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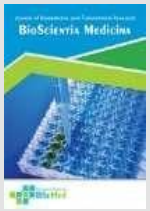

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The Oral-Skin Axis in Autoinflammation: A Case Report of Severe Refractory Generalized Pustular Psoriasis (GPP) Resolved by Comprehensive Periodontal Intervention

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A B S T R A C T

Background: Generalized pustular psoriasis (GPP) is a severe, IL-36-driven autoinflammatory dermatosis, distinct from psoriasis vulgaris. Chronic periodontitis (CP) is a dysbiotic inflammatory disease sharing pathogenic pathways (IL-1, IL-17). An "oral-skin axis" has been hypothesized, but definitive clinical evidence of CP driving a GPP flare is scarce. **Case presentation:** We present a 37-year-old male with a history of plaque psoriasis who developed a severe, refractory GPP flare (GPPASI 35.8) with high-grade fever (38.9°C), profound neutrophilic leukocytosis (22.5 x 10^3/µL), and markedly elevated CRP (150 mg/L). The flare was resistant to maintenance methotrexate. Workup revealed severe CP with multiple periapical abscesses, culture from which grew *Porphyromonas gingivalis* and *Fusobacterium nucleatum*. The patient underwent a comprehensive dental intervention, including emergency extractions and full-mouth debridement, with concurrent peri-operative Amoxicillin-Clavulanate therapy. This combined intervention led to a rapid resolution of fever, neutrophilia, and cutaneous pustulation within 72 hours, without any escalation of systemic immunomodulators. He achieved complete remission (GPPASI 1.0) at 3-month follow-up. **Conclusion:** This case provides a strong temporal association supporting the oral-skin axis, highlighting severe periodontitis as a potent trigger and amplifier for GPP. The rapid resolution following a *combined* surgical and antibiotic intervention suggests that targeting the oral inflammatory and microbial reservoir is a critical, actionable strategy. We strongly recommend consideration of a comprehensive dental/oral screening in patients with refractory GPP.

1. Introduction

Generalized pustular psoriasis (GPP) is a rare, life-threatening, and severe systemic inflammatory disease of the skin, characterized by recurrent, widespread episodes of sterile, non-follicular pustules.[1] These pustules often coalesce into "lakes of pus," arising on a background of painful, fiery erythema. Unlike the more common psoriasis vulgaris (PV), GPP is almost invariably accompanied by systemic symptoms, including fever, malaise, arthralgia, and significant hematological disturbances, most notably a profound neutrophilic leukocytosis. If unmanaged, GPP can lead to life-threatening complications, including sepsis, high-output cardiac failure, and electrolyte imbalances, highlighting its status as a true dermatological emergency.[2]

For decades, GPP was considered part of the spectrum of PV. However, a wealth of immunological and genetic research has now firmly established GPP as a distinct clinical and immunologic entity, driven by a pathophysiology fundamentally different from that of classic plaque psoriasis.[3] While PV is a quintessential T-cell-mediated adaptive immune disease, dominated by the IL-23/Th17 axis, GPP is a quintessential autoinflammatory disease of the innate immune system.[4]

The dominant pathogenic driver in GPP is the Interleukin-36 (IL-36) cytokine family. In healthy skin, the activity of IL-36 cytokines (IL-36α, β, and γ) is tightly regulated by the IL-36 receptor antagonist (IL-36Ra).[5] In a significant subset of GPP patients, this balance is genetically broken by loss-of-function mutations in the IL36RN gene, which encodes IL-36Ra. This monogenic condition, known as DITRA (Deficiency of IL-36 Receptor Antagonist), leads to unopposed IL-36 signaling and the characteristic GPP phenotype. However, even in genetically wild-type patients, a massive, trigger-induced upregulation of IL-36 ligands is observed, overwhelming the available IL-36Ra and initiating the same inflammatory cascade.[6]

This unopposed IL-36 signaling, amplified by other innate cytokines like IL-1β and TNF-α, activates keratinocytes and dendritic cells via the NF-κB and MAPK pathways. This activation creates a vicious, self-amplifying feed-forward loop: activated keratinocytes produce more IL-36, along with a torrent of neutrophil-recruiting chemokines (CXCL1, CXCL2, CXCL8). This "IL-36 signature" results in the massive influx of neutrophils from the vasculature into the epidermis, forming the pathognomonic sterile spongiform pustules of Kogoj. These neutrophils, in turn, release proteases that cleave and further activate IL-36 precursors, perpetuating the cycle. This cutaneous inflammation spills systemically, driving the fever and emergency granulopoiesis (neutrophilia) seen clinically.[7]

Given this autoinflammatory nature, GPP flares are notoriously precipitated by various triggers, including pregnancy, certain medications, and the rapid withdrawal of systemic corticosteroids. Infections are a well-established trigger.[8] While acute infections like streptococcal pharyngitis are known, the role of chronic, localized, dysbiotic inflammatory conditions as a primary trigger and sustainer of GPP is less defined.

