Review Article

The Koebner Phenomenon in Sarcoidosis

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ABSTRACT. The isomorphic response of Koebner can be observed not only in psoriasis, but also in several diseases including lichen planus, vitiligo vulgaris, and further in systemic diseases; such as in SLE (systemic lupus erythematosus) or sarcoidosis.

Some important clinical findings in sarcoidosis are presented and discussed in this paper with special references to Koebner phenomenon. Several intriguining examples; such as mutual-, microscopical-, internal-, or intra-lesional- Koebner phenomena are introduced and presented with related cases and figures.

As the pathophysiology of Koebner phenomenon, it could be speculated that the 1st step of non-specific inflammations locally induced by some environmental stimuli to the normal-appearing skin including trauma, heat, cold, sun exposure, metal, tattoo, dermatitis, infections, etc might be followed by the 2nd step of the disease-specific reactions based upon genetic, immunologic or inflammatory backgrounds after latent periods.

The understanding and investigation of these Koebner phenomena are important to clarify the natures of sarcoidosis of unknown etiology.

Key words ① **Sarcoidosis** ② **Koebner phenomenon**
③ **Mutual Koebner phenomenon**
④ **Microscopical Koebner phenomenon**
⑤ **Internal Koebner phenomenon**

Koebner phenomenon in sarcoidosis with special consideration of clinical findings.

Sarcoidosis is a chronic systemic non-caseative epithelioid granulomatosis of unknown nature. Cutaneous sarcoidosis can be a good model to understand its pathophysiology. The isomorphic response of Koebner was originally found in psoriatic skin by Prof. Heinlich Köbner[1] in Breslau in 1876, who described the newly-appearing psoriatic lesion on the normal healthy skin after horse-bites. He observed further that this phenomenon could be provoked by puncturing the normal-appearing skin in psoriatic patients after certain latent periods (3 weeks to several months).

This phenomenon was confirmed not only in psoriasis but also in lichen planus, vitiligo vulgaris, and autoimmune blistering dermatoses, and has been accepted as the "Köbner Phänomen" (Koebner phenomenon) or isomorphic response[2)~6)]. This Koebner phenomenon has been further reported also in various systemic

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diseases including systemic lupus erythematosus (SLE), discoid LE, systemic sclerosis, dermatomyositis, necrobiosis lipoidica, and even in sarcoidosis. All are non-infectious inflammatory diseases of which causes are unknown, and most are diseases accompanying autoimmune phenomena. Provocating factors involved in the Koebner phenomenon are reported to be needling, scratch, trauma, sun exposure, heat, cold, pressure, drug administration, tattooing, scars, and inflammatory dermatoses, as shown in Table 1. These are

Table 1. Causes of Koebnerization

Trauma		
Animal bites	Burns	Electrodessication
Excoriation	Freezing	Friction
Gunshot wounds	Insect bites	Lacerations
Nail manicuring	Needle scarification	Poor fitting shoes
Pressure	Shaving	Skin grafts
Surgical incision	Tape stripping	Thumb sucking
Allergic/irritant reactions		
BCG vaccination		
Drug reaction		
Hair spray	Hair tints	Influenza vaccination
Photosensitivity	Positive patch testing	Scratch skin test
Tattoos	Tuberculin skin test	Urticaria
Dermatoses		
Carbuncles/furuncles	Dermatitis	
Dermatitis herpetiformis	Dermatophytosis	
Diaper dermatitis secondary to Candida infection		
Eczema	Epidermal inclusion cyst	
Folliculitis	Herpetic involvement	
Herpes zoster	Lichen planus	
Lymphangitis	Measles	Miliaria
Perianal Corynebactenum minutissium infection		
Perianal neurodermatitis		Pityriasis rosea
Psoriasis	Scabies	Seborrhoeic dermatitis
Syphillis	Varicella	Vitiligo
Therapeutics		
Grenz ray therapy	High-energy irradiation	
Immunosuppression	Iodine application	
Pulsed dye laser	Roentgen therapy	
Ultraviolet light	Ultraviolet B treatment	
Withdrawal of methotrexate therapy		

non-specific factors, in which inflammatory reactions are common.

The author is particularly interested in the fact that this phenomenon is observed not only in inflammatory dermatoses but also in the skin with systemic diseases, such as collagen diseases and sarcoidosis[5)~7)]. This finding raises the question of whether this phenomenon is limited to the skin and whether it can occur in oral mucosa and various internal organs. Usually, the Koebner phenomenon as well as clinical symptoms can be suppressed in patients with collagen diseases by systemic administration of glucocortico-steroid hormones. Therefore, in this article, patients with sarcoidosis to whom steroids have not usually been administered are reported, and some points of interest, peculiarity, and pathophysiology are discussed.

