Incidence, Mortality, and Disease Associations of Pyoderma Gangrenosum in the United Kingdom: A Retrospective Cohort Study

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Pyoderma gangrenosum (PG) is an important disease with significant complications. The objectives of this study were to determine incidence and mortality of PG and strength of reported associations. A retrospective cohort study was completed using computerized medical records from the General Practice Research Database, a large representative UK database. Patients with PG and three groups of age-, sex-, and practice-matched controls—general population, rheumatoid arthritis (RA), and inflammatory bowel disease (IBD) controls—were included in the study. Incidence and mortality were determined and validation undertaken to inform diagnostic accuracy. In all there were 313 people with the median age of 59 (interquartile range 41–72) years, and of them 185 (59%) were female. The adjusted incidence rate standardized to European standard population was 0.63 (95% confidence interval (CI) 0.57–0.71) per 100,000 person-years. The risk of death was three times higher than that for general controls (adjusted hazard ratio = 3.03, 95% CI 1.84–4.73, $P<0.001$), 72% higher than that for IBD controls (adjusted hazard ratio = 1.72, 95% CI 1.17–2.59, $P=0.013$), with a borderline increase compared with RA controls (adjusted hazard ratio = 1.55, 95% CI 1.01–2.37, $P=0.045$). Disease associations were present in 110 (33%) participants: IBD, $n=67$ (20.2%); RA, $n=39$ (11.8%); and hematological disorders, $n=13$ (3.9%). To our knowledge, there are no previous population-based studies of the epidemiology of PG, an important disease with significantly increased mortality.

Journal of Investigative Dermatology (2012) **132,** 2166–2170; doi:10.1038/jid.2012.130; published online 26 April 2012

INTRODUCTION

Pyoderma gangrenosum (PG) is a rare ulcerative neutrophilic condition usually affecting the skin, with rare extracutaneous involvement. The pathogenesis of PG is poorly understood. This disorder requires intensive multidisciplinary management, involving dermatologists, plastic surgeons, gastroenterologists, and immunologists, as well as other specialists depending on the disease location (Callen, 1998). It is a challenging diagnosis requiring the presence of a classical clinical presentation with biopsies excluding other important pathology (Weenig *et al.*, 2002; Brooklyn *et al.*, 2006). Delayed diagnosis or misdiagnosis can lead to serious morbidity (Brooklyn *et al.*, 2006).

The epidemiology of PG has never been formally assessed in a population-based study (Powell *et al.*, 1996). Thus, estimates of the epidemiology of this disorder are based on case reports, case series, and cohort studies of individuals with inflammatory bowel disease (IBD; Farhi *et al.*, 2008; Vavricka *et al.*, 2011). As a result of these studies, PG has been estimated to have an incidence rate of 3–10 per million population per year. Similarly, mortality has been reported in case reports and case series, with some estimates quoting a mortality rate of 30% (Saracino *et al.*, 2011). Previous studies have reported associations with systemic disease in 50% of cases, most commonly with IBD, rheumatoid arthritis (RA), and hematological disorders (Powell *et al.*, 1985). PG has been reported in ~2% of individuals with IBD in a variety of cohorts, but the number of individuals with PG in these large cohorts is small ($n=8$ and $n=17$; Farhi *et al.*, 2008; Yüksel *et al.*, 2009). As the epidemiology of PG has never been formally studied outside the context of IBD, the population-based incidence, associated mortality, and disease associations are unknown. These estimations are critically important to enable a better understanding of disease epidemiology, which is important for planning clinical trials of interventions, service planning, and education of healthcare professionals.

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Abbreviations: CI, confidence interval; GP, general practitioner; GPRD, General Practice Research Database; IBD, inflammatory bowel disease; PG, pyoderma gangrenosum; PPV, positive predictive value; RA, rheumatoid arthritis

Received 15 November 2011; revised 18 January 2012; accepted 9 February 2012; published online 26 April 2012

The aims of this study were to determine the incidence and mortality of PG in the United Kingdom and to assess what proportion of individuals had associated underlying systemic disease.

