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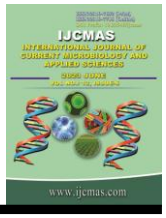

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The Effect of Cercarial Antigen Vaccine against Murine *Schistosomiasis mansoni*

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A B S T R A C T

Schistosomiasis is one of the most common parasitic diseases worldwide. Because of the low bioavailability of praziquantel and the appearance of drug resistant strains, the development of an effective vaccine is crucial to control schistosomiasis. To test the effect of cercarial antigen as a potential vaccine against *Schistosoma mansoni* -infected mice. Methods: 90 mice divided into 2 groups: group I: (Control group) (40 mice) subdivided into subgroup Ia (15 mice): Non-infected mice (normal control) and subgroup Ib (25 mice): *Schistosoma* infected mice (infected control). Group II: (50 mice) (The vaccinated group): received cercarial antigen then infected with *S. mansoni* three weeks after the first immunization dose. Vaccine efficacy was assessed by parasitological and histopathological studies. The vaccinated group caused significant reduction in adult worms count, intestinal egg countand intestinal granulomas size and number compared to the infected control group. Cercarial antigen vaccine is a promising schistosomal antigen that has a protective effect against *Schistosoma mansoni* as proved by parasitological and histopathological examination.

Introduction

Schistosomiasis is the second infectious disease next to malaria in Africa (Hailegebriel *et al.*, 2020). It is caused by trematode parasites of the genus *Schistosoma*, of which three major species - *Schistosoma mansoni*, *S. japonicum*, and *S.haematobium* - cause severe disease in humans (WHO, 2013). *Schistosoma mansoni* has a wider spread involving Africa, the Middle East, South America, and the West Indies (Barakat, 2013). More than 200 million individuals are infected and about half of them are children (Hotezand Fenwick, 2009). It is estimated that about39 million disability adjusted life years (DALYs) are lost each year due to schistosomiasis (Koroma *et al.*, 2010). Humans are infected after direct contact with water sources containing infectious cercariae (Wilson, 2009). There are 2 stages of schistosomiasis; either acute schistosomiasis that develops within a few weeks

after exposure, or chronic schistosomiasis that occurs after a few years of heavy infection (Gryseels *et al.,* 2006). The chronic phase occurs as a result of the formation of granulomas around the eggs. The size of a granuloma can be a hundred times larger than the size of the egg (Coon, 2005).

Schistosomiasis control aims to reduce the propagation of various life cycle stages (McManus *et al.,* 2010). Praziquantel (PZQ); an isoquinoline derivative, is the drug of choice against all *Schistosoma* species (Utzinger and Keiser, 2004). Moreover, this efficacious, low-cost drug has achieved a significant decrease in disease prevalence and infection intensity in several endemic areas by decreasing worm burden, egg burden and granuloma size and number (Evans *et al.,* 2011 and ElAhwany *et al.,* 2006). However, Praziquantel (PZQ) has poor efficacy against the juvenile forms and resistance to the drug has been reported (da Silva *et al.,* 2017). Therefore, vaccination can be integrated with chemotherapy in order to control the pathological consequences, reduce the associated mortality and eliminate schistosomiasis (Alves *et al.,* 2015). The effectiveness of a schistosomiasis vaccine depends on its ability to decrease the adult worm count, egg count as well as the ability to downregulate granulomatous responses to the trapped eggs in the tissues which are the main reasons of morbidity (Rezende *et al.,* 2011). Many vaccine candidates have been identified, but none of them have yielded significant protection levels (Abdel-Hakeem *et al.,* 2020). Therefore, it's a critical task to identify new antigens to produce an efficient vaccine against schistosomiasis (Oliveira *et al.,* 2008).

Materials and Methods

The present study was done in the Medical Parasitology Department, Faculty of Medicine, Tanta University and the Biological Unit at Theodore Bilharz Research Institute (TBRI), Imbaba, Giza, Egypt.

Experimental animals: The study was performed on 90 male laboratory bred mice, 5 weeks old, weighing ±20 grams, free of any parasitic infection. They were kept on a commercial pellet diet and animal house temperature of 20-22ºC. They were infected subcutaneously with 60 *Schistosoma mansoni* cercariae as described by Peter and Warren (1969).

Antigens

Schistosomal cercarial antigen was obtained from Schistosome Biological Supply Center, TBRI.

