Skin Therapy Letter ©

Volume 18 • Number 4 • May-June 2013

Indexed by the US National Library of Medicine and PubMed

EDITOR: DR. STUART MADDIN

Selected Skin Diseases with Systemic Involvement

Marcelo Ruiz, MD[1]; Pilar Valdés, MD[1]; Kenneth Tomecki, MD[2]

[1]Department of Dermatology, Hospital Clínico Universidad de Chile, Santiago, Chile

[2]Department of Dermatology, Cleveland Clinic, Cleveland, OH, USA

ABSTRACT

The skin is often a window to systemic disease that is available to the trained eye of the dermatologist. Herein, we focus on four dermatoses with associated systemic conditions of interest: scleromyxedema and monoclonal gammopathy, nephrogenic systemic fibrosis in the setting of renal insufficiency, dermatitis herpetiformis and celiac disease, and psoriasis as a risk factor for cardiovascular disease. Dermatologists can play a crucial role in recognizing the cutaneous manifestations linked with these conditions. Identifying the related underlying disorder will contribute to appropriate diagnosis and improved management.

Key words: systemic disease, skin signs, cutaneous manifestations, dermatitis herpetiformis, nephrogenic systemic fibrosis, psoriasis, scleromyxedema

Introduction

Dermatologists can play an integral role in the diagnosis and management of an array of systemic diseases that manifest in skin symptoms. Recent advances in elucidating pathogenic mechanisms and described associations hold the potential for early identification and treatment, thereby possibly modifying the disease course. A detailed discussion covering the spectrum of skin conditions with underlying systemic dysfunction is beyond the scope of this review, instead a look at the hematologic, renal, gastrointestinal, and cardiovascular systems is undertaken, with a focus on four skin disorders with systemic involvement.

Scleromyxedema and Monoclonal Gammopathy

Scleromyxedema (SM), also known as generalized lichen myxedematosus (LM), is a cutaneous mucinosis. Although LM is considered a chronic nonlethal disease, its generalized form (SM) is associated most frequently with monoclonal gammopathy and other systemic disorders that may result in death.[1,2] By contrast, the more localized forms of LM are not associated with paraproteinemia and usually have no systemic manifestations. SM is a rare disease of unknown etiology that usually affects middle-aged adults between 30 and 80 years of age.[3] It is characterized by a generalized papular and sclerodermoid eruption, mucin deposition, increased fibroblast proliferation, fibrosis, and monoclonal gammopathy, in the absence of thyroid disease. An increased production of hyaluronic acid by fibroblasts occurs, possibly due to paraprotein stimulation.[2,3]

Clinically, SM appears as a generalized eruption of 2 mm to 3 mm waxy lichenoid (flattopped) papules, often in a linear arrangement; lesions are most common on the hands, elbows, forearms, upper trunk, face, and neck. These lichenoid lesions coalesce, leading to induration of the underlying tissue that resembles scleroderma. Typical involvement of the glabella with deep longitudinal furrows can be reminiscent of leonine facies[1,4] and a characteristic elevated rim with central depression can be seen on the proximal interphalangeal joints ("doughnut sign"). Histologic examination of involved skin demonstrates fibroblast proliferation, fibrosis, and dermal deposition of mucin.[4] Systemic manifestations of SM are serious and have been fatal in some cases, secondary to mucin deposition in various organs. It may involve the cardiovascular, gastrointestinal, pulmonary, rheumatologic, and central nervous systems. Dysphagia is the most common extracutaneous manifestation of SM.[2,3] Up to 83% of cases have an associated paraproteinemia, predominantly an immunoglobulin G (IgG) lambda subtype, and a minority of these patients develop a plasma cell dyscrasia or multiple myeloma (10%).[1,2] Other associated diseases include Waldenstrom's macroglobulinemia as well as Hodgkin's and non-Hodgkin's lymphomas.[1,2]

Work-up, including serum protein electrophoresis, immunofixation electrophoresis, and measurement of immunoglobulin levels, is critical in all patients with suspected SM. Follow-up should be done at least every 6 months.[4] SM is characteristically quite resistant to therapy, although anecdotal reports attest to the efficacy of melphalan, thalidomide, and intravenous immunoglobulins (IVIG).[2,3] Autologous stem cell transplantation could be beneficial in some cases.[4,5]

Nephrogenic Systemic Fibrosis in Renal Insufficiency

Nephrogenic systemic fibrosis (NSF), or formerly known as nephrogenic fibrosing dermopathy, is a scleroderma-like fibrosing disorder that develops in the setting of renal insufficiency. It

ALSO IN THIS ISSUE: **Topical Agents for Hair Growth Promotion: What Is Out There?** *(page 5)* & **Update on Drugs** *(page 8)*

occurs predominately in patients with end-stage renal disease on dialysis (80%) and occasionally in patients with acute renal failure or after kidney transplantation.[6] The cause remains unclear, but most cases are related to the use of gadolinium-based contrast agents (GBCA) in magnetic resonance imaging (MRI), such as gadodiamide and gadopentetate. These gadolinium (Gd) chelates tend to easily release free Gd into the surrounding tissue.[7] In patients with renal insufficiency, increased retention of GBCA leads to increased free Gd that could ultimately trigger NSF.[6] A concomitant proinflammatory event (e.g., infection and major surgery) can confer additional risk.[8]

