Seborrheic Dermatitis: An Update

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SUMMARY Seborrheic dermatitis is a chronic relapsing inflammatory skin disorder clinically characterized by scaling and poorly defined erythematous patches. The prevalence of adult seborrheic dermatitis is estimated at 5%. Although the exact cause of seborrheic dermatitis has yet to be understood, Malassezia yeasts, hormones (androgens), sebum levels and immune response are known to play important roles in its development. Additional factors including drugs, winter temperatures and stress may exacerbate seborrheic dermatitis. A variety of treatment modalities are available, including antifungal agents, topical low-potency steroids and calcineurin inhibitors (immunomodulators). This review summarizes current knowledge on the etiopathogenesis and therapy of adult seborrheic dermatitis.

KEY WORDS: seborrheic dermatitis, Malassezia yeast, sebum, antifungal agents

INTRODUCTION Seborrheic dermatitis (SD) is a common chronic relapsing inflammatory skin disorder clinically characterized by poorly defined erythematous patches and scaling. SD primarily affects sebum rich areas, including scalp, face, upper chest and back (1).

The prevalence of adult SD is estimated at 5% (2). This condition is more common in males than in females. Among adults, the peak incidence is in the third and fourth decades of life. Although the exact cause of SD has yet to be understood, Malassezia yeasts, hormones (androgens), sebum levels and immune response are known to play important roles in its etiopathogenesis (3). Some researchers propose a pivotal role for Malassezia yeasts (formerly called Pityrosporum ovale) in seborrheic dermatitis (4). Antifungal therapy leads to decreased colonization with Malassezia spp. and concomitant disappearance of skin lesions, which is probably the strongest evidence that Malassezia spp. have momentous role in the development of SD (5). Other therapeutic options include corticosteroids, immunomodulators and antibiotics.

ETIOLOGY AND PATHOGENESIS Despite quite a high prevalence of this disorder, the exact cause is poorly understood. However, several factors (Malassezia yeasts, hormones, sebum levels, immune response, neurogenic factors, external factors) seem to be involved in SD etiopathogenesis, but the exact pathogenetic mechanism still remains controversial.
Malassezia species

Growing evidence indicates that Malassezia spp. are a major etiologic factor in SD development. The number of Malassezia spp. decreases after antifungal therapy with disappearance of skin lesions. This is probably the strongest evidence that Malassezia spp. have an important role in the development of SD. Malassezia spp. are lipophilic yeasts that are ubiquitous residents of the skin (8). They are predominantly situated on lipid-rich anatomic areas. Whereas eleven species have been identified, seven of them are associated with human skin flora and SD. Malassezia (M.) furfur, M. restricta, M. sympodialis, M. globosa, M. obtusa and M. slooffiae have been detected on affected skin (9). However, M. globosa and M. restricta predominate in SD lesions, particularly on the scalp (10).

Since Malassezia spp. have the ability to produce lipases, they can initiate inflammatory response by releasing oleic and arachidonic acid from the sebum lipids (11,12). Both of these unsaturated fatty acids have direct irritative and desquamative effects on keratinocytes. Furthermore, arachidonic acid metabolized by cyclooxygenase serves as a source of proinflammatory eicosanoids (particularly prostaglandins), leading to inflammation and consequent damage of stratum corneum. Keratinocytes at affected areas are stimulated to produce proinflammatory cytokines that further enhance and maintain the inflammatory response. Malassezia-driven pathogenetic “vicious circle” closes owing to the fact that saturated fatty acids, released by Malassezia lipases, are used as a “proliferative fuel” for these yeasts.

Hormones and skin lipids

SD is not always associated with excessive secretion of sebum (13). However, 50% of patients have oily, sebum rich skin. As mentioned above, sebum lipids are essential for Malassezia proliferation and synthesis of initial proinflammatory factors, so a certain amount of sebum is always required in order to provide permissive conditions for SD development. Therefore, SD lesions are predominantly located on skin areas rich in sebaceous glands. SD is most common in puberty and adolescence, during periods of highest sebum production. There is also a possible hormonal link: not only does the disease occur in puberty, but SD is more common in males than in females, suggesting an influence of androgens on the pilosebaceous unit (14).

