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Infection with *Plasmodium chabaudi* diminishes plasma immune complexes and ameliorates the histopathological alterations in different organs of female BWF1 lupus mice

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Abstract. – OBJECTIVE: To determine the effect of *Plasmodium chabaudi* infection on the plasma level of circulating immune complexes (CICs), haemoglobin (Hb) content, urine profile, and histological features of female BWF1 mice, the murine model of systemic lupus erythematosus (SLE).

MATERIALS AND METHODS: A total of 30 female BWF1 lupus mice were randomly divided into three groups as follows: group (I) control group (*P. chabaudi* uninfected); group (II) lupus mice infected with live *P. chabaudi*; group (III) lupus mice infected with irradiated *P. chabaudi*. Urine samples were daily collected from the second week-post infection. Mice from the three groups were killed at day 14 post-infection and heparinized blood was collected for further haemoglobin contents and plasma analysis. Paraffin-embedded kidney, liver, lung, heart, brain, ovary and skin tissues were stained with Hematoxylin and Eosin (H&E) and examined under light microscope.

RESULTS: Our results reveal that infection of lupus mice with live *P. chabaudi* was associated with an increase in urinary Hb and a decrease in plasma Hb and CIC levels. Interestingly, infection of lupus mice with live *P. chabaudi* ameliorates the histopathological alterations mediated by lupus disease in kidney tissues. Although no parasite sequestration was observed in any of the investigated organs, *P. chabaudi* pigment deposition was observed in the liver of both live and irradiated *P. chabaudi* infected groups.

CONCLUSIONS: This study in lupus prone BWF1 mice indicated that gamma-irradiated *P. chabaudi* infection has the desired lupus ameliorating effect without negative effects of malaria which assist the understanding of different responses to plasmodium sp. infection in human lupus patients.

Key Words:
BWF1, Haemoglobin, Immune complexes, Lupus, Malaria.

Introduction

Autoimmune diseases are the third most prevalent cause of morbidity and mortality in the industrialised world, surpassed only by cancer and heart diseases[1]. Despite the high prevalence of autoimmune diseases, the aetiology of most such disorders remains obscure and a number of factors have been implicated in their pathogenesis[2]. Among these key elements, the impact of infections on the development of autoimmunity is substantial and the relationship between infections and autoimmunity is a complex phenomenon that has been the focus of much research[3,4]. Epidemiological and clinical data support the hygiene hypothesis, according to which the decrease of infections observed over the last three decades is the main cause of the parallel, and incessant, increase in auto immune disorders[5,6]. Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by the production of numerous auto antibodies and the involvement of skin, joints, kidneys, brain, serosal surfaces, blood vessels, blood cells, lungs and heart[7]. The (NZB×NZW) F1 (BWF1) mouse develops a spontaneous autoimmune disease process with striking similarities to human SLE. In female BWF1 mice, the production of IgG antinuclear antibodies, including antibodies

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to double-stranded DNA (dsDNA), is associated with the development of severe immune complex-mediated glomerulonephritis that results in death from renal failure in virtually all animals by 12 months of age[8]. Although various studies have explored the factors responsible for the onset of autoimmunity in these mice[9], little is known regarding the histological changes in different organs of this model. Malaria is a parasitic protozoan disease that has many pathological signs, including severe anaemia and histopathological alterations in a variety of tissues[10]. It has been speculated that Hb loss during malaria infection is caused by the destruction of normal uninfected red blood cells (uRBCs)[11]. On the other hand, malaria may offer a protective effect against autoimmune diseases by diminishing their severity or by either preventing or retarding their expression[12]. Greenwood et al[13] described a higher survival rate in young lupus-prone mice infected with *Plasmodium berghei yoelii*. In normal mice, *P. chabaudi* infection induces the production of natural auto antibodies, probably with immune-regulatory properties[14]. Circulating immune complexes (CICs) are the result of the host's defence against endogenous or exogenous antigens. Chronically elevated concentrations of CICs, however, induce inflammatory organ or tissue damage. CICs are detectable in a variety of systemic autoimmune diseases (such as SLE), allergies and infectious diseases[15] and have, therefore, been acknowledged as useful tools for the diagnosis of inflammatory diseases and for the provision of clinical information regarding immunopathology, prognosis and follow-up. Recently, the presence of CICs in the blood of SLE patients has attracted many research groups and its correlation with disease activity is now well documented[16]. In addition to its well-known role in SLE disease activity, CICs are also associated with malaria disease activity and a reduced clearance of CICs has been associated with cerebral malaria[17]. Although histopathological changes during SLE and during malaria have been studied in detail before, these pathological changes have not been explored in respect to the organs of female BWF1 lupic mice after *P. chabaudi* infection. Nor has consideration been given to the comparison between the effects of live and gamma irradiated parasites. Here, therefore, we have tried to study this comparison between live and gamma irradiated parasites and their effects on lupus associated pathology in female BWF1 mice.

Materials and Methods

Animals

A total of 30 female BWF1 29-week-old mice were purchased from Jackson Laboratory (Bar Harbor, ME, USA) and were maintained and monitored in a specific pathogen-free environment as previously described[18-26]. All animal procedures were performed in accordance with the standards set forth in the Guidelines for the Care and Use of Experimental Animals issued by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The study protocol was approved by the Animal Ethics Committee at King Saud University. All animals were allowed to acclimatize in plastic cages (five animals per cage) inside a well-ventilated room for one week prior to the experiment. The animals were maintained under standard laboratory conditions (temperature of 23°C, relative humidity of 60-70%, and a 12-hour light/dark cycle), fed a diet of standard commercial pellets, and given water *ad libitum*.

