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Psoriasis: Epidemiology, Clinical and Histological Features, Triggering Factors, Assessment of Severity and Psychosocial Aspects

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1. Introduction

Psoriasis, a chronic erythematosquamous dermatitis that affects about 2-3% of the population, is characterized by abnormal keratinocyte hyperproliferation, resulting in thickening of the epidermis and of the stratum corneum. Psoriasis *vulgaris* accounts for 90% of the psoriasis cases and is characterized by well delineated reddish and scaly papules and plaques, typically on the elbows, knees and scalp or in other cutaneous surfaces.

Psoriatic skin changes have been described since biblical times. The first documented description is found in the Old Testament in the third book of Moses. It was confused with leprosy for hundred of years, and, therefore, many people with psoriasis was ostracised in the Middle Age. At the beginning of the 19th century, Robert Willan, an English physician, was the first to clinically describe psoriasis (Crissey and Parish 1998). Humankind suffered and studied this disease for at least 3000 years, and, naturally, several possible causes for the disease have been hypothesized.

Nowadays it is accepted that psoriasis is a chronic, recurrent, immune-mediated inflammatory disease, with a recognised genetic predisposition. The primary immune defect appears to be an increase in cell signalling via chemokines and cytokines that act up-regulating gene expression, causing keratinocyte hyperproliferation. T lymphocytes and their cytokines and chemokines appear to be the driver of lesion development and persistence, although other cells, such as endothelial cells, dendritic cells, neutrophils and

keratinocytes play also an important role, along with other cytokines and growth factors (Chen, de Groot et al.; Wollenberg, Wagner et al. 2002; Sano, Chan et al. 2005). Currently, it is proposed that psoriasis development depends on skin infiltration of T helper (Th)1/Th17 cells that stimulate macrophages and dermal dendritic cells to release mediators that sustain inflammation and cause abnormal keratinocyte proliferation. Interleukin (IL)-23 has the potential to activate Th17 cells, stimulating their survival and proliferation and serving as a key master cytokine regulator in psoriasis (Blauvelt 2008). Th17 cells secrete IL-17, IL-21 and IL-22, with the latter mediating IL-23 induced acanthosis and dermal inflammation (Zheng, Danilenko et al. 2007; Kunz 2009).Therefore, the IL-23/Th17 axis seem to play an important role in psoriasis and explains the hyperplasia of psoriatic keratinocytes (by IL-22), and why neutrophils appear in a chronic inflammatory disease, such as psoriasis (IL-8 production induced by IL-17) (Di Cesare, Di Meglio et al. 2009). More recently, functional interactions between IL-33 and mast cells were also found to contribute to inflammatory conditions, such as psoriasis (Xu, Jiang et al. 2008; Castellani, Kempuraj et al. 2009; Theoharides, Zhang et al. 2010). Nonetheless, the immunologic target molecule that would allow to classify psoriasis as an autoimmune disease, as well as, the events that trigger the inflammatory process, remain to be determined.

Patients with psoriasis require an individual management and long-term planning of therapeutic strategies. The ratio risk *versus* benefit, and the cost-effectiveness of the different treatments should be carefully evaluated. The therapy is chosen in accordance with skin type, clinical history, patient's age, severity of psoriasis and the response to previous treatments. Topical agents are, usually, chosen for milder forms and limited psoriasis; phototherapy, photochemotherapy and systemic agents for moderate and severe psoriasis. Biological therapies, the more recent therapies for psoriasis, are particularly used for severe psoriasis.

2. Epidemiology

Psoriasis affects about 125 million of people worldwide (National Psoriasis Foundation), is common in Caucasians and affects equally men and women. The prevalence of psoriasis in the population of Northern Europe and Scandinavia is 1.5-3%. While relatively common in Japanese, it is less common in Chinese, Eskimos, West Africans and North American blacks, and very uncommon in North American and South American natives and aboriginal Australians (Langley, Krueger et al. 2005). The causes for these variations are likely to be genetical and environmental; actually, population-based and twin studies indicate psoriasis as an heritable disease with a polygenic mode of inheritance, with variable penetrance (Elder, Nair et al. 1994). The prevalence of psoriasis seems to be affected by latitude (Vazquez, Carrera et al. 2006).

The onset of psoriasis can be at any time of life and, afterwards, it usually persists for life. The mean age of onset of psoriasis *vulgaris* is at 33 years, and 75% of the patients develop psoriasis before 46 years of age (Nevitt and Hutchinson 1996). It has been also suggested that psoriasis onset is bimodal, with a peak at 16- 22 and the other peak at 57-60 years of age. The age of onset is slightly earlier in women than in men.

Psoriasis is a relapsing disease, although natural remission occurs in about one-third of the psoriatic patients (Farber and Nall 1974).