Chronic periodontitis (CP) is one of the most prevalent human inflammatory diseases, affecting a significant portion of the global adult population. Like GPP, CP is increasingly understood as a disease of aberrant host-immune response rather than a simple infection. It is initiated by a dysbiotic polymicrobial biofilm, orchestrated by "keystone pathogens" such as *Porphyromonas gingivalis*.[9] These pathogens and their virulence factors (lipopolysaccharide [LPS], gingipains) subvert the host immune response, resulting in a chronic, destructive, and neutrophil-dominated inflammation. This inflammation, strongly driven by IL-1β and a Th17-skewed T-cell response (producing IL-17), leads to the progressive destruction of the periodontal ligament and alveolar bone.

An epidemiological link between psoriasis and periodontitis has been robustly established in numerous meta-analyses. This strong association suggests shared pathogenic mechanisms, including overlapping cytokine pathways (IL-1, IL-17, TNF-α) and shared genetic loci. This has given rise to the concept of an "oral-skin axis," a bidirectional pathway where inflammation in one compartment can influence the other. It is hypothesized that the chronically inflamed periodontal pocket, with a massive cumulative surface area, acts as a "systemic inflammatory reservoir," continuously "spilling" pro-inflammatory cytokines, microbial components (Pathogen-Associated Molecular Patterns, or PAMPs), and activated immune cells into the systemic circulation. This systemic inflammatory load is thought to lower the activation threshold for cutaneous inflammation, effectively "priming" the skin for a flare.

While this link is established, reports demonstrating the resolution of severe, life-

threatening GPP (not just PV) following periodontal treatment are exceptionally rare. The precise mechanisms by which chronic oral inflammation fuels the IL-36-specific axis of GPP remain to be fully elucidated.[10] This case report aims to provide a detailed clinical, immunological, and histopathological description of such a case, exploring the pathophysiological links and highlighting the therapeutic implications of a comprehensive dental intervention. We present a patient with severe, refractory GPP whose flare was temporally and immunologically linked to an active, severe chronic periodontitis, and which resolved rapidly only after a combined surgical and antimicrobial oral intervention.

2. Case Presentation

A 37-year-old male accountant presented to our emergency department with a one-week history of a rapidly progressive, painful, and pustular rash accompanied by high-grade fever and severe malaise. The patient had a 15-year history of well-controlled, mild-to-moderate plaque psoriasis (psoriasis vulgaris), affecting <5% of his body surface area (BSA), primarily on the elbows, knees, and scalp. His disease had been stable for years on topical corticosteroids (Clobetasol propionate 0.05% ointment as needed) and intermittent phototherapy. Ten years prior to presentation, he experienced his first episode of GPP, which required hospitalization and was successfully treated with oral acitretin. Since that time, he had been managed on maintenance oral methotrexate (MTX) 15 mg weekly, with folic acid supplementation. This regimen had kept his disease quiescent, with only minor, self-limiting flares.

The patient's relevant medical history included being overweight (Body Mass Index [BMI] 29.05 kg/m^2). He was a current smoker (one pack per day, 15-pack-year cumulative history) and reported regular social alcohol consumption (4-5 glasses of ethanol-based drinks per weekend). Approximately three months prior to admission, the patient noted increased gingival bleeding when brushing and a persistent, dull ache in his jaw, which he attributed to "sensitive teeth." He did not seek dental consultation. Two months prior to admission, he noticed his maintenance MTX seemed less effective, with new erythematous plaques and scattered pustules appearing on his trunk. In the week leading up to admission, the rash "exploded," spreading rapidly across his entire trunk, back, and extremities, becoming intensely painful and "burning." He developed fever, chills, and profound fatigue. He denied any recent medication changes, withdrawal from corticosteroids, or preceding viral illness.

