Clinical, Cosmetic and Investigational Dermatology

Dovepress

open access to scientific and medical research

Open Access Full Text Article

COMMENTARY

Exploring the Clinical Features, Immunopathogenesis and Approach to Diagnosis for Generalized Pustular Psoriasis [Podcast]

Tina Bhutani[1,*], Jason E Hawkes[2,*]

[1]Psoriasis and Skin Treatment Center, Department of Dermatology, University of California at San Francisco, San Francisco, CA, USA; [2]Department of Dermatology, University of California at Davis, Sacramento, CA, USA

*Both authors contributed equally to this paper

Correspondence: Dr. Jason E Hawkes, Email hawkes3@gmail.com

Abstract: Generalized pustular psoriasis is a rare presentation of psoriatic disease and is characterized by the acute onset of diffuse superficial pustules on the skin. These pustules can often coalesce, forming what's known as 'lakes of pus' that are most often seen on the trunk and on skin folds. GPP flares are often accompanied by systemic symptoms, including fever, malaise, and edema. The interleukin (IL)-36 pathway plays a central role in the development of GPP, although several other genes may be associated. The rarity of GPP makes its diagnosis challenging and it could be mistaken for an infectious condition or other types of pustular psoriasis, including unstable forms of plaque psoriasis that may present with pustules. Performing a thorough skin examination and obtaining a detailed history are vital to exclude these differential diagnoses. Incorrect or late diagnosis, inadequate or delayed treatment, and lack of specialist referrals may contribute to increased disease severity and can have a debilitating impact on patients' quality of life. In this podcast, two US-based dermatologists discuss the clinical characteristics of GPP, highlight the central role of IL-36 in immunopathogenesis, and share practical approaches to recognizing and diagnosing the disease.

Keywords: Diagnosis, generalized pustular psoriasis, genetics, immunopathogenesis, interleukin-36 pathway, quality of life

This podcast is brought to you by Boehringer Ingelheim.

Dr. Uwe Wollina: Hello to our listeners. I'm Dr Uwe Wollina, the head of the department of dermatology and allergology at the Academic Teaching Hospital, Dresden. I have the pleasure of moderating today's podcast. I would like to welcome Drs. Bhutani and Hawkes, both board-certified dermatologists in California. We discuss their experiences in treating generalized pustular psoriasis, also referred to as GPP. Can you share your background in managing patients with this disease?

Dr. Jason E. Hawkes: Sure. My name's Dr. Jason Hawkes. I'm an associate professor of dermatology and medical dermatology at UC Davis in Sacramento, where I specialize in the care and treatment of complex and chronic inflammatory skin diseases like psoriasis and eczema. Throughout my career, I've cared for several patients with GPP in both inpatient and outpatient hospital settings, and I'm looking forward to today's podcast.

Dr. Tina Bhutani: Hi, everybody. Thanks for having me. My name's Dr. Tina Bhutani. I'm an associate professor of dermatology at the University of California, San Francisco, and I also co-direct our psoriasis and skin treatment center. Most of the patients that I see in clinic have complex psoriatic disease, so I have seen several patients in my practice with GPP.

Dr. Uwe Wollina: Thank you for your introductions. It's a pleasure to join you today. We can all recognize the importance of discussing this rare disease, as it is debilitating for our patients. Today, we are going to discuss the clinical characteristics, immunopathogenesis, and approach to diagnosing GPP.

Received: 2 June 2023
Accepted: 2 June 2023
Published: 16 June 2023

Since other pustular conditions can mimic GPP, we'll review how to distinguish GPP from other subtypes of psoriasis. In addition, interleukin-36 signaling occurs in GPP, and genetic variants may act as immune drivers of GPP.

[00:2:00]: Lastly, we'll discuss a typical clinical course for GPP and some practical steps for establishing a diagnosis in this population. With that being said, can you talk about the typical clinical features of GPP and where it fits with other psoriasis variants, so we can better understand GPP?

Dr. Tina Bhutani: So, as we know, there are many subtypes of psoriasis that exist, ranging from plaque psoriasis to inverse psoriasis, and even to erythrodermic psoriasis. Generalized pustular psoriasis is a rare presentation of psoriatic disease and it's characterized by the acute onset of diffuse superficial pustules on the skin. These pustules can often coalesce, forming what's known as 'lakes of pus' that are most often seen on the trunk and also in the intertriginous areas.

