had multiple enlarged lymph nodes. Forty-eight subjects (69.6%) had a lymph node diameter of <3 cm, 13 (18.8%) and a diameter of 3-6 cm and 8 (11.6%) had a diameter >6 cm.

On histopathology, 38 subjects (55.1%) had granulomatous

Table 1

Demographic data and selected characteristics of study subjects (N = 69)

Characteristics	Value
Mean (±standard deviation) age in years	43.1 (±13.7)
Female sex, *n* (%)	49 (71.0)
Human Immunodeficiency Virus infection, *n* (%)	4 (5.8)
Abnormal chest X-ray, *n* (%)	10 (14.5)

Table 1 (cont)

Characteristics	Value
Duration of cervical lymph node enlargement, *n* (%)	
<4 weeks	27 (39.1)
4-8 weeks	13 (18.8)
>8 weeks	29 (42.0)
Lymph node tenderness, *n* (%)	27 (39.1)
Constitutional symptoms, *n* (%)	12 (17.3)
Cough	5 (7.2)
Fever	7 (10.1)
Weight loss	6 (8.7)
Site of involvement, *n* (%)	
Unilateral	54 (78.3)
Bilateral	15 (21.7)
Number of enlarged lymph nodes, *n* (%)	
1	33 (47.8)
>1	36 (52.2)
The largest size of involved lymph node in centimeters, *n* (%)	
<3	48 (69.6)
3-6	13 (18.8)
>6	8 (11.6)
Lymphadenopathy clinical presentation, *n* (%)	
Solid lymph node	57 (82.6)
Abscessed lymph node	12 (17.4)
Fistula/sinus	0 (0.0)
Histopathology results, *n* (%)	
Granulomatous inflammation with caseous necrosis	38 (55.1)
Granulomatous inflammation with nonspecific necrosis	23 (33.3)
Granulomatous inflammation without necrosis	8 (11.6)

inflammation with caseous necrosis, 23 (33.3%) had granulomatous inflammation with nonspecific necrosis and 8 (11.6%) had granulomatous inflammation without necrosis.

Treatment outcomes among study subjects according to histological results were summarized in Table 2. Sixty-three subjects (91.3%) responded to ATT: 54 (78.3%) responded to the standard ATT regimen and 9 (13.0%) responded to an extended ATT regimen. No MDR-TB infections were detected in our study.

All 38 subjects with granulomatous inflammation with caseous necrosis responded to ATT.

Nineteen of the 23 subjects with granulomatous inflammation with nonspecific necrosis, (82.6%) responded to ATT; of the 4 who failed to respond, 1 was diagnosed with having diffuse large B-cell lymphoma confirmed by repeat lymph node biopsy and 3 were finally diagnosed with having non-tuberculous mycobacteria (NTM) lymphadenitis (based on response to NTM treatment).

Six of the 8 subjects with granulomatous inflammation without necrosis (75.0%) responded to ATT. Of the 2 subjects who did not respond to treatment, 1 was subsequently diagnosed as having lymph node metastases from thyroid cancer and in the other subject who did not respond no diagnosis was made.

When classifying subjects as either having (n = 38) or not having (n = 31) caseous necrosis, 100% of those with caseous necrosis responded to ATT whereas 80.6% of those without caseous necrosis responded to treatment (p=0.006).

Table 2

Treatment outcomes among study subjects by histopathological results (N = 69)

Response to treatment	Granulomatous inflammation with			
	Total patients (N = 69)	Caseous necrosis (N = 38)	Nonspecific necrosis (N = 23)	No necrosis (N = 8)
Responder, *n* (%)	63 (91.3)	38 (100)	19 (82.6)	6 (75.0)
Non-responder, *n* (%)	6 (8.7)	0 (0)	4 (17.4)	2 (25.0)

DISCUSSION

In our study, all the patients with caseous necrosis on pathology responded to ATT suggesting they were all tuberculous cervical lymphadenitis. A previous study (Asano, 2012) had reported tuberculous lymphadenitis is characterized on histopathology by having caseous necrosis. This also suggests empiric treatment of CTL in patients with granulomatous inflammation with caseous necrosis at the study institution with ATT is reasonable.

In this study, 9% of subjects did not respond to ATT suggesting non-caseating granulomatous lymphadenopathy is not pathognomonic for CTL. The differential diagnosis of etiological organisms includes non-tuberculous mycobacteria (such as Mycobacterium scrofulaceum, Mycobacterium avium, and Mycobacterium haemophilum), lymphoma, fungal disease, cat-scratch disease and neoplasms (Asano, 2012; Patel, 2019). Cervical granulomatous lymphadenopathy without caseous changes should be monitored carefully when treating empirically with ATT due to the risk of having another etiological organism.

Our study had some limitations. First, it was conducted at a single center consisting of only Thai patients. Second, it was a retrospective study. All variables were evaluated by reviewing medical charts, which inevitably carries a risk of misclassification bias and missing data. Third, the population size in the present study was relatively small. A large multicenter prospective study is needed to confirm the effectiveness of ATT for empiric treatment of cervical granulomatous lymphadenitis without evidence of evidence of *M. tuberculosis* infection.

In summary, the great majority of subjects with cervical granulomatous lymphadenopathy and all those with caseous lymphadenopathy, were treated successfully with ATT. We conclude, patients with cervical granulomatous lymphadenitis at the study institution can be treated with ATT, even if there is no evidence of *M. tuberculosis*. Further studies at other institutions need to be conducted to determine if this finding can be applied to other institutions in Thailand.

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CONFLICT OF INTEREST DISCLOSURE

All authors declare no conflict of interest.

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