Pathological changes of immunized mice with *Trichophyton mentagrophyte* lyophilized antigen

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Summary

The study was carried to investigate the pathological effect of lyophilized antigen of *Trichophyton mentagrophytes* in mice. Fifty mice were divided into three groups. The first group 20 mice were immunized subcutaneous (s/c) with 0.5 ml of *T.mentagrophyte* antigen 20 µgm/ml, by two doses, 14 day intervals, between them. The second group 20 mice and third group 10 mice considered as positive and negative control groups respectively. After 30 days post immunization first and second groups were challenged intradermal I/d. with 0.1 ml of fungal suspension contain (1×10^7 ml) of viable virulence *T.mentagrophyte* while the third group injected intraperitoneally I/P. with 0.5 ml of sterile phosphate buffer saline. All mice of the first and second groups were sacrificed at (5, 14, 30 and 60) days post challenge for gross and histopathological examination. Histopathologically the second group showed epidermal hyperkeratosis with appearance of crust lesions seen with abscess formation especially in early stage of lesion, while the main feature of advance cases were characterized by folliculitis with fungal hyphae invasion in all epidermal and dermal layers together with eosinophilic infiltration. Mild pathological changes were seen in the 1st immunized group characterized by infiltration of mononuclear cells mainly macrophages in dermal connective tissue with dense proliferation of collagenous fibers , appearance of young fibroblasts together with cellular hypodermal infiltration of eosinophil no evidence of clear follicular lesions were seen. Lyophilized antigen of *T.mentagrophyte* can be considered as an effective immunogen for protecting mice against *T.mentagrophyte* infection and it is synchronized with its dose.

Keywords: *T.mentagrophyte* lyophilized, mice, pathology.

Introduction

Trichophyton mentagrophytes is a group of the most common zoonotic worldwide fungi generally grow only in keratinized tissues such a hair, nails and outer layers of skin, The fungus adheres, proliferates usually digging into the epidermis and entering through hair follicles causing an infection that may vary from mild to very intense (1 and 2), these fungi produce keratinases, proteolytic enzymes that enable them to hydrolyze keratin (3) where *T.mentagrophytes* contacts to living cells or areas of inflammation but mucus membranes are not affected (4).

The skin lesions are usually characterized by inflammation that is most severe at the edges, with erythema, scaling and occasionally blister formation, central clearing is sometimes seen particularly in tinea corporis, and this results in the formation of a classic ringworm lesion (5 - 7). The lyophilized vaccine used to increase the resistance of vaccinated animals to experimental challenge infection. The lyophilized vaccine is designed to protect (i.e., increase resistance to infection) bearing animals against *T.mentagrophytes* infection and there by decrease zoonotic infection exposure to their human attendants. This broader lyophilized antigenic base and the antigenic cross protection between dermatophyte genera and species (8). The aims of this study was to investigate the pathological effected of lyophilized antigen of tem entire aphids a mice.

Materials and Methods

The isolate of *T.mentagrophyte* was obtained from the Microbiology department in the College of Veterinary Medicine/Baghdad University; which was confirmed by the macroscopical, microscopical and biochemical tests which maintained in dextrose agar for preparation of lyophilized antigens according to (8) and the concentration of protein was measured by Biurete method. A total number of 50 mice from both sexes with ages ranged

from (4–8) weeks old which were obtained from the (National Center of Researches and Drugs Monitor in Baghdad), then divided into three groups. The 1st group 20 mice immunized by *T.mentagrophyte* antigen, 2nd group 20 mice and third group 10 mice considered as positive and negative control groups respectively.

Whole Killed Lyophilized Antigen was prepared from sediment of centrifuged virulent *T.mentagrophyte* according to (8), after that it was sonicated above antigen and kept it under 4˚C until it used in a skin test according to Al-Haddad, (9). The first group was immunized by 0.5 ml subcutaneously each ml contanin 10 µgm/ml of *T.mentagrophyte* antigen, the second group considered as positive control while the third group gave 0.5 ml of phosphate buffer saline as control negative. After two weeks the animals of the 1st group gave same dose of immunization as a booster dose first and second groups were challenge at day 30 at dose 0.1 ml of fungal suspension contain 1×10^7 cell/ml of virulence *T.mentagrophyte*, between (5, 14, 30 and 60) days. All animals were scarified for gross and histopathological examination of skin, about $1cm^3$ was taken and fixed in 10% formalin saline for histopathology section which was dose according to (10).

