PSORIASIS AND ANESTHETIC CONSIDERATIONS

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Introduction

Psoriasis is an inflammatory skin disease. It is the most common chronic disease of the skin, often a debilitating dermatological ailment that affects up to 3 percent of the world's population. The disease exhibits the characteristics of a high epidermal turnover rate accompanied with epidermal hyperplasia and accumulation. The dermal papillae and epidermis undergo hypertrophy and form cutaneous lesions that develop thick, loosely adherent scales (chronic plaque psoriasis). The epidemiology is due to complex genetics and the disease is known to erupt due to many environmental factors including infection, bone marrow transplantation, stress, and malignancy[1]. Lesions usually appear on the scalp, elbows, knees and the sacral region. In some cases, psoriasis can spread throughout the entire integument including the oral mucosa, palms, soles and even finger nails. Symptoms are cyclical, peaking usually during young adulthood (16 to 22 years of age) and during older ages (57 to 60 years of age)[2].

Genetics

Psoriasis has strong genetic ties. One study of 3,717 families identified the relationship of psoriasis among patients and siblings[3]. The lifetime risk for developing psoriasis is 4% for an individual if the parents of the individual do not have psoriasis. However, the risk increases to 28% if one of the parents is afflicted and to 65% if both parents have psoriasis.

It is believed that genomic imprinting of the psoriasis gene passes the disease from parent to child. Penetrance of psoriasis can be variable according to the sex of the carrier, and is much higher if the carrier is the father[4,5]. The genetics of psoriasis exhibit characteristics of autosomal dominant and recessive gene traits, and it is therefore difficult to pinpoint the underlying cause. It is most likely that psoriasis expresses traits by 3 to 4 autosomal dominant genes while one gene acts in a recessive manner. If two of the predisposed genes are expressed, there is an increased likelihood for the development of psoriasis[6]. In simplified terms, early-onset psoriasis with severe progression is associated with human leukocyte antigen (HLA) factors whereas the milder, late-onset counterpart is not.

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Psoriasis has many patterns associated with genetics which can best be appreciated by understanding its relations to HLA factors. Different HLA associations can determine many variant forms of psoriasis and also indicate other factors such as time of onset and severity of the disease. For example, pustular psoriasis has dissimilar HLA association from psoriasis vulgaris. P. vulgaris is associated with HLA A13 and A17, and this different association is one of the factors that determine findings such as how pustular psoriasis can arise at any age, even in childhood[7, 8]. HLA associations can also be seen when examining PsA, which also shows evidence of heredity. Occurrence of psoriasis increases by 8.3% for an individual if first degree relatives have PsA[9]. Patients with PsA show increased frequencies of HLA A26, B38, and DR4[10].

Clinical Presentation

Psoriasis is best observed as a disease that exhibits sharply demarcated erythematosquamous lesions, which are in several forms and demonstrate a variable cycle of growth and regression (Table 1). Psoriatic lesions follow a distinct pattern, starting as small pinpoint papules, which in turn grow larger and develop into a polycyclic outline with sharp demarcations but with no change to the unaffected skin. Occasionally, psoriasis shows a white blanching ring around the lesion. Macromorphical elements include scaling, erythema and induration. The scaling is silvery, and can be studied using a curette. Scratching the scaling repetitively, removes the last membrane.

This examination can expose a wet surface which shows pinpoint bleeding, due to the upward growth of the dermal papillae with increased vasodilation. Some extracutaneous manifestations are exemplified in the nails and include separation of the nail plate from the bed (onycholysis), dimpling, and pitting[11].

There are several risk factors associated with the onset of psoriasis. A recent study shows that there is an association of psoriasis with smoking, obesity, and infectious diseases. Clinical and immunological evidence supports streptococcal infection and the subsequent development of psoriasis, mainly in young people. There is an increased risk of psoriasis in patients with recent infectious disease, and the risk is greater within the first month after an upper respiratory tract infection, in particular among individuals aged 21 to 40 years[12].

There is no specific diagnostic test for psoriasis, as it is partly genetic. A family history of predisposition and knowledge of the presentation are important to the diagnosis.

Pathogenesis

The pathogenesis includes a variety of abnormalities that involve the epidermis, the stroma, intracellular communication, the immune system, and numerous aspects of cutaneous inflammation. The earliest stage begins with stromal changes. Later, an inflammatory infiltrate is found. Finally, an increased recruitment of cycling epidermal cells is observable.

