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6

Head and Neck Psoriasis

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1. Introduction

Psoriasis is an immuno-mediated condition whose pathogenesis is still unclear and that in head and neck area presents six specific aspects that justify the title of this chapter: 1) visibility of the lesions and their impact on quality of life (QOL); 2) the very common involvement of the scalp; 3) the difficulty of the treatment; 4) the aberrant epidermal-mesenchymal interactions theory; 5) the rare mucous occurrence and the PPP-tonsil-related disease; 6) the significantly increased risk of head and neck cancer in men with Psoriasis.

2. Visibility and the impact on quality of life

Visibility of head and neck Psoriasis has a considerable impact on patients' QOL. The differential diagnosis for pustular skin disorders is extensive but facial Psoriasis more commonly affects eyebrows, the skin between the nose and the upper lip, the upper forehead and the hairline. Scalp Psoriasis is very common. Multiple instruments have been used to determine the severity of scalp Psoriasis and tools for patient self-assessment have also been developed (Psoriasis Area and Severity Index or PASI, Psoriasis Scalp Severity Index or PSSI, Body Surface Area or BSA, Physicians' Global Assessment or PGA, Lattice Physician Global Assessment or LS-PGA, and Self-assessed Psoriasis Area and Severity Index or SAPASI) but none of the severity scores used for Psoriasis meets all of the validation criteria required for an ideal score. However the PASI score is the most extensively studied (Puzenat & al, 2010).

While head represents only 10% of the whole body's surface, consequences of scalp Psoriasis are disproportionate to its extension as it can be seriously debilitating inducing important social and emotional distress.

Although it is unclear why initial scalp involvement is so common, scalp tissue has unique features that may promote its vulnerability to psoriatic lesions. For example, its high follicular density provides a dark, warm and moist environment that reduces environmental UV exposure which normally would limit lesion development. In addition, inflammation-

promoting microorganisms flourish in the sebum-rich setting of the scalp and, as seen in one study, an association with the severity of scalp disease was suggested to be related to isolation of Malassezia globosa yeast from patients scalp (Gupta & al., 2004).

Additional inflammation may be triggered or exacerbated by frequent friction and trauma to the scalp (Koebner phenomenon: psoriatic lesions as consequence of trauma in psoriatic patients) from brushing or use of styling implements.

Psoriasis of the eye is extremely rare. When it does occur, it can cause inflammation, dryness and discomfort. It may cause vision impairment. When Psoriasis affects the eyelids, scales may cover lashes and topical antibiotics may be used to treat infection.

Psoriasis generally affects the external auditory canal without involvement of the ear or behind the eardrum but can cause scale buildup that can block the auditory canal with subsequent temporary hearing loss.

Rarely Psoriasis appears on the gums, the tongue, inside the cheek and the nose or on the lips. The lesions in these areas are usually white or gray and can be relatively uncomfortable as they can cause chewing and swallowing discomfort.

When Psoriasis involves the face, it can be much more disabling and can severily decrease patient's QOL. Facial Psoriasis is difficult to treat and is associated with severe cutaneous disease. In fact, patients who have a long history of Psoriasis or an early age of onset are more likely to suffer from facial involvement. Facial Psoriasis may also be associated with pruritus, psoriatic arthritis, and with a family history of Psoriasis.

Various clinical manifestations of Psoriasis make it more than a dermatological nuisance, as it interferes with many normal daily activities, such as use of hands, walking, sleeping, and sexual activity. At least 30% of patients contemplate suicide, which places Psoriasis on par with other major medical diseases such as depression, heart disease and diabetes (Krueger, 2001).

Alexithymia was originally defined as the inability to recognize and verbalize emotions. It is characterized by an emptiness of feelings, poverty of imagination or of a life fantasy and by difficulties in communicating with other peoples, as well as lack of positive emotions and a high prevalence of negative emotions. Its presence has been incriminated in genesis and maintenance of various psychosomatic pathologies.

As patient's psychological dimension seems to be related to the onset of the illness, to its evolution and to its prognosis, Psoriasis is classified among psychosomatic pathologies too.

In this perspective Alexithymia does not appear to be simply a condition related to Psoriasis, but a worsening of patient's condition, exposing him to other psychosomatic diseases and alcoholism and to a worsening of his global prognosis. That's why psychological approach in treatment favouring expression of patient's emotions and opening a symbolic dimension is as important as the biological approach and is necessary for improvement (Masmoudi, 2009).

A recent cohort study (Gelfand & al., 2011) has also shown that severe Psoriasis (defined as Psoriasis patients with a history of systemic therapy) is associated with an increased risk of mortality as male and female patients in the study died 3.5 and 4.4 years younger

respectively than those without Psoriasis (even after adjustment for classical risk factors of mortality). Hence Psoriasis is a major public health problem.

The data analysis suggests that a minimum of two summary scores (one for skin and one for joints), and potentially a third for nails, are required to accurately assess severity across the full spectrum of psoriatic disease. The optimal design of such assessment tools remains the objective of many research projects, with efforts continuing to identify the most meaningful contributing elements that define the full spectrum of the psoriatic disease state (Wittkowski & al., 2011).

2.1 Addictions and Psoriasis

Association between Psoriasis and addictive disorders is a longtime suspect and several studies are supporting association of Psoriasis and alcohol, and of Psoriasis and tobacco. Association between Psoriasis and alcohol seems not to be influenced by gender and shows a dose-effect relation. The most striking link between cigarette smoking and Psoriasis has been established in Palmo-Plantar Pustulosis (PPP). This link also seems to exist for other forms of Psoriasis with a dose-effect relation.

The relationship between cigarette smoking and Psoriasis has been the subject of several studies. It was showed that cigarette smoking represents a significant risk factor for appearance of Psoriasis, especially in women, in a case about five, and it has been pointed out that risk increases with the number of cigarettes consumed per day and increases in those who smoke 20 or more daily. The risk would increase further in those who have a family history of this disease. Also for PPP seems to be a relation to cigarette smoking, with a risk factor 7.2 times higher in smokers than in non smokers. The report is based on leukocyte neutrophil counts: PPP is a neutrophilic dermatosis and cigarette smoke increases peripheral neutrophil counts and alters it in morphological and functional way.

Cigarette smoking may be involved in the high prevalence of lung and oral cancer and cardio-vascular disorders in psoriatic patients. The association between alcohol and development of plaque-type Psoriasis is complex and confusing because many of the initial studies did not control for confounding factors such as tobacco use.

There are a number of difficulties in the assessment of the correlation between Psoriasis, cigarette smoking and alcohol, and even more so in establishing a causal or etiologic relationship between the three because of several confusing factors (Meyer &al., 2008).

Alcohol-controlled studies suggest that women who are smokers have an up to 3.3-fold increased risk of developing plaque-type Psoriasis. Men who are smokers do not exhibit such an increased risk, but studies have shown that smoking more than 10 cigarettes per day by men who are Psoriasis patients may be associated with a more severe expression of disease in their extremities. In addition, smoking among both men and women who are Psoriasis patients has been shown to reduce improvement rates.

Dermatologists are not only the sentinels for early diagnosis of psoriatic arthritis, but also for metabolic complications such as dyslipidemia or diabetes. Moreover, they need to keep in mind interactions between (systemic) anti-psoriatic drugs and the co-medication of their patients as well as possible consequences of these co-medications on the course of Psoriasis (Behnam & al., 2005).

The association between Psoriasis and alcoholism represents one of the major psychodermatological issues where a multidisciplinary approach (including dermatologist, psychiatrist, psychologist and others) is crucial for optimal outcome. Psoriasis is associated with an increased risk of comorbidity and mortality compared to the general population. It appears that patients with Psoriasis have a higher prevalence of metabolic disorders such as diabetes, hypertension, obesity, and hyperlipidemia, as well as a higher frequency of cigarette smoking. These concomitant diseases can complicate the treatment of Psoriasis.

3. The very common involvement of the scalp

The estimated prevalence of Psoriasis worldwide is 0.3-5%, depending on ethnic origin (Naldi, 1994; Valdimarsson, 2007). In a retrospective analysis in children was present scalp involvement in 48% on 125 patients by Stefanaki & al. (2011) and in 50.3% on 137 patients (most common initial site affected) by Wu & al. (2010) .