According to Henseler and Christophers (Henseler and Christophers 1985) there are two types of psoriasis, defined by the age of psoriasis onset: type I, when it occurs at or before 40 years of age, and type II, when it occurs after the age of 40 years. Type I disease accounts for more than 75% of the cases. These patients are much more likely to express susceptibility alleles at the human leukocyte antigen (HLA) *loci*, to have affected first-degree relatives and to experience a more severe and recurrent disease than patients with type II psoriasis.

The course and progress of psoriasis is apparently unpredictable.

3. Clinical features

Psoriasis *vulgaris* or chronic plaque psoriasis, is the classic and the most common form of psoriasis presentation. The other forms of psoriasis include guttate, erythrodermic and pustular psoriasis. It is characterized by papulosquamous plaques well-defined from surrounding normal skin (Figure 1A). These plaques are red or salmon pink, covered by white or silvery scales, and the plaques may be thick, thin, large or small. They are more active at the edge and are, usually, symmetrically distributed, occurring commonly on elbows, knees, scalp, lumbosacral region and umbilicus.

Psoriasis *vulgaris* may have a variable course, presenting chronic stable lesions or plaques with a rapid onset and widespread involvement. It is, usually, symptomatic, with patients complaining of intense pruritus or burning; about 30% of the patients suffer from itch and pain, mostly due to the dryness and cracking of the psoriatic area.

Early lesions frequently start as small pinpoint papules, which, soon in their evolution, show scaling. The amount of scaling varies among patients, and at different body areas on a given patient, and its removal may reveal tiny bleeding points (Auspitz sign) (Murphy, Kerr et al. 2007). A white blanching ring, known as Woronoff`s ring may be observed in the skin surrounding a psoriatic plaque.

In inactive disease, the few existing plaques remain with the same size, and new ones do not appear.

Worsening of the disease is associated with enlargement of existing lesions and appearance of new, small lesions. With gradual peripheral extension, the plaques may develop different configurations: in psoriasis gyrata, a curved linear pattern predominates; in annular psoriasis, ring-like lesions develop secondary to central clearing; and in psoriasis follicularis, minute scaly papules are present at the opening of the pilosebaceous follicles (Langley, Krueger et al. 2005). The terms rupioid and ostraceous are related to distinct morphological subtypes of plaque psoriasis. Rupioid plaques are small and highly hyperkeratotic, resembling limpet shells. Ostraceous psoriasis refers to hyperkeratotic plaques, with concave centres, similar in shape to oyster shells (Langley, Krueger et al. 2005).

Site-specific variants of psoriasis *vulgaris* exist. Flexural or inverse psoriasis occurs in intertriginous sites. Seborrhoeic psoriasis occurs in eyebrows, nasolabial folds, postauricular and presternal sites. Psoriatic nail disease is most commonly found in patients with psoriatic arthritis. Fingernails are more commonly affected than toenails, and the clinical manifestations range from pitting, yellowish discoloration, and paronychia, to subungual hyperkeratosis, onycholysis, and severe onychodystrophy (Salomon, Szepietowski et al. 2003).

Fig. 1. Psoriasis clinical manifestations: A - chronic plaque psoriasis, B - guttate psoriasis, C - pustular psoriasis, D - erythrodermic psoriasis (With permission of Américo Figueiredo, PhDMD, and of Hugo Oliveira, MD).

Psoriatic arthritis is a seronegative inflammatory arthritis that occurs in the presence of psoriasis *vulgaris*. Five types of this psoriasis have been proposed: distal interphalangeal

joint only, asymmetrical oligoarthritis, polyarthritis, spondylitis and arthritis mutilans (Wright 1956; Wright 1959a; Wright 1959b). Gladman expanded the five sub-groups to seven: distal disease, oligoarthritis (<4 joints), polyarthritis, spondylitis only, distal disease plus spondylitis, oligoarthritis plus spondylitis and polyarthritis plus spondylitis (Gladman, Shuckett et al. 1987). About 10-30% of patients with psoriasis *vulgaris* develop psoriatic arthritis. It is controversial whether or not the skin condition and arthritis represent a different manifestation of the same disease. Immunological studies, genetic evidence and different responses to treatment, suggest that they might be different conditions with a similar underlying inflammatory process (Pitzalis, Cauli et al. 1996; Ho, Bruce et al. 2005).

Psoriasis *vulgaris* can be classified in accordance with the configuration of the lesions and their localization. It is also classified, according to the severity of clinical presentation, in mild, moderate and severe (see Assessing psoriasis severity).

Guttate psoriasis (Figure 1B), an acute form of psoriasis that develops especially in children, adolescents and young adults, is characterized by papules with less than 1 cm in diameter that erupt in the trunk and extremities, about 2 weeks after a β-haemolytic streptococcal or a viral infection, and/or after acute stressful life events. Usually, it is self-limited, resolving in 3-4 months, however its long-term prognosis is unknown. Some affected individuals may progress to a chronic form of plaque psoriasis and sparkles of guttate lesions may appear during the course of chronic plaque psoriasis (Martin, Chalmers et al. 1996).