Patients may also have a history of plaque psoriasis. However, to have true GPP, they need to have pustules present outside of the previous plaques. Many times, patients may appear ill or have systemic symptoms such as fever, chills, malaise, or arthritis. The skin is classically very painful and can also be very itchy both during the acute phase and in the healing phase. They may also have laboratory abnormalities, such as leukocytosis or elevated inflammatory markers, such as ESR and CRP,[1] so these patients are classically very sick.

The most common age of onset is between 40 and 60 years, although cases have been described in childhood.[2] Many patients may present with a relapsing-remitting history, with recurrent episodes of pustulosis with systemic symptoms occurring throughout their life.

Dr. Jason E. Hawkes: To follow up on Dr. Bhutani's comments, it's really crucial that we also differentiate GPP from unstable forms of psoriasis, which can also present with pustules and mimic GPP. So, for example, severe erythrodermic psoriasis, or even TNF-induced psoriasis, can also present with pustules and similar systemic symptoms. Palmoplantar pustular psoriasis, or PPP, is really a more localized pustular disease of the palms and soles, where the pustules are a little different, though. They tend to be deeper-seated and not always associated with any of the systemic symptoms that Dr. Bhutani mentioned.[3]

[00:4:09]:

Dr. Uwe Wollina: Now that we have discussed how GPP clinically differs from other forms of psoriasis, can you talk more about the underlying cause of GPP and the factors contributing to this pustular condition?

Dr. Tina Bhutani: Sure. So, as I already discussed, as inferred by the name, diffuse or generalized pustules are really the hallmark of this condition, and they can present in the form of either individual lesions, like individual pustules, or more extensive confluent pustular collections or those 'lakes of pus' that I already discussed.[1]

These primary lesions are formed by the infiltration and collection of neutrophils into the epidermis and dermis,[4] so when we look at path (pathology), we see these collections of neutrophils superficially in the epidermis and also in the dermis. And we now understand that the IL-1 cytokine family, which includes the IL-36 alpha, beta and gamma cytokines, are essential components of the innate immune response and cutaneous protection conferred by keratinocytes[5] and are really important in the pathogenesis of this disease.

Jason, do you want to talk more about this?

Dr. Jason E. Hawkes: Yes. We're just starting to understand this pathway, but the key concept here is that, when you have unopposed IL-1 or IL-36 signaling due to genetic mutations, it may lead to hyperproliferation of keratinocytes in diffuse pustular disease, with these reoccurring systemic symptoms that we already talked about. We see this in some of the genetic conditions, specifically the autosomal recessive conditions like DIRA and DITRA, which are considered a subgroup of GPP,[6] so these serve as a nice template.

So, this unopposed signaling sets up this self-amplifying, or this auto-inflammatory, response in the skin as IL-36 can crosstalk with the adaptive arm in the immune system, like the T lymphocytes, and this stimulates other immune responses in the skin and the body, like the increased production of IL-17 cytokines.[4]

[00:6:00]: So, this overexpression and dysregulation of IL-36 signaling, which is primarily from the keratinocytes, is really what is driving the recruitment of the neutrophils forming these pustules in these patients who have GPP.[4]

Dr. Uwe Wollina: That is very interesting to learn how dysregulation in interleukin-36 signaling can lead to disease manifestation. Indeed, mutations in the gene interleukin-36 receptor antagonist (*IL-36RN*) have been identified in patients with GPP. Can you elaborate on the genetic basis of pustular forms of psoriasis such as GPP?

Dr. Jason E. Hawkes: Yes. This can be quite confusing. When we talk about the genetic mutations, it explains a portion of psoriasis patients who have the disease. About 60–75% of patients have known susceptibility loci that are associated with psoriasis.[7] However, in some instances, genetics alone don't determine disease, but they require the presence of other factors. We often refer to these as environmental exposures or stimuli, even infections can trigger psoriasis in these susceptible patients.

It was in a 2011 publication, in the *New England Journal of Medicine*, that the discovery of the *IL-36RN* gene was found in nine Tunisian pedigree families who had autosomal recessive disease. It really gave us insight into the underlying immunopathophysiology of GPP, making it really its own distinct clinical variant within the range of psoriasis or psoriatic disease.[8]

New genetic data suggests that specific genes that are found in GPP or pustular forms of psoriasis do not typically occur in non-pustular forms of psoriasis, but, very interestingly, *IL-36RN* gene mutations account for only about 21% of GPP cases.[9] We see a much higher likelihood of *IL-36RN* mutations in patients with GPP who have no history of plaque psoriasis, and only a small percentage of patients with both GPP and plaque psoriasis have identifiable *IL-36RN* mutations.[10]

[00:8:09]: So, we're still looking at the exact genetic causes and we've found some other genes that may contribute or play a role in GPP, like *AP1S3, CARD14, TNIP1, SERPINA3* and *MPO*. These are all genes that have some role in the immune response[11] and may also contribute to disease in a subset of patients.

