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ORIGINAL RESEARCH

Is pyoderma gangrenosum associated with solid malignancies? Insights from a population-based cohort study

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ABSTRACT

Background: The question of whether solid malignancies (SMs) are associated with pyoderma gangrenosum (PG) remains to be conclusively answered.

Objective: To evaluate the risk of SM among patients with PG and the odds of PG after a diagnosis of SM.

Methods: A population-based retrospective cohort study was conducted to study the risk for SM in patients with PG (n = 302) as compared with age-, sex- and ethnicity-matched control subjects (n = 1799). A case–control design was used to estimate the odds of PG in those with a preexisting history of SM.

Results: The prevalence of a preexisting SM was comparable in patients with PG and controls (7.5% vs. 8.8%, respectively; P = 0.490). The odds of having PG following a diagnosis of a SM was not statistically increased (OR, 0.85; 95% CI, 0.53–1.36). The incidence of SM was 6.8 (95% CI, 3.5–12.2) and 7.9 (95% CI, 6.1–10.1) per 1000 person-years among patients with PG and controls, respectively. Patients with PG were not more likely to develop SM as compared to controls (HR, 0.86; 95% CI, 0.44–1.69). Patients with a dual diagnosis of PG and SM were older and had more frequent comorbid conditions and increased mortality.

Conclusions: SM is not associated with provoking PG, and patients with PG are not at an increased risk of developing SM. A thorough routine screening for SM in patients with new-onset PG is an unnecessary approach based on the study findings.

Key words: case–control study, cohort study, Pyoderma gangrenosum, solid malignancies.

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare noninfectious, neutrophilic dermatosis. The typical clinical manifestation begins with sterile pustules that rapidly progress and turn into painful ulcers of variable depth and size with compromised violaceous borders. The clinical subtypes of PG include classic ulcerative, pustular, bullous and vegetative PG. PG mostly affects the legs, but also other parts of the skin and mucous membranes might be involved.[1-3] In addition to severe painful morbidity, PG has been linked with an increased risk for mortality.[4] Overexpression of pro-inflammatory cytokines as interleukin (IL)-8 and IL-1β leading to autoinflammation, adaptive and innate immune system dysregulation and abnormal neutrophil function takes part in the pathomechanism underlying the disease.[5]

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PG may present alone, in syndromic forms or associated with systemic diseases.[1,5] Current knowledge about associated comorbidities in PG is inadequate and based essentially on small-scale case series and few retrospective cohort studies, rather than on controlled observational studies. In a recent meta-analysis summarising 31 case series and cohorts, 57% of patients with PG experienced an underlying systemic disease at the onset of their cutaneous disease.[6] While PG was historically linked with haematological malignancies, namely monoclonal gammopathy and acute myeloid leukaemia, this meta-analysis provided evidence that 7.4% of reported PG patients had a solid malignancy (SM) at the onset of their disease.[6] However, it remains to be decisively determined whether the presence of SM among patients with PG triggers the cutaneous disease or merely represents an incidental coexistence. The question is yet to be answered since no controlled studies were held to compare the prevalence and incidence of SM in patients with PG relative to the general population.

The question of whether patients with PG experience an increased burden of SM is of substantial clinical implication, as it may dictate whether patients with PG should be screened for SMs. Additionally, investigating the association between PG and SM may facilitate comprehension of additional aspects of the pathophysiology of PG.

The aim of the current study was to investigate the bidirectional association between PG and SM. To elaborate, we aimed to evaluate whether a history of SM predisposes individuals to develop subsequent PG and whether patients with PG have an increased risk of developing subsequent SM. A granular analysis was performed to delineate the association between PG and a wide array of different SMs. We additionally sought to characterise PG patients with SMs relative to the remaining patients with PG.