Table 1. **Clinical Presentation of Psoriasis**

- *CHRONIC INFLAMMATION CONSISTING OF ERYTHEMATIC PAPULES AND PLAQUES*
- Silver scaling
- Sharp demarcation of lesions
- Involvement of scalp, sacral areas, knees, elbows, fingers (psoriatic arthritis)
- Epidermal proliferation without differentiation
- Association with severe rheumatoid arthritis type lesions (psoriatic arthritis)

Systemic Factors

Direct evidence for involvement of systemic factors in the development of psoriasis is provided by two observations: the response of the patient's skin to injury and systemic factors that aggravate the condition. The symptomless skin of a psoriatic patient responds with genesis of a new lesion at the site of trauma known as the Koebner response. It is an all-or-none phenomenon where either all or none of the injury sites on uninvolved skin will respond with psoriatic plaques. The mechanism for this response can possibly be explained via the release of proinflammatory cytokines, the unmasking of autontigens, or both[13]. In fact, some treatments for psoriasis that have proinflammatory potential (e.g., anthralin and phototherapy) appear to trigger psoriasis if applied too aggressively - for example, in high initial doses[14]. Aggravating factors such as psychological stress, focal infections, and a few medications also point to an underlying systemic pathogenesis for psoriasis. Although many systemic abnormalities have been described, the extent to which the abnormalities determine the underlying cause of the disease is unclear[11]. Other findings that show a systemic pathway include capillary abnormalities and epidermal hyperplasia - two key features of psoriasis whose mechanisms are still unknown[15].

Abnormal intracellular communication

Abnormal intercellular communication is another identifying feature of psoriasis. Many of the molecules expressed in psoriatic plaques are restricted or even absent in normal skin. SKALP (skin-associated antileukoprotease) is expressed in other hyperproliferative states and is also found in the psoriatic patient[16]. The SKALP protein actually binds to proteases, especially elastase, the enzyme released by neutrophils that enables penetration into the skin by collagen type IV degradation[17]. Other molecules have also been reported as increased in plaques, such as TGF-α, calmodulin, epidermal growth factor receptor, IL-1α, IL-1β, IL-6, IL-8, GRO-α, -β, and -γ[11].

Immunopathogenesis

While many of the factors that promote the generation of psoriatic lesions still remain obscure, compelling evidence suggests a primary T-lymphocyte based immunopathogenesis[18]. Experimental treatment of psoriasis began in 1979, with a compound that acts on lymphocytes called cyclosporine[19]. The primary action of CSA is to inhibit lymphokine release and proliferation of T cells, which led many scientists to believe that the T-cell is a key component of a psoriatic lesion. As aforementioned, the actual cause of psoriasis still remains unknown, but an enhanced immune response is now known to be an essential factor in the progression of the disease[20].

Variant Forms of Psoriasis

The term psoriasis encompasses a broad spectrum of diseases with different manifestations (see Table 2). These diseases have many similarities, but must still be distinguished from each other given that they have different systemic effects and severities.

Table 2

Variant Forms of Psoriasis	Characteristics
Chronic Plaque	Most common: scalp, sharp demarcations
Unstable	Transition phase
Guttate	Erythematosquamos papules, "droplets," involves trunk, spares palms and soles, common in children
Pustular	Macroscopic pustules, affects mucosal membrane and oral cavity, general and localized form
Erythrodermic	Generalized erythema and scaling replaces traditional plaques, systemic disregulation, increased blood flow in plaques can lead to high-output congestive heart failure

Differential Diagnosis

There are several skin disorders that resemble the clinical presentation of psoriasis based on macromorphology. One must be aware of the distinct traits of psoriasis that sets it apart from these other similar diseases, and that knowledge is usually sufficient for an accurate diagnose (see Table 3).

Other diseases that resemble psoriasis and are best differentiated by the use of histopathology include: Pityriasis lechenoides chronica, hypertrophic lichen planus and Bowen's disease. In addition to using histopathology, some conditions are best diagnosed by obtaining cultures and using potassium hydroxide (dermatophytic infections, candidiasis). Some diseases,

such as pre-malignancies, mycosis fungoides, and premycotic eruptions are very difficult to differentiate and may require multiple skin biopsies[11].

Table 3

Differential Diagnosis	Characteristics that differ from Psoriasis
Seborrheic Dermatitis caused by Pityrosporon proliferation	- Erythema localizations on the scalp that can spread to the face - Yellowish scarring
Pityriasis Rubra Pilaris	- "Islands" of unaffected skin surrounded by involved skin - Hyperkeratotic papules - Yellowish scarring
Eczema	- Vesiculations
Syphilis	- Resembles guttate psoriasis (to differentiate check serology)
Candidiasis	- Combination of colarette scaling and pustules

Complicating Factors

Extended disease control of psoriasis is tough to achieve due to difficulty in application of topical medicines, hence leading to reduced compliance, as well as a limit of the long-term use of many topical treatments due to safety issues[21]. The psoriatic condition is further complicated by environmental, emotional, and systemic factors. The underlying pathology can be exacerbated by infections, alcohol, smoking, stress and various drugs.

