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COVID-19 outbreak and autoimmune bullous diseases: A systematic review of published cases

To the Editor: Autoimmune bullous diseases (AIBDs) are potentially life-threatening disorders requiring long-term immunomodulatory therapies.[1,2] As the coronavirus disease 2019 (COVID-19) has emerged as a widespread public health emergency since December 2019,[3] we have published recommendations for their management during the outbreak.[4] However, there is currently only sparse evidence-based information on how the pandemic affects this special patient population, considering that AIBDs are rare conditions and that it is difficult to collect large cohorts. Therefore, a rapid systematic review of published cases has been conducted.

Literature was comprehensively screened using the PubMed database from inception to July 28, 2020. Search terms were "pemphigus" or "pemphigoid" or "bullous" or "blistering" combined with "COVID-19" or "SARS-CoV-2" or "coronavirus." Inclusion criteria were English-language clinical and epidemiologic reports related to AIBD cases in association with the COVID-19 outbreak and indexed in the mentioned database. Pure review/recommendation articles and articles not related to both AIBDs and COVID-19/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were excluded. The main endpoints were the proportion of patients with AIBDs with COVID-19 symptoms and confirmed COVID-19 as well as the rate of related hospitalizations and deaths. Screening and review of articles were performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig 1).

Eight articles (7 case series and 1 case report) with a pooled total of 732 patients with AIBDs (211 pemphigus, 112 pemphigoid, 409 not specified) from 3 countries were included in the final analysis (Table I). Except for 1 report, all information was collected via telephone/telemedicine visits that have been performed instead of in-person encounters during the COVID-19 outbreak. COVID-19 symptoms were reported in 70 (9.5%) patients, and in 16 (2.1%) patients the diagnosis was confirmed. Six (0.8%) patients had severe symptoms requiring

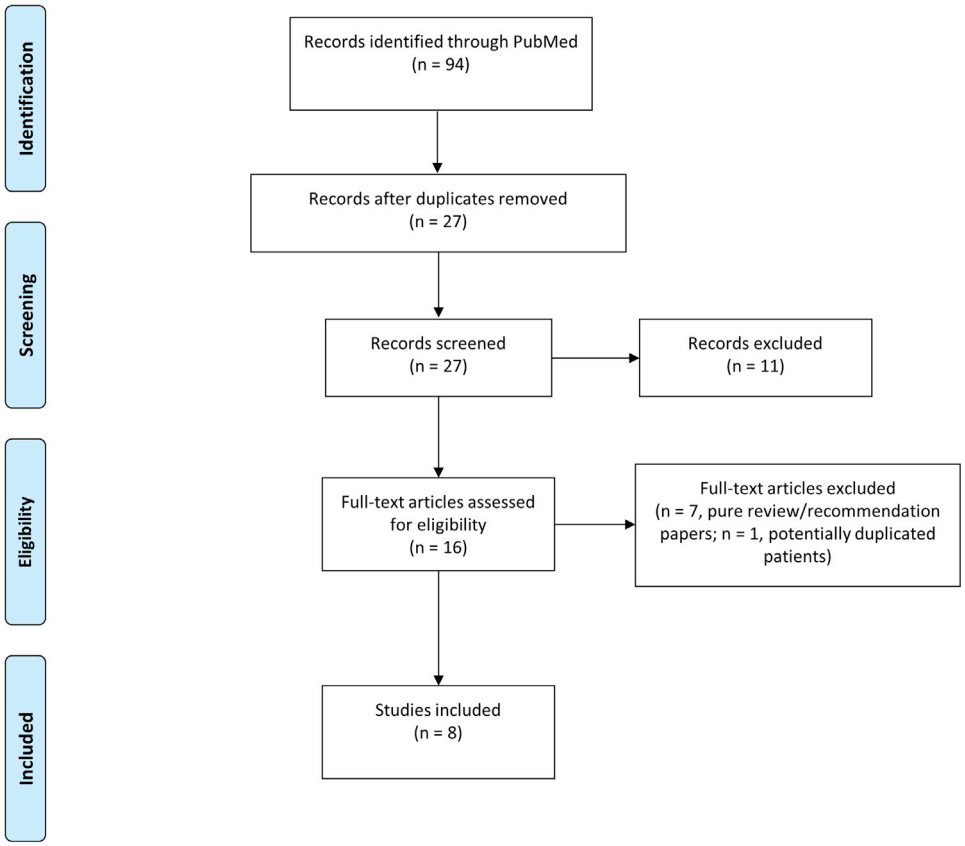

Fig 1. PRISMA flow diagram—inclusion of records.

