

Scar Sarcoidosis can be an Expression of the Isomorphic Response of Koebner against the Scar

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ABSTRACT. Two cases of scar sarcoidosis are presented with a proposed new insight into its pathomechanism. This type of sarcoidosis is well known to reflect the clinical and laboratory activities of sarcoidosis. The clinical observation of scar sarcoidosis was reminiscent of expression of the isomorphic response of Koebner in sarcoidosis. The generally accepted findings of scars are the presence of inflammatory cells and substances including fibroblasts, histiocytes, lymphocytes, mast cells and their released cytokines, lymphokines, enzymes, etc.

Some locally activated unknown factors such as interferon- α may activate and attract sarcoidosis into scar tissues. Certain common substances in scars and also in the Kveim antigen should be explored in sarcoidosis.

Key words: sarcoidosis — isomorphic response — Koebner phenomenon — scar — foreign body

Sarcoidosis is a chronic, non-infectious, epithelioid cell granulomatous disease of unknown etiology.¹⁾ Scar sarcoidosis and a positive Kveim reaction are recognized to be signs of active systemic activity.¹⁾

The pathomechanism of the cutaneous changes in sarcoidosis remains unclarified. Although silica or silicate-compounds can often be found within granulomatous lesions of scar sarcoidosis, there are also cases having no silicate materials.²⁻⁴⁾ Some scar sarcoidosis can also appear on the moxa scars, burn scars or infectious scars. On the other hand, specific lesions of sarcoidosis are reported to localize linearly along the scratch lines or on the area pressed by an eyeglass-pad. Some components within scars or traumatic lesions may have unknown causative factors for sarcoidosis.

Two cases of scar sarcoidosis are described below.

CASE REPORT

Case 1. 63-year-old house-wife.

The patient was operated, because of right ovarian cyst at the age of 34 years, and also of cholecystitis at the age of 58 years. She had no unremarkable family history. On 1980, the patient noticed a high fever, general fatigue, loss of appetite, right parotid swelling and sight disturbances. At the same time, she recognized cutaneous changes such as non-tender, non-itching macular indurated erythema with slight dark red, brown pigmentation, which were observed on her trunk, patellar areas and lower thighs.

As general and physical findings, fever 38.5 C, anisocoli, Velcro rales in the both lower lung fields, heart palpitation, right parotid swelling and slight abdominal pain were noted. Special organs examinations showed the presence of acute myocardial insufficiency, uveitis, lung fibrosis and acute pancreatitis.

As the cutaneous changes, several finger-tip sized dark-red nodules and plaques were scattered on the skin of the back and lower extremities. Some of these nodules were localized on moxa scars (Fig 1) and also on scars in patellar regions (Fig 2).

Laboratory examinations in our clinic revealed elevated ESR (erythrocyte sedimentation rates) 35 mm/hr, peripheral RBC count $428 \times 10^4/\text{mm}^3$, WBC count 7,100/mm³, serum γ -globulin value 24.8%, serum angiotensin converting enzyme 33.3 IU/l, serum lysozyme 28.7 $\mu\text{g}/\text{ml}$, and Mantoux reaction 9×10 mm/48 hrs. Chest X-ray showed diffuse lung fibrosis with positive bilateral hilar lymph node enlargement (BHL).

The biopsy specimens from nodular plaques on moxa scars (Fig 3, 4)



Fig 1. Fingernail-sized, dark red infiltrated plaques on the back skin, some of which are located on old moxa-scars.