It has been well documented that infections trigger psoriasis. For example, streptococcal infections can trigger the disease and usually result in the guttate form. Psoriasis can also be aggravated by upper respiratory tract infections. A survey showed psoriasis exacerbation in 50% of children with upper respiratory tract infections[22-24].

Other local triggering factors include: contact dermatitis and certain eczemas, irritant dermatitis, impetigo contagiosa, herpes zoster, mycotic infection, mechanical trauma and sunburn. There are many known drugs that can also aggravate the disease (see Table 4): antimalarials, non-steroidal anti-inflammatory drugs, lithium, beta –adrenergic antagonists, and systemic corticosteroids[15,25,26]. It has been reported that the skin condition can even be triggered by emotional stress.

Treatment

The symptoms of psoriasis can be ameliorated in a variety of ways that can include moderate doses of UV light, tars, psoralen, anthralin, methotrexate, hydroxyurea and steroids[27]. There is no one standard cure for psoriasis and treatments vary based on the status of the disease. Both topical and systemic regimes are used. A wide array of antipsoriatic treatments is available that range from mild treatments with minimal side effects to drugs used to treat severe psoriasis with severe adverse effects. Various combinations are possible and the physician must individually design the treatment based on the patient's individual case and presentation of psoriasis.

Table 4

Drugs that exacerbate Psoriasis	Common Examples
Antimalarials	Chloroquine, Primaquine, Quinine, Sulfadoxine, Tetracyclines, Mefloquine, Artemisinin, Halofantrine, Proguanil
Non-Steroidal Anti-Inflammatory Drugs	Indometacin, Aspirin, Ibuprofen, Naproxen
Lithium	
Beta Adrenergic Antagonists	Acebutolol, Bisoprolol, Esmolol, Propranolol, Atenolol, Labetalol, Carvedilol, Metoprolol, and Nebivolol
Systemic Corticosteroids	Prednisone, Prednisolone, Methylprednisolone, Betamethasone, Dexamethasone, Triamcinolone and Hydrocortisone

Topical Treatments

While the severity of the psoriasis determines its treatment, approximately 70 to 80 percent of all patients with psoriasis can be successfully treated via topical treatments, while more severe cases require a combination therapy of systemic drugs and phototherapy[14]. A variety of topical treatments have been successful in the treatment of psoriasis. Patients have responded favorably to the following topical treatments:

Vitamin D_3 analogues (calcipotriol and tacalcitol), corticosteroids, dithranol, phototherapy (UVB) and

photo (chemo) therapy (PUVA).

Topical corticosteroids can be useful in managing psoriasis, especially when used to soothe the irritation that psoriasis causes in the genital and flexure areas, an effect due to anti-inflammatory, immunosuppressive and antimitogenic actions. Steroids regulate inflammation by binding to the DNA region called glucocorticoid responsive element (GRE)[29]. Another effect of steroids is that they hamper the transcription of cytokines[30]. Corticosteroids hinder inflammation by stopping vascular permeability, an effect that can further inhibit problems such as dermal edema and inflammatory cell movement within the skin. Unfortunately, steroids must be given under close observation because side effects may occur if the corticosteroids bind to other steroid receptor sites and cause acne and hypertrichosis at the application site[31]. Also, the side effects are proportional to the potency of the application; high potency may be the source of epidermal, dermal, vascular and systemic side effects[11].

Phototherapy (UVB) and photo (chemo) therapy (PUVA) are long term treatment devices to manage moderate to severe psoriasis. Psoriasis responds favorably to photo chemotherapy that utilizes 8-methoxypsoralen (8-MOP) plus UVA radiation (PUVA). UVB or PUVA are usually used in combination with other topical or systemic treatments[11].

Systemic Treatments

A variety of systemic treatments are available including methotrexate, retinoids and cyclosporine A and S.