RESULTS

Our cohort included 313 people with incident PG contributing 1,452 person-years. There were 313 matched general controls who did not have either RA or IBD, contributing 1,624 person-years, 309 matched RA controls contributing 1,770 person-years, and 303 matched IBD controls contributing 1443 person-years, respectively. The median age at presentation for PG was 59 (interquartile range 41–72) years, and 185 (59%) patients were women (Table 1). The median length of follow-up for individuals with PG was 3.3 years (interquartile range 1.1–7.5 years). Comorbidity rates, measured using the Charlson comorbidity index, were higher in cases compared with general controls, with one or more comorbidities being present in 43% of cases compared with only 31% of controls. On examining the components of the Charlson index, significant differences were observed: increased rates of uncomplicated diabetes in cases (10%) compared with controls (3%), increased congestive cardiac failure (5% compared with 1%), and leukemia in 2% of the cases and not in controls. There was no significant difference in overall comorbidity rates compared with IBD controls (43% compared with 41%) or RA controls (43% in both groups). On examining the components of the Charlson index, it was found that leukemia was increased in cases compared with all control groups (2% vs. 0%), whereas stroke was increased in IBD controls (6%) compared with cases (2%).

Validation

Questionnaires were sent to the general practitioners (GPs) of 80 individuals with diagnoses of PG in the 2 years before the study end date. Of these, 53 were returned reporting individuals with ''PG'' codes; 11 GPs either did not respond or the response was not valid. Of the 42 cases coded as ''PG'' for whom we received a valid response, 32 were confirmed to have a diagnosis of PG (positive predictive value (PPV) 76%, 95% CI 61–87%). For the 27 questionnaires

Table 1. Demographics of study population

Category	Number of cases	Person-time	Incidence rate (confidence interval) per 100,000 person-years standardized to European standard population
Overall incidence	313	428.71	0.63 (0.58–0.71)
Incidence by gender			
Male	128	211.47	0.55 (0.46–0.65)
Female	185	217.24	0.71 (0.61–0.82)
Incidence by year			
1992–1994	39	45.71	0.83 (0.60–1.13)
1995–1997	30	56.90	0.46 (0.33–0.66)
1998–2000	32	75.98	0.37 (0.26–0.53)
2001–2003	61	92.14	0.55 (0.43–0.71)
2004–2006	87	98.09	0.75 (0.61–0.93)
2007–2008	64	59.88	0.90 (0.70–1.15)
Incidence by age category (years)			Age-specific incidence rates per 100,000 population
<10	3	47.94	0.06 (0.02–0.19)
10–19	13	50.88	0.26 (0.15–0.44)
20–29	19	53.90	0.35 (0.22–0.55)
30–39	36	65.49	0.55 (0.40–0.76)
40–49	42	62.46	0.66 (0.48–0.89)
50–59	47	54.74	0.86 (0.65–1.14)
60–69	54	42.41	1.27 (0.98–1.66)
70–79	70	31.62	2.25 (1.78–2.83)
80 (maximum)	29	19.28	1.50 (1.04–2.16)

returned reporting individuals with ''pyoderma'' codes, we received 16 valid responses and 8 were confirmed to have a diagnosis of PG, giving a PPV of 50% (95% CI 26–74%). Among the confirmed cases with both ''PG'' and ''pyoderma'' codes, the majority of GPs reported disease involvement of the legs in 25 (74%), the trunk in 6 (19%), the arms in 5 (16%), and stomal disease in two patients (6%). A total of 18 GPs (56%) described a rapid onset, and 12 (38%) described severe pain.