Results and Discussion

The results of skin test in the present study appeared at 24 and 48 hrs. post inoculation that the mean result values of skin thickness and duration in mice immunized with *T.mentagrophyte* antigens against sonicated lyophilized antigen (SLA) were (2.89 ± 0.06) mm after 24hrs. and (2.80 ± 0.04) mm after 48hrs. post-inoculation while at 72hrs. (2.43 ± 0.04) mm these values were significantly increased than those of control group (P≤0.05) which were, (2.26± 0. 02) mm after 24hrs. and decreased to (2.24 ± 0.02) mm after 48hrs. and (2.25 ± 0.02)mm at72hrs (Table,1).

Table, 1: The mean values of skin thickness in immunized mice with *T.mentagrophyte* Ags (1st group) and control(2nd group) at 24,48 and 72hrs. After immunization.

Hours Groups	24 hours	48 hours	72 hours
Immunized with *T.mentagrophyte Ag.*	Aa 2.89 ± 0.06	Ab 2.80 ± 0.04	Ac 2.43 ±0.04
Control positive	Ba 2.26± 0. 02	Bc 2.24 ± 0.02	Ca 2.25 ± 0.02

The development of DTH against dermatophyte antigens has been documented in humans and some animal species. Cutaneous reactivity to trichophytin antigen extracted from fungal cultures, has been described in dermatophytosis patients, even in those with severe infections (11) Antigens derived from trichophyton exhibit unusual immunologic properties based on their ability to induce distinct skin test reactions in different individuals (12). According to above observation it was found that the cell mediated response which is characterized by induration of skin at the injection of food pad which is maximum at 24-48 hrs. in immunized animals and similar observation was seen by (12) whom investigated DTH to trichophyton antigens which associated with maximum at 24-48 hrs. and this suggested that trichophyton infection results in the development of distinct immune responses in which the ultimate effector cell is the activated macrophage, activation of macrophages is mediated by gamma interferon-(IFN-γ)-producing (Th1) CD4+T- lymphocytes. These T cells recognize and respond to foreign antigen presented in the form of peptide (T-cell epitopes) complex molecules expressed on the surface of antigen-presenting cells (APCs) including potentiation of their Ag presenting capacity migration of APCs is probable initiated by different cytokines produced by keratinocyte however the type of cytokines and mechanisms involved have not been determined there create favorable conditions in skin for specific immunological activity as Langerhans' cells have poor phagocytic capacity macrophages may have a role in the uptake and degradation of the fungi into smaller fragments. It has also

been proposed that keratinocytes, which are able to phagocytize and degrade antigens, may process antigens that can be transferred to Langerhans' cells and directly presented to T cells. They are in a unique position to capture exogenous antigen upon exposure to antigens, they migrate as veiled cells to lymph nodes draining the skin, where the antigens are presented to T-lymphocytes in a major histocompatibility complex (MHC) class II-restricted fashion (13).

At 72 hrs. the result showed that the mean thickness was lessor than 24 – 48 hrs., and this observation was in consistence to recent study by (14) which explained this decline in median thickness may be possible indicate that *T. mentagrophytes* antigens induced release of suppressor cells and/or factor, which inhibited development of cellular immune response suppression of the hypersensitivity to dermatophyte Ags could be an important mechanisms for resolving cutaneous *T.mentogrophytes* infection and limiting tissue damage (15 and 16).

The cellular branch of the immune system is crucial for protective immunity against dermatophyte infections, vaccination stimulated a cellular immune response, as assessed by a skin test and aleukocyte migration inhibition test (17). Although several studies (18) showed that infection with dermatophyte presented two patterns of cellular immune response that an acute inflammatory response correlated with positive DTH skin test to Trichophyton and clearing of infection.

The main clinical signs in the 2nd group observed during 30-60 days post-inoculation with heavy fungal isolation from external organ (skin) was characterized by ruffled haircoat, scaly ovoid type lesions with crusty edge and patch of hair loss mostly seen on the back and itching was reported these results may indicate that the animal exposed to an infective dose of highly virulent *T.mentagrophyte* while in the immunized group (1st group) there is no fungal isolation as in (Table, 2).

Table, 2: Show fungal isolation in immunized and non-immunized mice with *T.mentagrophyte* Ags (1st group) and control(2nd group) after 5 ,14, 30,and 60 day post challenge.

