Discovery of resident memory T cells in inflammatory vitiligo
A case report

YanLi Xu, MMab, Bao-Xiang Zhang, MD, PhDab,*, Mao Lin, MD, Phdc, Lu Zhang, MMb

Abstract
Rationale: The purpose of this report was to describe resident memory cluster of differentiation 8 (CD8) + T cells may contribute to the progression of inflammatory vitiligo.

Patient concerns: A 32-year-old male has a stable vitiligo for 1 year, then some patches present inflammatory erythema. Two years later, the inflammatory patches enlarged and joined together, and the remaining 2 common patches showed repigmentation and no change respectively. Both CD69 + CD8 + T cells and CD103 + CD8 + T cells showed marked increase in inflammatory vitiligo than common vitiligo.

Diagnosis: Histological findings show that the numbers of lymphocytes are increased in inflammatory vitiligo than common vitiligo. Immunofluorescence staining show that the numbers of CD69 + CD8 + T cells demonstrated a marked increase in inflammatory vitiligo than common vitiligo.

Interventions: Without any intervention.

Outcomes: The previous upper 2 patches on the abdomen with erythematous rim were enlarged and joined together. However the lowest lesion with uninfamed common rim on the abdomen remained static, the one on the right groin showed spot-like repigmentation.

Lessons: This case report demonstrates that resident memory CD8 + T cells may contribute to the progression of inflammatory vitiligo.

Abbreviation: CD = cluster of differentiation, TRM = resident memory T cells.

Keywords: case report, CD8 positive T lymphocytes, inflammatory vitiligo, resident memory T cells, vitiligo

1. Introduction
Inflammatory vitiligo described as having a rim of raised erythema at the periphery of the depigmented patches is a rare subtype of vitiligo,[1] and the etiology is poorly understood. Resident memory cluster of differentiation 8 (CD8) + T cells may be active players in disease maintenance. However, there is no clear relationship between inflammatory vitiligo and resident memory CD8 + T cells. We report a case of a 32-year-old male has a stable vitiligo for 1 year, then some patches present inflammatory erythema. Two years later, the inflammatory patches enlarged and joined together, and the remaining 2 common patches shows repigmentation and no change respectively. Both CD69 + CD8 + T cells and CD103 + CD8 + T cells showed marked increase in inflammatory vitiligo than common vitiligo.

2. Case report
Two years ago, a 32-year-old Chinese male presented to our department of dermatology complaining of his white patches. Most patches remained unchanged for 1 year except 2 patches on the right abdomen which were enlarged and joined together. However the lowest lesion with uninfamed common rim on the abdomen remained static, the one on the right groin showed spot-like repigmentation.

The authors have no conflicts of interest to disclose.

This study was supported by the technological development project of medical and health of Shandong province (202004121432), scientific research and innovation fund of Yidu central hospital of Weifang (ydky20210509), national natural science foundation of China (81402601), Chongqing medical scientific research project (Joint project of Chongqing Health Commission and Science and Technology Bureau) (2022DBXM007).

The Ethics Committee of Yidu Central Hospital approved the publication of this case report, and participants provided informed consent for publication of this work.
rim were enlarged and joined together. However the lowest lesion with uninflamed common rim on the abdomen remained static, and notably, the one on the right groin showed spot-like repigmentation (Fig. 1c, d).

Both the biopsies revealed mild spongiosis, interface dermatitis, focal basal vacuolization and subtle perivascular lymphocytic infiltration. However the numbers of lymphocytes are increased in inflammatory vitiligo than common vitiligo (Fig. 2e, f). The numbers of CD69 + CD8 + T cells demonstrated a marked increase in inflammatory vitiligo than common vitiligo (Fig. 2g, h), so as to the numbers of CD103 + CD8 + T cells (Fig. 2i, j).

3. Discussion

Inflammatory lesions is one of characterized clinical markers of active vitiligo besides Koebner phenomenon, trichrome lesions, inflammatory lesions and confetti-like depigmentation, and the inflammatory response may occur in the early stage of vitiligo.[2] And the occurrence rates of this form of vitiligo can be estimated at 0.5% of all vitiligo cases.[3] Different patches may be increased in size, decreased in size or stayed the same in I vitiligo patient.[4] So inflammatory vitiligo may coexist with common vitiligo in clinical consequences, however the mechanism needs further study.

Figure 1. The white patches (a, b), and the changes two years later (c, d).