Cutaneous lesions of NSF usually develop over a variable period of time (few days to several months) and subsequently assume a chronic, unremitting course. Approximately 5% of patients experience NSF that is rapidly progressive (fulminant).[6] The primary skin lesions are usually papules or nodules that are erythematous and coalesce to form indurated irregular plaques. These areas may appear slightly edematous with peau d'orange and erythematous surface features, and can be easily confused with cellulitis, lymphangitis or chronic lymphedema.[6] They are often symmetrical, commonly involving the lower extremities up to the knees and the upper extremities up to the elbows. The face is usually spared. Over time, the skin tends to develop a "cobblestone" appearance and browny hyperpigmentation. Affected areas and subcutaneous tissues are extremely hard ("woody"), warm, and tender, as well as often accompanied by pruritus and burning sensation. Yellow scleral plaques are found in some cases.[6,9-11] Differential diagnosis is made with several other fibrosing processes, including scleroderma and scleromyxedema.[11] The clinical distribution of lesions in NFS, which favors the extremities and spars the face, is opposite to that seen in scleromyxedema, and paraproteins are not detected in the serum of NFS patients.[6] Histopathology of NFS is very similar to scleromyxedema, including their immunohistochemical staining profiles. A scoring system, based on clinical and histopathological criteria, has been recently proposed to aid diagnosis.[11]

Major organ or systemic involvement can include muscles, joints (contractures), and viscera, such as the pulmonary, cardiovascular, gastrointestinal and renal systems.[6] The chronology of the visceral involvement is not clear, but is more common in patients exhibiting extensive skin symptoms. The severity and rapidity of progression of the cutaneous lesions correlate with poor prognosis and death.[12]

Therapeutic modalities include oral and topical steroids, pentoxifylline, photopheresis, plasmapheresis, psoralen plus ultraviolet light, IVIG, sodium thiosulfate, and physical therapy, however, all with little benefit. Improvement of renal function can terminate the progression of NSF, so renal transplantation is the best option for these patients. Implementation of preventive strategies, including the use of alternatives to Gd-enhanced MRI, has been shown to reduce the risk of NSF.[6,8-10]

Dermatitis Herpetiformis and Celiac Disease

Dermatitis herpetiformis (DH) is a chronic, intensely pruritic blistering disease characterized by symmetric grouped vesicles, papules, and wheals on the elbows, knees, scalp, and buttocks. It has a clear relationship to celiac disease (CD) and is considered the cutaneous manifestation of gluten sensitivity.[13] Despite this, the majority of DH patients have silent or mild gastrointestinal CD. Pathophysiologies of both disorders are closely related, involving genes and the environment. Human leukocyte antigens (HLA) DQ2 and DQ8 have been identified as predisposing factors.[13,14] Tissue transglutaminase (tTG or TG2) and epidermal transglutaminase (eTG or TG3) are thought to be the main autoantigens in CD and DH, respectively. tTG, an ubiquitous enzyme, plays a role in gluten intolerance by modifying gliadin (fraction of gluten) into an efficient autoantigen and forming tTG-gliadin immunogenic complexes. eTG is homologous to tTG, localized in the epidermis to maintain the cornified envelope integrity.[13,14]

Clinically, the primary lesions of DH (papules and vesicles) are often absent, replaced by erosions and excoriations, sometimes leading to lichenification. Purpura on the fingers and toes is an interesting clinical finding but not always present. It rarely has mucosal involvement.[13,14] Evolution with symptom-free months during summer occurs in some patients due to a beneficial sun exposure effect.[14]

Biopsy reveals a subepidermal cleft with neutrophils and a few eosinophils at the tips of dermal papillae, and direct immunofluorescence is confirmatory, by demonstrating pathognomonic granular deposition of IgA at the dermal-epidermal junction.[13] Serologic tests are useful to aid diagnosis and monitor disease activity, looking for IgA-TG or antiendomysial antibodies. In DH, IgA antibodies can be specific for eTG, making the detection of specific IgA-eTG antibodies a promising tool that needs further validation.[13,14] Genetic testing for HLA DQ2 and DQ8 can be useful in some cases to rule out DH. Differential diagnosis includes linear IgA dermatosis, bullous pemphigoid, scabies, contact dermatitis, and bullous lupus erythematosus.[13]

A wide range of autoimmune disorders are associated with DH, such as diabetes type I or hypothyroidism, the latter being the most common. Screening for common autoimmune disorders is generally indicated. Clinical examination of the skin may reveal a concurrent autoimmune disease, such as vitiligo, primary biliary cirrhosis (jaundice), pernicious anemia, alopecia areata or lupus erythematosus.[14] Clinical signs of malabsorption may also be present, such as anemia due to iron, folate, or B12 deficiency, and caries or diffuse alopecia due to zinc deficiency. DH patients may also have a higher risk of developing non-Hodgkin lymphoma, particularly enteropathy-associated T-cell lymphoma. This is an important comorbidity to rule out, especially in longstanding, untreated DH or CD.[14,15]

Therapy is always based on a gluten-free diet. Skin lesions and pruritus of DH are rapidly responsive to oral dapsone. Other treatments include sulfasalazine and sulfamethoxypyridazine.[15]