P. chabaudi Infection

The blood stage forms of *P. chabaudi* parasites were stored in liquid nitrogen after *in vivo* passage in 3-month-old BALB/c mice according to a previously described protocol[27]. Female BWF1 mice (30 weeks old) were infected by the i.p. injection of 10^6 parasitized erythrocytes obtained from an infected mouse of the same strain as previously described[27]. Parasitaemia was monitored by Giemsa-stained thin blood smears. The experimental animals were assigned to three groups (10 mice/group) as follows: group (I) lupus group (uninfected with malaria); group (II) live *P. chabaudi* infected group (lupus + live *P. chabaudi* infection); group (III) irradiated *P. chabaudi* infected group (lupus + irradiated *P. chabaudi* infection). Group III was infected i.p. with 10^6 gamma irradiated red blood cells (RBCs) infected with *P. chabaudi*. Prior to injection, the blood cells were exposed to a dose of 200Gy gamma-radiation from a Gamma Cell 200 Irradiator (Atomic Energy of Canada, Ltd., Ottawa, Canada) utilizing a 60^oC source located at the Research Center of College of Science, King Saud University, Saudi Arabia. This radiation dose was applied based on experiments conducted by Ferreira-da-Cruz et al[28] who provided evidence that a 200Gy gamma-irradiation dose is able to abolish the original replication of erythrocytic forms of the Palo Alto *P. falciparum* strain,

most likely by inactivating their infectivity. According to their data, neither 100 nor 150Gy irradiation doses were able to inactivate the parasite, despite a reduction of parasitaemia. All animals were sacrificed at day 14 post infection.

Sample Collection

Blood was collected from the heart in heparinized tubes for the determination of haemoglobin content. The organs were removed and cut into small pieces in sterile saline. The pieces were fixed in 10% neutral buffered formalin, and then embedded in paraffin. Sections were cut and stained with haematoxylin and eosin and analysed under light microscopy.

Urine Analysis

From the second week post infection, urine collections were obtained in metabolism cages every 24 hours. Urine parameters were evaluated semi-quantitatively using a Combur 10 Test kit (Roche Diagnostics GmbH, Mannheim, Germany).

Haemoglobin Content

Whole blood samples were analysed with an automatic Vet abc Animal Blood Counter (Horiba ABX, Montpellier, France) using the haematology kits specified for that instrument (Horiba ABX, France) according to the manufacturer's instructions. ELISA Assay for Circulating Immune Complexes (CICs) Detection. For CICs detection, plates coated with C1q to detect CIC (Alpha Diagnostic International Inc., San Antonio, TX, USA) were used with plasma diluted in the sample buffer. Subsequent procedures were performed according to the manufacturer's instructions. The ELISA plates were read with a micro plate reader (Multiskan ASCENT ThermoH).

Histological Analysis

Pathological evaluation of H/E stained tissue sections was carried out by a pathologist blinded to the experimental regimen. To further ensure the validity of our results, not less than ten fields per organ with similar microscopic fields were observed carefully for histopathological changes, such as *P. chabaudi* pigment deposition, tissue inflammation and red blood cell sequestration.

Statistical Analysis

One-way ANOVA was carried out, and the statistical comparisons between the groups were performed with Duncan's test using a statistical package program (SPSS version 17.0, SPSS Inc., Chicago, IL, USA). All p-values are two-tailed and $p < 0.05$ was considered as significant for all the statistical analyses in this study.

Results

Infection of Female BWF1 Mice with Either Live or Gamma Irradiated *P. chabaudi* was Associated with a Changed Urine Biochemical Parameters

Urine analysis was carried out for the three experimental groups as shown in Table I. The specific gravity and the level of urobilinogen (mg/dL) were nearly similar in the urine samples of all groups. In the live *P. chabaudi* infected group, RBCs (Ery/µL) and haemoglobin (gm/ml) content were detected in highly elevated levels, compared to either the control or the gamma irradiated *P. chabaudi* infected groups. Similarly, leukocytes (Leuko/µL) were higher in the live *P. chabaudi* infected group in comparison to either the control or the gamma irradiated *P. chabaudi* infected groups. Conversely, the urine pH in the

Table I. Urine parameters in female BWF1 mice infected or non-infected with *P. chabaudi* (live or gamma irradiated).

Parameter	Lupus	Lupus + Live *P. chabaudi*	Lupus + gamma irradiated *P. chabaudi*
Specific gravity	1.010	1.020	1.025
pH	7.3	4.5	5.5
Leukocytes (Leuko/µL)	> 500	< 500	500
Nitrites	Negative	Positive	Positive
Glucose (mg/dL)	800 ± 85	300 ± 32	300 ± 28
Ketones (mg/dL)	30 ± 7	10 ± 4	10 ± 3
Urobilinogen (mg/dL)	Normal	Normal	Normal
Bilirubin	Negative	Positive	Positive
Blood (Ery/µL)	Negative	250	5-10
Haemoglobin (Hb) gm/ml	Negative	250	10

live *P. chabaudi* infected group was lower in comparison to either the control or the gamma irradiated *P. chabaudi* infected groups. Glucose and ketone levels were lower in both the *P. chabaudi* infected groups in comparison to the control group. Nitrites and bilirubin exhibited a similar pattern in both *P. chabaudi* infected groups.

