Autopsy findings from patients diagnosed with COVID-19 demonstrate unique morphological patterns in bone marrow and lymph node

Ali AlJabban,[1,2] Mark G Evans,[1] Geoffrey G Fell,[3] Jack P Guccione,[4] Robert A Edwards,[5] Geraldine S Pinkus,[1] Robert F Padera,[1] Olga Pozdnyakova ,[1] Annette S Kim [1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/jcp-2023-208875).

[1]Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts, USA
[2]Department of Clinical Investigation, Harvard Medical School, Boston, Massachusetts, USA
[3]Department of Biostatistics, Dana-Farber Cancer Institute, Boston, Massachusetts, USA
[4]Los Angeles County Department of Medical Examiner-Coroner, Los Angeles, California, USA
[5]Department of Pathology and Laboratory Medicine, University of California Irvine, Irvine, California, USA

Correspondence to
Dr. Annette S Kim, Pathology, Brigham and Women's Hospital, Boston, Massachusetts, USA; Askim@bwh.harvard.edu

Received 7 March 2023
Accepted 30 April 2023
Published Online First 8 June 2023

To cite: AlJabban A, Evans MG, Fell GG, *et al*. *J Clin Pathol* 2024;**77**:622–627.

ABSTRACT

Aims The identification of haemophagocytosis in bone marrow (BM) is recurrently identified in patients with severe COVID-19. These initial COVID-19 autopsy studies have afforded valuable insight into the pathophysiology of this disease; however, only a limited number of case series have focused on lymphoid or haematopoietic tissues.

Methods BM and lymph node (LN) specimens were obtained from adult autopsies performed between 1 April 2020 and 1 June 2020, for which the decedent had tested positive for SARS-CoV-2. Tissue sections (H&E, CD3, CD20, CD21, CD138, CD163, MUM1, kappa/lambda light chains in situ hybridisation) were examined by two haematopathologists, who recorded morphological features in a blinded fashion. Haemophagocytic lymphohistiocytosis (HLH) was assessed based on HLH 2004 criteria.

Results The BM demonstrated a haemophagocytic pattern in 9 out of 25 patients (36%). The HLH pattern was associated with longer hospitalisation, BM plasmacytosis, LN follicular hyperplasia and lower aspartate aminotransferase (AST), as well as ferritin at demise. LN examination showed increased plasmacytoid cells in 20 of 25 patients (80%). This pattern was associated with a low absolute monocyte count at diagnosis, lower white cell count and lower absolute neutrophil count at demise, and lower ferritin and AST at demise.

Conclusions Autopsy results demonstrate distinct morphological patterns in BM, with or without haemophagocytic macrophages, and in LN, with or without increased plasmacytoid cells. Since only a minority of patients met diagnostic criteria for HLH, the observed BM haemophagocytic macrophages may be more indicative of an overall inflammatory state.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Literature has suggested that a potential cause of death in COVID-19 is an excessive inflammatory response which some researchers have attributed to haemophagocytic lymphohistiocytosis (HLH), a condition that can arise in some cases in context of some infections and cause death.

WHAT THIS STUDY ADDS

⇒ This study analysed bone marrow and lymph node tissues from 25 autopsies from patients with COVID-19 and identified two recurrent histological patterns correlated with clinical and laboratory parameters. Increased macrophages were identified in the bone marrow tissues and 36% of cases demonstrated bona fide haemophagocytosis although the majority did not meet diagnostic criteria for HLH. Lymph nodes demonstrated haemophagocytosis and plasmacytosis with the majority expressing excess kappa light chain and associated with higher Sequential Organ Failure Assessment scores including the cases meeting criteria for HLH.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study identifies the histological correlates of a deranged inflammatory system in COVID-19 infection and mortality, including the laboratory and clinical parameters associated with these findings pre-mortem.