Days Groups	No.	Day 5	Day 14	Day 30	Day 60
Immunized with *T.mentagrophyte*	**20**	**–**	**–**	**–**	**–**
Control positive	**20**	**_**	**+**	**++**	**++++**

- negative growth, + mild growth ++ moderate growth +++ heavy growth ++++ very heavy growth.

In regard to fungal isolation our present observation is similar to that noticed by (19) who explained that most rodents infected with *T.mentogrophytes* are asymptomatic or have few clinical signs, in mice, partial or complete areas of alopecia, erythema, scale, and scab may be seen, often on the tails (20) because the *T.mentogrophytes* have the ability to invade keratinized layer of the skin mainly the stratum corneum and produce proteolytic enzymes that enable them to hydrolyze keratin to induce active infection caused by this organisms (3 and 21).

The first microscopic observation in the skin at 5 day was focal epidermal hyperkeratosis with moderate polymorphonuclear cells infiltration in sub epidermal and upper dermal with evidence of abscess formation together with appearance of slight keratohyaline layer covered the stratum cornium (Fig. 1) .In another section there was evidence of follicular invasion by neutrophilic infiltration around the hair follicle (Fig. 2) together with focal of epidermal ulceration contain necrotic debris (Fig. 3).

At day14 post challenge cutaneous lesion revealed epidermal hyperkeratosis and acanthosis (Fig. 4) in addition to present balloonic degeneration of some prickle cell accompanied with formation clumps of pyknotic nuclei nearly adjacent to stratum cornium (Fig. 5) with sever dilation and destruction of some hair follicle (Fig. 6) as well as dermal odema which characterized by fragmentation of dermal collagen fiber at 30 days post challenge together with mononuclear cells infiltration around some degenerated hair follicle (Fig. 7), in another section follicular destruction appeared with degenerated keratin that replace by compact mass of red purplish microfilament hyphae mainly seen in the

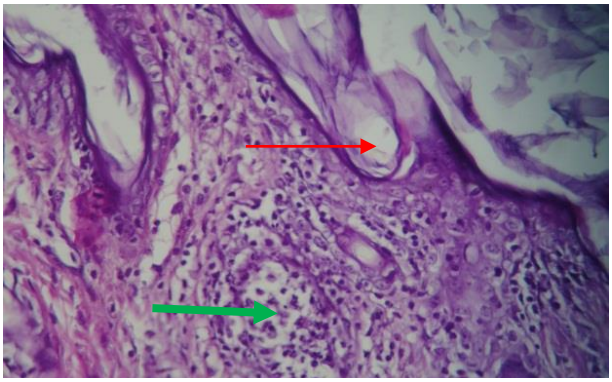
portal end and basement membrane of hair follicle (Fig. 8) as well as fragmentation and separation of dermal collagen with eosinophilic infiltration and congested blood vessels (perivascular dermititis) (Fig. 9 a and b).

At day 60 post challenge the main characteristic pathological changes was dense fungal growth with hyphae that appeared red with PAS stain spreading in both dermal and epidermal involving hair follicle (Fig. 10). The immunized group at 5 day was characterized by no clear pathological changes post challenge, except fragment separation of dermal collagen fiber with edema and congestion of blood vessels with scattered infiltrate of young fibroblast seen mainly at 14 day (Fig. 11) as well as polymorph nuclear cells around some degenerated follicles. At 30 day the lesion characterized by slight acanthosis with fibrotic and granulated tissue (evidence of dermal healing) associated with intact hair follicle (Fig. 12 and 13).

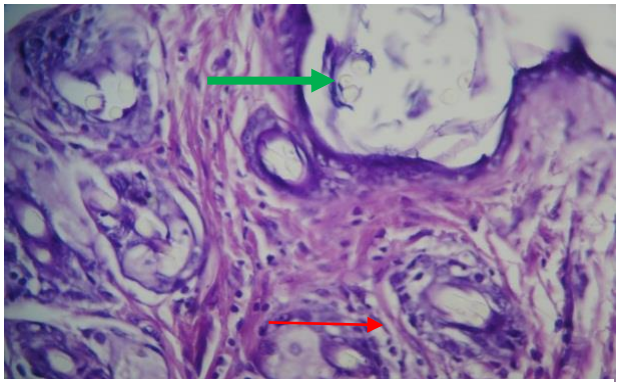
At day 60 showed massive mononuclear cells infiltration in dermis and hypodermis (fatty dermis) with proliferation of collagen fiber in the upper dermis together with vascular dermatitis (Fig. 14) in another section there was the epidermal acanthosis accompanied with intracellular odema together with vascular dermatitis (Fig. 15) in addition to present follicular plugging with slight perivascular dermatitis (Fig. 16) also the result reveals intense proliferation of mononuclear cells in dermal and hypodermal tissue with proliferation of hair follicle and sebaceous gland (Fig. 17), as well as dilation and congestion of blood vessels. There is no clear characteristic change in the epidermis.