Dr. Tina Bhutani: Yeah, really, based on the work that's been done, we now have clinical trials that are assessing the efficacy of an anti-IL-36 drug, spesolimab, so, specifically a biologic that's targeting anti-IL-36. And the clinical trials showed that patients responded to treatment, whether they carried an *IL-36RN* gene mutation or not. So, as Jason mentioned, this kind of makes sense. Even without mutations in the gene, overexpression of IL-36 is important for this clinical presentation, and targeting this cytokine can lead to improvement, regardless of mutation status.[12,13] So regardless of whether they have the gene mutation or not, we know that IL-36 is still important in the pathogenesis of this disease, and these clinical trials really confirm that.

While discovering that *IL-36RN* was an important milestone in our understanding of GPP, this genetic testing is not routinely done, nor is it readily available commercially.[3] It's pretty difficult to find, but genetic testing can be considered in clinical situations if there's a strong family history of pustular disease or when clinical features suggest a strong genetic basis for the disease, such as earlier onset of disease in infants or young children, or disease with intraoral manifestations.[14]

Dr. Uwe Wollina: Yes, we know the disease burden is significant in patients with GPP. In your experience, how would you describe the typical journey for patients with GPP?

Dr. Tina Bhutani: Yeah, so because GPP is a lesser recognized subtype of psoriasis, patients are often misdiagnosed or undertreated, and this often leads to really severe disease presentations, with patients presenting to the emergency room or other acute settings in order to get care.[15]

[00:10:08]: They're often hospitalized, due to their systemic symptoms, for pain management and also to rule out infections, because they present with a picture that really looks like they might be infected, and many patients are even started on empiric antibiotics.

Because of this problem with diagnosis and delay in diagnosis, patients are often seen by many different doctors and have had multiple hospital visits before they finally get to see a dermatologist and the diagnosis is made.[16] This treatment delay can profoundly impact quality of life due to the pain and symptoms associated with this disease,[16] and also the recurrent hospitalizations.

Studies indicate that pustular psoriasis has a significant psychological impact on patients, more so than even plaque psoriasis.[16–18] And also, potential complications of untreated disease can include secondary infection or sepsis, renal and liver dysfunction, and even death,[1] and so it's really critical to get these patients diagnosed and treated as soon as possible.

Dr. Jason E. Hawkes: And to add to that, as we discussed earlier, some of these patients will have these episodic flares of their disease, and we don't always find an obvious trigger, but there are some common

triggers that listeners should be aware of, including infections, pregnancy, hypocalcemia, or even starting or suddenly stopping medications, including psoriasis medications.[1,19]

Dr. Uwe Wollina: That's very interesting. The rarity of GPP contributes to the challenge of diagnosing this condition. Can you expand on how a patient with GPP is diagnosed and what clinicians should be aware of when seeing these possible GPP patients?

Dr Jason E. Hawkes: Yes, the differential diagnosis for GPP really is broad, and it includes a number of conditions.[3,6] The first I'll talk about is drug-induced eruptions. One specifically, which we call acute generalized exanthematous pustulosis, or AGEP, can certainly mimic this condition. Impetigo herpetiformis – as I mentioned, pregnancy is a risk factor, so impetigo herpetiformis is this pustular eruption that can occur during pregnancy.

[00:12:06]: Tina mentioned primary infections that can be bacterial, like bullous impetigo, viral, or even fungal infections, like tinea pedis, which is commonly referred to as athlete's foot. Other inflammatory conditions that are pre-existing – for example, atopic dermatitis in the setting of a secondary bacterial infection, also known as impetiginized atopic dermatitis, can also mimic the pustular eruption in GPP. Eosinophilic pustular folliculitis, IgA pemphigus, subcorneal pustular dermatosis or Sneddon-Wilkinson disease – these are some other conditions that we think about in the differential diagnosis for GPP.

