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Widespread pustular eruption following probiotic use

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Abstract

A 26-year-old woman with Crohn disease and palmoplantar psoriasis on ustekinumab presented with a diffuse and intensely pruritic rash with a few pin-point pustules within days after initiation of an over-the-counter Align brand probiotic. Biopsy revealed psoriasiform and spongiotic dermatitis with spongiform subcorneal pustules and scattered eosinophils, consistent with acute generalized exanthematous pustulosis. Our case highlights a unique presentation of acute generalized exanthematous pustulosis following probiotic exposure with fewer than usual pustular lesions. IL23 suppression by ustekinumab may have contributed to the patient's reduced pustular presentation.

Keywords: acute generalized exanthematous pustulosis, drug reaction, probiotic, pustules, ustekinumab

Introduction

Acute generalized exanthematous pustulosis (AGEP) is rare, affecting 1-5 people per million per year. It manifests as an abrupt eruption of small, non-follicular, sterile pustules on an erythematous background often with associated fever, neutrophilia, and occasional eosinophilia [1]. Histopathologic findings in AGEP include spongiform subcorneal and/or intraepidermal pustules. Other features include edema of the papillary dermis, neutrophilic perivascular infiltrates, and eosinophil exocytosis [2]. The differential diagnosis for subcorneal pustules includes AGEP,

pustular psoriasis, IgA pemphigus, and Sneddon-Wilkinson syndrome. To the best of our knowledge, this report represents the first case of AGEP following probiotic exposure.

Case Synopsis

A 26-year-old woman with Crohn disease and palmoplantar psoriasis on ustekinumab 90mg subcutaneous injection every six weeks for the past year was admitted for pneumonia and new-onset intensely pruritic rash. The eruption began one day prior, initially on the abdomen, with rapid progression to the chest, neck, shoulders, and gluteal regions with associated redness of the upper mucosal lip (**Figure 1**). Physical examination revealed numerous thin, pink, edematous-appearing papules coalescing into plaques with scattered few central pinpoint pustules. Work-up demonstrated leukocytosis ($16.0 \times 10^9/L$) and elevated neutrophil count (84.3%). Mycoplasma PCR was negative. Her only new medication preceding rash onset was an over-the-counter Align brand probiotic started five days earlier and stopped one day prior to admission. She began taking the probiotic for her "well-being" after receiving a free sample from a friend. Antibiotics were initiated for presumed atypical pneumonia after the eruption had developed. Biopsy of the left lower back revealed psoriasiform and spongiotic dermatitis with spongiform subcorneal pustules and scattered eosinophils (**Figure 2**), consistent with a diagnosis of acute generalized exanthematous pustulosis (AGEP). In