On admission, the patient was in moderate distress, appeared ill, and was febrile to 38.9°C (102.0°F). His heart rate was 110 beats/min, blood pressure was 130/85 mmHg, and respiratory rate was 18 breaths/min. Cutaneous examination revealed widespread, confluent, "fiery red" erythematous patches covering approximately 40% of his BSA. Superimposed on this erythema were innumerable, 1-3 mm, discrete and confluent, sterile pustules. These pustules were most dense on the trunk, where they coalesced into large, 5-10 cm, purulent "lakes of pus". Annular lesions with a peripheral "collarette" of scale and trailing pustules were present on the extremities. The skin was exquisitely tender. Generalized Pustular Psoriasis Area and Severity Index (GPPASI) was 35.8 (severe), and Dermatology Life Quality Index (DLQI) was 28/30. Oral examination revealed severe halitosis, generalized, edematous, and erythematous gingiva that bled profusely on contact. A thick plaque and calculus buildup were visible. Purulent exudate could be expressed from the periodontal pockets of multiple teeth. Several teeth exhibited Grade 2-3 mobility.

The patient's initial laboratory workup revealed a profound systemic inflammatory state, reflecting the severity of the GPP flare. The hematological analysis was dominated by a striking neutrophilic leukocytosis, with a total white blood cell (WBC) count of 22.5 x $10^3/\mu L$ (Normal: 4.1-11.0). This was overwhelmingly comprised of neutrophils, with an absolute count of 19.8 x $10^3/\mu L$ (Normal: 2.5-7.5), constituting 88% of

the total circulating leukocytes. This finding provides objective, systemic evidence for the "emergency granulopoiesis" characteristic of a neutrophil-driven disease. This profound leukocytosis was mirrored by a massive elevation in acute-phase reactants. The C-Reactive Protein (CRP) was markedly elevated at 150 mg/L (Normal: <5), and the Erythrocyte Sedimentation Rate (ESR) was 88 mm/hr (Normal: <15). Critically, this picture of severe inflammation, which might otherwise be mistaken for bacterial sepsis, was clarified by a low procalcitonin level of 0.3 ng/mL (Normal: <0.5). The low procalcitonin, combined with two sets of sterile blood cultures (no growth at 5 days) and a sterile culture from an aspirated pustule, strongly argued against systemic bacterial sepsis and pointed towards a sterile, autoinflammatory process.

Evidence of the systemic burden of this chronic inflammatory state was abundant. The metabolic panel was significant for hypoalbuminemia (Albumin: 2.9 g/dL), a negative acute-phase reactant reflecting both systemic inflammation and potential transepidermal protein loss. The patient also exhibited a mild anemia of chronic disease (Hemoglobin: 10.5 g/dL) and a reactive thrombocytosis (Platelets: 480 x $10^3/\mu L$), both common hematological sequelae of a sustained, high-grade inflammatory condition. All other metabolic markers, including creatinine and liver function tests, were within normal limits. The cellular signature was definitively confirmed at the tissue level. A 4-mm punch biopsy obtained from an active pustular lesion on the trunk was pathognomonic for Generalized Pustular Psoriasis. Histopathological examination revealed prominent acanthosis, parakeratosis with neutrophil collections, and a significantly reduced granular layer. The cardinal finding was a large, subcorneal, multilocular spongiform pustule of Kogoj, which was inundated with a massive influx of neutrophils. The underlying papillary dermis was markedly edematous and contained a dense, perivascular inflammatory infiltrate composed of lymphocytes, histiocytes, and abundant neutrophils, thus completing the classic histopathological picture of GPP.

A panoramic radiograph (orthopantomogram) revealed severe, generalized horizontal and vertical alveolar bone loss, consistent with advanced chronic periodontitis. Multiple periapical abscesses (radiolucent areas) were noted at the apices of teeth #11, #21, #25, #28, and #32. Dental diagnosis was severe chronic periodontitis, with multiple acute periapical abscesses. During the emergency dental procedure, purulent material from the periapical abscess of tooth #21 was aspirated under sterile conditions and sent for anaerobic culture and 16S rRNA sequencing. Anaerobic culture grew *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, both known "keystone pathogens" in severe periodontitis.

The patient was admitted to the dermatology inpatient unit for aggressive supportive care (IV fluids, wound care, emollients). His 15 mg weekly MTX was deemed a therapeutic failure. The primary clinical challenge was the trigger. The fever and profound neutrophilia strongly suggested an underlying infection, yet blood and pustule cultures were sterile. Escalation to biologic therapy (an IL-36R inhibitor like Spesolimab) was considered, but there was significant concern about initiating profound immunosuppression in the setting of a potential occult infection.