Regimen of vaccination: Vaccination was done according to the method of Nabih and Soliman, (1986). First, each mouse was injected subcutaneously with 200 µl of the antigen with total antigen concentration of 30 µg protein. Two weeks later, the mice were injected subcutaneously with 200 µl of the same antigen with total antigen concentration containing 20 µg proteins; therefore, each mouse received a total antigen dose of 50 µg protein.

Study design

The mice were divided into two main groups: GI (Control group): forty mice that were further subdivided into 2 subgroups: Subgroup Ia (Fifteen mice): non-infected mice (Negative control) and subgroup Ib (Twenty-five mice): *Schistosoma* infected mice (Positive control). GII (Vaccinated group): Fifty mice that received cercarial antigen then infected subcutaneously with *S. mansoni* cercaria three weeks after the first immunization dose.

Five mice from each control group and ten mice from the vaccinated group were euthanized at the 1st, 6th, 8th, 10th and 12th weeks post infection (P.I.). Normal mice were sacrificed at the end of the experiment. The lungs were removed from each euthanized mouse at the 1stweek PI. The large intestine from mice euthanized at the 6th, 8th, 10th and 12th weeks P.I. were removed. The infected mice were subjected to parasitological examination and histopathological examination.

Parasitological examination

Adult worm count was done using a perfusion pump to suck the worms from the liver and the intestinal tissues. The recovered worms were then counted at 10 weeks P.I. according to the method described by Smithers and Terry (1965). Egg count was done in the intestinal tissues according to Cheever (1968) as follows; half gram of each of the colon was put in a glass bottle containing 2 ml of 5% KOH and left for 12 hours at room temperature. On the second day, it was put in the incubator at 37°C for 6 h, then, the glass bottle was shaken well. 0.1 ml was taken from the bottle and put on a glass slide, covered with a coverslip and examined microscopically for *S. mansoni* ova count.

Histopathological examination

Early evaluation: Lung samples were fixed in 10% formalin then processed and stained with hematoxylin and eosin (H & E). Late evaluation: Samples of the large intestine were fixed in 10% formalin then processed and stained with H & E according to Bancroft and Stevens (1975). The greatest granuloma diameter and its perpendicular diameter were calculated, and their mean is the diameter of the granuloma. The number and size of the granulomas were then determined in ten high power fields (Jacobs *et al.,* 1997).

Statistical analysis

Data were analyzed using Statistical Program for Social Science (SPSS) version 22.0 Quantitative data were expressed as mean± standard deviation (SD). Independent-samples T-test of significance was used when comparing between two means.

Results and Discussion

Parasitological studies

A significant reduction in the mean number of *Schistosoma mansoni* adult worms was reported in GII (vaccinated group) at week 10 P.I. compared to the infected control group (GIb)(Table 1). Regarding the mean intestinal egg count, there was a significant reduction in the vaccinated group (GII) as compared to the infected control group (GIb) at all weeks P.I. (Table 2).

Histopathological studies

Regarding early evaluation of the efficacy of vaccine, the lung tissue sections of the infected groups at one-week P.I. and the normal control group were examined. The lung tissues of the normal control group (GIa) including alveolar wall and capillaries, the pneumocytes, alveolar lumina, blood vessels, bronchial walls and their epithelial cells were normal. At the first week P.I., the changes in the lungs of the infected control group (GIb) were restricted to the interstitial tissues, especially those around large and medium size bronchi, and also in the subpleural region. There was mild to moderate mononuclear infiltration mainly by lymphocytes and macrophages. The alveolar spaces showed marked congestion and were filled with RBCs. No *Schistosoma* stages were seen in the examined sections. Regarding the vaccinated group (GII), there was mild congestion of the bronchi and the alveolar tissues with mild mononuclear infiltration mostly formed of lymphocytes as compared to the infected control group (GIb) (Figure 1).

Concerning the intestinal granuloma, there was a statistically significant difference in the mean number and size of intestinal granulomas between the infected control group (GIb) and the vaccinated group (GII) at all weeks P.I. (Table 3 & 4).

