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Update on Alopecia Areata

Speaker: Dr. Vera H. Price

Alopecia areata (AA) is an autoimmune disease resulting in reversible dysfunction of the hair growth cycle. There is no obvious destruction of hair follicles in AA, and the potential for full hair regrowth always remains. AA affects about 2% of the population in the United States. All ages are affected although it occurs more frequently in children and young adults. Males and females are equally affected and it occurs in all races, worldwide. It can affect any hair bearing area in the body and can cause stippling and dystrophy of nails. Patients with AA have a higher incidence of atopy, thyroid disease, and vitiligo. They are otherwise generally healthy. Family members have a higher incidence of atopy, thyroid disease, vitiligo, insulin-dependent diabetes, lupus erythematosus, rheumatoid arthritis and other autoimmune diseases. If a first degree relative has AA, the chance of developing the condition is approximately 20%. Laboratory tests are not usually needed in patients with AA with the exception of a thyrotrophin level in young children or in patients with a strong family history of thyroid disease.

Two types of alopecia areata

Two forms of AA are now recognized: an early-onset form and a late-onset form. Early-onset AA occurs before the age of 30. It is of greater severity and longer duration. Thirty-seven percent of patients have a family history. Late-onset AA is less severe and has a shorter duration, only 7% of patients have a family history.

HLA and animal models

Certain human leucocyte antigen (HLA) markers identify a general susceptibility for AA (the HLA alleles DQ3 and DRB1*1104) and others identify susceptibility to long-standing AA or alopecia universalis (DRB1*0401 and DQB1*301).

There are 2 animal models for AA: the C3H/HeJ mouse developed at the Jackson Laboratory in Bar Harbor, Maine, and the DEBR rat developed at the University of Dundee. The most compelling evidence that AA is an autoimmune disease followed the work of Gilhar, et al. who transferred AA by autologous T lymphocytes to human scalp explants on mice with severe combined immune deficiency (J Clin Invest 101: 62-67, 1998). Subsequent work suggests that a target of the autoimmune attack in AA may be a melanocyte-derived protein.

Treatment

Current treatments for AA do not change the course of the condition. All treatments must be continued till the disease enters a remission. Patients should be told the unpredictable nature of AA and be prepared for its remissions and recurrences. They should be reassured that complete hair regrowth can occur with or without treatment even in patients with 100% scalp hair loss.

Children under the age of 10 are treated with single or combination therapy of topical 5% minoxidil solution with or without a mid-potency topical steroid twice per day or short contact anthralin.

Treatment of individuals over the age of 10 is based on the extent of AA. Patients with <50% scalp involvement are treated with intralesional corticosteroids and/or 5% minoxidil solution and/or high potency topical steroid twice per day. Anthralin is less practical in mild AA because the remaining hair is an obstacle. For patients with more than 50% scalp

involvement, a scalp prosthesis should be offered. Topical immunotherapy with dinitrochlorobenzene (DNCB), squaric acid dibutyl ester (SADBE), or diphenylcyclopropenone (DPCP) for at least 24 weeks should be considered. One side of the scalp is treated first in order to establish definitive response. If successful, the opposite side of the scalp is also treated. Side effects include lymphadenopathy of the neck and behind the ears, allergic contact dermatitis on the scalp, severe blistering and auto-eczematization. Pigment changes such as hyperpigmentation, hypopigmentation, a combination of both ("dyschromia in confetti") and vitiligo may also occur. Extreme caution should be exercised when treating patients with darker skin. Forty to sixty percent success rates have been reported in severe AA. Patients with alopecia totalis and universalis have a lower successful response (25%). Refractory patches can be injected with intralesional corticosteroids. Alternative modalities include 5% minoxidil solution, with or without high potency topical corticosteroids or short contact anthralin therapy for at least 6 months. Initial response usually takes 12 weeks.

Because of potential side-effects, systemic prednisolone should only be used in special circumstances. For active disease of greater than 50% scalp involvement, one treatment regime is to use 40mg prednisolone per day for one week then one week of 30mg prednisolone per day followed by tapering doses over 4 weeks. For active but less extensive AA, 20mg prednisolone per day or every other day may help to slow the activity while using intralesional corticosteroids every 4 weeks or 5% minoxidil solution twice daily. With long-term use, an every other day regimen tapering slowly by 1mg is recommended.

