Drug-Induced Rosacea-like Dermatitis

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ABSTRACT Rosacea is a common, chronic cutaneous disorder with a prevalence of 0.5-10%, predominantly affecting women. The disease presents with a heterogeneous clinical picture characterized by transient flushing, persistent facial redness, telangiectasias, and, in more severe clinical forms, the presence of inflammatory papules and pustules in the central third of the face. Although its pathophysiology is complex and still remains unknown, factors that exacerbate the disease are well defined. They include genetic predisposition as well as external factors such as exposure to UV light, high temperature, and diet. Besides these well-known factors, recent studies suggest that drugs and vitamins could also be possible factors inducing rosacea-like dermatitis or aggravating pre-existing rosacea. Although these are less common possible triggering factors, the aim of this article is to present the current knowledge on the association between use of certain drugs or vitamins and rosacea.

KEY WORDS: drugs, rosacea-like dermatitis

INTRODUCTION

Rosacea is a chronic skin inflammatory condition affecting the blood vessels and pilosebaceous units. Although it has many different clinical presentations, in the majority of cases it presents with centrofacial erythema and the presence of telangiectasia, occurring more frequently in persons with fair complexion and light eyes (1). Although numerous studies have identified possible risk and triggering factors that induce or exacerbate rosacea, the pathophysiology of rosacea still remains unknown (2). The contributing factors include family history of the disease, very light skin phototype, exposure to sun and high temperature, and diet (3,4). Apart from well identified possible contributing factors for rosacea, recent studies show emerging evidence that some drugs and vitamins aggravate rosacea or induce rosacea-like symptoms. These agents include topical corticosteroids, topical immunomodulators, oral parabens, epidermal growth factor receptor inhibitors (erlotinib, geftinib, cetuximab), calcium channel blockers, selective phosphodiesterase inhibitors, and vitamin B complex (5-9). Although the exact mechanism of how each of these agents contributes to the development of rosacea is not yet fully understood, some studies suggest that drug induced rosacea-like dermatitis occurs primarily in genetically predisposed individuals (6,10).

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TOPICAL CORTICOSTEROIDS

The regular and excessive use of topical corticosteroids is identified as a potential risk factor that can aggravate or induce rosacea (11-13). Patients usually start using this topical therapy for the treatment of common dermatoses such as seborrheic dermatitis, acne, or melasma, usually as a result of recommendations from nonmedical personnel or through self-prescribing (12). Young women are the most affected population by this problem (12). After diminishing signs of the primary dermatitis due to the vasoconstrictive and anti-inflammatory effects of the steroids, persistent use of these agents leads to epidermal atrophy, degeneration of dermal structure, and deterioration of collagen, consequently leading to the skin disorder resembling rosacea (11,12,14). Skin atrophy can be observed on the centrofacial area, together with erythema, telangiectasia and possible papulopustular eruptions, photosensitivity, and vulnerability to bacterial, viral, and fungal infections (11,13,15). Furthermore, the immunosuppressive effects of corticosteroids facilitate an overgrowth of bacteria, which may act as superantigens, inducing formation of follicular granulomatous lesions (16). This relatively new dermatosis was given various names by different authors, such as perioral dermatitis, rosacea-like dermatitis, steroid rosacea, steroid dermatitis resembling rosacea, and steroid-induced rosacea-like dermatitis (13-15,17). Pathological mechanisms that are thought to be responsible for development of rosacea-like symptoms include dilatation of blood vessels, release of proinflammatory cytokines, and accumulation of nitric oxide (12,18). Although some researchers suggest that the minimum duration needed to develop rosacea-like symptoms was 3 months of continuous use, the average duration of persistent use of topical corticosteroids required to produce these adverse effects is in most cases 6 months or more (11,12). This variability is largely conditioned by individual genetic predisposition as well as the potency of the local corticosteroid used (11,13,15). Consequently, high-potency topical corticosteroids such as clobetasol propionate, betamethasone, fluticasone, and mometasone are more likely to induce this condition (11).