Regarding the histopathological changes of the intestine, as regards to the infected control group (GIb), the intestinal sections showed a high degree of accumulation of inflammatory cells in the submucosa in the form of histiocytes, eosinophils and macrophages around the *schistosoma* eggs leading to the formation of large granulomas which were mainly fibrocellular and fibrous with marked increase in the fibrous content as the duration progressed. In addition, there was hyperplasia of the

glands (Figure2). Concerning the vaccinated group (GII), the granulomas were smaller in size, and number compared to the infected control group (GIb). The granulomas were mainly fibrocellular and cellular with more reduction in the fibrous content as the duration progressed (Figure 3).

Schistosomiasis is still one of the most significant endemic diseases in the world (Fenwick and Webster, 2006). Poverty and lack of sanitation are the major contributing factors to the high incidence and prevalence of schistosomiasis (Adenowo *et al.,* 2015). Chemotherapy alone could not control the disease or prevent reinfection (Hotez and Ferris, 2006). In addition, resistance to chemotherapy was reported (Neves *et al.,* 2015). Vaccines, and/or chemotherapy, are considered the best strategy for long-term sustained control of schistosomiasis (Kupferschmidt, 2013). Hence, in the present study, cercarial antigen was tested as a potential vaccine against *Schistosoma mansoni* infected mice.

Regarding the adult worm count, the present work showed a statistically significant reduction in the vaccinated group (GII) at week 10 ($p<0.05$) as compared to the infected control group (GIb) with percentage of reduction of 66.1%. This is slightly higher than the findings of De Melo *et al.,* (2013) who used schistosomula tegument (Smteg) in association with the adjuvant CpG-ODN (CpG oligodeoxynucleotides) and reported a (43-48 %) reduction in the mean adult worm burden.

Regarding the intestinal egg count, there was a statistically significant reduction in the mean intestinal egg count in the vaccinated group (GII) at all weeks P.I.as compared to the infected control group (GIb). The maximal percentage of reduction in the vaccinated group (GII) was recorded at week 8 P.I., reaching 43.9%. Similar results were observed by Abdel-Hakeem *et al.,* (2020) who immunized mice using soluble egg antigen and soluble adult worm antigen preparation (SEA+SWAP) with percentage of reduction of 67.32% at week 10 P.I.

In reference to the histopathological findings, the current study demonstrated that the changes in the lungs of the infected control (GIb) one-week P.I. consisted of mild to moderate cellular infiltration of mainly lymphocytes and a few macrophages which were restricted to the interstitial tissues. No *Schistosoma* stages were seen in the examined sections. Similar results were observed by Souza *et al.,* (2007) who found moderate edema and focal or diffuse infiltration with predominant lymphocytes and a few macrophages in the peri bronchial space during the acute phase of *Schistosoma mansoni* infection in mice. The mechanism of lung inflammation was attributed to the triggering of inflammatory responses by host tissue damage resulting from breaching of the capillary-alveolar barrier by schistosomules as mentioned by Kassim *et al.,* (1992). This was further explained by Kumar *et al.,* (2017) who attributed this pathology to the effect of TH2 cells that stimulate an inflammatory response in the form of recruitment of monocytes into the interstitium of the lungs. As regards to the effect of the vaccinated group (GII), there was mild congestion of the bronchi and the alveoli with mild mononuclear infiltration mostly formed of lymphocytes. As the duration progressed, there was amelioration in lung pathology with restoration of normal appearance of most alveoli and bronchioles. The same lung pathological findings were observed by El Gawish *et al.,* (2006) who immunized mice using schistosomula antigen.

Concerning the intestinal granulomas, there was a statistically significant reduction in the number and size of intestinal granulomas at all periods of sacrifice in the vaccinated group (GII) as compared to the infected control group (GIb). The highest reduction was recorded at week 12 P.I. in the vaccinated group reaching 53.8% and 26% in number and size of granulomas, respectively. These percentages are slightly higher than those observed by Abdel-Hakeem *et al.,* (2020) who immunized mice with SEA+SWAP resulting in reduction of intestinal granuloma size to 18.1% and number to 23.3% at week 10 P.I.

Table.1 The mean adult *Schistosoma mansoni* worms count (mean ± SD) recovered from the infected groups at week 10 P.I.