INTRODUCTION

As of February 2023, the number of deaths from COVID-19 has exceeded 6 800 000 globally, with a mortality rate of 1.1% in the USA.[1] Many recent studies have documented the manifestations of COVID-19 at time of autopsy on end organs, such as heart and lung, but less is understood of its effects bone marrow (BM) nor lymph node (LN) involvement. One study focused on the similarities between the COVID-19 immune response and secondary haemophagocytic lymphohistiocytosis (HLH), with histological evidence of HLH in the BM.[2 3] These initial COVID-19 autopsy studies have afforded valuable insight into the pathophysiology of this disease; however, only a limited number of case series have focused on the effects of COVID-19 in haematolymphoid tissues. As a result, this study has focused on these latter tissues and provides correlation with other pre-mortem clinical parameters documented in the victims of COVID-19.[2 4]

MATERIAL AND METHODS

Patients and study design

Internal review boards of each participating institution approved collection and use of samples of all patients in this study. The study included 25 autopsy cases from patients who had tested positive for SARS-CoV-2 prior to their demise. Consent was obtained from relatives prior to autopsy. In all 25

cases, the demographic information as well as available clinical and laboratory data were documented (see online supplemental tables 1 and 2 for detailed list of parameters). The Sequential Organ Failure Assessment (SOFA) score was used to assess the severity of organs failure. HLH was documented based on following criteria: (1) prolonged fever, (2) splenomegaly, (3) cytopenias (haemoglobin <100 g/L, platelets $<100\times10^9$/L, neutrophils $<1.0\times10^9$/L), (4) low or absent natural killer (NK) cell function, (5) triglycerides ≥3.0 mmol/L or fibrinogen ≤1.5 g/L in the blood, (6) ferritin ≥500 µg/L, (7) morphological evidence of haemophagocytosis in BM, spleen or LNs and (8) soluble CD25 (sIL2-R) ≥2400 U/mL. Presence of at least five of the eight criteria were required to confirm the diagnosis.[5]

BM and LN examination

Microscopy was performed by two haematopathologists, who each independently recorded morphological features in a double blinded fashion (blinded to each other and to other patient data). Each morphological feature (see online supplemental tables 1 and 2 for the list) was independently assigned an m-score (morphological score) on an 8 point scale (0–7, with 4 representing the expected finding of that cell type/feature in normal tissue, 5–7 increased, 1–3 decreased, 0 absent). Scores between the two pathologists were averaged when within 2 points of each other. All discrepancies >2 points or spanning the normal level (increased vs decreased) were adjudicated by consensus with a third haematopathologist. The immunohistochemistry was performed using a panel for CD3 (clone MRQ39, Cell Marque), CD20 (clone L26, Agilent Dako), CD21 (clone 2G9, Leica Biosystems), CD138 (clone MI15, Leica Biosystems), CD163 (Leica Biosystems) and MUM1 (clone MUM1p, Agilent Dako). Kappa and lambda light chain in situ hybridisation was also performed (Ventana Medical Systems) with a kappa:lambda (κ:λ) ratio determined by visual inspection. Immunohistochemical stains were scored on a 4-point scale (0–3+, defined as strong positive (3+ staining intensity, black (nuclear) or dark with complete circumferential staining (membrane)), positive (2+, brown (nuclear) or moderate with complete circumferential (membrane)), weak positive (1+, faint gray-brown (nuclear) or partial circumferential (membrane)) and negative (0)). Normal BM levels of B and T cells were considered to be 5%–10% and 10%–15% of cellularity as scattered single lymphocytes, respectively.

Statistical methods

Differences in morphological and haematological parameters were assessed using a two-sided Wilcoxon rank-sum test with a 5% type I error. After analysing possible discriminating clinicopathological features, the two parameters considered for further analysis were (1) haemophagocytic macrophages in the BM and (2) plasmacytosis in the LNs. To account for multiple testing concerns, the false discovery rate (FDR) is also reported along with the Wilcoxon rank-sum p value.

Co-expression of markers, and their corresponding p values were estimated using Pearson correlation coefficients and test of correlations, respectively. χ^2 analysis was used for categorical variables. The results of both analyses are depicted as heatmaps. Only markers with less than three missing values were included in the analysis of correlations. Missing values were imputed using each marker's respective average. Differences with p values <0.05 were considered statistically significant.

All analyses were performed using R V.4.0.4 using the R packages base, dplyr, psych, ggplot2, and power Mediation.