METHODS

Study design and database

The current study was conducted to assess the bidirectional association between PG and SM. To outline the risk of developing SM during the course of PG, a retrospective cohort study design was chosen, in which patients with PG were longitudinally followed to estimate the incidence of SM. To elucidate the odds of having PG in individuals with a history of SM, a case–control study design was implemented to investigate the prevalence of preexisting SM (exposure) in patients with subsequent PG (outcome).[7] The rare disease assumption theorises that estimates produced by case–control studies investigating rare diseases (defined as those with a prevalence rate<10%) approaches that produced by cohort studies.[7] Therefore, the case–control study design utilised in the current study enables to evaluate the risk of PG in subjects with a history of SM.

The computerised database of Clalit Health Services (CHS) was the origin of the current study. Ensuring 4 927 000 enrollees as of October 2018, CHS is the largest health maintenance organisation in Israel, providing healthcare services for 57% of the general Israeli population. The characteristics of the utilised data set are further detailed in our previous publications.[8] The current study was approved by the institutional review board (IRB) of Ben-Gurion University in accordance with the declaration of Helsinki.

Study population and main variables

The data set of CHS was systematically checked for all individuals with a diagnosis of PG between the years 2000 and 2018. Cases were individually checked, and only those meeting at least one of the following eligibility criteria were eventually included: (i) a documented diagnosis of PG registered at least twice by a community board-certified dermatologist and/or (ii) documentation of the diagnosis of PG in discharge letters of patients with hospitalisations in dermatological wards.

The diagnosis of each one of the SMs was based on its documentation in the cancer registry of the CHS. This registry is cross-linked with the National Cancer Registry and undergoes continuous updates and logarithmic checks. The SM variable was defined as the occurrence of any of the 19 SMs available in the cancer registry of CHS. In those having more than single isolated SM, the date of the first cancer was considered for the calculation of time to an event.

Outcome measures were adjusted for the Charlson comorbidity index (CCI), an epidemiological tool estimating the degree and severity of the comorbid condition. The latter is widely utilised in epidemiological studies and was evidenced to reliably predict mortality.[9] To avoid bias, we used a modified version of the score following the exclusion of the malignant component of the scoring system. Patients with a CCI of 1-2 were defined to have moderate comorbidities, while those with a score ≥3 were considered to experience severe comorbidities.

Statistical analysis

Baseline characteristics were described by means and standard deviations (SDs) for continuous variables, while categorical values were signified by percentages. A comparison of sociodemographic and clinical factors between cases and controls was performed using the chi-square test and t-test for categorical and continuous variables, respectively.

In the cohort study design, incidence rates of SMs were calculated for both PG patients and controls and expressed as the number of events per 1000 person-years. Hazard ratios (HRs) for the risk of incident SM were obtained by the use of the Cox regression model. Differences in the cumulative survival of PG patients with and without SM were evaluated using Kaplan–Meier method and stratified log-rank test. In the case–control study design, logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) to compare cases and controls regarding the presence of preceding SM. The association was calculated based on individuals who developed PG after the diagnosis of each SM, given that a temporal

relationship exists between exposure and outcome in case–control studies. Two-tailed P-values less than 0.05 were considered as statistically significant. All statistical analyses were performed using SPSS software, version 25 (SPSS, Armonk, NY: IBM Corp).

RESULTS

Characteristics of the study population

The study population included 1,799 individuals, of whom 302 were patients with PG and 1,497 were age-, sex- and ethnicity-matched control individuals. The mean (SD) age of the study participants was 54.0 (20.8) years, 57.9% of them were females, and 84.4% were of Jewish ancestry. Case and control subgroups were comparable with regard to the prevalence of smoking and the mean body mass index (BMI; Table 1). The mean (SD) CCI score was higher in cases than in controls (2.3 [2.7] vs. 1.3 [1.8], respectively; $P < 0.001$). Severe comorbidities were encountered more frequently among cases as compared to controls (37.4% vs. 19.2%, respectively; $P < 0.001$). The characteristics of the study population are outlined in Table 1.

Do solid malignancies predispose individuals to the development of subsequent pyoderma gangrenosum?