hospitalization, and 3 (0.4%) died of COVID-19, all of whom were elderly people and/or had comorbidities. Only 3 (0.4%) patients were reported to have some limited control of their AIBD.

Although old age and certain comorbidities such as hypertension and diabetes represent well-described risk factors for complicated COVID-19, the role of immunosuppression remains controversial.[3,5] Taking into account that approximately 15% of COVID-19 cases are of a severe nature in the general population and that the overall mortality rate associated with COVID-19 is 1.5% to 3.6%,[3] this preliminary systematic analysis suggests that patients with AIBDs receiving immunomodulatory therapies are basically not at increased risk of severe or fatal COVID-19. This assumption, which may potentially be at least partly associated with enhanced disease prevention in this patient cohort, is in line with previous reports about other immunosuppressed patient populations during the present and past coronavirus outbreaks.[5] The results further indicate that the pandemic generally does not seem to negatively affect the course of AIBDs. Therefore, although surveillance of and precautions for this particular patient group must remain, delays or obstructions in important immunomodulatory treatment should be avoided during the pandemic. Nevertheless, data from this brief systematic review need to be interpreted with caution until more comprehensive investigations such as international registries further define the influence of COVID-19 on patients with AIBDs.

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Table I. Summary of published reports relating to COVID-19 and autoimmune bullous disease cases

Study type/origin	Patient population	Demographic characteristics	Comorbidities	Treatment	COVID-19	Course of AIBD	Other main findings
Case series/Italy	371 with AIBD (NS)	202 women and 169 men Mean age: 55.8 y Disease duration NR	NR	Azathioprine, cyclophosphamide, cyclosporine, dapsone, doxycycline, mycophenolate mofetil, methotrexate, prednisone/prednisolone, rituximab (n = 12), topical corticosteroids	Symptoms: 47 patients with COVID-19–related symptoms (NS) Confirmed diagnosis by PCR: 3 patients (NS) Hospitalization/death: NR	NR	None of the patients had discontinued the prescribed therapies on their own accord or because urged by their general practitioners; none of the 12 patients actively on rituximab had COVID-19–related symptoms or positive testing results.
Case series/Italy	30 with BP, 9 with pemphigus (NS), and 4 with MMP	Pemphigus: 1 woman Age: 65 y Disease duration: 40 mo Other patients NR	NR	Mycophenolate mofetil (n = 1); other NR	Symptoms: 1 patient with nausea, fever, anorexia, and asthenia; other patients NR Confirmed diagnosis by PCR: 1 patient (woman, 65 y) with pemphigus receiving mycophenolate mofetil Hospitalization/death: NR	Remission in the patient with confirmed COVID-19, some posterior tongue discomfort; other patients NR	—
Case series/Italy	5 with BP and 4 with pemphigus (NS)	7 women and 2 men Age range: 60-83 y (mean: 71.1 y) Disease duration NR	NR	Prednisone (n = 9), topical corticosteroids (n = 6), rituximab (n = 1)	Symptoms: 8 patients with good general status Confirmed diagnosis by PCR: 1 patient (NS) Hospitalization/death: NR	Stable disease (all)	—

