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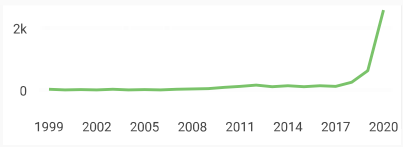

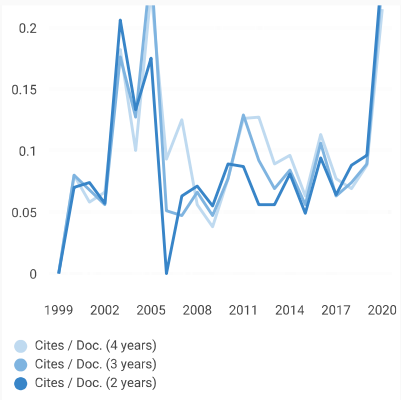

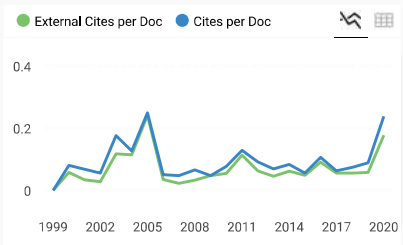

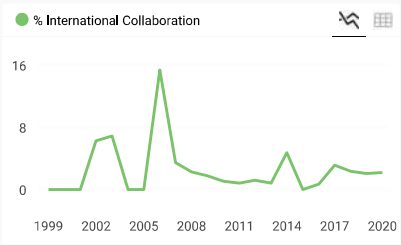

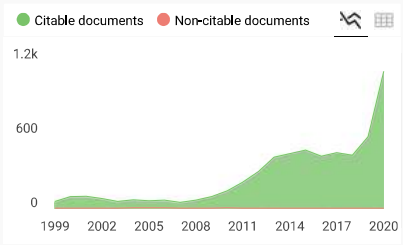

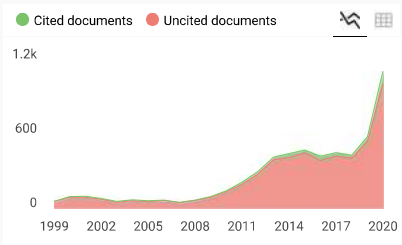

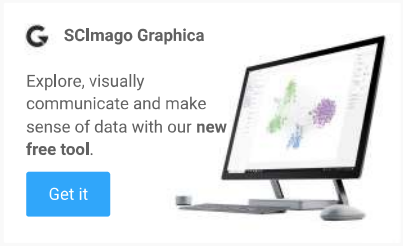

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Contents

Volume 14, Number 2 **April-June 2020**

Macrophage Activity and Histopathological Differences of Lung Tissue on Sequential Co-infections of Heligmosomoides Polygyrus Nematode on Mycobacterium Tuberculosis Infection

Laksmi Wulandari[1,2], Muhammad Amin[1], Soedarto[3], Gatot Soegiarto[2,4], Kenji Ishiwata[5]

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Abstract

Background: Tuberculosis is a chronic infection caused by Mycobacterium tuberculosis, a facultative intracellular parasite, that can be eliminated by cellular immunity played by macrophages. It has become a debate whether the co-infection of nematodes will affect the immune response of macrophages towards mycobacterium infection.

Objective: To reveal macrophage activity and histopathological difference of lung tissue in sequential co-infection of *Heligmosomoides Polygyrus* towards Mycobacterium tuberculosis infection.

Method: This study used 49 mice divided into 7 treatment groups with *Mycobacterium tuberculose* infection by inhalation and *Heligmosomoides polygyrus* orally within 8 and 16 weeks, and observed by immunohistochemical staining.

Result: Infection for 8 weeks showed polarization of macrophages towards M1 macrophage, whereas in 16 weeks, the macrophage polarization more towards M2 macrophages, supported by histopathological changes of lung tissue: peribronchiolitis, perivaskulitis, alveolitis, and granuloma formation with counts of acid-resistant germs +3. There was a difference of expression of arginase1 to each group ($p < 0.001$) and there was a difference of T CD4+ Th1 lymphocyte ($p < 0.001$).