Pustular psoriasis (Figure 1C) is an acute form of psoriasis, in which small, monomorphic, sterile pustules develop in painful inflamed skin. It can be generalized and potentially life-threatening or it can be localized, presenting as palmoplantar pustulosis or acrodermatitis continua of Hallopeau. Acrodermatitis continua is a rare, chronic, pustular eruption of the fingers and toes. Palmoplantar pustulosis is characterized by hyperkeratosis and clusters of pustules over the hands and/or feet; some authors claim, however, that this form is not really a psoriasis form (Asumalahti, Ameen et al. 2003). Patients with generalized pustular psoriasis may have pre-existing plaque psoriasis or develop it after pustular episodes. An intercurrent infection, or the abrupt withdrawal of systemic and, occasionally, of ultrapotent topical corticosteroids may also trigger this form of psoriasis.

In erythrodermic psoriasis (Figure 1D), more than 90% of the skin surface area is affected, which may lead to hypothermia, due to an impairment in the thermoregulation of the skin, high output cardiac failure, infection and metabolic changes. These changes include hypoalbuminaemia and anaemia due to loss of iron, vitamin B_{12} and folate. This form of psoriasis can be a life-threatening condition. It may present as chronic plaque psoriasis that gradually worsens, as plaques become confluent and extensive. Erythroderma may also be precipated by infection, tar, drugs, or withdrawal of corticosteroids (Langley, Krueger et al. 2005).

4. Genetic predisposition

A genetic predisposition to develop the disease appears to exist. Indeed, psoriasis develops in bone marrow transplant recipients from donors with psoriasis, and clears in recipients from donors without psoriasis (Wahie, Alexandroff et al. 2006).

About 30% of psoriatic patients present a family history of the disease in a first or second-degree relative. In fact, the probability to develop psoriasis is raised when first-grade relatives

suffer from the disease. The risk to develop psoriasis appears to be about 20% if one parent has psoriasis and about 75% if both parents are affected (Watson, Cann et al. 1972).

Psoriasis has been associated with certain HLA-types (HLA-Cw6, HLA-B13, HLA-B17, HLABw57, HLA-DR4), and those with HLA-Cw6 seem to have a 10-fold higher risk to develop the disease. A collaborative genome-wide association study of psoriasis involving thousands of cases and controls revealed association between psoriasis and seven genetic loci: HLA-C, IL12B, IL23R, IL23A, IL4/IL13, TNFAIP3, and TNIP1 (Elder, Bruce et al. 2010). Moreover, a family history of psoriasis, an early-onset of the disease and the presence of HLA-Cw*0602 (the major determinant of phenotypic expression), have been associated to a more unstable and severe clinical course, as compared to those patients with late onset psoriasis and negative for HLA-Cw*0602 (Henseler and Christophers 1985; Gudjonsson, Karason et al. 2006).

The molecular genetic basis of psoriasis is complex, with evidence that multiple genes are involved. At least nine chromosomal susceptibility *loci* have been revealed (PSORS1-9). The PSORS1 gene, in the major histocompatibility complex region on chromosome 6 (6p21), appears to be associated with most cases of psoriasis. However, the exact location of PSORS1 gene remains controversial. Furthermore, the penetrance of PSORS1 *locus* is estimated to be less than 15%, implying that other genetic and/or environmental factors may also contribute to the liability of the disease. Moreover, an association of PSORS with functional polymorphisms in modifier genes that mediate inflammation (e.g., tumour necrosis factor (TNF)-α) and vascular growth (e.g., vascular endothelial growth factor), has been found (Capon, Munro et al. 2002).

Thus, whereas the existence of a genetic component in psoriasis is certain, the exact location of the genes involved remains to be determined.

Psoriatic patients present a substantial genetic heterogeneity and it is likely that this genetic heterogeneity could lead to subtle differences in disease pathogenesis, explaining the different responses to treatment observed in the patients.

5. Triggering factors

Psoriasis has a complex genetic predisposition, with a complex inheritance pattern, plus an environmental component. The development and exacerbation of psoriasis appears to involve an interaction between multiple genetic and environmental risk factors. Usually, psoriasis is triggered by infection, inflammation, stress, skin injury and drugs.

Several microbial infections are associated with the development and/or worsening of psoriasis. A strong association is the induction of guttate psoriasis by a preceding tonsilar *Streptococcus pyogenes* infection. Disease exacerbation has been associated with skin and/or gut colonization by *Staphylococcus aureus, Malassezia* and *Candida albicans* (Noah 1990; Waldman, Gilhar et al. 2001). Streptococcal infections precede the development or worsening of psoriasis in more than 90% of patients with type I psoriasis (Weisenseel, Laumbacher et al. 2002). The role, if any, of viruses (papilomaviruses, retroviruses, endogenous retroviruses) present in lesional skin is unknown.