Fig 2. Dark red nodules on old patellar mature scars.

showed histologically non-caseative epithelioid granulomas with foreign body giant cells throughout the dermis, where any polarizable material suggesting silica or metal compounds was not recognized. Lymphocytic infiltrations around the granulomas were rare. In the areas surrounding the sarcoidal

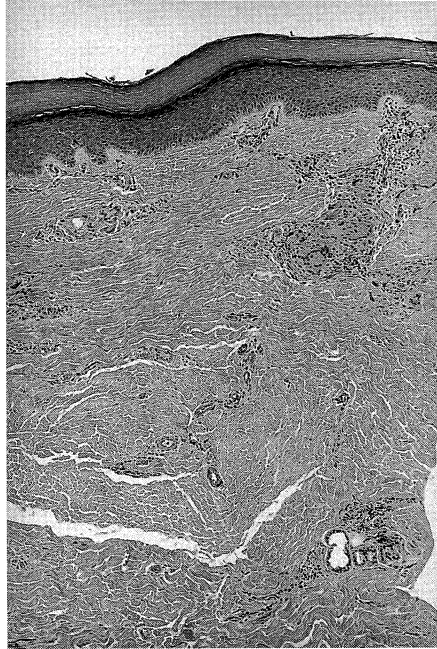


Fig 3. Histopathology of the infiltrated nodule on the scar. The epidermis is atrophic and the rete ridges have disappeared. The epithelioid cell granulomas are found in the middle dermis, surrounded by fibrotic tissues. (H-E staining, original magnification $\times 100$)

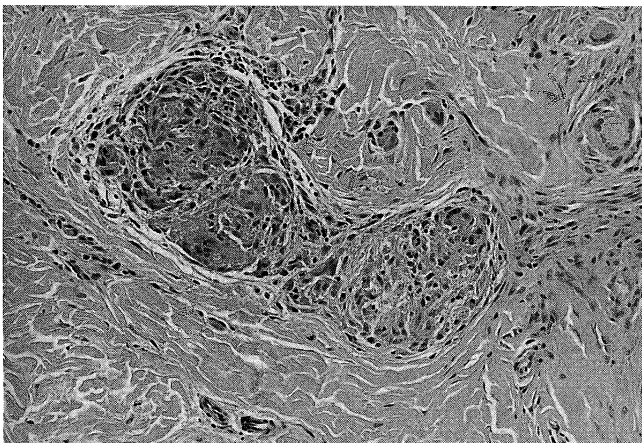


Fig 4. A higher magnification of Fig 3. Naked epithelioid granulomas with asteroid body. Fibrotic tissues are also observed. (H-E staining, original magnification $\times 600$)

granulomas, there was pallasading fibrosis consisting of collagen bundles, fibroblasts, histiocytes and mast cells, whose findings are compatible with those of scars.

The patient was treated with 30 mg daily of the oral steroid prednisolon. In two months, the scar sarcoidosis, lung fibrosis, uveitis, pancreatitis, myocardial insufficiency and parotitis were dramatically improved. After the scar sarcoidosis disappeared, only mature scars remained without any infiltration.

Case 2. Y.F. 68-year-old housewife.

The patient had no remarkable medical past history. Since January 1980, the patient noticed several dark red non-tender granulomatous nodules on old mature scars of the left patellar region, and some subcutaneous nodules on the four extremities, which enlarged gradually. In February 1980, she visited our clinic. Her general conditions were good. Slight abdominal pain (pancreatitis), coughing and bilateral chorioretinitis were noted. There was no sign suggestive of active heart disorders.

On an old mature scar in the left patellar region, a dark red elastic-hard node (4 cm×2 cm) was found (Fig 5). A non-tender, egg-sized subcutaneous nodule was observed in a surgical scar on the right thigh. Chorioretinitis was also observed in both eyes.

The main laboratory findings were as follows; peripheral blood RBC count $514 \times 10^4/\text{mm}^3$, WBC count $6,900/\text{mm}^3$, platelet count $65 \times 10^4/\text{mm}^3$, ESR 10 mm/hr, SP 7.2 g/dl, FBS 83 mg, A/G ratio 1.40, serum ACE (angiotensin converting enzyme) 81 IU/l, serum lysozyme $28.3 \mu\text{g}/\text{dl}$, serum IgG 1189 mg/dl, IgA 229 mg/dl, IgM 211 mg/dl, LDH 118 IU/l, CPK 20 IU/l, urinalysis normal. BHL (bilateral hilar lymph node enlargement) and miliary nodules throughout the lung fields were found on the chest x-ray.