Psoriasis of the scalp is estimated to occur in 40-90% of patients with Psoriasis. Up to 79% of patients with chronic plaque Psoriasis may have scalp involvement (Farber & Nall, 1992). It can be mild to severe, frequently itchy and so cosmetically embarrassing to affect patient's QOL adversely. Treatment is often prolonged for a long period of time and can be another cause of worsening of patient's QOL because of hair staining, face irritating, messy, time-consuming and cosmetically unacceptable applications prescribed.

As with Psoriasis elsewhere on the body, skin cells grow too quickly on the scalp and cause red lesions to be covered with scales. Scalp Psoriasis can be very mild with slight and fine scaling but can also be severe with thick, crusted plaques covering the entire scalp. Psoriasis can extend beyond the hairline onto the forehead, the back of the neck and around the ears.

The scalp is frequently involved in patients with Psoriasis vulgaris but rarely it is the only site affected. Lesions look like an erythematous crown with net margins covered by dry silvery-white scales. They are located at the hairline in the fronto-temporal, parietal or occipital areas (where, often, the erythematous component is more pronounced) and are associated to scaling-scratching squamous lesions. In the fronto-temporal regions, particularly in young subjects, the spots extend beyond the scalp involving the skin of the forehead and ear. In patients with a long history of scalp Psoriasis the confluence of many spots and the scant evidence of the erythematous component leads to the formation of a real shell that can cover the entire scalp. In other cases, silvery-white scales are seen on a widespread dry pityriasiform furfuracea-like desquamation, sometimes showing follicles. The spots do not produce alopecia and hairs are not incorporated by squamous heaps but in the less restrictive forms the pseudotinea amiantacea can be seen. This lesion, once considered a variant of impetigo, is characterized by the presence of small opaque white adherent scales similar to asbestos, that incorporate the proximal part of the hair shaft.

Psoriasiform lesions localized to the face often represent the extension of scalp lesions to the brow, the temporal regions, the ears and the retroauricular fold where it is observed a tendency to fissures. The involvement of the face in the course of Psoriasis is considered an index of extended or severe disease as in the case of erythrodermic Psoriasis. Rarely small droplike lesion in the face can be seen in case of eruptive Psoriasis; in case of mild forms of Psoriasis Vulgaris (minimal Psoriasis) instead, the eyelid involvement by small patches of whitish scales is characteristic. Psoriasis of the ear is characterized not only by the

involvement of the auricle but also by the involvement of external auditory canal by heaps of scales that can stamp it. Diagnosis of SeboPsoriasis, that is characterised by the presence of yellowish-white unctuous scales can be put when psoriasiform lesions are localized exclusively in seborrheic areas of the face (naso-labial fold, glabella and eyebrows, auricle and retroauricular fold) and are associated with similar lesions of the hairline and the presternal area. This clinic form, on the border between Psoriasis Vulgaris and Seborrheic Dermatitis, is considered a Psoriasis arisen on patches of Seborrheic Dermatitis because of the Koebner phenomenon.

Family history may predispose patients to scalp Psoriasis. In an analysis of Psoriasis genes in an Icelandic patient population, 296 of 1,000 Psoriasis patients experienced onset of Psoriasis on the scalp. Cluster analysis (Karason & al., 2005) of this subset of patients determined that 198 patients fit within 79 families and determined a linkage to chromosome 10. The familial nature of Psoriasis has long been recognized with evident intra and interfamilial variability. Thirty nine individual with Psoriasis (25 men and 14 women) from 9 Tunisian unrelated multiplex families (in Tunisian population the estimated prevalence of Psoriasis is of 3%) were investigated during a study period of 1 year (Ammar & al., 2009). The common form of Psoriasis was discovered in 37 cases. The nails, the scalp, the mucous membranes were involved respectively in 21, 12 and 13 cases. The Psoriasis was severe in 11 cases.

Methods used to diagnose scalp Psoriasis vary in sensitivity, reproducibility, and invasiveness. Recently has been introduced a videodermoscopy scalp Psoriasis severity index (VSCAPSI) for evaluation of scalp Psoriasis (Rossi &al., 2011). This index is particularly useful in mild and moderate forms that often are not clinically appreciable. VSCAPSI takes into account extension of the area of the scalp affected, the presence and morphology of vascular patterns, erythema and desquamation. Videodermoscopy images obtained between November 2009 to June 2010 from 900 participants with various scalp and hair disorders were reviewed for distinguishing features. During the 2010 Italian congress on Psoriasis, in order to assess the reproducibility and efficacy of the VSCAPSI, 146 dermatologists were asked to evaluate 16 videodermoscopy images of scalp Psoriasis using the VSCAPSI. Of the 900 patients, 85 new cases of scalp Psoriasis were diagnosed. The other 815 patients were found to be suffering from different scalp and hair diseases. Of 146 dermatologists, 28 did not recognize erythema, 15 desquamation and 7 the vascular patterns. The VSCAPSI provides an important tool for early diagnosis, differential diagnosis and follow-up and screening.

3.1 Histology of head and neck Psoriasis: Gross findings

Head and neck Psoriasis (in the form of the so-called Psoriasis vulgaris or plaque type of Psoriasis and guttate Psoriasis) commonly involves the skin surface of the scalp and the face (eyebrow, nose, upper lip, forehead, and hairline) and presents as papules, well-demarcated erythematous plaques with a scaly surface or as papulo-squamous lesions covered by fine silvery-white and loosely adherent scales. The amount and thickness of the scales is variable such are the plaques, ranging in size from few to several centimeters, with coalescence of smaller plaques into larger and sometimes fissured lesions. On the other hand, less thick plaques and less scaly lesions are commonly encountered in children with face psoriatic localization compared with adults. Pustular forms of Psoriasis are rarely described on the

face as annular or circinnate and pustular lesions on an erythematous background with an acute, subacute or chronic clinical course. Pustular eruptions are frequently associated with a classic form of skin Psoriasis, and both hair loss and involvement of tongue mucosal surface may be appreciated. Oral localizations, less commonly observed in children than in adults, appear as pustular and hyperemic lesions within a geographic and fissured tongue. In such a localization, infections, smoking and physical agents all may affect the course and duration of Psoriasis and may cause dysphagia. Unusual mucosal (nose, oral cavity) or ocular localizations are commonly described in patients with otherwise usual skin psoriatic dermatitis. Mucosal lesions show a non-specific macroscopic appearance ranging from erythematous and slightly raised lesions to a white annular, serpiginous and ulcerated pattern that may disappear quickly, with no obvious clinical symptoms, or may have exacerbations and remissions similar to skin lesions. Pustular forms, mixed white and erythematous lesions, ulcerative, vescicular and indurated lesions, multiple annular coin-sized lesions, gray, yellowish, translucent and silvery-white forms are described with macroscopic findings similar to several so-called psoriasiform benign and malignant conditions involving the oral cavity. In this setting, the diagnosis mainly rely on an interdisciplinary clinical and histological approach with a crucial role played by the microscopic findings on mucosal biopsy. Psoriasis vulgaris may also be associated to oral localizations such as the case of geographic tongue and the stomatitis areata migrans. Patients with Psoriasis rarely develop uncommon ocular manifestations such as uveitis, blepharitis and conjunctivitis as a result of changes, alterations and dysfunctions of conjunctival surface, tear film and meibomiam gland changes.

3.2 Microscopic findings

Variabilities in clinical macroscopic findings of Psoriasis reflect different histologic pictures with relation to the stage of the disease. Generally, early stages show more typical and pathognomonic microscopic clues to the diagnosis than that of the advanced and fully developed lesions. Moreover, histologic differences could also be noted in psoriatic lesions affecting mucosal surfaces.

In its classic histologic appearance, cutaneous Psoriasis shows achantosis (thickened of epidermal layers) and parakeratosis (retention of cell nuclei in stratum corneum) of the epidermis, with thin or loss of granular cell layer, downward elongation of rete ridges and thinning of the epidermis overlying the dermal papillae that shows edema and small vessels close to the epidermis. The latter condition underlies the so-called Auspitz sign: when the silvery scales (parakeratotic layers) are removed from the plaque (epidermal achantosis), small pinpoint bleeding (from dermal capillaries) is seen.

The inflammatory cutaneous infiltrate of Psoriasis is characterized by neutrophils and lymphocytes throughout the superficial papillary dermis. Activated CD3+ T cells are mainly observed around small papillary vessels and are admixed with neutrophils and macrophages. Neutrophils and lymphocytes can migrate upwards from the dermis to the epidermis and in parakeratotic layers (exocytosis). Collections of intraepithelial neutrophils (Munro abscesses) and those arranged in the epidermis in a network of degenerated keratinocytes (spongiform pustule of Kogoj) are characteristics of Psoriasis but not always present nor specific to the disease.