So, it's very important that we perform a thorough skin exam and obtain a detailed history from our GPP patients, really to help us rule out the above diagnoses. Asking about prior disease, flares, and family history can also be important and help guide some management decisions. Some tests can be helpful. Although they are not routinely done, you may consider, given the specific clinical situation, a skin biopsy or wound culture, KOH preps from pustules to rule out fungal infections, labs such as erythrocyte sedimentation rate or ESR, or C-reactive protein or CRP, a complete blood count with differential, comprehensive metabolic panel or CMP, and calcium levels can be helpful in those triggered by hypocalcemia.[20]

Dr. Tina Bhutani: Yeah, and so just to add to that, as Jason mentioned, the first step in evaluating a possible case of GPP is to exclude other causes and mimics of pustular disease, so we should consider the list that was just mentioned. Also, it's really important to distinguish GPP from other forms of psoriasis[1] – firstly, other forms of pustular psoriasis like palmoplantar pustulosis and also acrodermatitis continua of Hallopeau or ACH – but more critical is to distinguish GPP from unstable plaque psoriasis or erythrodermic psoriasis that may present with pustules.

[00:14:03]: Sometimes, this can occur when psoriasis treatments are abruptly withdrawn or discontinued, such as treatment with cyclosporine or even TNF inhibitors. Oftentimes, patients with psoriasis who get an oral prednisone taper that might be tapered very quickly or discontinued, they can also present with unstable plaque psoriasis that has pustular features. Psoriasis patients who get primary infections, and also TNF-induced psoriasiform dermatitis, can present with pustular features. So, it's important to differentiate those subtypes from classic GPP.

Dr. Uwe Wollina: Thank you so much for taking the time to speak with us today. Based on your clinical experience, what main takeaway on GPP is important for healthcare providers to know?

Dr. Tina Bhutani: Yeah, so I think, for me, I want healthcare providers to know that GPP is an under-recognized form of psoriasis and, as I mentioned before, it needs rapid diagnosis and treatment to prevent complications from the disease. Therefore, increasing our awareness is the first step to improving quality of care for these patients.

Dr. Jason E. Hawkes: Totally agree. And for me, it's really been through the ongoing research, that we're just now beginning to understand how all the unique subtypes or variants of psoriasis, like GPP, differ from the conventional plaque psoriasis that we're all familiar with, and also how IL-36 plays a role in driving the disease phenotype outside of IL-17 and IL-23.

You know, while we can't fully explain the underlying genetics, disease triggers or clinical course of these patients, the treatment success associated with selective inhibition of the IL-36 receptor for GPP, as was mentioned, really is a major breakthrough for patients suffering with this variant, and it truly is an exciting time to be in medical dermatology.

Dr. Uwe Wollina: Thanks so much to both Drs. Bhutani and Hawkes for sharing your expertise today in diagnosing GPP. We appreciate your time today.

[00:16:00]: To our listeners, please join us on upcoming podcasts that focus on GPP treatment and management, and on the patient perspective in managing GPP.

Acknowledgments

This podcast was sponsored by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI).

The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors received no direct compensation related to the development of the manuscript. Editorial support was provided by Katie Crosslin, PhD, and Allison Craig, PharmD, both of Elevate Scientific Solutions, which was contracted and compensated by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) for this service. BIPI was given the opportunity to review the discussion points for medical and scientific accuracy as well as intellectual property considerations. The authors thank Dr. Uwe Wollina for serving as the moderator and for reviewing the transcript prior to journal submission.

Funding

Medical writing support, which was provided by Elevate Scientific Solutions, was contracted and funded by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI).

Disclosure

TB is currently aprincipal investigator for studies being sponsored by AbbVie, Castle, CorEvitas, Dermavant, Galderma, Mindera, and Pfizer. She has additional research funding from Novartis and Regeneron. She has served as an advisor for AbbVie, Arcutis, Boehringer-Ingelheim, Bristol Myers Squibb, Janssen, Leo, Eli Lilly and Company, Pfizer, Novartis, Sun, and UCB.

JEH has served as a consultant and/or advisor for AbbVie, Arcutis, Boehringer Ingelheim, BMS, Janssen, LearnSkin, LEO, Lilly, Novartis, Pfizer, Regeneron-Sanofi Genzyme, and UCB. He also currently serves on the medical board and scientific advisory committee of the National Psoriasis Foundation and is a councilor in the International Psoriasis Council.