Live P. chabaudi Infection Caused Anaemia in Female BWF1 Lupus Mice

Infection of female lupus mice with 10^6 *P. chabaudi* parasitized erythrocytes had a direct impact on the blood picture and this was largely dependent on the viability of the parasites. Live *P. chabaudi* infection caused severe anaemia, as indicated by the marked decrease in Hb concentration in the blood samples of the live *P. chabaudi*-infected group (Figure 1). On the other hand, the gamma irradiated *P. chabaudi* infected group showed Hb concentrations that were close to the control values.

Live P. chabaudi Infection Decreased Plasma Concentration of CICs in Female BWF1 Mice

Elevated levels of CICs have been implicated in SLE. Plasma concentrations of CICs in the three experimental groups were measured by ELISA (Table II). Although the control BWF1 Lupus mice are known to give positive result for CICs detection in their plasma, experimental infection of female BWF1 mice with live *P. chabaudi* resulted in a negative result for CICs detection in their plasma samples. In the gamma irradiated *P. chabaudi* infected group, however, the result of plasma CICs detection resembled that of the control group with positive CIC detection.

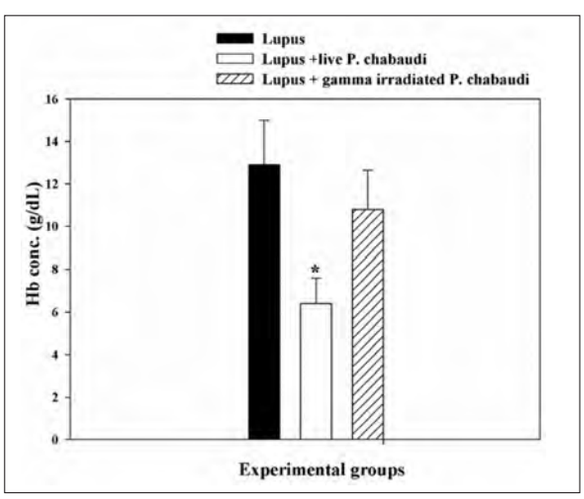

Figure 1. Effect of live or gamma-irradiated *P. chabaudi* infection on Hb concentration in blood of female BWF1 mice. The data are the mean ± SEM for 6 mice per group. *$p < 0.05$ for live *P. chabaudi*-infected BWF1 mice vs. lupus mice.

Table II. Effect of live or gamma irradiated *P. chabaudi* infection on the level of CIC in plasma of BWF1 mice.

Experimental group	CIC
Lupus	Positive
Lupus + Live *P. chabaudi*	Negative
Lupus + gamma irradiated *P. chabaudi*	Positive

Improvement of Kidney Tissue After Live, but not Gamma Irradiated P. chabaudi Infection

When histopathological examination was performed on H/E stained renal tissue sections of lupus mice, the characteristic lupus associated glomerulonephritis was evident (Figure 2). Glomerular inflammation (arrow), necrosis and degeneration were observed and haemorhagia (star) was predominant. Infection of female BWF1 mice with live *P. chabaudi* was accompanied with a clear improvement in these symptoms. Nevertheless, these improvements were not evident in the gamma-irradiated *P. chabaudi* infected group, whose renal tissue sections resembled those from the control group.

Hepatic tissue histological Alterations Due to live P. chabaudi Infection

Since the liver is the target organ for malaria parasites, hepatic changes after *P. chabaudi* infections are of special relevance. The H/E stained liver sections of lupus mice revealed clear architecture and colour while hepatocyte necrosis (star), cholestasis, granulomatous lesions, congested sinusoids, increased lymphocyte infiltration and *P. chabaudi* pigment deposition (arrow) were observed in both *P. chabaudi* infected groups. These symptoms were more severe in the live *P. chabaudi* infected group than in the gamma irradiated *P. chabaudi* infected one (Figure 3).

Increased Interstitial Lymphocytic and Neutrophilic Infiltration in Alveolar Tissue was Associated with Live P. chabaudi Infection

The lung is among the organs affected during the course of human SLE[29]. Interstitial lung

