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VIEWPOINT – Vitiligo and alopecia areata: Apples and oranges?

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Abstract

Vitiligo and alopecia areata are common autoimmune diseases of the skin. Vitiligo is caused by the destruction of melanocytes and results in the appearance of white patches on any part of the body, while alopecia areata is characterized by patchy hair loss primarily on the scalp, but may also involve other areas as well. At first glance, the two diseases appear to be quite different, targeting different cell types and managed using different treatment approaches. However, the immune cell populations and cytokines that drive each disease are similar, they are closely associated within patients and their family members, and vitiligo and alopecia areata have common genetic risk factors, suggesting that they share a similar pathogenesis. Like apples and oranges, vitiligo and alopecia areata have some obvious differences, but similarities abound. Recognizing both similarities and differences will promote research into the pathogenesis of each disease, as well as the development of new treatments.

Keywords

Vitiligo; alopecia areata; treatment; autoimmunity; T cell; autoantigen; innate immunity; adaptive immunity; cytokine; IFN- γ

Comparing apples and oranges

The phrase, “like comparing apples and oranges” or, in some languages, “apples and pears”, is commonly used to refer to comparisons of two different objects or concepts that are thought to be so unrelated that they are not directly comparable. However, in his book *Sex, Drugs, and Cocoa Puffs: a Low Culture Manifesto*, Chuck Klosterman criticizes this interpretation - “Apples and oranges aren’t that different really. I mean they’re both fruit. Their weight is extremely similar. They both contain acidic elements. They’re both roughly spherical...So how is this a metaphor for difference? I could understand if you said ‘That’s like comparing apples and uranium’ or ‘That’s like comparing apples with baby wolverines’ ...Those would all be valid examples of profound disparity.” (1) Others have made similar arguments, even contributing experimental, albeit whimsical, data revealing chemical and structural similarities between the two fruit (2, 3). Therefore, while the fruits have some differences, they share many important similarities as well.

Vitiligo and alopecia areata – Clinically different

Vitiligo and alopecia areata, while both affecting the skin, have very different outward appearances. Vitiligo is characterized by white patches, while alopecia areata presents as

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patchy hair loss. Treatments for vitiligo are primarily topical steroids, topical calcineurin inhibitors, or narrow-band UVB light therapy (4). In contrast, alopecia areata is primarily treated with intralesional steroid injections or by inducing contact dermatitis with chemicals such as squaric acid or diphenylcyclopropenone (DPCP) (5). However, DPCP has been reported to *induce* depigmentation (6, 7), and therefore it is not an effective treatment for vitiligo. Differences in treatment approach may be more due to the location of inflammation within the skin, rather than the pathogenesis of each disease. Melanocyte destruction in vitiligo is primarily limited to the epidermis, so topical immunosuppressants and nbUVB light therapy are effective (4) despite their limited penetration. Inflammation in alopecia areata is localized around the hair bulb deep in the dermis, so steroids are most effective when injected intradermally, and topical steroids are limited in efficacy unless used under occlusion (5). It may be the depth of inflammation in alopecia areata that makes nbUVB ineffective as a treatment while PUVA, which penetrates deeper into the dermis, has had modest success (8). The mechanism of contact immunotherapy with chemicals like squaric acid or DPCP is currently unknown, however it may rely on refocusing the immune response in the skin toward the epidermis and toward a separate, T_H2 response (8). Despite these obvious clinical differences, the two diseases share much in common, and understanding those commonalities may help us to better hypothesize about their pathogeneses, test those hypotheses, and develop new treatments for our patients.

Approaches to categorizing autoimmune diseases

Autoimmune diseases may be categorized by target tissue and medical specialty, which is primarily useful for clinical purposes, since diagnostic and treatment expertise are often tailored by organ system. Alternatively, autoimmunity can be categorized based on immune pathogenesis, such as cytokine expression, T cell infiltrate, or both. This can be very helpful for developing new treatments, as diseases sharing a similar mechanism may respond to similar drugs. This is nowhere more evident than with the use of TNF- α blockers in psoriasis, rheumatoid arthritis, and inflammatory bowel disease (9). Above I have discussed the clear differences between vitiligo and alopecia areata, just like those existing between apples and oranges. However, like the fruit, they share much in common, particularly when contrasted with other autoimmune diseases in the skin that represent the “baby wolverines” of profound disparity. Psoriasis, for example, appears starkly different from either vitiligo or alopecia areata, and recognizing these relative differences will help in this discussion.