Conclusion: There is a difference in macrophage activity in lung tissue; however, it does not cause different levels of histopathological changes in lung tissue and does not affect the immune response to *Mycobacterium tuberculosis* infection.

Keywords*: Heligmosomoides polygyrus*, *Mycobacterium tuberculosis*, macrophage, *Immunohistochemistry*

Introduction

Tuberculosis (TB) is a chronic infection caused by *Mycobacterium tuberculosis*. According to WHO report in early 2012, it is estimated that 8.7 million individuals in the world suffer from TB infection especially in developing and low income countries [1]. Most areas of the country with high TB incidence and low BCG vaccination effectiveness are also areas of high prevalence of worm infections [2–4]. Worm infections cause changes in the immune response that harm the body's defenses against TB infection [5,6].

Each year, there are 8.7 million new TB cases, with a mortality rate of around 1.4 million per year [1]. *Mycobacterium tuberculosis* is a paracitic intracellular facultative bacillus [7]. An appropriate immune response to

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eliminate TB is cellular immunity played by macrophages; $CD4^+$ T-lymphocytes that secrete IFN-g; $CD8^+$ T lymphocytes that eliminate infected macrophages with TB germs; as well as Tgd lymphocytes. This response requires a strong Th1 type cytokine. In contrast, worm infections stimulate the activation of eosinophil cells, mast cells, basophile cells, and IgE formation, which are Th2-type immune responses [8]. The dominant Th2-type immune response suppresses the Th1 type immune response through suppression by IL-4 [9].

Sequential research is certainly not ethical in human populations, because it can only be conducted with the standard model of nematode worm infection in mice that is *Heligmosomoides polygyrus*, and *Mycobacterium tuberculosis* sequentially. To describe the chronicity of a worm infection requires an interval of infection for at least 8 weeks [10]. Chronic worm infection is known to trigger the onset of regulatory T cells (Treg) [11,12]. Treg may affect the balance of Th1 and Th2 immune responses. Th1-Th2 balance will also affect macrophage function in overcoming mycobacteria infection [13,14]. If it is proven that chronic infection of the worms stimulates the onset of Treg cells that are capable of altering the balance of Th1 - Th2 type immune responses and macrophage functional activity, then the debate about the effect of worm infection on histopathological changes in TB infection will be resolved. This study aimed to identify the effect of sequential co-infection of *Heligmosomoides polygyrus* nematodes on pulmonary histopathological changes in *Mycobacterium tuberculosis* infection [15].

Method

The research was conducted for 6 (six) months at Experimental Animal Cage of the Clinical Parasitology Division, Faculty of Medicine, Universitas Brawijaya and in Bacteriology Laboratory of Tuberculosis Infection Study Group of Tropical Diseases Institution, Universitas Airlangga, Surabaya, Indonesia. The research sample used 49 male (*Mus musculus*) mice of wild type aged 8-12 weeks with body weight of 30-35 grams. The sample was divided into 7 groups consisting of: a group infected with tuberculosis (TB) for 8 weeks (M.tb8), a group infected with TB (*Mycobacterium tuberculosis*) for 16 weeks (M.tb16), a group infected with a worm (*Heligmosomoides polygyrus*) for 8 weeks (H.pg8), a group infected with a worm (*Heligmosomoides polygyrus*) for 16 weeks (H.pg16), the group of mice treated with helminth co-infection (*Heligmosomoides polygyrus*) followed by TB infection (*Mycobacterium tuberculosis*) (H.pg + M.tb), a group of mice treated with TB co-infection (*Mycobacterium tuberculosis*) followed by a helminth infections (*Heligmosomoides polygyrus*) (M.tb + H.pg), as well as control group without infection treatment [16]. Prior to conducting the research, the researchers conducted ethical test (151-KE) at the Faculty of Veterinary Medicine, Univeristas Airlangga, Surabaya, Indonesia.

Result

The activity of alternatively activated macrophage (AAMØ) also known as M2 macrophage was characterized by the expression of Arginase1 protein. It was explained that macrophages with brown cytoplasm and Arginase1 protein were blue (arrows) and seen with a 400x light magnification microscope. Group 1: *H. polygyrus* infection for 8 weeks; group 2: *H. polygyrus* infection for 16 weeks; group 3: *H. polygyrus* infection for 16 weeks + *M. tuberculosis* for 8 weeks; group 4: infection of *M. tuberculosis* for 16 weeks + *H. polygyrus* for 8 weeks; group 5: 16 weeks of tuberculosis infection; group 6: *M. tuberculosis* infection for 8 weeks (figure 2). The level of Ariginase 1 expression by macrophages in lung tissue showed in Table 1.