Duration / Groups	10 W P.I.			
	Mean ± SD			R
GIb	12.4	±	2.30	
G II	4.2	±	1.48	66.1%
T test	8.441			
P value	0.001*			

GIb: Infected control GII: Vaccinated P: GIb vs GII *Significant (*P<0.05*) R: Reduction %

Table.2 The mean number of *S. mansoni* eggs/gm intestine in all infected groups at different durations P.I

Duration Groups	6 W P.I.				8 W P.I.				10 W P.I.				12 W P.I.			
	Mean ± SD			R	Mean ± SD			R	Mean ± SD			R	Mean ± SD			R
G Ib	3116.8	±	827.56		4123	±	762.62		4529.2	±	832.69		8201.6	±	1172.94	
G II	1950.2	±	815.04	37.4 %	2311.2	±	735.74	43.9 %	3729.6	±	917.65	17.7 %	6396	±	1767.46	22 %
T test	3.182				5.412				2.892				2.689			
P value	0.005*				0.001*				0.012*				0.015*			

GIb: Infected control GII: Vaccinated P: GIb vs GII *Significant (*P<0.05*) R: Reduction %

Table.3 The relation between the mean number of granulomas / intestinal section in all infected groups at different durations post infection.

Duration / Groups	Week 6 P.I.		Week 8 P.I.		Week 10 P.I.		Week 12 P.I.	
	Mean ± SD	R	Mean ± SD	R	Mean ± SD	R	Mean ± SD	R
GIb	8.2±1.2		8.6±1.1		9.1±1.5		11.62±2.25	
GII	6.8±1.3	17.1	6.5±1.2	24.4	6.3±1.7	31	5.37±2.10	53.8
T test	2.502		4.082		3.912		6.421	
P value	0.022*		0.001*		0.001*		0.001*	

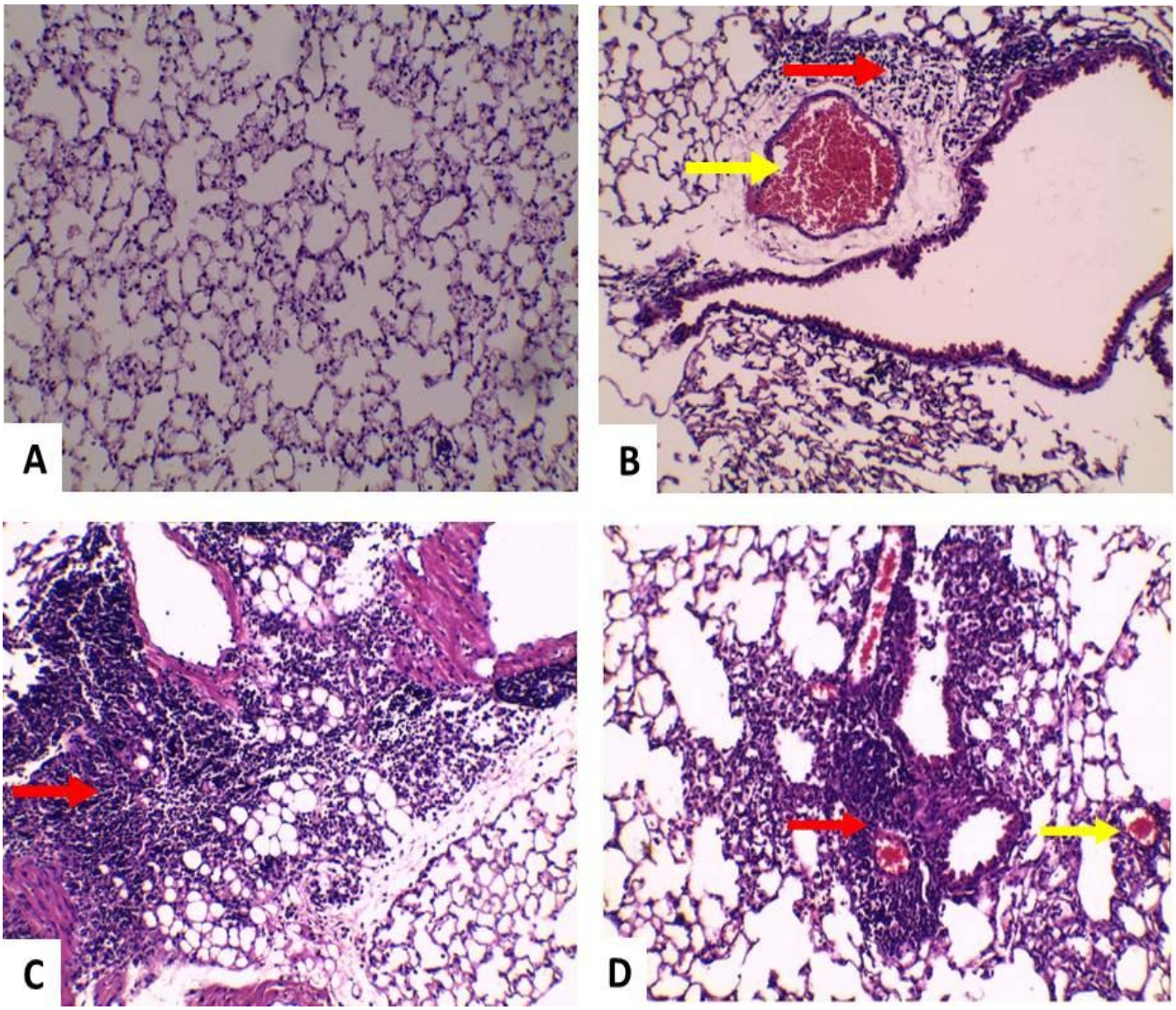
GIb: Infected control GII: Vaccinated P: GIb vs GII *Significant (*P<0.05*) R: Reduction %