Psoriasis and Cardiovascular Disease

Psoriasis is a chronic relapsing inflammatory disease of the skin that affects 1-3% of the population.[16,17] Dermatologists are well familiarized with the clinical presentation, subtypes, and histologic features of psoriasis, but there is still much to learn about disease physiopathology, systemic consequences, and how these factors influence therapy. At present, there is great interest in elucidating the potential link between psoriasis and

significant comorbidities, such as an increased risk for metabolic dysfunction and cardiovascular disease (CVD), which could be explained by a systemic inflammatory process. As we know, a complex interplay between environmental and genetic factors sets the scene for psoriasis-initiating events, allowing activation of the immune system and generation of effector T cells that reside in the skin and interact with keratinocytes. Chronic inflammation is maintained through the action of key cytokines (e.g., tumor necrosis factor-alfa).[18] Systemic inflammation could be responsible for subsequent insulin resistance, endothelial cell dysfunction, and atherosclerosis.[17,19-21]

Different population-based cohort studies indicate that there is a higher risk for myocardial infarction (MI) in psoriasis patients,[22-27] with increased risk of cardiovascular death and all-cause mortality.[28,29] These findings are independent to the presence of other major cardiac risk factors and comparable to them in the magnitude of risk, similar to diabetes mellitus. However, there is also controversial evidence against these results.[30-32] According to most of the studies that found an increased risk, clinical characteristics of psoriasis patients that are related to a higher risk are young age (<50 years), severe skin affection (defined by Psoriasis Area and Severity Index or the need of systemic therapy) and psoriatic arthritis (PsA). The incidence of cerebrovascular and peripheral vascular disease could also be higher among psoriasis patients compared to the general population.[23,33,34]

In light of this evidence, it is critical to know whether systemic therapies do have a cardioprotective effect and a preventive role in the development of CVD in severe psoriasis patients, as this answer could change current paradigms of treatment. There are already some published studies addressing this issue. By measurements of biomarkers of cardiovascular risk (e.g., C-reactive protein, homocysteine, and lipid profile), direct evaluation of atherosclerotic progression (e.g., carotid ultrasonography), and assessment of MI risk, promising results have been reported showing beneficial effects of different systemic agents when compared to patients using only topical therapy.[35-39] However, a recent study that compared MI risk in psoriasis patients after being treated with phototherapy, traditional systemic agents, or different biologics, found no overall relevant changes in MI risk.[35] At the moment, there is still a lack of evidence supporting the use of systemic therapies for the prevention of CVD in psoriasis patients. Therefore, larger multicenter studies are needed to confirm this data and the long-term safety profiles of biologic drugs.

Regular screening for CVD risk factors is recommended in psoriasis,[40,41] especially for patients with severe disease and PsA, but the fact that other cardiac risk factors (e.g., obesity or metabolic syndrome) are more common in psoriasis[42-44] points out that this practice could be beneficial for all psoriatics, allowing early implementation of preventive measures.[45] A detailed history inquiring about diabetes, dyslipidemia or hypertension should be performed, together with the evaluation of blood pressure, body mass index and waist circumference at least every 2 years. Fasting serum lipoproteins, blood glucose and glycosylated hemoglobin should be determined at least every 5 years, or every 2 years if other risk factors are present. Another recommended approach is to undertake these assessments every 6 months in patients receiving systemic therapy and yearly in those undergoing topical treatment.[40,41,45]

Conclusion

Scleromyxedema, nephrogenic systemic fibrosis, dermatitis herpetiformis, and psoriasis are skin diseases associated with well-recognized systemic disorders that may result in significant morbidity and mortality. Although important progress has been made in understanding the physiopathology of these conditions, precise disease mechanisms remain unknown and treatment challenges persist. To improve therapeutic outcomes, dermatologists should be aware of these associations and pathogenic cofactors, in order to ensure that both skin and systemic abnormalities are properly addressed.[45]