Table 1 Demographic and clinical characteristics

Demographic and hospitalisation characteristics	
Age in years, mean (range) (n=25)	66 (45–96)
Gender (male:female) (n=25)	1.6:1
Hospitalisation length in days, mean (range) (n=25)	11 (1–36)
Highest body temperature (°C), mean (range) (n=25)	38.7 (35.3–40.2)
Hepatomegaly (n=25)	12 (48%)
Splenomegaly (n=25)	16 (64%)
Complete blood count at diagnosis (n=25)	
White cell count (K/µL), mean (range)	6.9 (1.5–39.5)
Absolute neutrophil count (K/µL), mean (range)	4.6 (0.03–37.1)
Absolute lymphocyte count (K/µL), mean (range)	0.7 (0.0–2.9)
Absolute monocyte count (K/µL), mean (range)	0.3 (0.0–2.0)
Haemoglobin (g/dL), mean (range)	12.5 (5.5–19.7)
Platelets (K/µL), mean (range)	156 (6–450)
Complete blood count at demise (n=25)	
White cell count (K/µL), mean (range)	11.8 (0.3–64.9)
Absolute neutrophil count (K/µL), mean (range)	8.6 (0.03–42.2)
Absolute lymphocyte count (K/µL), mean (range)	0.8 (0.1–2.9)
Absolute monocyte count (K/µL), mean (range)	0.8 (0.01–5.2)
Haemoglobin (g/dL), mean (range)	8.9 (5.7–17.9)
Platelets (K/µL), mean (range)	166 (10–642)
Cause of death (n=25)	
COVID-19 pneumonia (primary)	19/25 (76%)
COVID-19 pneumonia (secondary)	3/25 (12%)
Primary causes: acute leukaemia (2), gall bladder perforation (1)	
With COVID-19 infection	2/25 (8%)
Primary causes: trauma, severe abdominal aortic atherosclerosis	
In the setting of documented COVID-19 PCR positivity	1/25 (4%)
Primary cause: systemic amyloidosis with bilateral aspiration bronchopneumonia	

RESULTS

Demographic and clinical characteristics

The mean age of the patients was 66 years old (range 45–96), and the male:female ratio was 1.6:1. The majority of the deceased presented with acute COVID-19 (48%) with a mean hospitalisation stay of 11 days (range 1–36 days). The mean highest body temperature was 38.7°C (range 35.3–40.2°C). Physical examination showed that 48% and 64% of patients had hepatomegaly and splenomegaly, respectively (table 1).

BM examination

At autopsy, the BM cellularity in patients with COVID-19 ranged from 50% to 90% (mean 73%) with most of the cases demonstrating mildly increased myeloid-to-erythroid ratio (19 of 25; 76%; average m-score 5.1, see the Material and methods) (figure 1A,B). Megakaryocytes were present in normal numbers (m-score of 4.0) in 22 of 25 all cases.

B cells, marked by CD20 expression, were decreased in 24 of 25 (96%) of cases. CD138-positive plasma cells co-expressing MUM1 were overall decreased as well in the BMs (19 of 25, 76%; average m-score 2.6). By contrast, T cells expressing CD3 showed only a mild increase (15 of 25, 60%; average m-score 4.5). Lymphoid aggregates were rare (found in only 6 of 25 cases, 24%). In addition, there were increased BM macrophages expressing CD163 in 20 cases (80%; average m-score 5.1), with nine cases demonstrating haemophagocytic macrophages (determined by the presence of multiple cell nuclei within the CD163-positive cells) (figure 1C,D). The other 16 cases (with

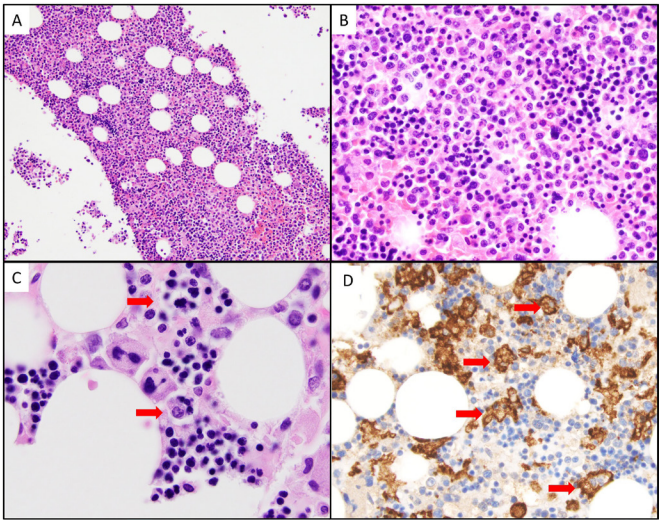

Figure 1 Bone marrow histological assessment. Bone marrows of the patient with COVID-19 demonstrate hypercellularity with mildly elevated myeloid:erythroid ratio (A, H&E, 100×; B, H&E, 600×). Haemophagocytic macrophages are evident (arrows, C, H&E, 1000×). CD163 highlights the increased activated macrophages with ingested cells (arrows, D, CD163, 600×).

and without an increase in macrophages) did not demonstrate haemophagocytic macrophages.