CASE PRESENTATION

Sarcoidosis is non-caseative-epithelioid granulomatosis of unknown nature, and generally shows non-infectious inflammatory reactions often associated with autoimmune phenomena. However, whether it is non-infectious remains unsolved. Sarcoidosis was considered to be caused by mycobacterium infection in the past, but currently, propionibacterium acnes infection is proposed as the cause, mainly in Japan[8)]. Sarcoidosis is a systemic disease, and the main affected organs are the lungs, hilar lymph nodes, eyes, skin, salivary glands, heart, bone, liver, or alimental canals.

It has been reported that provocating factors of the Koebner phenomenon in sarcoidosis are trauma, scratch[9)], pressure[10)] (Fig. 1), post-herpetic skin, scars[11)] (Fig. 2), tattooing[12)~14)] (Fig. 3), needling[15),16)], and silica-granuloma in the patella (Fig. 4). Common targeting factors of the phenomena may be inflammatory reactions or products. In the case of tattooing, inflammatory swelling occurs gradually in the regions where a red dye was injected, and $HgCl_2$, or $HgSo_4$ which is generally used as a red dye, has superantigen activity[17)]. Also in silica-granuloma, silica is the superantigen[18)], and induces persistent inflammatory reactions. The specific inflammatory reactions in sarcoidosis may be induced by targeting inflammatory products, such as IL-1, IL-6, TNF-α, hsp, adhesion molecules, neuropeptidase, and various auto-antigens, however there has been no detailed evidence.

The latent period from the induction of the Koebner stimuli to the occurrence of lesions is as long as several weeks to several years. After improvement of sarcoidosis, initial scars, tattoos, and silica-granuloma remain usually unchanged. The Koebner phenomenon is observed mainly in the active disease stage, but not during the administration of high-potency drugs or in the remission stage.

IMPRESSIVE CASES

Some interesting modified examples of the Koebner phenomenon in sarcoidosis are described in this chapter; such as the mutually-provocated Koebner phenomenon, the microscopical Koebner phenomenon, the oral and genital Koebner phenomenon, and the internal Koebner phenomenon. The reverse Koebner phenomenon[19),20)] in psoriasis vulgaris and the negative Koebner phenomenon[5)] in lupus erythematosus are already reported in the literatures.

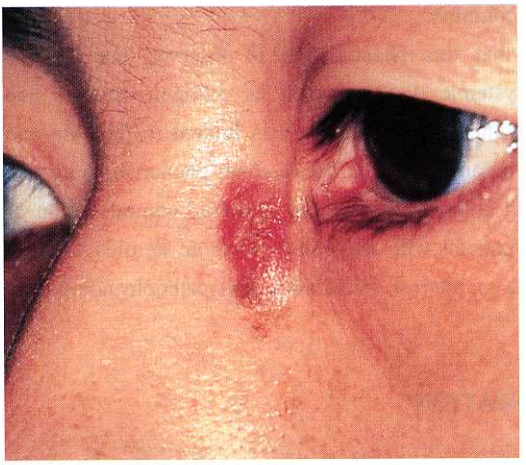

Fig. 1. Sarcoidosis on the left nose-root area pressed by the eyeglass-pad (by courtesy of Dr. I. Takahashi)

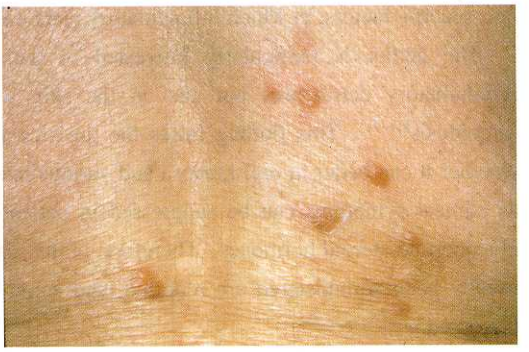

Fig. 2. Sarcoidosis on the old mature scars in the back

Fig. 3. Sarcoidosis on the red areas of a tattoo (by courtesy of Prof. K. Hanada)