In about 30% of patients, the lesions appear at sites of skin injury - the Koebner phenomenon (Holzmann, Werner et al. 1992). This phenomenon is an indicator of disease

activity and may have a prognostic value, as it is, usually, associated with early onset of psoriasis. Interestingly, light-induced psoriasis, resulting from an excessive sun exposure (that may improve psoriasis if used appropriately), is also a form of Koebner phenomenon.

There is a growing list of drugs that may aggravate existing psoriasis or induce it for the first time. The frequency of this adverse event varies between drugs. The most commonly proposed causative agents are β-blockers, lithium, synthetic anti-malarial drugs, non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors and tetracycline antibiotics (Wolf, Lo Schiavo et al. 1997; O'Brien and Koo 2006).

Evidences confirm that the onset of plaque psoriasis is highly associated with a preceding stressful life event (Mallbris, Larsson et al. 2005); indeed, chronic psychological stress may influence the development of psoriasis and affect its clinical expression (Naldi, Chatenoud et al. 2005).

Diet is sometimes referred as a possible triggering factor for psoriasis, but no consistent data exist. Apparently, fish oil diet or a diet consisting predominantly of glucose and unsaturated fatty acids has beneficial effects on psoriasis (Lithell, Bruce et al. 1983; Caspary, Elliott et al. 2005).

Alcoholism, cigarette smoking, obesity, type 2 diabetes *mellitus*, and metabolic syndrome increase the risk for developing psoriasis (Naldi, Chatenoud et al. 2005; Neimann, Shin et al. 2006). These factors may influence clinical severity and prognosis of psoriasis and, as risk factors for cardiovascular diseases (CVD), may underlie the increased morbidity and mortality for CVD events observed in psoriatic patients.

Some authors stated (Mallbris, Larsson et al. 2005; Naldi, Chatenoud et al. 2005) that obesity precedes and may represent a risk factor to develop psoriasis. Moreover, after the onset of psoriasis, obesity seems to contribute to its exacerbation (Sterry, Strober et al. 2007). We found (Coimbra, Oliveira et al. 2010a) that the prevalence of overweight/obesity in psoriatic patients is high, with overweight/obese patients presenting higher leptin, resistin, TNF-α and IL-6 levels, and lower adiponectin values, as compared to patients with a normal body mass index. Obesity itself, by increasing friction and trauma in the waistline and intertriginous areas, may worsen psoriasis by the Koebner phenomenon (Higa-Sansone, Szomstein et al. 2004). Furthermore, obesity may favour the onset of the disease, by providing a chronic level of low-grade inflammation that may contribute to trigger the development of psoriasis and may account for its severity (Hamminga, van der Lely et al. 2006).

Indeed, inflammation seems to be a central key in psoriasis onset and exacerbation. Studies in our lab (Coimbra, Oliveira et al. 2010b; Coimbra, Oliveira et al. 2010c) showed that worsening of psoriasis is linked to an enhanced inflammatory response with neutrophil activation and in which the cytokine network is disturbed. We also found that after a successful treatment the inflammatory markers levels decreased. Nonetheless, at clearing of the disease, a residual inflammatory response still persists, what may be important for the relapse episodes that are characteristic of psoriasis.

6. Psoriasis *vulgaris* histological features

Psoriasis presents three main histological features: epidermal hyperplasia (acanthosis), dilated and prominent blood vessels in the dermis, and an inflammatory infiltrate of leukocytes, predominantly in the dermis (Gonzalez, Rajadhyaksha et al. 1999; Werner,

Bresch et al. 2008). The histopathological findings in psoriasis lesions, however, may vary as a consequence of the recurrent courses of exacerbation of the disease. The increase in epidermal proliferation and in inflammation are not uniform, even within the same lesion of chronic plaque type psoriasis. Typically, they are higher at the centre of the pinpoint of early lesions, whereas in more developed plaque lesions these changes are found at the border.

A sparse superficial perivascular T-lymphocytic infiltrate of the dermis is, usually, the earliest alteration observed in the lesions. This is followed by the development of dilated and tortuous blood vessels within dermal papillae, by mild dermal oedema, and by minimal spongiosis, with rare T-lymphocyte and/or neutrophil exocytosis. Subsequently, a slight epidermal hyperplasia, with higher neutrophil exocytosis and small mounds of parakeratosis (retention of nuclei in cells of the stratum corneum) containing neutrophils are observed. The infiltrate in the dermis at this early plaque stage is, usually, composed of lymphocytes, histiocytes and neutrophils, in addition to red blood cells.