LN examination

The nodal architecture from COVID-19 autopsy patients demonstrated significant sinus expansion (100% of samples, average m-score 6.0) and sinus histiocytosis (100% of samples, average m-score 5.9) (figure 2A). Concomitantly, there was mild follicular hyperplasia (21 of 25, 84%; average m-score 5.8) and interfollicular hypoplasia (21 of 25, 84%; average m-score 3.4) with near-total absence of germinal centres in 17 of 25 cases (68%; average m-score 2.5). Follicles were marked by CD20-positive B cells with follicular dendritic meshworks highlighted by CD21. Interfollicular regions included T cells marked by CD3 as well as increased apparent plasma cells identified in 20 of 25 cases (80%, average m-score 5.6) (figure 2B). The majority of plasma cells were robustly positive (2+ to 3+) for MUM1 expression (88%) but were negative for CD138 in the majority of cases (56%) with only partial/rare weak positivity (44%, grade 1+) in the remainder (figure 2C,D). The kappa:lambda ratio by in situ hybridisation showed elevated kappa:lambda ratios greater than 3:1 in 72% (18/25) of cases with only 16% polytypic cases and only one case with definitive lambda excess (table 2 and figure 2E,F). Cytomorphological atypia was also observed with large atypical immunoblastic, hyperchromatic, or multinucleated cells in 23 of 25 cases (92%; average m-score 5.5) which mark with strong MUM1 and subset dim CD20 expression, most consistent with B cells (figure 2G,H). Finally, 20 of 25 autopsies (80%) demonstrated histological evidence of haemophagocytic macrophages marked by CD163 (figure 2I).

Factors associated with dominant BM and LN patterns

Each histological feature was examined as a single discriminator of the various clinical and laboratory findings recorded for the patients at first diagnosis of COVID-19 and the last values available before their demise (online supplemental figure 1). The histological feature with the most clinical/laboratory correlates was used to separate patients into high-risk and low-risk groups.

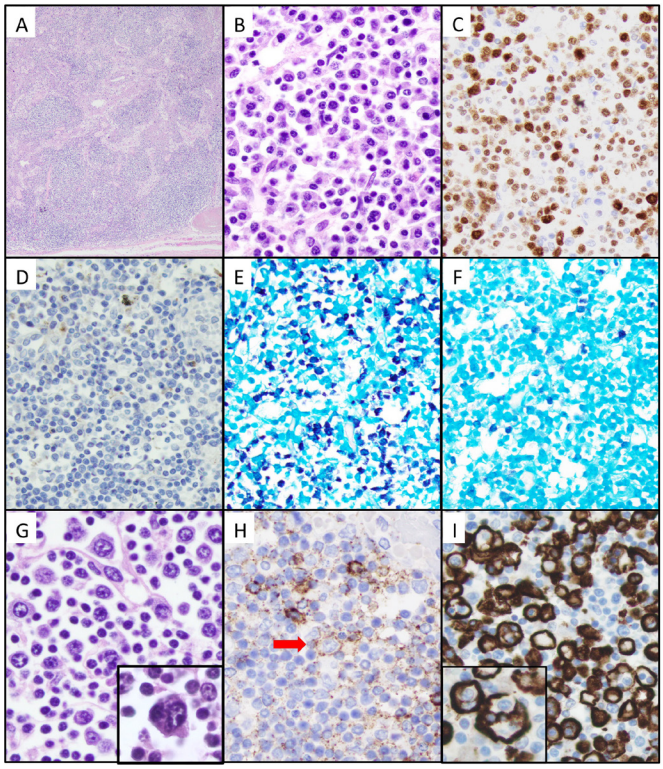

Figure 2 Lymph node histological assessment. Lymph nodes of the patient with COVID-19 demonstrate follicular hyperplasia with expanded sinus histiocytosis (A, H&E, 20×). The interfollicular regions contain significant expansion of plasmacytoid cells (B, H&E, 600×) which are positive for MUM1 (C, 400×), but negative for CD138 (D, 400×). The plasmacytoid cells demonstrate kappa surface light chain predominance by in situ hybridisation (E, kappa, 400×; F, lambda, 400×). In addition, there are increased immunoblasts (G, H&E, 600×, with magnified inset of a multi-nucleated cell) marked by dim CD20 (arrow, H, 600×) and haemophagocytic macrophages highlighted by CD163 (I, 400×, with magnified inset).

