

## Alopecia Areata Associated with Adalimumab Administration

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### Abstract

It is not widely appreciated that the administration of TNF- $\alpha$  blockers can be associated with the development of alopecia areata. We report herein a dramatic case of severe alopecia areata which arose in conjunction with adalimumab administration. There were no other obvious etiologic factors. Notably, the hair loss developed rather rapidly and was recalcitrant to standard therapy. Prior reported cases of this phenomenon strongly suggest that the association is more than fortuitous and, thus, should be mentioned specifically as part of the informed consent discussion before initiation of TNF- $\alpha$  blocker therapy. A previous episode of either alopecia areata or another presumably immune-mediated disorder (such as vitiligo) may indicate an increased risk for this devastating side effect. Neither age and gender, nor the underlying disease state warranting TNF- $\alpha$  blockade, seem to be predisposing. Best practice therapy for alopecia areata in this situation remains uncertain, and hair regrowth may occur with either cessation or continuation of TNF- $\alpha$  antagonist therapy.

### Keywords

Alopecia areata; Hair loss; Adalimumab; TNF- $\alpha$  blockers

### Abbreviations

Tumor necrosis factor- $\alpha$ : TNF- $\alpha$ ; AA: Alopecia areata

### Introduction

Hair loss, most often classic alopecia areata (AA), has been associated with administration of the major tumor necrosis alpha (TNF- $\alpha$ ) blocking medications [1-24]. This phenomenon has been reported from Asia, Europe, North America and South America. There are three substantial case series from France [14,20,22], but all others are individual case reports or very small case series. We report herein a dramatic instance of alopecia areata which appeared in temporal association with adalimumab administration and review key prior literature in an attempt to identify clinically relevant trends.

### Case Report

A 32 year-old Caucasian female presented in June, 2012, with refractory constipation which eventually led to the diagnosis of Stage IIA, moderately well-differentiated adenocarcinoma of the rectosigmoid. Pertinent past medical history included pan-colonic Crohn's disease since high school, treated with periodic infliximab infusions at the standard dose of 5 mg/kg. Colon cancer treatment consisted of: pre-operative radiotherapy, complete colectomy with ileo-anal anastomosis and J-pouch

formation, and post-operative capecitabine chemotherapy. With the exception of several serious urinary tract infections, she did well until January, 2015, when she developed peristomal pyoderma gangrenosum and concomitant recurrent Crohn's disease involving the J-pouch. For both of these reasons, she was then placed on adalimumab injections at a dose of 40mg once weekly. After eight months of adalimumab monotherapy, hair loss was first noted. Initially limited to widening of the central part and patchy loss lateral to the central part (Figure 1), the hair loss rapidly expanded in extent (Figure 2). Three months after AA onset and despite adalimumab discontinuation, there was near alopecia totalis (Figure 3 and Figure 4), as well as partial loss of eyebrow, axillary and pubic hair. At all times, hair pull was positive, hairs removed being tapered and hypopigmented at the root. "Exclamation hairs," classic and pathognomonic for alopecia areata, were easily seen during this process. There was no evidence of psoriasisform plaques in the scalp or elsewhere. Treatment to date has consisted of: adalimumab discontinuation, frequent application of potent topical corticosteroids (flurandrenolide 0.05% lotion), and multiple intralesional injections of triamcinolone acetonide suspension (3-4 mg/ml concentration). Hair regrowth has been sparse.

It should be noted that the patient did not experience alopecia of any kind during cancer therapy, post-operatively, or in relationship to numerous life-threatening febrile infections. There was no prior history of alopecia in either the patient or any first degree family members. The patient also had not previously suffered from any other autoimmune disease (e.g. vitiligo, thyroiditis).

## Discussion

The most important question is whether the occurrence of alopecia areata in conjunction with TNF- $\alpha$  antagonist therapy is merely a coincidence or whether there is a true causal relationship. Using sophisticated statistical disproportionality and sensitivity analyses of the nationwide French Pharmacovigilance Database, Béné and co-workers [22] concluded that, indeed, there exists a strong link between TNF- $\alpha$  blockade (class effect) and the occurrence of alopecia, particularly alopecia areata. Supporting such statistical analyses are instances where simply stopping the presumed etiologic anti-TNF- $\alpha$  drug has led to hair regrowth [8,14,18,19,20,22], as well as instances where re-challenge with the same suspected agent led to AA recurrence [22]. Despite the fact that the association between TNF- $\alpha$  blockers and alopecia areata is almost certainly not fortuitous, the mechanism by which TNF- $\alpha$  antagonists induce alopecia is not well understood. Because TNF- $\alpha$  inhibits hair growth [25], alopecia induced by TNF- $\alpha$  antagonists would appear paradoxical. Other paradoxical autoimmune reactions to TNF- $\alpha$  blockade, such as worsening or development of psoriasis, are well known. It is possible that autoimmunity (in this case, alopecia areata) is mediated by inhibition of suppressive regulatory T-cells. [5,26].