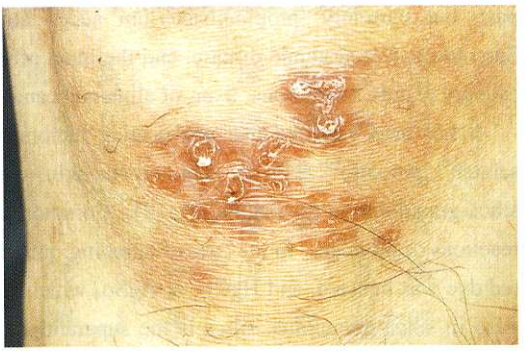

Fig. 4. Sarcoidosis on the old patellar silica-granuloma

(a) Mutual Koebner phenomenon

Patients showing a vicious cycle caused by mutually eliciting stimuli of 2 inflammatory diseases causing the Koebner phenomenon that occurred in the same region have been reported. The coincidental occurrence of psoriasis and leucoderma vulgaris[21], leucoderma vulgaris and sarcoidosis[22], or psoriasis and sarcoidosis[23] in the same region have been reported. Burgoyne[23] considered the last case as an example of sarcoidosis developing as a Koebner reaction in an already existing psoriasis. Mizukawa *et al*[24] described lesions of discoid lupus erythematosus (DLE) in the upper cutaneous layer and sarcoidosis in the lower dermal layer immediately below DLE in the same region, which was histologically confirmed. We speculate that DLE might be targeting the inflammatory products of sarcoidosis, while sarcoidosis induced the Koebner

phenomenon by targeting inflammatory products of DLE. However, the natures of inflammatory products for koebnerization are unknown, and may vary depending on diseases.

(b) Microscopical Koebner phenomenon

The Koebner phenomenon can be macroscopically observed, while it may be possible to find the microscopical Koebner phenomenon, which cannot be macroscopically observed because of its mildness. In sarcoidosis, the positive Kveim-Siltzbach test might be compatible with the microscopical Koebner phenomenon. In this test, tissue extracts collected from the spleen and lymph nodes of patients with sarcoidosis are intracutaneously injected into patients in whom sarcoidosis is suspected, and after 4-6 weeks, the injected site can be examined by biopsy. When an epithelioid granulomatous reaction is histologically detected, the patients are diagnosed as having sarcoidosis. In this test, tissues are examined at the microscopical level by microscopy. Conventionally, this test was considered as a specific diagnostic tool of sarcoidosis, but it is currently considered non-specific[25),26)] because it is positive only in the active stage and negative in the remission stage. Furthermore, other tests, such as the tuberculin test, sometimes show positive reactions[25),27)]. Based on the results obtained throughout the world, this may be the Koebner phenomenon, which can be called the microscopical Koebner phenomenon. It can be understood that the positive Kveim test is the Koebner phenomenon provoked on the injected site after 4-6 weeks by the injected Kveim solution.

(c) Oral and genital Koebner phenomenon

If the Koebner phenomenon occurs in the skin with active sarcoidosis, it would be reasonable to speculate whether it may occur in organs other than the skin. In the oral mucosa, there have been reports on the occurrence of sarcoidosis in the tongue[28)] and the lower lip[29)], which are most likely to have trauma, and in the buccal mucosa[28)], which is likely to contact artificial teeth. This resembles lichen planus, in which the Koebner phenomenon also occurs in the oral mucosa. In lichen planus, lesions occur in the genital mucosa, and similar observations have been also reported with sarcoidosis, in which lesions were observed in the glans penis[30)~32)] and urethral openings[33)]. It is necessary to examine the relationship between such lesions and the life style or sexual life in detail.

(d) Internal Koebner phenomenon

Since the Koebner phenomenon occurs in the skin and adjacent mucosa in the oral cavity and pudendum with sarcoidosis, a similar phenomenon might occur also in other internal organs. However, it is not easy to obtain clinical and histological evidences from internal organs where macroscopic and also microscopic observations are difficult. Clinically, we sometimes experience the occurrence and aggravation of lung fibrosis in patients with collagen diseases and sarcoidosis after recovery from common cold, bronchitis, or pneumonia, which might be considered to be the Koebner phenomenon in the alveolar bronchus. Here is an interesting observation of hilar lymph nodes in patients with sarcoidosis. In sarcoidosis, it is well-known that hilar lymph nodes are characteristically swollen in the early active stage (bilateral hilar lymphadenopathy: BHL). As silica-granuloma is often observed in the patellar skin of adults, it exists also in hilar lymph nodes in healthy adults (Fig. 5). Figure 6 shows the results of X-ray microanalysis of epoxy section. Two high peaks of Si and Mg are detected. If sarcoidosis occurs, specific infiltration may occur by targeting silica-granulomas in hilar lymph nodes. So we can understand that BHL may be an example of the internal

Koebner phenomenon in sarcoidosis. Similarly, specific infiltration occurs on the silica-granuloma in the patellar skin, what is described as scar sarcoidosis in published papers[11].

