

Response to Adjuvant Therapy of Granulomatous Lymphadenitis: Evidence from High Burden Country

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ABSTRACT

Introduction: A granulomatous lymphadenitis is a form of inflammation of the lymph nodes that are often found. Until now, effective treatment of granulomatous lymphadenitis is still inconsistent, namely between surgical intervention, antibiotics, or adjuvant therapy.

Objective: This study aims to determine the response to adjuvant therapy in patients with granulomatous lymphadenitis at RSUD Prof. Dr. Margono Soekarjo in 2019 – 2020.

Methods: The research was a descriptive observational study with a retrospective approach that used secondary data from the medical records of the polyclinic and inpatient ward of RSUD Prof. Dr. Margono Soekarjo Purwokerto.

Results: A total of 5 patients with tuberculous granulomatous lymphadenitis (66,7%) experienced a complete response to therapy after surgical excision followed by administration of anti-tuberculosis adjuvants an average of $6,5 \pm 3,6$ times and a mean duration of administration of $22,5 \pm 14,7$ weeks. A total of 14 patients with non-tuberculous granulomatous lymphadenitis (73,7%) experienced a complete response to therapy after surgical excision, incision drainage followed by adjuvant antibiotic therapy alone or in combination with 1-3 times and the median duration of administration was 3,5 weeks.

Conclusion: Surgical excision followed by adjuvant therapy in tuberculous and non-tuberculous granulomatous lymphadenitis has good cure rates.

KEYWORDS: Adjuvant Therapy; Granulomatous Lymphadenitis, Tuberculosis

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INTRODUCTION

Lymphadenitis is inflammation of the immune cells of the lymph nodes. Histologically, the most common inflammatory response to lymphadenitis is non-specific reactive hyperplasia and granulomatous inflammation[1][2]. According to the research of Ismail and Muhammad (2013), 74.5% of patients who had enlarged cervical lymph nodes were diagnosed as tuberculous lymphadenitis (TB), which includes non-suppurative infectious granulomatous lymphadenitis[3]. According to the World Health Organization (WHO) in 2020, Indonesia ranks the 3rd highest TB incidence in the world with around 845,000 sufferers and the most common form of extrapulmonary TB is lymphadenitis[4]. Therefore, Indonesia is categorized as high

TB burden Asian countries[5][6]. The prognosis of TB lymphadenitis is poor if it is allowed to become an abscess until fistula forms into the skin[7][8].

Management of lymphadenitis is still inconsistent between the combination or single use of macrolides, antituberculosis therapies (ATTs), and surgical treatment. Surgical intervention often requires additional therapy due to its recurrence and increased risk of postoperative complications [2]. Past study indicated that non-tuberculous granulomatous cervical lymphadenitis showed a good response to the administration of macrolide antibiotics single or in combination so that they can be used for preoperative therapy or postoperative adjuvant therapy [9]. Zeharia et al.'s research. (2008) showed that single therapy or combination

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of antibiotics did not have an effective response in curing non-tuberculous granulomatous lymphadenitis [10].

Based on the above background, the authors are interested in examining the effect of excision and adjuvant therapy on granulomatous lymphadenitis at RSUD Prof. Dr. Margono Soekarno.

MATERIALS AND METHOD

This study is a descriptive observational study with a retrospective approach using secondary data from medical records at RSUD Prof. Dr. Margono Soekarjo Purwokerto. The population is granulomatous lymphadenitis patients who have undergone a biopsy and received adjuvant therapy in 2019-2020. Inclusion criteria were lymphadenitis patients who were histopathologically proven as granulomatous inflammation and received adjuvant therapy and had been evaluated after adjuvant therapy. Patients with immunocompromised and disseminated infection were excluded.

Data collection was conducted for 3 weeks, October 11, 2021 – October 30, 2021. Patients were divided into 2 groups, namely the tuberculosis-specific granulomatous inflammation group and the non-specific/non-tubercular granulomatous inflammation group. Data analysis using SPSS 25.

RESULT

Invasive measures in the subjects of this study were excision and fine needle aspiration (FNA) in the TB group, drainage incisions in the NTB group with a diagnosis of abscess, FNA and excision in some of the NTB group [11]. Antituberculosis therapies (ATTs) were given to all patients in the TB group, preceded by excision of the biopsy or FNA of the lesioned lymph nodes.

Evaluation of therapeutic response is based on subjective assessment of the doctor in charge by looking at

the lumps that have disappeared and based on adjuvant therapy that has been discontinued and replaced with roborantia therapy. The results of the response to therapy are divided into complete (the lump is gone) and incomplete (the lump is still there or worsens due to lymphadenitis). Complete response in 20 patients (74.1%), in the NTB group that had excision, as many as 9 patients (90%), in the NTB group that had FNA performed there were 3 patients (50%), in the NTB group the incision had been made 100% drainage. In the TB group, excision showed a complete response in 5 patients (62.5%), and a complete response in 100% in the TB group undergoing FNA and adjuvant ATTs.