The histopathology of murine dermatophytosis showed presence of cutaneous abscess and ulceration to primary infection with *T.mentogrophytes* during 5 days post challenge which closely compaired with description of primary irritant dermatitis (22 and 23). The presence of these abscesses could be a consequence of the fungal components over the complement system, once it has been reported that *T. mentagrophytes* activates this system generating anaphylotoxin C5a, even in non-immune animals, through the alternate via (24). Many of these infected individuals have no cell-mediated immunity against *Trichophyton* antigens and do not develop DTH evaluated through the intradermic test with trichophyton. It has also been suggested in these cases that polymorph nuclear cells migrate to the area of follicle rupture after complement activation and C5a generation besides C5a, soluble factors released by keratinocytes, including IL8, have also been involved in this process (25). The necrotic feature in the upper dermis which may be initiated by production of toxic product by this fungi (26 and 27). A similar histopathological picture is observed in guinea pigs skin when skin sensitizing hapten (DNCB) when toxic concentration is applied to the skin of non-sensitized animals (22 and 26), the area of sever epidermal necrosis are invaded by neutrophils (28). The role of neutrophils in the defense mechanisms against dermatophytes is not totally clear. It has been demonstrated in experimental models that neutrophil infiltration occurs before the peak of infection (29) and these are capable of inhibiting fungal multiplication, even in the absence of immune response (30). Therefore, the presence of neutrophils during primary *T.mentogrophytes* infection (day 5) could also be attributed to early tissue damage caused by expression of contact hypersensitivity (22). Because neither granulocytes nor monocytes were observed in physical contact with hyphae in lesion biopsies, the elimination of the fungi may be mediated by soluble fungi static serum mediators, as postulated by (31). Contact sensitivity would damage the epithelial barrier causing the release of fungi static or fungicidal factors (from serum or cells), contact sensitivity is thought to be mediated by the inter action of peripheral T-lymphocyte with soluble foreign antigens which diffused into viable tissues (32). This mechanism could also provide a rapid anamnestic recognition of a microbial invasion of the keratinized layers of the skin (33-35). Authors (H) was demonstrated that in immune animals, as well as non-immune, the time required for lesions to resolve was longer when leukopeny was induced concomitantly with inflammation. The delayed cure was more noticeable in non-

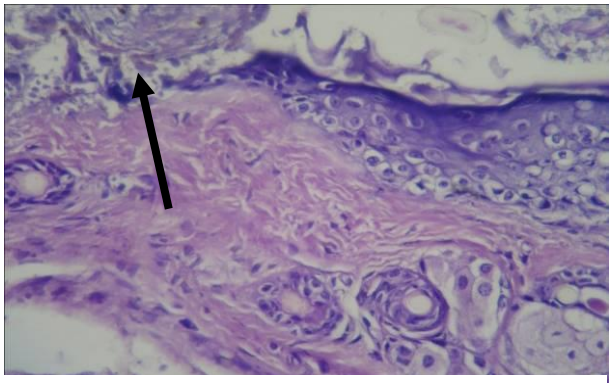
immune animals. At day14 and 30 post challenge the amount of mononuclear cells was larger than observed at day 5 mainly in immunized groups, proliferation of vessels and increased interstitial collagen fiber together with eosinophil infiltration. In general, the most lesions exhibited hyalinized collagen and dense mononuclear cells that concentrated in upper dermis and hypodermis these may correspond to the memory cells described by (36 and 37) and may be responsible for facilitating the secondary response mechanism as inflammatory cell infiltrates appeared faster than on primary immunity. Other investigator (38) found that when mice infected with dermatophyte, increase cell proliferation suggest that the changes could be initiated in the absence of an effective T-cell mediated immunity. According to our observation in mice it found that mononuclear cells secreting cytokines which attract other effector cells involving plasma cell and lymphocyte together with fibroblats proliferation.



