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Follicular occlusion triad: an isotopic response or adverse effect of rituximab?

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Abstract

Follicular occlusion triad is a symptom complex of three conditions with a similar pathophysiology including hidradenitis suppurativa (HS), dissecting cellulitis of the scalp, and acne conglobata. Although the exact pathogenesis of the triad is unknown, it appears to be related to follicular occlusion in areas with apocrine glands. Wolf isotopic response refers to the occurrence of a new dermatosis at the site of another, unrelated, previously healed dermatosis. We present a 26-year-old man with a history of pemphigus foliaceus (PF) who developed large draining nodules with scarring and sinus tracts, compatible with follicular occlusion triad, preferentially at areas previously affected by PF thirteen months after treatment with rituximab. To the authors' knowledge there are no reported cases of follicular occlusion triad or HS manifesting as an isotopic response. However, one member of the triad, HS, has been reported to occur infrequently following the use of biologic agents such as adalimumab, infliximab, tocilizumab, and rituximab for chronic immune-mediated inflammatory diseases (psoriasis, Crohn disease, rheumatoid arthritis, and ankylosing spondylitis).

Keywords: hidradenitis suppurativa, biologic agent, rituximab, anti-CD20, pemphigus foliaceus, isotopic response

Introduction

Recent studies and case reports have shown the paradoxical development of hidradenitis suppurativa (HS) after starting treatment with a monoclonal antibody or biologic agent to treat chronic immune-mediated inflammatory disease (psoriasis, rheumatoid arthritis, Crohn disease), with TNF inhibitors being the most common [1-4]. However, the authors found only two other cases of paradoxical HS after initiation of anti-CD20 antibody treatment (rituximab). The mechanism of the paradoxical development of HS and autoinflammatory diseases following treatment with anti-CD20 antibodies is not well understood. Anti-CD20 antibodies may play an immune-modulating role similar to TNF inhibitors through their effects on multiple arms of the immune system including humoral and cell-mediated immunity leading to the development of HS in susceptible individuals [2, 5, 6].

Various dermatoses have been reported to occur at the site of different, previously healed dermatoses including lichen planus, psoriasis, granuloma annulare, and acne comedones [7]. There are several theories proposed to explain the pathogenesis of the isotopic response involving the interplay of vascular, neural, and immunologic factors [7].

Case Synopsis

A 26-year-old man with history of pemphigus foliaceus (PF) presented with painful nodules, cysts, and draining sinus tracts (arrows) on the scalp, face, and chest. At the age of 17 the patient developed superficial blistering of the scalp, face, and upper trunk after starting doxycycline for acne. The patient was subsequently diagnosed with PF via direct (DIF) and indirect immunofluorescence (IIF) with an anti-intercellular antibody titer of 1:5120 on monkey esophagus and ELISA for desmoglein-1 positive at 178U (index<15). He was initially treated with prednisone and high dose mycophenolate mofetil