The dental consultation identified the oral cavity as a massive, active focus of infection and inflammation. An interdisciplinary decision was made: the periodontal disease was the most likely driver of the patient's systemic inflammation and GPP flare. The treatment plan was to "turn off the tap" of this inflammation. The patient was taken for an emergency dental procedure under local anesthesia. This involved: (1) Full-mouth debridement and scaling/root planning; (2) Extraction of all non-viable, abscessed teeth (#11, 21, 25, 28, 32, 33, 47). Crucially, he was concurrently placed on a 7-day course of oral Amoxicillin-Clavulanate 875/125mg BID as peri-operative antimicrobial therapy to control the identified polymicrobial infection.

Table 1. Summary of clinical findings on admission.

CATEGORY	PARAMETER / TEST	PATIENT'S RESULT	NORMAL RANGE / REFERENCE	SIGNIFICANCE
Clinical Severity	Systemic Fever	**38.9°C (102.0°F)**	< 38.0°C	**High-Grade Fever**
	GPPASI Score	**35.8**	0-72	**Severe Disease**
	DLQI Score	**28 / 30**	0-30	**Extremely Large Effect on Quality of Life**
Hematology	WBC Count	**22.5 x $10^3/\mu L$**	4.1-11.0	**Profound Leukocytosis**
	Absolute Neutrophil Count	**19.8 x $10^3/\mu L$**	2.5-7.5	**Severe Neutrophilia**
	Hemoglobin	**10.5 g/dL**	(Varies)	**Anemia of Chronic Disease**
	Platelets	**480 x $10^3/\mu L$**	150-450	**Reactive Thrombocytosis**
Inflammatory Markers	C-Reactive Protein (CRP)	**150 mg/L**	< 5.0	**Marked Systemic Inflammation**
	Erythrocyte Sedimentation Rate (ESR)	**88 mm/hr**	< 15	**Marked Systemic Inflammation**
	Procalcitonin	0.3 ng/mL	< 0.5	Argues Against Overt Bacterial Sepsis
Metabolic Panel	Albumin	**2.9 g/dL**	~3.5-5.5	**Hypoalbuminemia (Negative AP)**
	Creatinine & LFTs	Within Normal Limits	Per lab reference	Normal Renal & Hepatic Function
Microbiology (Systemic)	Blood Cultures (2 sets)	No Growth at 5 days	No Growth	Sterile
	Pustule Culture	Sterile (No organisms)	No Growth	Confirms Sterile Pustulosis
Dermatopathology	Trunk Biopsy (4-mm)	**Spongiform Pustule of Kogoj**	N/A	**Pathognomonic for GPP**
Dental & Oral Microbiology	Panoramic Radiograph	**Severe Bone Loss & Abscesses**	N/A	**Severe Chronic Periodontitis**
	Abscess Culture (Tooth #21)	**Grew *P. gingivalis & F. nucleatum***	No Growth	**Identified Keystone Pathogens**

The patient's response to this combined intervention was rapid and dramatic. On 24 hours post-intervention, the patient reported a significant reduction in skin pain and "burning". Forty-eight hours post-intervention, the fever resolved (temperature 37.1°C). No new pustules were forming. The "lakes of pus" began to dry. On 72 hours post-intervention, the patient was afebrile and systemically well. The GPP flare had clearly "broken". This dramatic improvement occurred without any addition or escalation of his systemic immunomodulators (biologics), though it was concurrent with the initiation of both surgical debridement and systemic antibiotic therapy. The patient's objective inflammatory markers mirrored his clinical improvement (Table 2). The patient was discharged on Day 10, with only residual post-inflammatory erythema. His GPPASI score had fallen from 35.8 to 10.5. He was continued on his maintenance MTX 15mg/week and referred for long-term dental rehabilitation. He was also counseled on smoking and alcohol cessation. At 3-month follow-up, he was in complete remission (GPPASI 1.0) and had experienced no further flares.

Table 2. Treatment, follow-up, and outcome of the patient.