Vitiligo and alopecia areata – Pathogenically similar

In contrast to more inflammatory diseases of the skin like psoriasis and lichen planus, vitiligo and alopecia areata are relatively asymptomatic (10, 11). The histopathological appearances of vitiligo and alopecia areata reflect this, as lesions are less inflammatory than other inflammatory diseases like psoriasis or lichen planus. While psoriasis contains a heterogeneous mixture of cell types within the infiltrate, including T cells, dendritic cells, neutrophils, and others, the comparably modest infiltrates in vitiligo and alopecia consist primarily of T cells, which include both $CD8^+$ and $CD4^+$ subtypes. The $CD8^+$ cells are commonly found infiltrating the epidermis in vitiligo, and the follicular epidermis in alopecia areata, while the $CD4^+$ T cells remain dermal (5, 12–14).

Targeted cell killing by $CD8^+$ cytotoxic T cells with the help of $CD4^+$ T helper cells reflects a T_H1 -mediated immune response, which is usually dependent on the production of IFN- γ to drive that response (15). Association of each disease with thyroiditis, also considered a T_H1 -mediated disease (16), is well-documented, and anti-thyroid antibodies are more common in both vitiligo and alopecia areata patients when compared to the general population (17, 18). Both vitiligo and alopecia areata have also been described as T_H1 -driven diseases, based on

the involvement of CD8⁺ T cells and the clear, consistent production of IFN- γ within lesional skin (19, 20). Human CD8⁺ T cells are both necessary and sufficient for melanocyte destruction in vitiligo (21), and innate-like T cells (including CD8⁺ populations) are both necessary and sufficient for hair loss in a humanized model of alopecia areata (22). Supporting these observations in human tissue, we recently reported that a mouse model of vitiligo requires autoreactive CD8⁺ T cells and IFN- γ for epidermal depigmentation (23), and others have made similar observations in a mouse model of alopecia areata (24, 25).

In sharp contrast to psoriasis (26), a role for cytokines that reflect a T_H17 response (IL-17, IL-23, and IL-22) is not clear in vitiligo or alopecia areata, as they are reportedly associated in some studies but not in others (21, 27–30). TNF- α , a highly inflammatory cytokine, is consistently elevated in T_H17-mediated diseases and appears to be required for their pathogenesis, revealed through the efficacy of TNF- α blockers in treating psoriasis (9). While modest TNF- α is reportedly elevated in vitiligo and alopecia areata (31–35), attempts to treat both vitiligo and alopecia areata with TNF- α blockers have been unsuccessful (36–38), and both diseases have been reported to develop or worsen following this treatment (39, 40). Therefore, vitiligo and alopecia areata appear to depend primarily on IFN- γ , while psoriasis and other T_H17 diseases (inflammatory bowel disease, rheumatoid arthritis) require IL-17, IL-23, IL-22, and TNF- α . Based on these data, it may be better to focus future therapeutic strategies in vitiligo and alopecia areata on targeting the T_H1/IFN- γ pathway rather than testing treatments that have been effective in psoriasis.

One expectation for diseases that share a similar pathogenesis is that they might be found together in patients and their family members due to shared genetic risk factors. Direct overlap of associated genes between vitiligo and alopecia areata are few, including HLA alleles, IL2RA, and possibly CTLA4, and all are shared with other autoimmune diseases as well. In addition to direct overlap, they share common gene categories, as both adaptive and innate immune-related genes predominate in both diseases (41, 42). Clinically, I have observed patients with both vitiligo and alopecia areata (Figure 1a,b), although only formal, prospective studies can determine whether these occurrences are found more often than would be expected by chance. For example, patients presenting with both vitiligo (prevalence of ~0.5–2%) (43) and alopecia areata (prevalence of ~0.1%) (5) at the same time would occur with a frequency of ~0.001%, or 1:100,000 people within the general population. Within a specialty clinic like mine where I see patients with either disease, they would represent 1:1000 vitiligo patients and 1:100 active alopecia areata patients. Prospective studies of disease overlap in large populations are difficult to perform due to limited reporting of skin diseases in general, as well as the characteristically short duration and spontaneous remission of alopecia areata. Some have reported no increased coincidence of vitiligo and alopecia areata (44), however three studies do support this concept – patients with alopecia areata had a higher risk for developing vitiligo than the general population (18, 45), and vice versa (46). Interestingly the Smyth line chicken, an animal model of spontaneous vitiligo, develops loss of feathers at an incidence that is increased over those without vitiligo, and both diseases are dependent on the immune system (47).

Case Report – Vitiligo and alopecia areata at the same location

Even more intriguing are reports of patients in whom both vitiligo and alopecia coexist at the same anatomical site in the skin, with lesional overlap. I have observed one patient with this presentation: BH is a 33 year-old man with depigmentation on his face, trunk, arms and legs, as well as alopecia on his trunk and extremities. At the age of 16, he noticed small patches of hair loss on his arms. Three years ago he noted a small macule of depigmentation on his right hand. The depigmentation progressed to involve his face, trunk and extremities. His family history is significant for his mother and grandmother who have thyroid disease,

but no other known family members with autoimmune diseases. He has no known allergies, takes no medications, and denies vision/hearing changes or vertigo. On physical exam, patches of depigmentation were visible on his face, trunk and extremities, highlighted by Wood's lamp examination. Patches of non-scarring alopecia were visible on his extremities, but not his scalp. Notably, patches of depigmentation and alopecia were present in an identical, overlapping distribution on his extremities, with hair loss primarily limited to depigmented skin (Figure 1c).