Immune response

Since SD is an inflammatory condition, largely accompanied by the presence of Malassezia yeast, it is reasonable to assume that inappropriate immune response may contribute to the pathogenesis. Although the immunopathogenetic mechanism involved in the development of SD is not clearly understood, several studies indicate immune dysfunction in SD patients. The strongest evidence for immunodeficiency as an etiologic factor comes from findings that SD prevalence is significantly higher (34%-83%) among HIV positive and AIDS patients compared to general population (approximately 3%). Furthermore, in HIV positive patients, a more severe clinical presentation of SD (often affecting even extremities) has been observed; hence, SD in these patients is considered by some authors as a distinctive entity (“seborrheic-like dermatitis of acquired immunodeficiency syndrome”). Studies conducted by Bergbrant et al. have directly shown impaired function of T cells and increased number of NK cells in peripheral blood of SD patients compared to control group (15). The same study showed increased levels of total serum IgA and IgG antibodies in patients with SD, which was also confirmed by several other studies. Interestingly, despite the presence of hypergammaglobulinemia in SD patients, there were no elevated titers of antibodies specific to Malassezia antigens, suggesting that increased immunoglobulin production occurs as a response to yeast toxins and lipase activity. Faergemann et al. found infiltration of NK cells and macrophages in SD affected skin areas, with concomitant local activation of complement and proinflammatory cytokine induction, which all together can result in epidermal devastation (16). Considering the fact that Malassezia may be present on the skin commensally, without provoking any immune reaction or inflammation, it could be concluded that in SD patients an abnormal immune reaction to the yeasts occurs, which is influenced by the interplay of other pathogenetic factors that may govern and modulate an individual immune response.

Neurogenic factors

The frequent occurrence of SD in patients with Parkinson’s disease has long been clinically observed, particularly in those with prolonged and severe seborrhea, which provides permissive conditions for Malassezia proliferation (17). Since bilateral seborrhea occurs in patients with unilateral parkinsonism, it seems that these changes in sebum level are provoked endocrinologically rather than neurologically (18). This is supported by the findings of increased plasma α-melanocyte stimulating hormone (α-MSH) levels in patients with Parkinson’s disease, probably due to the lack of MSH-inhibiting factor as a consequence of insufficient dopaminergic neuronal activity (19).
Namely, treatment with L-dopa successfully restores MSH-inhibiting factor synthesis and reduces sebum secretion in parkinsonian patients. This sebostatic effect of L-dopa is limited exclusively to patients with Parkinson’s disease, whereas in other seborrheic conditions such as acne, L-dopa has no effect on sebum production (19). Furthermore, facial immobility of Parkinson’s disease patients (mask-like face) can secondarily lead to the increased sebum accumulation, thus additionally contributing to the tendency of SD development.

Similar mechanisms may be, at least partially, responsible for the frequent occurrence of SD in patients treated with neuroleptic drugs, as well as in patients with tardive dyskinesia, central nervous system trauma and facial nerve palsy.

Frequent occurrence of SD is also observed in depressive disorders, but this could be attributed to the tendency of depressed patients to remain indoors, as well as to altered hygiene habits.

**Other factors**

SD has a seasonal aspect; relapse of the disease is more common in low fall and winter. The condition can be triggered by emotional stress; a high rate of seborrhea is reported among combat troops in war times (20). Traditionally, diet is blamed for the development of SD. A severe zinc deficiency in patients with acrodermatitis enteropathica and acrodynatitis-like conditions can produce a seborrheic dermatitis-like rash (20). Common SD does not respond to supplementary zinc therapy.

**CLINICAL FEATURES**

Typical SD lesions are erythematous patches, with greasy large scales. The disorder has a predilection for areas with numerous sebaceous glands, such as scalp, forehead, eyelid, eyebrow, glabella, nasolabial folds, ears, upper chest, back, axillae, umbilicus and groins. Patients often report pruritus, especially on the scalp and in the ear canal. Scalp lesions may extend into the forehead skin and form scaly erythematous border called “corona seborrhoeica”. Two forms of SD may occur on the chest, a common petaloid type and quite rare pityriasisiform type (6). The petaloid type starts with red to brown follicular and perifollicular papules, which develop to patches that resemble the shape of flower petals or medallion. The pityriasisiform type is probably an acute severe form of petaloid SD (7). This type has generalized maculae and patches that follow the skin lines mimicking pityriasis rosea. In some individuals, chronic dermatitis of the ear canal may be the only manifestation of SD. Another common symptom of SD is blepharitis with honey-colored crusts along the rim of the eyelid. When only this manifestation is present, the diagnosis is not simple. A serious variant of this skin disorder is generalized exfoliative erythroderma (seborrheic erythroderma).