TIME POINT	INTERVENTION / OBSERVATION	KEY CLINICAL & LABORATORY OUTCOMES	STATUS / SIGNIFICANCE
Day 0-1 (Intervention)	Surgical Intervention	Full-mouth debridement & scaling. Extraction of 7 abscessed/non-viable teeth.	Removal of Inflammatory Nidus
	Medical Intervention	Start 7-day course of Amoxicillin-Clavulanate 875/125mg BID.	Control of Bacterial Load
Day 1-3 (Acute Response)	24 Hours Post-Op	Patient reports significant reduction in skin pain and "burning" sensation.	Rapid Symptomatic Improvement
	48 Hours Post-Op	Fever resolved (Temp 37.1°C). No new pustule formation.	Systemic Inflammation Breaking
	72 Hours Post-Op	Afebrile and systemically well. "Lakes of pus" drying and crusting.	GPP Flare "Broken"
Day 4-10 (Lab Evolution)	72 Hours Post-Op (Day 4)	WBC: 11.2 (from 22.5) Neutrophils: 7.5 (from 19.8) CRP: 32.5 (from 150.0)	Rapid Decrease in Inflammatory Markers
	Discharge (Day 10)	WBC: 8.1 Neutrophils: 4.9 CRP: 6.2	Lab Markers Normalized
Long-Term Follow-up	Discharge (Day 10)	GPPASI Score: 10.5 (from 35.8) Residual erythema and scaling.	Cutaneous Disease Resolving
	2-Week Follow-up	GPPASI Score: 4.2	Near Remission
	3-Month Follow-up	GPPASI Score: 1.0 No flares since intervention.	Complete Clinical Remission

3. Discussion

This case provides a striking and unusually clear-cut example of the "oral-skin axis" in action, offering a rare, "n-of-1" experimental model of a complex immunopathological interplay. We report a patient with severe, life-threatening generalized pustular psoriasis (GPP), whose disease was refractory to maintenance methotrexate, a standard systemic immunomodulator. The patient's condition, characterized by a profound systemic inflammatory signature (fever, neutrophilia, high CRP) and severe cutaneous disease (GPPASI 35.8), resolved rapidly and completely only after a comprehensive dental intervention to manage a severe, comorbid chronic periodontitis.[11]

The case is scientifically exceptional for its clear and rapid temporal relationship; (1) Therapeutic Failure: The patient's established GPP was resistant to conventional, T-cell-centric immunomodulation (methotrexate), suggesting the flare was driven by a non-T-cell pathway; (2) Trigger Identification: A massive, active, and infectious inflammatory focus was identified in the oral cavity; (3) Rapid Resolution: A dramatic resolution of all systemic and cutaneous parameters occurred within 72 hours of the dental intervention; (4) Absence of Confounders: This resolution occurred without the escalation of systemic immunosuppressive therapy, such as the initiation of a biologic. This absence of confounding by new dermatological therapies is what isolates the dental intervention as the key therapeutic variable. This report, therefore, moves beyond the simple epidemiological associations that have long linked psoriasis and periodontitis.[12] It provides a strong, mechanistically plausible model suggesting that chronic periodontitis, in certain patients, can act as a primary driver and systemic amplifier for a severe GPP flare. The subsequent discussion will focus on deconstructing the intricate pathophysiological mechanisms that bridge these two seemingly disparate inflammatory diseases and will analyze the nature of the successful, multi-pronged intervention.[13]

To understand the connection, one must first appreciate the unique and specific pathophysiology of GPP. It is now definitively established that GPP is not merely a severe variant of psoriasis vulgaris (PV), but a distinct autoinflammatory disease of the innate immune system, in contrast to the adaptive, T-cell-driven nature of PV.[14] The dominant pathogenic driver in GPP is the Interleukin-36 (IL-36) cytokine family, which includes the agonists IL-36α, IL-36β, and IL-36γ, and their specific receptor, IL-36R. In healthy skin, the activity of these potent pro-inflammatory cytokines is tightly controlled by the high-affinity IL-36 receptor antagonist (IL-36Ra). This antagonist, encoded by the IL36RN gene, is co-expressed with the agonists in keratinocytes and acts as a biological "brake" on the pathway.[15]

In a significant subset of GPP patients, this "brake" is genetically broken by loss-of-function mutations in IL36RN, a condition known as DITRA (Deficiency of IL-36 Receptor Antagonist). In DITRA, the lack of a functional antagonist leads to unopposed, high-potency IL-36 signaling, which is sufficient to drive the GPP phenotype. However, even in genetically wild-type patients, an overwhelming environmental or inflammatory "trigger" can lead to a massive over-production of IL-36 agonists, effectively "saturating" and overwhelming the available IL-36Ra, thereby initiating the same pathogenic cascade.[16]