The most discriminatory BM histological pattern was the presence of haemophagocytic macrophages (table 3). Morphologically, both BM plasmacytosis (average m-score of 3.2 vs 2.0; p=0.005) and more prominent germinal centres in the LNs (average score of 3.2 vs 1.0; p=0.030) were significantly higher among patients with BM haemophagocytic macrophages. Clinically, haemophagocytic macrophages were identified more frequently in patients with a longer hospital stay prior to demise (mean 17 days vs 9.5 days; p=0.035), lower last AST (34 vs 74.5 U/L, p=0.023), and lower last ferritin (612 vs 1669 µg/L, p=0.028).

By contrast, in the LNs, the most discriminatory feature was the presence of increased plasmacytoid cells (table 4). There was 100% correlation between those patients without plasmacytosis and those without any haemophagocytic macrophages in either the LN or the BM, and 100% correlation between those patients with plasmacytosis and those with haemophagocytic macrophages in the LN. In these patients with LN plasmacytosis, the absolute monocyte count was significantly lower on hospitalisation (0.25 vs 0.8×10^9/L, p=0.016). At demise, these patients had less elevated AST (44.5 vs 389 U/L, p=0.018), WBC (11.06 vs 18.81×10^9/L, p=0.018), neutrophil count (7.62 vs 16.92×10^9/L, p=0.023) and ferritin (662 vs 7922 µg/L, p=0.033).

Table 2 Lymph node plasma cell analysis for MUM1, CD138 and Kappa:Lambda ratio

Marker	Frequency
MUM1	
3+	1 (4%)
2+	21 (84%)
1+	3 (12%)
CD138	
0 (Predominantly negative)	14 (56%)
1+	11 (44%)
Kappa:lambda	
Polytypic	4 (16%)
>3:1; kappa excess	18 (72%)
<1:2; lambda excess	1 (4%)
Too few to assess	2 (8%)

Due to the level of disability in terminal patients with COVID-19, the score for SOFA was calculated as well as the percentage of patients who met criteria for HLH (table 5). There were 22 (88%) who had a SOFA score of ≥9 with a significant correlation observed between these poor prognostic SOFA scores and the plasmacytoid LN pattern (p=0.002), while BM histological features were not associated with elevated SOFA scores (p=0.2). For HLH assessment, out of the eight criteria for diagnosis, two laboratory tests were not ordered in any of the 25 cases (NK-cell activity and CD25 count); however, the calculation was made based on remaining available six criteria. Out of 16 cases with sufficient available data, only four cases (25%) fulfilled HLH diagnostic criteria in this study. All four patients (100%) were included in the group with LN plasmacytosis, while 3 of the 4 (75%) were among those cases demonstrating BM haemophagocytic macrophages.

DISCUSSION

Our findings indicate that there are histological correlates to the clinical findings in the BM and LNs of COVID-19 autopsies. Documentation of these findings is critical to avoid unexpected and protracted work-up for results that should be expected in the disease course of these morbid patients. In addition, these clinicopathological findings may signal imminent demise. The two dominant observed histological patterns were BM histiocytosis with haemophagocytosis and LN plasmacytosis. The patients segregated into these two patterns independent of whether they had COVID-19 pneumonia as primary (76%) or secondary causes of death (12%) or if they had only documented COVID-19 infection without overt pneumonia (12%).

This study identified several histological features in the BM. A recurrently elevated myeloid:erythroid ratio was not surprisingly associated with BM cellularity. This finding may explain the observed neutrophilia associated with more severe COVID-19 infection, although neutrophil counts can vary during the course of disease and hospitalisation.[6 7] More globally, general leukocytosis has been associated with patient demise across multiple studies.[8–10]

However, the dominant BM histological pattern involved increased macrophages (20 of 25 cases, 80%) with evidence of haemophagocytosis in 9 of 25 cases (36%). Importantly, haemophagocytosis can be identified without meeting the diagnostic criteria (a total of 5 of 8 criteria required) of HLH, a life-threating inflammatory condition that can be associated with infection, malignancy or genetic predisposition.[5 11 12] Indeed, as shown by Rosado *et al*, many of the criteria for HLH can be met in any patient with a systemic inflammatory disorder, highlighting the need to redefine the diagnostic criteria for HLH in the adult population.[13 14]