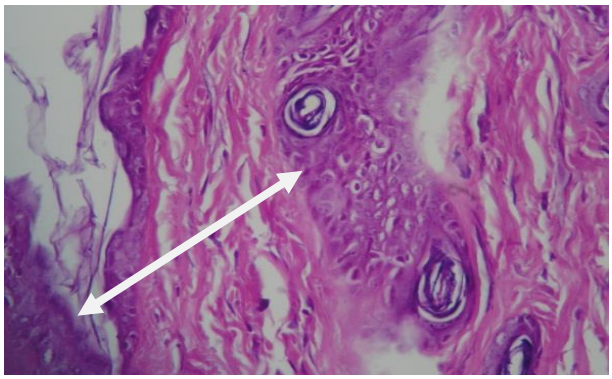
Figure,1: Section in the skin of infected non-immunized animal at day 5 post challenge showed slight keratohyalin layer covered stratum cornium → with neutrophil producing abscess in the upper dermis → (H&E stain400X).



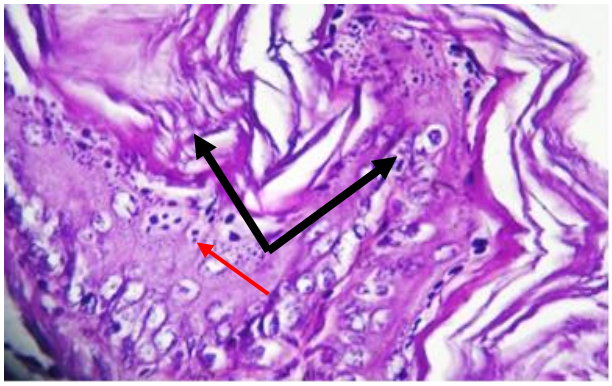
Fig,2: Section in the skin of infected non-immunized animal at day 5 post challenge showed neutrophil infiltrate around hair follicle in the dermis → with keratin debris seen in the follicular opening → (H&E stain 400X).



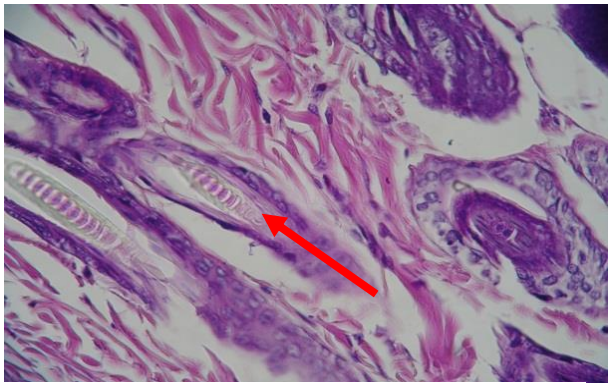
Figure,3: Section in the skin of infected non-immunized infected animal at day 5 post challenge showed focal epidermal ulceration (H&E stain 400X).



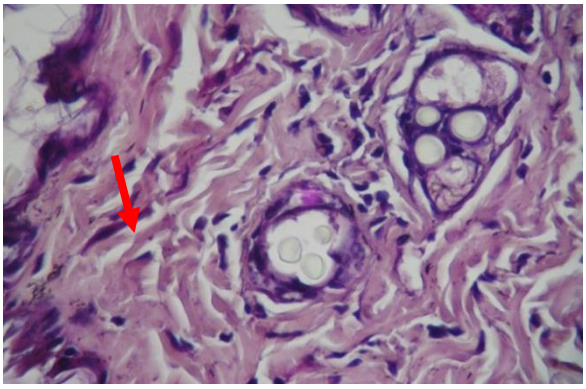
Figure,4: Section in the skin of infected non-immunized animal at day 14 post challenge showed epidermal hyperkeratosis and acanthosis (H&E stain 400X).



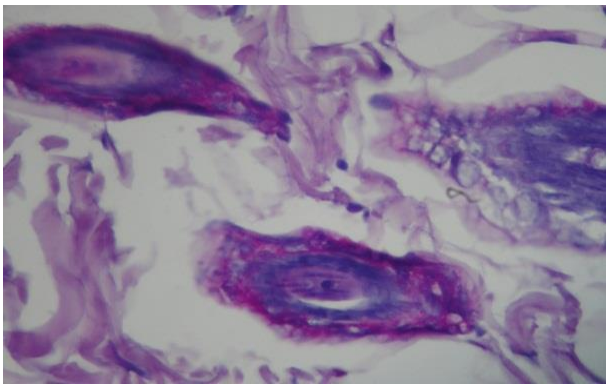
Figure,5: Section in the skin of infected non-immunized animal at day 14-post challenge showed epidermal hyperkeratosis and acanthosis → In addition to present balloonic degeneration of some prickle cell accompanied with formation clumps of pyknotic nuclei → (H&E stain 400X).