Learning points:

Topical immunotherapy is reserved for severe long standing alopecia areata. Considerable experience is required for its administration and extreme caution should be exercised when treating patients with darker skin.

Scarring Alopecias: Trichologic Emergencies

Speaker: Dr. Jerry Shapiro

Introduction

Scarring alopecia is characterized by destruction of hair follicles, leading to permanent hair loss. The follicular stem cells are located in the 'bulge' area, where the arrector pili muscle inserts just below the sebaceous gland. The hair follicles can be saved from irreversible damage if peri-bulge inflammatory infiltrate can be controlled. All scarring alopecia can thus be regarded as trichologic emergencies.

Classification of scarring alopecia

Scarring alopecia can be classified by clinical or pathological criteria. The former rests on the presence of inflammatory lesions (Figure 1) and the latter by the nature of primary infiltrate. The pathological classification has important bearing on treatment. Biopsy site selection is crucial in this aspect. Site representative of clinical manifestation and active disease should be chosen, for example, primary lesion at the edge, but not secondary changes like excoriations.

Lymphocyte-mediated scarring alopecias

The lymphocyte-mediated scarring alopecias are mainly discoid lupus erythematosus (DLE), lichen planopilaris and pseudopelade. Both DLE and lichen planopilaris have inflammation and follicular hyperkeratosis clinically. The hyperkeratosis is centrally located in DLE and peripherally located in lichen planopilaris. Pseudopelade is non-inflammatory and there is no follicular hyperkeratosis. Pathologically DLE shows vacuolar degeneration, perivascular and periadnexal infiltrate and an increase in dermal mucin. Direct immunofluorescence demonstrates C3 and IgG at the dermo-epidermal junction. Lichen planopilaris shows a band-like lichenoid lymphocytic infiltrate. Pseudopelade may show a minimal infiltrate at the level of the follicular infundibulum without interface alternation in the early stage but no infiltrate in the late lesion. Direct immunofluorescence is negative.

Neutrophil-mediated scarring alopecias

The neutrophil-mediated scarring alopecias mainly include folliculitis decalvans and dissecting cellulitis. Folliculitis decalvans is characterized by irregular- to oval-shaped patches of alopecia with pustules present