The developed plaques show marked epidermal hyperplasia, with regular elongation of epidermal rete ridges with characteristic bulbous enlargement of their tips; elongation of intervening dermal papillae containing dilated and tortuous capillaries; fine fibrillary collagen and thinning of epidermis that lies immediately above the dermal papillae. Additionally, there is pallor of the superficial layers of the epidermis and spongiosois is minimal or absent. There is marked hyperkeratosis, as well as, hypogranulosis subjacent to areas of parakeratosis. In most cases, neutrophils within the parakeratosis are present (Munro's microabscesses). Spongiform pustules of Kojog may be formed, due to the migration of neutrophils from the papillary capillaries that aggregate beneath the stratum corneum and in the upper Malpighian layer between degenerating and thinned keratinocytes (Mehta, Singal et al. 2009). Subsequently, the keratynocytes at the centre of the pustule degenerate, with formation of a large single cavity surrounded by thinned keratinocytes.

Both T cell subsets, CD4+ and CD8+ T cells, are present in early stage and developed lesions, but, whereas CD8+ T cells are preferentially present within the epidermis (Bos, Hagenaars et al. 1989), CD4+ T cells are mainly in the dermis. Currently, it is also believed that a separate population of T-helper (Th) cells beside the Th1 cells, namely, the Th17 cells, are present at psoriatic lesions (Lowes, Kikuchi et al. 2008).

The characteristic massive scaling is a consequence of a thickened, irregular stratum corneum with parakeratosis and epidermal thickening with acanthosis, papillomatosis, and absence of granular layer. Epidermal thickening is caused by increased keratinocyte proliferation, reflecting the increased mitotic activity within the basal and suprabasal layers. In normal skin, the maturation of keratinocytes from the basal layer to the cornified layer takes about 28 days, whereas in the psoriatic lesion, it is shortened to 5 days. This shortened maturation is associated with massively disrupted terminal differentiation of keratinocytes and is mainly reflected by parakeratosis.

As referred, the psoriatic plaque is characterized by profound histological disturbances and by the presence of different and unusual cell types. There is a marked infiltration of mononuclear leukocytes, the development of elongated/hyperplastic blood vessels in the papillary dermal region that accounts for the visible redness of psoriatic skin lesions. At the early stage of the plaque, infiltration of T cells, dendritic cells and monocytes/macrophages occurs. Later, the cellular density of these infiltrates increases, and infiltrates of CD8+ T cells

and neutrophilic granulocytes occur, particularly in the epidermis. Many lymphocytes, monocytes, and neutrophils are clearly adherent to endothelial cells.

Leukocytes can gain skin parenchyma by transmigration through reactive blood vessels, and resident skin leukocytes might increase creating the dense infiltrates, observed in psoriatic lesions. Although Langerhans cells and dermal dendritic cells have long been recognized as the main types of dendritic cells in skin, only more recently the types of dendritic cells in psoriatic lesions were identified, such as, CD11c+ (myeloid) and plasmocytoid dendritic cells. CD11c+ dendritic cells correspond to interstitial dendritic cells in other tissues and are the most abundant dendritic cell type in the dermis (Lowes, Chamian et al. 2005; Nestle, Conrad et al. 2005).

Polymorphonuclear neutrophils seem to play a pivotal role in the acute inflammatory changes of psoriatic lesions. Areas of parakeratosis appear to contain abundant neutrophils (Cox and Watson 1972). In addition, it is known that pronounced parakeratosis is associated with the presence of neutrophils and that Munro's microabscesses are located exclusively within areas of parakeratosis (van de Kerkhof and Lammers 1987). Coexistence of neutrophils and parakeratosis is in part explained by the tissue destructive properties of active oxygen intermediates and proteolytic enzymes that are released by activated neutrophils attached to the stratum corneum (Terui, Ozawa et al. 2000).

It is of interest, the fact that resolving or treated plaques of psoriasis show initially a progressive reduction of neutrophils within the stratum corneum and of the parakeratosis, with regeneration of the granular zone. The epidermal changes resolve later. The histopathologic clue of the disease that may remain is a residual mild superficial dermal fibrosis with persistence of papillary dermal capillary dilatation and tortuosity (Murphy, Kerr et al. 2007).

In summary, histologically, in psoriasis, there is marked acanthosis, accompanied by parakeratosis and a mixed dermal infiltrate, including CD4+ T cells, dendritic cells, macrophages, and mast cells. Indeed, by immunostaining for IL-17A and IL-22, it has been shown numerous cells present in the psoriasis lesions which are able to produce these cytokines (Harper, Guo et al. 2009). In the epidermis, neutrophilic exudates and CD8+ T cells are often seen. Dermal papillary blood vessels are dilated and tortuous.

7. Assessing psoriasis severity

In clinical practice, broad global assessments of psoriasis activity and its effect on patient's quality of life are used to define the severity of patient's disease and to define the more appropriate treatment. Furthermore, in clinical trials, the quantification of the disease severity is critical to measure the efficacy of the treatment under study, by comparing the severity of disease before and after the treatment.