A case–control design was followed to clarify whether a history of SM places patients at an increased risk of developing PG. The prevalence of preexisting SM was comparable among patients with PG and controls (7.5% vs. 8.8%, respectively; $P = 0.490$). Therefore, the odds of having PG following a diagnosis of SM were not found to be significantly different among patients with PG as compared to controls (OR, 0.85; 95% CI, 0.52–1.36). In stratified analyses across different sex, age and ethnicity strata, no association was found between a history of SM and the subsequent development of PG (Table 2).

To identify whether an independent association exists between preexisting SM and subsequent PG, we performed a multivariate logistic regression analysis. In accordance with the univariate analysis, no independently significant association was found between SM and subsequent PG after adjusting for demographic variables and comorbidities (adjusted OR, 0.85; 95% CI, 0.51–1.41; $P = 0.522$).

Table 1 Descriptive characteristics of the study population

Characteristic	Patients with pyoderma gangrenosum ($N = 302$)	Controls ($N = 1497$)	P value
Age, years			
Mean (SD)	54.0 (20.8)	54.0 (20.8)	1.000
Median (range)	55.8 (0.2–95.1)	55.9 (0.2–95.6)	
Male sex, N (%)	157 (57.9%)	629 (58.0%)	0.974
Ethnicity, N (%)			
Jews	255 (84.4%)	1264 (84.4%)	1.000
Arabs	47 (15.6%)	233 (15.6%)	
BMI, mg/kg^2			
Mean (SD)	28.0 (6.3)	27.8 (6.2)	0.614
Smoking, N (%)	115 (38.1%)	521 (34.8%)	0.274
Charlson comorbidity score			
Mean score ± SD	2.3 (2.7)	1.3 (1.8)	**<0.001**
None (0)	111 (36.8%)	777 (51.9%)	**<0.001**
Moderate (1–2)	78 (25.8%)	432 (28.9%)	0.276
Severe (≥3)	113 (37.4%)	288 (19.2%)	**<0.001**

BMI, body mass index; N, number; PG, pyoderma gangrenosum; SD, standard deviation.

Bold indicates significant values.

Are patients with pyoderma gangrenosum are at an increased risk of developing solid malignancies?

A retrospective cohort study followed patients with PG and controls for 1468.8 and 7688.4 person-years, respectively. Overall, 10 cases of new-onset SM occurred among patients with PG and 61 cases among controls. Taken together, the incidence rate of SM was 6.8 (95% CI, 3.5–12.2) and 7.9 (95% CI, 6.1–10.1)/1000 PY among patients with PG and controls, respectively.

The crude risk of developing SM was comparable between cases and controls (HR, 0.86; 95% CI, 0.44–1.69). The aforementioned risk was of no statistical significance in both sexes and also following adjustment for demographic variables (adjusted HR, 0.99; 95% CI, 0.50–1.93) and for demographic variables and comorbidities (adjusted HR, 1.02; 95% CI, 0.52–2.02; Table 3).

Granular analysis of the association between pyoderma gangrenosum and different solid malignancies

Table 4 demonstrates the association between PG and 19 different types of SMs. While the univariate analysis revealed a significant association between PG and ovarian cancer (OR, 9.97; 95% CI, 0.91–110.34), this association lost its statistical significance in a multivariate analysis adjusting for demographic variables and comorbidities (adjusted OR, 8.54; 95% CI, 0.72–101.56). No significant associations were found between PG and any of the remaining different solid malignancies (Table 4).

The clinical characteristics of patients with coexistent pyoderma gangrenosum and solid malignancies relative to other patients with pyoderma gangrenosum

The last endpoint of the current study was to investigate whether patients with coexistent PG and SM had unique features relative to other patients with PG. Patients belonging to the former subgroup were significantly older at the onset of PG (71.7 [12.2] vs. 51.9 [20.7]; $P < 0.001$), were

Table 2 The risk of pyoderma gangrenosum among patients with a preexisting history of solid malignancy, stratified by age, sex and ethnicity (case–control study design)