Continued

Table I. Cont'd

Study type/origin	Patient population	Demographic characteristics	Comorbidities	Treatment	COVID-19	Course of AIBD	Other main findings
Case series/Italy	62 with BP and 31 with PV	BP: 28 women and 34 men Age range: 52-98 y (mean: 78.6 y); Disease duration: 1-123 mo PV: 14 women and 17 men Age: 19-95 y (mean: 62.5 y) Disease duration: 5-411 mo	BP: diabetes (n = 22), hypertension (n = 17), neurologic/psychiatric diseases (n = 14), cardiovascular diseases (n = 21), chronic kidney failure (n = 6), dyslipidemia (n = 9), neoplasia (n = 4) PV: diabetes (n = 3), hypertension (n = 1), neurologic/psychiatric diseases (n = 5), cardiovascular diseases (n = 2), dyslipidemia (n = 1), neoplasia (n = 2)	BP: azathioprine (n = 4), doxycycline (n = 6), systemic corticosteroids (<20 mg/d prednisone equivalent; n = 52) PV: azathioprine (n = 3), cyclophosphamide (n = 4), dapsone (n = 2), rituximab (n = 1), systemic corticosteroids (<20 mg/d prednisone equivalent; n = 22)	Symptoms (BP): 6 patients with mild/moderate symptoms (eg, flu-like symptoms, cough, low-grade fever, and/or anosmia/ageusia); 4 patients with severe symptoms (eg, pneumonia with respiratory failure) Confirmed diagnosis by PCR (BP): 4 patients Hospitalization/death (BP): 4 and 3 (mean age, 85 y; all 3 with severe cognitive impairment) patients, respectively Symptoms (PV): 6 patients with mild/moderate symptoms (eg, flu-like symptoms, cough, low-grade fever, and/or anosmia/ageusia); 1 patient with severe symptoms (NS) Confirmed diagnosis by PCR (PV): 1 patient (69 y; previous breast cancer) Hospitalization/death (PV): 1 and 0 patients, respectively	Remission (all)	Main risk factor of developing suspected COVID-19 symptoms was contact between the patient and an individual with known/suspected COVID-19; longer disease duration was more frequently associated with suspected COVID-19 symptomatic patients.
Case series/China	38 with AIBD (NS)	NR	NR	NR	NR	Mild disease (all)	17 patients discontinued their therapy; 21 patients admitted that they were worried about COVID-19 infection.

Case report/Iran	1 with MMP	1 man Age: 43 y Disease duration: 4 mo	Diabetes, hypertension, and benign prostatic hypertrophy	Intravenous immunoglobulins (5 × 30 g), mycophenolate mofetil (2 g/d), prednisolone (up to 50 mg/d), rituximab (4 × 500 mg)	Symptoms: fever, chills, malaise, dry cough, dyspnea, dizziness, decreased oxygen saturation, pneumonia, and laboratory test result abnormalities (ie, lymphopenia, positive CRP, and high LDH and ESR) Confirmed diagnosis: yes (by spiral chest CT scan; PCR negative) Hospitalization/death: yes and no, respectively	Initial disease progression, but improvement with intravenous immunoglobulins	Improvement of both MMP and COVID-19 with adjuvant intravenous immunoglobulins
Case series/Italy	10 with BP	6 women and 4 men Median age: 68.5 y Disease duration: NR	Diabetes, hypertension, malignancy (n = 3)	Azathioprine (n = 3), systemic corticosteroids (n = 8), topical corticosteroids (n = 8)	NR	Mild to moderate grade (n = 7) and severe grade (n = 3) of the disease; almost all patients (n = 8) had good control of their disease	—
Case series/Iran	167 with PV	Mean age: 48.6 y Sex and disease duration NR for most patients	NR	Rituximab (all), corticosteroids and other immunosuppressants (NS; n = 165)	Symptoms: 4 patients with fever, nausea, vomiting, myalgia, dry cough, and/or dyspnea Confirmed diagnosis by CT scan: 5 patients, 1 of whom was asymptomatic (4 women and 1 man; mean age, 41.8 y; all without a past medical history) Hospitalization/death: NR	None of the patients with confirmed COVID-19 experienced disease recurrence	45 (26.9%) patients received rituximab within 1 year of the pandemic, and none of them developed COVID-19; 150 (89.8%) patients adhered to home quarantine, and all used face masks in public places.