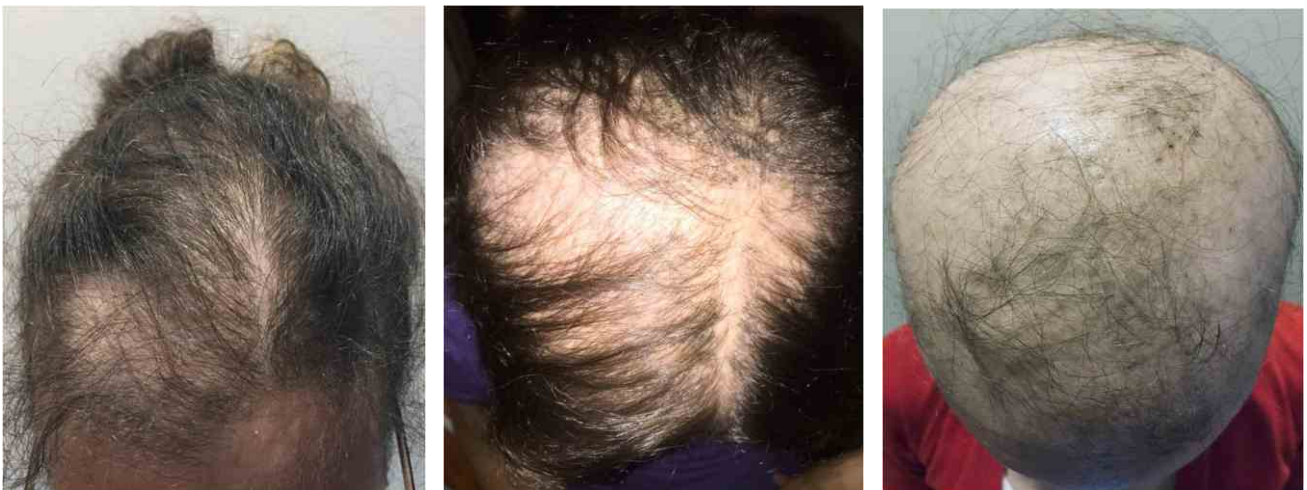
Prior reports of TNF- $\alpha$  blocking drugs related to alopecia, predominantly alopecia areata, are summarized in Table 1. AA may be mild and patchy (most common), or involve the whole scalp/face (alopecia totalis) or all hair-bearing areas (alopecia universalis). Adalimumab, etanercept, and infliximab are almost equally associated; there are only two reported instances each implicating certolizumab [22] and golimumab [24]. Underlying disease states are essentially equally divided amongst the assorted immune-mediated disorders for which the anti-TNF- $\alpha$  drugs are indicated. Neither age nor gender appears to be a major predisposing factor in the development of TNF- $\alpha$  blocker-associated alopecia areata. Similarly, duration of drug therapy is not a clearly predisposing factor, as AA

has developed as early as one month and as late as 48 months after institution of TNF- $\alpha$  blockade (See Table 1). Prior episodes of AA or the current or past history of another autoimmune disease has been often noted, and may be predisposing. Among the concurrent drugs given to such patients, there is one which appears most frequently: leflunomide [3,10,11,17,18,21,24]. The latter agent alone has been associated with alopecia areata [27], and the combination of TNF- $\alpha$  blockade with leflunomide may be particularly predisposing to this adverse event.

The treatment for AA associated with anti-TNF- $\alpha$  drugs remains controversial. While stopping the TNF- $\alpha$  antagonist is highly recommended by some [4,8,14,17,19], this strategy does not always induce hair re-growth [6,17,20]. Moreover, stopping anti-TNF- $\alpha$  therapy may not be medically feasible. In the latter instance, TNF- $\alpha$  blockade may be entertained using an alternate drug; cases have been reported where this “switching” technique has been both clinically effective (for the underlying disease state) and well tolerated (no exacerbation or recurrence of AA) [8,15,19]. Specific AA treatments reported in this particular situation have primarily included: topical, intralesional and systemic corticosteroids and topical minoxidil. While partial to complete regrowth has occurred in many individuals, it has not occurred in others following traditional AA management. Since the response to stopping an incriminated TNF- $\alpha$  antagonist as well as the response to specific AA therapeutic interventions are so variable, the prognosis remains difficult to predict.

Finally, while the authors firmly believe that AA in this reported case is due to the administration of adalimumab, the same medication has been rarely reported efficacious in treating AA, including very severe cases [28,29].