References

1. Rongioletti F, Rebora A. Updated classification of papular mucinosis, lichen myxedematosus, and scleromyxedema. *J Am Acad Dermatol.* 2001 Feb;44(2):273-81.
2. Rongioletti F. Lichen myxedematosus (papular mucinosis): new concepts and perspectives for an old disease. *Semin Cutan Med Surg.* 2006 Jun;25(2):100-4.
3. Cokonis Georgakis CD, Falasca G, Georgakis A, et al. Scleromyxedema. *Clin Dermatol.* 2006 Nov-Dec;24(6):493-7.
4. Thiers BH, Sahn RE, Callen JP. Cutaneous manifestations of internal malignancy. *CA Cancer J Clin.* 2009 Mar-Apr;59(2):73-98.
5. Heymann WR. Scleromyxedema. *J Am Acad Dermatol.* 2007 Nov;57(5):890-1.
6. Waikhom R, Taraphder A. Nephrogenic systemic fibrosis: a brief review. *Indian J Dermatol.* 2011 Jan;56(1):54-8.
7. High WA, Ayers RA, Cowper SE. Gadolinium is quantifiable within the tissue of patients with nephrogenic systemic fibrosis. *J Am Acad Dermatol.* 2007 Apr;56(4):710-2.
8. Sadowski EA, Bennett LK, Chan MR, et al. Nephrogenic systemic fibrosis: risk factors and incidence estimation. *Radiology.* 2007 Apr;243(1):148-57.
9. Zou Z, Zhang HL, Roditi GH, et al. Nephrogenic systemic fibrosis: review of 370 biopsy-confirmed cases. *JACC Cardiovasc Imaging.* 2011 Nov;4(11):1206-16.
10. Zou Z, Ma L. Nephrogenic systemic fibrosis: review of 408 biopsy-confirmed cases. *Indian J Dermatol.* 2011 Jan;56(1):65-73.
11. Girardi M, Kay J, Elston DM, et al. Nephrogenic systemic fibrosis: clinicopathological definition and workup recommendations. *J Am Acad Dermatol.* 2011 Dec;65(6):1095-106 e7.
12. Mendoza FA, Artlett CM, Sandorfi N, et al. Description of 12 cases of nephrogenic fibrosing dermopathy and review of the literature. *Semin Arthritis Rheum.* 2006 Feb;35(4):238-49.
13. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part I. Epidemiology, pathogenesis, and clinical presentation. *J Am Acad Dermatol.* 2011 Jun; 64(6):1017-24.
14. Karpati S. Dermatitis herpetiformis. *Clin Dermatol.* 2012 Jan-Feb;30(1):56-9.
15. Bolotin D, Petronic-Rosic V. Dermatitis herpetiformis. Part II. Diagnosis, management, and prognosis. *J Am Acad Dermatol.* 2011 Jun;64(6):1027-33.
16. Gelfand JM, Weinstein R, Porter SB, et al. Prevalence and treatment of psoriasis in the United Kingdom: a population-based study. *Arch Dermatol.* 2005 Dec;141(12):1537-41.
17. Alexandroff AB, Pauriah M, Camp RD, et al. More than skin deep: atherosclerosis as a systemic manifestation of psoriasis. *Br J Dermatol.* 2009 Jul;161(1):1-7.
18. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med.* 2009 Jul 30;361(5): 496-509.
19. Boehncke WH, Boehncke S, Tobin AM, et al. The 'psoriatic march': a concept of how severe psoriasis may drive cardiovascular comorbidity. *Exp Dermatol.* 2011 Apr;20(4):303-7.
20. Kremers HM, McEvoy MT, Dann FJ, et al. Heart disease in psoriasis. *J Am Acad Dermatol.* 2007 Aug;57(2):347-54.
21. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. *J Eur Acad Dermatol Venereol.* 2012 Mar; 26(Suppl 2):3-11.
22. Ahlehoff O, Gislason GH, Charlot M, et al. Psoriasis is associated with clinically significant cardiovascular risk: a Danish nationwide cohort study. *J Intern Med.* 2011 Aug;270(2):147-57.

23. Brauchli YB, Jick SS, Miret M, et al. Psoriasis and risk of incident myocardial infarction, stroke or transient ischaemic attack: an inception cohort study with a nested case-control analysis. *Br J Dermatol.* 2009 May;160(5):1048-56.
24. Gelfand JM, Azfar RS, Mehta NN. Psoriasis and cardiovascular risk: strength in numbers. *J Invest Dermatol.* 2010 Apr;130(4):919-22.
25. Gelfand JM, Mehta NN, Langan SM. Psoriasis and cardiovascular risk: strength in numbers, part II. *J Invest Dermatol.* 2011 May;131(5):1007-10.
26. Gelfand JM, Neimann AL, Shin DB, et al. Risk of myocardial infarction in patients with psoriasis. *JAMA.* 2006 Oct 11;296(14):1735-41.
27. Li WQ, Han JL, Manson JE, et al. Psoriasis and risk of nonfatal cardiovascular disease in U.S. women: a cohort study. *Br J Dermatol.* 2012 Apr;166(4):811-8.
28. Abuabara K, Azfar RS, Shin DB, et al. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. *Br J Dermatol.* 2010 Sep;163(3):586-92.
29. Gelfand JM, Troxel AB, Lewis JD, et al. The risk of mortality in patients with psoriasis: results from a population-based study. *Arch Dermatol.* 2007 Dec;143(12):1493-9.
30. Stern RS. Psoriasis is not a useful independent risk factor for cardiovascular disease. *J Invest Dermatol.* 2010 Apr;130(4):917-9.
31. Stern RS, Huibregtse A. Very severe psoriasis is associated with increased noncardiovascular mortality but not with increased cardiovascular risk. *J Invest Dermatol.* 2011 May;131(5):1159-66.
32. Wakkee M, Herings RM, Nijsten T. Psoriasis may not be an independent risk factor for acute ischemic heart disease hospitalizations: results of a large population-based Dutch cohort. *J Invest Dermatol.* 2010 Apr;130(4):962-7.
33. Prodanovich S, Kirsner RS, Kravetz JD, et al. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. *Arch Dermatol.* 2009 Jun;145(6):700-3.
34. Gelfand JM, Dommasch ED, Shin DB, et al. The risk of stroke in patients with psoriasis. *J Invest Dermatol.* 2009 Oct;129(10):2411-8.
35. Abuabara K, Lee H, Kimball AB. The effect of systemic psoriasis therapies on the incidence of myocardial infarction: a cohort study. *Br J Dermatol.* 2011 Nov;165(5):1066-73.
36. Boehncke S, Salgo R, Garbaraviciene J, et al. Effective continuous systemic therapy of severe plaque-type psoriasis is accompanied by amelioration of biomarkers of cardiovascular risk: results of a prospective longitudinal observational study. *J Eur Acad Dermatol Venereol.* 2011 Oct;25(10):1187-93.
37. Prodanovich S, Ma F, Taylor JR, et al. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid arthritis. *J Am Acad Dermatol.* 2005 Feb;52(2):262-7.
38. Strober B, Teller C, Yamauchi P, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. *Br J Dermatol.* 2008 Aug;159(2):322-30.
39. Wu JJ, Poon KY, Channual JC, et al. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. *Arch Dermatol.* 2012 Nov 1;148(11):1244-50.
40. Kimball AB, Gladman D, Gelfand JM, et al. National Psoriasis Foundation clinical consensus on psoriasis comorbidities and recommendations for screening. *J Am Acad Dermatol.* 2008 Jun;58(6):1031-42.
41. Dauden E, Castaneda S, Suarez C, et al. [Integrated approach to comorbidity in patients with psoriasis. Working Group on Psoriasis-associated Comorbidities]. *Actas Dermosifiliogr.* 2012 Jan;103(Suppl 1):1-64.
42. Azfar RS, Seminara NM, Shin DB, et al. Increased risk of diabetes mellitus and likelihood of receiving diabetes mellitus treatment in patients with psoriasis. *Arch Dermatol.* 2012 Sep 1;148(9):995-1000.
43. Gisondi P, Tessari G, Conti A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. *Br J Dermatol.* 2007 Jul;157(1):68-73.
44. Langan SM, Seminara NM, Shin DB, et al. Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. *J Invest Dermatol.* 2012 Mar;132(3 Pt 1):556-62.
45. Fernandez-Torres R, Pita-Fernandez S, Fonseca E. Psoriasis and cardiovascular risk. Assessment by different cardiovascular risk scores. *J Eur Acad Dermatol Venereol.* 2012 Jun 25. [Epub ahead of print]