Histopathologic features and iNOS expression rates indicated that *M. tuberculosis* infection for 8 weeks resulted in infiltration of large amounts of macrophages into the infected lung tissue of mice and most of the macrophages infiltrating the tissue express iNOS (macrophage M1) activated in the atmosphere of Th1 cytokine. In infection with M. tuberculosis for 16 weeks, the number of macrophages that infiltrated the lung tissue was relatively decreased, and the level of iNOS expression in the macrophage group (4) whereas, histopathological features and levels of Arginase 1 expression indicated that M2 macrophages were also present in lung tissue, either in M. tuberculosis infection for 8 weeks or for 16 weeks. However, the level of Arginase1 expression by macrophages in mice for 8 weeks of M. tuberculosis infections (Fig. 3.-D) was lower than in the 16 weeks group of M. tuberculosis infections (Figure 3.-E).

To ascertain whether the duration of M. tuberculosis infection affected the level of expression of iNOS and Arginase1 by macrophages in lung tissue, MANOVA test was performed. From the statistical calculation, Box's Test of Equality of Covariance Matrices obtained p value = 0.148 ($p > 0.05$) which means homogeneous

data. From the Multivariate Test table on Hotelling's Trace, p = 0.00 (p <0.05) showed that the duration of M. tuberculosis infection significantly affected the level of expression of iNOS and Arginase1 by macrophages in lung tissue.

Histopathological Changes of Lung Tissue

The calculated percentage of T $CD4^+$ Th1 lymphocytes in peripheral blood showed a significant difference (p = 0.000). The percentage of $CD4^+$ T1 T lymphocytes in the highest lung tissue was found in M. tuberculosis infection for 8 weeks (4.508 ± 0.947) and then decreased in M. tuberculosis infection for 16 weeks (2.058 ± 0.845). The group treated with the last co-infection in the form of M. tuberculosis infection had a significantly higher percentage of $CD4^+$ Th1 T lymphocytes than the opposite co-infection. In addition to assessing histopathologic changes in pulmonary tissue, it was also calculated the acid-resistant M. tuberculosis bacteria in the lung tissue sieves preparation stained with Ziehl Neelsen staining (Table 1).

There was a correspondence between germination scores and histopathological lung rate change scores, wherein *H. polygyrus* co-infection did not affect acid-resistant bacteria count nor the rate of histopathological changes of lung tissue. The correlations between polarization of macrophage activity in lung tissue (ie, iNOS or Arginase1 expression) with histopathologic lung tissue change rate (ie Dormans scale score and acid-resistant bacteria count) were evaluated by Spearman test (Table 2).

Table 1. Levels of arginase expression1 by macrophages and the number of M. tuberculosis in lung tissue

Group	Arginase1 Expression		CDC/ATS	p
	Mean±SD	Min-Max		
H.pg 8	19.20±0.45c	19.00-20.00	-	0.000
H.pg 16	23.40±1.14d	22.00-25.00	-	
H.pg + M.tb	10.00±1.41 b	9.00-12.00	+3	
M.tb + H.pg	25.00±2.00d	23.00-28.00	+3	
M.tb 16	25.20±1.64d	24.00-27.00	+3	
M.tb 8	8.80±0.45b	8.00-9.00	+3	
Control	3.80±0.45a	3.00-4.00	-	

Note: H.pg = H. Polygyrus infection; M.tb = M. tuberculosis infection; 8 and 16: infection for 8 and 16 weeks; The letters a, b, c, d: indicate that groups with the same letter marks have insignificant differences, whereas groups with different letter marks have significant differences.

