Possible Role of Cellular Immunity: A Case of Cellulitis

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On the basis of the observation that there was a “skip” area in an otherwise diffuse drug eruption where cellulitis had previously occurred, it is theorized that both delayed hypersensitivity type of dermatologic drug reaction and cellulitis share pathogenic mechanisms.

Cellulitis is one of the most common maladies seen, and it occurs in individuals in all age groups. It is fortunate that the majority of patients with cellulitis make an uneventful recovery after receiving appropriate antibiotic therapy; however, many of these patients are at risk for subsequent bouts of cellulitis.

It is surprising that so little is known about the pathogenesis of cellulitis, because it is so common and it recurs so often. Successful therapy, coupled with a low rate of complications, may have resulted in part in a limited interest in examining the pathogenic mechanisms involved in the production of cellulitis. Long-term clinical experience and case-control data [1, 2] indicate that several factors predispose patients to cellulitis and are probably operative in the pathogenesis of the illness. How these factors predispose patients to cellulitis is currently unknown.

We present a case report that provides an important clue for the diagnosis of cellulitis pathogenesis. Clinical features of this case prompt us to hypothesize that delayed (type IV) hypersensitivity mechanisms involved in the pathogenesis of maculopapular drug reactions also account for the local skin and soft tissue changes associated with cellulitis.

A 61-year-old man presented with acute onset of swelling of the left lower-extremity and erythema associated with fever and chills. He was mentally retarded and lived in a group home. He had no previous history of cellulitis. Pertinent findings on physical examination included a temperature of 37.3°C, a heart rate of 71 beats/min, and focal changes of the left tibial area. There was confluent macular erythema of the anterior, lateral, and posterior tibial regions. There was also diffuse swelling of the tibial region and of the dorsum of the left foot. Scaling and maceration of the toe webs of both feet were noted. At admission, the peripheral leukocyte count was 14,500 cells/mm³. The streptozyme antibody titer was abnormally elevated at 1:200 units.

The patient subsequently developed severe and diffuse maculopapular eruptions associated with the acute onset of fever. He had also had desquamation of the buccal mucosae and conjunctival hyperemia. The cutaneous eruptions were first noted on the ninth hospital day (9 days after the start of nafcillin therapy and 3 days after the start of piperacillin-tazobactam, vancomycin, and clindamycin therapy). It is of interest that a “skip” area, an area with no skin lesions, was evident in the left lower extremity (figure 1). This skip area had distinct margins (figure 2), and its distribution exactly matched that of the previously noted cellulitis. Permission to obtain skin biopsy specimens was not granted. The patient recovered from the allergic reaction when vancomycin and piperacillin-tazobactam therapy was discontinued and antihistamine and corticosteroid therapies were begun. Clindamycin was continued and levofloxacin was added; both drugs were administered for 5 days.

The pathogenesis of cellulitis is probably complex [3]. We know that underlying venous and lymphatic compromise is critical in many cases [1, 2]. Pathogenic bacteria, although present, are usually found in relatively low concentrations. Bacterial products, such as streptococcal and staphylococcal exotoxins, are probably important: they may combine with fungal antigens from accompanying tinea pedis (in cases of lower-extremity cellulitis) to induce the local inflammatory changes of cellulitis seen in the sensitized host (reviewed by Baddour...
[3]). Specific immune and inflammatory mediators that account for the local findings of cellulitis remain undefined.

Still, some have advocated that trials of anti-inflammatory agents administered with antibiotic therapy should be done to see whether clinical response could be hastened [4]. Such trials would provide feedback regarding how important immune or inflammatory mediators are in disease production. In at least 3 cases [5, 6] of chronic breast cellulitis for which prolonged antibiotic therapy failed to completely clear local skin changes, anti-inflammatory agents (including aspirin, indomethacin [5], and topical corticosteroids [6]) were used and resulted in clinical improvement. The effect of corticosteroid therapy on cellulitis (erysipelas) was more formally addressed in a randomized, double-blind, placebo-controlled trial [7]. Patients were administered antibiotics and were randomized to receive either prednisolone or a placebo. Findings included a significant reduction in the time to clearance of local skin changes and systemic toxicity in the group receiving combined antibiotics and prednisolone therapy. Moreover, unlike the corticosteroid-treated group, this group had no increase in the short-term relapse rate.