References

1. Gooderham MJ, Van Voorhees AS, Lebwohl MG. An update on generalized pustular psoriasis. *Expert Rev Clin Immunol*. 2019;15(9):907–919. doi:10.1080/1744666X.2019.1648209
2. Augey F, Renaudier P, Nicolas JF. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. *Eur J Dermatol*. 2006;16 (6):669–673.
3. Ly K, Beck KM, Smith MP, Thibodeaux Q, Bhutani T. Diagnosis and screening of patients with generalized pustular psoriasis. *Psoriasis*. 2019;9:37–42. doi:10.2147/PTT.S181808
4. Marrakchi S, Puig L. Pathophysiology of generalized pustular psoriasis. *Am J Clin Dermatol*. 2022;23(Suppl 1):13–19. doi:10.1007/s40257-021-00655-y
5. Johnston A, Xing X, Wolterink L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. *J Allergy Clin Immunol*. 2017;140 (1):109–120. doi:10.1016/j.jaci.2016.08.056
6. Sussman M, Napodano A, Huang S, Are A, Hsu S, Motaparthi K. Pustular Psoriasis and Acute Generalized Exanthematous Pustulosis. *Medicina*. 2021;57(10). doi:10.3390/medicina57101004
7. Lønnberg AS, Skov L, Skytthe A, Kyvik KO, Pedersen OB, Thomsen SF. Heritability of psoriasis in a large twin sample. *Br J Dermatol*. 2013;169 (2):412–416. doi:10.1111/bjd.12375
8. Marrakchi S, Guigue P, Renshaw BR, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. *N Engl J Med*. 2011;365(7):620–628. doi:10.1056/NEJMoa1013068
9. Hussain S, Berki DM, Choon SE, et al. IL36RN mutations define a severe autoinflammatory phenotype of generalized pustular psoriasis. *J Allergy Clin Immunol*. 2015;135(4):1067–1070 e1069. doi:10.1016/j.jaci.2014.09.043
10. Sugiura K, Takemoto A, Yamaguchi M, et al. The majority of generalized pustular psoriasis without psoriasis vulgaris is caused by deficiency of interleukin-36 receptor antagonist. *J Invest Dermatol*. 2013;133(11):2514–2521. doi:10.1038/jid.2013.230
11. Samotij D, Szczech J, Reich A. Generalized pustular psoriasis: divergence of innate and adaptive immunity. *Int J Mol Sci*. 2021;22(16):9048. doi:10.3390/ijms22169048
12. Bachelez H, Choon SE, Marrakchi S, et al. Trial of spesolimab for generalized pustular psoriasis. *N Engl J Med*. 2021;385(26):2431–2440. doi:10.1056/NEJMoa2111563
13. Bachelez H, Choon SE, Marrakchi S, et al. Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis. *N Engl J Med*. 2019;380(10):981–983. doi:10.1056/NEJMc1811317
14. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol*. 2019;143 (3):1021–1026. doi:10.1016/j.jaci.2018.06.038
15. Strober B, Leman J, Mockenhaupt M, et al. Unmet educational needs and clinical practice gaps in the management of generalized pustular psoriasis: global perspectives from the front line. *Dermatol Ther*. 2022;12(2):381–393. doi:10.1007/s13555-021-00661-2

16. Reisner DV, Johnsson FD, Kotowsky N, Brunette S, Valdecantos W, Eyerich K. Impact of generalized pustular psoriasis from the perspective of people living with the condition: results of an online survey. *Am J Clin Dermatol*. 2022;23(Suppl 1):65–71. doi:10.1007/s40257-021-00663-y
17. Okubo Y, Kotowsky N, Gao R, Saito K, Morita A. Clinical characteristics and health-care resource utilization in patients with generalized pustular psoriasis using real-world evidence from the Japanese Medical Data Center database. *J Dermatol*. 2021;48(11):1675–1687. doi:10.1111/1346-8138.16084
18. Sampogna F, Tabolli S, Söderfeldt B, Axtelius B, Aparo U, Abeni D. Measuring quality of life of patients with different clinical types of psoriasis using the SF-36. *Br J Dermatol*. 2006;154(5):844–849. doi:10.1111/j.1365-2133.2005.07071.x
19. Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. *Int J Dermatol*. 2014;53(6):676–684. doi:10.1111/ijd.12070
20. Umezawa Y, Ozawa A, Kawasima T, et al. Therapeutic guidelines for the treatment of generalized pustular psoriasis (GPP) based on a proposed classification of disease severity. *Arch Dermatol Res*. 2003;295(Suppl 1):S43–54. doi:10.1007/s00403-002-0371-6