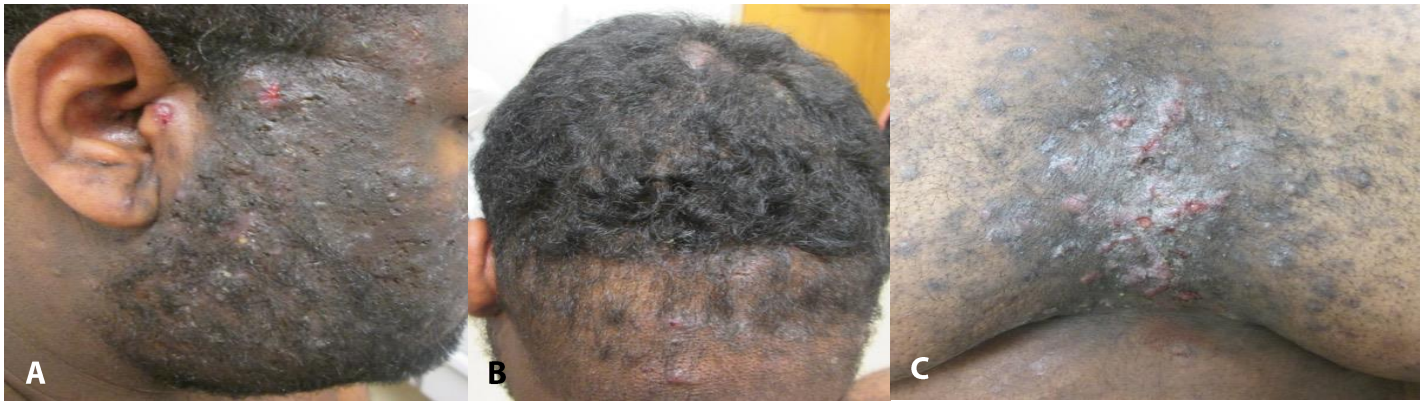

Figure 1. *March 2017, cystic acne.* ***B)*** *March 2017, dissecting folliculitis of the scalp.* ***C)*** *March 2017, hidradenitis suppurativa on the trunk.*

(3g per day) followed by azathioprine 200mg per day with no improvement. The patient continued to develop extensive verrucous and proliferative lesions on his scalp, face, neck, chest, and back. After failing multiple immunosuppressive medications, rituximab was initiated. The patient underwent four infusions of 1125mg of rituximab over four weeks.

Seven months following treatment with rituximab, no active PF lesions were noted, but the patient had developed severe tinea pedis and onychomycosis. Thirteen months after treatment, the patient developed severe cystic acne-like draining lesions on the face, scalp, chest, and intertriginous areas including the flanks, pannus, and upper abdomen. He was subsequently diagnosed with follicular occlusion triad including dissecting folliculitis of the scalp, acne conglobota on the face, and HS on his trunk (**Figures 1, 2**). Of note, the patient did not develop lesions in his axillae or groin.

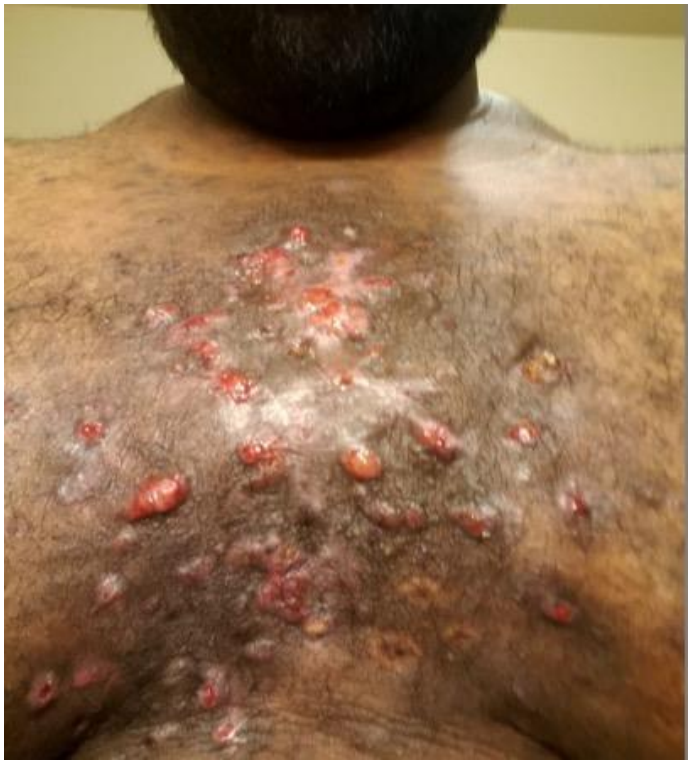

Figure 2. *January 2018, hidradenitis suppurativa on the trunk.*

The patient was started on a combination of clindamycin and rifampin with initial improvement and subsequently low dose isotretinoin for management of follicular occlusion triad lesions with some improvement. The patient's PF lesions recurred prompting initiation of intravenous immunoglobulin (IVIG). Retreatment with rituximab for PF was considered but ultimately deferred owing to the onset of follicular occlusion triad following his previous treatment with rituximab.