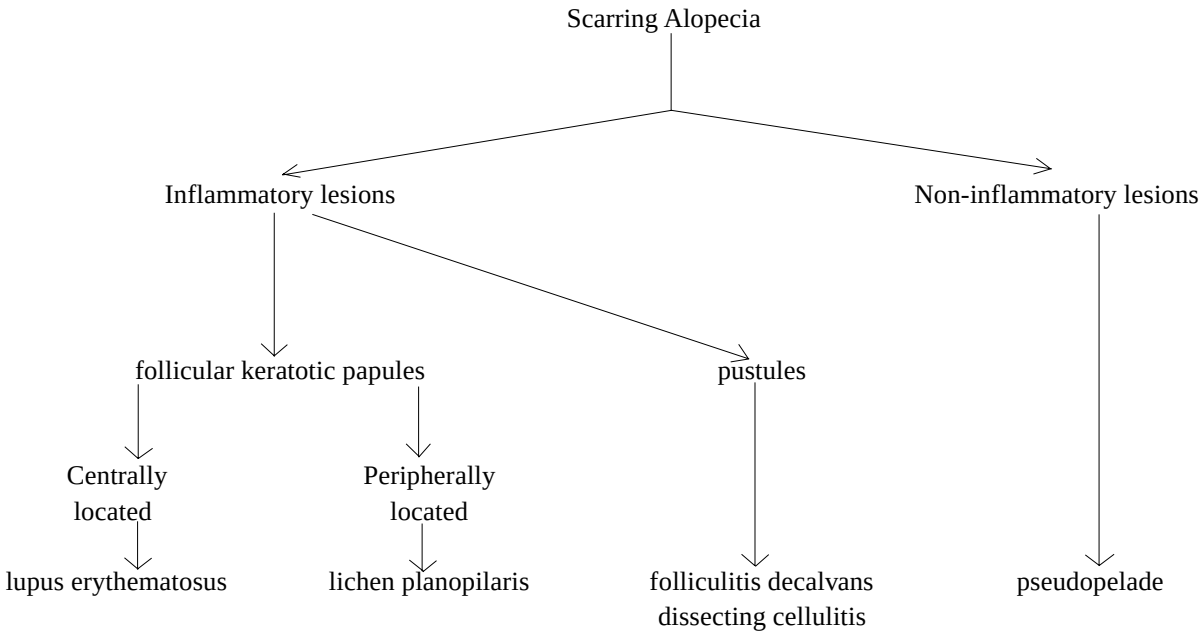

Figure 1. A simplified clinical classification of scarring alopecia

at the peripheral advancing edge. Tufted folliculitis is common. Dissecting cellulitis shows numerous interconnected deep-seated fluctuant abscesses and sinus tracts with overlying crusts and pustules. Pathologically there is infundibular destruction with a neutrophilic infiltrate.

Management of scarring alopecia

The goals of management in scarring alopecia are three folds: to arrest the disease process, decrease peri-follicular inflammation and prevent further fibrous replacement of follicles. Treatment depends on the nature of infiltrate: lymphocytic or neutrophilic.

Lymphocyte-mediated scarring alopecias

For lymphocyte-mediated scarring alopecia with less than 10% scalp involvement, monthly intralesional corticosteroid injection to active edge and superpotent topical corticosteroid therapy can be given. If the lesions do not improve within 8 weeks, antimalarial like hydroxychloroquine can be added for at least 6 months. If the lesions are very rapidly progressive, inflamed and symptomatic, a course of prednisone 1mg/kg/day, tapering over 2 months may be considered.

If scalp involvement is more than 10%, one can give intralesional corticosteroid injection, together with superpotent topical corticosteroid and hydroxychloroquine for at least 6 months. If the lesions are very rapidly progressive, inflamed and symptomatic, one should consider a course of systemic corticosteroid for 8 to 12 weeks. If the patient does not respond after 6 months, the following can be considered: isotretinoin, dapsone and thalidomide. Surgical procedures like hair transplantation and scalp reduction are possible but the lesions should be inactive or burnt-out for at least 2 years. Wearing a hairpiece may be an option for some patients.

Neutrophil-mediated scarring alopecias

Oral antibiotics like cloxacillin, cephalexin, minocycline, erythromycin, etc. are often given initially. Isotretinoin may be necessary for dissecting cellulitis.

In conclusion, the following are important for the management of scarring alopecia: accurate diagnosis with clinical and histopathologic assessment, aggressive treatment if the disease is extensive, and a multi-modality approach.

Learning points:

Scarring alopecias are truly trichologic emergencies and should be treated as such. Clinical and histopathologic assessment are essential to guide the management.

Recent Advances in Contact Dermatitis

Speaker: Prof. C. L. Goh

Irritant contact dermatitis

Despite being the commonest form of contact dermatitis, there are few publications on the epidemiology and mechanism of irritant contact dermatitis (ICD). Manifestation of this multi-factorial disease depends on an individual's susceptibility and exposure to various irritants. Unlike allergic contact dermatitis (ACD), there is no diagnostic model and ICD is usually a diagnosis of exclusion. The molecular biology of ICD has been studied recently. It has been shown that rather than a pure physical injury, ICD is an immunological reaction resulting from an interplay of cellular cytokines released from damaged keratinocytes. Various cytokines including ICAM-1, TNF-α, IL-6, IL-1β, G-CSF have been identified. Studies comparing the histochemistry of ICD and ACD showed that their cytokine profiles were almost identical, suggesting that they may have similar pathways of manifestation. TNF-α in particular, plays an important role in the development of ICD by inducing ICAM-1 expression. Studies have shown that individuals with genetic predisposition for TNF-α expression have a lower threshold for developing ICD. The gene for TNF-α expression has also been identified recently. It may become an identifiable "risk factor" for ICD in pre-employment examination and counseling. Though it is postulated that individuals with high trans-epidermal water loss are more susceptible to develop ICD, repeated studies have shown that it is a poor indicator.

Allergic contact dermatitis

The afferent and efferent pathways for ACD are well known. Various cytokines particularly TNF-α, are released from keratinocytes. These are responsible for facilitating the passage of Langerhans cells through the basement membrane and their migration to local lymph nodes where sensitization of T-lymphocytes occurs. Molecular research are now underway to find ways to block Langerhans cell migration into the lymphatic system from which new treatment for ACD may be developed.