Subgroup	SM in patients with PG *n* (%)[†]	SM in controls *n* (%)[†]	OR (95% CI)	Univariate *P* value
All	22 (7.5%)	126 (8.8%)	0.85 (0.53-1.36)	0.490
Age, years				
<54	1 (0.7%)	2 (0.3%)	2.51 (0.23-27.84)	0.439
≥54	21 (13.7%)	124 (16.7%)	0.79 (0.48-1.31)	0.361
Sex				
Male	8 (6.6%)	45 (7.5%)	0.87 (0.40-1.89)	0.719
Female	14 (8.2%)	81 (9.7%)	0.84 (0.46-1.51)	0.552
Ethnicity				
Jews	21 (8.6%)	123 (10.2%)	0.83 (0.51-1.34)	0.439
Arabs	1(2.1%)	3 (1.3%)	1.64 (0.17-16.10)	0.669

[†]The prevalence of SM in cases when SM preceded PG (in cases) or preceded recruitment (in controls). Bold: significant value. CI, confidence interval; *n*, number; OR, odds ratio; and PG, pyoderma gangrenosum; SM, solid malignancy.

Bold indicates significant values.

Table 3 The risk of solid malignancies among patients with pyoderma gangrenosum (retrospective cohort study design)

	PG	Controls
Follow-up time, PY	1468.8	7688.4
Median follow-up time, years (range)	4.8 (0.0–17.8)	5.4 (0.1–17.8)
Number of events	10	61
Incidence rate/1000 PY (95% CI)	6.8 (3.5–12.2)	7.9 (6.1–10.1)
Crude HR (95% CI)	0.86 (0.44–1.69)	Reference
Male-specific crude HR (95% CI)	0.93 (0.36–2.41)	Reference
Female-specific crude HR (95% CI)	0.80 (0.31–2.05)	Reference
Adjusted HR (95% CI)[†]	0.99 (0.50–1.93)	Reference
Adjusted HR (95% CI)[‡]	1.02 (0.52–2.02)	Reference

[†]Multivariate logistic regression model adjusting for age, sex and ethnicity.

[‡]Multivariate logistic regression model adjusting for age, sex, ethnicity and comorbidities. CI, confidence interval; HR, hazard ratio; *N*, number; PG, pyoderma gangrenosum; PY, person-years. Bold: significant value.

Bold indicates significant values.

more likely to be of Jewish ethnicity (96.9% vs. 83.0%; $P = 0.049$) and had higher modified Charlson comorbidity score (2.6 [2.0] vs. 1.6 [2.1]; $P = 0.009$). Relative to the remaining patients with PG, those with SM-associated PG demonstrated higher probability of all-cause mortality (HR, 1.00; 95% CI, 1.06–3.76; $P = 0.033$; Figure 1).

DISCUSSION

The current population-based study revealed no significant association between PG and SM. To elaborate, patients with PG do not experience an overall increased risk of developing SM, and a preexisting diagnosis of SM does not predispose individuals to PG. The latter held true for all the different analysed organ-specific SMs. Relative to the remaining patients with PG, those with PG and coexistent SM were older at the diagnosis of PG and had more frequent comorbid conditions.

Scattered case reports and case series anecdotally depicted the coexistence of PG and SMs. Shahi et al.[10] characterised five patients with PG and SMs identified throughout seven years of follow-up. Of those, two (40%) developed SM prior to PG, two (40%) presented with SM following PG, whereas the fifth patient manifested with SM in parallel to PG. Three (60%) patients responded to PG-related drugs independently of the neoplasm course.[10] Subsequently, the same group has systematically reviewed the literature and found 19 patients reported to have coexistent PG and SM, with their majority (78.9%) having the SM prior to PG. Of note, all these patients were reported to achieve clinical remission, either with anti-neoplastic or anti-inflammatory therapy.[11] In 2019, Gupta et al.[12] reviewed the literature and summarised a total of 186 individual case reports of patients with PG and malignancy. Overall, 33 (17.7%) patients had SM, in whom the latter preceded the diagnosis of PG in 71.0% of cases.

