GENERALIZED PUSTULAR PSORIASIS – A CASE REPORT AND THERAPEUTIC PERSPECTIVES

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Summary

Generalized pustular psoriasis (GPP) has traditionally been considered a variant of psoriasis vulgaris, especially since the two conditions often occur in the same patient.

However, recent research has proven that different pathological mechanisms are involved in the two conditions. The IL-36 in excessively activates in GPP and lead to an aberrant inflammatory response. Thus, GPP should be reclassified as a separate entity.

We present the case of a 51 year old patient, with a personal history of psoriasis vulgaris, who was admitted to our hospital for a generalized erythematous eruption, with overlying scales and pustules, occurring after emotional distress and excessive sun exposure. The patient's history, clinical and histopathological examination were consistent with the diagnosis of GPP. Corticosteroids and methotrexate treatment was prescribed and the cutaneous eruption significantly improved during hospitalisation.

At the moment, the first line treatments for GPP are acitretin, methotrexate, cyclosporine and biological therapies. A better understating of the underlying physio-pathological mechanisms involved in this disease and the development of new drugs that specifically target the involved pathways could lead to a more effective disease management in the future.

Key words: *generalized pustular psoriasis, case report.*

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Introduction

Pustular psoriasis (PP) is a rare chronic inflammatory disease that is characterized by the apparition of sterile pustules on an erythematous background, with or without accompanying systemic inflammation. The outcome of this condition can potentially be severe, exacerbation episodes even leading to death in some cases. The incidence of the disease is highest in the 30-39 years age group [1].

PP is traditionally considered to be part of the psoriasis vulgaris spectrum, mainly because the two conditions often occur simultaneously in the same patient. However, in the light of recent research regarding the pathological mechanisms involved in PP, the old classification systems are starting to be questioned, some authors suggesting that PP should more appropriately be considered part of the neutrophilic dermatoses group [2,3]. Nevertheless, around 65% of PP patients also have clinical manifestations of PV [4,5].

PP was first described by Leopold von Zumbusch, in the case of two siblings who had PV and later developed recurring episodes of generalized erythema associated with edema and multiple sterile pustules, as well as fever and systemic inflammation. The exacerbation episodes were self-limiting and extensive desquamation occurred during healing [6].

The primary lesion seen in PP is the sterile pustule, which is defined as a macroscopically visible collection of neutrophils in the epidermis, with or without associated eosinophils. Very small pustules that can only be seen on micro-

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scopic examination are also compatible with the diagnosis of pustular psoriasis [6].

Pustules and microabscesses of Munro can also be seen in PV, but in this condition, they are only present within the psoriatic plaque or at its periphery. This histopathologic picture is not suggestive of PP [6].

Several *clinical subtypes* of PP have been described, although no consensus has been reached and classifications are slightly different from one group of authors to the other. We mention here the following subtypes of PP: palmoplantar pustulosis (PPP), acrodermatitis continua of Hallopeau (ACH), generalized pustular psoriasis (GPP) and impetigo herpetiformis. In order to avoid confusion, some authors choose to simply divide PP into localized or systemic disease. [6–8]

A great part of PP cases has characteristics of more than one subtype and should be classified according to the dominant clinical picture. All subtypes of PP are often associated with plaques of PV. [6–8]

The European consensus [6] defines GPP as the occurrence of macroscopically visible sterile pustules on non-acral skin (excluding cases when the pustules appear on psoriasis plaques or at their periphery), which may or may not be associated with systemic inflammation or PV and which are recurring (more than one episode) or persistent (for more than 3 months) in nature. The lesions have a sudden onset and, in most cases, spontaneously remit after a few weeks. PP is generally seen in adults, but cases in children have also been reported. The disease is more prevalent among Asian populations than among Caucasians [6,7,9].

According to the Japanese guide [1] for the management and treatment of GPP, the definite diagnosis of GPP can be made if the following four criteria are simultaneously met:

1. The presence of systemic symptoms such as fever and fatigue.
2. The occurrence of generalized or nearly generalized erythema along with multiple sterile pustules, that may or may not be confluent, creating lakes of puss.
3. The presence, on histopathologic examination, of subcorneal neutrophilic pustules - spongiform pustules of Kogoj.
4. The recurrence of the above-mentioned clinical and histopathological pictures.