Methotrexate treats psoriasis and psoriatic arthritis effectively. This folic acid antagonist is a popular choice among patients and is one of the oldest systemic treatments for this ailment. In fact, this drug improves psoriasis by 75% in 90% of patients. Up to 60% of psoriatic arthritis patients saw great improvement while 30% experienced moderate improvement[32]. Even though methotrexate treats psoriasis efficaciously, there has been a decline in its use due to its known liver toxicity and an increased incidence of cirrhosis and fibrosis[33]. Even though the liver damage by methotrexate is not extremely severe, patients using this drug should be followed by liver

biopsies. If methotrexate dosages are controlled and patients are monitored properly, methotrexate is an excellent drug where the benefits outweigh the risks and it is still considered one of the most valuable agents in psoriasis treatment.

Topical and systemic retinoids can limit psoriasis by enhancing retinoic acid cytoplasma levels. The topical antipsoriatic retinoid, tazarotene, and the systemic P-450 inhibitor liarazole both work in a similar fashion. Retinoids are classified as anti-inflammatory agents due to their influence on the arachidonic acid cascade and migration of PMNs. Acitretin is also used among these drugs, and is beneficial in hampering cell proliferation[34].

Cyclosporine A and S are cyclic peptides that are used to treat psoriasis by inhibiting certain calcium dependent cellular processes such as the transcriptional activation of lymphokine genes (IL-2 in helper T cells that follows T cell receptor mediated signal transduction. Cyclosporine A is usually tried in patients with severe psoriasis that have not responded to other treatments[35]. The medication is nephrotoxic and can be detrimental to those with impaired kidney function and hypertension. Side effects are dose and duration related. It is advised that patients should not take the medication for more than 1 year. Although the drug is effective, its potency comes with adverse side effects such as the aforementioned nephrotoxicity and hypertension, malignancies, tumors and infections.

New Drugs

Some relatively new medications are available: efalizumab (Raptiva®), alefacept (Amevive®), etancercept (Enbrel®), and infliximab (Remicade®).

Efalizumab is a humanized monoclonal antibody that inhibits T cell activation and is used to treat adults with moderate to severe chronic plaque psoriasis. Use and effectiveness can be seen based on the results of a clinical study involving 597 psoriatic patients. These patients were treated with efalizumab once a week and the trial resulted in a 75% improvement in the Psoriasis Area and Severity Index (PASI) over the 12 week period. However, this improvement occurred in only 22% of patients at 1 mg dosage, 28% with the 2 mg dosage and 5% in the placebo group. The

adverse side effects consist of initial reactions that are basically composed of mild constitutional symptoms like headache, chills, fever, nausea and myalgia. The psoriasis may worsen in 0.7% of patients, and can worsen when drug usage is discontinued. Moreover, acute or chronic infection may develop.

In early 2003, the FDA approved alefacept, a drug that also inhibits T-cell activation and can reduce the count of memory T cells. Another treatment that may be approved soon for general psoriasis is the TNF-alpha inhibitor etanercept. This medication has been used to treat both rheumatoid and psoriatic arthritis since 1998. Another TNF-alpha inhibitor is infliximab. This drug was also a treatment for rheumatoid arthritis, similar to that of etanercept.

Efalizumab (Raptiva), alefacept (Amevive) and etancercept (Enbrel) are effective in about 30% of patients with moderate to severe psoriasis. Etanercept has been widely used to treat rheumatoid arthritis and has a good safety rating. Currently, results of comparative trials are not available[36].

Perioperative Anesthetic Considerations

During the preoperative period, since chronic corticosteroid therapy is involved in the psoriatic patient, stress-dose corticosteroids should be provided to those patients who are taking these agents. Physical examination and laboratories should explore any evidence of any acute infection or inflammation related to psoriasis. Renal and liver function should be assessed when immunosuppressants and/or methotrexate have been utilized in the psoriatic patient[37].

Intraoperatively, trauma, e.g. instrumentation of any kind to psoriatic skin should be avoided. There are no specific agents that are contraindicated or indicated for this disease other than to protect the skin. In addition, anesthesiologists must be aware of the high incidence of pruritus with neuraxial opioids, especially when dealing with psoriatic patients - for pruritus exacerbates their disease[38].

Skin Trauma

It has been well documented that psoriatic plaques can be elicited artificially by inducing trauma to the skin[39]. Further investigation of this phenomenon revealed an isomorphic all-or-none response, with approximately 25% of patients developing psoriatic plaque at all injured sites[40]. It should also be noted that trauma to the dermis alone is not sufficient to elicit a response; the epidermis must also be injured[41]. Thus, the anesthesiologist must protect the skin in the areas of the psoriatic lesions. Tape should be used only in the most necessary cases, as even such a non-invasive step as tape-stripping has been reported to provoke a psoriatic lesion. An enhanced proliferative response in the epidermis has been reported within 48 hours[42] and also in the late phase (6-9 hours)[43]. Intravenous catheters should be sutured in place or wrapped with web roll[44].

