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REVIEW

Update on Frontal Fibrosing Alopecia☆

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KEYWORDS
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Update

Abstract Frontal fibrosing alopecia (FFA) is an increasingly common acquired primary scarring alopecia, first described by Kossard in 1994. Clinically it is characterized by frontotemporal hairline recession, frequently accompanied by eyebrow loss. FFA was initially thought to have a hormonal origin as it was first described in postmenopausal women and premenopausal women with a history of hysterectomy or early menopause. This origin, however, has been questioned in recent years due to the publication of cases in men and premenopausal women. Although FFA has a highly characteristic clincal pattern, it is histologically similar to lichen planopilaris, and is currently believed to be a clinical variant of this condition. No clinical trials to date have investigated the efficacy of treatments for FFA. Numerous drugs, however, have been assessed in observational studies, and the best results to date have been reported for 5-αreductase inhibitors and intralesional corticosteroids, followed by antimalarials and calcineurin inhibitors. In this article, we review the latest data on the etiology, pathogenesis, clinical presentation, diagnosis, and treatment of FFA.

PALABRAS CLAVE
Alopecia frontal fibrosante;
Liquen plano pilaris;
Actualización

Actualización en alopecia frontal fibrosante

Resumen La alopecia frontal fibrosante (AFF) es un tipo de alopecia cicatricial primaria adquirida, descrita por Kossard en 1994, cuya incidencia ha aumentado en los últimos años. Se caracteriza clínicamente por una recesión de la línea de implantación frontotemporal del cabello, acompañada frecuentemente por alopecia de las cejas. La AFF fue inicialmente descrita en mujeres posmenopáusicas y premenopáusicas con antecedentes personales de histerectomía o menopausia precoz, por lo que se propuso un origen hormonal de la enfermedad. Sin embargo, en los últimos años se han publicado estudios en varones, así como en mujeres premenopáusicas que cuestionan dicha etiología. A pesar de que las manifestaciones clínicas de la AFF son muy características, desde el punto de vista histopatológico los hallazgos son similares al liquen plano pilaris, por lo que actualmente es considerada como una variante clínica

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de este último. Hasta el momento no se han realizado ensayos clínicos sobre las diferentes alternativas de tratamiento en pacientes con AFF. En los estudios observacionales publicados se valora el uso de múltiples fármacos, siendo los inhibidores de la 5-alfa-reductasa y los corticoides intralesionales los que mejor resultado han obtenido hasta el momento, seguidos por los antipalúdicos y los inhibidores de la calcineurina. Esta revisión analiza de forma exhaustiva la información más recientemente publicada sobre la etiopatogenia, la clínica, el diagnóstico y el tratamiento de los pacientes con AFF.

Introduction

Frontal fibrosing alopecia (FFA) is an increasingly common acquired primary cicatricial alopecia,[1] first described by Kossard in 1994.[2] Clinically, it is characterized by frontotemporal hairline recession, frequently accompanied by eyebrow loss.[2,3] As this is a cicatricial alopecia, hair loss is irreversible, with a major impact on the confidence and quality of life of the affected patients.[4] Although the clinical manifestations of FFA are very characteristic, the histopathological findings are identical to those observed with lichen planopilaris (LPP),[3] and so some authors consider FFA as a variation of LPP.[1]

Pathogenesis

FFA mainly affects postmenopausal women with a mean age of 60 years, although it has also been reported in men[5–10] and premenopausal women.[8–14] Indeed, the youngest woman reported to have the condition was 23 years old.[10] Despite the notable increase in incidence since it was first described,[2] the etiology of FFA is still unknown. The role of sex hormones in the development of FFA has been proposed by several authors. These chemicals are thought to act by inducing a decrease in hair growth resulting from stimulation of the transition of hair follicles from anagen to telogen.[15,16] Subsequent studies have supported this hypothesis in that a favorable response has been obtained with the use of antiandrogen drugs in patients with this disease.[10,11,16–18] Furthermore, among patients with FFA, there is a high proportion of patients with early menopause (14% versus 6% in the general population),[10] hysterectomy patients (11%-21%),[10,12,14] associated androgenetic alopecia (AGA) (40% in some series),[10,15] and oophorectomy (although no consistent association has been demonstrated to date).[19] However, studies published in men and in premenopausal women have brought into question this hormone theory. Of note, the pathogenic mechanism for AGA and FFA differs (miniaturization versus inflammation and fibrosis).[20] It has also been demonstrated that hormone replacement therapy does not prevent or slow disease progression[3] and hormone studies in patients with FFA have confirmed that androgens are not elevated and other hormone imbalances are not present in peripheral blood.[3,19]

The association of FFA with autoimmune diseases such as hypothyroidism (11%-23% of patients with FFA versus 4.2% in the general population),[9,10,12,13] vitiligo,[21] or Sjörgren syndrome[13] may point an autoimmune origin. In the case of LPP, good response to corticosteroid therapy, presence of antibodies in some cases, and the influence of certain drugs in the presentation of epitopes in the hair follicles to the immune system have been reported. However, FFA differs from LPP in this point, as no specific antibodies have been detected with sufficient titer in these patients, and to date, there is no evidence in the literature to support the autoimmune origin of the disease.[22]

Likewise, it has not been possible to demonstrate a genetic component in the pathogenesis of FFA, although a family association has been suggested by some series, with a reported family history in approximately 8% of the patients.[9,10,21,23] A recent study of 4 families affected by the disease with 8 cases in mother and daughter with FFA found that all mothers had postmenopausal FFA and all daughters had developed the disease before menopause, suggesting that family history could be associated with an earlier presentation of the disease.[24]

Finally, although reports have been published of isolated cases of FFA associated with surgical procedures such as hair transplantation or face lifts, in which an immune response secondary to a Koebner process was postulated as a possible etiologic factor, the number of patients is still too small to establish a consistent relationship.[3,14,25,26]

The pathogenesis of FFA, like its etiology, is still unclear. There would appear to be a set of multiple processes that trigger and lead to disease progression. Laboratory experiments in mice have shown that FFA reversibility depends exclusively on damage to epithelial stem cells in the hair follicles.[27] Notable, the highest density of inflammatory infiltrate is observed around these cells. In addition, decreased expression of cytokeratin 15, a marker of epithelial stem cells in hair follicles, has been observed in FFA biopsies.[28,29] Epithelial stem cells are located in the region of the hair follicle known as the bulge. This region constitutes a niche with immune privilege,[4,22,28,30,31] as it is surrounded by T lymphocytes, Langerhans cells, macrophages, and antimicrobial peptides such as β-2-defensin, psoriasin, cathelicidin, and RNAase 7, which block the passage of toxic external agents.[32] The above processes, along with local immunosuppression induced by the absence of major histocompatibility complex (MHC) class I and II molecules and β-2-microglobulin in stem cells[4,33] and by secretion of endogenous immunosuppressants such as transforming growth factor β, melanocyte-stimulating hormone α, and cortisol,[31,33,34] impede excessive inflammation that may damage stem cells in the hair follicles. Along these lines, Harries et al.[35] demonstrated an increase in MHC class I and II molecules, β-2-microglobulin, and interferon γ in