According to the same guide, the suspicion of PP can be formulated if the second or the third criteria are present.

The *differential diagnosis* with acute generalized exanthematous pustulosis (AGEP) must be made. The personal history of the patient is extremely useful to this end, since the clinical picture of the two conditions is very similar. AGEP is generally caused by the administration of drugs such as pristinamycin, ampicillin, amoxicillin, quinolones, sulfonamides, terbinafine and diltiazem. Although AGEP and GPP are classically considered to be different diseases, recent studies have uncovered mutations of the IL-36RN in AGEP as well, indicating similar pathogenic mechanisms in the two entities. It may thus be possible that AGEP and GPP be different clinical manifestations of the same disease [6,9–11].

Several *triggering factors* of GPP exacerbations have been identified: infections, especially streptococcal and viral upper airway infections, vaccination, pregnancy, hypocalcemia, hypoparathyroidism, certain drugs, corticosteroid or cyclosporine treatment discontinuation, UV radiation exposure etc. [6–9,12–17]. Paradoxical GPP cases, triggered by biologic medications, have also been reported [9,18–21].

GPP generally has an intermittent course, with sudden onset of exacerbation episodes that then completely resolve in a matter of weeks and are followed by remission periods that last for months or even years. Sometimes, however, GPP can have a persistent course, with some characteristic lesions present even between exacerbation episodes. GPP can be associated with lesions of PV or with systemic inflammation and fever [6,7,9].

The characteristic *laboratory findings* are leukocytosis with neutrophilia and elevated inflammatory markers. If antistreptolysin O antibodies are raised, we can presume that a streptococcal infection triggered the exacerbation. The patient should also be evaluated for the presence of tonsilitis or another infection. If complications occur, hypocalcemia and hypoproteinemia can also be seen. IgA and IgG levels can be elevated. The choice of treatment

should take into account the presence of kidney or liver function abnormalities [1].

Potential *complications* are bacterial superinfections and respiratory, liver or kidney failure. GPP is frequently associated with systemic inflammation, mucosal manifestations and arthritis. Respiratory failure, eye manifestations and secondary amyloidosis can also occasionally occur [1].

GPP can potentially be fatal. The cause of death is usually cardiac or respiratory failure or is related to bacterial superinfections. Estimated disease mortality is of 3-7% [9,22].

Hepatic cytolysis or cholestasis can often be seen during or after acute episodes of exacerbation. In these patients, neutrophilic infiltrates have been shown in the biliary ducts as well as in the portal and periportal spaces and imaging studies have demonstrated the presence of strictures on the biliary ducts. This presentation has been named neutrophilic cholangitis and it seems to have a benign, self-resolving nature [7,23,24].

The presence of extensive cutaneous manifestations, high levels of inflammatory markers or edema indicates the increased severity of the episode of exacerbation. The presence of edema has been associated with complications such as cardiac failure, respiratory distress syndrome or capillary leak syndrome [1].

It is recommended to perform a histopathologic exam of the lesions in order to formulate the definite diagnosis [1].

Although PP has long been considered just another clinical presentation of PV, recent research has uncovered differences in the inflammatory pathways involved in the two diseases.

The inactivating mutation of IL-36RN, a gene that codes for the IL-36 receptor antagonist, has been well studied in PP, even though it is only responsible for a minority of cases. IL-36RN, as well as other cytokines involved in the innate immunity, is part of the IL-1 family. It has an anti-inflammatory role, through inhibition of NF-kβ (*nuclear factor 'kappa-light-chain-enhancer' of activated B-cells*) [2,6]. When IL-36RN is inactivated, this leads to the abnormal activation of the IL-36 pathway and, consequently, to the stimulation of keratinocytes and antigen presenting cells and the activation of the inflammatory pathways involved in PP [25].

Even though IL-36RN has an autosomal recessive mode of transmission, GPP has also been described in patients that only had one mutant allele. In these cases, the disease was likely caused by mutations occurring in additional loci [6,25].

IL-36RN mutations were found in about 25% of GPP cases and 20% of ACH cases. Its association with PPP is less clear and some authors even deny its existence [3,6].