Pruritus induced by Neuraxial Opioids

The onset of pruritus after the adminstration of neuraxial opioids has been a longstanding adverse effect with an incidence ranging from 0-100%[45,46]. This incidence of pruritus is lower in epidural opioids vs spinal opioids (8% vs 46%), and the greatest incidence has been shown when using neuraxial morphine[47]. Opioid-induced pruritus is not only difficult to manage and extremely uncomfortable, but it also has a poor response to histamine (H1) blockers and other conventional treatments. However, naloxone and propofol are two drugs proven to be effective against opioid-induced pruritus[48].

Staph Aureus Complications

Staphylococcus aureus is found in the lesions of 20 to 50 percent of patients with psoriasis[49,50] although many may not exhibit any pyodermic symptoms. For comparative purposes, this bacterium is carried by less than 10 percent of the normal population. Since psoriatic lesions are commonly associated with S. aureus, regional anesthesia or intravenous cannulae should not be directed at these sites. Doing so may lead to septicemia and further complicate the case[44].

Methotrexate

Clinical observations of cancer patients that were placed on methotrexate after anesthesia later showed unexpected signs of myelosuppression and mucosal damage. This observation led to the discovery that nitrous oxide, which inactivates the cobalamin

coenzyme of methionine synthase, and methotrexate, which inhibits dihydrofolate reductase in folate metabolism, has a synergistic effect. Studies performed on Wistar rats demonstrated that no substantial kidney or liver toxicity occurred in the rats with the combination; however, the lethal dose of methotrexate decreased by 83.3% when nitrous oxide was administered previously for 48 hours. Furthermore, the administration of 5-formyl-tetrahydrofolate completely protected the rats from the synergistic effect of the two drugs. It was concluded that nitrous oxide potentiated the cytotoxic effects of methotrexate on proliferating cells and therefore the use of nitrous oxide before or even during methotrexate administration should be avoided[51].

Erythroderma Variant

Severe cases of erythroderma can present a challenging case for. In this inflammatory disorder, generalized erythema and scaling occur. Furthermore, this variant form may disturb the cardiovascular, thermoregulatory, and metabolic systems[52]. Increased incidence of vascular diseases such as thrombophlebitis, pulmonary embolism, cerebrovascular accidents, and myocardial infarction has been described[53]. It is recommended that the psoriatic patient undergo full systemic management throughout the perioperative period[52]. One of the most important preventative steps in management includes evaluation for undiagnosed high-output congestive heart failure[45].

The presentation of systemic scales can cause difficulty in placing ECG electrodes on the patient. Systemic scaling can also complicate endotracheal tube placement and may lead to postoperative dyspnea[52]. For example, pustular psoriasis can be accompanied by relapsing polychondritis; this phenomenon can complicate intubation due to reasons such as cartilage degeneration and a smaller glottis due to edema[54,55].

Steroid and Antidepressant Treatment of Psoriasis; Compatibility with Anesthesia

Many patients are managed with steroid therapy to limit the psoriatic lesions and impede recurrences. Prednisolone is a popular choice used to treat psoriasis as well as other dermatologic diseases that exhibit lesions[56]. There are no serious problems of steroid therapy causing complications reported during the perioperative procedure[57] and typically 100 mg of hydrocortisone is administered to prevent Addisonian crises.

Patients afflicted with psoriasis related psychological symptoms such as social phobias often are given agents including tricyclic antidepressants (TCAs) or the selective serotonin reuptake inhibitor (SSRI) antidepressants[58]. Neuromodulators including antidepressants can alleviate inflammation. Psoriatic inflammation can be due to an abnormal proliferation of neuropeptides such as Substance P and may be used to treat depression as well as reduce psoriatic inflammation[59-61].

Summary

Psoriasis can be extremely debilitating for the patient due to the fact that it can affect the whole integument, and, because of its chronic nature, can afflict the individual for most of his/her life. In some cases such as erythrodermic psoriasis, the disease can even be fatal due to complications such as high-output congestive heart failure. The anesthesiologist must take many factors into consideration such as the severity of the disease, where to place regional anesthesia, and the anesthetic complications associated with certain types of psoriatic medications. Although certain mechanisms such as differentiating keratinocytes while impeding their proliferation, immunosuppressive therapy, regulating transcription via steroids and the use of extra-cellular oxygen radicals have been used to manage psoriasis, no "miracle" cure exists. Even though psoriasis is usually treated by dermatologists, anesthesiologists must be careful and prepared because the disease is chronic, variable, and patients must be carefully handled in the operating room.

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