The severity of psoriasis can be defined by the percentage of body surface area involved. In mild cases, the lesions cover less than 10% of the body surface, in moderate cases 10-20% and in the severe cases the lesions affect more than 20% of skin surface (Naldi and Gambini 2007).

There are several other approaches to measure the severity of psoriasis, which consider not only the affected skin surface, but also the degree of scaling and the type of infiltration.

The Psoriasis Area and Severity Index (PASI) is the prototype for such measures, and is the most widely used tool to assess psoriasis severity in clinical trials and in clinical practice. It was developed as an outcome measure in clinical trials on oral retinoids in 1978 (Frederiksson T 1978).

The PASI score ranges from 0 to 72. It combines the assessment of four body areas: head and neck, upper limbs, trunk and lower limbs. To assess affected body surface area, the proportion of skin affected in each area is given by a numerical score, representing the proportion involved. Within each area the severity of the lesions is assessed by three signs, erythema, thickness/induration, and desquamation/scaling; each of the three signs is assessed on a five-point scale. Finally, the PASI score is calculated according to an appropriate formula (Figure 2).

Score	0	1	2	3	4	5	6
Erythema Induration Desquamation	none	mild	moderate	severe	very severe	—	—
True Area (%)	0	1-9	10-29	30-49	50-69	70-89	90-100

Fig. 2. Psoriasis Area and Severity Index (PASI) score assessment (H, head; LL, lower limbs; T, trunk; UL, upper limbs).

A PASI score below 10 defines psoriasis as mild, between 10 and 20 as moderate, and above 20 as severe (Naldi and Gambini 2007). The evaluation of PASI presents some subjectivity, which is reduced when patients are evaluated always by the same dermatologist.

The PASI system has two major advantages: it is sensitive to changes in the area of the affected skin and in the severity of the lesions; therefore, the changes in PASI score reflect improvement or worsening of the disease. Its widespread use in the research setting means that it is possible to compare information from different studies. When conducting a clinical trial for treatment of psoriasis, a predetermined endpoint is required, on which the efficacy

of the drug will be assessed. It is established that a 75% improvement in PASI, defined as PASI 75, is a clinically meaningful endpoint for clinical trials, and there is strong evidence demonstrating that 50% improvement in PASI (PASI 50) could also be a clinically meaningful endpoint (Carlin, Feldman et al. 2004). A major limitation of the PASI is that it is not routinely used by clinicians and, therefore, is poorly understood by both clinicians and patients. It also presents poor sensitivity to changes in small areas of involvement. Therefore, PASI is not the best tool to be used in patients with mild disease.

Another traditional assessment tool to evaluate psoriasis severity is the Physician's Global Assessment (PGA), a simple instrument that provides a subjective global evaluation. There are several variants for PGA. Typically, the patient is asked to rate the disease, using a scale of seven categories, "clear", "almost clear", "mild", "mild to moderate", "moderate", "moderate to severe" and "severe". It is less objective than PASI, but the result is more easily understood by the patient (Berth-Jones, Grotzinger et al. 2006).

The Lattice System Physician's Global Assessment (LS-PGA), formerly known as Lattice System Global Psoriasis Scale, applies a more objective approach to global assessment of disease severity than PGA, because it considers the body surface area involved and the morphological characteristics of the plaques (Berth-Jones, Grotzinger et al. 2006). Total body surface area involved is estimated using a scale of seven categories (0, 1-3, 4-9, 10-20, 21-29, 30-50, $\geq$ 51%). Then, using a matrix system, the average of plaque characteristics (elevation, erythema and scaling) will be evaluated. The categories, on an eight-point scale, are: "clear", "almost clear", "mild", "mild to moderate", "moderate", "moderate to severe", "severe", and "very severe".

Despite the importance of the evaluation of psoriasis severity, there is a lack of consensus on the most appropriate measures (van de Kerkhof 1997; Chalmers and Griffiths 2003; Langley and Ellis 2004), though PASI, PGA, and LS-PGA appear to be highly correlated with each other (Langley and Ellis 2004). Despite the referred limitations, the PASI score is the most accepted and widely used measure in clinical trials and in clinical practice (Ashcroft, Wan Po et al. 1999).

Other important psoriasis measurement tools are under development, especially those that also measure the patient's perception of well-being. The National Psoriasis Foundation has developed the National Psoriasis Foundation Psoriasis Score, a responder index, that include six subdomains: induration at two target sites, current and baseline body surface area, physician global assessment, patient global assessment, and patient assessment of itch (Gottlieb, Chaudhari et al. 2003).