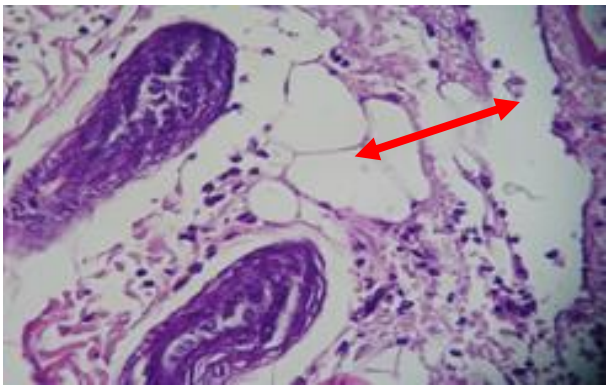
Figure,6: Section in the skin of infected non-immunized animal at day 30 post challenge showed sever dilation and degeneration of hair follicles (H&E stain 400X).



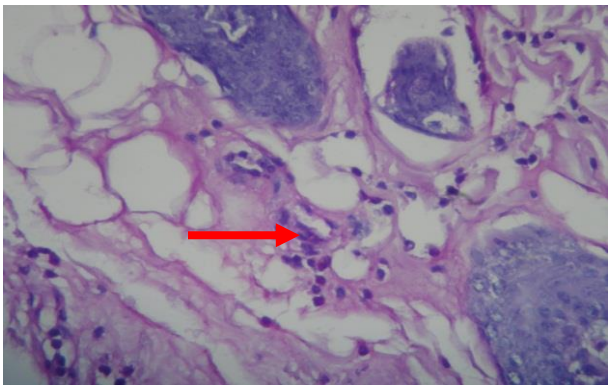
Figure, 7: Section in the skin of infected non-immunized animal at day 30 post challenge showed mononuclear cells infiltration around degenerated hair follicle (H&E stain 400X).



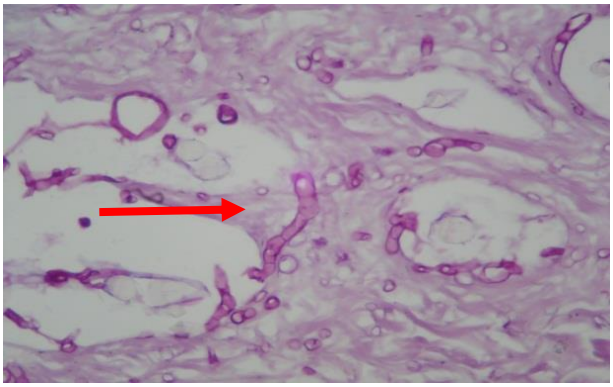
Figure, 8: Section in the skin of infected non-immunized animal at day 30post challenge show hair follicle invasion with red purplish microfilament hyphae with dermal edema (PAS stain 400X).



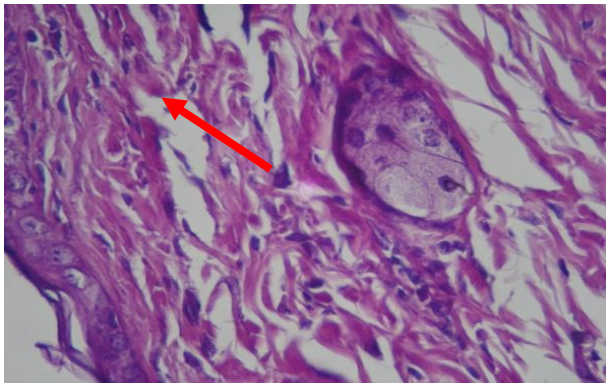
Figure, 9a: Histological section in the skin of infected non- immunized animal at day 30 post challenge showed hypodermal odema with eosinophilic infiltration and congested blood vessel (H&E stain 400X).



