SHORT COMMUNICATION

MJS PUBLISHING

Patient Journey of Generalized Pustular Psoriasis: A Real-world Study Using Data-mining Methods and Japanese Claims Data

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Generalized pustular psoriasis (GPP) is a chronic, rare, autoinflammatory skin disease characterized by widespread eruption of sterile pustules with or without systemic symptoms (1, 2). Owing to the rarity of GPP, there is a lack of international consensus on diagnosis and management, and a paucity of standardized global guidelines (3). Although there are established GPP guidelines in Japan (2), disease understanding among general dermatologists is limited. Moreover, several pustular skin conditions have similar clinical presentations, which contribute to the diagnostic complexity of GPP (3).

A greater understanding of disease trajectory before GPP diagnosis may be key to improving the timeliness and accuracy of diagnosis, and subsequently, patient outcomes. However, thus far, disease trajectories in patients with GPP have not been ascertained on a population level.

Using population data from a Japanese health insurance database, this study describes the journey of patients with GPP and explore other diagnoses received before GPP. Notably, the methods used in this study (Appendix S1) may be used to mine databases from other countries.

MATERIALS AND METHODS

This retrospective cohort study used two data mining and machine-learning models with different medical foci to evaluate anonymized claims data from the Japan Medical Data Center (JMDC), from 1 January 2005 to 29 February 2020. Eligible patients with an incident diagnosis of GPP (International Classification of Diseases 10th Revision code L40.1) and ≥1 year of continuous insurance enrolment before their index date were followed from the first confirmed diagnosis of any disease to the first confirmed GPP diagnosis (index date; Fig. S1); their journey before GPP diagnosis was analyzed. This study was approved by the ethics committee of the Nishi-Umeda Clinic for Asian Medical Collaboration, Osaka, Japan; approval number AMC-BI-21-009.

Data were analyzed using network analysis and sequential pattern mining. Baseline covariates, including age and sex, are presented descriptively.

RESULTS

Of the 435 patients in the JMDC database with GPP diagnosis, 189 met the inclusion criteria. The median age was 39 (range 1–74) years and 42.9% of patients were female (Table SI).

Overall, 31/607 diseases diagnosed before a GPP diagnosis appeared in the network pattern with a direct or indirect connection to GPP. Twenty-two diseases were diagnosed in ≥20% of patients (**Fig. 1**; Table SII), including atopic conditions (e.g. conjunctivitis and atopic dermatitis; Table SII). Fifteen diseases were directly linked to GPP (Fig. S2); the most common being allergic rhinitis (53.5%), acute bronchitis (52.9%), and acute upper respiratory tract infection (48.1%; Fig. 1).
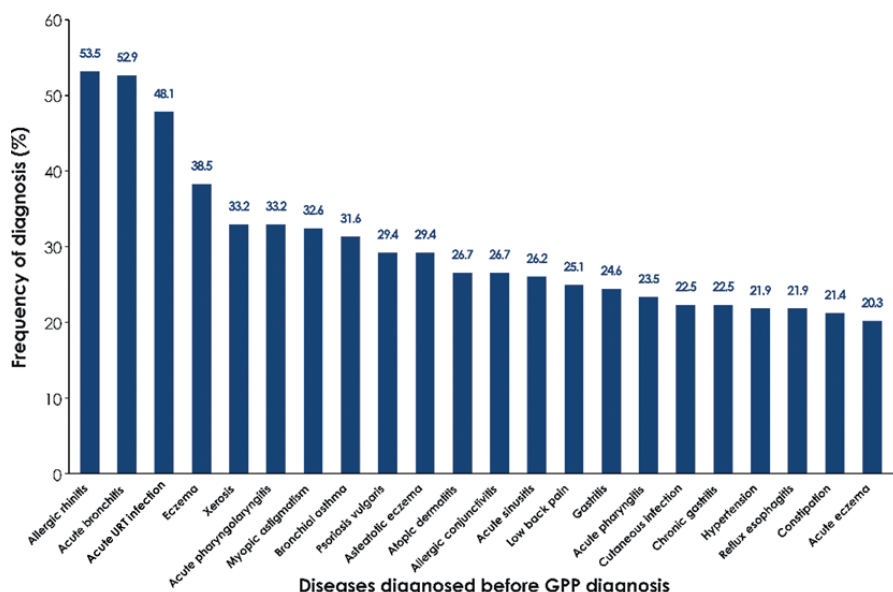
Fig. 1. Diagnoses (*n* = 22) before a generalized pustular psoriasis (GPP) diagnosis occurring in ≥ 20% of patients. URT: upper respiratory tract.

Psoriasis vulgaris (PsV) was a pre-diagnosis in 29.4% of patients. Time to GPP diagnosis for patients with any of the 15 diseases directly linked to GPP is shown in Fig. S3 and Table SII. Sixty-seven sites were identified as making pre-GPP diagnoses of interest, with clinics (any type of clinic including but not limited to dermatology and internal general medicine) and other hospitals (any hospital that is not a clinic, public hospital, or University hospital) the most frequent settings ($n=38/67$ [56.7%] and $n=14/67$ [20.9%], respectively (Fig. S4)).