In the pustular form of Psoriasis, such a collection of neutrophils occurs as characteristic macropustules (abscesses), while epidermal and dermal changes are similar to those seen in Psoriasis vulgaris. The so-called eruptive or guttate Psoriasis, with small and numerous red papules and an acute onset on clinical examination, shows similar microscopic findings to that of early Psoriasis vulgaris lesions unless the same degree of achantosis.

Mucosal localizations show a more variable histological presentation ranging from classic hyperparakeratotic lesions, with thinning of the suprapapillary plate and mixed inflammatory infiltrate with neutrophils exocytosis to mild and quickly self-limited erythematous inflammatory conditions with capillaries engorgement but without microabscess formation. Similar microscopic characteristic are shared by different inflammatory mucosal diseases generally known as psoriasiform mucositis or psoriasiform lesions. In such instances, histological distinction between Psoriasis and other inflammatory mucosal entities cannot be made with confidence unless mucosal lesions are associated to or are coincident with cutaneous psoriatic dermatitis and additional data (family history, HLA typing) are available.

3.3 Differential diagnosis

Although the diagnosis of Psoriasis mainly rely on clinical settings, histological evaluation should be used to confirm the diagnosis as well as to evaluate unusual clinical lesions and to exclude benign and malignant conditions that may mimic Psoriasis or may be associated to it.

On the other hand, microscopic findings alone should pose problems in differential diagnosis with other inflammatory disorders as well as in the evaluation of the phase of Psoriasis normally evolving through early, advanced and later lesions with a different microscopic variability with lesion's age and activity.

Skin psoriatic manifestations should sometimes require a differential diagnosis from dermatoses such as lichen planopilaris, florid seborrheic dermatitis and discoid lupus erythematosus.

On the other hand, differential diagnosis of oral localization of Psoriasis could also consider Reiter's syndrome, erythema migrans, benign migratory glossitis, oral lichen planus and other inflammatory conditions generally described as psoriasiform lesions.

Clinical data alone may be inadequate such as the case of Koebner phenomenon that could be present in lichen planus.

In this settings, the macroscopic characteristics of cutaneous psoriatic lesions (well defined elevated lesions, with silvery-white or micaceous scale), the clinical data (symmetrical distribution, Auspitz sign, patient's history reporting itchy, skin scaling and peeling, lesions at site of injury or trauma) and the classic histologic findings may all contribute to a definitive diagnosis of Psoriasis.

Oral lichen planus, mainly occurring in adults, appears as bilateral plaques, papules and erythematous-atrophic or ulcerated lesions on the oral mucosa, gingivae (desquamative gingivitis) and tongue. Oral white striations (so-called Wickham striae) may coincide with cutaneous lesions on the scalp, laryngeal and esophageal mucosa or less frequent

conjunctival lesions. Skin involvement of the scalp (lichen plano-pilaris) appears as scarring alopecia and violaceous and erythematous papules with hair loss. On histologic examination, more irregular acanthosis, prominent granular cell layer and dense sub-epithelial T-cell CD8+ inflammatory infiltrate along with damage of basal keratinocytes represent clues to the diagnosis in contrast to Psoriasis. Moreover, since patients with oral lichen planus could develop oral squamous cell carcinoma and commonly show a significant local morbidity with negative impact on QOL, a proper diagnosis based on clinical and histological findings is mandatory.

Discoid lupus erythematosus may sometimes be responsible for unusual manifestations in head and neck localizations that can mimic several skin diseases (Psoriasis, acne rosacea, lichen planopilaris) or be associated with liken planus-like lesions and Psoriasis. Nonetheless, clinical findings are usually characteristic as erythematous papules and plaques that progress to scaling lesions with pigmentary changes (central hypopigmentation and peripheral hyperpigmentation) in a centrifugal spread. Cutaneous scalp lesions may result in permanent alopecia with atrophy and scarring (localized form of discoid lupus erythematosus) with histologic picture similar to that of lichen planopilaris. Rare mucosal involvement are described with clinical and microscopic characteristic that may simulate lichen planus lesions. In this setting, laboratory data (hematologic and serologic abnormalities frequently observed in widespread discoid lupus erythematosus) along with meticulous clinical attention and microscopic findings (essentially dependent on familiarity with these lesions) can pose a correct diagnosis.

Psoriatic lesions may also not look much different from those caused by seborrheic dermatitis, a papulo-squamous disease of the scalp, face and trunk. In its facial localization, the disease may be associated with squamous blepharitis, a chronic inflammation of the lid margins with small white scales accumulated among the lashes, or may present as mild scaling to widespread crust adherent to the skin of the scalp, forehead, neck and postauricolar skin. Secondary infections may occur as eczematoid dermatitis. Microscopic picture shows a more irregular acanthosis than that seen in psoriatic lesions along with spongiosis and follicular ostia involvement.

The guttate variety of Psoriasis may appears as an acute exanthema in young adults, often associated to streptococcal pharyngitis, with papules on the face similar to those seen in psoriasiform drug eruption. The latter condition is also known as localized drug reactions related to medications and usually involving the face, chest and back with a papulo-erythematous or vescicular and pustular appearance. Similarly, psychogenic and emotional factors, infections and environmental factors may all contribute to the development of cutaneous lesions similar to those seen in Psoriasis or may be related to increase in Psoriasis activity and severity.

Histologic overlapping in such cases, with lacking of microscopic characteristic features, require a correct clinical evaluation in the differential diagnosis of these conditions.

Differential diagnosis of head and neck Psoriasis, in both cutaneous and mucosal localizations, should also consider preneoplastic and neoplastic conditions. Since head and neck Psoriasis is more often a chronic and long standing process, frequently associated with severe cutaneous disease and difficult treatment, a significant risk of cancer has been noted. Such an association could be related to the reactive epidermal hyperproliferation seen in

psoriatic lesions along with keratinocytes activation and expression of molecules involved in cell proliferation. In particular, basal cell and squamous cell carcinomas are frequently reported and should be taken into account when evaluating psoriatic patients.

Moreover, malignant conditions should be ruled out as is the case of the rare acrokeratosis paraneoplastica (Bazex syndrome). The disease can be associated with head and neck and upper aerodigestive tract squamous cell carcinomas and differs from Psoriasis in its localizations (erythematous squamous plaques or scaly patches of earlobes, helices and tip of the nose along with similar lesions in the extremities and nail dystrophy) and lack of histological findings typical of Psoriasis.

Investigators use several physical examination measures to assess clinical features and severity of Psoriasis and psoriatic arthritis (PsA) in clinical trials, clinical registries, and clinical practice; however, no relevant training modules are widely available to teach and standardize the performance of these measures. At a GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) meeting adjacent to the 2009 International Federation of Psoriasis Associations in Stockholm, members were updated on the development status of online training videos of Psoriasis and PsA examination measures. Dermatology assessment modules include the PASI, the PGA, the BSA, the original and modified Nail Psoriasis Severity Index (NPSI), the Palmar-Plantar Pustular Psoriasis Area and Severity Index (PPP-PASI), and the PSSI. Rheumatology modules include assessment of tender and swollen joint counts used in the American College of Rheumatology criteria, Disease Activity Score, and other composite arthritis scores; enthesitis assessment used in various enthesitis scoring systems; dactylitis; and spine disease. Each module will include background information for each measure, diagrams and photographs to emphasize teaching points, demonstration video of examination where applicable, and an optional examination at the end. Future plans include evaluating the modules for their influence on interrater and intrarater reliability and development of additional modules (Callis Duffin & Mease, 2011).

4. The difficulty of the treatment

Head and neck Psoriasis treatment is still a challenge because its difficult to get topical agents through hair to be absorbed by the scalp. In fact, scalp is not susceptible to many topical Psoriasis treatment or phototherapy because hair prevent adequate contact with the affected tissue. Moreover current therapies can only bring some relief to the symptoms without any cure to the disease and treatments can carry important side effects in face of high therapeutic costs.

Medications for scalp Psoriasis include those to be left on the scalp and wash off products. Left on products are gels, lotions and ointments containing steroids, coal tar, salicylic acid or vitamin D analogs.

Wash off products are shampoos containing coal tar, salicylic acid, sulfur, selenium, ketoconazole or zinc pyrithione. Recently, Handa (2010) proposed a treatment algorithm for scalp Psoriasis (see Tab. 1), dividing a first line and a second line therapies.