Case Discussion

Our patient's history of obesity and PF placed him at an increased risk for subsequent development of HS assuming a similar presentation between biologic agent-induced and classic HS [2]. A recent study showed an association between HS and PF with a statistically significant odds ratio of 5.34, as well [8]. However, the onset of follicular occlusion triad following treatment with rituximab and the preferential development of lesions at areas previously affected by PF (scalp, face, chest) while sparing other areas more typically affected by HS including the groin, back, axillae, and buttocks are both peculiar suggesting a possible adverse effect of

rituximab treatment and aspects of an isotopic response, as well.

In a review of the literature, we found 34 published reports (**Table 1**), [1-4, 9, 10], of HS paradoxically induced by biologic agents. Of the 34 cases, 20 were associated with adalimumab, 6 with infliximab, 5 with etanercept, 2 with rituximab, and 1 with tocilizumab [1-4, 9, 10]. The male-female ratio was 1:4.5, slightly higher than that of non-biologic agent-induced HS, which is reported to range from 1:2.7-3.3 [11]. The median age of diagnosis was 29 years (average 34.5, range 11-57), also slightly higher than the reported average age at onset of 23 years [11]. The median duration of biologic agent exposure prior to onset of HS was 12 months (range 1-120). Faivre, et al. also noted that four of 25 patients documented presented with additional symptoms consistent with follicular occlusion tetrad at time of HS onset (HS, acne conglobate, dissecting cellulitis of the scalp, and pilonidal sinus), [2]. Of the underlying conditions, 14 of the patients were being treated for Crohn disease, 7 for rheumatoid arthritis, 7 for ankylosing spondylitis, 2 for psoriasis, 1 for psoriatic arthritis, 1 for synovitis-acne-pustulosis-hyperostosis-osteitis syndrome, 1 for juvenile idiopathic arthritis, and 1 for chronic juvenile arthritis. Of those that reported biologic agent discontinuation or switch, 7 reported complete resolution, 3 partial resolution, 2 stable disease, and 1 worsening of HS. On the contrary, of those that maintained biologic agent use, 7 reported worsening of HS, 2 stable disease, 5 partial resolution, and 2 complete resolution.

We also reviewed rituximab-associated adverse cutaneous events (ACEs), (**Table 2**), [2, 12-27] and found 18 reported cases, of which the most commonly reported ACE was serum sickness (N=4). The median age of diagnosis was 50 years (range 23-77). The median duration of rituximab exposure prior to onset of ACE was less than 1 month (range 12 hours-120 months). Of the 18 cases, 15 reported complete resolution of the ACE following discontinuation of rituximab.

Two other patients were reported to develop HS after receiving rituximab. The patients were 43 and 50 years old at time of onset of HS and both were being treated for rheumatoid arthritis. They were exposed to rituximab for 12 and 120 months prior to onset of HS. Of the two, one achieved resolution of HS after stopping treatment with rituximab and the other continued treatment with addition of a different biologic agent with no reported outcome [2].

The mechanism by which anti-CD20 antibodies induce autoinflammatory disease is not well understood. Takahashi et al. presents a case of improvement of HS following treatment with rituximab as part of anti-rejection therapy following renal transplant [28]. Interestingly, chronic HS lesions have a marked increase in CD20+ B cells [29]. Weber et al. proposes a mechanism by which anti-CD20 therapy may effectively treat autoinflammatory disease in some and lead to exacerbation in others depending on whether the disease process is being driven by antigen-presenting B cells, in which anti-CD20 therapy effectively reduces the number of B cells thereby treating the disease, or a T cell-dependent response in which B cells are effectively regulating the response and thus depletion leads to exacerbation of disease [30].

On the other hand, Wolf isotopic response is hypothesized to involve various factors including altered vascular, neural, and immunologic functions, which may have contributed to the development of our patient's disease, as well. Alterations in microcirculation, connective tissue, regional immune system function, and innervation at sites previously affected by PF may have predisposed him to the chronic autoinflammatory follicular occlusion triad. herpes zoster virus appears to be the most common primary dermatosis implicated in Wolf isotopic response and lichen planus the most common secondary dermatosis [7]. In a review of the literature, no cases were found of Wolf isotopic response with pemphigus as the primary dermatosis or with follicular occlusion triad or HS as the secondary dermatosis.

