

Koebner Phenomenon in Rheumatoid Arthritis

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Abstract

Koebner phenomenon indicates the newly appearance of isomorphic lesions at the sites of mechanically stimulated or injured skin. This phenomenon can be seen in various inflammatory, auto-immune, viral, fibrotic, and even tumoral disorders. Also, rheumatic diseases such as lupus erythematosus, dermatomyositis, and rheumatoid arthritis (RA) often present with cutaneous manifestations with isomorphic response of Koebner. RA presents with various skin conditions as extra-articular manifestations. Rheumatoid nodule is the representative specific skin lesion which frequently occurs on the hand, elbow, sole, sacrum, occipital area, and so on. These sites are susceptible to both outer and inner mechanical stress. Rheumatoid nodules involve not only skin but internal tissues such as spine, lung, heart valves, and gastrointestinal tract, which are also susceptible to mechanical stress. This isomorphic response may be induced at deeper levels than skin, and thus considered to be “deep” or “internal” Koebner phenomenon. Other than rheumatoid nodules, several specific skin conditions are associated with RA, such as palisaded neutrophilic granulomatous dermatitis and rheumatoid neutrophilic dermatitis, which can be seen on the fingers, elbows, knees and sole. Also, there are various other skin lesions in association with RA, which show Koebner phenomenon, such as neutrophilic dermatosis and autoimmune bullous diseases. Koebner phenomenon may be closely associated with the induction of various specific or nonspecific conditions, not restricted to the skin, in association with RA.

Keywords: Rheumatoid nodule; Koebner phenomenon; Isomorphic response; Drug

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory systemic disorder which primarily involves the joint synovial membrane. It is well-known that patients with RA exhibit various cutaneous conditions [1-4]. The most representative characteristic cutaneous lesion is rheumatoid nodule, and a number of specific and nonspecific cutaneous lesions are additionally seen. Many of those lesions occur at sites easily susceptible to mechanical stimuli.

The Koebner phenomenon is the newly development of isomorphic lesions in the mechanically stimulated or injured skin [5-8]. The Koebner phenomenon was originally described in psoriatic skin by Prof. Heinrich Köbner in 1876. Thereafter, Koebner phenomenon is well-known to be seen in various skin disorders other than psoriasis, and sometimes seen in association with autoimmune diseases such as dermatomyositis, lupus erythematosus, morphea, vitiligo, autoimmune bullous dermatosis, sarcoidosis, and so on. In this review, we discuss Koebner phenomenon in the representative skin lesions associated with RA.

Koebner Phenomenon

The Koebner phenomenon can be seen in various disorders, such as psoriasis, lichen planus, and vitiligo, following extrinsic exposure to minor trauma, such as heat, cold, X-rays, and ultraviolet. Furthermore, there are a number of similar conditions to Koebner response, including true Koebnerization, pseudo-Koebnerization, occasional lesions, and poor/questionable trauma-induced processes [6]. The pathogenesis of the Koebner phenomenon is still not fully elucidated as yet. Upon epidermal injury, several proinflammatory cytokines, i.e. interleukin-1 (IL-1), tumor necrosis factor- α (TNF- α) and granulocyte macrophage-colony stimulating factor (GM-CSF), are released [9], which may induce further inflammation. Ueki [10] proposed a second-step theory, a first non-specific inflammatory step and a second disease-specific

step, in Koebner phenomenon. In the first step, many environmentally induced factors such as cytokines, stress proteins, adhesion molecules, or autoantigens translocated from intracellular areas are involved in the inflammatory phase. Subsequently, in the second step, there may be disease-specific reactions mediated by T-cells, B-cells, autoantibodies and immune complex deposition under the susceptible backgrounds. However, analysis on genetic roles in the induction of Koebner phenomenon is difficult and has not been performed at all, because of diversity of the disorders showing Koebner phenomenon. Also, this phenomenon is frequently influenced by disease activity.

Nerve growth factor (NGF) is a neurotrophic factor, and has many functions including the activation of T-cells, recruitment of inflammatory cells, and degranulation and migration of mast cells [11]. The binding of NGF to its receptor initiates the activation of nuclear factor kappa B (NF- κ B), and regulates inflammation cascades. In the lesional skin of psoriasis, a representative disease showing Koebner phenomenon, a marked upregulation of NGF was induced by tape-stripping, followed by TNF- α expression [12]. In addition, it is frequently experienced that psoriatic lesions occur on the old scar, which is histologically characterized by hypervascularity and fibrosis containing a number of mast cells. Thus, mast cells may play an important role in the etiology of isomorphic response.

Basic fibroblast growth factor (bFGF) is one of angiogenic

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Received August 07, 2013; **Accepted** August 21, 2013; **Published** August 23, 2013

Citation: Yamamoto T, Ueki H (2013) Koebner Phenomenon in Rheumatoid Arthritis. J Genet Syndr Gene Ther 4: 173. doi:10.4172/2157-7412.1000173

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cytokines, and produced by keratinocytes and endothelial cells, as well as mast cells. Also, bFGF induces proliferation and chemotaxis of fibroblasts [13] and collagenase expression in fibroblasts [14], and has a mitogenic activity for keratinocytes and endothelial cells. bFGF binds to heparin sulfate proteoglycan and is associated with extracellular matrix in basement membrane. Extracellular matrix also serves as a storage depot for FGFs. Displacement of bFGF by physical stimuli such as scratching or rubbing, may explain Koebnerization [15].

