

CORRESPONDENCE

Seven cases of vitiligo complicated by atopic dermatitis: suggestive new spectrum of autoimmune vitiligo

A recent report strongly suggests that genetic polymorphisms such as the *NALP1* gene are closely associated with generalized vitiligo, especially when complicated with autoimmune or auto-inflammatory diseases possibly related to aberrant innate immune responses to microorganisms [1]. However, the complication of atopic dermatitis (AD) with vitiligo vulgaris (VV) has rarely been reported [2, 3]. Therefore, we would like to present 7 patients with VV complicated by atopic dermatitis and evaluate the infiltration pattern of immunocompetent cells on the basis of the results of immunohistochemical staining.

The representative patient is a 27-year-old female who complained of multiple white-colored guttate macules on the whole body except the face (*figure 1A*). HE staining on the edge of vitiligo on Lt. cubital fossa showed mild acanthosis and irregular elongation of the rete ridge with perivascular inflammation mimicking chronic dermatitis. The leading edge clearly showed the borders of pigmented and depigmented sites (*figure 1B*). To compare the inflammation patterns among lesional, bound and peri-lesional skin, immunostaining for CD1a, CD8, merged CD4 and IL-17A, and Foxp3 (*figures 1C-D*) was performed. The number and size of CD1a⁺ Langerhans cells appeared to increase in vitiligo lesional and bound skin compared to perilesional skin. CD4⁺T cells had perivascular and interfibrous infiltration mainly on the upper dermis containing CD4⁺/IL-17A⁺ Th17 cells (*figure 1D*).

Vitiligo lesions of 7 combined patients were mainly located on the intertriginous areas such as the neck and cubital fossa, indicating the association with vitiligo and atopic eczema. The number of infiltrating immunocompetent cells was compared between vitiliginous and the surrounding non-vitiliginous lesions, in addition to those from VV and Sutton's nevus (SN) patients and normal individuals

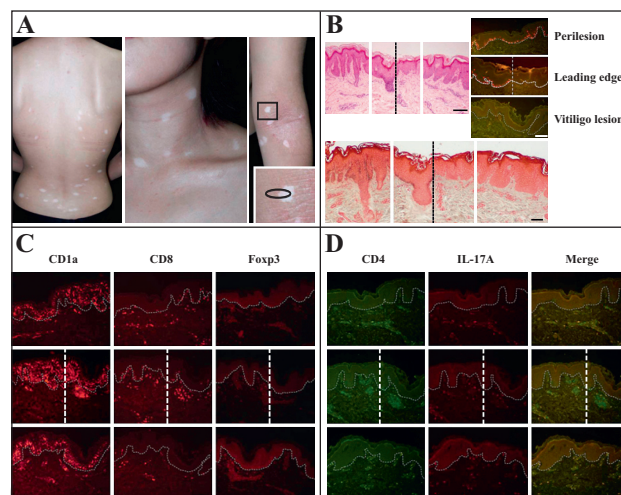


Figure 1. The clinical feature of a representative case.

A) Well-defined whitish macules, which were round-to-ovoid shaped and within 3 cm in diameter, were scattered on the whole body. The vitiligo lesions tended to be more obvious on the intertriginous area. **B)** **Histological findings.** HE showed perivascular inflammatory cell infiltration among vitiligo lesional, bounded, and non-lesional skin (upper left panel). Fontana-Masson staining clearly defined the border of melanosomal deposition (lower panel, center). Melan-A positive melanocytes are completely lacking on the vitiligo lesion (upper right panel). Bar indicates 100 μ m. **C)** Immunohistochemical staining for CD1a (left lane), CD8 (center lane), and Foxp3 (right lane) on each lesion. Bar indicates 100 μ m. **D)** Immunohistochemical staining for CD4 (left lane, green), IL-17A (center lane, red) on each lesion. Merged figures are placed on the right lane. Bar indicates 100 μ m. Upper, middle and lower panels in Figures 1C and 1D are perilesion, leading edge and vitiligo lesion, respectively.

(*table 1*). All of the disease cases examined were infiltrated by higher number of inflammatory cells compared to normal skins. In the combined cases, while the numbers

Table 1. The comparison of inflammatory cell numbers among each group. Mean cell numbers counted in 3 independent high power fields ($\times 100$) were represented.

	CD1a ⁺	CD8 ⁺	CD4 ⁺	CD4 ⁺ IL-17A ⁺	Foxp3 ⁺
Vitiligo lesion in the present cases (n=7)	34.2	88.0	42.5	30	35.1
AD lesion in the present cases (n=7)	19.2	54.4	61.1	22.3*	54.8*
VV (n=3)	15.7	134	41.2	20.5	69
SN (n=3)	30.9	102	29.1	22.6	22.1
Normal (n=3)	13.2	21	6.1	3.1	19.0

*: significant difference compared to that of normal skin analyzed by the Mann-Whitney test.

of CD1a+ Langerhans cells and CD8+ T cells were apparently higher in vitiligo lesions compared to the atopic lesions, the trend of Foxp3+ Treg cells number was the opposite. This is similar to vitiligo vulgaris and Sutton's nevus rather than atopic dermatitis. This result suggests that Th1 cell lineages may be predominant and activated in vitiligo lesions, even overlying atopic eczema. An increase in CD1a+ cell numbers and sizes in vitiligo lesions indicates a change in their distribution and activity in the process of depigmentation. CD4+IL-17A+ cells, considered as Th17 cells, infiltrated most densely in vitiligo lesions complicated with or without AD. Functional Th17 cells have been identified in autoimmune inflammatory skin disorders such as psoriasis and atopic dermatitis [4]. Th17 cells were infiltrated not only in the atopic skins but also in the vitiligo and VV skins and the numbers were slightly higher in vitiligo skin compared to AD and VV skins. We have reported the functional involvement of Th17 cells in the pathogenesis for auto-immune vitiligo (data in submission). Depigmentation in the vitiligo arising from atopic dermatitis may also be affected by Th17 cells in addition to cytotoxic T cells. Considering these results, anti-microbial immunity may somehow be more activated in the vitiligo lesion and sequentially trigger for preferential shifting to Th1 cells from a Th2-dominant condition.

To our knowledge, few cases have been reported presenting vitiligo complicated by atopic dermatitis [2, 3, 5], while Fregert *et al.* reported that vitiligo was seen more frequently in patients with atopic dermatitis [5]. Although it is not fully explained how vitiligo arises on atopic skin, the incidence of vitiligo in atopy seems to be higher than that of vitiligo with mutual antagonism in the same patients. ■

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