Others have reported similar cases (48–53), and while coincidence of vitiligo and alopecia areata without overlap is expected to occur in the general population, lesional overlap is highly significant because lesional patterns in each disease have nearly infinite possibilities, and therefore perfect overlap is very unlikely to occur by chance. In addition, the fact that pigmented hairs appear to be specifically targeted in alopecia areata while non-pigmented hairs are spared, and that hairs regrowing within a former lesion are often initially depigmented (5), further connects alopecia areata to melanocytes and pigmentation. Many have hypothesized that melanocytes are primary immune targets in vitiligo, although this view remains controversial (54). These overlapping presentations of depigmentation and hair loss in patients with both vitiligo and alopecia areata suggest a similar pathogenesis, and may depend on any number of mechanisms due to the close proximity of melanocytes and hair follicles within the skin, including localized epitope spreading during inflammation, or the targeting of melanocytes both in the epidermis as well as the hair follicle (54). According to the immunopathogenesis of both vitiligo and alopecia areata discussed above, it is also possible that overlapping lesions are co-driven by IFN- γ and its downstream targets. An inverted presentation of this phenomenon has been reported, where patients with psoriasis and alopecia areata on similar areas of the body presented with patches of alopecia but normal hair growth within plaques of psoriasis that appear at the same site. This suggests that psoriatic inflammation is protective against alopecia areata, and is referred to as the Renbök, or “reverse Köbner” phenomenon. I described one patient with this presentation, and hypothesized that this was due to cytokines expressed in psoriasis (T_H17) suppressing inflammation in alopecia areata (T_H1) (55). Such cross-regulation of cytokines is well-recognized *in vitro*, as immune responses become “polarized” toward one type due to cytokine-mediated suppression of other types (15). The fact that vitiligo and alopecia areata overlap within the skin, rather than antagonize one another like psoriasis and alopecia, further suggest that their pathogenesis are similar.

Vitiligo and alopecia areata – learning from each other

As mentioned above, adaptive immunity, and in particular cytotoxic CD8⁺ T cells, plays a key role in the destruction of melanocytes in vitiligo (21) and hair loss in alopecia areata (20, 22). Consistent with this, melanocyte-specific autoantigens targeted by CD8⁺ T cells in vitiligo have been well-characterized, including tyrosinase, gp100, and MART-1 (56). However in contrast, no T cell autoantigens have yet been definitively identified in alopecia areata (20), although trichohyalin or keratin 16 may be autoantibody targets (57). Based on the similarities between vitiligo and alopecia areata, I would hypothesize that T cell target autoantigens do exist in alopecia areata, and further efforts to identify them are worthwhile.

In addition to adaptive immunity, genetic and functional genomic studies have implicated innate immunity in both diseases (42, 58, 59), however the precise mechanisms vary between them. Understanding the exact contributions in one disease may inform our understanding of the other. For example, NLRP1 was implicated as a susceptibility gene for vitiligo in a genome-wide linkage study (60), and a recent follow-up study revealed that a high-risk allele for NLRP1 increased the processing and secretion of the innate pro-inflammatory cytokine IL-1 β , suggesting hyperactivation of NLRP1 as a causative factor in

vitiligo (59). Likewise, NKG2D ligands, which drive innate immune cytotoxic responses, have been reported as susceptibility genes for alopecia areata (42). NKG2D is expressed on infiltrating cytotoxic T and NK cells within scalp lesions (61), and may specifically identify those cells that directly participate in cytotoxicity to the hair follicle (22). Inflammatory dendritic cells have been implicated in vitiligo pathogenesis (62, 63), yet a role for a similar population in alopecia areata has not yet been identified. Immune privilege of the hair follicle is thought to be protective against alopecia areata (20), and may prove to be responsible for protecting hair from depigmentation in vitiligo. These cutting-edge studies may reveal important clues about the role of innate immunity in vitiligo and alopecia areata, and similar mechanisms may be active in each.

