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Post SARS-CoV-2 vaccination effluvium

In December 2020, the FDA issued emergency use authorization for Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) SARS-CoV-2 vaccines. Cutaneous reactions reported after vaccination include: injection site reactions, urticarial and morbilliform eruptions, pernio/chilblains, reactions to cosmetic fillers, herpes zoster, herpes simplex flares, and pityriasis rosea-like rashes [1]. Reactions related to the hair have so far not been reported. We originally reported patients with COVID-19 [2], in whom the onset and acuity of hair shedding were associated with severity of the disease and fever. Our observations have been confirmed by others, while the underlying pathogenic mechanisms remain elusive [3-6].

The term "cytokine storm syndrome" is perhaps one of the critical hallmarks of COVID-19 severity, with a prominent role of type I and II interferons (IFN), tumour necrosis factor (TNF), and members of the interleukin (IL) family [7].

Many factors can lead to pathologically increased hair loss. Whatever the cause, the follicle tends to behave in a similar way. Dystrophic anagen effluvium is an early-onset hair loss condition that results from the shedding of large numbers of hairs from the anagen phase of growth. A major characteristic of anagen is that the epithelial hair follicle compartment undergoes proliferation, with the hair matrix keratinocytes showing the highest proliferative acti-

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Table 1. Demographic data, vaccine type, and hair manifestations of patients with SARS-CoV-2 vaccine-related post-febrile effluvium[1] and matched non-febrile controls[2] seen at the Center for Dermatology and Hair Diseases who received vaccination with Moderna or Pfizer/BioNTech vaccines (March – November 2021).

Patient No.	Sex/age	Type of vaccine	Date of 2nd Vaccination	Fever in °C	Onset of hair loss after vaccination	Comorbidities
1	F/46	Moderna	03/2021	39	1-2 months	None
2	F/60	Moderna	05/2021	38.5	1-2 months	Crohn's disease
3	F/38	Moderna	05/2021	38	1 month	Polycystic ovary syndrome
4	F/61	Moderna	05/2021	39.5	3 months	Hypothyroidism
5	F/69	Moderna	07/2021	39	1-2 months	None
6	F/29	Moderna	08/2021	39	1-2 months	None
7	F/52	Moderna	07/2021	38.3	1 month	Diabetes mellitus
8	F/63	Moderna	06/2021	38	1-2 months	None
9	F/24	Moderna	07/2021	38.5	1-2 months	None
10	F/25	Moderna	07/2021	39.4	2-3 months	Acne
11	F/39	Moderna	04/2021	38.2	2 months	Autoimmune thyroiditis
12	F/48	Moderna	06/2021	39	2-3 months	None
13	F/56	Moderna	07/2021	38	2-3 months	None
14	F/68	Moderna	05/2021	39	3 months	None
15	F/65	Moderna	07/2021	39	3-4 months	None
16	F/53	BioNTech/Pfizer	07/2021	38.5	1-2 months	None
17	F/64	Moderna	05/2021	none	none	Chronic bronchitis
18	F/63	Moderna	06/2021	none	none	None
19	F/68	Moderna	06/2021	none	none	None
20	F/70	BioNTech/Pfizer	05/2021	none	none	None
21	F/43	Moderna	06/2021	none	none	None
22	F/61	BioNTech/Pfizer	02/2021	none	none	Hypothyroidism, primary biliary cholangitis
23	F/67	Moderna	05/2021	none	none	None
24	F/65	Moderna	06/2021	none	none	Ankylosing spondylitis
25	F/70	BioNTech/Pfizer	04/2021	none	none	Arterial hypertension
26	F/44	Moderna	05/2021	none	none	None
27	F/34	BioNTech/Pfizer	07/2021	none	none	None
28	F/65	BioNTech/Pfizer	05/2021	none	none	None
29	F/75	BioNTech/Pfizer	04/2021	none	none	Breast cancer
30	F/37	Moderna	07/2021	none	none	Hypercholesterolaemia
31	F/52	Moderna	06/2021	none	none	None
32	F/73	BioNTech/Pfizer	04/2021	none	none	Myositis

