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Letter to the Editor

High prevalence of heterotopic ossification in critically ill patients with severe COVID-19

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ARTICLE INFO

Article history:

Received 14 September 2020

Received in revised form

5 December 2020

Accepted 21 December 2020

Available online 15 January 2021

Editor: A. Kalil

To the Editor,

We describe ten out of 52 patients with severe COVID-19 requiring prolonged mechanical ventilation who developed extensive heterotopic ossification (HO) around the shoulder, the elbow and the hip.

Basic demographic characteristics, laboratory data, clinical presentation and treatment of acute respiratory distress syndrome (ARDS) were compared using the chi-squared test or Fisher's exact test for categorical variables, and the Mann–Whitney test for continuous variables. Odds ratios of developing HO were investigated using logistic regression models. Written informed consent was obtained from all patients.

Between 29 February and 20 April 2020, 82 patients were admitted to our intensive care unit (ICU) because of ARDS due to

SARS-CoV-2 infection requiring invasive mechanical ventilation. Of these, 52 patients had more than one computed tomography (CT) scan during the hospitalization and were included in the analysis. During the recovery period, five patients reported severe shoulder, elbow and hip pain with decreased joint mobility. CT performed at a median of 43 days (interquartile range (IQR) 35–48) after admission showed in these and in additional five asymptomatic patients extensive HO around the shoulder, the elbow and the hip, corresponding to a HO prevalence of 19.2%. Baseline characteristics according to HO are shown in Table 1. Most patients were males (8/10) and had at least one comorbidity. The median age was 71 years (IQR 67–74). Treatment of severe ARDS consisted of mechanical ventilation during a median of 36 days (IQR 25–45) with prone positioning during 12 days (IQR 7–16) in 8/10, neuromuscular blockade in 9/10, and a 3-week course of steroids (mean dosage prednisone equivalent of 0.6 mg/kg/day) in 3/10 patients. On CT scans we observed either an asymmetric enlargement with inhomogeneous density and mild calcifications of the muscles (early phase) or more advanced calcifications (mineralization phase), mainly with a linear morphology. We observed an involvement of the muscles of the hip in seven cases, posteriorly and medially located (gluteus minimus, gemellus superior and inferior, quadratus femoris, piriformis and obturator internus muscles in six cases, four bilateral and two monolateral) and anteriorly located (ileo-psoas muscle in one case, monolateral); an involvement of the muscles of the shoulder in three cases, anteriorly located (subscapularis muscle in two cases, monolateral) and circumferentially located (rotator cuff, deltoid, biceps and triceps in one case, bilateral); and an involvement of the elbow in one case, posteromedially (medial head of the triceps, monolateral). One patient, showing HO in the elbow region, reported severe pain with immobility of the right arm that was refractory to conservative treatment. In this patient, surgical intervention with neurolysis and transposition of the

DOIs of original article: <https://doi.org/10.1016/j.cmi.2020.12.038>, <https://doi.org/10.1016/j.cmi.2021.02.004>.

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<https://doi.org/10.1016/j.cmi.2020.12.037>

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Table 1
Characteristics of 52 patients with severe COVID-19 and ARDS requiring mechanical ventilation according to the development of heterotopic ossification

Characteristic	Heterotopic ossification		No heterotopic ossification		p
	N = 10		N = 42		
	n	%	n	%	
Age (median, IQR)	71	67–74	69	60–73	0.530
Male gender	8	80	34	81	0.945
Body mass index, kg/m ² (median, IQR)	31.9	24.4–34	27.7	25.7–30.8	0.174
Arterial hypertension	7	70	26	61.9	0.633
Type 2 diabetes mellitus	3	30	13	31	0.953
Cardiovascular disease	4	40	11	26.2	0.308
Duration of mechanical ventilation, days (median, IQR)	36	25–45	22	7–36	<0.001
Prone positioning	9	90	32	76	0.477
Time of prone positioning, days (median, IQR)	12	7–16	5	4–12	0.105
Steroids for ARDS treatment	6	60	20	47	0.479
Minimal lymphocyte count, × 10 ⁹ /μL (median, IQR)	0.66	0.62–0.73	0.57	0.43–0.79	0.093
Maximal C-reactive protein, mg/L (median, IQR)	352	331–377	392	304–481	0.673
Maximal creatine kinase, U/L (median, IQR)	820	262–1114	295	154–507	0.037
Minimal ionized calcium, mmol/L (median, IQR)	0.97	0.92–1.02	0.93	0.90–1.04	0.834
Ventilator-associated pneumonia	9	90	28	66.7	0.102
Catheter-related blood stream infection	6	60	22	52.4	0.470
Duration of hospitalization (days) (median, IQR)	53	43–58	33	24–42	0.002

IQR, interquartile range.

right ulnar nerve was needed. No vascular compression was observed.

In a multivariate analysis, HO was associated with longer mechanical ventilation (odds ratio (OR) 2.64 for each additional week, 95% confidence interval (CI) 1.26–5.51, p 0.009) and longer hospitalization (OR 2.1 for each additional week, 95% CI 1.3–3.4, p 0.004), suggesting that prolonged immobilization might have played a crucial role in the occurrence of HO. We also observed a trend towards higher maximal creatine kinase values in patients who developed HO (OR 1.22 for each creatin kinase (CK) increase of 100 U/L, 95% CI 1.01–1.47, p 0.043).

Heterotopic ossification, the formation of bone outside the skeletal system, is a rare but potentially debilitating condition, usually associated with paralysis and immobilization following trauma, neurologic injury, ARDS, surgery and burn [1,2]. The pathogenesis is still unclear, possibly resulting from an imbalance between certain neuro-humoral factors, calcium homeostasis, autonomic dysregulation, micro-bleedings, osteoporosis and muscle atrophy [2,3]. The main complications of HO are functional impairment of the involved anatomic districts and peripheral nerve entrapment [4,5].

The prevalence of HO in our population was about fourfold higher than that reported in patients with ARDS (5%) [5]. We assume that prolonged immobilization as a result of longer sedation and neuromuscular blockade for severe ARDS has played a decisive role for HO in our patients. However, it is plausible that other factors, such as the deranged calcium metabolism, systemic inflammatory condition and local myositis, possibly due to the SARS-CoV-2 virus, might have contributed to the higher prevalence of HO.

Clinicians should be aware of this debilitating complication in critically ill patients with severe COVID-19, particularly if severe muscular and articular pain arise in the recovery period. We recommend early passive mobilization during ICU stay to prevent HO in patients with COVID-19.

Transparency declaration

The authors declare that they have no conflicts of interest and no external funding related to this study.

Author contributions

E.S., L.E., A.F.C. conceived and designed the study. L.E. performed statistical analysis. E.S., L.E., R.G., C.P. and A.F.C. collected patients' data. All authors interpreted the data and wrote the manuscript. All authors read and approved the final manuscript.

Appendix A. List of collaborators

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