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## **Comparison of pyoderma gangrenosum and hypertensive ischemic leg ulcer Martorell in a Swiss cohort**

Kolios, Antonios G A; Hafner, Jürg; Luder, C; Guenova, Emmanuella; Kerl, K; Kempf, Werner; Nilsson, J; French, L E; Cozzio, A

**Abstract:** Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis presenting with painful and sterile skin ulcerations (1). Its aetiology remains largely unknown although an autoinflammatory background seems possible. Several comorbidities as well as triggering factors such as surgery, trauma or pharmacological therapies have been associated with the development of PG (2). Different topical and systemic treatments are recommended for PG, most commonly topical steroids or calcineurin inhibitors as well as systemic steroids, dapsone, infliximab and others, as well as by our group and others canakinumab and ustekinumab (3, 4). This article is protected by copyright. All rights reserved.

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## Comparison of pyoderma gangrenosum and hypertensive ischemic leg ulcer Martorell in a Swiss cohort

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**Short title:** PG HYTILU Switzerland

**Keywords:** Pyoderma gangrenosum, hypertensive ischemic leg ulcer Martorell, systemic inflammation, neutrophilia, CRP

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Pyoderma gangrenosum (PG) is a rare neutrophilic dermatosis presenting with painful and sterile skin ulcerations (1). Its aetiology remains largely unknown although an autoinflammatory background seems possible. Several comorbidities as well as triggering factors such as surgery, trauma or pharmacological therapies have been associated with the development of PG (2). Different topical and systemic treatments are recommended for PG, most commonly topical steroids or calcineurin inhibitors as well as systemic steroids, dapsone, infliximab and others, as well as by our group and others canakinumab and ustekinumab (3, 4). Pyoderma gangrenosum is a diagnosis of exclusion and often misdiagnosed at initial manifestation. Hypertensive ischemic leg ulcer Martorell (HYTILU) was previously investigated by our group showing that 50% of the patients with a referral diagnosis of PG were found to have HYTILU (5). HYTILU is caused by ischemic subcutaneous arteriosclerosis and all patients showing arterial hypertension and up to 58% diabetes mellitus. Typical clinical presentation of HYTILU is a latero-dorsal lower leg ulceration with central black necrosis and purple inflamed ulcer borders (5, 6). This appearance can clinically be misleading for PG and immunosuppression could be fatal in HYTILU as it strongly increases the risk of septicaemia. (5) In the current study we compare our PG with a HYTILU cohort and focus on clinical data, laboratory findings and comorbidities to develop diagnostic clues for both diseases.

In the patient files of the Department of Dermatology, University Hospital of Zurich (USZ), Cantonal Hospital of Sankt Gallen (KSSG), and in the private practice of Prof. Werner Kempf (USZ) a keyword search for “pyoderma” and/or “gangrenosum” was conducted for all patients who were hospitalized between 01.01.2002 and 31.12.2012. 179 patients were identified with an initial suspected differential diagnosis of PG, of which 38 patients were diagnosed as PG. We performed a histopathological re-assessment of these 38 patients and identified three patients with histopathological signs of HYTILU and one with morphea, leading to exclusion of these four patients from further analysis. The remaining 34 patients fulfilled the criteria for PG as established by Su et al. and were included in our study (7). These PG patients were retrospectively compared to a cohort of 32 HYTILU patients diagnosed at the USZ during the same time period. Medical records and laboratory findings were analysed for both cohorts in order to identify features which support clinical distinction (**Table 1**). The study was approved by the local ethics committee (KEK-ZH 2014-0432). For statistical analysis GraphPad Prism® 7.0b, 2016, and Microsoft Excel® 14.3.2, 2011, were used.

Compared to PG, HYTILU appeared less frequent in women, at later age, more often in smokers, showed higher CRP but lower levels of blood leukocytes and neutrophils, lesion localization only at the lower leg, more cardiovascular comorbidities such as arterial hypertension, diabetes mellitus, peripheral artery occlusive disease, metabolic syndrome and more microbial superinfection (**Table 1**).