Moreover, increased BM haemophagocytic macrophages were paradoxically associated with lower, not higher, ferritin and AST levels in this series, despite the reported association of high ferritin levels with more severe COVID-19 disease.[6 12] In this study, most patients did not have results for NK-cell activity or soluble CD25 levels, so the determination of HLH required five of six diagnostic criteria—which was met in only four patients (16%), possibly an underestimation of the incidence of cases meeting standard criteria of HLH. HLH was identified at comparable rates, in 25% of COVID-19 autopsies, by Harris *et al*, with a similar caveat that some data elements were not available.[8] Wood *et al* showed that only 7.5% of intensive care unit-admitted patients with COVID-19 had HLH (in which all of their patients received cytokine directed therapies, such as tocilizumab),[15] while Prieto-Pérez *et al* were not able to reach a final diagnosis of HLH in any of the deceased patients in their series, although, interestingly, three survivors did fulfil criteria for an HLH diagnosis.[16] Thus, most studies seem to point to a low rate of bona fide HLH. By contrast, Núñez-Torrón *et al* identified HLH at much higher rates (8 out of 10, cases), more closely matching our macrophage hyperplasia rates.[2] Nonetheless, macrophages serve as a source of cytokines which, even if not associated with diagnostic HLH, can contribute to morbidity and mortality in patients with COVID-19.[17] Indeed, the presence of haemophagocytic macrophages in the BM correlated in our study with broader systemic reactive findings, such as increased BM plasmacytosis and LN follicular hyperplasia.

In the LNs, the dominant histological pattern found in 20 of 25 cases (80%) was an plasmacytosis. In a different study of 20 COVID-19 autopsies, Haslbauer *et al* identified mild to moderate

Table 3 Factors associated with BM haemophagocytic macrophages

	BM haemophagocytic macrophages		Wilcoxon rank-sum test	
	Yes (n=9)	No (n=16)	P value	FDR
BM plasmacytosis (m-score)	4	2	0.019	0.424
AST last (nl: 10–50 U/L)	34*	74.5*	0.023	0.424
Ferritin last (nl: 30–400 µg/L)	612*	1669*	0.028	0.424
LN follicular hyperplasia (m-score)	5	0	0.030	0.424
Hospitalisation (days)	20*	9.5*	0.035	0.570

*Median value for this histological category.
AST, aspartate aminotransferase; BM, bone marrow; FDR, false discovery rate; last, the last available clinical data on the patient prior to demise; LN, lymph node; m-score, the morphology score on an 8-point scale; N, number; nl, normal range; U, units.

Table 4 Factors associated with LN plasmacytosis

	LN plasmacytosis		Wilcoxon rank-sum test	
	Yes (n=20)	No (n=5)	P value	FDR
Monocyte count first (nl: 0.16–1.10 k/µL)	0.25*	0.8*	0.016	0.209
AST last (nl: 10–50 U/L)	44.5*	389*	0.018	0.209
WBC count last (nl: 4.00–10.00 k/µL)	11.06*	18.81*	0.018	0.209
Neutrophil count last (nl: 1.92–7.60 k/µL)	7.62*	16.912*	0.023	0.224
Ferritin last (nl: 30–400 µg/L)	662*	7922*	0.033	0.278

*Median value for this histological category.
AST, aspartate aminotransferase; FDR, false discovery rate; first, the first available clinical data on the patient at the time of hospitalisation; last, the last available clinical data on the patient prior to demise; LN, lymph node; m-score, the morphology score on a 8-point scale; N, number; nl, normal range; WBC, white blood cell.

LN plasmacytosis in all cases with plasmablast activation.[18] These plasmablasts demonstrated heterogeneous positivity CD138 and MUM1.[12] In our series, the majority of our plasma cells were not light chain restricted and positive for MUM1, but negative for CD138. It is unclear if this is related to the level of autolysis or degradation of markers after patient demise as CD138 expression is rapidly lost when sample processing is delayed.[19 20] Moreover, while the plasma cells were overall not restricted by surface light chain expression, 72% demonstrated kappa:lambda ratios greater than 3:1. This finding has been reported recently in an individual who successfully recovered from COVID-19, in which the extent of kappa light chain restriction was concerning for a plasma cell neoplasm.[21] Of note, the plasma cells described in that patient were similarly negative for CD138 in freshly obtained tissue from a live patient and positive for MUM1, which raises the possibility of CD138-loss being associated with SARS-CoV-2 infection.