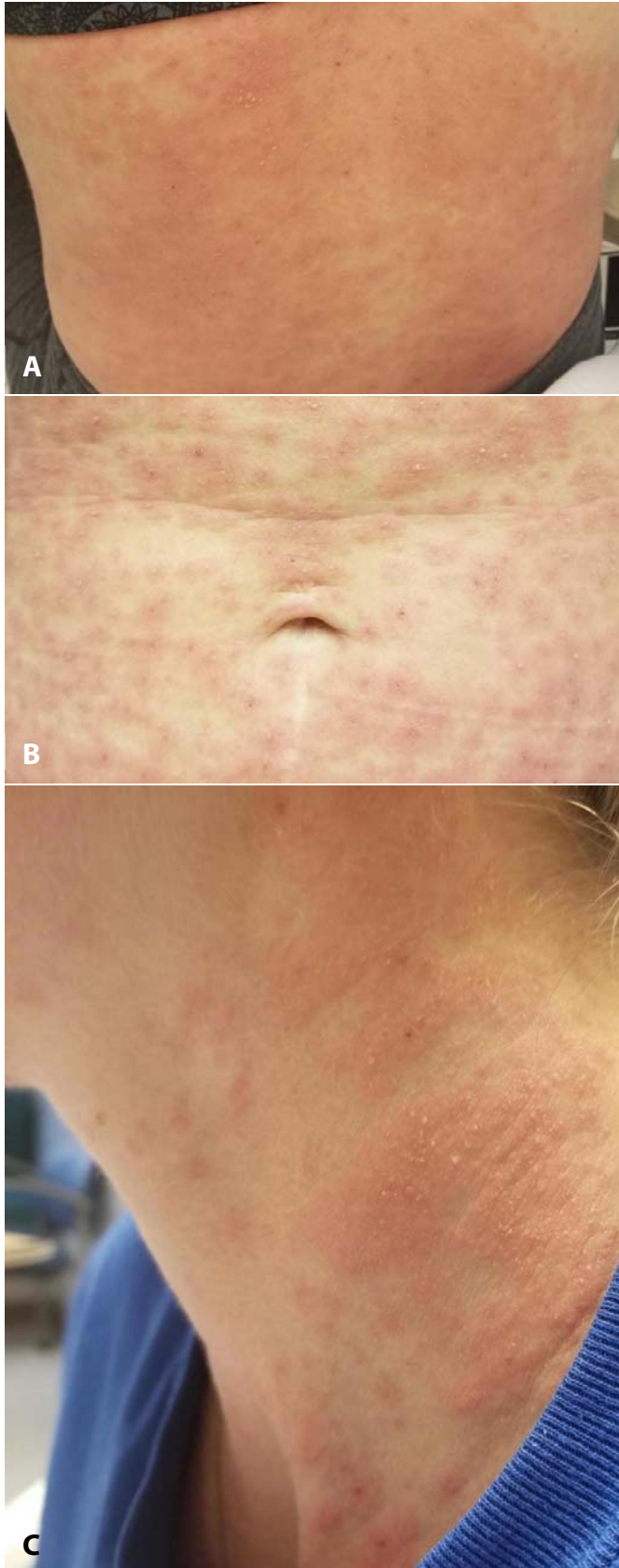


Figure 1. Clinical presentation. Numerous thin, pink edematous-appearing papules and plaques located on the **A)** back, **B)** abdomen, and **C)** neck.

this case, the probiotic was discontinued prior to admission and the patient received diphenhydramine and clobetasol 0.05% ointment for pruritus and acetaminophen for pain. The pustules quickly resolved. At 10-day follow-up, only post-inflammatory hyperpigmentation remained with over 90% clearance of erythematous papules and plaques. The patient did not report recurrence at both 12 and 18-month follow-ups.

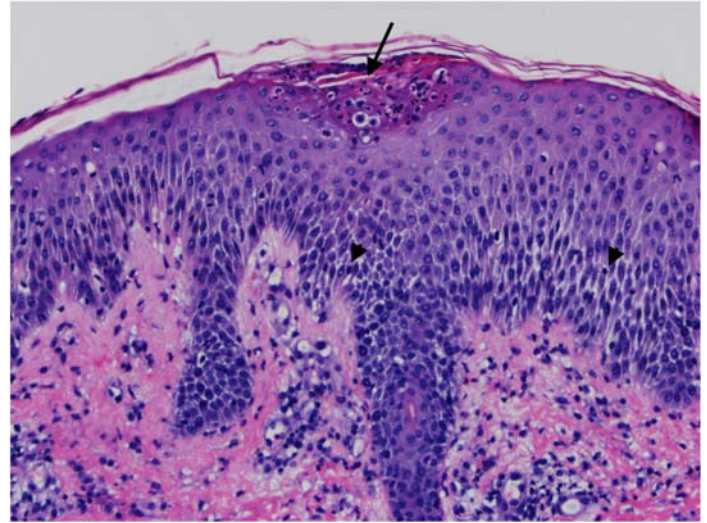


Figure 2. Histopathologic findings. Psoriasiform and spongiotic dermatitis (arrowheads) with spongiform subcorneal pustules (arrow) and scattered eosinophils. H&E, 20x.

Case Discussion

Approximately 90% of AGEP cases are caused by drugs, most commonly aminopenicillins, sulfonamides, and antimalarials [3]. Antibiotic reactions typically occur within 24 hours of exposure, whereas the median onset of AGEP with other associated drugs is 11 days [3]. The remainder of cases are attributed to infectious triggers including parvovirus B19, cytomegalovirus, and *Mycoplasma pneumoniae* [1], which was initially suspected in this patient. According to the Naranjo adverse drug reaction probability scale, the probiotic is considered a probable cause of AGEP (**Table 1**), [4]. To the best of our knowledge, there are no previous reports of AGEP following probiotic initiation. Align probiotics (Procter & Gamble, Cincinnati, OH) contain a strain of bacteria known as *Bifidobacterium* 35624™.