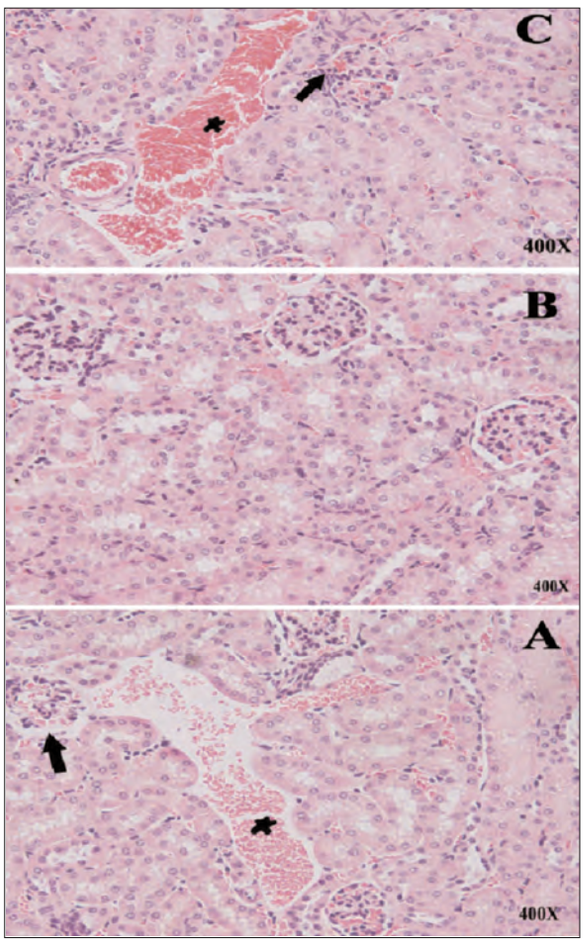

Figure 2. Effect of live or gamma-irradiated *P. chabaudi* infection on kidney histopathology in female BWF1 mice. Hematoxylin-eosin (H/E) staining of kidney of uninfected control ***(C)***, live *P. chabaudi* infected ***(B)***, and gamma irradiated *P. chabaudi* infected ***(A)*** group. The organs were removed at day 14 p.i. Sections of these organs were stained with H/E and analyzed under light microscopy. Arrow indicates glomerulonephritis; Star indicates haemorrhage.

disease (ILD), acute lupus pneumonitis, diffuse alveolar haemorrhage, pulmonary arterial hypertension, acute reversible hypoxia and shrinking lung syndrome (SLS) are known manifestations of human lupus. Figure 4 shows the pathological features in pulmonary tissue of the three investigated groups. The lung tissues of the control mice showed pulmonary haemorrhage, interalveolar septal thickening (star), and interstitial lymphocytic and neutrophilic infiltration (arrow). The group infected with live *P. chabaudi*, on the other hand, showed, besides alveolar wall thickening, increased interstitial lymphocytic and neutrophilic infiltration, while in gamma irradiated *P. chabaudi* infected group, these pathological features were less clear. Similar features, such as normal RBCs, were also observed in the alveolar walls and blood vessels of all the three groups.

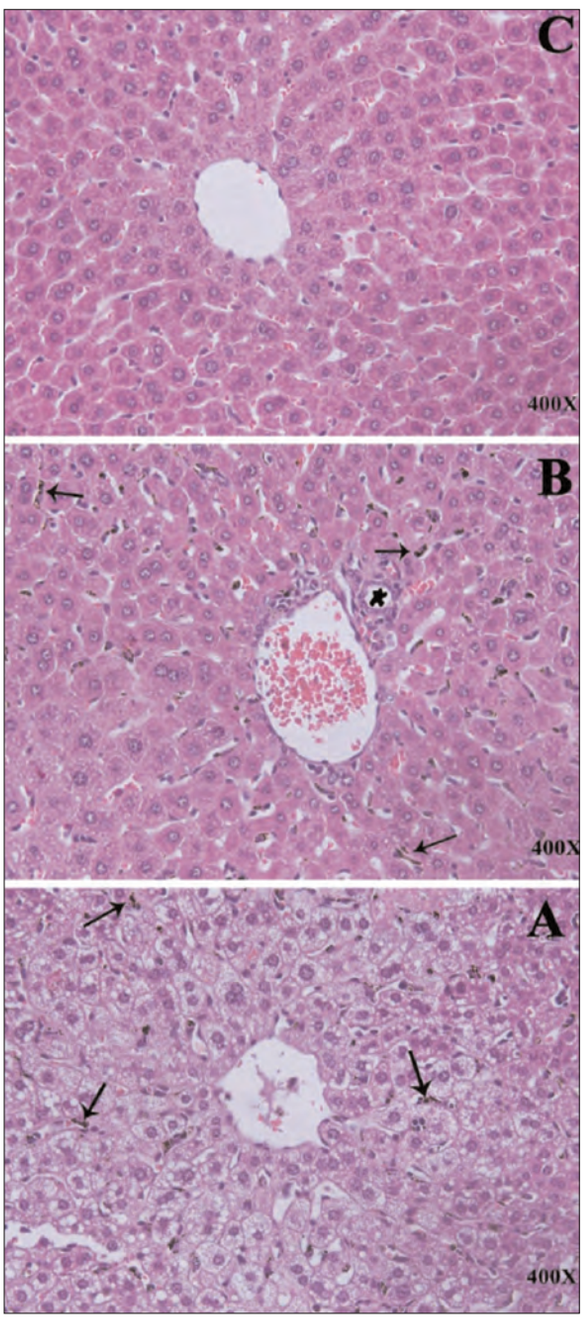

Figure 3. Effect of live or gamma-irradiated *P. chabaudi* infection on liver histopathology in female BWF1 mice. Hematoxylin-eosin (H/E) staining of liver of uninfected control ***(C)***, live *P. chabaudi* infected ***(B)***, and gamma irradiated *P. chabaudi* infected ***(A)*** group. The organs were removed at day 14 p.i. Sections of these organs were stained with H/E and analyzed under light microscopy. Arrows indicates *P. chabaudi* pigment deposition in the liver. Star indicates hepatocytes necrosis.

