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Impact of the COVID-19 pandemic on hospital admissions of patients with rare diseases: an experience of a Southern Italy referral center

Dear Editor,

Rare diseases are defined by the European Community as pathologies which present a frequency $\leq$ 1 case per 2000 people (5 cases per 10,000 people). Rare syndromic and nonsyndromic diseases which affect the skin, seeking dermatology attention, are numerous. Certainly, autoimmune bullous diseases (pemphigus vulgaris and bullous pemphigoid) and keratinization disorders (ichthyosis) represent the most common. In fact, it is estimated a prevalence of 18.0/100.000 for pemphigus, 26.0/100.000 for bullous pemphigoid, and 16.6/100.000 for X-linked recessive ichthyosis.[1,2] Currently, the Section of Clinical Dermatology, Department of Integrated Activities of Public Health, Pharmacology and Dermatology of the University of Naples Federico II, is one of the Italian accredited centers specifically identified by the National Health System to provide diagnostic and therapeutic services for rare diseases. This center is an active actor of the Technical Working Group for the drafting of Italian guidelines and shares treatment algorithm for rare diseases in dermatology. Actually, our center deals with 293 cases of rare diseases: congenital ichthyosis (16.38%), lichen sclerosus et atrophicus (17.96%), bullous pemphigoid (55 patients), bullous epidermolysis (9.89%), pemphigus (64 patients), Darier disease (6.48%), ectodermal dysplasia (4.09%), and Hailey-Hailey disease (5.96%). All patients who had been referred to the specific outpatient clinic of rare diseases of our facility have been followed through a multidisciplinary approach. Unfortunately, the COVID-19 pandemic had complicated the assistance to this fragile class of patients. We have implemented telemedicine services for all patients who could not seek our attention, with e-mails, WhatsApp, and Zoom mediated telemedicine playing a key role during the COVID-19 pandemic.[3,4] Obviously, during the COVID-19 pandemic, we followed strict precautionary measures for the management of these fragile patients: they had to perform a molecular swab 48 hours preceding the visit or hospitalization and could not be accompanied by other caregivers except for minors. All these measures led to a significant reduction in the number of accesses at the dedicated outpatient clinic and at our day hospital in the year 2020 (Table 1). We have provided vaccinations for almost all our patients, reaching about 92% with the three doses with the remaining 8% deciding not to vaccinate for personal concerns, and all the administrations have been carried out at our facility in day hospital ensuring the patient a certain safety.[5] Certainly, the vaccination campaign has allowed us to ensure a greater number of accesses. In fact, in 2021, we recorded an increase in the first accesses at our facility around 50% (Table 1), and now patients can freely access our facility with a certificate of vaccination or with a negative swab of the previous 48 hours if they are not vaccinated; if a patient is positive, we guarantee the visit in telemedicine, in this way we can reach all our patients. In conclusion, comparing these 2 years of the pandemic (2020 and 2021), we observed a huge reduction of rare diseases patients seeking our attention. Fortunately, in 2021 thanks to COVID-19 vaccines and restriction measures reduction, we were able to almost double the number of visits compared to the previous year. COVID-19 has unfortunately had a great impact on fragile and delicate patients who require multidepartment commitment, follow-up, and frequent visits, such as patients with rare diseases, so new strategies must be implemented to reduce such emergencies. The limit of our study is certainly the sampling and the monocentric character, but, nonetheless, enabling easy access and emphasizing high-quality medical and telematics care for patients, especially those with rare diseases, could reduce long-term complications and prevent irreversible damage.

Table 1 Hospital admissions of patients with rare diseases in 2020 compared with those in 2021

Clinical setting	2020	2021
Day hospital and ambulatory outpatients		
Total, *N*-293	153	293
Males, *N*-183		
Females, *N*-110		
Disease		
Epidermolysis bullosa, *N*-29	11	29
Ichthyosis, *N*-48	24	48
Bullous pemphigoid, *N*-55	25	55
Pemphigus, *N*-64	30	64
Darier disease, *N*-19	9	19
Lichen sclerosus et atrophicus, *N*-50	35	50
Others, *N*-28	9	28

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Patients gave the consent for publication.