Table.4 The relation between the mean size of granulomas / intestinal section (diameter/µm) in all infected groups at different durations post infection.

Duration / Groups	Week 6 P.I.		Week 8 P.I.		Week 10 P.I.		Week 12 P.I.	
	Mean ± SD	R	Mean ± SD	R	Mean ± SD	R	Mean ± SD	R
Group Ib	320.5±10.6		317.32±11.2		312.8±9.8		306.1±10.7	
GII	294.5±10.3	8.11	287.4±9.6	9.4	267.3±12.3	14.6	226.4±8.6	26
T test	5.562		6.405		9.152		18.362	
P value	0.001*		0.001*		0.001*		0.001*	

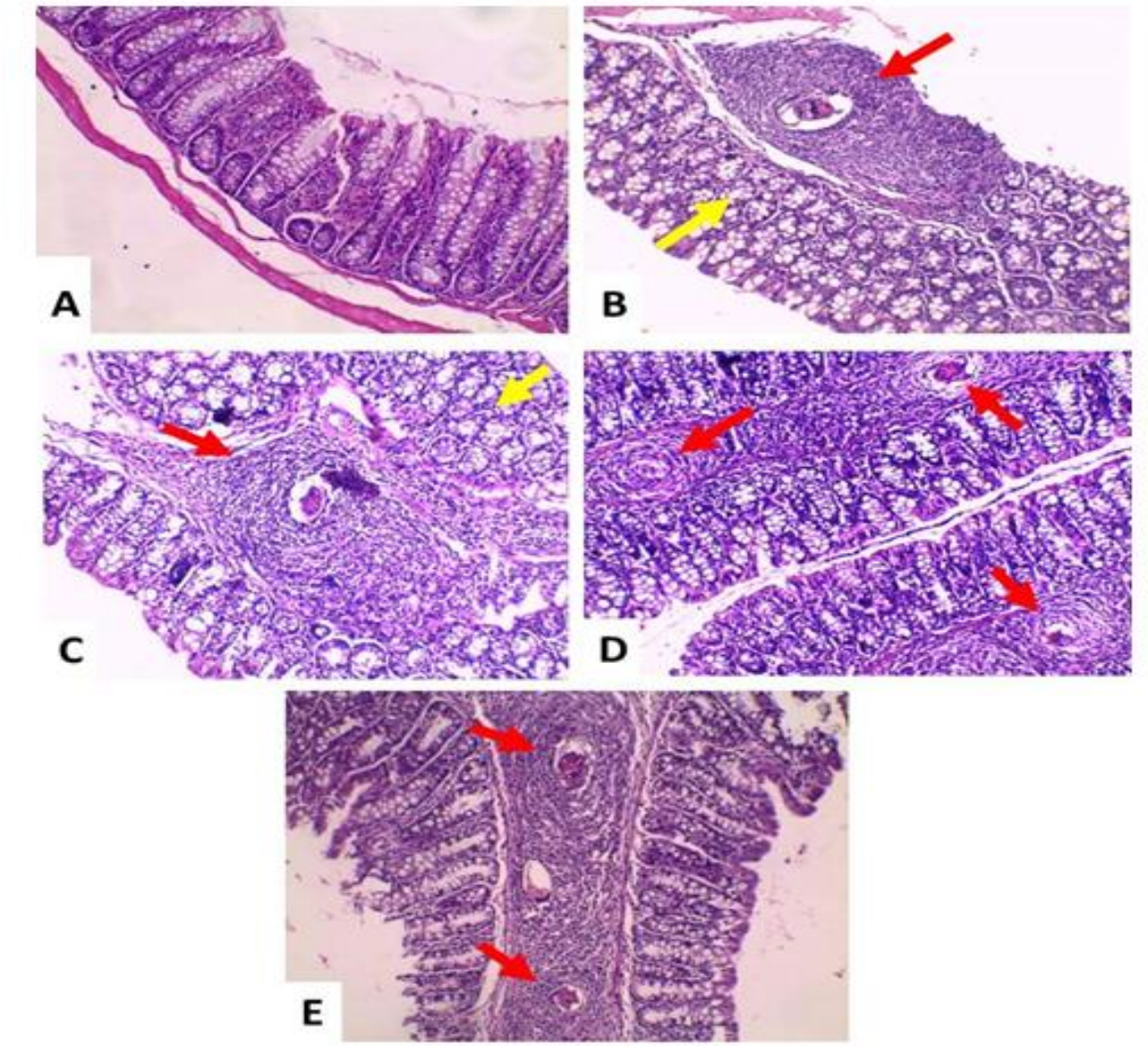
GIb: Infected control GII: Vaccinated P: GIb vs GII *Significant (*P<0.05*) R: Reduction %