While recent genetic and mechanistic studies clearly identify vitiligo as an autoimmune disease, additional studies also implicate the melanocyte-intrinsic cellular stress response as contributing to pathogenesis. Indeed, both *in vitro* and *in vivo* studies reveal increased levels of reactive oxygen species, oxidation of cellular organelles, and activation of the unfolded protein response within melanocytes from vitiligo patients (62, 64–69). Similar changes have been reported in other autoimmune diseases as well (70) (71) and, based on the similarities between vitiligo and alopecia areata, future studies may find that the stress response within the hair follicle also participates in the pathogenesis of alopecia areata. Therefore, basic and translational mechanistic studies in alopecia areata can benefit from progress made in vitiligo, and vice-versa. The relative ease of culturing both melanocytes (72) and hair follicles (73) *in vitro* make translational studies using these tissues particularly attractive, and may not only advance our understanding of vitiligo and alopecia areata, but also of autoimmune diseases that affect other organ systems as well.

Conclusions

So, are vitiligo and alopecia areata similar or different? Is comparing them like comparing apples and oranges? The interpretation may depend on your point of reference as a clinician, melanocyte or hair biologist, geneticist, or immunologist. All views are valid, and the question remains whether categorizing them as similar would be advantageous in some way. Systemic therapies for vitiligo and alopecia areata are not widely used, and research into identifying new treatments with improved efficacy and safety profiles is the focus of a number of labs, including ours. Developing targeted therapies that interfere with IFN- γ and its downstream effectors is a promising treatment strategy for both. If a new therapeutic agent can be delivered systemically, then the anatomic differences in location of the inflammatory infiltrate may not determine efficacy, and if new therapies target shared pathways, significant benefit may be gained from progress made in one disease for the other, and vice versa. The Table lists the discussed similarities and differences between vitiligo and alopecia areata, and Figure 2 summarizes the concepts discussed here. Comparing vitiligo and alopecia areata *is* like comparing apples and oranges, but not like comparing apples and baby wolverines. The differences are important, yet focusing on the similarities and fostering collaboration among research groups with interest in vitiligo and alopecia areata may provide an opportunity to understand disease pathogenesis, as well as to develop new treatments, more efficiently.

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Figure 1.

Coincident vitiligo and alopecia areata. (a, b) Non-overlapping lesions: Thirty-five year-old woman with longstanding, widespread vitiligo responding to treatment with nbUVB. Depigmented patch on her right areola and breast with some repigmentation (a). During treatment with nbUVB and while pregnant, she developed a patch of nonscarring alopecia on her occipital scalp, now with some regrowth (b). Overlapping lesions: Thirty-three year-old man with overlapping vitiligo and alopecia areata on the forearm. Arrowheads mark the border of both depigmentation and alopecia, highlighted by illumination with Wood's lamp (c).

Figure 2. Summary of a working hypothesis that describes similarities and differences between vitiligo and alopecia areata

Inflammation includes T cell and innate populations. In vitiligo T cell infiltrates are superficial near the epidermis, but in alopecia areata are located in the deep dermis near the hair bulb. Consequently, topical steroids and other immunomodulatory agents are first-line therapies for vitiligo, while alopecia areata requires intralesional steroids. Both diseases are driven by a CD8⁺ T cell-mediated attack that is dependent on IFN- γ , suggesting that targeting this cytokine pathway may be an effective treatment strategy for both. So far, cellular stress has only been identified in melanocytes in vitiligo. Antigens have been well-characterized for vitiligo, yet remain elusive in alopecia areata. Systemic treatments could target both vitiligo and alopecia areata, as they are not limited by the depth of inflammation. The differences between diseases offer insight into new research opportunities, yet the similarities provide hope that future, targeted therapies may be effective for both vitiligo and alopecia areata. UVB, ultraviolet B; UVA, ultraviolet A.

Table

Summary of differences and similarities between vitiligo and alopecia areata.

Differences	Vitiligo	Alopecia Areata
Clinical appearance	Patches of depigmentation	Patches of alopecia
Treatment	Topicals, UVB	Intralesional steroids, PUVA
Location of immune infiltrate	Superficial dermis/epidermis	Deep dermis/follicular bulb
T cell autoantigens	gp100, MART-1, tyrosinase	Unknown
Abnormalities in cellular stress	Present in melanocytes	Unknown
Inflammatory dendritic cells	Important in pathogenesis	Unknown
Hair follicle immune privilege	Unknown	Important to prevent disease

Similarities	Vitiligo & Alopecia Areata
Primarily asymptomatic	Mild pruritus in minority
Histopathology	Infiltrate of CD8 ⁺ and CD4 ⁺ T cells characteristic
Immune mechanisms	Both innate and adaptive cell populations implicated
Cytokine response	T _H 1/IFN- γ dependent TNF- α present at low levels but TNF- α inhibitors ineffective as treatments
Shared genetic risk alleles	HLA, IL2RA, CTLA4
Coincidence without overlap	Patients with vitiligo at increased risk for alopecia areata and vice versa
Coincidence with lesional overlap	Case reports, pigmented hairs targeted in alopecia areata

UVB, ultraviolet B; PUVA, psoralen plus ultraviolet A.