Alopecia Areata, triggered by psychological stress and successfully treated with a Janus kinase inhibitor. Case report

Alopecia Areata, desencadenada por estrés psicológico y tratada con éxito con un inhibidor de las Janus quinasas. Reporte de un caso

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Abstract

Alopecia areata is an autoimmune disease that causes a non-healing form of hair loss. Stress is one of the crucial factors, which contributes to its development as it increases the corticotropin releasing hormone, creating an inflammatory environment and the immune privilege loss around the hair follicle. Case report: A 37-year-old woman with a history of alopecia areata, who presents progressive hair loss after a twin pregnancy announcement, which triggers a considerable level of psychological stress. The physical examination shows absence of hair on the entire body surface. Once lactation ended, treatment with topical corticosteroids and tofacitinib (janus kinase inhibitor) was started, resulting in hair recovery. Within the environmental factors that contribute to the development of alopecia areata, stress is one of the most important ones. Therefore, knowing about its physiopathology allows for the understanding of how stress triggers some autoimmune diseases, as well as why novel therapies including janus-kinase inhibitors are useful for treating them.

Keywords: Alopecia areata; Psychologic stress; Autoimmune disease; Corticotropin-releasing hormone; Tofacitinib.

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Resumen

La alopecia areata es una enfermedad autoinmune que genera la caída del pelo de forma no-cicatrizante. El estrés psicológico es uno de los factores que pueden contribuir en su etiopatogenia al incrementar las concentraciones de la hormona liberadora de corticotropina, la cual genera un ambiente altamente inflamatorio y la pérdida del privilegio inmune alrededor del folículo piloso. Presentación del caso: Mujer de 37 años con antecedente de alopecia areata, quien presenta pérdida progresiva del pelo después del anuncio de un embarazo gemelar, el cual le desencadena un nivel de estrés psicológico considerable. El examen físico evidencia ausencia de pelo en toda la superficie corporal. Terminada la lactancia, se inicia manejo con corticoides tópicos y tofacitinib (inhibidor de las janus kinasa) con el cual consigue recuperar el pelo capilar y corporal. Dentro de los factores medioambientales, que pueden contribuir al desarrollo de Alopecia Areata, el estrés es uno de los más importantes. Por ende, conocer la fisiopatología del estrés permite entender cómo este factor ambiental dispara la aparición de enfermedades autoinmunes y por qué terapias como los inhibidores de las janus kinasas son útiles en su tratamiento.

Palabras clave: Alopecia areata; Estrés psicológico; Enfermedades autoinmunes; Hormona liberadora de Corticotropina.

Introduction

Alopecia areata is an autoimmune disease that affects the normal development of the hair follicle resulting in hair loss, it also corresponds to a 0.7 to 3.8% of dermatological examination findings and affects 0.1 to 0.2% of the world population, without sexual dichotomy. According to the affected body areas, it is classified as: *totalis, universalis, sisaipho, incognita, patchy, ophiasis and Marie Antoinette type*[1,2]; in this article, a case report of alopecia areata universalis is going to be addressed.

Under physiological conditions, the hair follicle has an immune privilege, characterized by a low expression of major histocompatibility complex and high expression of guardian molecules such as: transforming growth factor β and α-melanocyte stimulating hormone. On the other hand, under stress conditions there is an increase in the releasing of corticotropin-releasing hormone, reactive oxygen species and interferon gamma, which promote an inflammatory environment around the peribulbar region[3].

Genetic susceptibilities and epigenetic dynamics may also produce the loss of the immune privilege in the hair follicle, triggering immunoreactive responses against self-proteins. Moreover, an infiltration of mastocytes, Langerhans cells and T cells (mainly natural killer group 2 member D+ cluster of differentiation 8+ T cells) is described in skin biopsies of patients with alopecia areata[4]. It is worth to mention that due to the response against immunoreactive self-proteins, cytotoxic T cells have been established as the most important effectors in this disease, favoring a proinflammatory state[5].

