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Alemtuzumab-induced halo nevus-like hypopigmentation – New insights into secondary skin autoimmunity in response to an immune cell-depleting antibody

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Alemtuzumab is an antibody directed against the Cluster of Differentiation (CD)52. It depletes B and T lymphocytes and is approved for treatment of active relapsing-remitting multiple sclerosis (RRMS). Secondary autoimmunity is an important risk of alemtuzumab-treated patients and can affect different organs. 41% of patients develop autoimmune thyroid disease[2]. Skin autoimmunity under alemtuzumab has but reported only in the neurological literature[3,4].

We describe a 33-year-old male patient who developed hypopigmentation around his melanocytic nevi with disappearance of the nevi in August 2018. In June 2016 he had been diagnosed with highly active RRMS and treated with alemtuzumab in September 2016 for the first time. In September 2017 another cycle of alemtuzumab was administered. The patient´s family history for vitiligo was unremarkable and he had no autoimmune thyroid disease. At time of the occurrence of the hypopigmented spots the number of his circulating leukocytes in the blood was normal. Upon examination he showed sharply demarcated hypopigmented spots around his melanocytic nevi (Fig. 1A). Some of the nevi within the white spots had already disappeared. There were no other signs of skin hypopigmentation. A biopsy specimen from one of the halo-like nevi (insert of Fig. 1A) revealed absence of epidermal melanocytes (Fig. 1B) which was confirmed by immunohistochemistry with an anti-Pan Mel antibody (Fig. 1C). In contrast, melanocytes were detected within the nevus (Fig. 1C). Immunostaining with an anti-CD3 antibody disclosed a sparsely scattered infiltrate of T lymphocytes within the upper dermis (Fig. 1D, E). To shed light into the pathogenesis of the halo nevus-like lesions we wondered whether alemtuzumab might directly attack epidermal melanocytes. CD52 immunohistochemistry of normal skin and a melanocytic nevus from a healthy person did not show immunoreactivity in melanocytes in contrast to lymphoid tissues used as positive control (data not shown).

Since autoimmune thyroid disease is characterized by circulating anti-thyroid antibodies, we hypothesized whether anti-melanocyte antibodies may be generated following alemtuzumab treatment. In patients with non-segmental vitiligo (NSV) antibodies against tyrosinase (TYR), the key enzyme of melanin synthesis, were also detected[5]. Therefore, a TnT® T7-Coupled Reticulocyte Lysate System (Promega, Southampton, UK) was used to produce various [^{35}S]-labelled melanocyte antigens *in vitro* from the translation of cDNA in the appropriate plasmid. Serum samples of the patient before and after alemtuzumab therapy were then analysed for circulating antibodies against these antigens by radioligand binding assays[5]. An almost 6-fold increase in anti-TYR antibodies and a ~3-fold increase in antibodies against TYR-related protein 1 were detected following alemtuzumab (Table 1). In contrast, anti-thyroid antibodies were not detected throughout the patient´s history. In accordance with this TSH levels were always normal.

Our findings are puzzling as alemtuzumab depletes both B and T cells but still evokes an autoimmune attack against melanocytes. Recently, three patients with RRMS have been described who developed NSV 14, 18 and 52 months after initiation of alemtuzumab[6]. The immune-mediated destruction pathways of melanocytes in classic halo nevus and NSV may be different[7]. It has been suggested that secondary autoimmunity induced by alemtuzumab is related to proliferation of chronically activated, oligoclonal, effector memory CD8+ T cells[8]. Interestingly, resident and effector memory T cells have been identified in non-active skin of patients with NSV[9]. Previous studies showed that alemtuzumab depletes all T cells from the blood but does not deplete skin-resident memory T cells[10]. Thus, production of anti-melanocyte-specific antibodies may be secondary to initial destruction of melanocytes by melanocyte-specific CD8+ T cells.

In summary, alemtuzumab-induced skin autoimmunity is a condition a dermatologist should be aware of. Our report underscores the complex pathogenesis of immune-mediated destruction of epidermal melanocytes that may follow even upon depletion of both T and B cells.

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The patient in this manuscript has given written informed consent to the publication of his case details.