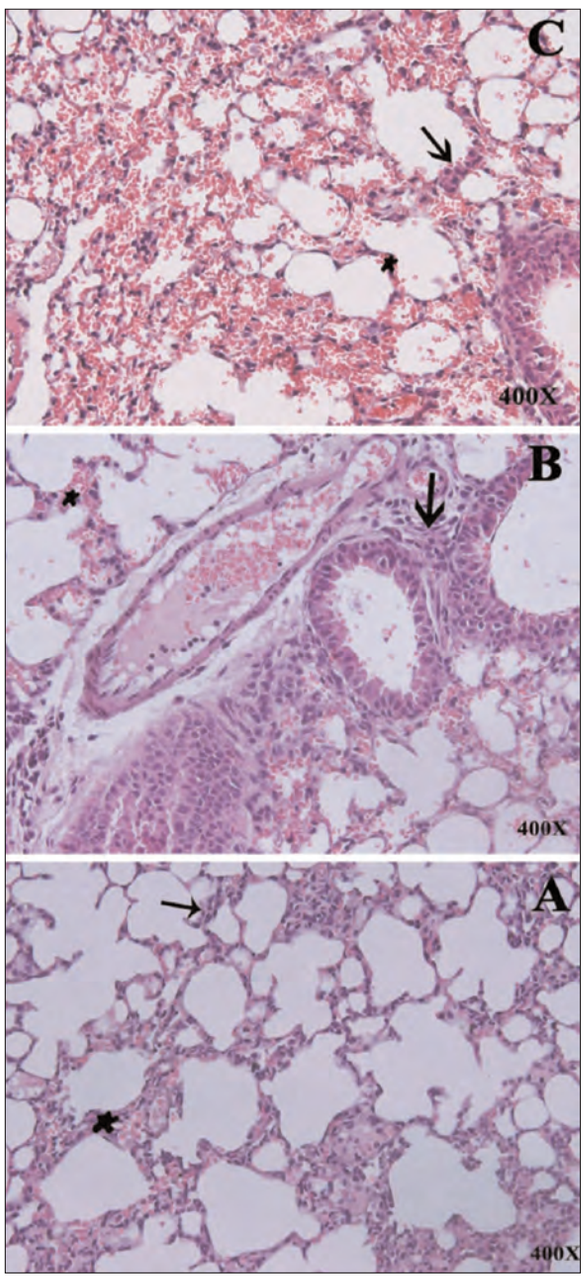

Figure 4. Effect of live or gamma-irradiated *P. chabaudi* infection on lung histopathology in female BWF1 mice. Hematoxylin-eosin (H/E) staining of lung of uninfected control ***(C)***, live *P. chabaudi* infected ***(B)***, and gamma irradiated *P. chabaudi* infected ***(A)*** group. The organs were removed at day 14 p.i. Sections of these organs were stained with H/E and analyzed under light microscopy. Arrow indicates lymphocytic infiltration. Star indicates interalveolar septal thickening.

Pathological Alterations in the Corpus Luteum After P. chabaudi Infection

SLE is a female biased disease so investigating ovarian changes during SLE is interesting. In Figure 5, the ovaries of control mice can be seen to contain an increased number of atretic follicles. Deformed and pyknotic oocytes (arrow) were observed in all groups and an unhealthy corpus luteum (star) was observed in both the *P. chabaudi* infected groups.

Cardiac, Cerebral and Dermatologic Tissue Responses After P. chabaudi Infection

Cardiac involvement during the course of SLE is well documented[30]. In Figure 6, H/E stained cardiac sections from control mice showed the char-

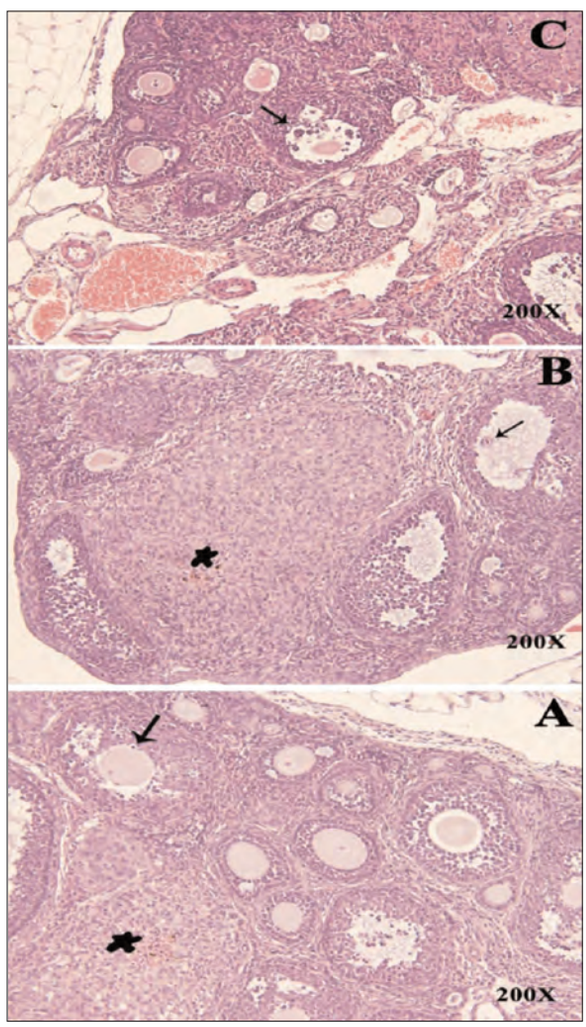

Figure 5. Effect of live or gamma-irradiated *P. chabaudi* infection on ovary histopathology in female BWF1 mice. Hematoxylin-eosin (H/E) staining of ovary of uninfected control ***(C)***, live *P. chabaudi* infected ***(B)***, and gamma irradiated *P. chabaudi* infected ***(A)*** group. The organs were removed at day 14 p.i. Sections of these organs were stained with H/E and analyzed under light microscopy. Arrow indicates deformed oocyte. Star indicates unhealthy corpus luteum.