In a meta-analysis aiming to summarise the prevalence and distribution of underlying diseases among patients with PG, the prevalence of SM ranged between 0%[13-17] and 20.7% (95% CI, 8.2–37.0)[18] in different study populations.[6] Summarising 21 studies encompassing 2611 PG patients, this quantitative synthesis revealed that the pooled prevalence of SM among patients with PG was estimated at 7.4% (95% CI, 5.8–9.1).[6] Of great interest, the aforementioned pooled outcome measure precisely accords with the prevalence of preexisting SM in our study population (7.5%). To the best of our knowledge, no controlled observational studies were carried out to assess the

Table 4 The association between PG and different solid malignancies

	OR (95% CI)	Univariate *P* value	Adjusted OR (95% CI)[†]	Multivariate *P* value
Breast cancer	0.70 (0.33–1.48)	0.350	0.80 (0.37–1.76)	0.586
Bone cancer	NA	0.525	NA	0.994
Brain and CNS cancer	3.32 (0.55–19.95)	0.164	2.39 (0.36–16.16)	0.369
Cervix cancer[†]	1.65 (0.17–15.96)	0.660	1.04 (0.09–11.86)	0.973
Colorectal cancer	1.79 (0.86–3.74)	0.112	1.89 (0.88–4.04)	0.101
Oesophagus cancer	2.48 (0.22–27.48)	0.443	2.73 (0.24–30.94)	0.417
Kidney cancer	2.99 (0.71–12.59)	0.116	3.47 (0.80–15.08)	0.097
Larynx cancer	NA	0.653	NA	0.138
Liver and bile ducts cancer	0.71 (0.09–5.77)	0.745	0.69 (0.08–5.80)	0.736
Lung cancer	0.38 (0.05–2.91)	0.332	0.40 (0.05–3.15)	0.387
Ovary cancer[†]	**9.97 (0.91–110.34)**	**0.021**	8.54 (0.72–101.56)	0.090
Pancreas cancer	1.99 (0.38–10.30)	0.403	2.05 (0.38–10.95)	0.403
Pharynx cancer	0.62 (0.08–4.96)	0.648	0.63 (0.08–5.18)	0.667
Prostate cancer[‡]	NA	0.118	NA	0.994
Stomach cancer	NA	0.368	NA	0.994
Sarcoma and soft tissue cancer	NA	0.525	NA	0.994
Thyroid cancer	0.49 (0.06–3.87)	0.493	0.48 (0.06–3.84)	0.488
Uterus cancer[†]	0.76 (0.17–3.39)	0.719	0.83 (0.18–3.78)	0.808
Urinary bladder cancer	0.35 (0.05–2.69)	0.292	0.34 (0.04–2.64)	0.301

[†]Multivariate logistic regression model adjusting for age, sex, ethnicity and comorbidities. NA was specified where OR could not be calculated due to lack of positive cases among cases or controls. CI, confidence interval; CNS, central nervous system; *n*, number; NA, not applicable; OR, odds ratio; PG, pyoderma gangrenosum.

[‡]Female study participants only.

Bold indicates significant values.