Two other quantitative ways of measuring psoriasis are biopsies and photographs. Biopsies are attractive because they are objective, however, their major limitation is that psoriasis does not resolve in a uniform way, and, therefore, biopsies may not provide a representative sampling of lesions. In theory, photographs could be used to confirm real time assessments of disease severity. It is not clear, however, if thickness/induration or even scaliness of lesions can be accurately assessed using the photographs. Nevertheless, photographs do make a strong impact in educating physicians and, therefore, they are commonly incorporated into clinical trials.

Most of these tools do not include a measure about the quality-of-life or considers the patient's perception of well-being. Thus, any direct information about psychological and/or

social disease consequences is not provided. Indeed, a major component in the assessment of psoriasis should be the measurement of the quality of life, because the improvement in patients' lives is the primary goal of therapy. The term quality of life, or health related quality of life (HRQOL), refers to a quantitative estimation of the global impact of a disease on physical, social, and psychological well-being of a patient. It appears that there is not always a strong correlation between the HRQOL and the severity of the disease, as defined by PASI. For instance, the visibility of psoriatic lesions or the impairment of daily activities may incapacitate a patient to work; itch and pain may cause severe impairment of HRQOL.

The estimation of quality of life is obtained through standardized questionnaires exploring the relevant dimensions of the patient's life that may be affected by the disease. Non-specific queries, such as the Medical Outcome Survey Short Form 36 (SF-36) and the Euro QOL, are used to assess patients' overall quality of life (Ware and Sherbourne 1992; Brazier, Jones et al. 1993).

There are more specific instruments, focusing on aspects of quality of life that are affected by skin disease. These, include the Dermatology Life Quality Index (DLQI) and the Skindex (Finlay and Khan 1994; Chren, Lasek et al. 1997). There are even more specific measures for psoriasis. For instance, scores that include psychological impact along with the severity of the skin lesions are the Salford Psoriasis Index and the Psoriasis Disability Index (Kirby, Fortune et al. 2000). A psoriasis-specific study of QOL, the PSORIQOL, is a recently introduced 25-item instrument (McKenna, Cook et al. 2003).

The DLQI and the SF-36 have been previously used to evaluate the HRQOL on psoriatic patients (Feldman, Gottlieb et al. 2008; Reich and Griffiths 2008). The generic queries, such as the SF-36, are useful to show the impact of psoriasis. The SF-36 has showed that the impact of psoriasis was similar or higher than that imposed by many other serious medical conditions.

The DLQI has been most widely used in psoriasis trials as a measure to assess the quality of life related to skin disease. Indeed, it has been used in more than 35 psoriasis studies, and it has been used very extensively over the last years in the study of the new generation of systemic therapies for psoriasis. Furthermore, it has been shown that the value of clinical research in psoriasis is improved in the DLQI, as the DLQI score banding proposes: 0-1 means "no effect on QOL"; 2-5, "small effect"; 6-10, "moderate effect"; 11-20, "very large effect"; 21-30, "extremely large effect". Apparently, a total DLQI higher than 10 represents a skin disease having a very large effect on patient's life, needing intervention, and, from the individual point of view, a DLQI of 5 or less is associated with improved QOL.

Quality of life clarified the multidimensional nature of disease assessment and outcome, which should include the evaluation of disease associated discomfort, level of disability, and social disruption. It is important to define the severity of psoriasis, but it is also important to identify psoriasis that severely affects the quality of life.

8. Psoriasis psychosocial aspects

A number of psychiatric/psychological comorbidities have been observed in psoriatic patients. Psoriasis deeply affects the well-being of the patient and has emotional and social consequences (Jobling and Naldi 2006). Thus, to define psoriasis as only a skin problem is a very restrictive approach.

Psoriatic patients present a variety of psychological problems, including poor self esteem, sexual dysfunction, anxiety and depression. Indeed, about 35% of psoriatic patients report symptoms of depression (Friedewald, Cather et al. 2008); about 80% of patients refer that the disease has a negative impact on their lives for a variety of reasons, including the physical symptoms, upsetting physical appearance (particularly because its onset is before 30 years of age in 60% of the cases), frustration, anger, anxiety, depression, and increased use of alcohol (Mease and Menter 2006). Since psoriasis is a persistent, disfiguring and stigmatizing disease, clinicians need to be aware of the emotional and psychological impact of psoriasis in the patient.

Major depression seems to be a significant predictor of CVD events. It may be an independent risk factor for death, after suffering an acute myocardial infarction (Carney, Blumenthal et al. 2003), and it may increase the risk for coronary artery disease (Barth, Schumacher et al. 2004). An association between depressive symptoms and the levels of serum inflammatory markers was also reported (Stewart, Janicki-Deverts et al. 2008). Acute or chronic psychological stress, may induce a chronic inflammatory process that may culminate in atherosclerosis (Black and Garbutt 2002).