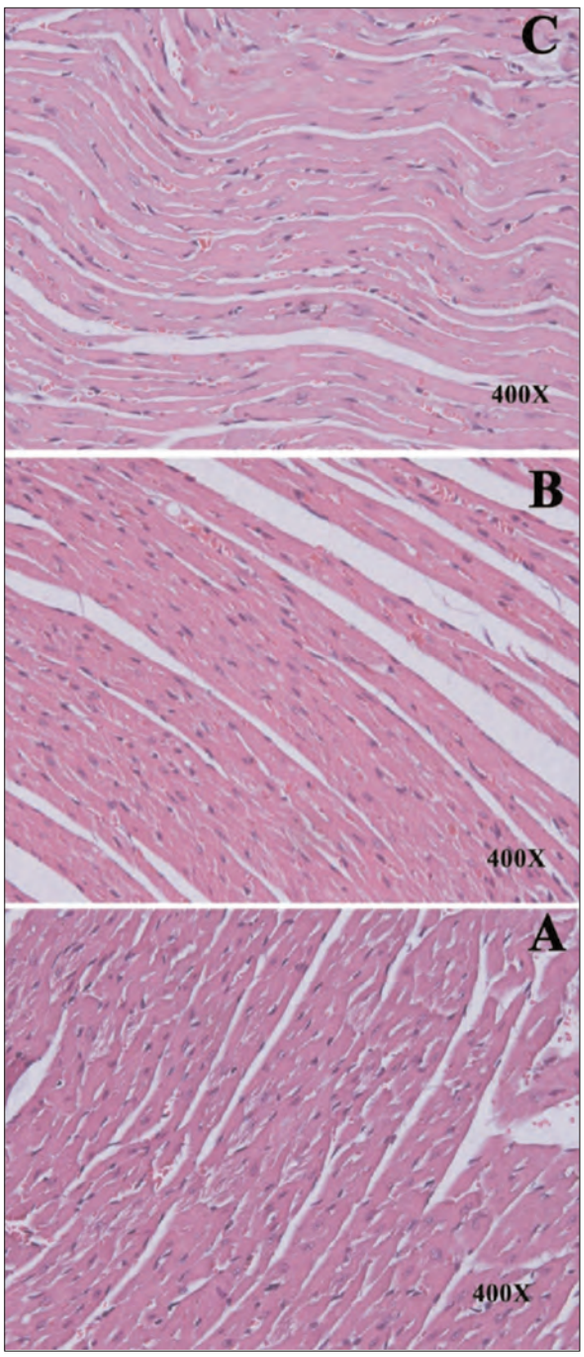

Figure 6. Effect of live or gamma-irradiated *P. chabaudi* infection on cardiac histopathology in female BWF1 mice. Hematoxylin-eosin (H/E) staining of heart of uninfected control ***(C)***, live *P. chabaudi* infected ***(B)***, and gamma irradiated *P. chabaudi* infected ***(A)*** group. The organs were removed at day 14 p.i. Sections of these organs were stained with H/E and analyzed under light microscopy.

acteristic heart muscle tissue structure with uninfected RBCs. H/E stained sections of both *P. chabaudi* infected groups also showed similar features with no sequestration of infected RBCs. In Figure 7, H/E stained brain sections from the three groups were compared. It was observed that the brain tissues of the three mice groups did not show any sign of leukocyte infiltration. Abnormal features, such as haemorrhage, were observed in all groups. Since skin manifestations of SLE are well known in both human and some experimental