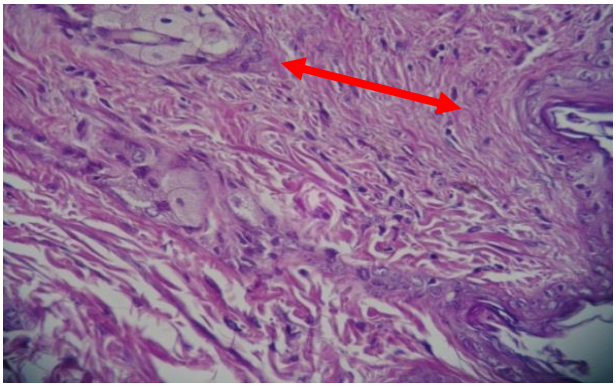
Figure, 9b: section in the skin of non- immunized animal at day 30 post challenge showed eosinophilic infiltration in hypodermis with appearance of some destructed follicle (PAS stain 400X).



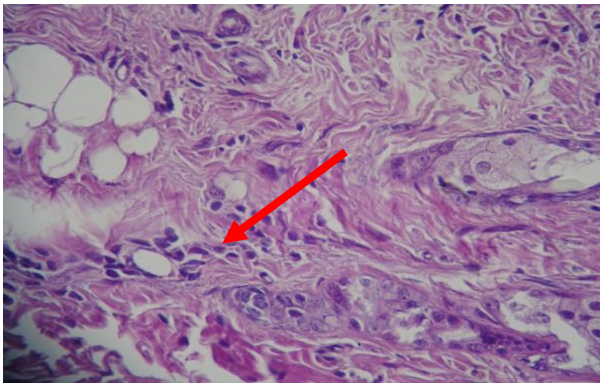
Figure, 10: Section in the skin of infected non-immunized animal at day 60 post challenge showed dense fungal growth with hyphae that stained red with PAS stain spreading in both dermal and epidermal involving hair follicle (PAS stain400X).



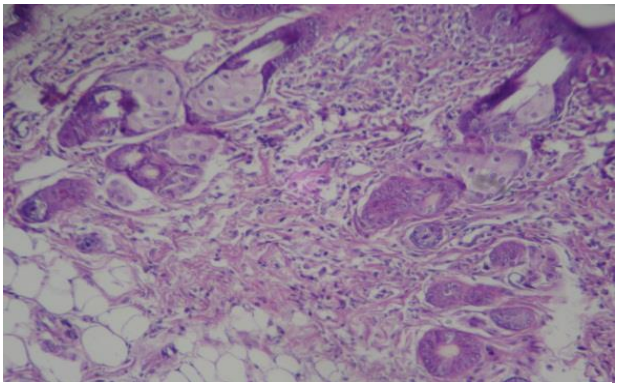
Figure, 11: Section in the skin of immunized animal at day 14 post challenge showed proliferation of dermal collagen fiber with appearance of young fibroblast (H&E stain 400X).



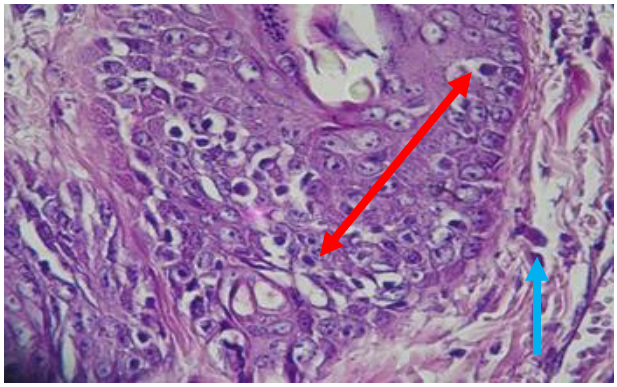
Figure,12: Section in skin of immunized animal at day 30 post challenge showed slight acanthosis with fibrotic and granulated tissue(dermal healing)with intact hair follicle (H&E Stain400X).



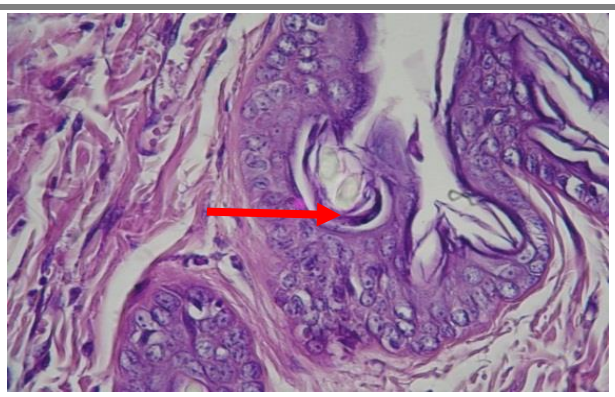
Figure,13: Section in skin of immunized animal at day 30 post challenge showed fibrotic and granulated tissue with moderate MNCs infiltration (H&E Stain400X).