**DIFFERENTIAL DIAGNOSIS**

Although in everyday practice SD can usually be diagnosed at the first sight, patients presenting with skin lesions suspect of SD should be thoroughly considered for the possible presence of other, more serious dermatologic disorders, which are clinically manifested with chronic eczematous and papulosquamous lesions. The patient’s age, gender, affected sites, presence of concomitant conditions and diseases (especially immuno-compromising), family history as well as everyday habits must be taken in consideration on differential diagnosis. A patient with erythematous and scaling plaques in the areas such as scalp, nasolabial folds, eyebrows and retroauricular regions has most likely SD, but these clinical features of SD may be confused with psoriasis, leading to misdiagnosis. To facilitate distinction, findings of sharply demarcated scalp plaques, nail pitting and distal onycholysis may be helpful, as they are typically present in psoriatic patients (21). The occurrence of so-called seborrhiasis could be found, indicating a condition with overlapping psoriasis and SD on the face. Facial SD lesions may resemble skin changes found in systemic lupus erythematosus (if suspected, immunologic assessment is required) and in certain photodermatoses. SD changes on the trunk sometimes may be misinterpreted as tinea versicolor that can easily be distinguished with Wood light examination and presence of hyphae on scraped KOH cytologic preparation. Furthermore, differential diagnosis also includes atopic and contact dermatitis, rosacea, dermatophytosis, candidiasis, and, uncommonly, cutaneous lymphoma or Langerhans cell histiocytosis. Skin biopsy is rarely needed to verify the diagnosis, and associated histologic changes may vary from acanthosis and parakeratosis to spongiosis.

**MANAGEMENT AND THERAPY**

Since the key underlying pathogenetic mechanisms of SD include excessive *Mallasezia* spp. proliferation with consequent induction of local skin inflammatory response, today’s therapeutic approach is commonly based on topical antifungal, antiinflammatory and immunomodulatory agents. Given that desquamation is regularly present, keratolytics are also highly effective. In some patients, significant improvement can also be achieved by antibiotics (met-
ronidazole), tar and phototherapy. Systemic therapy is rarely required, only in severe cases with strikingly outspread lesions, as well as in cases unresponsive to topical treatment. Some alternative therapeutic approaches have also been reported, such as tea tree oil and 90% honey diluted in warm water.

**TOPICAL THERAPY**

Topical agents are effective and well tolerated in the majority of SD cases, as shown and validated by multiple randomized clinical trials, but today also empirically well-known from everyday clinical practice.

**Antifungal medications**

Although earlier treatment approaches were focused on antiinflammatory agents, today it is generally accepted that initial therapy for SD should be based on topical antifungals. Azole class of antifungal agents (lanosterol 14 α-demethylase inhibitors) proved to be most effective in growth inhibition of *Malassezia* spp., associated with the development of SD.

Among the azoles, ketoconazole applied in various vehicles showed superior effects, and hence it is the first-line treatment for SD.

Ketoconazole is available in different topical over-the-counter preparations, such as shampoos, creams and gels. Ketoconazole shampoo 2% is effective in treating scalp SD, used twice weekly. Intermittent use of ketoconazole 2% shampoo (once weekly) has been shown to have a significant prophylactic effect (22). Ketoconazole 2% cream significantly improves SD lesions of the face and chest used twice daily (effective as hydrocortisone 1% cream) and, intermittently used, also effectively maintains remission (23). Ketoconazole also has slight antiinflammatory properties, and it is principally well tolerated in all available formulations.

Bifonazole 1% cream, used once daily, is usually effective in the treatment of SD of the scalp and face (24,25). A combination ointment containing 1% bifonazole and 40% urea helps reduce the symptoms of scalp SD (26).

Miconazole is an azole that can also be effectively used in the treatment of SD as a monotherapy or in combination with hydrocortisone (27).

Another topical antifungal agent, ciclopirox 1% cream, is likewise effective and provides a reduction of symptoms when used twice daily. Ciclopirox has both antifungal and antiinflammatory properties (28). Combinations of ciclopirox 1.5% shampoo with salicylic acid 3% or zinc pyrithione 1% are also effective (29). Recent studies show statistical non-inferiority of ciclopirox in comparison with ketoconazole (30).

**Corticosteroids**

In severe cases of SD, low to mild potency topical corticosteroids are effective in fast clearing of visible signs and associated symptoms (31). Topical corticosteroids can be used alone or in combination with antifungal agents. Often and prolonged use is not recommended because of their well-known side effects such as atrophy, telangiectasias, hypertrichosis and perioral dermatitis. Antifungal agents are still the first choice in the treatment of SD due to the fact that ketoconazole 2% has been shown to be superior to betamethasone dipropionate 0.05% in reducing symptoms and lowering the number of *Malassezia* spp. (32). There is a consensus that topical corticosteroids are useful in short term mainly to control erythema and itching.