Interestingly, in the past year there have been many reports documenting COVID-19-induced lymphadenopathy, mostly by imaging studies.[22] Rare studies that delved into LN morphological changes have reported findings similar to those identified in this study, with increased plasmacytoid cells in interfollicular areas as well as atypical follicular hyperplasia.[23 24] Another histological pattern of necrotising lymphadenitis in patients after COVID-19 vaccine has not been seen in this study.[25 26]

LN plasmacytosis was most highly associated with low monocyte counts at initial hospitalisation. The monocytes in patients with COVID-19 have been noted to be distinctly abnormal in morphology, particularly in milder disease, with some reports of monocytopenia noted in patients with more severe disease.[6 27 28] It has been hypothesised that that this is due to recruitment of the monocyte/macrophage cells to sites of inflammation.[29–31] The association of lower initial monocyte counts with terminal disease and atypical LN histology may be a manifestation of this process.

LN plasmacytosis was also associated with lower terminal white cell and neutrophil counts, although both counts were above the normal range on average, as has been documented previously for the more severe cases of COVID-19.[6] Since the patients with this histological presentation included all four who met criteria for HLH (using only six available criteria of the eight possible), this may represent the confounding influence of the typical cytopenias seen in HLH with the leukocytosis and specifically neutrophilia usually observed in patients with severe COVID-19.[6] As mentioned above, in many cases of adult HLH, the clinical findings overlap with systemic inflammatory response syndrome, and patients with poor outcomes more commonly have neutrophilia rather than the typical cytopenias seen in individuals congenitally predisposed to HLH, highlighting the complex picture of inflammation seen in these autopsies. In particular, the LN plasmacytosis was associated with increased SOFA scores, and all four cases meeting criteria for HLH (likely an underestimation since not all diagnostic data were available in all cases) fell within this morphological category.

In this series, there was also an overall increase in atypical large cells, multinucleated cells, and hyperchromatic cells, identified in 23 of 25 cases (92%). This finding is corroborated by the study of Elsoukkary *et al* that also identified larger transformed cells with prominent nucleoli and amphophilic cytoplasm in variable numbers within subcapsular and intraparenchymal sinuses.[32]

The SOFA score has been used to assess the clinical outcomes and to predict mortality among patients with multiorgan failure. Not surprisingly, in this autopsy study SOFA scores exceeded 9 in 22 of 25 cases (88%). Elevated SOFA scores were associated with the LN plasmacytosis, although BM histological features did not correlate statistically with elevated SOFA scores.[33]

CONCLUSION

This study identified several recurrent histological patterns within BM and LN specimens from patients who succumbed to COVID-19. Given the limited case numbers, associations with clinical parameters could only be determined for morphological features observed in a sufficient number of positive and negative cases. Of these, LN plasmacytosis was associated with several complete blood count and laboratory findings. Moreover, BM haemophagocytic macrophages were frequently identified but fulfilled diagnostic criteria for HLH in only a minority of cases and instead may be simply markers of a complex inflammatory state in COVID-19 mortality.

Table 5 SOFA score analysis with BM and LN patterns

		BM haemophagocytic pattern			LN plasmacytoid pattern		
Clinical features of patients with SARS-CoV-2-positive	All patients	Present (n=9)	Absent (n=16)	P value	Present (n=20)	Absent (n=5)	P value
SOFA Score (≥9), predictive of poor prognosis (n=25)*	22	8	14	0.20	18	4	**0.0028**

*P values determined by χ^2 analysis. All other analyses performed by Student's t-test.
BN, bone marrow; LN, lymph node; SOFA, Sequential Organ Failure Assessment.

Handling editor Vikram Deshpande.

Acknowledgements During these unprecedented times, the authors would like to acknowledge the deceased and their families for their losses during this pandemic and our colleague healthcare workers.

Contributors ASK and OP oversaw and designed the study. AA analysed the data and drafted the manuscript. MGE, ASK and OP reviewed all slides. MGE did all medical record data collection. GGF performed all statistical analysis. RFP, JPG and RAE contributed cases. GSP performed all immunohistochemical stains. ASK was responsible for all major editing and for shepherding the process and served as the guarantor of the overall content. All authors reviewed and edited the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Brigham and Women's Institutional Review Board (#2018P000521). Consent was given by next of kin for autopsy and research. Patients were deceased and could not give consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All relevant data (de-identified and aggregated) are available in the article or uploaded as supplementary information. Data on a per-individual bases are not provided to protect the privacy of the individuals.