To our knowledge, no previous report of a case of a sparing phenomenon in a recent bout of cellulitis (and subsequent cutaneous drug reaction) has been published. A sparing phenomenon, however, has been described in association with other clinical syndromes. In one case of generalized granuloma annulare in a man with underlying chronic myelomonocytic leukemia and myelodysplasia [8], the cutaneous eruption spared vaccination sites. No possible explanation for this striking occurrence was included in the case report.

In another case report [9], a sparing phenomenon was described in an Indian woman with previously undiagnosed tuberculous leprosy and an acute hypersensitivity rash caused by ampicillin. The rash was generalized, intensely erythematous, and maculopapular, and it spared a hypopigmented patch on the left cheek of the patient. The asymptomatic patch had been present for 5 years. In addition to being hypopigmented, it was well defined and anesthetic, and was dry and devoid of hairs. Skin biopsy of the patch was performed and revealed a tuberculoid granuloma in the upper dermis that supported a diagnosis of tuberculoid leprosy. After resolution of the rash, intradermal histamine and ampicillin tests were conducted, and the contralateral cheek and a forearm were used as control injection sites. Wheal and flare responses were seen at both control sites, but no flare response was seen when the leprosy patch was injected with either histamine or ampicillin. The author concluded that because the histamine flare response was dependent on the dilation of minute blood vessels via sympathetic nerves in the skin, associated nerve damage was responsible for the lack of response in the patch of tuberculoid leprosy.

A local and systemic sparing phenomenon can be seen with the treatment of alopecia areata by use of topical sensitizers. Patients who are successfully sensitized by means of topical dinitrochlorobenzene can see a regrowth of hair in the affected areas. These effects are also found at distant, untreated sites that suggest a systemic effect [10, 11]. Although the mechanism is poorly understood, a decreased CD4:CD8 lymphocyte ratio and a reduced number of intrabulbar CD6+ lymphocytes and Langerhans cells are found in the treated skin [12]. Happle et al. [13] proposed the concept of antigenic competition in which suppressor CD8 T cells exhibit a nonspecific, inhibiting effect on the immune response against hair follicles, thereby permitting hair growth.

The patient’s lower-extremity changes were typical of β-hemolytic streptococcal cellulitis, although they did not resolve with nafcillin. Although this suggests a possible nonstreptococcal or staphylococcal etiology, a previously published report [14] described a case of acute cellulitis and lymphangitis caused by mucoid Streptococcus pyogenes that also failed to respond to initial β-lactam therapy. Even if the skin infection were due to another organism, such as an aerobic gram-negative bacillus, it is likely that the same sparing phenomenon would have occurred because, in general, the clinical presentation of cellulitis is the same, regardless of the bacterial etiology, and it probably involves similar mechanisms of pathogenesis.

Drug-induced rashes may be characterized by the clinical appearance of skin lesions and by the pattern of inflammation observed in skin biopsy specimens [15]. Our patient had generalized, fixed erythematous macules and papules without scale. They were not evanescent or hemorrhagic. These types of skin lesions are typically associated with dermal lymphohesinophilic infiltrates. Vasculitis, epidermal injury, and granulomas are not
Staphylococcal exotoxins have been associated with exacerbated T cell-mediated inflammatory responses. The kinetics of histamine release from activated mast cells in coculture with T cells. Unlike rapid anaphylactic degranulation, the kinetics of histamine release from activated mast cells in coculture with T cells was measured in hours. In other studies [22], one considers the complex interactions of T cells and mast cells such as histamine or an interleukin. This is plausible, when one considers the complex interactions of T cells and mast cells [21]. In particular, T cells can affect mast cell activation and mediator release via 2 mechanisms: release of T cell-derived cytokines and direct cell-to-cell contact between mast cells and T cells. Unlike rapid anaphylactic degranulation, the kinetics of histamine release from activated mast cells in coculture with activated T cells was measured in hours. In other studies [22], staphylococcal exotoxins have been associated with exacerbation of atopic dermatitis. IgE antibodies to staphylococcal-derived superantigens staphylococcal enterotoxin A and B are thought to cross-link on the surface of mast cells and to trigger release of histamine and other inflammatory mediators.