Table 2. The correlation between macrophage activity and histopathologic changes

Correlation between variables	r	p
iNOS and Dormans scores	0.523	0.001 *
Arginase1 and Dormans score	0.312	0.068
iNOS and acid-resistant bacteria count	0.723	0.000 *
Arginase1 and acid-resistant bacteria count	0.228	0.188
Dormans score and acid-resistant bacteria count	0.875	0.000 *
iNOS and Arginase1	0.058	0.739

*p<0.05

Discussion

In this study, we found an increase in the percentage of Th1 lymphocytes in lung tissue and in peripheral blood that correlated strongly with levels of IFN-g cytokines in peripheral blood serum. The increase occurred in M. tuberculosis infection for 8 weeks which then 'subside' at the time of infection lasted up to 16 weeks. Our results are consistent with the results of several other researchers who found that elevated IFN-g levels were primarily obtained in the early stages of the infection especially after the second week post infection [17]. The mobilized lymphocytes accumulate at the site of infection, proliferate and secrete cytokines, especially IFN-g. Protective immune responses to M. tuberculosis are more necessary for the role of Th1 type cytokines. Th1 type cytokines, including IFN-g, are required not only to activate macrophages but also to assist the activity of $CD8^+$ T lymphocytes [17,18].

Worm infection induces the emergence of T regulatory lymphocytes ($CD4^+$ $CD25^+$ $Foxp3^+$) in both the intestinal tract, peripheral blood and lung tissue. T regulatory activity can be assessed from elevated levels of IL-10 and TGF-b cytokines in peripheral blood serum, as well as T regulatory lymphocyte percentage in intestinal tissue, lung tissue and peripheral blood. Similarly, the findings of the Th1 and Th2 lymphocyte immune responses, the T regulatory lymphocyte response were only found in the worms infection group for up to 8 weeks. When the infection has lasted up to 16 weeks, the activity and the role of T regulatory lymphocytes also decreased [19].

Activation of T regulatory lymphocytes apparently also occurs in M. tuberculosis infections, especially in infections lasting up to 8 weeks [20].Thus, it can be concluded that the time interval between the infection of the nematode worms and tuberculosis, as well as the observation will greatly affect the outcome of the co-infection [18]. The success of the macrophage immune response is influenced by the balance of iNOS and Arginase expression [21] which describes the direction of polarization of macrophage activity. Worm infections induce Th2-type immune responses, such as IL-4 and IL-13, leading to macrophage polarization into M2 macrophages expressing Arginase1. The purpose of M2 macrophage activation is to evoke an anti parasitic response and repair tissue damage [22]. In the group who received the last co-infection treatment of M. tuberculosis, the Arginase1 expression decreased whereas iNOS expression increased sharply [23].

This can be explained through several arguments that sequential infection of M. tuberculosis and H. polygyrus at intervals of 8 weeks does not affect the balance of T lymphocyte activity in lung tissue, sequential infection of M. tuberculosis and H. polygyrus at intervals of 8 weeks does not affect the ability of macrophages to generate an appropriate immune response for M. tuberculosis infection in lung tissue, and histopathological changes occurring in lung tissue due to M. tuberculosis infection are slowly changing and evolving changes that cannot be detected in the observation process for 8 or 16 weeks [24].

Immune responses to M. tuberculosis often fail to eliminate germs because germs are able to use several ways to circumvent the host's immune response, among others by inhibiting the maturation and acidification of the phagosome, inhibiting the fusion of phagosome and lysosome, and escaping from the phagosome [25]. It triggers macrophages to work together with $CD4^+$ and $CD8^+$ T lymphocytes to form granulomas that aim to isolate M. tuberculosis [7]. However, M. tuberculosis can still survive in macrophages and beyond macrophages in granulomas [26]. Thus, granulomas are retained for long periods of time through delayed-type hypersensitivity (DTH) responses requiring Th1 lymphocyte competence. If there is a significant decrease in immune response as well as in patients with HIV-AIDS macrophage, it can decay that allows dissemination of M. tuberculosis [27].

Conclusion

There is a difference in macrophage activity in lung tissue; however, it does not cause different levels of histopathological changes in lung tissue and does not affect the immune response to *Mycobacterium tuberculosis* infection.

Conflict of Interest: There is no concflict of interest.

Source of Funding: This study is self-funded.

Ethical Clearance: This study was approved by Ethical Commission of Health Research (151-KE) at the Faculty of Veterinary Medicine, University of Airlangga, Surabaya, Indonesia.

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