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Figure 1

(A) Clinical appearance of the posterior trunk of the patient. The insert depicts the halo-like nevus from which the biopsy was taken; (B) Haematoxylin & eosin staining and (C) Pan Mel immunohistochemistry of the lesion (as shown in insert of Fig 1A). Note the absence of epidermal melanocytes; (D, E) CD3 immunostaining of the lesion. Note scattered T cells adjacent to the dermal melanocytes (D) and along the dermal-epidermal junction devoid of melanocytes (E).

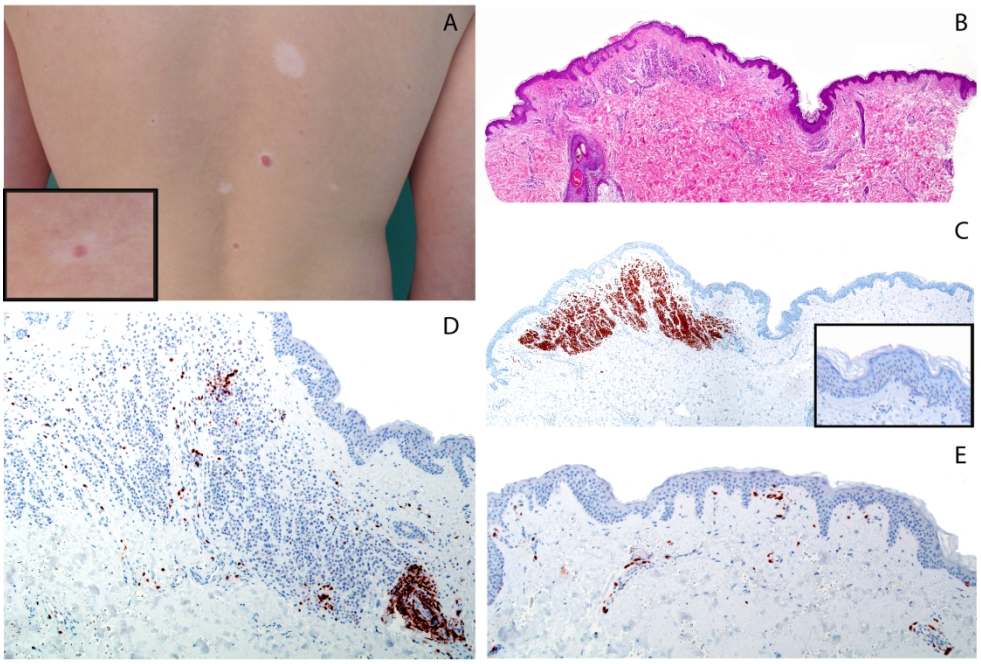
Table 1: Presence of circulating anti-melanocyte antibodies in the patient's serum before (Sept/2016) and after initiation of alemtuzumab (Aug/2018 and Feb/2019).

Antigen used in radioligand binding assay[1]	Before treatment antibody index[2]	After[2] treatment antibody index[2]	After[2] treatment antibody index[2]	Upper limit of normal for radioligand binding assay[3]
LMNA	1.23	1.09	1.15	1.59
TYR	**2.23**	**12.89**	**13.12**	1.72
TYRP1	1.25	**3.04**	**3.89**	1.57
DCT	0.95	0.99	1.03	1.36
PMEL	1.14	1.26	1.19	1.45
TH	1.09	1.12	1.15	1.84
MCHR1	0.95	0.94	0.98	1.48

[1]Radioligand binding assays (RLBA) were used to test for antibodies against LMNA, laminA, TYR, tyrosinase; TYRP1, TYR-related protein 1; DCT, dopachrome tautomerase; PMEL, premelanosome protein; TH, tyrosine hydroxylase; and MCHR1, melanin-concentrating hormone receptor 1.

[2]An antibody index for the patient's serum was calculated for each RLBA as: counts per min (cpm) immunoprecipitated by serum/mean cpm immunoprecipitated by 20 healthy control sera. Positive antibody indices are in bold.

[3]The upper limit of normal for the RLBAs was calculated using the mean antibody index + 3 SD of the population of 20 healthy control sera.



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