Conclusion

The onset and location of follicular occlusion triad in our patient are both curious. We propose a

mechanism of disease in our patient whereby rituximab effectively caused depletion of immune-regulating B cells and exacerbation of a T cell response in a patient predisposed to development of autoinflammatory follicular disease given the association between HS and PF. The preferential development of lesions at areas previously affected by PF may relate to underlying changes in local immune, vascular, and neural function. This case demonstrates the importance of a physician's awareness of potential immune dysfunction when starting biologic agents.

Potential conflicts of interest

The authors declare no conflicts of interests.

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Table 1. *Characteristics of patients with paradoxical hidradenitis suppurativa induced by biologic agents.*

Case	Sex/Age	Underlying Condition	BA	Onset of HS (mo)	Treatment	BA Course/HS Outcome	Reference
1	F/57	CD	ADA	12	ATB, CS	Switch to AZA/Worsening	Harvin, Kasarala (2016)
2	M/24	CD	ADA	9	ATB	Maintained/Worsening	Harvin, Kasarala (2016)
3	F/50	RA	RTX	12	Surgery, ATB	Stop/CR	Faivre, et al. (2016)
4	M/43	RA	ADA	2	Surgery, ATB	Switch to abatacept/CR	Faivre, et al. (2016)
5	F/35	RA	IFX	9	Surgery, ATB	Maintained/Worsening	Faivre, et al. (2016)
6	F/52	RA	TCZ	6	ATB	Maintained/Worsening	Faivre, et al. (2016)
7	F/54	RA	ETN	2	ATB	Maintained/Worsening	Faivre, et al. (2016)
8	M/43	RA	RTX	120	ATB	Maintained/ -	Faivre, et al. (2016)
9	F/27	RA	IFX	11	–	Maintained/Worsening	Faivre, et al. (2016)
10	F/17	CJA	ADA	48	ATB	Switch to ETN/CR	Faivre, et al. (2016)
11	M/33	AS	ADA	24	-	Stop/PR	Faivre, et al. (2016)
12	M/20	AS	ETN	10	ATB, retinoid, CS	Maintained/SD	Faivre, et al. (2016)
13	F/21	AS	ADA	18	-	Switch to UST/CR	Faivre, et al. (2016)
14	F/24	AS	ADA	57	Surgery, ATB	Maintained/PR	Faivre, et al. (2016)
15	F/46	AS	ADA	18	-	Maintained/Worsening	Faivre, et al. (2016)
16	F/28	Psoriatic arthritis	ETN	28	Surgery, ATB	Maintained/SD	Faivre, et al. (2016)
17	F/55	SAPHO	ETN	12	Surgery	Stop/CR	Faivre, et al. (2016)
18	F/35	CD	ADA	6	ATB	Stop/PR	Faivre, et al. (2016)
19	F/28	CD	ADA	10	ATB	Maintained/PR	Faivre, et al. (2016)
20	F/51	CD	ADA	12	Surgery, ATB, colchicine	Stop/SD	Faivre, et al. (2016)
21	F/29	CD	IFX	72	Surgery, ATB	Switch to ADA/SD	Faivre, et al. (2016)
22	F/23	CD	ADA	1	Surgery, ATB	Maintained/PR	Faivre, et al. (2016)
23	F/28	CD	ADA	3	Surgery, ATB	Maintained/PR	Faivre, et al. (2016)
24	F/22	CD	IFX	5	Surgery	Maintained/Worsening	Faivre, et al. (2016)
25	M/26	CD	IFX	42	ATB	Stop/CR	Faivre, et al. (2016)
26	F/50	CD	IFX	48	ATB	Maintained/SD	Faivre, et al. (2016)
27	F/49	Psoriasis	ADA	54	Surgery, ATB	Maintained/CR	Faivre, et al. (2016)
28	F/17	JIA	ADA	24	ATB	Switch to ETN/PR	Delobeau, et al. (2015)
29	F/29	CD	ADA	7	ATB	Maintained/PR	Delobeau, et al. (2015)
30	F/51	Psoriasis	ADA	12	ATB	Maintained/CR	Delobeau, et al. (2015)
31	F/11	AS and CD	ADA	24	ATB	Switch to UST/ -	Delobeau, et al. (2015)
32	F/40	CD	ADA	22	ATB	Stop/CR	Martina, et al. (2017)
33	F/21	AS	ADA	-	-	-	Toussirot, et al. (2016)
34	-	-	ETN	-	-	-	Pellegrino, et al. (2011)