[1] Age range: 24-68 years (mean: 49.75 ± 15 SD), [2] age range: 34-75 years (mean: 59.44 ± 13 SD).

vity in building up the hair shaft. The common pathogenesis which unites the different aetiologies of dystrophic anagen effluvium is a direct insult to the rapidly dividing bulb matrix cells. Telogen effluvium results from late-onset increased shedding of hairs from the telogen phase of the hair cycle and represents by far the commonest cause of hair loss. An increase in the percentage of follicles in telogen by >20% leads to increased shedding of hairs in telogen. This can either be due to synchronization phenomena of hair cycling, with shedding of hairs in the hundreds (in telogen effluvium), or to a decrease of anagen duration with variable shedding of hair and increasing diversity of hair shaft diameters (in androgenetic alopecia).

Post-infectious hair loss has traditionally been categorized as telogen effluvium, yet it may present with different pathomechanisms and clinical patterns. Evidence exists that the hair follicle may respond to infection with both shedding patterns, dystrophic anagen effluvium and telogen effluvium, depending on the type and intensity of the insult. Accordingly, the hair may fall out very quickly in clumps or gradually.

Savil originally reported that for post-febrile effluvium, the critical temperature should be 39-39.5°C [8], however, circulating pyrogenic cytokines appear to be the important determinant rather than body temperature.

The immune system is involved in both the regulation of hair follicle cycling and the pathogenesis of some immune-mediated hair pathologies. Immunomodulatory cytokines not only act as mediators of immunity and inflammation, but also regulate cell proliferation and differentiation and, as such, play a role in hair growth and shedding. Philpott *et al*. reported ILs and TNF to be potent inhibitors of hair follicle growth *in vitro* in a dose-dependent manner [9]. In addition, IFN-γ has been shown to be a potent inducer of catagen-like changes in cultured human anagen hair follicles [10].

The cytokine profiles generated by SARS-CoV-2 vaccination, particularly in those with febrile vaccine reactions, are yet to be established.

We observed sixteen patients who developed a similar pattern of hair loss following vaccination against SARS-CoV-2. All patients had a reduced density of hair and a positive hair-pull test. One patient, in whom a trichogram was performed, showed mixed telogen and dystrophic anagen effluvium. The demographic data, symptoms, and hair manifestations of the indicator cases with SARS-CoV-2 vaccine related to effluvium and sixteen control vaccinees without a febrile reaction are summarized in *table 1*. The age difference between the two groups may be explained by a reduced febrile response to infections with increasing age.

The observation and analogies related to effluvium following febrile SARS-CoV-2 vaccination reaction are in favour of COVID-19-related effluvium being due to the systemic inflammatory reaction rather than to a direct infection of the hair follicle with SARS-CoV-2. As yet, histopathological and ultrastructural evidence for a direct infection of the hair follicle with SARS-CoV-2 is lacking. ■

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Pseudallescheria boydii infection associated with IgG4-related disease

IgG4-related disease (IGRD) is a newly described immune-mediated fibro-inflammatory disease characterized by cutaneous and systemic manifestations associated with increased serum IgG4 levels [1, 2]. Patients with immune-mediated disorders are susceptible to infection because of the intrinsic immune dysregulation in relation to the disease process [3]. Here, we report the first case of *Pseudallescheria boydii* infection with massive infiltration of IgG4-producing plasma cells in a patient with IGRD and discuss the pathophysiology of this rare infectious disease.

A Japanese man in his 80s presented to our department with a month-long history of a subcutaneous tumour on the dorsum of his left foot. The patient was taking prednisolone, 5 mg/d, for thrombocytopenic purpura and had a history of chronic kidney disease associated with a history of IGRD. There was no history of skin disease. Physical examination revealed a dome-shaped subcutaneous tumour, 3 cm in diameter, located on the dorsum of the left foot (*figure 1A*). Laboratory workup showed a slightly increased white blood cell count (9,000/μL; normal: 3,300-