Topical Agents for Hair Growth Promotion: What Is Out There?

Omar S. Shamsaldeen, MD[1]; Thamer Al Mubki, MD[1,2]; Jerry Shapiro, MD, FRCPC[1,3]

[1]Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

[2]College of Medicine, Al Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia

[3]Department of Dermatology, New York University, New York, NY, USA

ABSTRACT

Hair loss is a widespread complaint that carries a significant psychosocial burden for affected individuals. Androgenetic alopecia (AGA) is the predominant cause of hair loss seen in the dermatology clinic. Although a range of therapies are available, minoxidil remains the only approved topical treatment for AGA. Promising new topical agents are under current investigation.

Key words: androgenetic alopecia, AGA, female pattern hair loss, male pattern hair loss, topicals

Introduction

Hair loss is a common dermatological problem that affects a large segment of the population both physically and psychologically. Although there are many different causes for hair loss, such as telogen effluvium and alopecia areata, androgenetic alopecia (AGA), i.e., male pattern hair loss and female pattern hair loss, is the most prevalent form in both men and women. Onset of AGA can occur anytime at or after puberty, but incidence and severity increases with advancing age in both genders, manifesting in at least 80% of Caucasian men and 40% of women.[1] Because of its considerable psychological impact many patients actively search for new treatments.[2]

Androgenetic Alopecia

Clinical Presentation

Male pattern hair loss (MPHL) affects androgen-sensitive follicles and features fronto-temporal recession and hair loss over the vertex while the occipital scalp is preserved, resulting in a classic M pattern. In women, female pattern hair loss (FPHL) typically presents with diffuse central thinning or frontal accentuation forming a "Christmas tree" pattern. A third and less common presentation is a male-like pattern with fronto-temporal recession/vertex loss, which may indicate excess androgen activity.[3] Diagnosis is easily determined from the clinical history, however, a scalp biopsy may be needed in situations where the cause of hair loss is uncertain. Extensive hormonal testing is usually unnecessary unless indicated by signs and symptoms of androgen excess, such as hirsutism, severe unresponsive cystic acne, virilization, or galactorrhea, which may point to the possibility of an underlying endocrine abnormality.[4]

Pathogenesis

The pathophysiology of AGA is not yet fully understood, but both genes and androgens appear to be involved. Inheritance is polygenic with input from either or both parents. Women with FPHL are less likely than men to exhibit a clear family history of the disorder.[5]

The androgens testosterone (T) and dihydrotestosterone (DHT) are the most important factors in regulating the anagen duration and hair matrix volume.

DHT, a potent metabolite of testosterone, enlarges follicles in the beard, chest and limbs, and miniaturizes follicles in the bitemporal region. In genetically susceptible individuals, DHT can cause miniaturization in the vertex and frontal hairline leading to AGA patterned thinning. The conversion of T to DHT occurs at the hair follicles elicited by a type II 5-alpha-reductase enzyme.

Topical Treatments

Minoxidil

Minoxidil is the current standard treatment for hair loss. It was initially used as an oral antihypertensive medication, but because of minoxidil's side effect of hypertrichosis it was subsequently developed as a topical treatment in 2% strength for hair loss. US FDA approval for the treatment of MPHL was granted to the 2% formulation in 1988 and the 5% in 1997, but only the 2% strength was approved for FPHL in 1997.[6]

The precise mechanism by which minoxidil induces hair growth is unknown. However, its vasodilatory, angiogenic, and enhanced cell proliferative effects are thought to be responsible. Minoxidil is an adenosine-triphosphate-sensitive potassium channel opener reported to stimulate the production of vascular endothelial growth factor, a possible promoter of hair growth.[7] Minoxidil prolongs duration of anagen of the hair cycle and increases miniaturized hair follicle size in addition to its significant ability to maintain and thicken preexisting hair.[8]

Minoxidil's efficacy in pattern hair loss has been proven in double-blind, placebo-controlled trials. In men with MPHL, minoxidil showed a rapid increase in hair count and weight peaking at 16 weeks. The average increase in target area hair count is about 8% with minoxidil 2% lotion and 10-12% with the 5% formulation. About 60% of men demonstrated improvement with the 5% formulation and 40% with the 2% formulation compared with 23% of placebo.[6]

In women with FPHL treated with minoxidil 2% solution, a 10-16% increase in regrowth compared with controls was shown, while greater effects may be derived at the higher 5% concentration.[9] This treatment is life-long and stopping minoxidil will shed all minoxidil-dependent hair growth within 4 to 6 months.[6]

The recommended dosing of either 2% or 5% minoxidil solution is twice daily application of 1 ml (25 drops) spread evenly over the entire top of the dry scalp. For the 5% foam formulation, half a capful is applied twice daily on the dry scalp and left in place for at least 4 hours. To minimize the risk of hypertrichosis of the face, especially in women, hands should be washed with warm water after application. The minoxidil 5% foam has only just recently become available in Canada as of November 2012.