DISCUSSION

In this study, the age of the subjects in both groups was classified as early adulthood, namely 29.5 years for the NTB group and 32.4 years for the TB group [12]. The results of this study are in line with the research of Fontanilla et al. (2011) that the highest tuberculous lymphadenitis occurs in adults, namely 30-40 years [13]. Tuberculous lymphadenitis can be associated with reactivation of the disease due to primary lesions acquired in childhood. Female sex dominated as the subject of this study (74.1%) in both the TB and NTB groups. The results of this study are in line with the research of Fontanilla et al. (2011) women have a higher risk factor for tuberculous lymphadenitis and non-tuberculous lymphadenitis due to hormonal influences, nutritional status, and the lower effect of Bacillus Calmette-Guerin (BCG) immunization in the early phase [13][14]. Predilection is most frequent. The granulomatous lymphadenitis in the study subjects was unilateral in the neck. These results are in line with the research of Koo et al. (2006) that granulomatous lymphadenitis is most commonly found in the cervical region and based on the research of Neven et al. (2020) Cervical lymphadenitis is most often unilateral, especially in the submandibular lymph nodes. [2],[10]

Table 1. Regimen and Response of Research Subjects Based on Invasive Treatment

Therapy and Evaluation	NTB		TB		Total N=27	
	Excision	Incision	FNA	Excision		FNA
Adjuvant						
ATTs	-	-	-	8 (100%)	1 (100%)	9 (33,3%)
Macrolides	2 (20%)	-	-	-	-	2 (7,4%)
Cephalosporins	2 (20%)	-	-	-	-	2 (7,4%)
Macrolides + Cephalosporins	-	1 (50%)	-	-	-	1 (3,7%)
Quinolones	3 (30%)	-	-	-	-	3 (11,1%)
Penicillin	1 (10%)	-	-	-	-	1 (3,7%)
Quinolones + steroids	2 (20%)	-	-	-	-	2 (7,4%)
Cephalosporins + steroids	-	1 (50%)	6 (100%)	-	-	7 (25,9%)
Amount of adjuvants						
Range	1 – 3	1 – 3	1 – 3	2 – 11	9	1 – 11
Median	1	2	3	7,5	-	3
≤ 3 times	10 (100%)	2 (100%)	6 (100%)	2 (25%)	-	20 (74,1%)
> 3 - ≤6 times	-	-	-	-	-	-
> 6 times	-	-	-	6 (75%)	1 (100%)	7 (25,9%)

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Response						
Complete	9 (90%)	2 (100%)	3 (50%)	5 (62,5%)	1 (100%)	20 (74,1%)
Incomplete	1 (10%)	-	3 (50%)	3 (37,5%)	-	7 (25,9%)
Duration (weeks)						
Range	1 – 24	4 – 12	2 – 56	2 – 36	21	1 – 56
Mean±SD			17,7±20,3			
Median	2,5	8	11,5	34	-	8
≤ 12 weeks	9 (90%)	2 (100%)	4 (66,7%)	2 (25%)	-	17 (63%)
>12 - ≤24 weeks	1 (10%)	-	1 (16,7%)	1 (12,5%)	1 (100%)	4 (14,8%)
> 24 weeks	-	-	1 (16,7%)	5 (62,5%)	-	6 (22,2%)

Table 2. Characteristics and Subject Therapy Regimen Based on Response to Therapy.