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Cutaneous symptoms of connective tissue diseases after COVID-19 vaccination: a systematic review

Dear Editor,

SARS-CoV-2 vaccination has been shown to substantially decrease COVID-19 morbidity and mortality.[1] However, reports have described the onset of autoimmune cutaneous symptoms after COVID-19 vaccination, usually in patients with pre-existing autoimmune diseases. No studies to date have analyzed the aggregate data. In this study, we systematically review cutaneous symptoms of connective tissue diseases after COVID-19 vaccination.

We searched PubMed/MEDLINE for articles in English published from December 11, 2020, to March 30, 2022, using key words "COVID-19 vaccin*" or "SARS-COV-2 vaccin*" and connective tissue disease-related search terms (e.g., "lupus," "systemic sclerosis," "scleroderma," "sclerotic skin," "dermatomyositis," "morphea"), yielding 126 articles (Figure 1). Screening and review of articles were completed according to Preferred Reporting Items for Systematic and Meta-Analysis (PRISMA) guidelines. Two independent reviewers (B.N. and M.J.L.) screened articles based on titles and abstracts to exclude duplicate, non-English, and review articles, yielding 116 reports. Of these, 30 articles (22 case reports, 3 case series, 2 cohort studies, 2 cross-sectional studies, and 1 clinical trial) encompassing 2020 patients (mean age 53.4 ± 19.9, 91.3% females) described 93 patients who developed post-vaccine cutaneous symptoms of connective tissue diseases.

The majority of affected patients had pre-existing autoimmune disease (77.4%, 72/93); new diagnosis of connective tissue disease after COVID-19 vaccination was uncommon (22.6%, 21/93). Females seemed to be affected more often (65.6%, 21/32), although the gender of most affected patients was not reported in larger studies.

The most common vaccines administered were Pfizer (60.5%, 1201/1984), Sinovac (19.6%, 388/1984), Moderna (10.8%, 215/1984), and AstraZeneca (9.1%, 180/1984). In non-case report and non-case series studies that described patients with and without cutaneous symptoms, the overall prevalence of cutaneous symptoms after vaccination ranged from 0.4% (1/265) to 4.4% (4/90), with a mean of 3.3% (65/1992) (Table 1).

The most common connective tissue diseases and cutaneous symptoms implicated after COVID-19 vaccination, when specified, were autoimmune sclerosing diseases (51.6%, 48/93), lupus (41.9%, 39/93), and dermatomyositis (6.5%, 6/93) (Table 2). When specified, 55.6% (45/81) of skin symptoms occurred after the 1st vaccine and 44.4% (36/81) after the 2nd

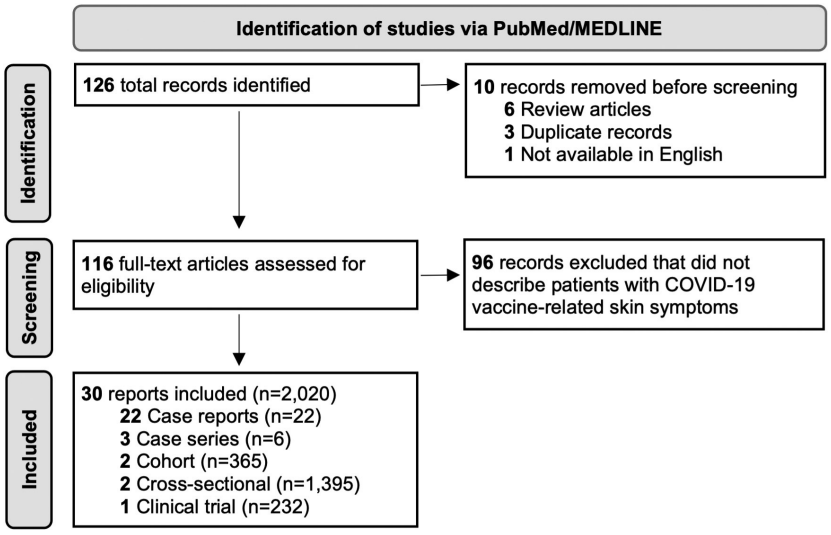

Figure 1 Flowchart of study identification via PubMed/MEDLINE according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