**Metronidazole**

There are contradictory data on the effectiveness of topical metronidazole 0.75% gel. In two trials, metronidazole showed better efficacy than placebo and was as effective as ketoconazole 2% cream (33,34). Conversely, Koca et al. found metronidazole not superior to placebo in patients with SD (35).

**Calcineurin inhibitors**

Topical calcineurin inhibitors, pimecrolimus 1% cream and tacrolimus 0.03% and 0.1% ointment decrease cutaneous inflammation by inhibiting T-lymphocyte driven cytokine production (36). These agents are not associated with the side effect profile of corticosteroids. In a randomized, double blind, vehicle-controlled 4-week efficacy trial of twice daily pimecrolimus 1% cream in 96 patients, topical calcineurin inhibitor therapy was effective and well tolerated in the treatment of SD (37). In two randomized clinical trials, pimecrolimus 1% proved to be as effective as topical corticosteroids (hydrocortisone acetate 1% cream or betamethasone 17-valerate 0.1% cream) (1). However, rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors. Due to this fact, long-term use is not recommended and application should be limited to lesions of SD (38).

**Zinc pyrithione**

Zinc pyrithione is a common active ingredient in most of the over-the-counter anti-dandruff shampoos and has both antifungal and antimicrobial effects (39). This agent is available in concentrations of...
1% and 2% in shampoos as well as a 1% cream formulation (40). Zinc pyrithione has shown inferior efficacy than ketoconazole in several trials, but it might still be effective to clear visible signs of the disease when used alone or in combination with ketoconazole (41).

Lithium salts

Topical lithium succinate and lithium gluconate are effective agents in treating SD in the areas other than scalp, probably due to their anti-inflammatory effects. In a randomized trial involving 12 patients, lithium succinate 8% ointment showed greater efficacy than placebo in the treatment of visible signs of the disease in HIV-positive patients (42). Lithium gluconate 8% ointment, used twice daily, was shown to be more effective than placebo in an 8-week trial involving 129 patients with facial lesions (43). Also, lithium gluconate 8% ointment is more effective than ketoconazole 2%.

Selenium sulfide

In a randomized double-blind trial involving 246 patients with moderate to severe dandruff, selenium sulfide 2.5% was tested against ketoconazole 2% and placebo. Both medicated shampoos showed greater efficacy than placebo, but ketoconazole was better tolerated (44).

Phototherapy

Many patients notice improvement during the summer. Phototherapy using UVB rays is sometimes considered as an option for severe or recalcitrant SD. In an open prospective study, 18 patients with severe SD were treated with narrow-band UVB three times per week until the clearance or upon completing 2 months of therapy (45). The median number of treatment sessions was 23 and the median cumulative UVB dose was 9.8 J/cm². All patients showed improvement, especially those with severe disease, but burning and itching may occur during phototherapy. The biggest drawback of UVB irradiation is rapid disease relapse appearing 2-6 weeks after treatment. Also, there are risks associated with exceeding the maximum lifetime allowable cumulative dose and carcinogenic effects on the skin.

SYSTEMIC THERAPY: ORAL ANTIFUNGAL MEDICATIONS

Data on the effectiveness of systemic antifungal therapy are not consistent. In a randomized, double blind, placebo-controlled study, 174 patients with SD received either 250 mg of terbinafine or placebo for 6 weeks. Oral terbinafine was not more effective than placebo in patients with facial SD, but in other areas terbinafine showed greater efficacy than placebo (46). In another double blind study involving 63 patients, oral fluconazole in a 300 mg single weekly dose showed no significant therapeutic effect (47). In one trial involving 19 patients, ketoconazole (200 mg daily dose for 4 weeks) showed significant improvement (48). On deciding on oral antimycotic therapy, the cost-benefit ratio must be carefully considered due to the possible hepatotoxic effect of systemic antifungals.

CONCLUSION

Seborrheic dermatitis is a chronic, relapsing, papulosquamous inflammatory skin disorder, which must be strictly distinguished from seborrhea. The etiology is still not completely understood, but among the many identified etiopathogenetic factors, *Malassezia* yeast has certainly a pivotal role. In the majority of cases, satisfactory therapeutic results are achieved by topical antifungal agents of theazole class that are principally well tolerated without significant side effects, and therefore today are considered as the first-choice treatment for SD. Local glucocorticoids are also effective, but long-term use should be avoided because of their well-known side effects. Although SD *per se* does not seriously disrupt the patient’s quality of life, it should be kept in mind that its occurrence, particularly in severe, therapy-resistant form, can be a predictor of some serious conditions such as HIV infection.

References