PATHOPHYSIOLOGY

When the pathophysiology of the Koebner phenomenon is discussed, it is important to evaluate other diseases together with individual diseases. The occurrence of the Koebner phenomenon has been reported with various diseases, and it's pathophysiology can be classified into non-specific inflammatory step (primary reaction) in local regions and subsequently specific inflammatory step (secondary reaction) after individual latent periods. As products of the primary inflammatory step, various cytokines (IL-1, IL-2, IL-6, IL-8, IL-10, IL-12, IL-18, TNF-α, INF-γ, etc.), adhesion molecules (ICAM-1), stress protein (hsp, molecular chaperon), degranulated substances from mast cells, or autoantigens are known, but there may be many unknown substances. These released substances might be considered to be non-specific. After individual latent periods depending on lesions followed by the primary inflammatory step, the secondary disease-specific inflammatory step may be induced by targeting some inflammatory products of the primary step. It has been described that sarcoidosis was induced and aggravated by the administration of INF-α [34),35)].

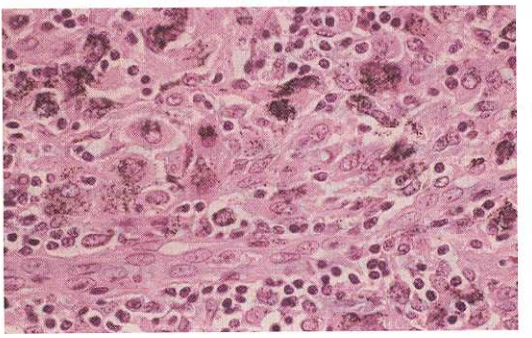

Fig. 5. Silica-granuloma in the hilar lymphnode of a healthy person (by courtesy of Prof. T. Manabe)

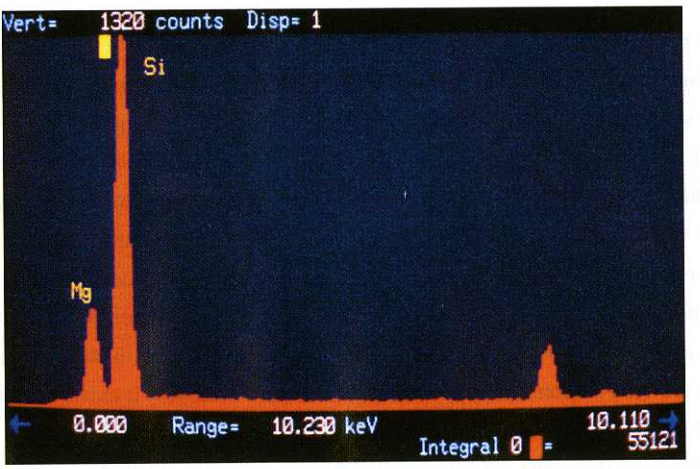

Fig. 6. Elemental composition of healthy human hilar lymphnodes using X-ray microanalysis of epoxy section. (by courtesy of Prof. K. Sasaki and chief technician of our EM research center; Mr. K. Uehira).

Substances released from silica-granuloma and scars would be readily tracked. Since there is infiltration of fibroblasts, mast cells, and lymphocytes even in mature scars, various inflammatory substances are generated and released by a very low degree of stimulation. Matrix metalloproteinases, which are activated even by mild inflammatory reaction, such as cold in pulmonary bronchiles and bronchitis, greatly affect collagen fibers, suggesting their involvement in fibrosing lung[36].

The presence of various autoantigens and immune complexes in sarcoidosis have been also reported[37]. Although their involvement cannot be excluded, the latent period from the primary step to the occurrence of the specific second step is far too long for simple immunoreactions. Interaction between cytokines, adhesion molecules, or superantigens must be involved in the occurrence. Figure 7 shows the speculative outlines of pathophysiology of the Koebner phenomenon.

In Europe and the USA, sarcoidosis has long been considered to be an infectious disease caused by mycobacteria. There is another hypothesis recently proposed in Japan that it may be caused by propionibacterium acnes[8], which is resident flora in the skin and other organs.

Reaction by the Kveim-Siltzbach test reagent described above is used for the clarification of its pathophysiology. An examination of bacterial DNA of Kveim extract suspension demonstrated that all were negative[38], and furthermore, positive reaction was observed even with sterile Kveim solution, both of which do not support the bacterial infection hypothesis. On the other hand, there have been studies showing that the incidence of sarcoidosis was high in patients exposed to crystalline silica[39], suggesting that sarcoidosis can be induced by continuous stimulation of the immune system.