Incidence

The crude overall incidence of PG was 0.73 (95% confidence interval 0.65–0.82) per 100,000 person-years. On standardizing this rate to the European standard population, the adjusted incidence rate was found to be 0.63 (95% CI 0.57–0.71) per 100,000 person-years. Incidence increased with age and was higher in women than in men (Table 1), but did not vary by calendar region or change over time. We estimate that the incidence of PG increased 12.13-fold (95% CI 7.15–20.57) between individuals aged <20 years and those aged >70 years.

The validation study gave a PPV of 76% for ''PG'' and 50% for ''pyoderma'' diagnostic codes. In all, 308 individuals were identified with ''pyoderma'' codes. As ~50% of these individuals and 76% of those with ''PG'' codes are likely to have PG, the true incidence rate is likely to be closer to 0.91 (95% CI 0.83–1.01) per 100,000 person-years.

Mortality

The risk of death for patients with PG varied according to the choice of the control group (Table 2)—the risk being three times higher compared with general population controls (adjusted hazard ratio = 3.03, 95% CI 1.84–4.73), 74% higher compared with IBD controls (adjusted hazard ratio = 1.74, 95% CI 1.17–2.59), and only a borderline statistically significant increased risk compared with RA controls (adjusted hazard ratio = 1.55, 95% CI 1.01–2.37). On adjusting for other comorbidities using the Charlson comorbidity index, the revised hazard compared with general population controls reduced to 2.87 (95% CI 1.83–4.50), as compared with 1.64 for IBD controls (95% CI 1.10–2.44), and a revised hazard of 1.49 compared with RA controls (95% CI 0.96–2.28). The borderline increased significance compared with that of RA controls disappeared in sensitivity analysis, excluding cases with leukemia (eight in total, two following PG) and lymphoma (five in total, two following PG).

Disease associations

Frequently reported disease associations were present in 110 (33%) individuals, the majority having IBD ($n=67$; 20.2%), with smaller numbers having RA ($n=39$; 11.8%) and hematological disorders ($n=13$; 3.9%), respectively. Similar disease associations were seen in individuals with ''pyoderma'' codes, but these were not as strong as those for individuals with specific codes. No increased association was seen for osteoarthritis, a disease not previously reported in association with PG (results not shown).

DISCUSSION

This study identified that PG was associated with significantly increased mortality rates, three times higher than that for the general population, almost twice as high as the mortality in IBD, and a 50% increase compared with that for RA, although the latter was of borderline significance and disappeared in sensitivity analysis excluding cases with leukemia and lymphoma. These results are in contrast with the disease-specific deaths recorded by the Office for National Statistics, which recorded only three deaths from PG in the United Kingdom in 2009. Adjusting for other comorbidities did not eliminate these increased mortality rates.

This is a large, population-based study that allows robust estimation of incidence and mortality and is less susceptible to selection bias than other study designs. The size of the data set gives sufficient power to exclude chance as the basis for the findings and allowed us to undertake the largest study of pyoderma gangenosum ever undertaken. The use of routinely collected data indicates that we could not assess the severity of disease, although it was possible for us to validate the diagnosis of PG using GP questionnaires.

Table 2. Mortality in pyoderma gangrenosum compared with three control groups

Group	Deaths	Person-years	HR	Adjusted HR (for age)	Adjusted HR (for age and gender)	Adjusted HR (for age, gender, and Charlson comorbidity index)	*P*-value
General controls without RA or inflammatory bowel disease (*n*=313)	30	1,624	1.0	1.0	1.0	1.0	
Cases (*n*=313)	70	1,452	3.75 (1.98–7.09)	3.03 (1.94–4.73)	3.03 (1.84–4.73)	2.87 (1.83–4.50)	<0.001
RA controls (*n*=309)	35	1,770	1.0	1.0	1.0	1.0	
Cases (*n*=309)	70	1,452	2.31 (1.51–3.51)	1.54 (1.00–2.36)	1.55 (1.01–2.37)	1.48 (0.96–2.28)	0.08
IBD controls (*n*=302)	40	1,647	1.0	1.0	1.0	1.0	
Cases (*n*=302)	70	1,443	1.97 (1.33–2.93)	1.72 (1.16–2.56)	1.74 (1.17–2.59)	1.64 (1.10–2.44)	0.02

Abbreviations: HR, hazard ratio; IBD, inflammatory bowel disease; RA, rheumatoid arthritis.