Minoxidil has a well-established safety profile.[10] Adverse effects are very infrequent and include skin irritation, contact dermatitis, facial hypertrichosis, scale, dryness, tachycardia, and transient increased hair shedding, which is more prominent in the first 4 weeks and results from induction of anagen from the resting phase. This may be viewed as an indication of minoxidil's efficacy, as such, patients should be advised to continue with treatment even if this side effect occurs.

Constituents of the vehicle (e.g., propoylene glycol and minoxidil) can cause irritant contact dermatitis, allergic contact dermatitis, or exacerbation of seborrheic dermatitis, which are more common with the 5% solution. An allergic reaction to minoxidil itself is very rare; the more common contactant inducing pruritus and scaling of the scalp is propylene glycol.[11] The 5% foam vehicle is propylene glycol free and, hence, reduces the potential for irritation and improves cosmetic acceptability.[12] Patch testing for propylene glycol can be performed. If positive, a less irritating butylene glycol vehicle can be substituted. If the contact dermatitis is due to minoxidil, then treatment with this agent may have to be abandoned.

The side effect of hypertrichosis is more frequently seen in female patients who already have hirsutism. It mostly affects the forehead, malar areas and sides of the face, but is totally reversible with cessation of the drug.

Systemic absorption of minoxidil is weak, with only 0.3-4.5% reaching the circulatory system, and excreted within 4 days. No changes in blood pressure or other hemodynamic effects were shown with minoxidil use,[13] however, caution should be exercised in patients with cardiovascular disease. Minoxidil has been assigned to pregnancy category C. Although there is no evidence of teratogenicity in rats and rabbits, studies are lacking in humans and it is secreted in human milk, therefore, use in pregnant or nursing women should be avoided.

Prostaglandins

Latanoprost and bimatoprost are prostaglandin analogues widely used to treat glaucoma and recently they have been investigated for eyelash alopecia. Studies have demonstrated variable success when used as eye drops to stimulate eyelash growth in alopecia areata.[14] Although their mechanism of action is not fully understood, these compounds likely work by interacting with the prostaglandin receptors in the hair follicle and inducing anagen (growth phase) in telogen (resting phase) follicles.[15]

The rationale for use in alopecia areata was predicated on bimatoprost's history of drug discovery. When administered as an eye drop for glaucoma, eyelash growth was noted in 42.6% of patients treated once daily for a year.[16,17] Initially, this effect was regarded as an adverse event, but the potential aesthetic benefits of eyelash growth were quickly recognized, leading to the development of bimatoprost for hypotrichosis of the eyelashes and culminating in US FDA approval for this indication in 2008.

A 24 week double-blind, randomized pilot study of 16 men with mild AGA showed a significant increase in hair density (terminal and vellus hairs) on the treated site with latanoprost 0.1% compared to baseline and the placebo-treated area.[14] Treatment was well tolerated, although erythema at the application site was observed in 5 patients.

More data is required to determine the optimal concentrations of these prostaglandin analogues. Bimatoprost may eventually be more effective at the right titrated concentration.[14]

Fluridil

Fluridil is a synthetic novel topical antiandrogen that is similar in structure to flutamide. Fluridil is a highly hydrophobic, systemically non-resorbable compound that demonstrates local tolerance and degrades into inactive metabolites without systemic antiandrogenic effects.[18,19] In a double-blind, placebo-controlled study of 43 men with AGA, application of fluridil for 3 months resulted in increased anagen percentage from 76% to 85% in the fluridil treated group, and at 9 months to 87%, with no change in the placebo group. Sexual function, libido, hematology and blood chemistry values were normal over the duration of the investigation.[19] Fluridil is being used throughout Europe but is still awaiting approval in the US.

Ketoconazole

Ketoconazole is an imidazole antifungal agent known to be effective for the treatment of seborrheic dermatitis and dandruff.[20] In a 21 month study comparing topical ketoconazole to minoxidil, the effect of ketoconazole 2% shampoo was compared to that of an unmedicated shampoo used in combination with or without minoxidil 2% therapy. Hair density and size as well as proportion of anagen follicles were improved almost similarly by both ketoconazole and minoxidil regimens.[20] The mechanism by which ketoconzole improves hair growth is unclear, but may be attributable to anti-inflammatory effects against T cells that are found in the balding area in AGA and activity against microflora of the skin by *Malassezia*. It also inhibits steroid synthesis and decreases DHT levels at the hair follicle by affecting androgen receptor activity.[21]

Spironolactone

Spironolactone is an aldosterone receptor blocker that reduces enzyme activity in the biosynthesis of testosterone. In a clinical study of 60 female patients with AGA, topical spironolactone 1% was found to be effective in promoting hair growth without hypotonia or hormonal disorders reported.[22] However, larger studies are necessary to determine the antiandrogenic properties of topical spironolactone and its potential utility for FPHL.