There are other potential explanations for the sparing phenomenon described in the present case report. For example, Schlievert et al. [23] speculated that exotoxins produced by group A streptococci may account for the clinical manifestations of erysipelas. If exotoxins were operative as superantigens in our patient, then one could anticipate that counterimmunomodulatory mechanisms that are operative in other types of inflammatory diseases could respond to the initial overstimulation of T cells caused by superantigens during infection, and could suppress the local skin changes induced by the subsequent drug reaction. It is conceivable that in our patient there was a suppression of release of inflammatory mediators or an up-regulation of anti-inflammatory cytokines, chemokines, or receptors to block the local skin response to drug allergy [24]. In addition, apoptosis of the superantigen-activated T cells could occur and result in a depletion of particular Vb subsets [25].

The theory that the mechanisms of pathogenesis chiefly associated with allergic diseases could also be operative in some presentations of cellulitis is not a novel one. In 1928, Birkhaug [26] proposed that allergic sensitization early in life to the products of *Streptococcus scarlatiniae (pyogenes)* could be responsible for recurrent episodes of erysipelas. He supported his theory with observations he made accidentally when he used streptococcal toxin to actively immunize patients against recurrent bouts of erysipelas. Within hours of im injection of toxin, 3 patients developed systemic complaints, including fever and chills, and local changes of erysipelas. Importantly, systemic and local changes of erysipelas both gradually disappeared with serial toxin injections administered over a period ranging in length from weeks to months. In addition, each patient remained free of erysipelas attacks for at least 2 years after receiving immunotherapy.

In 1979, Schlievert et al. [27] took exotoxins purified from group A streptococci and showed that hypersensitivity, and not direct toxic effects of the streptococcal proteins, was responsible for erythematous and edematous skin lesions in rabbits injected with exotoxins. Young rabbits had no obvious skin changes in response to the initial challenge injection of exotoxin. On subsequent challenge 2 weeks later, the animals developed intensely red and edematous skin reactions to the same exoprotein. The investigators concluded that these findings supported the belief that the Dick test, which was used in the past to identify individuals who were susceptible to scarlet fever [28], was an assay of hypersensitivity to certain streptococcal products. The test included broth culture filtrates from erythrogenic toxin-producing group A streptococci, and these were injected in-
tracutaneously. Twenty-four hours later, susceptible individuals would develop redness and swelling at the injection site; this was defined as a positive test result.

Athlete’s foot has been linked to lower-extremity cellulitis [29, 30]. Sulzberger et al. [31] hypothesized that hypersensitivity to trichophytin products could result in recurrent erysipelas of the lower extremity in some patients with dermatophytosis of the feet. They were able to reproduce the local findings of erysipelas with the intracutaneous injection of trichophytin in a patient who had recurrent erysipelas of the lower extremity and dermatophytosis of the feet. Naide [32] also believed that an allergic mechanism was responsible for the production of lower-extremity cellulitis-like changes in a patient with long-standing deep venous disease and dermatophytosis. The investigator was able to produce a severe cellulitis-like lesion that covered an area of ~10 cm in diameter after the local intradermal injection of trichophytin extract.

Because of the prompt response to antibiotics in patients with acute cellulitis and the recovery of bacteria from [33] or identification of bacterial products in [34, 35] infected tissue, a bacterial origin is suspected in most cases of cellulitis. Nevertheless, it is conceivable that a fungal-related origin of cellulitis could be operative in a small subset of patients. In some of these patients, a combined fungal-bacterial origin is plausible if one recognizes that streptococcal pyrogenic exotoxins have been shown to enhance hypersensitivity reactions to unrelated substances, including endotoxin, purified protein derivative of Mycobacterium tuberculosis, and bovine serum albumin [27].

The case of cellulitis with subsequent development of a drug reaction described in this report has provided a clue to the pathogenesis of cellulitis. We speculate that mechanisms involved in the production of a delayed hypersensitivity type of dermatologic drug reaction are shared in at least some cases of cellulitis. We also recognize that it is probable that there are other mechanisms involved in the production of local changes of cellulitis, although, to date, investigations have yet to clarify them. Subsequent studies should include skin biopsies of cellular lesions for examination of cellular and chemical mediators that could account for the striking focal dermatologic changes that we define as cellulitis.

References

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