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Our findings of an elevated CRP and neutrophilia in PG indicates the presence of systemic inflammation, which is also increasingly suggested by the field (8). Additionally the reduced likelihood of pathogenic bacteria in PG lesions could be explained by the exacerbated neutrophil response. Cardiovascular comorbidities like arterial hypertension, peripheral artery occlusive disease, metabolic syndrome and diabetes mellitus appear significantly more in HYTILU, which has also been reported previously by our group, as in PG. Upon age-adjustment the prevalence of cardiovascular comorbidities in our small PG cohort seems to correspond to the normal Swiss population, however this needs to be confirmed in bigger studies (5). Furthermore, all of the HYTILU patients in our cohort had an ulcer located on the lower leg and as such, a lesion localization outside of the lower leg could be a further clinical hint favouring the diagnose of PG (lower leg 67%, trunk 24%, upper limb 5%, head 4%). Both cohorts are however rather small and larger cohorts are needed to confirm our findings.

Pyoderma gangrenosum and HYTILU are important differential diagnosis for ulcerative skin disorders and should be carefully considered. In particular if the biopsy taken in PG and HYTILU is too small, the chance of visualizing “PG-like features” of neutrophilic infiltration and missing the typical features of HYTILU (subcutaneous stenotic arteriolosclerosis in 100% and medial calcification in 71% of cases) is high. Our findings suggest that differences in lesion localization, laboratory parameters and presence of comorbidities could also be utilized in order to accurately differentiate these disorders. We also identified increased inflammatory markers in a considerable proportion of our PG patients, which is an expected but not formally proven aspect of PG. Larger prospective studies or international registries on these rare ulcerative skin diseases are needed to confirm these findings.

**Table 1: Comparison HYTILU and PG**

	<b>HYTILU (n=32)</b>	<b>PG (n=34)</b>	<b>p value</b>
<b>Female gender</b>	50.0%	61.8%	ns
<b>Age at manifestation (years)</b>	73.5	61.2	***
<b>BMI (kg/m2)</b>	28.3	24.1	*
<b>Smoking</b>	25%	20.6%	ns
<b>Alcohol</b>	12.5%	11.8%	ns
<b>Laboratory (mean)</b>			

<b>CRP (mg/L)</b>	31.5	14.5	ns
<b>Leukocytes (G/L)</b>	9.9	10.5	ns
<b>Neutrophils (G/L)</b>	7.9	8.4	*
<b>Lesion localization lower leg</b>	100%	67%	***
<b>Cardiovascular comorbidities</b>	100%	79.4%	**
<b>Arterial hypertension</b>	100%	29.4%	****
<b>PAOD</b>	62.5%	5.9%	****
<b>Hypertensive heart disease</b>	40.6%	11.8%	**
<b>Myocardial infarction</b>	25.0%	5.9%	*
<b>Other cardiopathy</b>	12.5%	2.9%	ns
<b>Cerebrovascular infarction</b>	21.9%	2.9%	*
<b>Metabolic syndrome</b>	65.6%	2.9%	****
<b>Diabetes mellitus</b>	53.1%	8.8%	****
<b>Thrombosis</b>	3.1%	8.8%	ns
<b>Renal insufficiency</b>	28.1%	20.6%	ns
<b>Microbiological swab positive</b>	90.6%	44.1%	****

**Table 1: Comparison HYTILU and PG**

Comparison of 32 HYTILU patients (hypertensive ischemic leg ulcer Martorell) and 34 PG patients by demographic data, laboratory values, localization, comorbidities.

PAOD = peripheral artery occlusive disease, BMI = body mass index, CRP = C-reactive protein, kg = Kilogram, m = meter, mg = milligram, G/L = giga/liter =  $10^9/L$ , CRP reference value:  $<5\text{mg/L}$ , leukocytes reference value:  $3.5\text{-}9.6 \times 10^9/L$ , neutrophils reference value:  $1.4\text{-}8.0 \times 10^9/L$ , ns = not significant /  $p>0.05$ , \* =  $p\leq 0.05$ , \*\* =  $p\leq 0.01$ , \*\*\* =  $p\leq 0.001$ , \*\*\*\* =  $p\leq 0.0001$ ). Statistics: unpaired t test with Welch's correction.

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