To explore the short-term patient journey regardless of frequency, we extracted disease diagnoses first made ≤120 days before GPP diagnosis. Pre-GPP diagnoses occurring in ≥1% of patients included skin diseases or symptoms, and differential diagnoses; these occurred at a relatively low frequency (1.1–6.4%; Fig. S5). Table SIII shows diseases that were diagnosed ≤120 days before GPP diagnosis.

DISCUSSION

This real-world study was the first to explore disease trajectories and the pre-diagnosis history of patients with GPP. The study identified 22 diseases diagnosed in ≥20% of patients before GPP diagnosis, and highlighted direct links between 15 diseases and GPP. Five of the 15 diseases linked to GPP were last diagnosed ≤120 days before GPP diagnosis, including PsV (known to precede GPP in some patients (4)) and other diseases (e.g. impetigo) that often represent differential diagnoses for GPP. These data align with previous research from the Japanese Society for Psoriasis Research, reporting PsV prevalence of 31–78% among Japanese, Malaysian, and Portuguese patients with GPP (4–9).

The frequency of diseases that were first diagnosed ≤120 days before GPP diagnosis was low, indicating that they were minor diagnoses in the patient journey. Overall, several skin diseases and dermatological signs/symptoms were identified (Fig. S5) that may exhibit similar symptoms to those of early GPP. For example, fever is common to both cellulitis and GPP, and pustules, skin erosion, and erythema present at initial GPP onset (2). Additionally, patients experiencing severe itch can be mistakenly diagnosed with eczema. This highlights the difficulty in correctly diagnosing early GPP symptoms and the need for dermatologists to consider differential diagnoses. A high proportion of initial diagnoses in this study were made in clinics including but not limited to dermatology clinics. Unfortunately, data on the type of clinic were unavailable for the most of these diagnoses, so the impact of dermatologist involvement on misdiagnosis remains unclear. Overall, our findings highlight the challenge of accurate GPP diagnosis, similar to the results of a US patient survey, in which 59% of patients with GPP were misdiagnosed before receiving a confirmed GPP diagnosis (4, 10).

The short-term patient journey to a GPP diagnosis may include diseases that trigger GPP. Although there is some overlap between GPP symptoms and cellulitis that may lead to misdiagnosis (e.g. swelling, redness, and fever), other symptoms differ; cellulitis has been reported as a trigger for GPP (2). Pregnancy is a known trigger for GPP and this was reflected our study, with threatened premature delivery identified ≤120 days before GPP diagnosis (Table SIII). Conditions identified ≤120 days before GPP diagnosis included allergic contact dermatitis and allergic rhinoconjunctivitis, for which corticosteroids may be prescribed (11, 12). As corticosteroid withdrawal is a known trigger for GPP, the treatment, rather than the disease *per se*, could be the trigger. Indeed, it was difficult to establish a relationship between diseases directly connected to a GPP diagnosis with the onset of GPP, particularly for patients diagnosed several months before GPP. For example, diagnoses of myopic astigmatism and impacted cerumen occurred approximately 285 and 326 days prior to GPP diagnosis. Although there is currently no evidence for the link between these conditions and GPP, a potential correlation cannot be completely disregarded. In addition, as the most common diagnoses occurring in ≥5% of patients during the pre-GPP diagnosis period are relatively common conditions (allergic rhinitis, acute bronchitis, and acute upper respiratory tract infection) it is not easy to decipher their relevance to GPP onset.

This study included a representative sample of patients with incident GPP diagnoses; however, external validity may be limited due to the restriction to a single Japanese database that includes only 4 million of ~125 million people in Japan (13), and few individuals aged >65 years. Our study population comprised younger patients compared with other Japanese studies (7, 14) and a higher proportion of males than females. While most GPP studies observe a higher proportion of females versus males (15), a higher proportion of males has been observed in other Japanese studies (13), including one utilizing JMDC data (16). As employed individuals comprise the majority of patients captured in the JMDC database, older, unemployed or female patients (who make up a large proportion of the Japanese population) may be under-represented. There was also a potential risk of bias due to the retrospective study design, restricting the analysis to patients with ≥1 year of continuous insurance enrolment, and relying on the quality and availability of data in the database, all of which could have included inconsistencies or errors. Furthermore, using the JMDC database to analyse GPP diagnoses has not yet been validated.

This first real-world study exploring the short- and long-term disease trajectories in patients before their GPP diagnosis found that approximately 30% had received a prior PsV diagnosis. Other pre-GPP diagnoses in the patient journey may represent differential diagnoses that clinicians need to exclude when diagnosing GPP or that may trigger GPP.

ACKNOWLEDGEMENTS

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