In 2009 van de Kerkhof & al. divided treatment of scalp Psoriasis into four phases. First phase involves descaling using salicylic acid or urea preparations. The second phase is the

clearing phase in which topical corticosteroids, vitamin D analogs, tar, dithranol, antifungal treatment, ultraviolet B light therapy or systemic treatment are used. The third phase is stabilization using a steroid-sparing vitamin D analog during the week and a super potent topical corticosteroid at weekends. Finally, the fourth phase is maintenance, using a vitamin D analog alone or with a tar shampoo.

First line therapies
Salicylic acid/Urea
Topical corticosteroids (short term use)
Calcipotriol
Dithranol/Anthralin
Coal tar (Shampoo/pomade)
Tazarotene
Combination therapies
Second line therapies (for recalcitrant or severe disease)
Phototherapy
Systemic drugs (Methotrexate, Acitretin, Cyclosporine)
Biologics

Table 1. Treatment algorithm for scalp Psoriasis (from Hanna S., 2010)

4.1 Corticosteroids

Topical corticosteroids are the recommended first-line therapy for short-term use. Response to treatment is quick but high potential for side effects, such as atrophy, striae, telangiectasias and tachyphylaxis, limits the period of use. These side effects are virtually never seen in the scalp. Use of potent steroids (twice a day) should be limited to 4 weeks. The choice of preparation such as ointment, cream, gel, lotion, foam, spray or shampoo should be patient oriented.

In any single patient the lowest strength preparation that allows clinical clearing should be used for the shortest time, in order to minimize side effects and tachyphylaxis. Nevertheless, long-term use of mid-potency preparations or intermittent use of potent steroids is more commonly practiced by physicians. Clobetasol propionate (CP) 0.05% and betamethasone dipropionate 0.05% are the most potent topical corticosteroid preparations currently used. Exceptionally intralesional corticosteroids can be used for one or two localized patches not responding to topical steroids. Foam vehicles are the new alternatives to traditional topical preparations because of the advantage of minimal residue and increased ease of application. They are absorbed more rapidly, have a higher bioavailability, are not associated with suppression of the hypothalamic pituitary adrenal (HPA) axis and once-daily administration has been seen to be as effective as twice daily administration. They are also associated with better patient compliance. CP foam 0.05% is generally as effective as CP solution for scalp Psoriasis and may produce superior results against scaling. Dose is limited to 50 g/week. Mid-potency corticosteroid betamethasone valerate (BMV) has also become available in a new thermolabile, low-residue foam vehicle, BMV 0.12% foam. In a recent study BMV foam produced greater improvement in the primary signs of scalp Psoriasis than BMV lotion, placebo or other standard topical therapies (Stein, 2005). Shampoo preparations

are another new development. When clobetasol shampoo 0.05% was tried in a patient experience program, 50% of the patients said that the shampoo was easy to use and did not interfere with their daily routine. Almost 90% of patients found the shampoo better than other prescriptions they had used before for their scalp Psoriasis.

Medication used to treat facial Psoriasis should be applied carefully and sparingly; creams and ointments can irritate eyes. Because facial skin is delicate, prolonged use of steroids may cause it to become thin, shiny and/or prone to enlarged capillaries. Treatment with steroids is safe if a careful treatment schedule is followed.

4.2 Non steroidal topical preparations

This group includes: Calcipotriene/calcipotriol, Anthralin, Coal Tar, Tazarotene.

4.2.1 Calcipotriene/calcipotriol

These are vitamin D 3 derivatives used for chronic, moderately/severe Psoriasis of the scalp. The 0.005% solution is applied to the affected area and rubbed gently onto the scalp twice a day. Response to therapy takes about 8 weeks. It is not recommended in patients with acute psoriatic eruptions on the scalp, those with hypercalcemia or hypervitaminosis D. The main side effects are burning, itching, irritation and dryness. Irritation tends to decrease with time. Clearance has been observed even with 8 weeks of once a day treatment in up to 60% of patients.

4.2.2 Anthralin

Anthralin 0.1-3% cream has been used for long-term treatment of scalp Psoriasis. Concentration should be gradually increased according to body response and tolerance of the patient. Anthralin is applied in a thin layer to the psoriatic area once a day, rubbed in well and left on the scalp for 5-10 minutes before washing with a shampoo and rinsing well. It is not used for acutely inflamed scalp Psoriasis. Redness or irritation of the treated scalp is common. Anthralin may temporarily stain the fingernails, gray/white hair, skin and fabrics. Caution is advised in patients having history of allergy to anthralin or to condoms (e.g., parabens).

4.2.3 Coal tar

Coal tar is an effective and cheap treatment modality for scalp Psoriasis but staining and an acrid smell associated with its use may have an important impact on patients QOL. Topical tar solution (liquor picis carbonis-LPC, or liquor carbonis detergens-LCD) is widely available and commonly used for scalp Psoriasis. Newer preparations specifically meant for scalp include coconut oil compound ointment (coal tar solution with precipitated sulfur, salicylic acid, coconut oil, yellow soft paraffin and emulsifying wax) and tar pomades (contain LCD, Tween 20 and salicylic acid in a hydrophilic ointment). Compound ointment should be applied once at night and washed off the next morning with a coal tar shampoo. Coal tar shampoos contain 1-20% coal tar extract. They are used twice a week. A tar blend 1% shampoo Polytar (Steifel, Johannesburg, South Africa) is made of coal tar, juniper tar (cade oil) and pine tar. In a comparative 4-week study of tar blend 1% shampoo (Polytar)

and CP 0.05% shampoo (Clobex, Galderma, Ft. Worth, USA), the corticosteroid shampoo was significantly more effective and showed a better patient's compliance too.

Coal tar has been a very popular traditional treatment for various types of Psoriasis for over a century and still it's the first-line treatment for scalp, hand, and foot Psoriasis. However, application of coal tar on hair invariably causes staining, which results in a high degree of patient non-compliance, especially in patients with non-black hair. Thus, treatment of scalp Psoriasis with a topical coal tar formulation requires that special concern to be paid to product esthetics. A novel lecithinized coal tar (LCT) formulation seems to be less likely to stain hair and thus has excellent potential to be exploited in treatment of scalp Psoriasis (Bhatia & al. 2011).

4.2.4 Tazarotene

There are no controlled studies on the use of tazarotene in scalp Psoriasis. Response to tazarotene (0.1%) compared to topical calcipotriol or steroids is less effective but relapse rates are reported to be minor as well. Dryness and irritation are common side effects.

4.3 Combination therapies

Combining different treatment allows enhanced efficacy and minimizes toxicity. Corticosteroids, when combined with vitamin D analogs, require a minor total amount of dose and induce less skin irritation. In treatment of moderate to severe plaque Psoriasis of the scalp, the fixed-combination suspension containing betamethasone 0.05% and calcipotriene 0.005% is used once a day. In a randomized double-blind controlled trial over 8 weeks, 71.2% patients achieved "absent" or "very mild" disease with the two-compound scalp formulation, compared to 64% treated with betamethasone dipropionate, 36.8% with calcipotriene and only 22.8% with the vehicle alone. Pruritus was the only adverse event reported.

Topical steroids with Puvasol gave better results: 37.3% clearance versus 13.3% with Puvasol alone. LPC 10% along with 2% salicylic acid in a cream base along with Puvasol for 8 weeks gave a much better clearance rate than Puvasol alone. Tazarotene has also been found to be efficacious in combination with topical steroids and calcipotriol.

In a prospective non-interventional trial in German dermatological practices, 721 patients with scalp Psoriasis received Xamiol(®) gel (calcipotriol 50 µg/g, betamethasone 0,5 mg/g) topically for 4 weeks. Severity was assessed by physician's global assessment (PGA) and QOL was assessed by using a scalp-specific questionnaire at the beginning of the study and after 4 weeks treatment. The mean disease severity of scalp Psoriasis (PGA) improved from 4.26 to 2.49 (-41.8 %, $p < 0.0001$) during 4 weeks treatment and QOL improved from 10.57 to 3.22 (-69.5 %, $p < 0.0001$). Among patients with pre-treatment 89.5% of patients and 87.9% of dermatologists judged treatment response to Xamiol(®) gel as better/much better compared to previous therapy. Tolerability of Xamiol(®) gel was rated good/very good by 98 % of dermatologists and patients, respectively. The use of Xamiol(®) gel was found easy/very easy by 90.4 % of the patients (Mrowietz, 2011).