The presence of IL-36RN mutations seems to be associated with an earlier disease onset and higher levels of systemic inflammation. In heterozygous patients, the disease seems to have a later onset, but the systemic inflammation levels are similar to those seen in homozygous patients. IL-36RN mutations are less often seen in patients who have concomitant psoriasis vulgaris [6,25–27].

CARD-14 (*caspase recruitment domain family member 14 gene*) mutations have also been described in PP, as well as in PV and pityriasis rubra pilaris. This gene codes for a protein that is involved in apoptosis and NF-kβ signaling. When CARD-14 is mutated in PP, this leads to an abnormal activation of the NF-kB pathway [6].

Another gene involved in PP is AP1S3, which codes for the AP-1 (*activating protein-1*) subunit of the adaptor related protein complex. Its role is the promotion of vesicular transport between the Golgi apparatus and endosomes [6].

As opposed to PV, PP also has higher levels of IL-1 and the innate immune system is more active [28].

Case presentation

We hereby present the case of a 51-year-old female patient, who presented to our clinic for nearly generalized erythema with multiple pustules, that first appeared two days prior to the presentation and then rapidly extended. The patient presented with fatigue, but no fever. The symptoms developed a few days after an upsetting personal event and a week after a trip to the seaside. At the clinical examination there were areas of desquamation due to sun over-

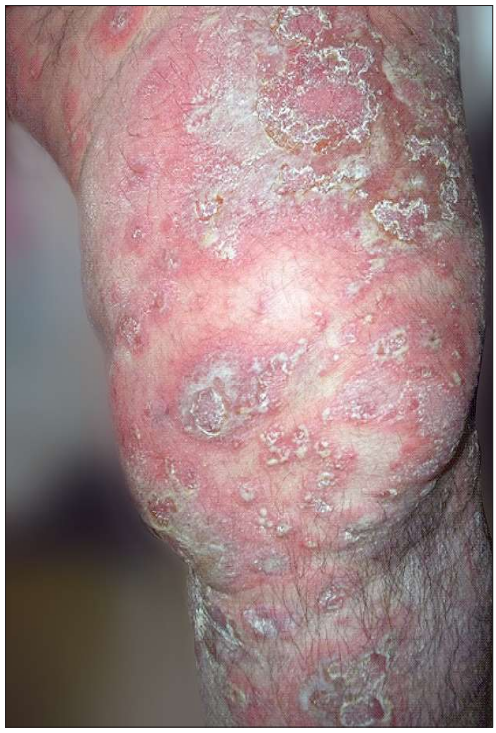

Figure 1. First exacerbation episode. Extensive erythema, scales, sterile pustules. The lesions have an annular configuration.

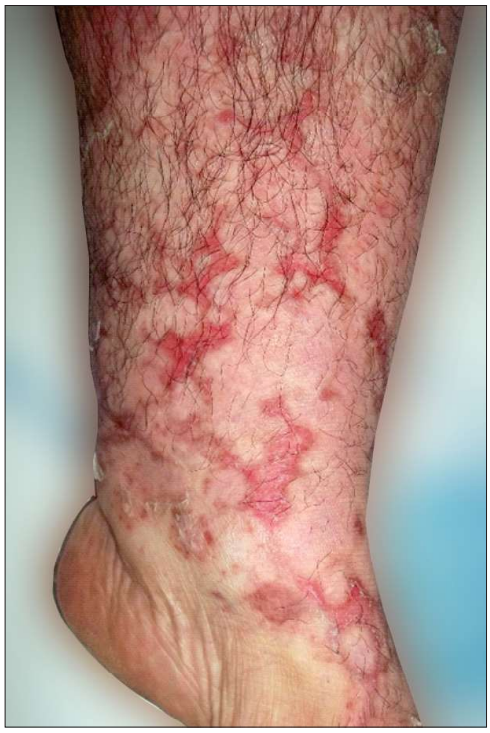

Figure 2. First exacerbation episode, after the initiation of systemic treatment. Remission of pustules. Some erythematous annular plaques are still evident.

exposure. In face of the clinical picture, it is decided that the patient be hospitalized for further investigations, monitoring and institution of systemic treatment.