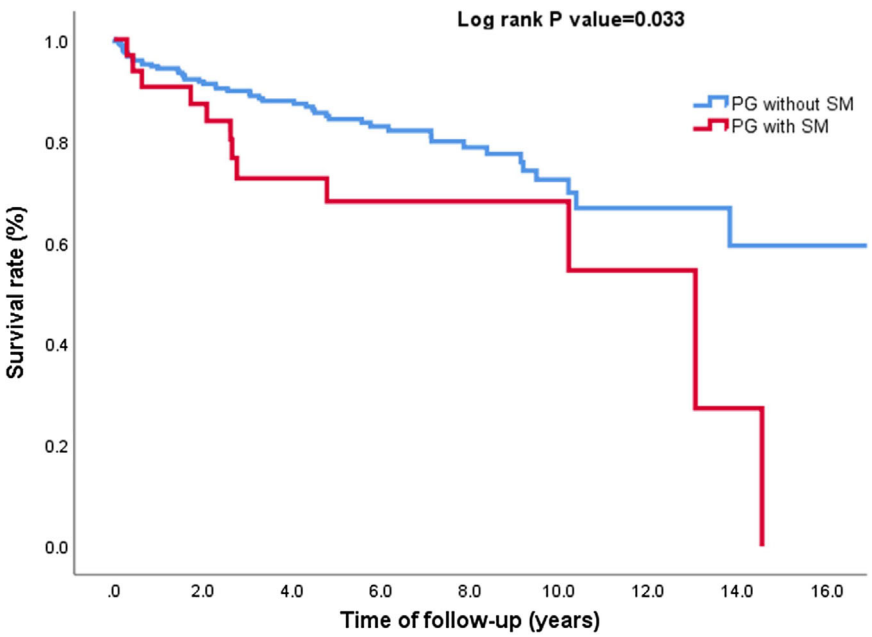

Figure 1 Kaplan–Meier curve demonstrating differences in survival rates between patients with PG and SM as compared to those with PG without SM.

association between PG and SM, leaving the literature inconclusive with regard to this question.

It is noteworthy that the aforementioned studies are methodologically improper to prove or refute the existence of a true association between PG and SM since they lacked comparison groups. Their findings, therefore, are underpowered to estimate the need for routine thorough cancer screening in patients with PG. Utilising a matched control group, the current study managed to overcome the main limitation of the previous studies and enabled to assess whether PG and SM are truly associated. Our findings indicate that patients with PG are associated with SM,

neither before nor after the onset of PG. Taken together, and in view that SMs are commonly encountered, it seems like their coexistence with PG in the current literature suggests a mere coincidence rather than a true epidemiological or pathophysiologic association.

Our findings may bear wide clinical implications since they argue against the performance of thorough routine screening for SM in patients with PG unless indicated by specific clinical history or suggestive symptoms. A thorough workup in search of haematological malignancy was suggested in patients with new-onset PG as it was proved helpful in improving survival outcomes.[19] Our results dispute a similar approach for SM and denote that patients with PG are not truly associated with SM.

Patients with coexistent PG and SM were found to be significantly older at the onset of PG relative to other patients with PG. This observation is thought to reflect the different age-related distribution of underlying diseases in PG. A considerable part of the remaining patients assumingly has underlying inflammatory bowel disease and inflammatory arthritis,[6,20,21] which tend to present at an earlier age.

The population-based setting of the study renders it less susceptible to ascertainment and selection biases, which frequently interfere with the findings of hospital-based studies. Addressing the temporal sequence in which the diagnosis appeared and the utilisation of two study designs enabled to evaluate the bidirectional association between the conditions. The limitations of the current study arise from lack of data concerning the morphological features of PG, as well as the precise histological type of each cancer. However, the diagnoses of both PG and malignancies in our study are of reliable validity since the diagnosis of BP relied only on documentation by certified dermatologists and dermatological wards and because the chronic disease registry of CHS is cross-linked with the Israel National Cancer Registry.

To conclude, the current population-based study excludes the presence of an epidemiological association between PG and SM. That is, our findings demonstrate that a history of SM is not associated with triggering subsequent PG and that patients with PG are not at an increased risk of SM. Patients with SM-associated PG were older and had higher comorbidities as compared to the remaining patients with PG. The current study argues against the performance of routine thorough SM screening in patients with incident PG. Further controlled studies are warranted to reproduce our findings in patients originating from other ethnic populations.