Patch test

Most have adopted the practice described by the International Contact Dermatitis Group by occluding for 48 hours and read at 96 hours. However, the optimal occlusion duration for patch test and the optimal time for patch test reading are still controversial. In hot tropical countries it is impossible to occlude patient for 48 hours, as perspiration causes the test patch to fall off. Studies have shown a concordance of 80% to 90% when comparing occlusion interval of 24 and 48 hours, thus it is agreed that a minimal of 24 hours of occlusion (preferably 48 hours) is required. Reading at 48, 72 hours and 96 hours will allow most true allergic contact dermatitis reactions to be identified. Reading at day 7 is necessary for certain allergens such as neomycin and corticosteroid. If not read at day 7, the chance of getting a false negative result is between 15-30%.

In patients with drug eruption, patch testing with the suspected agent is a simple way to confirm true drug allergy, though the yield is only about 25%. A positive test however, is particularly helpful for identifying the culprit in cases of polypharmacy thus sparing the need for provocation tests. A negative test does not however exclude drug eruption as the drug metabolite may not be available for patch testing and that the penetration of the tested agent may not be sufficient.

Fragrance allergy

Both Larsen's mix and balsum of Peru have been used as markers for fragrance allergy. Over the last few years the proportion of patients with synthetic aldehyde allergy has declined as the manufacturer have scaled down its use. Musk ambrette which caused photodermatitis has also been removed by most fragrance industry. The prevalence of fragrance allergy is about 8% in Singapore. A recent study has revealed that Asians are more likely to react to benzyl salicylate while westerners to isoeugenol and oak moss absolute. It is therefore appropriate when patch testing Asians to expand beyond the normal standardized fragrance series adding other exotic sensitizers.

Rubber latex allergy

The rising incidence of rubber latex allergy is probably due to the increased use of rubber gloves as a result of the HIV/AIDS epidemic. It is a form of type I hypersensitivity reaction and presentation varies from localized contact urticaria to generalized urticaria, angioedema or anaphylaxis. It can also present as allergic rhinitis, allergic conjuctivitis and asthma as the glove powder carries the latex protein. Subjects who are at risk include hospital workers (up to 15% in one

Finnish study), patients undergoing multiple surgery, those with atopic eczema and hand eczema and those with mucosal exposure. In glove users, contact urticaria can be caused by either the rubber latex protein or the corn starch. This can be distinguished by prick tests. Powder free gloves can reduce the risk of rubber latex allergy but they are more expensive. Diagnosis of rubber latex allergy requires a high index of suspicion. A careful and thorough history is the cornerstone. When prick test facilities are unavailable, the simple "usage test" can be done. Patient is asked to wear the rubber gloves. If it is a positive test, patient will develop tingling and itch, and on removing the gloves after 15-30 minutes, active whealing at area of contact may be observed. Latex-specific IgE tests are available but the low specificity of these tests limits clinical usefulness. Prohevein (20KD) and hevein (4.7KD) are the two major sensitizers, both derived from the rubber tree Hevea brailiensis. They have been used in the RAST and prick tests. Many other proteins have also been identified by electrophoresis and all have potential to cause type I hypersensitivity reactions.

Most patients experience only local symptoms but up to 34% of patients with rubber latex contact urticaria also had systemic symptoms. Thus they should be advised to avoid latex exposure. Cross-reactivity to fruits including kiwi, banana, chestnuts, avocado should also be warned. This is due to the cross-allergenic protein prolifin.

Preservative allergy

Preservatives are widely used in water-based products including cosmetics and toiletries. They generally cause more problems for the "leave-on" products e.g. foundation, and fragrance, rather than the "rinse-off" agents e.g. soap and shampoo, as the risk of sensitization is reduced due to the brief exposure time. Older allergens include chlorocresol, parabens and formaldehyde. Over the last two years a new preservative has been introduced: euxyl K 400 (with methyldibromoglutaronitrite {MDG} as the active ingredient). In a Dutch study, it is found in 30% of cosmetics and 66% of moisten-toilet tissues. Allergic contact dermatitis to euxyl K 400 has been reported and its addition to the standard patch test series should be considered.