The patient's history is positive for plaques of psoriasis vulgaris on the scalp and elbows, that she treated intermittently with topical corticosteroids, a previous episode of GPP, neglected hypertension and depression.

At the time of the current presentation the patient was not following any treatment.

Four years prior to the current presentation, the patient had a similar episode, of extensive erythema with overlying sterile pustules, associated fever and fatigue. At the time, the lesions had an annular configuration, that became more and more obvious once the treatment was started and the erythema started to fade. The triggering factors for that exacerbation episode were a concomitant upper respiratory tract infection, another upsetting personal event and excessive exposure to UV radiation.

During this first exacerbation episode the patient had leukocytosis of 22 000/mm^3 with neutrophilia and systemic inflammation (erythrocyte sedimentation rate, ESR=51 mm/h). A chest X-ray was performed, showing accentuation of the interstitial lung pattern, most apparent in the left lung, the partial opacification of the right costodiaphragmatic recess and the presence of an enlarged right hilar lymph node. For this first episode, treatment was started with clarithromycin, systemic and topical corticosteroids, methotrexate, as well as symptomatic treatment and the evolution of the patient was favorable.

Regarding the second, current, episode of exacerbation, blood work-up at admission showed leukocytosis of 16 200/mm^3 with neutrophilia, systemic inflammation (C reactive protein, CRP = 11,3 mg/dl), the presence of leukocytes and proteins on urinalysis, with frequent bacteria, but negative nitrites. The antigen test for the SARS-CoV-2 infection was negative, and the

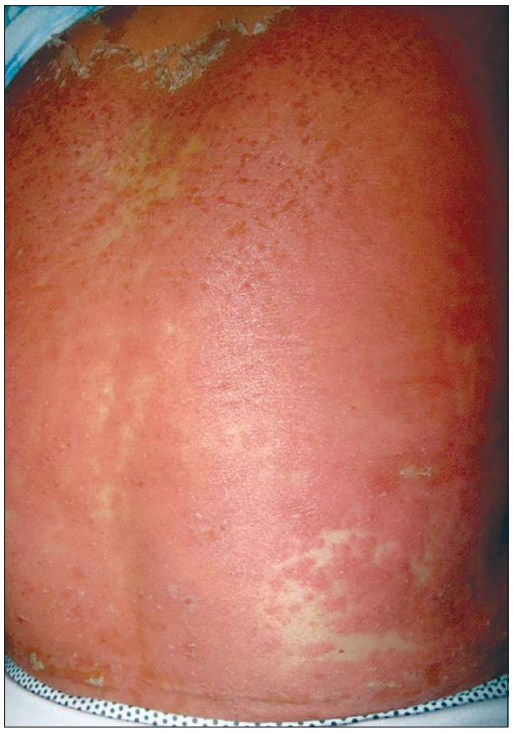

Figure 3. Current exacerbation episode, at presentation. Generalized erythema, with small sparing areas, associated edema, sterile pustules and desquamation due to actinic injury.

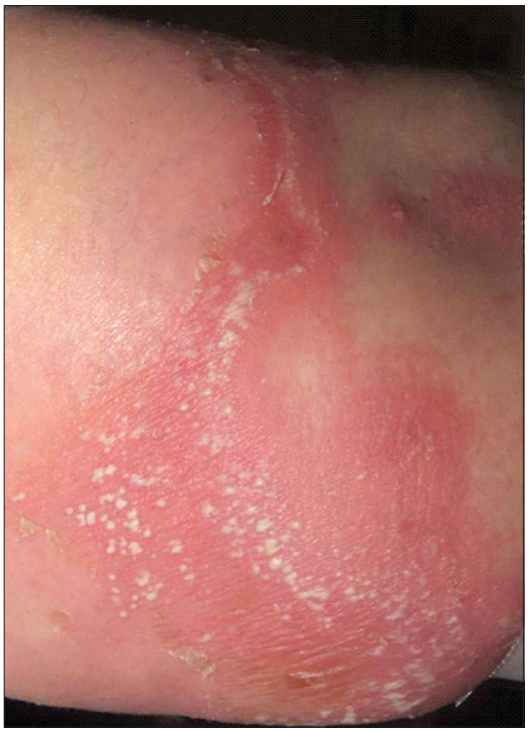

Figure 4. Current exacerbation episode, detail. Pustules on an erythematous background. The image is taken after the initiation of the systemic treatment. The area of erythema has reduced.

antistreptolysin O antibodies were in normal range.