AIBD, Autoimmune bullous disease; *BP,* bullous pemphigoid; *CRP,* C-reactive protein; *CT,* computed tomography; *ESR,* erythrocyte sedimentation rate; *LDH,* lactate dehydrogenase; *MMP,* mucous membrane pemphigoid; *mo,* month; *NR,* not reported; *NS,* not specified; *PCR,* polymerase chain reaction; *PV,* pemphigus vulgaris, y, year.
Due to the journal's policy, full references of the respective studies cannot be displayed due to limitation in citation numbers.

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Sites of distant metastasis in Merkel cell carcinoma differ by primary tumor site and are of prognostic significance: A population-based study in the Surveillance, Epidemiology, and End Results database from 2010 to 2016

To the Editor: Merkel cell carcinoma (MCC) is highly aggressive, with a propensity for recurrence and distant metastasis. Sentinel lymph node biopsy is critical for workup; however, optimal use of imaging is unclear.[1] A large institutional registry recently identified that liver metastases were more common with a head/neck primary compared with other sites, which could guide workup and surveillance strategies.[2] Thus, we sought to investigate the effect of the primary tumor site on metastasis patterns in a national cohort, hypothesizing that a relationship would exist.

We identified patients with MCC (code 8247/3) in the Surveillance, Epidemiology, and End Results (SEER)-18 registries. Our inclusion criteria consisted of patients with metastatic disease upon initial presentation based on American Joint Committee on Cancer 8th Edition staging, diagnosed between 2010 and 2016. Our cohort was stratified by primary lesion site, which consisted of the trunk, head/neck, upper/lower extremities, and other disease sites encompassing visceral or primary nodal disease.

We used χ^2 tests and Student t tests (2-tailed P values) to assess for differences in clinical and pathologic characteristics and metastatic disease distributions based on primary site and performed Kaplan-Meier analysis to analyze overall survival and disease-specific survival (DSS). We performed multivariate Cox proportional hazards analysis to assess for independent prognosticators of DSS.

Our cohort of 331 patients with M1 disease was predominantly male and White (Table I). Patients with a head/neck primary site had a higher proportion of liver metastasis (42.3%, $P = .0003$) relative to other primary sites, and patients with a trunk primary site had a higher proportion of bone metastasis (36.9%, $P = .0049$). Overall 5-year overall survival was 11.2%, and DSS was 16.2%. Increasing age and liver and brain metastases were independent prognosticators of poorer DSS by Cox proportional hazards analysis (Table II).

Our analysis corroborates findings by Lewis et al,[2] also suggesting that in metastatic MCC, a head/neck primary is associated with increased propensity for liver metastasis, generalizing this finding in a national cohort. Additionally, we demonstrate that a trunk primary is associated with bone metastasis compared with other primary sites and in our multivariate analysis that liver and brain metastases (although rare), but not lung or bone, are associated with poorer DSS.

These findings may guide further research regarding imaging in MCC. Current guidelines suggest whole-body positron emission tomography (PET)/computed tomography (CT) or PET/magnetic resonance imaging (MRI), or CT imaging of the chest, abdomen, and pelvis with contrast, with or without neck CT or brain MRI, for evaluation of regional or distant disease, when clinically indicated.[1] Guidelines however do not suggest that all clinically node-negative patients should be screened with PET/CT at the initial diagnosis, because PET/CT is more likely to change staging or management in those with features suggesting potential for advanced disease (large tumor size, lymphovascular invasion, immunosuppression).

Considering our findings, unexplained liver function abnormalities in head/neck primary MCC may particularly raise clinical suspicion for distant disease and guide imaging decisions. Furthermore, imaging methods differ in sensitivity and specificity for metastasis detection, and limited data suggest greater utility of PET/CT for detection of bone metastases in MCC and for liver metastases (although studied on other malignancies) compared with CT.[3] In addition, an area of potential interest is whole-body PET/MRI, which has shown better detection of liver metastases compared with PET/CT, although these data are not in MCC.[4] This may be particularly relevant for patients with a head/neck primary, but cost-effectiveness would be important to consider. In addition, given the rarity of brain metastasis, further studies could focus on optimal selection of patients for brain MRI. Ultimately, future prospective studies