REFERENCES

1. Marzano AV, Damiani G, Ceccherini I *et al*. Autoinflammation in pyoderma gangrenosum and its syndromic form (pyoderma gangrenosum, acne and suppurative hidradenitis). *Br. J. Dermatol.* 2017; **176**: 1588–98.
2. Marzano AV, Fanoni D, Antiga E *et al*. Expression of cytokines, chemokines and other effector molecules in two prototypic autoinflammatory skin diseases, pyoderma gangrenosum and sweet's syndrome. *Clin. Exp. Immunol.* 2014; **178**: 48–56.
3. Braswell SF, Kostopoulos TC, Ortega-Loayza AG. Pathophysiology of pyoderma gangrenosum (PG): An updated review. *J. Am. Acad. Dermatol.* 2015; **73**: 691–8.
4. Langan SM, Groves RW, Card TR *et al*. Incidence, mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: a retrospective cohort study. *J. Invest. Dermatol.* 2012; **132**: 2166–70.
5. Marzano AV, Borghi A, Meroni PL *et al*. Pyoderma gangrenosum and its syndromic forms: evidence for a link with autoinflammation. *Br. J. Dermatol.* 2016; **175**: 882–91.
6. Kridin K, Cohen AD, Amber KT. Underlying systemic diseases in pyoderma gangrenosum: a systematic review and meta-analysis. *Am. J. Clin. Dermatol.* 2018. May 2 [cited 2018 May 13]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/29721816
7. Greenland S, Thomas DC. On the need for the rare disease assumption in case-control studies. *Am J Epidemiol* 1982; **116**: 547–53.
8. Kridin K, Zelber-Sagi S, Comaneshter D *et al*. Coexistent Solid Malignancies in Pemphigus. *JAMA Dermatol.* 2018. Feb 16 [cited 2018 Apr 2]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/29453868
9. Charlson ME, Pompei P, Ales KL *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.* 1987; **40**: 373–83.
10. Shahi V, Wetter DA. Pyoderma gangrenosum associated with solid organ malignancies. *Int. J. Dermatol.* 2015; **54**: e351–e357.
11. Shah M, Sachdeva M, Gefri A *et al*. Paraneoplastic pyoderma gangrenosum in solid organ malignancy: a literature review. *Int. J. Dermatol.* 2020; **59**: 154–8.
12. Gupta AS, Ortega-Loayza AG. Pyoderma gangrenosum: a too often overlooked facultative paraneoplastic disease. *Annals Hematol.* 2019; **98**: 2247–8.
13. Vacas AS, Torre AC, Bollea-Garlatti ML *et al*. Pyoderma gangrenosum: clinical characteristics, associated diseases, and responses to treatment in a retrospective cohort study of 31 patients. *Int. J. Dermatol.* 2017; **56**: 386–91.
14. Suárez-Pérez JA, Herrera-Acosta E, López-Navarro N *et al*. Pyoderma gangrenosum: A report of 15 cases and review of the literature. *Actas Dermosifiliogr* 2012; **103**: 120–6.
15. Mlika RB, Riahi I, Fenniche S *et al*. Pyoderma gangrenosum: A report of 21 cases. *Int. J. Dermatol.* 2002; **41**: 65–8.
16. Hasselmann DO, Bens G, Tilgen W *et al*. Pyoderma gangrenosum: clinical presentation and outcome in 18 cases and review of the literature. *J. Dtsch. Dermatol. Ges.* 2007; **5**: 560–4.
17. Binus AM, Qureshi AA, Li VW *et al*. Pyoderma gangrenosum: A retrospective review of patient characteristics, comorbidities and therapy in 103 patients. *Br. J. Dermatol.* 2011; **165**: 1244–50.
18. Cabalag MS, Wasiak J, Lim SW *et al*. Inpatient management of pyoderma gangrenosum: treatments, outcomes, and clinical implications. *Ann. Plast. Surg.* 2015; **74**: 354–60.
19. Montagnon CM, Fracica EA, Patel AA *et al*. Pyoderma gangrenosum in hematologic malignancies: A systematic review. *J. Am. Acad. Dermatol.* 2020; **82**: 1346–59.
20. Kridin K, Damiani G, Cohen AD. Rheumatoid arthritis and pyoderma gangrenosum: a population-based case-control study. *Clin. Rheumatol.* 2020; **40**: 521–8.
21. Kridin K, Damiani G, Ludwig RJ *et al*. Quantification of the relationship between pyoderma gangrenosum and Crohn's disease: a population-based case-control study. *Scand J. Gastroenterol.* 2020; **55**: 814–8.