In order to establish the definite diagnosis and to ensure the clear documentation of the episode, a skin sample was taken to perform a histopathologic exam. The examination shows ortho- and parakeratosis, the presence of neutrophils and Munro microabscesses in the keratin layer, acanthosis and papillomatous, areas of agranulosis, Kogoj spongiform pustules in the upper Malpighian layer and a dense perivascular lymphocytic infiltrate in the dermis. The histopathologic aspects are compatible with the diagnosis of pustular psoriasis.

Thus, taking into consideration the clinical picture, the laboratory findings, the histopathologic pattern and the patient's personal history, the diagnosis of generalized pustular psoriasis is made.

It is decided that treatment be started with dexamethasone, prednisone, methotrexate at a dose of 15 mg/week, as well as symptomatic treatment and topical corticosteroids.

The patient has a good clinical course under treatment, with the improvement of the cutaneous lesions and of the general state and normalization of the blood tests (leukocytes 15 600/mm^3, CRP=0,42 mg/dl, normalization of urinalysis). Desquamation occurred during the healing of the lesions.

The patient is released from hospital with the recommendation to continue the treatment with 50 mg of prednisone daily, with tapering, 15 mg/week of methotrexate and topical corticosteroid treatment. She is also advised to seek psychiatric counselling in order to try to control her emotions, since they seem to be an important triggering factor in her case.

Even after the systemic corticoids were discontinued, the lesions continued to improve under methotrexate treatment. However, once the patient was clear of lesions, she stopped using methotrexate without seeking medical advice

and she was lost to follow-up. Six months later she recontacted her physician to report another, milder, GPP exacerbation, but she did not present to the clinic in order to receive a consultation and treatment recommendations. This episode admittedly resolved after methotrexate treatment as well.

Discussions and therapeutic perspectives

The clinical picture, the laboratory findings, the histopathologic description and the recurring character of the lesions in the case of our patient illustrate a typical GPP exacerbation episode.

The patient's exacerbations were treated with systemic corticosteroids in combination with methotrexate, with good results. A maintenance treatment with either methotrexate or biologics could be considered for our patient, considering the fact that the exacerbations were associated with systemic inflammation that can potentially lead to severe complications, that the last two exacerbation episodes occurred within a short time interval and that she also has PV plaques. Unfortunately, the patient does not wish to follow any long-time treatment.

GPP is an uncommon disease that has not been included in most of the clinical trials for psoriasis treatment. Thus, treatment in GPP is based on data from small studies or from case reports. Moreover, the natural course of the disease, with spontaneous resolution of the clinical manifestations a few weeks from onset, makes it difficult to evaluate the actual influence of treatments [7,29].

Given that the disease course can potentially be severe, systemic treatments are used for GPP.

The treatment goals are the quick control of the eruption and of the associated symptoms, as well as the prevention of long and short-term complications, such as acute kidney injury, respiratory distress, cholangitis, arthritis, cardiovascular disease, etc. [4]

In 2012, a task force of the National Psoriasis Foundation Medical Board achieved a consensus regarding treatment modalities for pustular psoriasis [30].

The choice of treatment should be made depending on the disease severity and extension. The patient characteristics or comorbidities also influence the treatment choice. For instance, if treating a pregnant woman, the teratogenic potential of the drugs should be taken into account [30].

Acitretin, cyclosporine, methotrexate and infliximab were designated as first line treatments [30].

Infliximab and cyclosporine have a short time interval until effect onset and are thus preferred for the treatment of acute, severe forms of GPP [30,31].

Second line treatments were adalimumab, etanercept and combined therapy (with a first line classic systemic agent together with a biologic agent). Topical corticosteroids or calcineurin inhibitors can be applied to the lesional skin. Psoralen and ultraviolet A light therapy (PUVA) can also be used and is more effective when acitretin or cyclosporine are used concomitantly [30].