Melatonin

Melantonin has long been known to modulate hair growth. Animal testing has shown that melatonin stimulates the anagen phase of hair growth.[23] In a double-blind, randomized, placebo-controlled study 40 women with diffuse alopecia (n=28) or AGA (n=12) were treated topically for 6 months with 1 ml daily of 0.1% melatonin-alcohol solution versus vehicle. Trichograms were used to determine efficacy in the frontal and occipital scalp areas. At the end of the study, the AGA group demonstrated a statistically

significant increase in anagen hairs in the occiput region compared to placebo (mean 78 to 82 hairs), but no difference was shown with placebo in the frontal area.[24] The group with diffuse alopecia showed a substantial increase in frontal hair. Plasma melatonin levels were elevated under treatment with melatonin, but did not exceed the physiological night peak.

Estrogens

Systemic estrogens increase production of the glycoprotein sex hormone-binding globulin (SHBG), leading to a decrease in free testosterone. A 6 month study of a topical 17α-estradiol 0.025% preparation applied by 7 women with FPHL reported stabilization of hair loss and/or increased telogen hair shedding compared to 2 female control subjects.[25] More studies are warranted to validate the use of topical estrogens in AGA.

Conclusion

Although the clinical diagnosis of AGA can be easily made, the array of topical treatments remains largely investigational and demonstrates variable rates of response. Hence, extensive and well designed studies are needed to confirm their efficacy and safety. Early intervention may be important to limit the associated significant psychological morbidity. Novel and more effective treatments are in persistent demand and may be developed once the pathogenesis of AGA is better understood.

References

1. Gan DC, Sinclair RD. Prevalence of male and female pattern hair loss in Maryborough. *J Investig Dermatol Symp Proc.* 2005 Dec;10(3):184-9.
2. Budd D, Himmelberger D, Rhodes T, et al. The effects of hair loss in European men: a survey in four countries. *Eur J Dermatol.* 2000 Mar;10(2):122-7.
3. Shapiro J. Clinical practice. Hair loss in women. *N Engl J Med.* 2007 Oct 18;357(16):1620-30.
4. Price VH. Androgenetic alopecia in women. *J Investig Dermatol Symp Proc.* 2003 Jun;8(1):24-7.
5. Olsen EA, Messenger AG, Shapiro J, et al. Evaluation and treatment of male and female pattern hair loss. *J Am Acad Dermatol.* 2005 Feb;52(2):301-11.
6. Banka N, Bunagan MJ, Shapiro J. Pattern hair loss in men: diagnosis and medical treatment. *Dermatol Clin.* 2013 Jan;31(1):129-40.
7. Li M, Marubayashi A, Nakaya Y, et al. Minoxidil-induced hair growth is mediated by adenosine in cultured dermal papilla cells: possible involvement of sulfonylurea receptor 2B as a target of minoxidil. *J Invest Dermatol.* 2001 Dec;117(6):1594-600.
8. Messenger AG, Rundegren J. Minoxidil: mechanisms of action on hair growth. *Br J Dermatol.* 2004 Feb;150(2):186-94.
9. Atanaskova Mesinkovska N, Bergfeld WF. Hair: what is new in diagnosis and management? Female pattern hair loss update: diagnosis and treatment. *Dermatol Clin.* 2013 Jan;31(1):119-27.
10. Olsen EA, Whiting D, Bergfeld W, et al. A multicenter, randomized, placebo-controlled, double-blind clinical trial of a novel formulation of 5% minoxidil topical foam versus placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol.* 2007 Nov;57(5):767-74.
11. Friedman ES, Friedman PM, Cohen DE, et al. Allergic contact dermatitis to topical minoxidil solution: etiology and treatment. *J Am Acad Dermatol.* 2002 Feb;46(2):309-12.
12. Blume-Peytavi U, Hillmann K, Dietz E, et al. A randomized, single-blind trial of 5% minoxidil foam once daily versus 2% minoxidil solution twice daily in the treatment of androgenetic alopecia in women. *J Am Acad Dermatol.* 2011 Dec;65(6):1126-34 e2.
13. Olsen EA, Dunlap FE, Funicella T, et al. A randomized clinical trial of 5% topical minoxidil versus 2% topical minoxidil and placebo in the treatment of androgenetic alopecia in men. *J Am Acad Dermatol.* 2002 Sep;47(3):377-85.
14. Blume-Peytavi U, Lonnfors S, Hillmann K, et al. A randomized double-blind placebo-controlled pilot study to assess the efficacy of a 24-week topical treatment by latanoprost 0.1% on hair growth and pigmentation in healthy volunteers with androgenetic alopecia. *J Am Acad Dermatol.* 2012 May;66(5):794-800.
15. Law SK. Bimatoprost in the treatment of eyelash hypotrichosis. *Clin Ophthalmol.* 2010;4:349-58.
16. Higginbotham EJ, Schuman JS, Goldberg I, et al. One-year, randomized study comparing bimatoprost and timolol in glaucoma and ocular hypertension. *Arch Ophthalmol.* 2002 Oct;120(10):1286-93.
17. Jones D. Enhanced eyelashes: prescription and over-the-counter options. *Aesthetic Plast Surg.* 2011 Feb;35(1):116-21.
18. Poulos GA, Mirmirani P. Investigational medications in the treatment of alopecia. *Expert Opin Investig Drugs.* 2005 Feb;14(2):177-84.
19. Sovak M, Seligson AL, Kucerova R, et al. Fluridil, a rationally designed topical agent for androgenetic alopecia: first clinical experience. *Dermatol Surg.* 2002 Aug;28(8):678-85.
20. Pierard-Franchimont C, De Doncker P, Cauwenbergh G, et al. Ketoconazole shampoo: effect of long-term use in androgenic alopecia. *Dermatology.* 1998;196(4):474-7.
21. Inui S, Itami S. Reversal of androgenetic alopecia by topical ketoconzole: relevance of anti-androgenic activity. *J Dermatol Sci.* 2007 Jan;45(1):66-8.
22. Dill-Muller D, Zaun H. Topical treatment of androgenetic alopecia with spironolactone. *J Eur Acad Dermatol Venereol.* 1997 Sep;9(Suppl 1):31.
23. Fischer TW, Slominski A, Tobin DJ, et al. Melatonin and the hair follicle. *J Pineal Res.* 2008 Jan;44(1):1-15.
24. Fischer TW, Burmeister G, Schmidt HW, et al. Melatonin increases anagen hair rate in women with androgenetic alopecia or diffuse alopecia: results of a pilot randomized controlled trial. *Br J Dermatol.* 2004 Feb;150(2):341-5.
25. Orfanos CE, Vogels L. [Local therapy of androgenetic alopecia with 17 alpha-estradiol. A controlled, randomized double-blind study (author's transl)]. *Dermatologica.* 1980;161(2):124-32.