This unopposed IL-36 signaling through the IL-36R on keratinocytes activates downstream signaling cascades, primarily via the NF-κB and MAPK pathways. This activation has two critical, self-amplifying effects that create a vicious feed-forward loop: (1) More IL-36: Activated keratinocytes are stimulated to produce even more IL-36 agonists, creating a local, self-perpetuating autoinflammatory cycle; (2) Neutrophil Chemokines: Activated keratinocytes and adjacent dendritic cells release a torrent of neutrophil-recruiting chemokines, most importantly CXCL1, CXCL2, and CXCL8 (IL-8). This "IL-36 signature" is the engine of GPP. The flood of chemokines results in the massive influx of neutrophils from the dermal vasculature into the epidermis. This was seen histologically in our patient as the pathognomonic sterile spongiform pustules of Kogoj. This cutaneous inflammation then spills systemically. The IL-36, IL-1, and IL-6 produced in the skin enter the circulation, acting on the hypothalamus to cause fever and on the bone marrow to induce "emergency granulopoiesis." This systemic effect was seen in our patient as the profound neutrophilic leukocytosis (WBC 22.5 x 10^3/μL). Furthermore, these newly recruited neutrophils release their own proteases (like elastase and cathepsin G), which have been shown to cleave and activate the inactive IL-36 precursors, thus adding yet another layer to the self-perpetuating cycle.[17]

Simultaneously, our patient had a severe, active chronic periodontitis (CP) with multiple periapical abscesses. It is crucial to understand that CP, like GPP, is not a simple infection but a complex, dysbiotic inflammatory disease. It is not caused by the mere presence of bacteria, but by a shift in the oral microbiome's composition and function, which subverts the host immune response.[18] This dysbiosis is often orchestrated by "keystone pathogens," such as *Porphyromonas gingivalis*, which we successfully cultured from our patient's abscess. *P. gingivalis* is a master of inflammation, not by its sheer numbers, but by its sophisticated virulence factors. Its gingipains (potent proteases), fimbriae, and uniquely modified Lipopolysaccharide (LPS) allow it to manipulate the host's innate immune response for its own benefit.

The host response to this dysbiotic biofilm is chronic, destructive, and, critically, mirrors the GPP response in its inflammatory signature. The bacterial PAMPs activate host Toll-like Receptors (TLRs), driving the production of a pro-inflammatory "cytokine soup," including IL-1β, IL-6, and TNF-α. This chronic antigen presentation also drives a strong, destructive Th17-skewed T-cell response. This IL-17, in turn, drives inflammation and, via the RANKL pathway, promotes the osteoclast activity that leads to the alveolar bone loss seen on our patient's radiograph.

The chronically inflamed periodontal pocket, which in severe disease can have a cumulative, ulcerated

epithelial surface area as large as the palm of the hand, acts as a systemic "factory" and "reservoir". It is an open wound that continuously spills two products into the systemic circulation, 24 hours a day: (1) Inflammatory Mediators: Pro-inflammatory cytokines (IL-1, IL-6, IL-17); (2) Microbial Products: Live bacteria, bacterial DNA, and PAMPs (LPS). This continuous systemic seeding places the entire host immune system on a "high alert" status, effectively "priming" it for a hyper-inflammatory response.[19]