Use of systemic corticosteroids in psoriasis is usually discouraged. In GPP, however, they can be used if other treatment modalities cannot be administered. Systemic corticosteroids have good efficacy in acute, severe GPP episodes, but when treatment is discontinued there is a risk of disease exacerbation because of a rebound effect. The risk of such exacerbations can be reduced when another systemic agent is used in conjunction with corticosteroids and is continued even after corticosteroid tapering. However, this concept has not yet been verified by large, good-quality studies [30,32].

Retinoids seem to be more effective than other treatments, but they also have a higher incidence of side effects. The rate at which side-effects appear is dose dependent [33]. Acitretin is the retinoid of choice in GPP, even though isotretinoin has also been used in females of reproductive age. Retinoids act by inhibition of keratinocyte proliferation and of Th17-cell activation. Moreover, they cannot be used during pregnancy because of their teratogenic potential. The benefic effects of treatment can generally be seen 7 to 10 days after treatment initiation [30,34,35].

In the case of methotrexate, treatment benefits occur slowly, in a few weeks' time. The maximum recommended dose is of 25 mg per week and patients need close monitoring for hematological and hepatic side effects [30,36].

Cyclosporine has a quick effect onset, at 2-4 weeks after treatment initiation. The mechanism

of action involves IL-2 synthesis inhibition and decreasing T-cell activation [28,30].

More recently, biologic drugs have started being used more and more in the treatment of PP. They have not yet been approved for this indication in the USA or in Europe, but they have already been approved for the treatment of GPP in Japan, Taiwan and Thailand, based on data coming from small, non-randomized studies and from the experience with these treatments in plaque psoriasis [1,30,37].

Several smaller studies have illustrated the rapid improvement of symptoms under infliximab treatment, either used as monotherapy or in combinations [30,31,38,39]. IL-17 inhibitors also seem to be effective in the treatment of GPP. Secukinumab, ixekizumab and brodalumab have all had good results in small studies, even though their effects were measured several weeks after the onset of the exacerbation episode [34,40–43].

IL-23 and IL-12/23 inhibition have also proven to be useful in GPP. Guselkumab and ustekinumab were effective even in patients that had not had a favorable response to the initial treatment with TNF-α inhibitors or with methotrexate [28,44–46]. IL-1 inhibitors, such as anakinra, canakinumab and gevokizumab, have also had good results in the treatment of GPP [28,47–50].

Topical treatments with corticosteroids, calcineurin inhibitors or vitamin D analogues can be used as adjuvant therapy [1,9,28,30,51,52].

PUVA can be used as a long-term maintenance treatment in GPP, once the control of the exacerbation episode is achieved [30].

Cyclosporine, systemic corticosteroids and topical treatments can be used as first-line treatments during pregnancy. Once the acute episode is controlled, PUVA or narrow band UVB phototherapy can also be employed [30].

In children, treatment recommendations are similar to those for adults. First-line treatments are acitretin, in monotherapy or in combination with systemic corticosteroids, methotrexate and cyclosporine. Etanercept could also be included in this category. Second-line treatments are adalimumab, infliximab, and UVB phototherapy. It is advisable that retinoids be used in doses of less than 1 mg/kg/day. They can potentially affect the skeletal system and they are relatively contraindicated for girls during puberty. Some authors advocate for the preferential use of cyclosporine in children, given that it is associated with fewer long-term side effects than corticosteroids, retinoids or methotrexate [30,53,54].

Recently, monocyte and granulocyte apheresis has been used for GPP treatment. This method filtrates the activated leukocytes in the patient's blood, thus decreasing the levels of interleukins and TNF. The method has been used in case of failure of other treatment methods, in very young or very old patients, in pregnant women or in patients with infectious hepatitis [8,55].

IL-36 inhibitors (spesolimab, imsidolimab), that specifically target the pathogenic pathways involved in GPP, are currently under development [37,56,57].

Conclusions

GPP is a potentially severe disease that can significantly affect the patients' quality of life, because of its recurring nature. Treatment should be started as soon as possible when exacerbations occur, and patients should be followed to ensure the early detection of complications. Complications can be due to either the disease itself or to the treatments used for it. The new IL-36 treatments that are under development bring hope for the more efficient treatment of this disease in the future.

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Conflict of interest
NONE DECLARED

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