McCormack (2001) reviewed the efficacy and tolerability of calcipotriol/betamethasone dipropionate in patients with Psoriasis vulgaris summarizing its pharmacological

properties. Calcipotriol/betamethasone dipropionate showed low systemic absorption and displayed local anti-inflammatory and immunoregulatory properties. It reduced hyperproliferation of keratinocytes and helped normalize keratinocyte differentiation. In large, well designed clinical trials, calcipotriol/betamethasone dipropionate, either as the ointment or the gel formulation, applied once a day for 4-8 weeks, was more effective than placebo, calcipotriol and tacalcitol, as well as betamethasone dipropionate in most instances, for the topical, symptomatic treatment of Psoriasis vulgaris of the trunk/limbs. Likewise, calcipotriol/betamethasone dipropionate gel applied once daily for 8 weeks was more effective than placebo or either component alone in the topical, symptomatic treatment of Psoriasis vulgaris of the scalp. Long-term, once a day, when required therapy with calcipotriol/betamethasone dipropionate for 52 weeks was more effective than calcipotriol alone for the treatment of scalp Psoriasis and was at least as effective as switching to calcipotriol for 48 weeks after 4 weeks of calcipotriol/betamethasone dipropionate or alternating between calcipotriol/betamethasone dipropionate and calcipotriol every 4 weeks for 52 weeks in the treatment of Psoriasis vulgaris of the trunk/limbs. Calcipotriol/betamethasone dipropionate also improved health-related QOL.

Calcipotriol/betamethasone dipropionate was generally well tolerated, with most adverse drug reactions being lesional or perilesional effects of mild or moderate severity (see Fig. 1).

Calcipotriol/betamethasone dipropionate was often associated with fewer lesional/ perilesional adverse reactions than calcipotriol or tacalcitol and did not appear to be

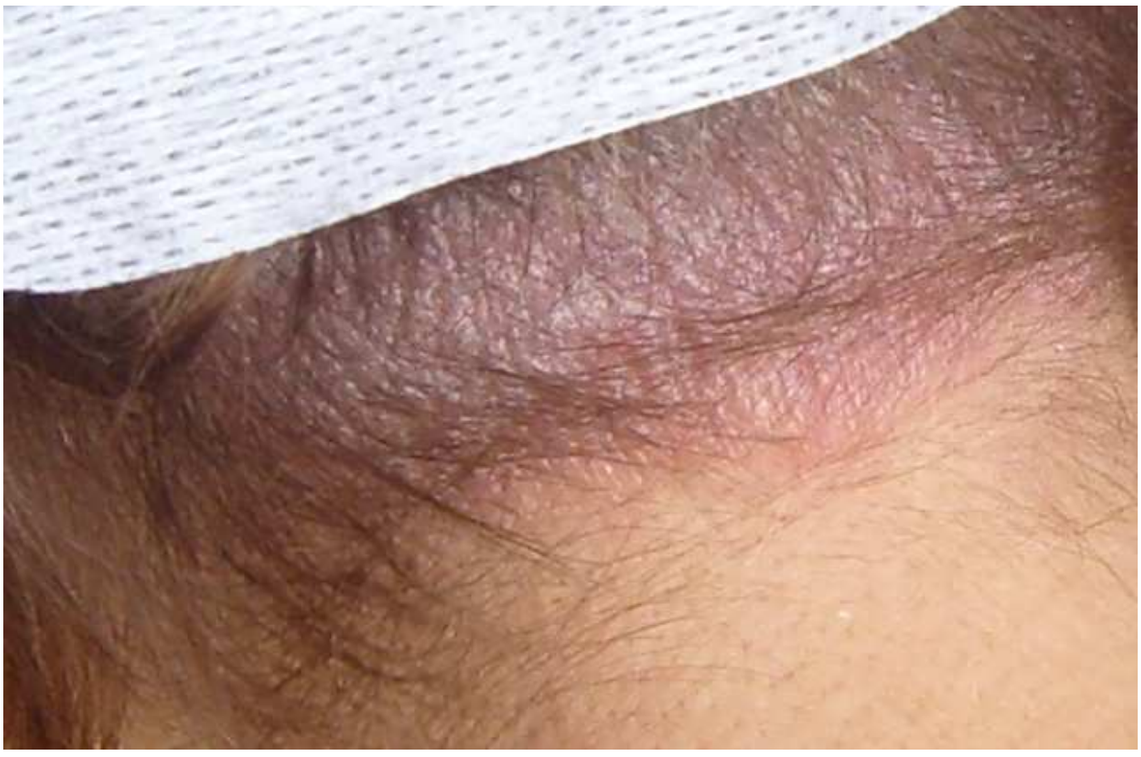

Fig. 1. Scalp Psoriasis after treatment with calcipotriol/betamethasone dipropionate gel formulation , applied once daily for 4 weeks.

associated with a higher incidence of corticosteroid-related adverse events during long-term therapy. Pharmaco-economic analyses predicted calcipotriol/betamethasone dipropionate to be more cost effective than other topical therapies.

Puig & al. (2010) reported the recommendations developed by an expert panel using the Delphi process to reach a consensus and then ratified by the members of the Psoriasis Group of the Spanish Academy of Dermatology and Venereology. The recommended induction therapy for scalp Psoriasis is either a topical corticosteroid or a topical treatment combining calcipotriol and betamethasone. The choice of an appropriate vehicle is crucial in improving effectiveness and patient adherence to treatment. The only formulations that have been studied in long-term treatment of scalp Psoriasis are a combination of calcipotriol and betamethasone in gel and calcipotriol alone in solution.

4.4 Second line treatments for recalcitrant disease

These are used when all topical treatments fail. No controlled studies exist regarding their use and include phototherapy and systemic drugs like methotrexate, retinoids, cyclosporine and biologics. They are used based on physician experience, choice and risk versus benefit ratio.

4.4.1 Phototherapy

Hair blocks adequate penetration of ultraviolet light. Better results are achieved with conventional UV units, if hair is parted in many rows or if the patient has thin hair or if the head is shaved. Hand-held devices (UV combs) deliver a higher intensity of UV light. There are reports of the use of targeted phototherapy with excimer laser which provides narrowband ultraviolet B (NB-UVB) (308 nm) phototherapy with a very high irradiance, allowing for a shorter treatment time.

4.4.2 Biologics

The emergence of biologic therapies as an effective modality for treatment of plaque Psoriasis may provide another option for patients. The biological agents employed in therapy of Psoriasis are classified into three groups (see Tab. 2).

Inhibitors of tumor necrosis factor-α
Adalimumab
Certolizumab
Etanercept
Golimumab
Infliximab
Inhibitors of Interleukin-12 and Interleukin-23
Ustekinumab
Briakinumab
T-cell modulating agents
Alefacept
Efalizumab

Table 2. Biological agents employed in scalp Psoriasis.

Recent findings suggest that Efalizumab may be effective for treatment of head and neck Psoriasis (Krell & al., 2008). Katsambas (2009) recorded a PSSI score for 1150 patients at baseline and by week 12; there had been a median improvement in PSSI score of 73.3% (IQR 33.3–94.3) compared with baseline. At week 12, PSSI 50 and PSSI 75 responses were achieved by 62.4% (718/1150) and 44.7% (514/1150) of patients, respectively. In many cases, a response to Efalizumab was apparent early in treatment, with over half of the patients classified as PSSI 50 responders at week 12 having already achieved this response by week 4 (n = 425).

However, Efalizumab has now been recommended for withdrawal in European market due to adverse effects. European Medicines Agency evaluated all safety data in light of post-marketing surveillance of patients with Psoriasis receiving Efalizumab continuously for more than 3 years that showed opportunistic infections and, in particular, cases of JC virus infection (polyomavirus) resulting in progressive multifocal leucoencephalopathy (PML). It was concluded that the benefits of Efalizumab treatment no longer outweighed the risks associated with the drug and was recommended suspension of marketing authorization on 19 February 2009. The drug has also been voluntarily withdrawn from the US market.

Adalimumab, a monoclonal humanized tumor necrosis factor alpha inhibitor proved to be successful in treatment of severe facial Psoriasis (Noiles & Vender, 2008).

Accumulating evidence supports efficacy and safety of ustekinumab for treatment of moderate to severe Psoriasis. There is some suggestion from head-to-head comparisons that ustekinumab may offer some advantage over TNF-α inhibitors. However, there is a need for larger and longer-term studies to assess the safety profile, cost-effectiveness and advantages of anti-interleukin 12 and 23 activity in the modern era of biological therapy (Garcia-Valladares & al., 2011).