TOPICAL IMMUNOMODULATORS

Local immunomodulator therapy is used for various skin diseases including atopic dermatitis, seborrheic dermatitis, asteatotic eczema, contact dermatitis, or psoriasis localized in sensitive areas such as the face (19-22). Although these agents have a good safety profile and adverse effects are generally rare, there have been case reports of rosacea-like dermatitis, rosacea-like demodicosis, and granulomatous eruptions associated with topical use of immunomodulators (16,19-21,23). Possible pathological mechanism responsible for the immunomodulator-induced rosacea-like dermatitis could include different factors, such as vasoactive properties of topical immunomodulator therapy, proliferation of *Demodex folliculorum* due to local immunosuppression, and an occlusive effect which is more pronounced with use of tacrolimus ointment than with pimecrolimus cream (16,20-23). Although clinical presentation is similar to rosacea caused by topical corticosteroids, it is important to emphasize the absence of skin atrophy during persistent use of topical immunomodulator therapy, unlike under corticosteroid therapy (16,24).

VITAMIN B

As far as vitamin B inducing rosacea is concerned, few studies have been conducted so far (10,25,26). Vitamin B3 (niacin) has been associated with skin flushing, while vitamins B2 (riboflavin), B6 (pyridoxine), and B12 (cyanocobalamin) have shown association with outbreak of acneiform lesions (5,10,25-29). There have also been reports of rosacea fulminans following the administration of vitamin B derivatives; however, the reactions were associated with daily intake of vitamin B6 that exceeded the recommended daily allowance (5,10). Regarding treatment modalities for vitamin B--triggered rosacea, clinical symptoms tend to improve rapidly after discontinuation of the agent, while other standard therapy for rosacea does not achieve optimal therapeutic response (10,27). This type of cutaneous side effect of vitamin B appears to be more common in women than in men (10). Although the pathological mechanism of vitamin B in development of rosacea-like dermatitis is not yet fully understood, the potential factor could be an irritation of the follicular epithelium, leading subsequently to an inflammatory reaction (5,10). In conclusion, vitamin B-triggered rosacea-like dermatitis is rare and usually associated with the intake of large doses of vitamins over a shorter period of time, with early presentation of clinical symptoms.

VASOACTIVE DRUGS

Vasoactive drugs, primarily vasodilators, could be possible triggers that can induce or exacerbate rosacea (30,31). Among this group of drugs, calcium channel blockers are most often associated with skin disorders, affecting dominantly the facial area. These agents are powerful peripheral arterial vasodilators and are frequently used in the treatment of ischemic heart disease or arterial hypertension (32). Although calcium channel blockers are in general rarely associ-

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ated with adverse skin reactions, flushing is a common adverse effect of these drugs experienced by 5% of patients, with greater incidence in women than in men (30,33). Side effects such as the appearance of subclinical rosacea as well as the exacerbation of pre-existing rosacea have been described much more rarely (30,34,35). Spoendlin *et al*. observed the association between use of calcium channel blockers, beta-blockers, and other antihypertensive drugs and incidence of rosacea (36). Their results confirmed the hypothesis that calcium channel blockers increase the risk of rosacea, whereas beta-blocker use is associated with a slightly decreased risk of rosacea (36,37). Considering that in all current clinical guidelines for the treatment of essential hypertension calcium channel blockers belong to the first line therapy and rosacea is one of the most common skin disorders seen in daily practice, this possible association should be additionally evaluated (30). Furthermore, when possible, in cases of pronounced clinical symptoms choosing another first-line antihypertensive drug instead of calcium channel blockers should be recommended (30). Additionally, a few reports have suggested an association between the use of calcium channel blockers and photosensitive reactions with telangiectasia appearing on the face (33,38-42). Although the underlying pathological mechanism of calcium channel blockers in provoking telangiectasia could be in the vasodilatory action of these drugs, it is not clearly understood how they may cause photosensitivity (32). Another vasoactive group of drugs associated with rosacea-like symptoms are selective phosphodiesterase (PDE) inhibitors. These agents have been successfully introduced in the oral treatment of erectile dysfunction (6,43,44). Although these drugs are rarely associated with development of cutaneous side effects, rosacea-like symptoms were described in a few case reports (6).