Epidermal injury is a danger signal which subsequently induces activation of the innate immune systems. Barrier disruption of the epidermis causes activation of the epidermal growth factor receptor (EGF-R). EGF-R is a member of transmembrane receptor tyrosine kinases family, encoded by the c-erb-B proto-oncogene. EGF-R consists of an extracellular ligand-binding receptor domain, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain. In the skin, EGF-R is expressed by basal keratinocytes, sebocytes, the outer root sheath and some endothelial cells [16,17]. EGF-R plays important roles in the regulation of differentiation, proliferation, apoptosis, attachment and migration of keratinocytes, inflammation, and wound healing [18]. EGF-R activation induced by physical triggers may contribute to the local inflammatory and immune response, leading to the development of new lesions.

RA-Associated Specific Skin Manifestations

Rheumatoid nodule

Rheumatoid nodule is the most representative specific cutaneous sign of RA. Rheumatoid nodules are firm and mobile subcutaneous nodules which develop most predominantly on the extensor surface of the elbows, olecranon, extensor tendons of the hands, proximal ulna, sacrum, occipital region, and sole (Figure 1 and 2). All of the sites are subjected to extrinsic mechanical irritation. In addition, the overlying skin above the joints is frequently exposed to friction stress from inner sides. These facts suggest the involvement of Koebner phenomenon in the induction of rheumatoid nodules. Sometimes they attach to deeper tissues such as the periosteum, fascia, tendons, or underlying inflamed rheumatoid synovium. They also occur at systemic sites, such as the spine, lung, heart valve, and gastrointestinal tract. Those internal organs are also susceptible to mechanical stress, and this isomorphic response may be more than skin deep and thus considered to be “deep” or “internal” Koebner phenomenon. Previously, Ueki [10] proposed that Koebner phenomenon occurs in internal organs, possibly triggered by not only mechanical stress but also inflammatory substances. Pulmonary rheumatoid nodules may be resulted in inflammatory process in the lung, i.e. repeated upper tract infection or bacterial pneumonitis.

Histopathological features show that rheumatoid nodule is composed of three parts, namely an inner zone of central necrosis/necrobiosis (mostly eosinophilic, but rarely basophilic), a surrounding cellular palisading zone, and an outer area with perivascular infiltration of chronic inflammatory cells. The major proportion of the palisaded cells consists of macrophages which are strongly positive for CD68. CD3 positive T-cells are seen among and surrounding the palisaded macrophages. The macrophages are activated by immune complexes [19], and secrete proinflammatory cytokines, such as IL-1 β and TNF- α , are thought to play a role in the induction of rheumatoid nodule [19,20]. Additionally, the cytokine profile of rheumatoid nodule includes Th1 cytokines such as interferon- γ (IFN- γ), IL-1 β , TNF- α , IL-12, IL-18, IL-15, and IL-10, which point to the possibility of a Th1 granuloma [21]. Local vascular damage is supposed to be caused by

repeated minor trauma because rheumatoid nodules predominantly occur on the pressured sites. Endothelial cell injury may result in local accumulation of IgM immune complexes on the small vessel walls, which subsequently activate monocytes/macrophages. Exceptionally, changes suggestive of focal vasculitis may be seen, such as fibrin deposition and nuclear debris. However, vasculitis is not essential in the pathogenesis of rheumatoid nodule, and which is the difference from rheumatoid vasculitis. Local secretion of cytokines, mediators, growth factors, proteases, and collagenases from those cells lead to inflammation, angiogenesis, necrobiosis, and granuloma formation. Expression of E-selectin is highly detected in the vessels of rheumatoid nodule, which suggest active inflammation and cell trafficking into the nodules [20].

RA patients receiving disease modifying anti-rheumatic drugs (DMARDs), among which methotrexate is the most common, occasionally develop multiple rheumatoid nodules on the hands [22-25]. Additionally, recent papers have reported the newly development of rheumatoid nodules during biologic therapies [26-29]. Apart from sufficient effects of biologics for joint symptoms, rheumatoid nodules are paradoxically induced following TNF- α targeting therapy. Although TNF-targeting therapies bring dramatic effects in RA, TNF- α plays an immunoregulatory role and unexpected conditions are occasionally induced. Several mechanisms have been suggested, i.e. i) the formation of rheumatoid nodule is TNF- α independent, ii) the binding of anti-TNF- α drugs to their target cells induces apoptosis followed by enhanced chemotaxis of inflammatory cells, leading to rheumatoid nodule, and iii) migratory inflammatory cells from the joints to other inflamed tissues induces rheumatoid nodule.



Figure 1: Multiple rheumatoid nodules on the metacarpophalangeal joints (70 y.o., female).