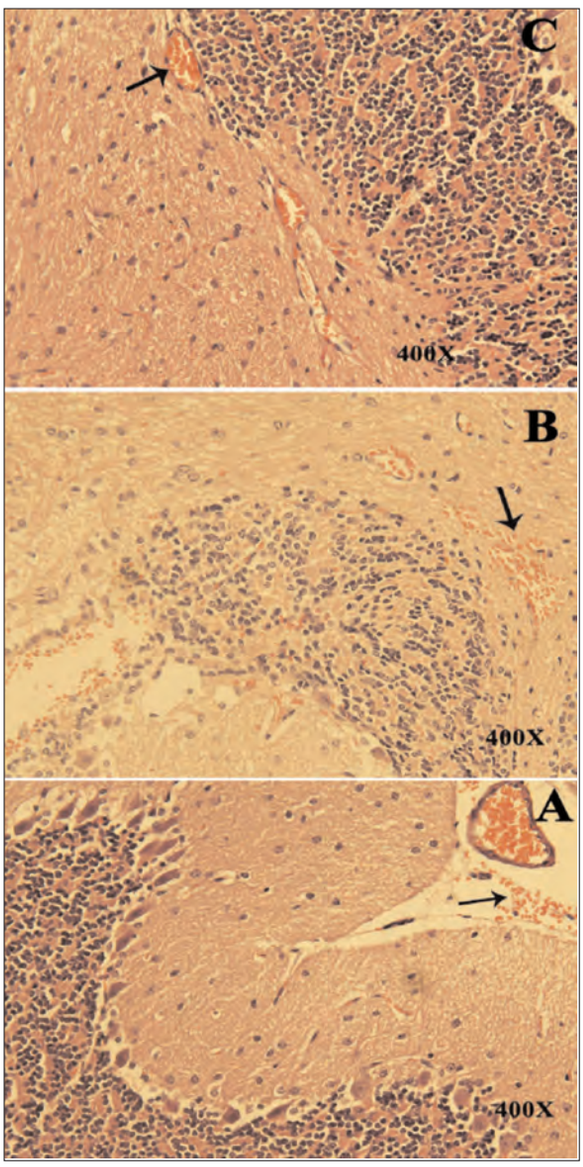

Figure 7. Effect of live or gamma-irradiated *P. chabaudi* infection on brain histopathology in female BWF1 mice. Hematoxylin-eosin (H/E) staining of brain of uninfected control ***(C)***, live *P. chabaudi* infected ***(B)***, and gamma irradiated *P. chabaudi* infected ***(A)*** group. The organs were removed at day 14 p.i. Sections of these organs were stained with H/E and analyzed under light microscopy. Arrow indicates hemorrhage.

SLE models we investigated the possible dermal changes between the three groups. In Figure 8, a comparison between the dermal tissues in the three groups reveals no obvious changes either in the live *P. chabaudi* infected group or in the gamma irradiated *P. chabaudi* infected group in comparison to the control group.

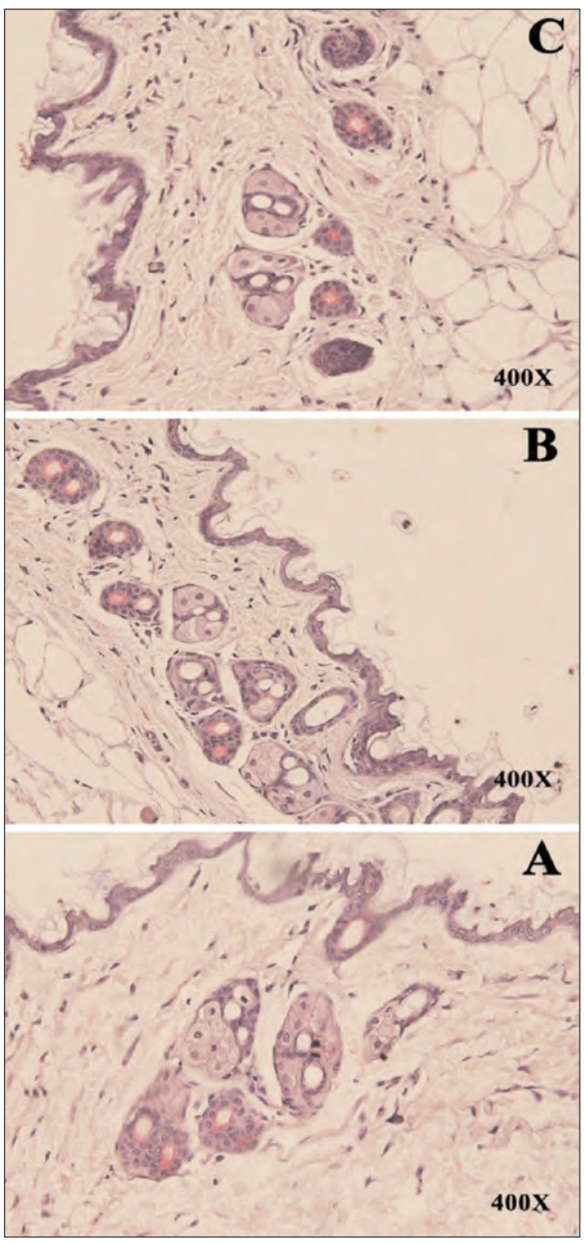

Figure 8. Effect of live or gamma-irradiated *P. chabaudi* infection on skin histopathology in female BWF1 mice. Hematoxylin-eosin (H/E) staining of skin of uninfected control ***(C)***, live *P. chabaudi* infected ***(B)***, and gamma irradiated *P. chabaudi* infected ***(A)*** group. The organs were removed at day 14 p.i. Sections of these organs were stained with H/E and analyzed under light microscopy.

Discussion

The deposition of the immune complex triggers a cascade of events in the inflammatory response that are accompanied by the generation of free radicals, which play a pivotal role in both acute and chronic glomerular injuries in lupus nephritis patients[31]. Detection of lipid oxidation, oxidative DNA damage, and protein oxidation in lupus patients provide strong evidence for the involvement of ROS in this disease[32]. Recently, it has been shown that antroquinonol a pure active compound from *Antrodia camphorata* mycelium inhibits renal inflammation and reduces oxidative stress in a mouse model of renal fibrosis[33]. Therefore, natural antioxidants play central roles in enhancing the immune system through mechanisms dependent on oxidative stress, which seems to play significant roles in many disorders including autoimmune diseases. In this context, we previously demonstrated the beneficial effects of thymoquinone (TQ) against insecticide-induced immunological and histological damages in rat model as well as in induction of growth arrest of multiple myeloma cancer cells and its protective anti-diabetic effects[19,34-37]. Moreover, we provided clear evidence for the effects of other natural antioxidants (camel whey protein and bee propolis) as immune-modulators in accelerating the healing process of diabetic wounds in experimental animal models[23-26,38-40]. Notably, we demonstrated that natural antioxidants isolated from snake and ant venoms enhanced normal lymphocyte functions and exerted antitumor effects in different human and animal cancer cells[20-22,41,42].