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Epidermal growth factor receptor inhibitors (EGFRI), including monoclonal antibodies (cetuximab and panitumumab) and the EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, and lapatinib), are amongst the most extensively used targeted agents in the treatment of the most common solid tumors. These agents avoid many of the classic side effects associated with cytotoxic chemotherapy, but their use is frequently associated with cutaneous adverse effects (8,45). The pathological mechanism that is responsible for these cutaneous adverse effects is the inhibition of EGFR in the skin, since EGFR is physiologically expressed in epithelial tissues and hair follicles (8,45,46). The earliest and most common skin side effect is an acneiform or papulopustular skin rash which is found in up to two thirds of patients receiving any of these agents (8,45-49). Clinical presentation is usually mild or moderate and dose dependent, developing within the first few weeks of treatment, predominantly in 2nd and 3rd week after initiation of therapy (48,50). Apart from these cutaneous side effects associated with EGFR inhibitors, less common ones have also been described, mimicking other dermatological conditions such as rosacea, seborrheic dermatitis, or folliculitis (9,46,49,53). Some researchers even suggest that the term acneiform rash should be changed to 'rosacea-like' or 'rosaceiform' (7,54). These hypotheses are based on the results of research that has shown increased density of *Demodex folliculorum* in the skin under EGFR inhibitors, although the role of this agent in dermatological conditions is still controversial (7). Additionally, satisfactory response of the skin lesions to topical treatment with metronidazole is another factor contributing this theory (55). It should be emphasized that the term "acneiform" or "papulopustular" rash does not describe these cutaneous side effects sufficiently, mostly because these lesions appear to be pathologically and etiologically distinct from acne vulgaris (7,45,49). Furthermore, heterogeneity in the definitions of skin toxicity/side effects is a result of different grading and reporting in trials, which are conducted primarily by oncologists and not by dermatologists. Consequently, when a "rash" or "acneiform rash" is reported, it may include a broad spectrum of different clinical presentations including: pustular rash, erythematous rash, rosaceiform dermatitis, acneiform dermatitis, exfoliative dermatitis, papular rash, pruritic rash, generalized rash, and maculo-papular rash (52,54). Therefore, many researches have emphasized the need for more accurate classification of EGFR inhibitor-associated cutaneous side effects (7,52,54).

CONCLUSION

Rosacea is commonly seen in daily dermatological practice. Its etiopathology still remains unknown. In this review, we focused on possible triggers of rosacea or rosacea-like dermatitis apart from those that have already been identified, such as exposure to sunlight and high temperatures, diet, and stress. Recent studies have demonstrated the association between the use of certain drugs or vitamins and development of rosacea-like dermatitis or exacerbation of preexisting rosacea. The mechanisms that are responsible for this effect can only be partially explained, but they mainly depend on the pathophysiologic mechanism of the drug or vitamin that is used. Since there is a

considerable number of potentially rosacea-inducing drugs that are used in frequent medical conditions such as hypertension and ischemic heart disease, solid tumors, erectile dysfunction, and atopic dermatitis, we emphasize the need for awareness of the fact that these incriminating agents could be possible triggering factors. In these specific situations rosacea-like dermatitis can also affect treatment compliance, consequently interfering with the therapeutic regimen. Furthermore, it can cause a significant psychological burden and have an impact on patient quality of life. Regarding treatment options for drug induced rosacea-like dermatitis, the only treatment modality is prompt discontinuation of the drug or vitamin, or in the case of a chronic medical disorder which requires uninterrupted therapy, choosing a drug with same action mechanism but from another class. It can be concluded that, considering recent evidence and observations on the influence of drugs or vitamins on rosacea development or aggravation, further research should be conducted to objectivize the role of these potential triggering factors.

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