This article presents the case of a patient with alopecia areata whom suffers from chronic stress after the announcement of a twin pregnancy and developed total hair loss. A close relation between alopecia areata and chronic stress can be inferred from the clinical manifestations and the exhaustive anamnesis. After eight months of treatment with tofacitinib, a biological anti-inflammatory medicament, the patient has efficiently recovered a great percentage of her hair.

Case report

The 37-year-old woman from Bogotá, D.C.- Colombia, who consulted after accelerated hair loss due to the announcement of a twin pregnancy. The hair loss was characterized by progressive scalp, eyelashes and pubic hair which started at the eighth week of gestation and progressed to complete hair loss at 28th week of pregnancy.

The patient was diagnosed with diffuse alopecia areata, after the birth of her younger brother, at the age of four. Later in adolescence, she developed depression and an associated eating disorder, which were addressed allowing her to become pregnant twice (G2P2C1V3). In the first pregnancy, she did not experience hair loss. In the second, the announcement of a twin pregnancy caused chronic stress that triggered alopecia in the first trimester of gestation. During the second pregnancy, the patient was admitted to the hospital twice: the first time was due to hyperemesis gravidarum, which generated inadequate weight gain during this period, and was successfully resolved with a continued management of oral antiemetics, gastric protectors, and multivitamins; the second time was because of preterm delivery risk.

However, she had a successful cesarean section after 32 weeks of gestation followed by a 6-month lactation period. Once it was over, the corresponding indagations of etiologies associated with hair loss were carried out showing the subsequent results.

Physical examination revealed the absence of hair on the entire body surface (**Figura 1a**) and a Body Mass Index of 15.1. The most relevant laboratory results showed an elevated globular sedimentation rate of 19 mm / hour indicating inflammation and an exacerbated immune response. On the other hand, normal thyroid-stimulating hormone (1.60 mcU / mL) and anti-thyroid peroxidase (16.95 mcU / mL) levels were observed which ruled out thyroid abnormalities (Hashimoto thyroiditis).

Following the suspicion of autoimmune diseases, several tests were performed: anti-DNAs, antinuclear antibodies, immunoglobulin A (316 mg / dL) and immunoglobulin G (1502 mg / dL) were normal, dismissing systemic pathologies (Amyloidosis and Lupus Erythematosus). Nonetheless, a polyclonal gamma (immunoglobulin M) and alpha-1 hyperglobulinemia proteins were evident, indicating a chronic inflammation state. Finally, to discard etiologies associated with the hypothalamic-pituitary-adrenal axis and to check on her nutritional status, early morning cortisol (11.13 ug / dl) and vitamin D (37 ng / ml) were tested and found normal.

Although clinical and laboratory results discarded different systemic diseases **Tabla 1**; an exhaustive anamnesis that evaluated psychological factors was needed to get a final diagnosis: Alopecia areata induced by chronic stress after a twin pregnancy announcement. Therefore, once breastfeeding was over, treatment with topical corticosteroids and tofacitinib began, resulting in a progressive recovery of eyebrows, eyelashes, and scalp hair after eight months **Figura 1b.**