However, opportunities for error in our study do exist. In our incidence study, although we have taken care to validate the diagnoses of PG (in effect determining the specificity of our code list for the diagnosis) and correct our results for the errors shown, we are unable realistically to provide a precise estimate of the sensitivity of our code list. Therefore, it is possible that a number of incident cases of PG have not been detected and that we have underestimated incidence. Given that this is a rare diagnosis without multiple alternate names, which is of great importance to patients and therefore their GPs, when it is present we think any such error is likely to be small. Misclassification of PG is always a difficult issue because it is a diagnosis of exclusion; this issue has been highlighted in series from tertiary care and may indeed be an issue for this data source despite our best efforts to validate the data (Weenig *et al.*, 2002). If some of the PG cases included are prevalent rather than incident cases, it might lead to an overestimation of incidence, as well as survival bias, thus leading to an underestimation of true mortality rates. Again, we believe that such an error is unlikely to have had a large effect given the previous validation of the algorithm used to determine incidence in another chronic disease (Lewis *et al.*, 2005). Conversely, studies of skin cancer incidence suggest undercoding and reporting of skin cancers; hence, true incidence could be higher than our study estimates (Bath-Hextall *et al.*, 2007).

There are no previous population-based studies of PG. Previous estimates of the epidemiology of PG have been based on case reports and case series from tertiary-care settings and cohort studies involving individuals with IBD (Powell *et al.*, 1985; Bennett *et al.*, 2000; Bernstein *et al.*, 2001; Farhi *et al.*, 2008). The estimated incidence usually quoted in the literature is 3–10 per million population per year. Our estimated incidence is consistent with these reports, with an incidence of 6 per million when standardized to the European standard population, i.e., 0.63 (95% CI 0.57–0.71 per 100,000 person-years). However, the true incidence rate is likely to be closer to 0.91 (95% CI 0.83–1.01) per 100,000 person-years when accounting for the PPV of a diagnostic code for ''PG'' and the fact that ~50% of those with ''pyoderma'' codes also have PG. Previous authors have suggested an increased incidence in women, which is consistent with our study findings (von den Driesch, 1997). The reasons for this are not clear and may warrant further study. Mortality rates of up to 30% overall have been reported in the literature, but there are no estimates of increases in mortality compared with controls. In our cohort, 22% of the study population died during the study, which translates into a 3-fold increased risk compared with the general age-, sex-, and practice-matched population. Previous reports from tertiary-care centers have described association with underlying systemic disease in up to 50% of those affected. In this study, we have found that 33% of the study population had underlying IBD, RA, or hematological disease. Ascertainment bias may have played a role in the higher number of reported associations in previous studies, as individuals in a tertiary-care setting may be more likely to be diagnosed with PG in a setting of concurrent disease, or equally might be more likely to have minor manifestations of associated disease or asymptomatic disease investigated once they are diagnosed with PG.

To our knowledge, there are no previous population-based cohort studies of PG. It provides useful information on incidence, mortality rates, the validity of a PG diagnosis in GPRD, and disease associations, which will be extremely useful data for planning clinical care and clinical trials. PG has recently been identified as a top priority for independent research by the UK Dermatology Clinical trials network (http://www.ukdctn.org/home/ and http://www.stopgaptrial.co.uk/).

Our study has shown high mortality associated with PG; mortality rates were three times higher than those in the general population, 70% higher than those in individuals with IBD, and 50% higher than those in age-, gender-, and practice-matched controls with RA. Factors leading to increased mortality in these individuals warrant further study. Previous measures have underestimated the burden of PG, in terms of risk of death.