Histopathology of the nodule on the patellar scar (Fig 6) revealed non-caseative epithelioid granulomas with polarizable materials in the middle and lower layers of the dermis. These granulomatous changes were directly surrounded by pallasading collagen bundles, spindle-shaped fibroblasts,

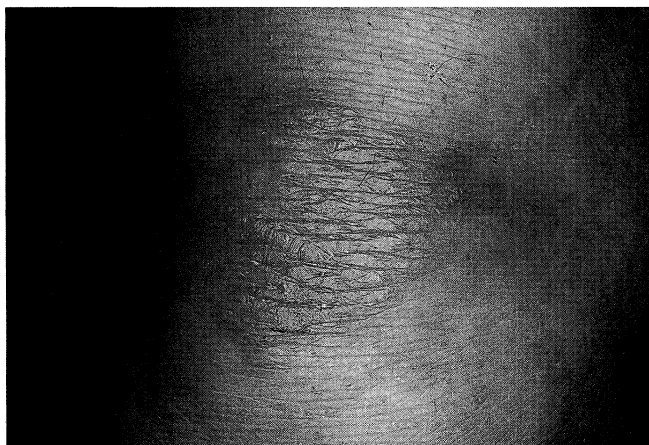


Fig 5. Dark red infiltration of an old patellar mature scar.

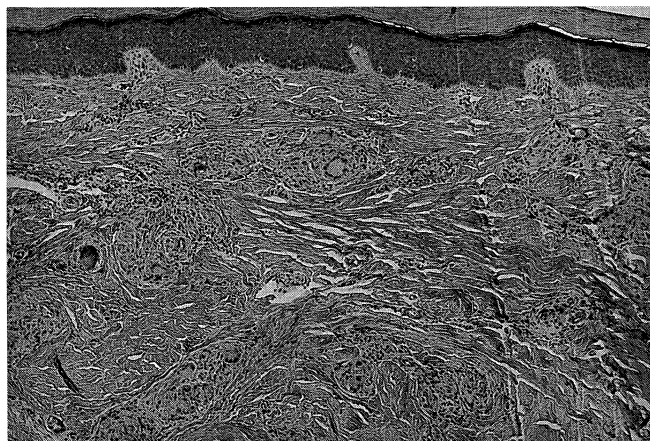


Fig 6. Histopathology from the patellar infiltration. Sarcoidal granulomas are located within fibrotic scar tissues. (H-E staining, original magnification $\times 100$)

histiocytes and mast cells.

The patient was treated by 40 mg with oral prednisolone. On September 22, 1980 (6 months later), the nodules had mostly disappeared and the laboratory findings were within normal ranges. The mature scar remained unchanged after the disappearance of sarcoidosis.

DISCUSSIONS

These patients showed typical sarcoidosis with characteristic systemic and cutaneous changes. On the skin, sarcoidosis is well known to appear as dark red nodules, infiltrated red plaques, lichenoid lesions, chilblain-like lesions on the nose or cheek, diffuse infiltration, subcutaneous nodules or scar sarcoidosis.¹⁾ Scar sarcoidosis means the occurrence of cutaneous sarcoidosis within a scar.¹⁾

Scar sarcoidosis reflects the systemic activity of sarcoidosis, and is observed in about 15% of all cutaneous sarcoidosis and is reported to occur on traumatic scars,¹⁾ silica-granulomas,⁵⁾ post-herpetic scars,^{6,7)} chicken pox scars,⁸⁾ surgical scars, injection sites⁹⁾ and burn scars.¹⁾ Some authors consider that scar sarcoidosis arising in the patellar regions may be a kind of sarcoidal reaction against implanted silica-compounds, which should be differentiated from real sarcoidosis.¹⁾ There have been conflicting discussions as to whether polarizable foreign particles can be found within sarcoidal granulomas.¹⁻⁴⁾

However, recent reports suggest that the presence of foreign bodies within the sarcoidal granulomas could not exclude the real sarcoidosis.²⁾ On the other hand, sarcoidosis can appear on tattooed areas.¹⁰⁻¹²⁾ Tattoos, minor traumas, or injections can also induce micro-scars in the dermis. Until now, most reports regarding the significance of the scar sarcoidosis are confused. In our cases, after the disappearance of systemic sarcoidosis by steroid treatment, the cutaneous lesions also improved, but the old mature scars remained unchanged. This is not unusual, but rather a common phenomenon.