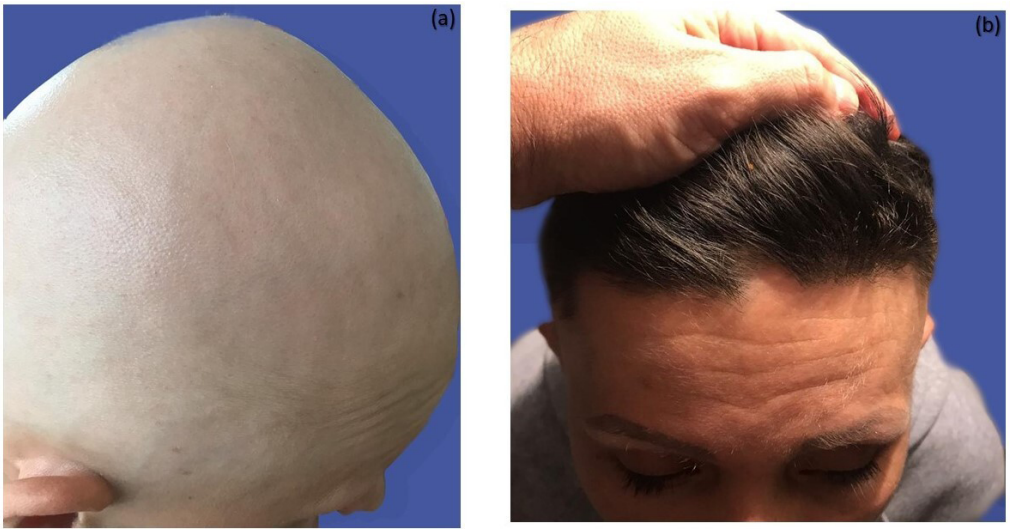

Figure 1. (a) Total hair loss in AA patient before treatment with tofacitinib, notice the absence of eyelashes. (b) Progressive hair recovery especially eyelashes and eyebrows, after 8 months of tofacitinib treatment.

Table 1. Laboratory results.

Test	Result	Normal value	Interpretation
Erythrocyte sedimentation rate	19 mm/hour	0-29 mm/hour	Normal
Thyroid-stimulating hormone	1.60 mcU/mL	0.5-5 mcU/mL	Normal
Thyroid peroxidase antibody levels	16.95 mcU/mL		Normal
Early morning cortisol	11.13 ug/dL	10-20 ug/dL	Normal
Vitamin D	37 ng/mL	20-40 ug/mL	Normal
Anti-DNAs and antinuclear antibodies	Negative		Normal
Immunoglobulin A	316 mg/dL	40-350 mg/dL	Normal
Immunoglobulin G	1502 mg/dL	650-1600 mg/dL	Normal
Immunoglobulin M	283 mg/dL	54-300 mg/dL	Normal
Gamma protein	Elevated		Abnormal
Alpha-1 protein	Elevated		Abnormal

Discussion

Alopecia areata is an autoimmune disease characterized by a transient hair loss and associated with nonscarring hair follicle conservation. This pathology has a 2.1% incidence risk and generally presents a first symptomatologic picture before the age of 20[6,7].

After a literature review[8-10], the analysis of the multiple clinical manifestations and laboratory findings in this case, it is concluded that this patient developed alopecia areata associated with a complicated multifactorial pathogenesis where stress, after the announcement of a twin pregnancy, lead to the loss of the immune privilege and the consequent hair loss in this patient.

Stress is defined as an adaptive reaction towards a certain stimulus, which induces hormonal changes to maintain homeostasis and improve survival probability[11]. During the stress response, different molecules are produced with the subsequent activation of neurobiological circuits in the central nervous system and trigger the release of neurotransmitters and hormones[12]. This process occurs in the paraventricular nucleus of the hypothalamus and the locus coeruleus, the regulatory centers of stress; where the corticotropin-releasing hormone and norepinephrine are respectively synthesized[13].

The paraventricular nucleus of the hypothalamus integrates information from stressful stimuli, circadian cycle, and central nervous system, leading to the activation of the hypothalamic-pituitary-adrenal axis causing corticotropin-releasing hormone production[14]. This hormone is transported by the hypophyseal portal system to the adenohypophysis, where it induces the synthesis of adrenocorticotropic hormone. Later, the adrenocorticotropic hormone travels in the bloodstream up to the adrenal gland, where it promotes glucocorticoids synthesis[15].

Under normal conditions, the hypothalamic-pituitary-adrenal axis function is regulated by the steroidogenic circadian rhythm and through negative feedback mechanisms, mainly constituted of glucocorticoids, that act on their hypothalamic and pituitary receptors[16].