Our case data, combined with the established literature, allows us to propose a "three-bridge" model to explain precisely how the chronic oral inflammation directly triggered and sustained the acute cutaneous GPP flare; (1) Bridge 1: Systemic Cytokine Spillover (Hypothesized but Supported). This bridge posits that the cytokines produced in the gingival "factory" did not remain localized. The high systemic levels of IL-1β, IL-6, and, critically, IL-17 (a hallmark of periodontitis) spilled into the circulation and traveled to the skin, lowering the activation threshold of the *entire* cutaneous immune system. This "priming" is not theoretical. IL-1β and IL-36, for example, share the MyD88 signaling pathway, and their signaling is known to be synergistic. Even more compellingly, IL-17 (originating from the mouth) is known to synergize with TNF-α (also from the mouth) to upregulate the expression of IL-36 in distant keratinocytes. The oral inflammation was, therefore, likely "pouring gasoline" on the cutaneous embers by providing the very cytokines needed to amplify the skin's own IL-36 loop; (2) Bridge 2: Systemic Neutrophil Priming (Directly Observed). This bridge is supported by direct, objective data from our patient. The chronic, high-demand for neutrophils in the gingival crevice, combined with the systemic spillover of G-CSF and IL-6 from the oral cavity, places the bone marrow in a constant state of "emergency granulopoiesis". This is precisely what we observed: a baseline state of profound neutrophilia (19.8 x $10^3/\mu L$). This is not just more neutrophils; it is primed neutrophils. These cells circulate in a "hair-trigger" state, already activated by the systemic inflammatory signals. When our patient's skin-level IL-36 axis was triggered, it did not have to slowly recruit and activate neutrophils from the bone marrow; it simply had to send out the "chemokine call" (CXCL8) to the massive, pre-existing, and hyper-responsive army already in his blood. This explains the rapidity and severity of the "lake of pus" formation. The dental disease provided the soldiers; the skin provided the battlefield. The rapid normalization of his WBC count post-intervention (Table 2) confirms this bridge; (3) Bridge 3: PAMPs and Pathogen-Specific Triggers (Hypothesized but Supported). This bridge, while speculative, is strongly supported by our novel abscess culture data. We did not measure systemic LPS, but we did identify the "keystone pathogens" (*P. gingivalis* and *F. nucleatum*) that produce it. This is the "spark." In severe periodontitis, simple acts like chewing can cause transient bacteremia and a showering of the bloodstream with PAMPs like LPS. These circulating PAMPs are potent activators of TLR-2 and TLR-4, which are expressed on keratinocytes and dermal dendritic cells. This PAMP signaling directly activates the NF-κB pathway in the keratinocyte. This is the exact same pathway that IL-36 uses. Therefore, the bacterial LPS from the dental abscess likely acted as the initiator of the flare, providing the initial, potent NF-κB signal that "lit the IL-36 autoinflammatory fire" in the skin, which then began its own self-perpetuating cycle.[20]

A critical point of discussion, and a central tenet of this paper's revised hypothesis, is the nature of the successful intervention. The patient's treatment was, in fact, two-pronged: (1) surgical extraction/debridement and (2) systemic Amoxicillin-Clavulanate therapy. This co-intervention introduces a significant, but highly informative, confounder. It is methodologically impossible to disentangle the two effects, and we must consider three possibilities for the patient's rapid resolution: (1) Hypothesis A: Resolution was driven by the Antibiotic. Amoxicillin-Clavulanate is a potent, broad-spectrum antibiotic with excellent coverage against the oral anaerobes we identified. In this model, the antibiotic directly

eradicated the bacteria (*P. gingivalis*), thereby immediately shutting down "Bridge 3" (PAMP production). This, in turn, caused a downstream, lagging cessation of the host's response: "Bridge 1" (cytokine spillover) and "Bridge 2" (neutrophil demand) powered down; (2) Hypothesis B: Resolution was driven by the Surgery. This model posits that a chronic, walled-off periapical abscess is a necrotic, avascular "factory." Systemic antibiotics may fail to penetrate this nidus effectively. The abscess contains not just live bacteria, but a massive reservoir of pre-formed cytokines and pre-formed PAMPs/virulence factors. In this model, it was the physical removal (debridement and extraction) of this "factory" that immediately "turned off the tap" and caused the rapid 72-hour collapse of the inflammatory load; (3) Hypothesis C: Resolution was Synergistic (The Parsimonious Conclusion). The most likely and parsimoniousexplanation is that the effects were synergistic, complementary, and addressed different facets of the problem. The surgery physically removed the core, necrotic, avascular reservoir that was likely resistant to antibiotic monotherapy. The antibiotics simultaneously "mopped up" the remaining bacterial load in the surrounding viable, perfused tissue and, critically, prevented the transient bacteremia from the extraction itself from causing a new systemic seeding.

We believe this third hypothesis is the correct one. This "turning off the tap" from two different directions simultaneously is what best explains the remarkable rapidity (72-hour) of the systemic inflammatory collapse. This nuanced interpretation does not weaken the "oral-skin axis" hypothesis; in fact, it strengthens it. It clarifies the mechanism by showing that the trigger is the infectious and inflammatory burden of the oral cavity, and it provides a clear, actionable therapeutic model: a comprehensive intervention, targeting both the physical source and the microbial load, is required for resolution. The failure of MTX, an anti-proliferative, T-cell-targeting drug, to control this innate, PAMP-driven flare further highlights this critical distinction.[17,18]

The implications of this case, even with its limitations, are profound. This report warrants a high index of suspicion for occult dental inflammation in GPP. The common patient complaint of "sensitive teeth" or "bleeding gums," often dismissed as a minor comorbidity, may in fact be a critical, overlooked clue to the primary driver of their systemic disease. We strongly recommend that clinicians maintain a low threshold for a comprehensive oral examination and panoramic radiography, especially in patients with refractory GPP, new-onset GPP, or flares of unknown origin.