Metal allergy

Nickel is the commonest contact allergen in the world. It has been postulated that oral nickel can aggravate eczema of sensitized patients. Provocation study in patients with nickel allergy has now refuted this theory. Ingestion of more than 5mg of nickel per day is required for exacerbation to occur. Such a concentration is non-existent in normal diet. Thus nickel-free diet is unnecessary for patient with nickel allergy. In Denmark, regulation introduced in 1996 strictly limited the concentration of nickel in manufactured products. This has reportedly led to a drop in the reported incidence of nickel allergy.

Gold allergy is rare. A Swedish study showed that 8.6% of 832 patients patch tested with gold sodium thiosulphate gave positive reactions. Up to 10% of patients in Singapore patch tested also gave positive reactions. Patients generally are asymptomatic when wearing gold jewellery but when given systemic gold, for example, intramuscular gold for rheumatoid arthritis, severe allergic reaction such as baboon syndrome may develop. Patient with contact allergy to gold should therefore be advised accordingly.

Learning points:

- ***Individuals with genetic predisposition for TNF-α expression are more susceptible to develop ICD.***
- ***The risk of rubber latex allergy can be reduced through the use of non-powdered, low protein latex and non-latex gloves.***
- ***Euxyl K 400 found in many moisten-tissue is a new preservative responsible for many cases of allergic contact dermatitis.***
- ***Nickel free diet is unnecessary for patients with nickel allergy.***

The Impact of HAART

Speaker: Dr. K. H. Wong

HAART

Highly active antiretroviral therapy (HAART) is the use of very potent regimen to control HIV disease. It usually means triple therapy with two nucleoside analogue reverse transcriptase inhibitors (NRTI) and one protease inhibitor (PI). This regimen has been used in Hong Kong since 1996-1997 (Table 1).

Table 1. Historical development of antiretroviral therapy in Hong Kong

Year	Treatment
1987	Monotherapy (AZT)
1994/95	Double therapy
1996/97	Triple therapy (HAART)

The impact of HAART

The impact of HAART can be described in three aspects: virologic, immunologic and clinical. The goal of HAART is to maximally suppress viral replication for as long as possible, often to an undetectable level.

Immunologically, HAART can reverse some of the changes induced by HIV infection, notably causing a rise in CD4 count. Immune re-constitution is characterised by a prompt rise in CD4 and CD8 lymphocytes, followed by a slower but persistent rise in CD4 lymphocytes as CD8 lymphocytes decrease. There is however no restoration of HIV-specific immunity. The magnitude of such changes is greater if there is a greater reduction in viral load. These changes are slower in advanced disease.

Clinically, the immune re-constitution as a result of HAART alters HIV disease progression and improves HIV-related complications. Incidence of opportunistic infections is decreased and their outcomes are improved. Chronic infections like cryptosporidiosis are better controlled or may even resolve. Other complications like Kaposi's sarcoma may also subside. Prophylaxis for opportunistic infections may be stopped if the CD4 count rises beyond a safety level. Overall there is a decrease in HIV-related morbidity and mortality.

HAART has caused a fall in hospitalisation and a shift to outpatient-based care. There is a rise in drug expenditure but a lower overall cost of patient care. More importantly the patient can re-gain productivity. As a result,HIV infection has become a treatable chronic condition.

Limitations of HAART

On the other hand, HAART has its limitations: suboptimal response or failure, drug toxicity and interaction, incomplete immune restoration and inability to eradicate the virus. Drug failure can occur in patients who are antiretroviral-experienced with development of drug resistance, non-compliant or very immuno-compromised.

A protease inhibitor-related lipodystrophy syndrome has been reported. It is characterised by body fat re-distribution (central obesity, peripheral fat wasting) and metabolic abnormalities (hyperlipidaemia, hyperglycaemia, insulin resistance).

Potential options to improve HAART for eradication of the virus include: more potent antiretroviral therapy, immunomodulatory treatment and therapeutic vaccine.

Conclusion

HAART has improved the mortality and morbidity of HIV infection in a cost-effective way though its limitations need to be addressed.

Learning points:

Drug compliance is crucial in HAART. The suboptimal response to HAART in advanced immunosuppression speaks for the importance of early diagnosis of HIV infection.