Under chronic stress conditions, body homeostasis is altered, producing a downregulation of corticotropin-releasing hormone receptor 1 expression, therefore an upregulation of corticotropin-releasing hormone secretion occurs. These changes are associated with a decrease of glucocorticoid receptors in the paraventricular nucleus of the hypothalamus and the consequent impairment of their negative feedback function[17].

Thus, literature reports describe the existence of a hypothalamic-pituitary-adrenal axis in the skin, due to the presence of corticotropin-releasing hormone, proopiomelanocortin and corticosterone in pilosebaceous units as well as in the epidermis[18]. This peripheral augmentation of corticotropin release hormone in patients diagnosed with alopecia areata, triggers the activation of mastocyte corticotropin-releasing hormone 2β receptor, and therefore stimulates their recruitment and degranulation all around the peribulbar region of the hair follicle[19]. This process releases histamine, tumoral necrosis factor α and proinflammatory cytokines, especially interleukin 1[20]. **Figura 2a**.

Furthermore, local inflammation caused by mastocyte degranulation enhances the release of substance P, which acts as a growth factor in normal conditions. Murine models of alopecia areata have revealed that a significant increase of substance P produces local vasodilation, chemokines and cytokines secretion that will enhance immune cells recruitment and the establishment of an inflammatory loop[21]. Besides, Substance P stimulates neurokinin 1 receptor in macrophage and cluster of differentiation 8+ T cells, increasing the cytotoxicity of these cells, thus producing a positive feedback loop of the inflammatory response[22].

Highly inflammatory environments produced by corticotropin-releasing hormone trigger a succession of events that decrease the immune privilege "guardians" (transforming growth factor β and α-melanocyte stimulating hormone); this causes an upregulation of the keratinocyte antigen presentation mediated by major histocompatibility complex and major histocompatibility complex class I-related chain A, allowing the immune cells, specially natural killer group 2 member D+ cluster of differentiation 8+ T cells, to react against the hair follicle proteins[23]. These T cells secrete cytokines, specifically interleukin-15 and interferon gamma (IFNγ), that act through Janus kinase pathways to activate immune cell proliferation, producing an upregulation of major histocompatibility complex class I respectively[24] (**Figura 2b**).