Probiotics are regulated by the U.S. Food and Drug Administration's Center for Food Safety and Applied Nutrition as "foods," not drugs, and only require

Table 1. Adapted from the Naranjo adverse drug reaction probability scale [4].

Questions	Yes	No	Do not know	Our Patient's Score
1. Are there previous conclusive reports on this reaction?	1	0	0	0
2. Did the adverse events appear after the suspected drug was given?	2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	1	0	0	1
4. Did the adverse reaction appear when the drug was re-administered?	2	-1	0	0
5. Are there alternative causes that could have caused the reaction?	-1	2	0	2
6. Did the reaction reappear when a placebo was given?	-1	1	0	0
7. Was the drug detected in any body fluid in toxic concentrations?	1	0	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	1	0	0	1*
Total				6

Scoring: ≥ 9 = definite, 5 to 8 = probable, 1 to 4 = possible, 0 = doubtful

*Biopsy results consistent with acute generalized exanthematous pustulosis (AGEP).

manufacturer safety approval [5]. Without formal testing and regulation, unknown interactions may exist.

In addition to the rarity of AGEP in association with probiotics, this case is unique in its presentation, which was less exuberant and pustular than typical AGEP. One contributing factor may be ustekinumab, a human IgG1k monoclonal antibody that binds the p40 subunit of IL12 and IL23 and modulates the downstream inflammatory cascade. Acute generalized exanthematous pustulosis is classified as a T cell-related sterile neutrophilic inflammatory

response (type IV hypersensitivity reaction), [1]. The exact pathogenesis of AGEP is unknown, but it is suspected that cytokines IL8, IL17, IL23, and IL36 are involved [1]. One study revealed the presence of IL23 expression in AGEP biopsies [6]. Ustekinumab-induced IL23 suppression may have contributed to the patient's less pustular presentation. Previous case reports have reported worsening of underlying psoriasis with ustekinumab including the appearance of generalized or palmoplantar pustules (Table 2), [7]. However, ustekinumab is less likely the inciting agent that resulted in the onset of these pustules because the patient used ustekinumab for

Table 2. Case comparison between the current case and a previous case of palmoplantar pustular psoriasis in a patient starting ustekinumab.

	Current Case	Benzaquen et al. [7]
Diagnosis	AGEP	Palmoplantar Pustular Psoriasis
Inciting agent	Align Probiotic (<i>Bifidobacterium</i> 35624™)	Ustekinumab
Ustekinumab use prior to symptoms	1 year	3 weeks
Significant medical conditions	Crohn's Disease	Crohn's Disease
Treatment	- Discontinuation of probiotic - Oral Diphenhydramine - Clobetasol 0.5% ointment - Acetaminophen	- Discontinuation of ustekinumab - Replacement of ustekinumab with golimumab

one year prior to onset and did not experience recurrence at 12- and 18-month follow-up with continued use of ustekinumab. The histopathologic findings in this case were also most consistent with AGEP.

The mainstay of AGEP treatment is withdrawal of the causative agent and future avoidance. Resolution of AGEP is generally seen within two weeks after inciting agent withdrawal [1]. Moist dressings, antiseptic solutions, and emollients can provide symptomatic relief and protection. In cases of severe pruritus and inflammation, medium potency topical corticosteroids are recommended. Systemic corticosteroids do not shorten the disease course [8].

Conclusion

To the best of our knowledge, this is the first reported case of AGEP following probiotic exposure. The short period between probiotic exposure and pustular

eruption and the histopathologic findings favor the diagnosis of AGEP from probiotic use. However, future reports are needed to confirm the frequency of this association. This case emphasizes the importance of comprehensively reviewing medications including supplements, which may contribute to unforeseen drug eruptions.

Potential conflicts of interest

VYS is a stock shareholder of Learn Health and has served as an advisory board member, investigator, and/or received research funding from Sanofi Genzyme, Regeneron, AbbVie, Eli Lilly, Novartis, SUN Pharma, LEO Pharma, Pfizer, Menlo Therapeutics, Burt's Bees, GpSkin, Altus Labs and Skin Actives Scientific. There were no incentives or transactions, financial or otherwise, relevant to this manuscript. KNP, AJH, MEG and JMK have no conflicts of interest to declare.

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