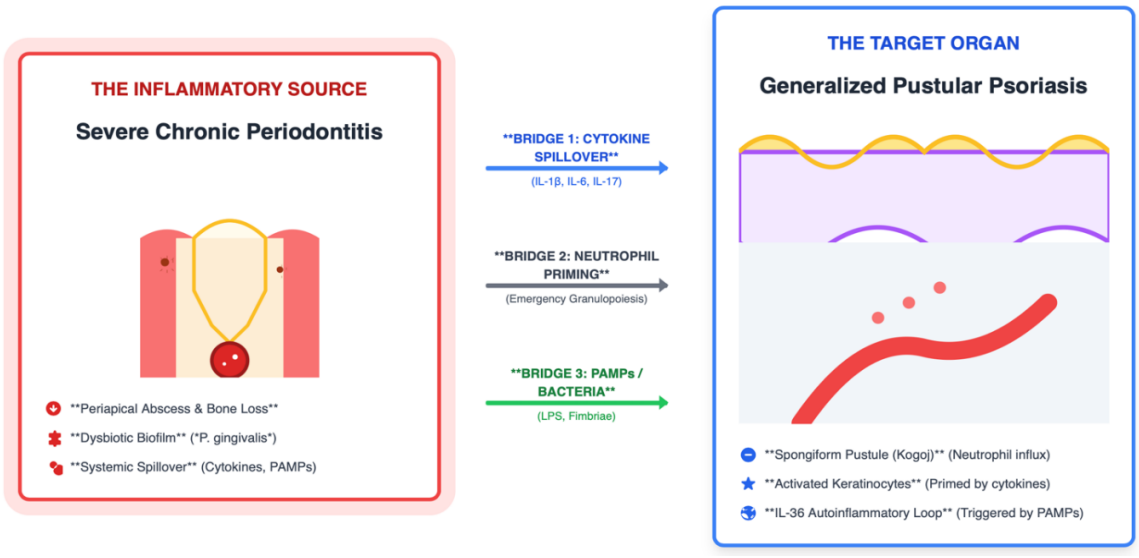

Figure 1. Pathophysiological model of the oral-skin axis.

This study, as a single case report, has inherent and significant limitations that must be acknowledged. An "n-of-1" report provides a strong temporal association but cannot definitively prove causality. It generates a hypothesis, but does not prove it. A major limitation is the lack of genetic testing for IL36RN mutations. This distinction is paramount for generalizability and must be a focus for future research. Though the 72-hour temporal link makes it exceedingly unlikely, the possibility of a rare, spontaneous remission of GPP coinciding exactly with the dental intervention cannot be formally excluded. As discussed in detail, the co-administration of antibiotics and surgery makes it impossible to isolate the precise therapeutic driver. A future study design might involve antibiotic-only therapy first, to see if it alone is sufficient. While we successfully cultured the pathogens from the abscess (a major strength), we did not measure the systemic "Bridge 3" components directly.[19,20] We did not measure serum LPS, anti-gingipain antibodies, or circulating bacterial DNA. Such data would have provided a "smoking gun" to definitively link the oral pathogens to the systemic circulation. Despite these limitations, the clear, objective, and rapid normalization of both clinical (GPPASI) and laboratory (WBC, CRP) markers following the oral-only intervention provides a compelling, hypothesis-generating model that demands further investigation.

4. Conclusion

This report details a case of severe, life-threatening Generalized Pustular Psoriasis, refractory to standard immunomodulation. The flare was driven by a massive, systemic inflammatory load originating from a severe chronic periodontitis. We provide strong evidence for the "oral-skin axis" by demonstrating the immediate and dramatic resolution of all systemic and cutaneous GPP manifestations following a comprehensive dental intervention (surgical debridement and systemic antibiotic therapy), *without* escalation of systemic immunosuppression. This case powerfully suggests that chronic oral inflammation is not merely an association but can be a primary, actionable *driver* of severe cutaneous autoinflammation. It underscores the necessity for clinicians managing severe psoriatic disease to "look in the mouth," as the oral cavity can be a potent, critical, and treatable inflammatory focus.

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