Fig.1 A photomicrograph of lung sections of mice of the infected groups at one-week P.I. and in the normal control group:



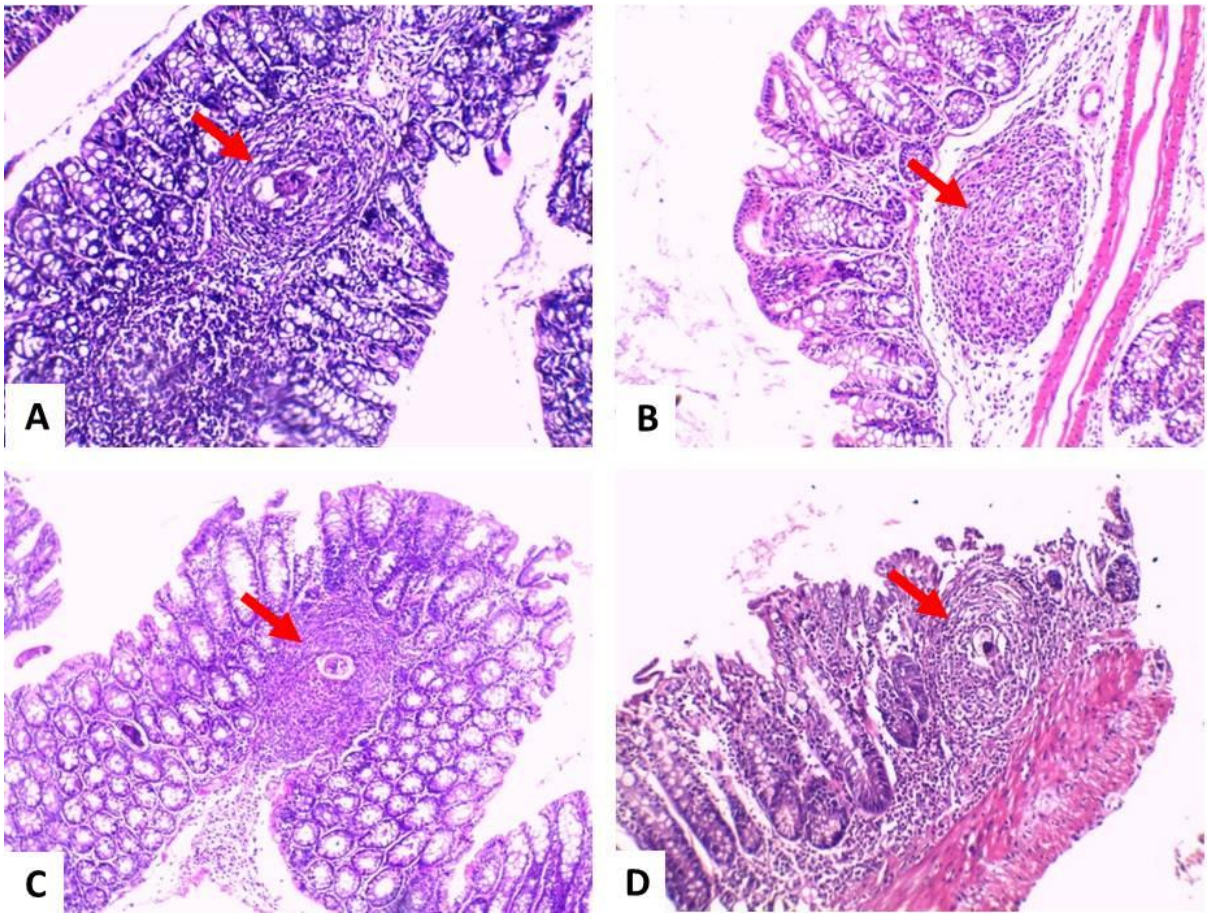
A) Normal control group (GIa) shows normal alveolar tissues.
B) Infected control group (GIb) shows congestion of the alveolar spaces (yellow arrow) and inflammation in the lungs (red arrow).
C)Infected control group (GIb) shows inflammation (red arrow) in the lungs, bronchi and alveoli.
D) Vaccinated group (GII) shows congestion (yellow arrow) and inflammation in the alveoli (red arrow) (H&E x200).