MATERIALS AND METHODS

The GPRD is the world's largest computerized database of anonymized longitudinal patient records from general practice, containing data on ~8% of the UK population. Data are obtained from >625 general practices for a currently registered population of >5 million people representative of the general UK population (General Practice Research Database, 2011). The data contain complete medical records of these individuals, including prescriptions and feedback from referrals, as well as hospitalizations. The validity of GPRD data has been widely demonstrated for epidemiological research, including research in IBD (Lewis *et al.*, 2002; Jick *et al.*, 2003; Herrett *et al.*, 2010).

Study population

Between 1992 and 2008, we identified all patients with a diagnosis of ''PG'' from the General Practice Research Database (GPRD) using diagnostic READ and OXMIS codes (M070200 and 6860GP). Individuals were also identified with ''pyoderma'' READ or OXMIS codes as a sensitivity analysis (M070.00, M070z00, and 6,860). To exclude prevalent cases, we imposed a lag period of 12 months after registration with their GP. This method has been previously validated by Lewis *et al.* (2005) to differentiate between incident and prevalent cases of disorders. We selected three control groups matched 1:1 randomly by age, sex, and general practice: one group had neither RA nor IBD, the second control group had RA, and the final group had IBD. Controls also had to be alive and contributing data to the GPRD on the date of diagnosis of the matched case. We assigned a date of ''pseudodiagnosis'' to controls, which was the date of diagnosis for the matched case.

Validation

A questionnaire was distributed to the GPs of all 80 individuals with a diagnostic code either for ''PG'' or ''pyoderma'' in the past 2 years of the study, who remained active in their practices to determine whether the individuals had a confirmed diagnosis of PG and to obtain descriptive data regarding diagnosis and presentation (Supplementary Material online).

Outcomes

We recorded incident diagnoses and dates of death. The follow-up period began on the date of first diagnosis, or the date of ''pseudodiagnosis'' for controls.

Statistical analysis

Incidence. We calculated incidences by age, categorized into 10-year age bands, sex, and calendar period. We used multivariate Poisson regression to model incidence rate ratios, adjusting for changes in age and gender structure over time. Incidence rates were standardized to the 2,000 European standard population. To provide the most accurate estimate possible, we also adjusted these rates for the PPV of a code for PG as established from our validation study. The impact of including individuals with ''pyoderma'' codes on the incidence rates was explored.

Mortality. All deaths in the case population and matched control groups were identified, and Kaplan–Meier techniques were used to calculate 1-year mortality and 5-year survival rates. We used Cox regression to compare the mortality of cases and the three groups of controls, adjusting for age, sex, and calendar period. We used Schoenfeld residuals to evaluate the proportional hazards assumption (Hess, 1995). Comorbidity was assessed using the Charlson comorbidity index to determine whether any observed differences in mortality related to underlying comorbidity (Charlson *et al.*, 1987). A sensitivity analysis was undertaken, excluding cases with leukamia and lymphoma in order to ensure that mortality was not explained by atypical PG.

Sample size

The size of the study sample was determined by the number of patients identified with PG in the UK GPRD. The study had about 80% power to detect a relative risk of mortality of 1.5.

Ethics

The study was approved by the Independent Scientific Advisory Committee of the GPRD.

Role of the funding source

Dr Langan is funded by an NIHR Clinician Scientist award from the UK Department of Health. The sponsor of the study reviewed the study protocol but had no role in the design, analysis or interpretation of data, writing of the report, or the decision to submit the paper for publication.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

This research was funded by a grant from Guy's and St Thomas's charity. SML is funded by an NIHR Clinician Scientist award. We thank Dr David Margolis, Dr Victoria Werth, Dr Misha Rosenbach, and Dr Joel Gelfand from the University of Pennsylvania for assistance and input into the validation questionnaire. SML, RWG, and MG were involved in the conception and design of this study. All authors were involved in analysis and interpretation of data. SML drafted the article and all authors revised it critically for important intellectual content and gave final approval of the version to be published. All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SML is the guarantor.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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