4.5 Miscellaneous agents

Salicylic acid 5-10% is combined with other topical therapies as a keratolytic. Many topical treatments do not work well until thick scales that reduce drug penetration are removed. Urea 10% and lactic acid 10% have been used as scalp moisturizers. In resistant cases topical imidazole derivatives are used to control the overgrowth of Pityrosporum in scalp Psoriasis.

Kircik (2011) stated that Salicylic acid 6% emollient foam provides a useful option that is highly effective, well tolerated and acceptable to patients. Efficacy, tolerability and patient acceptability of salicylic acid 6% emollient foam were assessed in an open-label pilot study of 10 subjects with scalp Psoriasis. All Psoriasis severity parameters were reduced with a significant decrease in PSSI score from 15.3 to 3.0 after four weeks of monotherapy ($P<0.001$). Sixty percent of subjects were either "completely cleared" or "almost cleared" from their Psoriasis. No adverse events were reported.

Psoriasis skin lesions can be secondarily infected with bacteria according with Brook (Brook & al., 1999). In this report the predominant aerobic and facultative bacteria were S. aureus, group D Enterococcus and Escherichia coli while the predominant anaerobes were Peptostreptococcus spp. and Bacteroides spp., Propionibacterium acnes and pigmented Prevotella spp. in two each. Nineteen of the micro-organisms isolated from 78% patients produced lactamase.

The U.S. Food and Drug Administration (FDA) has approved two drugs, Protopic and Elidel, for treatment of eczema which many dermatologists have found to work well in treating Psoriasis of the face or of other sensitive areas.

5. The aberrant epidermal-mesenchymal interactions theory

The normal adult epidermis is a self-renewing tissue consisting of 10 to 20 layers in which cell proliferation is primarily restricted to the basal layer. Orthokeratinized epithelium similar to that in skin is seen in the hard palate, whereas other regions are either parakeratinized (gingiva) or nonkeratinized (buccal mucosa) (Squier & al., 1976). Injury to the epidermis activates a homeostatic response resulting in inflammation, re-epithelialization, followed by tissue remodelling (Martin, 1997). Several studies have suggested release of interleukin-1 from keratinocytes at the wound site as the initial trigger for the inflammatory reaction. This serves as an autocrine signal to surrounding keratinocytes and paracrine signal to other cells, such as fibroblasts, endothelial cells, and lymphocytes resulting in a pleiotropic effect on them (Freedberg & al., 2001). The changes in gene expression that accompany re-epithelialization are similar to those seen in other disorders associated with hyperproliferation such as Psoriasis, contact dermatitis, and squamous cell carcinoma (SCC) suggesting considerable overlap in the signaling cascades. The development of a normal scar is dependent on the reversal of expression of these genes at the wound site. However, in some cases the inflammatory and proliferative signals persist even after wound closure resulting in pathological scars, such as hypertrophic (HTS) and keloid scars. Although most previous studies have considered these scars as dermal phenomena (Akagi & al., 1999), others have identified abnormalities associated with epidermal keratinocytes in HTS perhaps as a result of aberrant epidermal-mesenchymal interaction (Niessen & al., 2001). One of the most sensitive biochemical markers of terminal differentiation in keratinocytes is the keratin protein family that constitutes the major cytoskeletal architecture of all epithelia. In humans, the family consists of 30 polypeptides (including trichocytic keratins of hair and nail) that are divided into two types; type I is acidic and includes K9 to K20; type II is basic/neutral and includes K1 to K8. The normal expression of K2e in the upper spinous and granular layers of interfollicular epidermis is increased in keloid scars but showed distinct down-regulation in Psoriasis and hypertrophic scars where keratinocytes are known to undergo activation. Unlike normal and psoriatic skin, K2e expression in hypertrophic and keloid scars began in the deepest suprabasal layer. In cutaneous basal and squamous cell carcinomas, K2e was absent in most tumor islands but the overlying epidermis showed strong expression. In mild-to-moderate oral dysplasia with orthokeratinization, K2e was highly expressed compared with parakeratinized areas but in severe dysplasia as well as in oral squamous cell carcinoma, K2e expression was undetectable. Taken together, the data suggest that K2e expression in skin is sensitive to keratinocyte activation but its up-regulation in oral lesions is a reflection of the degree of orthokeratinization (Bloor & al., 2003). K 15 protein and mRNA are primarily located in the basal keratinocytes of stratified tissues (Waseem al., 1999) and the k 15 gene is upregulated in human subjects where both alleles for k 14 have beeen inactivated. In hyperproliferating epidermis, such as in Psoriasis, K 15 expression, both protein and mRNA, is downregulated, suggesting that K 15 expression may not be compatible with the activated phenotype.

6. The rare mucous occurrence and the PPP-tonsil-related disease

6.1 Mucous membrane localization

The occurrence of true psoriatic lesions on mucous membranes is disputed. For many years it has been claimed that this disease does not affect oral mucosa. Today it is thought that involvement of the oral cavity is rare but does exist. Oppenheim (1903) was the first to describe oral Psoriasis in a biopsy after histological examination. In a review of English-language and European non-English literature Younai and Phelan (1997) identified only 57 cases of oral Psoriasis. Since then, few new cases have been reported bringing the total to less than 100 cases described. The reports described a number of oral sites affected, such as lips, buccal mucosa, gums, palate, tongue and floor of the mouth. In the cases reviewed by Younai and Phelan, clinical presentation was a white intraoral lesion in 44% of patients, erythematous in 24% and red and white mixed in 13%. The remaining lesions appeared ulcerative, vesicular, pustular, or indurated. The histopathological findings in oral mucous membranes are assumed to be similar to those found in skin lesions. Epithelial parakeratosis, elongated rete ridges and the presence of an inflammatory infiltrate of the upper dermis were described in most cases. Differential diagnosis from other oral diseases such as benign migratory glossitis, fissured tongue, oral candidosis and the oral lesions of Reiter's syndrome may be subtle. The diagnosis is easily made when the clinical features of oral lesions parallels that of skin lesions and it is supported by histological investigation (Weathers et al., 1974; Younai and Phelan, 1997; Bruce and Rogers, 2003).

6.2 Recurrent streptococcal infection theory in pathogenesis of psoriasis

Recent immunological studies have shown that hyperactivation of tonsillar T cells is caused by a hyperimmune response to α-streptococci; recruitment of the T cells to lesions may be involved in the pathogenesis of PPP. ß1 integrin, expressed on T cells, not only provides a co-stimulatory signal for T-cell activation but also facilitates the accumulation of T cells in inflammatory skin lesions. In this study was found that expression of ß1 integrin on both tonsillar and peripheral blood CD4-positive T cells was higher in PPP patients than in non-PPP patients. It was demonstrated that ß1 integrin may play a key role in the pathogenesis of PPP (Ueda & al., 2010).

Psoriasis is a T-cell-mediated disease that can be triggered by group A beta-haemolytic streptococci infection.

The results of many experimental studies provide evidence that Psoriasis is largely a T-cell mediated disorder. It may result from antigen-specific activation of T cells in the skin of genetically predisposed individuals. These T cells apparently have a particular functional differentiation and promote the psoriatic skin changes by secreting a certain set of cytokines. Based on the fact that streptococcal throat infections are a trigger of guttate Psoriasis, the putative psoriatic antigens are assumed to be in keratinocyte proteins that share structural homologies with streptococcal proteins and thus induce cross-reactive responses of antibacterial T cells against skin components. Together with the particular phenotype of psoriatic skin lesions these findings can suggest that Psoriasis represents a sterile antibacterial tissue reaction, which is mediated by streptococci-specific T cells that cross-react against epidermal autoantigens.

Psoriasis is strongly associated with streptococcal throat infection and patients have increased occurrence of such infections. Psoriatic lesional T cells are oligoclonal, and T cells recognizing determinants common to streptococcal M-protein and keratin have been detected in patients' blood. The streptococcal association might reflect the concurrence of superantigen production promoting skin-homing of tonsil T cells, M-protein mimicking keratin determinants, and adjuvant effects of the peptidoglycan. Accordingly, improvement of Psoriasis after tonsillectomy should be associated with fewer T cells that recognize keratin and streptococcal determinants (Valdimarsson & al., 2009).

6.3 Tonsillectomy and antistreptococcal antibiotic therapy

Tonsillectomy may be a successful treatment modality in selected patients with recalcitrant guttate or chronic plaque Psoriasis. In the study of Hone & al. (1996) Psoriasis was cleared completely after tonsillectomy in five out of six patients (83%) with guttate Psoriasis and was improved in one patient. Two out of seven patients with plaque Psoriasis (29%) were cleared, two (29%) were improved and three (42%) were unchanged.

