Halo naevi, vitiligo and diffuse alopecia areata associated with tocilizumab therapy

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Abstract
We present a follow-up case report of a 33-year-old lady with juvenile onset arthritis who developed halo naevi while on treatment with tocilizumab. This case report describes the development of halo naevi, vitiligo and diffuse alopecia areata associated with tocilizumab therapy following infection with Methicillin-resistant Staphylococcus aureus (MRSA) and Panton–Valentine leukocidin positivity. This is the first case that describes these events and supports previous theories on cellular and humoral immunity as causative factors. The regression of melanocytes during treatment with tocilizumab could also implicate IL-6 and sIL-6R as future targets in the treatment of melanoma through its direct effect of melanocytic cytotoxicity, which supports previous studies.

INTRODUCTION
We present a follow-up case report of a 33-year-old lady with juvenile onset arthritis who developed halo naevi at the site of every mole while on treatment with tocilizumab (Fig. 1) [1].

CASE REPORT
Twenty years following diagnosis of juvenile onset arthritis, our patient was commenced on tocilizumab 8 mg/kg fortnightly. She was taking no other medication other than lanzoprazole and ibuprofen as required. Three years later, she went on to develop recurrent abscesses in her axilla requiring incision and drainage. Swabs confirmed Methicillin-resistant Staphylococcus aureus (MRSA) and Panton–Valentine leukocidin (PVL) positivity. Tocilizumab was withheld briefly, and the patient received phototherapy but failed to respond. Tocilizumab was restarted for disease control, and the patient went on to develop patches of vitiligo on her torso. Therefore, tocilizumab was discontinued and treatment switched to abatacept. On discontinuing tocilizumab, there was no further progression of depigmentation. Having failed abatacept (infusion reaction) and later certolizumab (primary non-response), tocilizumab was restarted 18 months later. While awaiting to restart tocilizumab, the patient was commenced on oral prednisolone, which was weaned down with regain of disease control. After 6 months of therapy, the patient reported loss of her eye lashes, eye brows and hair loss. A diagnosis of diffuse alopecia areata was made following dermatology review.

DISCUSSION
IL-6 is a pleiotropic cytokine that regulates the immune response. It is involved in autoimmunity by altering the balance between any underlying malignant melanoma. A skin biopsy was carried out, which demonstrated a benign intradermal naevus. Tocilizumab was withheld briefly, and the patient received phototherapy but failed to respond. Tocilizumab was restarted for disease control, and the patient went on to develop patches of vitiligo on her torso. Therefore, tocilizumab was discontinued and treatment switched to abatacept. On discontinuing tocilizumab, there was no further progression of depigmentation. Having failed abatacept (infusion reaction) and later certolizumab (primary non-response), tocilizumab was restarted 18 months later. While awaiting to restart tocilizumab, the patient was commenced on oral prednisolone, which was weaned down with regain of disease control. After 6 months of therapy, the patient reported loss of her eye lashes, eye brows and hair loss. A diagnosis of diffuse alopecia areata was made following dermatology review.
Th17 cells and Treg [2]. IL-6 is also involved in local inflammation leading to joint destruction and is thought to mediate many of the systemic inflammatory signs and symptoms related to rheumatoid arthritis. It exerts its biological activities via an IL-6-specific receptor and a signal transducer, gp130. The receptor exists in two forms: a transmembrane form and a soluble form (sIL-6R). Under physiological conditions, IL-6 is thought to act in a paracrine fashion. If IL-6 levels exceed the levels of sIL-6R and gp130, IL-6 can act systemically [3].

Tocilizumab is a humanized anti-IL6 receptor monoclonal antibody that blocks transmembrane as well as sIL-6R. This case was originally reported by Kuet and Goodfield [1] and is the first to describe halo naevi with tocilizumab therapy. This follow-up case report is the first case to describe the development of vitiligo and diffuse alopecia areata secondary to tocilizumab therapy.

Halo naevi are common benign skin lesions that represent melanocytic naevi in which an inflammatory infiltrate develops, resulting in a zone of depigmentation surrounding the naevus. The aetiology is unknown, although halo naevi are thought to share a similar autoimmune pathway to vitiligo.

Diffuse alopecia areata is a variant characterized by inflammatory-induced hair loss over a large scalp area without bald patches and has an unclear aetiology. Studies suggest that the autoimmune target may be related to the melanin pigment system and/or melanocytes.

The exact immune process involved in the destruction of melanocytes during the development of vitiligo is yet to be determined, although there is strong evidence of cellular immunity involvement and the role of IL-6.

IL-6 concentrations have been found to be significantly higher in patients with vitiligo [4], and IL-6 can induce the expression of ICAM-1 on melanocytes, thereby facilitating leucocyte–melanocyte attachment and immunological cytotoxicity. IL-6 also causes an imbalance of T regs and Th17, and this dysregulation may also contribute to the pathogenesis of vitiligo.

Tocilizumab therapy blocks IL-6R, thereby inhibiting the consumption of IL-6 by normal receptors, leading to an increase in serum IL-6 [5]. This increase in IL-6 could therefore act systemically and have a direct effect on melanocytes or cause a further imbalance of T regs and Th17 leading to vitiligo.

The role of IL-6 in alopecia areata is less well documented, although higher levels have been found in patchy alopecia areata [6]. There have been case reports of diffuse alopecia areata occurring following anti-TNF therapy and chemotherapy, and the pathogenesis is likely to involve a T-cell autoimmune-mediated process triggered by endogenous or exogenous stimuli that sustains an inflammatory reaction that leads to hair loss.

Cross-reacting antigens from infecting organisms may be implicated in vitiligo, and our patient only developed depigmentation on resuming treatment following infection with MRSA with PVL positivity. This infection may have been significant in the development of halo naevi, vitiligo and alopecia areata in combination with the cytokine disturbances created by tocilizumab.

This case report provides insights into the pathogenesis of halo naevi, vitiligo and diffuse alopecia areata and supports previous theories on cellular and humoral immunity as causative factors.

The regression of melanocytes during treatment with tocilizumab provides evidence for IL-6 and sIL-6R as future targets in the treatment of melanoma through its direct effect of melanocytic cytotoxicity supporting previous studies [7, 8].

CONFLICT OF INTEREST STATEMENT
None declared.

FUNDING
No sources of funding.

ETHICAL APPROVAL
No ethical approval required.

CONSENT
Informed patient consent.

GUARANTOR
K.N. is the guarantor of this article.

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