It is known that in psoriatic patients, psychological stress, by itself, can play a role in exacerbation of psoriasis, and that higher stress reactivity has been associated with the onset of psoriasis at an earlier age (Naldi, Chatenoud et al. 2005). Indeed, 31% of the patients reported the onset of psoriasis in periods of increased everyday life stress, and in 71% of patients, psoriasis symptomatology worsened during stressful life episodes (Griffiths and Richards 2001; Zachariae, Zachariae et al. 2004). The importance of stress in psoriasis has been further highlighted, since psychological distress affects treatment outcome in psoriatic patients. For instance, the level of stress may prolong the time taken for psoralen plus UVA (PUVA) to clear the symptoms of psoriasis (Fortune, Richards et al. 2003). Accordingly, stress reduction by stress management, relaxation or cognitive techniques shortened the time to clear psoriasis symptoms by PUVA, and, moreover, improved the clinical severity of psoriasis (Kabat-Zinn, Wheeler et al. 1998; Fortune, Richards et al. 2002). An interesting finding is the increase in the catecholamine levels after stress exposure in psoriatic patients (Buske-Kirschbaum, Ebrecht et al. 2006), pointing to a hyper responsive sympatho-adrenomedullary system in psoriasis.

The relevance of stress in psoriasis is broadly accepted, however, the underlying mechanisms, of how psychological distress exacerbates or triggers psoriasis, are poorly understood. It is known that psychological stress has the potential to regulate the immune response, and there is emerging evidence that abnormal neuroendocrine response to stress may contribute to the pathogenesis of chronic autoimmune diseases (Jorgensen, Bressot et al. 1995).

Psoriatic patients often manifest not only a profound psychosocial disability, but also a significant impairment of health related quality of life (Reich and Griffiths 2008). The lack of understanding by the family members may increase the level of anxiety in the patient; the QOL of relatives and partners of patients with psoriasis can also be significantly affected (Eghlileb, Davies et al. 2007).

Some authors believe that HRQOL is more determined by how an individual mentally copes with the disease than by the amount of skin affected (Stern, Nijsten et al. 2004;

Friedewald, Cather et al. 2008). Others, refer that the impact of the disease in HRQOL seem to be greater in patients with more extensive skin involvement (Gelfand, Feldman et al. 2004). Thus, clinicians need to try to perceive the severity of psoriasis from the patient's point of view. From the patient's perspective, psoriasis is usually considered as severe, if it causes embarrassment or anxiety, pruritus or soreness; if it affects relationships, everyday activities, working, studying or sport activities, or if there is joint involvement. In a survey of patients with severe forms of psoriasis, 79% reported that psoriasis had a negative impact on their lives, 40% felt frustration with recurrent treatments, and 32% did not perceive their treatment to be sufficiently aggressive (Krueger, Koo et al. 2001). The impact of psoriasis seems to be more severe for young adults (18-24 years old), particularly, for women, singles, patients with visible psoriasis, patients who developed psoriasis in early childhood, patients who have a negative state of mind as a result of psoriasis, or patients who have experienced additional problems due to psoriasis (Young 2005).

It is known that the stress caused by living with psoriasis can be manifested as avoidance behaviours. Active psoriasis seems to lead to a marked loss of productivity (Fowler, Duh et al. 2008). In fact, the two main contributors to stress in patients with psoriasis are engaging in avoidance behaviour and the belief that they are being evaluated on the basis of their skin disease, which may lead to low grade persistent stress. It has been reported that psoriatic patients present a reduction in physical and mental functioning comparable to that observed in patients with cancer, arthritis, hypertension, heart disease and depression (Rapp, Feldman et al. 1999). Furthermore, the general health status of the patient may be affected by all the diseases that associate with psoriasis, creating a substantial impact on HRQOL.

Psychological sequelae of the disease can impair the response to treatment, since patients with pathological levels of anxiety are less likely to respond to therapy (Fortune, Richards et al. 2003). Thus, stress in the form of pathological worry has a deleterious effect on response to therapy. In consequence, psychological intervention may play an important role in the management of psoriasis patients.

9. Acknowledgements

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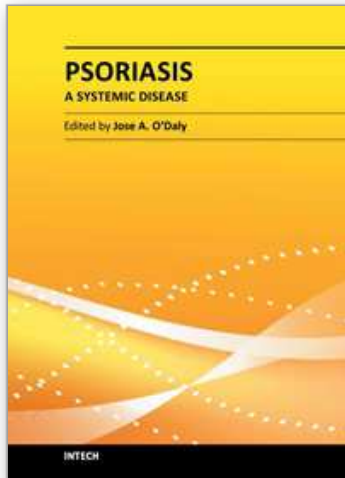
Psoriasis - A Systemic Disease

Edited by Dr. Jose O' Daly

The purpose of this book is to present a comprehensive analysis of Psoriasis, a disease that affects approximately 2-3% of humanity in all countries. Psoriasis existence is surveyed since the clay tablets of Assyrians and Babylonians 3.000-5.000 years ago, thru the middle ages, the renaissance, XIX and XX centuries.

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