Skin Therapy *Letter*© (ISSN 1201–5989) Skin Therapy *Letter*© is published 10 times annually by SkinCareGuide.com Ltd, 1004 – 750 West Pender, Vancouver, British Columbia, Canada, V6C 2T8.

Subscription Information. Annual subscription: Canadian $94 individual; $171 institutional (plus GST); US $66 individual; $121 institutional. Outside North America: US$88 individual; $143 institutional. We sell reprints in bulk (100 copies or more of the same article). For individual reprints, we sell photocopies of the articles. The cost is $20 to fax and $15 to mail. Prepayment is required. Student rates available upon request. For inquiries: info@SkinTherapyLetter.com

Update on Drugs

Name/Company	Approval Dates/Comments
Acyclovir 50 mg buccal tablets *Sitavig*® BioAlliance Pharma	The US FDA approved acyclovir buccal tablets in April 2013 for the treatment of recurring herpes labialis (cold sores). This novel formulation is available as a mucoadhesive tablet that is self-administered by placement on the gum, delivering a high concentration of acyclovir directly to the site of the cold sore infection. A Phase 3 international study of 775 patients showed that in addition to its efficacy, this treatment was unobtrusive and offered simplified dosing with a single application for the entire duration of an episode of herpes labialis. Sitavig® should be applied within 1 hour after experiencing prodromal symptoms (e.g., itching, redness, burning, or tingling, and before a cold sore appears). The buccal tablet should be applied to the upper gum, just above the incisor tooth on the same side of the mouth as the cold sore symptoms.
Acyclovir 5% + hydrocortisone 1% cream *Xerese*® Valeant Canada	Health Canada issued a Notice of Compliance (NOC) in March 2013 for this topical combination therapy indicated for the early treatment of recurrent herpes labialis to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time in adults and adolescents (≥12 years of age). Xerese® contains acyclovir, a synthetic nucleoside analogue active against herpes viruses, and hydrocortisone, an anti-inflammatory corticosteroid.
Botulinum toxin type A for injection *Dysport*® Ipsen Medicis/Valeant	Health Canada granted a marketing authorization in April 2013 for abobotulinumtoxinA (Dysport®) for the temporary improvement in the appearance of moderate to severe glabellar lines (frown lines) in adults <65 years of age. The active agent is a botulinum neurotoxin type A complex that acts at the level of the neuromuscular junction in the targeted muscle to block acetylcholine secretion, which reduces muscular spasm.
Desoximetasone 0.25% topical spray *Topicort*® Taro Pharmaceutical	The US FDA approved a New Drug Application (NDA) for this topical corticosteroid spray in April 2013, which is indicated for the treatment of plaque psoriasis in patients ≥18 years of age.
Carbinoxamine maleate extended-release oral suspension *Karbinal™ ER* Tris Pharma	In April 2013, the FDA approved carbinoxamine maleate extended-release oral suspension 4 mg/5 ml, the first sustained-release histamine receptor blocking agent indicated for the treatment of seasonal and perennial allergic rhinitis in children ages ≥2 years of age. Sanctioned uses include the symptomatic treatment of seasonal and perennial allergic rhinitis; vasomotor rhinitis; allergic conjunctivitis due to inhalant allergens and foods; mild, uncomplicated allergic skin manifestations of urticaria and angioedema; and dermatographism. Carbinoxamine, an H1 receptor antagonist, is a mildly-sedating antihistamine and may be a therapeutic option for allergy sufferers who are unresponsive to second-generation antihistamines or dissatisfied with dosing schedules associated with first-generation antihistamines.
C1-esterase inhibitor *Berinert*® CSL Behring	Health authorities in 23 European countries have approved an extended use of this C1-esterase inhibitor (C1-INH) concentrate in April 2013 for pre-procedure prevention (short-term prophylaxis) of acute episodes of hereditary angioedema (HAE) in adult and pediatric patients undergoing medical, dental or surgical procedures. In addition to short-term prophylaxis, Berinert® is indicated in Europe for the treatment of acute attacks of HAE at all body sites in adults and children. The therapy is self-administred by intravenous infusion for eligible and trained patients.