## Figures



**Figure 1:** Alopecia after eight months adalimumab therapy.

**Figure 2:** Worsening alopecia after nine months adalimumab therapy.

**Figure 3:** Progression to near alopecia totalis, two months after stopping adalimumab.

**Figure 4:** Progression to near alopecia totalis, two months after stopping adalimumab.



Table 1: Alopecia Areata Associated with Adalimumab

Cases Location	Age (years)	Gender	Disease State	TNF-alfa	Duration of Rx (months)	AA Type Prior AA?	Treatment	Outcome	Ref
1 USA	51	F	RA	Infliximab	11	AA-T No	NR	NR	1
1 USA	49	M	RA	Etanercept	36	AA-P Yes	Clobetasol Foam Topical minoxidil IL TAC	Slight regrowth	2
1 Germany	23	F	RA	Adalimumab	6	AA-U Yes	Topical steroids	No improvement	3
1 Italy	43	M	Psoriasis	Infliximab	4	AA-P No	Topical steroids	Regrowth	4
1 France	38	F	RA	Adalimumab	24	AA-U No	NR	NR	5
1 Switzerland	43	M	Psoriatic arthritis	Adalimumab	6	AA-U No	Topical steroids	No improvement	6
1 France	37	M	Ankylosing Spondylitis	Infliximab	1.5	AA-T Yes	NR	NR	7
1 Spain	20	F	Ankylosing Spondylitis	Infliximab	After each infusion	AA-P No	Switched to etanercept	Regrowth	8
1 Japan	69	F	RA	Infliximab	24	AA-P No	Cyclosporine	Regrowth	9
1 Canada	52	F	Psoriatic arthritis	Adalimumab	1	AA-P	NR	NR	10
1 Greece	30	F	RA	Adalimumab	9	AA-P No	Topical steroids Systemic steroid	No improvement	11
1 USA	48	M	Ankylosing spondylitis	Etanercept	48	AA-P No	IL TAC	No improvement	12
1 Italy	41	M	Behcet's Syndrome	Infliximab	12	AA-U No	Topical steroid Topical minoxidil	Partial regrowth	13
9 France	29-54 (Mean 39.2)	5 M 4 F	Various	Adalimumab 8 Etanercept 1	1.5-8	AA-P 5 AA-U 4 Yes (2)	Stopped TNF-a Systemic steroid	Regrowth 3 Partial regrowth 2	14
1 USA	21	F	Crohn's Dis	Infliximab	4	AA-P No	Topical steroids IL TAC	Partial regrowth	15

1	USA	27	F	Crohn's Dis	Infliximab	24	AA-P No	Switched to certolizumab	Regrowth	15
1	USA	39	F	Crohn's Dis	Adalimumab	NS	AA-P No	Topical steroids	Partial regrowth	15
1	Spain	39	M	Psoriasis	Adalimumab	12	AA-P No	Topical steroids	No improvement	16
1	Spain	24	F	Ankylosing spondylitis	Adalimumab	4	AA-T No	Topical steroids IL TAC	No improvement	17
1	Spain	46	F	RA	Etanercept	6	AA-P No	Topical steroids IL TAC	Slight regrowth	17
1	Spain	22	F	Juvenile Arthritis	Etanercept	2	AA-P Yes	Topical steroids IL TAC	Slight regrowth	17
1	Spain	52	M	Psoriatic arthritis	Etanercept	24	AA-P No	Topical steroids IL TAC	Slight regrowth	17
1	Spain	44	M	Psoriatic arthritis	Adalimumab	14	AA-P No	IL TAC	Partial regrowth	17
1	Spain	43	M	Psoriasis & Psoriatic arthritis	Adalimumab	12	AA-U No	None	Regrowth	18
1	Germany	46	F	Psoriasis & Psoriatic arthritis	Adalimumab	6	AA-P No	None (Switched to Etanercept)	Regrowth	19
29	France	22-59 (Mean 39.1)	17 M 12 F	Pso/PsA 16 Ankylosing spondylitis 8 Crohn's Dis 5 RA 4 Ulcerative colitis 2	Adalimumab 11 Infliximab 10 Etanercept 8	1-89 (Mean 22.5)	AA-P 23 AA-U 3 AA-T 3 Yes (3)	Split stop/continue ~70% topical and/or IL steroids	Partial to complete regrowth (76%)	20
1	Brazil	66	F	RA	Adalimumab	6	AA-U No	Minoxidil	Partial regrowth	21
52	France	Mean 39 Range NR	Both F>M	Ankylosing spondylitis 13 Crohn's Dis 12 Psoriasis 7	Infliximab 18 Adalimumab 17 Etanercept 15 Certolizumab 2	4 days-96 mo (Mean 11.3 mo)	Variable Yes (2)	Split stop/continue Various treatments	Where reported, most had some improvement	22
1	Portugal	24	F	Crohn's Dis	Adalimumab	7	AA-P No	Topical clobetasol	Regrowth	23
1	France	56	F	RA	Golimumab	5	AA-P No	IL betamethasone Topical minoxidil	Regrowth	24
1	France	46	F	RA	Golimumab	2	AA-P No	Topical minoxidil	Regrowth	24

## KEY

AA-P: Patchy alopecia areata; AA-T: Alopecia areata totalis; AA-U: Alopecia areata universalis; Dis: Disease; F: Female; IL: Intralesional; M: Male; NR: Not reported; Pso: Psoriatic arthritis; Pso: Psoriasis; RA: Rheumatoid arthritis; TAC: Triamcinolone acetonide

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