Characteristics	Response NTB group		Response TB group	
	Complete, n=14	Incomplete, n=4	Complete, n=6	Incomplete, n=3
Age				
Range	15 – 56	17 – 74	14 – 54	19 – 56
Mean±SD	30,4±13,7	40,5±24,5	28,8±14,2	39,7±18,9
Sex				
Male	5 (35,7%)	1 (25%)	-	1 (33,3%)
Female	9 (64,3%)	3 (75%)	6 (100%)	2 (66,7%)
Location				
Neck	13 (92,9%)	3 (75%)	6 (100%)	3 (100%)
Mesentery	1 (7,1%)	1 (25%)	-	-
Side				
Unilateral	13 (92,9%)	4 (100%)	4 (66,7%)	1 (33,3%)
Bilateral	1 (7,1%)	-	2 (33,3%)	2 (66,7%)
Therapy and Evaluation	NTB		TB	
	Complete	Incomplete	Complete	Incomplete
Operative				
Excision	9 (64,3%)	1 (25%)	5 (83,3%)	3 (100%)
Incision Drainage	2 (14,3%)	-	-	-
FNA	3 (21,4%)	3 (75%)	1 (16,7%)	-
Adjuvant				
ATTs	-	-	6 (100%)	3 (100%)
Macrolides	2 (14,3%)	-	-	-
Cephalosporins	2 (14,3%)	-	-	-
Macrolides + Cephalosporins	1 (7,1%)	-	-	-
Quinolones	3 (21,4%)	-	-	-
Penicillin	1 (7,1%)	-	-	-
Quinolones + steroids	1 (7,1%)	1 (25%)	-	-
Cephalosporins + steroids	4 (28,6%)	3 (75%)	-	-
Amount of Adjuvants				
Range	1 – 3	1 – 3	2 – 10	7 – 11
Median	-	2,3±0,9	6,5±3,6	8,7±2,1
≤ 3 times	1	-	-	-
> 3 - ≤6 times	14 (100%)	4 (100%)	2 (33,3%)	-
> 6 times	-	-	-	-
Range	-	-	4 (66,7%)	3 (100%)
Duration (weeks)				
Range	1 – 56	2-24	2 – 36	15 – 36
Mean±SD	-	15,3±10,4	22,5±14,7	28,7±11,8
Median	3,5	-	-	-
≤ 12 weeks	13 (92,9%)	2 (50%)	2 (33,3%)	-
>12 - ≤24 weeks	1 (7,1%)	2 (50%)	1 (16,7%)	1 (33,3%)
> 24 weeks	-	-	3 (50%)	2 (66,7%)

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Neven et al. (2020) Cervical lymphadenitis is most often unilateral, especially in the submandibular lymph nodes.^{[2],[10]}

Adjuvant therapy for granulomatous lymphadenitis in this study more fully responded to various adjuvant therapy regimens. This is because the complete response patients in this study underwent excision so that they had a high cure rate (88.5%).^[2] In the research of Neven et al. (2020) showed that complete excision early in granulomatous lymphadenitis can accelerate healing and have good therapeutic and aesthetic results.^{[2],[8]} The most common comprehensive treatment regimen for complete response NTB lymphadenitis is excision followed by adjuvant quinolone therapy. Other types of adjuvant therapy in granulomatous lymphadenitis in West Nusa Tenggara can be seen in Table 3. The results of this study are in line with the research of Luong et al. (2005) that macrolide antibiotics given single, in combination, adjuvant after or before excision, can show a good therapeutic response in curing cervicofacial NTB lymphadenitis.^[5]

The number of adjuvant therapy given to the complete response NTB group ranged from 1-3 times. The duration of adjuvant therapy in the complete response NTB group ranged from 1-56 weeks. The results of this study are in line with the research of Luong et al. (2005) single macrolide therapy of NTB lymphadenitis in children showed resolution at 1 month afterward, then to complete resolution at second month. In addition, within approximately a month, adjuvant antibiotic therapy showed good resolution in postoperative patients with multiple lymphadenitis or residual lymphadenitis, or recurrent lymphadenitis.^[5] Tuberculous lymphadenitis that responded completely after adjuvant therapy in this study were 6 subjects (66.7%) from all TB groups. This is of course preceded by surgical intervention in the form of excision which has the potential to produce better resolution, especially in persistent lymphadenopathy, worsening symptoms, less response to antibiotics and/or steroids.^[2]

Excision was performed in the complete response TB group as many as 5 patients (83.3%), in the incomplete response TB lymphadenitis as many as 3 patients (100%). The comprehensive treatment regimen for complete response TB lymphadenitis is excision followed by adjuvant ATTs. The number of adjuvant ATTs for complete response TB lymphadenitis ranges from 2-10 times. The duration of adjuvant ATTs in complete response TB lymphadenitis ranges from 2-36 weeks. These results are in line with the research of Fontanilla et al. (2011) that excision of TB lymphadenitis early in the disease followed by adjuvant ATTs for 6 months showed a cure rate of 89% and if continued for 9 months the cure rate increased to 94%.^[8] In Table 3. it can be seen that the incomplete response to TB lymphadenitis was more common in bilateral lesions as many as 2 patients (66.7%). The Infectious Disease Society of America (IDSA) does not recommend the use of steroids in the treatment of tuberculous lymphadenitis.

CONCLUSION

Complete response to non-tuberculous granulomatous lymphadenitis was 14 patients (73.7%) with surgical excision, incision drainage, followed by single or combination antibiotic adjuvant therapy. Complete response to tuberculous granulomatous lymphadenitis in 5 patients (66.7%) with surgical excision followed by ATTs.

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