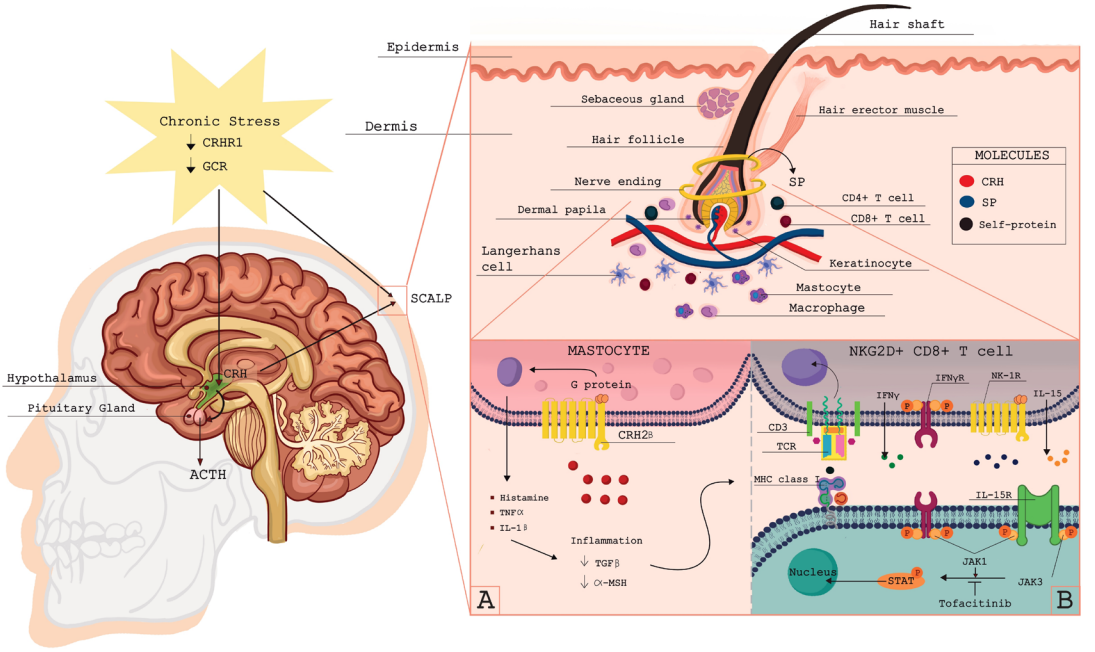

Figure 2. Physiopathology of alopecia areata induced by chronic stress Chronic stress induces corticotropin-releasing hormone (CRH) secretion by hypothalamus, which will promote an upregulation of adrenocorticotropic hormone (ACTH), as well as the downregulation of corticotropin-releasing hormone receptor 1 (CRHR1) and glucocorticoid receptor (GCR). As shown in section 2A, corticotropin-releasing hormone (CRH) activates corticotropin-releasing hormone receptor 2 beta (CRH2β) in mastocytes causing their degranulation to liberate histamine, tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β), enhancing an inflammatory response and a reduction of immunosuppressors molecules (transcription grow factor beta TGFβ and alpha-melanocyte stimulating hormone (αMSH)). Meanwhile in section 2B, substance P (SP) activates neurokinin 1 receptor (NK-1R) in cluster of differentiation 8 positive (CD8+) T cells to promote the inflammatory environment, causing an upregulation of major histocompatibility complex class I (MHCI) expression on follicle cells. This autoimmune response secretes interferon gamma (IFN-γ) and interleukin 15 (IL-15), which signalize via Janus kinase (inhibited by tofacitinib) for promoting the major histocompatibility complex class I (MHCI) expression that creates an inflammatory loop.

Nowadays, the patient is being treated with tofacitinib, a novel drug that was first used in 2014[25]. This medicine is an inhibitor of Janus kinase-1 and 3, that attenuates the activation signals produced by interleukin-15 in immune cells, and in consequence, it suppresses the exacerbated response against the hair follicle[26] **Figura 2b**. Since then, the patient has presented satisfactory hair recovery without adverse effects after 8 months under treatment (**Figura 3**); therefore, tofacitinib can be suggested as an effective option for alopecia areata patients.

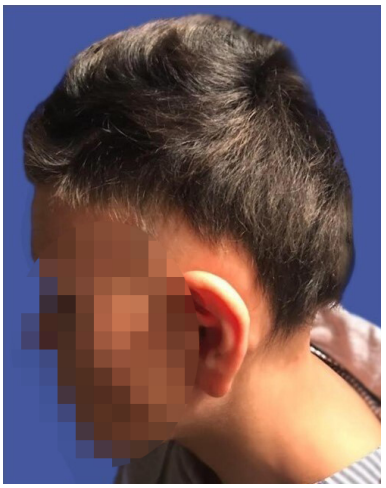

Figure 3. Total hair recovery excepting in temporal regions, after 8 months of tofacitinib treatment

Conclusion

Currently, the mechanisms by which alopecia areata is developed are not totally understood; however, this case, as well as some other articles found in the literature, suggest that stress could play a key role in alopecia areata etiology. In consequence, we recommend that psychological and environmental factors, which may participate in the onset of autoimmune diseases, should be considered in the anamnesis. Therefore, we encourage the performance of new investigations, from different fields of knowledge, aimed to clarify the alopecia areata physiopathology and its relationship with chronic stress. All these efforts are worthy since they will establish the basis of future medicaments, such as tofacitinib, which may aid the patient´s moral, physical and social integrity that is affected in most alopecia areata cases due to the lack of hair and the beauty paradigms.

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Conflicts of interest

The authors report that there are no financial conflicts of interest to disclose.

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