Together with the present cases and a variety of findings from the

literature, it can be considered that scar sarcoidosis reflects real sarcoidosis arising on the scars, where some unknown components are targeted by active factors including immuno-competent cells of sarcoidosis after some time delay.

This phenomenon is reminiscent of the isomorphic response of Koebner (Koebner phenomenon) in psoriasis. The Koebner phenomenon was originally observed and described by Prof. Heinrich Koebner¹³⁾ of Breslau in the normal skin of a psoriasis vulgaris patient, who showed psoriatic lesions on normal healthy skin following horse bites. This phenomenon has been recognized and confirmed only in active psoriatic patients by many authors. Today, this phenomenon is well known to appear also in other inflammatory dermatoses, including lichen planus, vitiligo vulgaris, lupus erythematosus, xanthoma, granuloma annulare, necrobiosis lipoidica, keloid, also in sarcoidosis.¹⁴⁻¹⁸⁾ Nowadays, the isomorphic response is widely accepted as the same lesions, which occurred on the healthy skin following traumatic inflammations; such as heat, sun exposure, dermatitis, etc. When we can identify scar sarcoidosis as an expression of the Koebner phenomenon against the scar, our understanding of this disease of unknown etiology will be greatly furthered.

The pathomechanism of the Koebner phenomenon is very interesting and important, however it may differ from disease to disease. Although the precise mechanism of the histopathology of Koebner phenomenon remains unclarified, it can be speculated that there may be two steps to elicit this phenomenon. The first step must be non-specific inflammatory stimuli against the skin, which are recognized as Koebnerization. The second step is each specific response against the locally produced substances, which may be regulated by genetic factors. Generally, as stimuli of Koebner phenomena (Koebnerization), a variety of causative agents are described in the literature, including trauma, scratching, sun exposure, x-ray exposure, tape-stripping, dermatitis, patch tests, tattooing, burns, scars and so on. Among agents, scars may be the most simple cause. Some unknown components within scars may act as stimuli or targets of sarcoidosis. Within the scars, there are fibroblasts, cell matrices, mast cells, lymphocytes and their related substances including lymphokines, cytokines, chemokines etc. Recently, Cariotta *et al*¹⁹⁾ reported the increased IL-15 in the hypertrophic scars. This IL-15 can activate T- and B-lymphocytes and also attract lymphocytes by chemokines, thus play an important role in the pathophysiology of autoimmune diseases. Interestingly, a variety of inflammatory cytokines are activated within hypertrophic scars and fibrotic tissues.²⁰⁾ Target materials within scars should be explored to analyze sarcoidosis in the future.

Regarding the responses of sarcoidosis patients, some interesting immune and inflammatory factors have been presented. T cells recognizing as yet unknown antigens are considered to play an important role in the development and perpetuation of the sarcoidosis disease process. Prasse *et al*²¹⁾ detected Th1 cytokine pattern in sarcoidosis by bronchoalveolar CD4+ and CD8+ T cells. Sawabe *et al*²²⁾ found common T cell clones in separated sites from different organs of sarcoidosis patients.

Finally, there have been also important reports that sarcoidosis can recur or develop following interferon- α therapy for other diseases including malignant tumors^{23,24)} or chronic hepatitis C.²⁵⁾ Interferon or its related substances may induce or stimulate sarcoidosis *in vivo*.

Together with the above findings, some locally activated factors in scars may activate and attract sarcoidosis into the scars.

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