ADA, adalimumab; AS, ankylosing spondylitis; ATB, antibiotherapy; AZA, azathioprine; BA, biologic agent; CD, Crohn disease; CJA, chronic juvenile arthritis; CR, complete remission; CS, corticosteroid therapy; ETN, etanercept; F, female; HS, hidradenitis suppurativa; IFX, infliximab; M, male; PR, partial remission; RA, rheumatoid arthritis; RTX, rituximab; SAPHO, synovitis-acne-pustulosis-hyperostosis-osteitis syndrome; SD, stable disease; TCZ, tocilizumab; UST, ustekinumab

Table 2. *Rituximab-associated adverse cutaneous events.*

Case	Sex/Age	Underlying Condition	ACE	Onset of ACE (mo)	ACE Treatment	RTX Course/ACE Outcome	Reference
1	M/63	FL	Vasculitis	-	CS	Stop/CR	Abe, et al. (2019)
2	F/50	RA	HS	12	Surgery, ATB	Stop/CR	Faivre, et al. (2016)
3	M/43	RA	HS	120	ATB	Maintained/ -	Faivre, et al. (2016)
4	-	MP	Cutaneous Sarcoidosis	-	-	-	Pescitelli, et al (2017)
5	F/43	FL	Oral Lichen Planus	-	CS	Stop/CR	Kuten-Shorrer, et al. (2014)
6	F/77*	FL	Paraneoplastic Pemphigus	<1	CS	Stop/CR	Higo, et al. (2015)
7	M/44	CLL	Vasculitis	<1	None	Stop/CR	Dereure, et al. (2001)
8	- /60	PV	TEN	12 hours	ETN	Stop/CR	Didona, et al. (2015)
9	M/36	FL	SJS	-	CS	Stop/Worsening	Lowndes, et al. (2002)
10	M/58	WM	Proinflammatory syndrome	1	CS	Stop/CR**	Buda-Okreglak, et al. (2003)
11	M/38	RA	Vasculitis	1 day	None	Stop/CR	Kim, et al. (2009)
12	F/53	MN	Urticarial dermatitis	<1	CS	Stop/CR	Radhakrishnan, et al. (2017)
13	M/69	CLL	Necrotizing fasciitis	3	Surgery	Stop/CR	Abdulkareem, et al. (2017)
14	F/67	FL	Vasculitis	<1	None	Stop/CR	Kandula, et al. (2006)
15	F/48	ITP	Serum sickness	-	CS	Stop/CR	Herishanu, et al. (2002)
16	F/60	MC	Serum sickness	<1	CS	Stop/CR	Catuogno, et al. (2005)
17	F/23	SLE	Serum sickness	48 hours	CS	Stop/CR	Hellerstedt, et al. (2003)
18	M/45	AP	Serum Sickness	10 days	CS	Stop/CR	D'Arcy, Mannik (2001)

ACE, adverse cutaneous event; AP, autoimmune polyneuropathy; CR, complete resolution; CS, corticosteroid therapy; CLL, chronic lymphocytic leukemia; ETN, etanercept; FL, follicular lymphoma; HS, hidradenitis suppurativa; ITP, immune thrombocytopenia; MC, mixed cryoglobulinemia; MN, membranous nephropathy; MP, microscopic polyangiitis; PV, pemphigus vulgaris; RA, rheumatoid arthritis; RTX, rituximab; SJS, Stevens-Johnson syndrome; SLE, systemic lupus erythematosus; WM, Waldenstrom's macroglobulinemia

*The patient was simultaneously started on bendamustine and rituximab.

**The patient was re-challenged with rituximab resulting in recurrence of symptoms.