Figure 2. Histological findings from marginal lesion of inflammatory vitiligo (e) and common vitiligo (f), low magnification (hematoxylin and eosin, ×40); immunofluorescence staining (original magnification, ×200) (inflammatory vitiligo, common vitiligo) of CD69 + CD8 + T cells (g, h) and CD103 + CD8 + T cells (i, j). CD = cluster of differentiation.
Recently the resident memory T (TRM) cells in vitiligo, one of the current research interest, is at the emerging stage.\textsuperscript{5,6} TRM cells marked by the expression of surface markers CD69 and CD103 are responsible for the recurrence of many autoimmune diseases.\textsuperscript{11} CD69 is the hallmark to define TRM in tissues through downregulation of surface expression of sphingosine 1 phosphate receptor 1. CD103, aka \( \alpha E \) integrin, is another TRM marker.\textsuperscript{11} CD69 + CD103 + TRM and CD69 + CD103-TRM accumulate in the perilesional skin of vitiligo patients.\textsuperscript{9} Previous studies have shown CD8 + T cells are responsible for the destruction of melanocytes in vitiligo, and multiple groups identified CD8 + T cells possessing a TRM cell phenotype within vitiligo lesions.\textsuperscript{10} The proportion of CD69 + CD103 + CD8 + T cells accounted for 20% of CD8 + T cells in peripheral blood mononuclear cells, whereas 80% were found in the skin lesions of vitiligo.\textsuperscript{11} However, the expression of CD8 + TRM in inflammatory vitiligo has not been report. In this case, the numbers of both CD69 + CD8 + T cells and CD103 + CD8 + T cells are increased in the inflammatory vitiligo more than common vitiligo. Two years later, the patches of inflammatory vitiligo developed obviously. The results indicate that the CD8 + TRM cells in vitiligo may not be only related to relapse of vitiligo but also the progression of the disease. Under the stimulation of interleukin 15, the CD8 + TRM cells secrete perforin, granzyme-B and IFN-\( \gamma \), which may induce melanocyte apoptosis directly.\textsuperscript{12} On the other side, CD8 + TRM cells produce chemokines C-X-C motif ligand 9 and C-X-C motif ligand 10 which bind to C-X-C-Motif Receptor 3 on the surface of recirculating memory T (TRCM) cells for the recruitment of TRCM to the skin.\textsuperscript{8}

4. Conclusion
To our knowledge, this is the first report of an association between inflammatory vitiligo and CD8 + TRM cells. And it is interesting that there are 3 different outcomes in the neighboring three lesions in the same patient, however we had not an biopsy from the lesion on the right groin, this is an limitation of the paper. Further investigations are needed to unravel the underlying mechanism of TRM cells, which may be an effective therapeutic target.

Author contributions
Conceptualization: BaoXiang Zhang,
Data curation: Lu Zhang,
Writing – original draft: YanLi Xu,
Writing – review & editing: Mao Lin, BaoXiang Zhang.

References
[1] Gunasekera N, Murphy GF, Sheh VM. Repigmentation of extensive inflammatory vitiligo with raised borders using early and aggressive treatment. Dermatology. 2015;230:11–5.
[2] Bergqvist C, Ezzedine K. Vitiligo: a review. Dermatology. 2020;236:571–92.
[3] Le Poole IC, van den Wijngaard RM, Westerhof W, et al. Presence of T cells and macrophages in inflammatory vitiligo skin parallels melanocyte disappearance. Am J Pathol. 1996;148:1219–28.
[4] Webb KC, Lyon S, Nardone B, et al. Influence of pregnancy on vitiligo activity. J Clin Aesthet Dermatol. 2016;9:21–5.
[5] Shah F, Patel S, Begum R, et al. Emerging role of tissue resident memory T cells in vitiligo: from pathogenesis to therapeutics. Autoimmun Rev. 2021;20:102868.
[6] Riding RL, Harris JE. The role of memory CD8+ T cells in vitiligo. J Immunol. 2019;203:11–9.
[7] Willemsen M, Linkutė R, Luiten RM, et al. Skin-resident memory T cells as a potential new therapeutic target in vitiligo and melanoma. Pigment Cell Melanoma Res. 2019;32:612–22.
[8] Khalil S, Bardawil T, Kurban M, et al. Tissue-resident memory T cells in the skin. Inflamm Res. 2020;69:245–54.
[9] Boniface K, Jacquemin C, Darrigade AS, et al. Vitiligo skin is imprinted with resident memory CD8 T cells expressing CXCR3. J Invest Dermatol. 2018;138:355–64.
[10] Frisoli ML, Essien K, Harris JE. Vitiligo: mechanisms of pathogenesis and treatment. Annu Rev Immunol. 2020;38:621–48.
[11] Richmond JM, Strassner JP, Rashighi M, et al. Resident memory and recirculating memory T cells cooperate to maintain disease in a mouse model of vitiligo. J Invest Dermatol. 2019;139:769–78.
[12] Richmond JM, Strassner JP, Zapata L, Jr, et al. Antibody blockade of IL-15 signaling has the potential to durably reverse vitiligo. Sci Transl Med. 2018;10:eaam7710.