Numerous studies implicate subclinical or recurrent streptococcal infection as a trigger or maintenance factor in the pathogenesis of Psoriasis in children but the study of Wilson & al. (2003) stated that the available evidence does not demonstrate the efficacy of either antibiotic therapy or tonsillectomy in treatment of childhood Psoriasis. Clinical trials assessing the efficacy of antibiotics or tonsillectomy as treatments for childhood Psoriasis were identified with a search of the medical literature and the results were compared. Only one controlled clinical trial was identified and it did not find a significant effect of antibiotic treatment on Psoriasis. In other studies, the percentage of Psoriasis patients who experienced a disease clearance with antibiotic therapy ranged from 0% to 55%, with no patients experiencing disease worsening during treatment. No controlled trials of tonsillectomy for Psoriasis were identified. The percentage of patients who experienced a disease clearance after tonsillectomy in uncontrolled trials ranged from 32% to 53% and a similar percentage reported significant improvement in their Psoriasis, with a maximum of 7% noting worsening of the disease after operation.

Owen & al. (2000) agreed on the previous conclusions. They searched the Cochrane Clinical Trials Register (Cochrane Library, Issue 3, 1999), Medline (1966- September 1999), Embase (1988-September 1999), the Salford Database of Psoriasis Trials (to November 1999) and the European Dermato-Epidemiology Network (EDEN) Psoriasis Trials Database (to November 1999) for terms [STREPTOCOCC* or ANTIBIOTIC* or TONSIL*] and PSORIASIS using the Cochrane Skin Group search strategy. The only one eligible trial identified compared the use of two oral antibiotic schedules in 20 Psoriasis patients, predominantly of guttate type, who had evidence of beta-haemolytic streptococcal colonisation. Either rifampicin or placebo was added to the end of a standard course of antistreptococcal antibiotic (phenoxymethylpenicillin or erythromycin). No patient in either arm of the study improved during the observation period. No randomised trials of tonsillectomy for Psoriasis were identified. Although both antibiotics and tonsillectomy have frequently been advocated for patients with recurrent guttate Psoriasis or chronic plaque Psoriasis, there is no good evidence that either intervention is beneficial to date.

Because these treatments are relatively benign compared to other treatments for severe Psoriasis, the use of antibiotic therapy or tonsillectomy may still be worth considering, especially for those patients with recurrent streptococcal infections that seem to trigger or maintain their skin disease.

6.4 Psoriasis as T cell-mediated disease and correlation with PPP

Another item of correlation between Psoriasis and inflammatory disease of the upper aerodigestive tract is represented by PPP. PPP is a tonsil-related disease and tonsillectomy is somewhat effective in treating the condition. However, aetiological association between tonsils disease and PPP has not been elucidated fully. Recently, some chemokines and chemokine receptors, including CC chemokine receptor (CCR) 4, CCR6 and CX chemokine receptor (CXCR) 3, have been reported to play important roles in the development of Psoriasis, which is related closely to PPP. Chemokines and chemokine receptors have been known to play a crucial role in directing the movement of mononuclear cells throughout the body, contributing to the pathogenesis of several skin diseases. In the skin lesions of PPP and/or Psoriasis, IL-8 and regulated upon activation normal T cell expressed and secreted are reported to be up-regulated on epidermal keratinocytes, suggesting that such chemokines may play an important role for migration of leucocytes and T cells.

Yoshizaki & al.(2009) have demonstrated that: (1) CCR6 expression was up-regulated in both tonsillar and peripheral blood T cells; (2) CCR6 expression on tonsillar T cells was enhanced by in vitro stimulus with a-streptococcal antigens; (3) tonsillar T cells exhibit more intense chemotactic responses to CCL20; (4) the number of CCR6-positive peripheral blood T cells decreased after tonsillectomy and this reduction was correlated with an improvement in skin lesions; and (5) CCR6 expression of T cells and CCL20 expression of epidermal cells were up-regulated in PPP skin lesions.

These results indicate that CCR6 may be induced by a novel immune response to α-streptococci in tonsillar T cells in PPP patients. CCR6-positive tonsillar T cells may be recruited to the skin via peripheral blood circulation and then attracted to keratinocytes expressing CCL20 in the epidermis. Therefore, CCR6 may act as an important factor, bridging the tonsils and PPP. CCR6-positive tonsillar T cells may move and circulate in the peripheral blood, being recruited ultimately to the skin lesions of PPP patients. The mechanism underlying the manner in which CCR6-expressing tonsillar T cells are recruited to the skin lesions of PPP patients remains obscure; the skin-specific homing receptor CLA may play an important role.

The pathogenic role of T lymphocytes and immune cross-reaction between human-HSP60 and bacterial-HSP65 in PPP was also revealed (Hayashi & al. 2009).

The evidence that T lymphocytes play a key role in the pathogenesis of Psoriasis is now compelling. Eruption of psoriatic skin lesions coincides with epidermal infiltration and activation of T cells and spontaneous or treatment-induced resolution of the lesions is preceded by the reduction or disappearance of epidermal T cells. An up-regulation has also been demonstrated for various molecules associated with T-cell mediated inflammation and treatments selectively directed against T cells have proved to be very effective. Infections with group A beta-haemolytic streptococci have been associated with onset of acute Psoriasis and exacerbation of chronic Psoriasis. Such infections are also

frequently accompanied by erythematous skin rashes. Also, recent reports indicate that streptococcal superantigens can induce expression of cutaneous lymphocyte antigens (CLA), believed to play a major role in enabling T cells to migrate to the skin. A novel immune response to alpha-streptococci may enhance CLA expression on tonsillar T-cells through TGF-beta production in patients with PPP, resulting in moving of CLA-positive tonsillar T-cells to skin and tissue damages. This may play a key role in pathogenesis of PPP (Nozawa & al., 2005).

Helper T-cells are frequently activated in tonsils from PPP patients and this activation may be related to unresponsiveness of TGF-beta1 by overexpression of Smad7. Such hyper-activation of T-cell may increase the risk of elicitation of self-reactive T-cell, being associated with pathogenesis of PPP (Takahara & al., 2005).

Furthermore, T-cell lines isolated from psoriatic lesions may show strong reactivity to streptococcal antigens. It was demonstrated that active Psoriasis is associated with a Th1 type response to short peptides with epitopes shared by streptococcal M-protein and keratin. This is consistent with the hypothesis that Psoriasis may be induced and exacerbated in susceptible individuals by M-protein-specific Th1-like cells that cross-react with human epidermal keratin (Valdimarsson & al., 1997).

6.5 Interaction between epidermal keratinocytes and the immune system

Psoriasis is associated with an increase of Th17 cytokines, such as IL-17, IL-22, IL-21, and TNF-α, which are produced by Th 17 cells. Adipokines are peptide hormones or cytokines secreted from adipose tissues and involved in the pathogenesis of metabolic syndrome. Psoriasis patients have a high prevalence of metabolic syndrome. Increased serum levels of IL-22 and adiponectin were positively correlated with PASI. In contrast, serum high molecular weight adiponectin levels were decreased in Psoriasis and negatively correlated with PASI (Nakajima & al. 2011).

Th 17 cells have crucial functions in host defense and dysregulated Th17 responses mediate a variety of autoimmune and inflammatory conditions. Th17 cells coexpress interleukin-22 and its receptor is expressed on epidermal keratinocytes. IL-17 and IL-22 cooperatively enhance some immunological responses. A close relationship between IL-17 and the cutaneous milieu has been suggested by a number of observations. IL-17 induces the production of certain cytokines, chemokines and antimicrobial peptides by keratinocytes, and its cooperation with IL-22 has been documented. Recent findings have suggested that Th17 cells profoundly participate in the pathogenesis of certain skin disorders, in particular, Psoriasis. The concept of the subsets of T cells responsible for Psoriasis has been modified in the order of Th1, T cytotoxic 1, and again Thl, and Thl7 cells. IL-22 is the strongest cytokine in the keratinocyte-proliferative ability. Since IL-22 is produced by Th17 cells, they are crucial for the proliferation of keratinocytes. Furthermore, IL-22 with the help of IL-17 can induce the critical events of Psoriasis, including signal transducer and activator of transcription 3 (STAT3) activation, cytokine/chemokine (IL-8 etc.) production, and antimicrobial peptide elaboration. For maintaining Th17 cells, IL-23 is required and is released from tumor necrosis factor-alpha (TNF-alpha) and inducible nitric oxide synthetase (iNOS)-producing dendritic cells (TIP-DCs). TIP-DCs are activated via an autocrine mechanism by virtue of TNF-alpha.