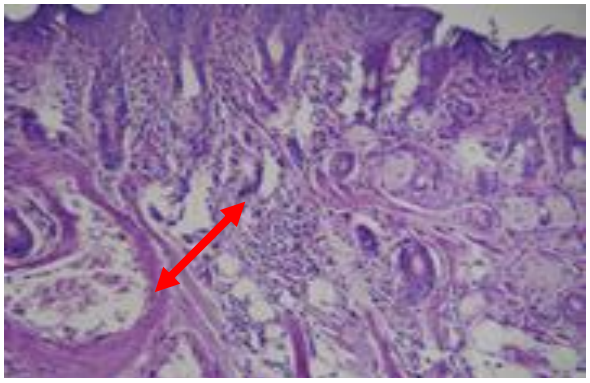
Figure, 14: Section in skin of immunized animal at day 60 post challenge showed mononuclear cells infiltration in dermis and hypodermis with proliferation of collagen fiber in the upper dermis together with vascular dermatitis (H&E Stain 400X).



Figure, 15: section in skin of immunized animal at day 60 post challenge showed intense epidermal acanthosis ↔ accompanied with intracellular odema → together with vascular dermatitis (H&E Stain 400X). .



Figure,16. Section in skin of immunized animal at day 60 post challenge showed follicular plugging with slight perivascular dermatitis (H&E Stain400X).



Figure, 17: Section in skin of immunized animal at 60 day post challenge show reveals intense proliferation of MNCs in dermal and hypodermal tissue with proliferation of hair follicle and sebaceous gland as well as dilation and congestion of blood vessels (H&E Stain 400X).

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التغيرات المرضية في الفئران الممنعة بمستضد الفطرالشعري المجفد*Trichophyton mentagrophytes*

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الخلاصة

اجري البحث لدراسة التأثيرات المرضية لمستضد *T. mentagrophyte* المجفد في الفئران وقد تم استخدام 50 فأر قسمت الى ثلاث مجاميع. المجموعة الاولى(20) فأرمنعت مرتين ب 0.5 مل تحت الجلد من مستضد الشعروية الحاوي على20 مايكروغرام/ مل وبفاصل زمني مقداره اسبوعين بين الجرعتين. المجموعتين الثانية(20) والثالثة (10) فأراعتبرتا مجموعتي سيطرة موجبة وسالبة على التوالي. بعد30 يوم من التمنيع حقنت المجموعة الاولى والثانية بجرعةالتحدي والبالغة 0.1 مل في الادمة من العالق الفطري الحاوي على 1× 10^{7} من فطر *T.mentagrophytes* الضاري. اما المجموعة الثالثة حقنت ب 0.5 مل بمنطقة الخلب من المحلول الملحي المتعادل. جميع حيوانات المجموعتين الاولى والثانية قتلت في الايام (30,14,5 و60) بعد جرعة التحدي للتعرف على التغيرات العيانية والمجهرية. أظهر الفحص المرضي النسيجي في المجموعة الثانية فرط التقرن في منطقة البشرة مع ظهور القشرة وملاحظة تكوين خراج خاصة في المراحل الاولية من ظهور الافة،في حين ان الصفة الرئيسية التي تتميز بها الآفة في الحالات المتقدمة التهاب الجريبة مع غزو الخيوط الفطرية لطبقتي البشرة و الادمة معا مصحوبة بارتشاح الحمضات . اما التغيرات المرضية في المجموعة الاولى الممنعة كانت معتدلة تمثلت بأرتشاح الخلايا وحيدة النواة ولاسيما البلاعم الكبيرة في الادمة مع زيادة الألياف الكولاجينية بكثافة و ظهور الخلايا الليفية الناضجة فضلا عن ارتشاح الحمضات في منطقة اللحمة كذلك لا يوجد دليل على حدوث الآفات الجرابية. يمكن ان يعد مستضد الشعروية مستضد فعال لحماية الفئران من الاصابة بالفطريات الشعروية وله تأثير تناغمي مع الجرعة المعطاة.

الكلمات المفتاحية: المستضد الفطرالشعري المجفد, الفئران ,التغيرات المرضية.