Interestingly, the Kveim test described above is useful for examining specific lesions induced at the site with intracutaneous injection, which differs from intracutaneous tests as simple immune reaction. This test

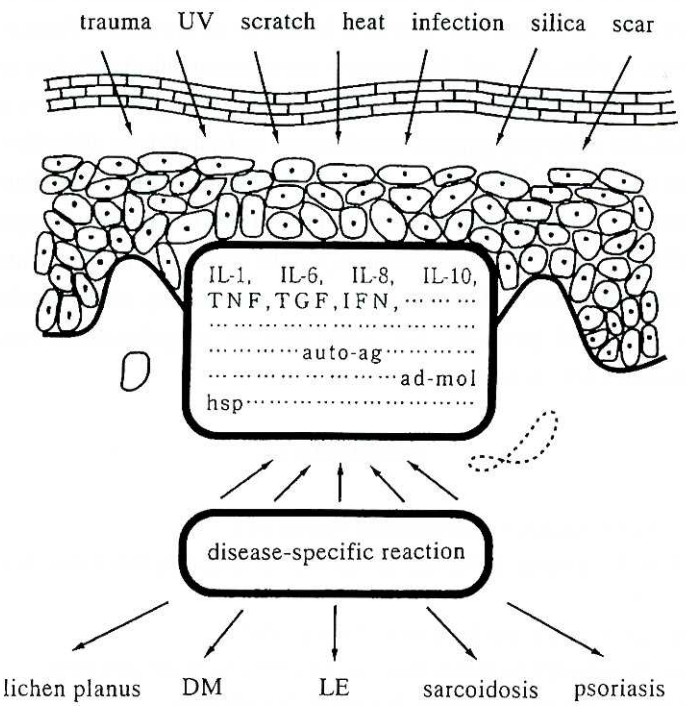

Fig. 7. A proposed pathophysiology of the Koebner phenomenon

fundamentally differs from immediate immune reaction (type Ⅰ immune reaction) and even from the tuberculin reaction (type Ⅳ reaction), Mitsuda reaction (type Ⅳ reaction), and Arthus reaction (type Ⅲ reaction). What we observe here is the total sarcoidosis lesion consisting of macroscopic and microscopic reactions. There are total histological reactions in the Kveim reaction-positive site, and analysis of infiltrated lymphocytes demonstrated the presence of oligoclonal Vβ-specific T cells[40], indicating that the involvement of immunoreaction cannot be excluded. The Koebner reaction is the specific disease itself generated after a certain latent period irrespective of provocations, such as injection or trauma, and it is important that the similar reactions as the primary step are induced in sarcoidosis, psoriasis, lichen planus, lupus erythematosus, and leucoderma vulgaris after individual stimulation. Interestingly, most diseases causing the Koebner phenomenon are accompanied by autoimmune phenomena. In addition, as described in the former chapters, if the reactions of the second step would target the inflammatory products of the first step, these continuous reactions may be usually occurring within the chronic lesions of sarcoidosis. Within these chronic lesions, there are always the mixed reactions of the non-specific inflammations of the first step and the disease-specific inflammations of the second step. Thus, the non-specific and the specific inflammatory reactions would be inter-acted each others continuously. This phenomenon can be recognized and understood as the intra-lesional Koebner phenomenon.

CONCLUSIONS

It is difficult to clarify the pathophysiology of diseases of unknown causes, such as sarcoidosis, even with the most recent findings, if detailed informations from the clinical fields are not used. As dermatologists have the advantage of observing lesions directly and macroscopically, it is considered necessary to understand the dynamics and characteristics of lesions and to observe lesions in other organs. Dermatologists can observe the Koebner phenomenon clinically, and informations about environmental factors involved in the skin surface and stimulation to the oral and genital mucosa obtained from the patients is very useful. For example, false dentures as a stimulus to the oral mucosa, autochewing, and autolicking of the lips are often observed. Under careful questioning from the physician, patients often recognize their habits. Since there are diseases which can be understood only by expanding the view from local area to the systemic organs, cooperation with physicians of other clinical fields should be developed. On the basis of such cooperation, it may be possible to accumulate effective evidences. The knowledge and understanding of the Koebner phenomenon in sarcoidosis may be useful and productive for clarification of its patho-mechanism, and also for the management and/or treatment of sarcoidosis.

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