The above cytokine network in the pathogenesis of Psoriasis has been proven by the therapeutic effectiveness of cytokine-blocking biologics. Antibodies against TNF-alpha or its soluble receptor have already been widely used in the treatment of Psoriasis.

The involvement of Th17 cells has also been shown in allergen-specific immune responses. The percentage of Th17 cells is increased in the peripheral blood of patients with atopic dermatitis (AD) and associated with the severity of AD. Drug eruption is another disease where Th17 cells are involved in the pathogenesis. The percentage of circulating Th17 cells are increased in drug-induced hypersensitivity syndrome, etc. Th17 cells and IL-22 are increased in patients with acute generalized exanthematous pustulosis. Since IL-17 and IL-22 cooperatively stimulate keratinocytes to produce IL-8, keratinocyte-derived IL-8 contributes to the accumulation of neutrophils in the lesional epidermis of this drug eruption (Tokura & al., 2010).

In conclusion, more recent data suggest that Psoriasis is caused by an interaction between epidermal keratinocytes and the immune system and that one possible candidate linking the immune system and epidermal keratinocytes is IL-22, a T-cell-derived cytokine that is produced by Th17 polarized T cells that are stimulated by IL-23, but that acts on epidermal keratinocytes to induce acanthosis and differentiation toward a psoriatic phenotype. Regardless of the specific underlying pathogenesis, Psoriasis is characterized by a disregulated epidermal acanthosis, dermal and epidermal leukocytic infiltration, and dilatation of dermal blood vessels—lesions that are maintained by the complex interplay between T cells and their cytokines, other leukocytes, vascular endothelium, and epidermal keratinocytes. As noted above, epidermal keratinocytes as well as vascular endothelial cells are active participants in the psoriatic inflammatory process via secretion of cytokines and growth factors, and the up regulation of signaling and adhesion molecules on their surfaces (Danilenko, 2008).

6.6 SAPHO syndrome and CMRO

SAPHO (synovitis, acne, pustulosis, hyperostosis, osteitis) syndrome and CMRO (chronic recurrent multifocal osteomyelitis) represent pathologic entities related to Psoriasis and PPP in regard to the relationship between infection and autoimmunity. In genetically susceptible individuals, environmental factors (mainly infections) play a critical role in the pathogenesis of autoimmune diseases. Molecular similarity of microbial and host antigens has recently been proposed as a promoting factor for pathogen expansion when microbial agents are not recognized as alien and not completely eliminated (Rozin, 2009).

SAPHO syndrome is now recognized as a distinct medical entity: a reactive infectious osteitis. Infectious agents isolated from SAPHO patients have gained special attention for many years. Their possible etiological role is supported by the pathogen isolation from different sites: anterior chest wall, spine, synovial fluid, bone tissue and skin pustules. A range of pathogens have been found, including Staphylococcus aureus, Hemophilus parainfluenzae, Actinomyces, and even Treponema pallidum (Arnson, 2008). Propionibacterium acnes is a much more frequent pathogen and plays a particular role. Multiple affected members who segregated a SAPHO syndrome-like phenotype had neutrophil dysfunction and reduced internal oxydant production (Ferguson & al., 2008). That may explain the inability of the innate system to eliminate the pathogen from

affected sites and justifies long-term or permanent antibiotic therapy (Rozin, 2009; Magrey, 2009). Treatment of SAPHO syndrome remains empirical as the underlying aetiopathogenesis is unclear.

A growing body of literature has identified the association between neutrophilic dermatoses and multifocal, aseptic bone lesions in children, termed chronic recurrent multifocal osteomyelitis (CRMO). Classically, patients present with swelling, pain, and impaired mobility of the affected area, with skin lesions developing concurrently or in the future. Bone biopsy reveals inflammatory changes consistent with infectious osteomyelitis, but cultures and histologic staining invariably fail to identify an infectious source. Patients are refractory to antibiotic therapy, but dramatically respond to systemic steroids and may need to be maintained on low-dose steroids to prevent relapse. Numerous authors have suggested that CRMO and SAPHO syndrome lie along the same clinical spectrum (Tlougan, 2009; Shilling, 2000).

7. Psoriasis and tumours in head and neck area

Overexpression of S100A7 (psoriasin), a small calcium-binding protein, has been associated with the development of Psoriasis and carcinomas in different types of epithelia but its precise functions are still unknown. Using human tissue specimens, cultured cell lines and a mouse model it was found (Zhou & al., 2008) that S100A7 is highly expressed in preinvasive, well-differentiated and early staged human squamous cell carcinoma of the oral cavity (SCCOC), but little or no expression was found in poorly differentiated, later-staged invasive tumors. Interestingly those researchers showed that S100A7 inhibits both SCCOC cell proliferation in vitro and tumor growth/invasion in vivo. Furthermore, they demonstrated that S100A7 is associated with the beta-catenin complex, and inhibits beta-catenin signaling by targeting beta-catenin degradation via a non canonical mechanism that is independent of GSK3beta-mediated phosphorylation. More importantly their studies also indicated that beta-catenin signaling negatively regulates S100A7 expression. Thus, this reciprocal negative regulation between S100A7 and beta-catenin signaling implies their important roles in tumor development and progression. Despite its high levels of expression in early stage of SCCOC tumorigenesis, S100A7 actually inhibits SCCOC tumor growth/invasion as well as tumor progression. Downregulation of S100A7 in later stages of tumorigenesis increases beta-catenin signaling, leading to promotion of tumor growth and tumor progression.

Significantly increased risk of cancer was demonstrated in patients with Psoriasis at an average of 9.3 years after discharge from hospital. This risk, amounting to 1.4 times that in the general population, is mainly relative to skin and lung cancer in both sexes and to pharynx and larynx cancer in men. Still this data are not definitive as no studies have been published with bias correction for smoke and alcohol consumption. Non-melanoma skin cancer is the most common malignancy, occurring in 196 of 795 patients with cancer: standardized incidence ratio 2.4 for men and 2.6 for women. This means an overall lifetime risk (up to the age of 75 years) of 14.1%. Women run the highest risk of basal cell carcinoma in the age range 20-40 years, while men in the age range 30-60 years run a particularly high risk of squamous cell carcinoma (Frentz & Olsen, 1999).

Standardized incidence ratios (SIR) was found to be 2.80 (95% CI 1.96, 3.87) for oral cavity and pharynx cancer in a nationwide series of psoriasis patients from Sweden with a hospital discharge diagnosis of psoriasis made during 1965–83, who were alive and free from malignancy 1 year after first discharge, compared with the national population (Boffetta & al., 2001). Psoriasis was associated with a significantly increased prevalence ratio of lip, oral cavity and pharynx cancer (1.49; [1.22, 1.80]), in a national database in Taiwan (Tsai & al. 2011).

8. Conclusion

Psoriasis is a disease treated near exclusively from dermatologists. Nevertheless some factors indicate the need for a new attention by the head and neck area specialists, especially by the otorhinolaringologists and maxillofacial surgeons.

Recent literature focuses on relationship between autoimmunity and infection, the latter representing the prince environmental factor that could play a critical role in the pathogenesis of autoimmune diseases in susceptible individuals with the production of cross-reacting antibodies and the induction of the inflammatory second hit. When infectious agents are not recognized as alien and not completely eliminated, pathogen expansion could be promoted by molecular similarity of microbial and host antigens.

As above mentioned important relationship has been demonstrated between tonsillar T cells and skin lesion in PPP patients with immune response to α-streptococci.

Further investigations with translation from bench research to clinical knowledge and vice versa and with interrelation between dermatologists and head and neck specialists could result in considerable progress in understanding immunopathogenesis of Psoriasis and other immuno-mediated diseases.

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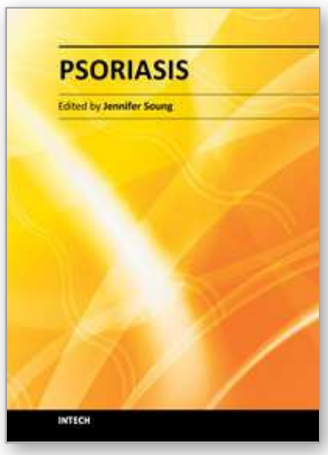

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