Fig.2 A photomicrograph of intestinal sections of mice of the infected control group (GIb) at different durations P.I. and in the normal control group (GIa) (H&Ex200):



A) Normal control group (GIa) shows normal intestinal mucosa.
B) Infected control group (GIb) at 6 weeks P.I. shows a *Schistosomal granuloma* surrounding eggs (red arrow) and hyperplasia of the mucosal glands (yellow arrow).
C) Infected control group (GIb) at 8weeks P.I. shows a *Fibrocellular granuloma* surrounding a schistosomal egg (red arrow) and gland hyperplasia (yellow arrow).
D) Infected control group at 10 weeks P.I. shows multiple *Fibrocellular granulomas* surrounding schistosomal eggs (red arrows).
E) Infected control group at 12 weeks P.I. shows multiple fibrous granulomas (red arrows).

Fig.3 A photomicrograph of intestinal sections of mice of the vaccinated group (GII) at different durations (H&Ex200):



A) At 6 weeks P.I. shows a *Schistosomal granuloma* surrounding eggs (red arrow).
B) At 8 weeks P.I. shows a fibrocellular *Schistosomal granuloma* (red arrow).
C) At 10 weeks P.I. shows a small *Fibrocellular granuloma* surrounding a schistosomal egg (red arrow).
D)At 12 weeks P.I. shows reduction in the cellular *Schistosomal granuloma* size (red arrow).

Regarding the infected control group (GIb), there were prominent histopathological changes in the form of submucosal granulomas which were fibrocellular or fibrous with hyperplastic colonic glands and polyposis. As the duration progressed, the size of granuloma decreased due to fibrosis while the number of granulomas increased.

Similar results were observed by Yang *et al.*, (2021) who found hyperplasia and polyposis in the colon of *S. mansoni*-infected mice in addition to the intestinal granulomas in the submucosa of the infected mice.As regards to the vaccinated group (GII) in the current study, the intestinal granulomas were mainly fibrocellular and cellular with decrease in size and reduction in fibrosis as the duration progressed. Ewaisha *et al.*, (2014) referred the reduction in the inflammatory reaction to the biological interactions between both parasite antigen and host tissues resulting in the dampening of egg metabolites with regeneration of the hepatic tissue.

In this work, vaccination with cercarial antigen resulted in significant reduction in adult worm count, intestinal egg count and intestinal granuloma number and size. Moreover, early protective effect

was induced by cercarial antigen as shown by the preserved lung tissue one-week P.I. Since immunization with cercarial antigen protected mice against challenge infection with *Schistosoma mansoni*, it can be considered as a promising vaccine against schistosomiasis.

Conflict of interest

Authors declare that there was no conflict of interest regarding the publication of this paper.

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