Figure 2: Sacral rheumatoid nodule (64 y.o., female).

Palisaded neutrophilic granulomatous dermatitis

Palisaded neutrophilic granulomatous dermatitis is a pathological condition including different termed disorders, such as rheumatoid papules, Churg-Strauss granuloma, linear subcutaneous bands, and superficial ulcerating rheumatoid necrobiosis [30]. Palisaded neutrophilic granulomatous dermatitis is usually presented with crusted, umbilicated papules and nodules on the extensor surfaces of the fingers, elbows, and knees (Figure 3). Also, clinical manifestations vary and include linear cords or bands on the trunk, urticarial lesions on the extremities, annular lesions, nodules or asymptomatic papules. By contrast, histological features are common, and early lesions demonstrate leukocytoclastic vasculitis with dense neutrophilic infiltrates and focal collagen degeneration. Fully developed lesions develop into palisading granulomas surrounding leukocytoclastic debris, fibrin, and altered collagen. Late lesions show palisaded granulomas with dermal fibrosis and scant neutrophilic debris [31]. Necrobiosis is the major pathologic condition of cutaneous involvement associated with RA, and may be closely associated with the pathogenesis of RA, i.e. collagen degeneration, recruitment of activated neutrophils, various cytokine production, and vascular injury [32].

Rheumatoid neutrophilic dermatitis

Rheumatoid neutrophilic dermatitis clinically presents with symmetrical erythematous papules, wheal-like erythema, nodules, plaques, and rarely, vesicles, over the extremities and trunk [33-35]. Bullous type rheumatoid neutrophilic dermatitis occurs predominantly on the lower legs. Rarely, bullous formation can be seen in a ray, possibly due to scratching (Figure 4). Histological features demonstrate dense and diffuse infiltration of lymphocytes and neutrophils with nuclear dust in the dermis. Some authors regard rheumatoid neutrophilic dermatitis as included in palisaded neutrophilic granulomatous dermatitis, however, rheumatoid neutrophilic dermatitis does not show palisaded granuloma.

Rheumatoid Vasculitis

Cutaneous rheumatoid vasculitis may present with digital infarcts, livedo, palpable purpura, bulla, ulcerations, painful nodules, or gangrene. Histologically, rheumatoid vasculitis involves blood vessels of the small arteries, and all layers of the vessel wall are infiltrated by neutrophils, lymphocytes and plasma cells. Jorizzo and Daniels [36] classified cutaneous rheumatoid vasculitis into three grades: severe, moderate and mild. The severe type presents with digital gangrene, nail fold infarcts, large cutaneous ulcers; the moderate type presents with palpable purpura; and the mild type presents with nail fold



Figure 3: Slightly elevated reddish nodules forming a plaque on the elbow (67 y.o., female).



Figure 4: Bullous rheumatoid neutrophilic dermatitis showing multiple bullae in a ray (63 y.o., female).



Figure 5: Pyoderma gangrenosum on the knee in a patient with RA (83 y.o., female).

telangiectasias with thromboses, minute digital ulcerations, petechiae, and livedo reticularis. Minor bleeding from the nail folds, finger pulp, and the edge of the nails results from digital infarcts (isolated nail fold vasculitis). Cutaneous rheumatoid vasculitis is seen most frequently on the lower legs, and triggered by minor trauma.

Neutrophilic Dermatoses

Neutrophilic dermatoses with neutrophilic activation are often associated with RA, e.g., pyoderma gangrenosum (especially the ulcerative type) (Figure 5), erythema elevatum diutinum, Sweet's syndrome (neutrophilic dermatosis), pustular panniculitis, subcorneal pustular dermatosis, psoriasis, palmoplantar pustulosis, and erosive pustular dermatosis of the scalp [4]. Pyoderma gangrenosum is occasionally triggered by minor trauma (pathergy), which means hyper-reactivity of the skin in response to minor trauma. EGF-R stimulation leads to the production of several chemokines such as IL-8 [18], which may play an important role in the induction of neutrophilic dermatosis.

Concluding Remarks

Due to the joint deformity, patients with RA suffer from impaired burden of weight on the sole, as well as the hand and elbow. The clinical management is to avoid the frequent overload on the joints and to protect skin of those sites. Epidermis functions as the outer barrier. Epidermal injury can lead to subsequent pathways via inflammatory cascades involving cytokines, chemokines, neurotransmitter, and stress proteins. Recent investigations suggest the activation of anti-microbial peptides and toll-like receptors upon keratinocytes stimulation. Furthermore, mechanical stress is not restricted to the outer irritation,

but inner mechanical stress also exists, which contributes to dermal injury. Thus, epidermal and/or dermal injury induces the Koebner phenomenon in susceptible individuals. It is speculated that the similar mechanisms may occur more than skin deep, which develop disease-related conditions in RA. Further studies are necessary to clarify the detail pathogenesis of the Koebner phenomenon and also genetic backgrounds.

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This article was originally published in a special issue, [Autoimmune Diseases](#) handled by Editor(s), Dr. Kenneth Blum, University of Florida, USA