Despite the fact that experimental animal models cannot reproduce all the features of human disease, they do contribute to the understanding of some phenomena in human situations. Animal studies have also been useful in understanding the pathogenetic basis of various disease conditions, thereby informing prophylactic or therapeutic interventions. Female BWF1 mice spontaneously develop a severe autoimmune disease that closely resembles human SLE[43]. In the current study, live *P. chabaudi* infection had a direct impact on the urine profile of female BWF1 lupus mice, with the most obvious change being that of haemoglobin level. The highly elevated level of haemoglobin in urine samples of live *P. chabaudi* infected BWF1 mice was associated with severe anaemia in plasma samples of this group of

mice. This is in accordance with the results of Evans et al[11], who reported severe *P. chabaudi* related anaemia in rodent models and concluded that this is a result of accelerated clearance of uninfected erythrocytes. In a previous study we demonstrated a decrease in RBC count in plasma samples after live *P. chabaudi* infection of this mouse strain[44]. Likely, here, the erythrocytic concentration in urine samples of live *P. chabaudi* infected BWF1 mice was higher than that of either the control or gamma irradiated P. chabaudi infected groups. The data presented in this study showing a dramatic decrease in Hb concentration after infection of BWF1 mice with live *P. chabaudi*, when taken together with our previous data, goes further to substantiate the assertion that the Hb loss in the plasma of this SLE mice model may be related to increased RBC leakage from plasma to urine.

Deposition of immune complexes (ICs) is considered to be an important pathogenic mechanism in SLE[45]. Granular deposits of immunoglobulins and complement components, which are presumptive evidence of ICs, are frequently found in the renal glomeruli, skin, choroid plexus and lungs of patients with SLE. Also, CICs have been detected in over half of SLE patients[46]. These studies have, in general, demonstrated a correlation between immune complex levels and clinical disease activity[47]. On the other hand, a decrease in CICs during malaria infection has been observed by many research groups[17]. In the present study, control BWF1 lupus mice exhibited increased level of CICs in plasma but infection with live *P. chabaudi* diminished the level of CICs in plasma, and this could be a possible mechanism for the amelioration of lupus in female BWF1 mice. It seems that the immune system directs its machinery towards producing anti-malarial antibodies which, in the absence of live malaria, serve to reset its auto reactivity, and this is the reason why CICs appeared in the gamma irradiated *P. chabaudi* infected group in an almost identical fashion to the control group.

Renal involvement is the major cause of morbidity and mortality in both human and murine SLE[48]. This study has shown that infection with live *P. chabaudi* can serve to ameliorate the histopathological signs of lupus nephritis in BWF1 lupic mice while gamma-irradiated *P. chabaudi* did not have the same positive effect. In comparison to control uninfected mice, the observed improvement in renal tissue sections after infection of BWF1 mice with live *P. chabaudi* is consistent with other studies[13]. As observed in our previous study, the decreased oxidative stress and apoptosis in renal tissue after infection of this strain with live *P. chabaudi* may represent the mechanism through which the live *P. chabaudi* infection is able to ameliorate the histopathological signs of lupus in renal tissue sections[44]. Variation in *P. chabaudi* pigment deposition has been observed in some of the organs of this mice model. The high *P. chabaudi* pigmentation in the liver of infected BWF1 mice is consistent with other studies[49]. Furthermore, the extent of *P. chabaudi* pigment deposition in the liver may help to explain the hepatic dysfunction during *P. chabaudi* infection that has been reported in this mice strain[44].

Central nervous system (CNS) involvement is frequently observed in patients with SLE[50] and, recently, intracranial and sub-arachnoid haemorrhage has been reported in human SLE[51]. Brain haemorrhages are a well-known sign of cerebral malaria[52] and, here, CNS involvement in BWF1 mice is manifested by the persistent presence of haemorrhage in both *P. chabaudi* infected groups. These findings are in agreement with those of Cangoli et al[53] who reported cerebral pathologies such as oedema, haemorrhage, and central thrombosis in Neuropsychiatric lupus (NPSLE). SLE is a female biased disease and has been observed to have obvious effects on ovarian structure and the ovarian histopathological signs of lupus seen in the current study are consistent with other reports[54].

Conclusions

Our findings regarding gamma-irradiated *P. chabaudi* infection are interesting because the high dose of gamma radiation used in this study was sufficient to kill the parasite, resulting in a group that resembled the lupus non-infected group in many aspects. Experimentation with different radiation doses offers the potential to arrive at a clinical dose that has the desired lupus ameliorating effect without negative effects of malaria.

Overall, although both malaria infection and SLE exhibit their own pathological changes in many organs, the concurrent occurrence of both has different outcomes that are to some extent interesting, with infection-associated amelioration in some of the pathological features of SLE.

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Conflict of Interest

All authors have read and agreed the contents of the manuscript and have approved its submission. The authors declare no conflicts of interest and state that the manuscript has not been published or submitted elsewhere, that the work complies with the ethical policies of the journal and that the work has been conducted according to internationally accepted ethical standards after the relevant ethical review.

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