ORCID iDs
Olga Pozdnyakova http://orcid.org/0000-0001-8376-0344
Annette S Kim http://orcid.org/0000-0002-8699-2439

REFERENCES

1 COVID-19 dashboard by the center for systems science and engineering (CSSE) at Johns Hopkins University. Note, on March 10, 2023, the Johns Hopkins Coronavirus resource center ceased its collecting and reporting of global COVID-19 data. n.d. Available: https://coronavirus.jhu.edu
2 Núñez-Torrón C, Ferrer-Gómez A, Moreno Moreno E, *et al*. Secondary haemophagocytic lymphohistiocytosis in COVID-19: correlation of the autopsy findings of bone marrow haemophagocytosis with Hscore. *J Clin Pathol* 2022;75:383–9.
3 Kumar B, Aleem S, Saleh H, *et al*. A personalized diagnostic and treatment approach for macrophage activation syndrome and secondary hemophagocytic lymphohistiocytosis in adults. *J Clin Immunol* 2017;37:638–43.
4 Purohit A, Vaswani S, Vishwajeet V, *et al*. Evaluation of bone marrow findings of COVID-19 by minimally invasive autopsies: a single tertiary care centre experience from India. *Indian J Hematol Blood Transfus* 2022;38:416–21.
5 Rosado FGN, Kim AS. Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol* 2013;139:713–27.
6 Pozdnyakova O, Connell NT, Battinelli EM, *et al*. Clinical significance of CBC and WBC morphology in the diagnosis and clinical course of COVID-19 infection. *Am J Clin Pathol* 2021;155:364–75.
7 Zini G, Bellesi S, Ramundo F, *et al*. Morphological anomalies of circulating blood cells in COVID-19. *Am J Hematol* 2020;95:870–2.
8 Harris CK, Hung YP, Nielsen GP, *et al*. Bone marrow and peripheral blood findings in patients infected by SARS-Cov-2. *Am J Clin Pathol* 2021;155:627–37.
9 Huang C, Wang Y, Li X, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
10 Mo P, Xing Y, Xiao Y, *et al*. Clinical characteristics of refractory coronavirus disease 2019 in Wuhan, China. *Clin Infect Dis* 2021;73:e4208–13.
11 Mostaza-Fernández JL, Guerra Laso J, Carriedo Ule D, *et al*. Hemophagocytic lymphohistiocytosis associated with viral infections: diagnostic challenges and therapeutic dilemmas. *Rev Clin Esp (Barc)* 2014;214:320–7.
12 Vargas-Vargas M, Cortés-Rojo C. Ferritin levels and COVID-19. *Rev Panam Salud Publica* 2020;44:e72.
13 Rosado FG, Rinker EB, Plummer WD, *et al*. The diagnosis of adult-onset haemophagocytic lymphohistiocytosis: lessons learned from a review of 29 cases of bone marrow haemophagocytosis in two large academic institutions. *J Clin Pathol* 2016;69:805–9.
14 Leverenz DL, Tarrant TK. Is the Hscore useful in COVID-19? *Lancet* 2020;395:e83.
15 Wood H, Jones JR, Hui K, *et al*. Secondary HLH is uncommon in severe COVID-19. *Br J Haematol* 2020;190:e283–5.
16 Prieto-Pérez L, Fortes J, Soto C, *et al*. Histiocytic hyperplasia with hemophagocytosis and acute alveolar damage in COVID-19 infection. *Mod Pathol* 2020;33:2139–46.
17 Chandrakasan S, Filipovich AH. Hemophagocytic lymphohistiocytosis: advances in pathophysiology, diagnosis, and treatment. *J Pediatr* 2013;163:1253–9.
18 Haslbauer JD, Matter MS, Stalder AK, *et al*. Histomorphological patterns of regional lymph nodes in COVID-19 lungs. *Pathologe* 2021;42:89–97.
19 Ahmann GJ, Chng WJ, Henderson KJ, *et al*. Effect of tissue shipping on plasma cell isolation, viability, and RNA integrity in the context of a centralized good laboratory practice-certified tissue banking facility. *Cancer Epidemiol Biomarkers Prev* 2008;17:666–73.
20 Hartmann L, Biggerstaff JS, Chapman DB, *et al*. Detection of genomic abnormalities in multiple myeloma: the application of FISH analysis in combination with various plasma cell enrichment techniques. *Am J Clin Pathol* 2011;136:712–20.
21 Evans MG, Crymes A, Crombie JL, *et al*. Monotypic Plasmacytoid cells mimicking lymph node malignancy in the setting of COVID-19 recovery. *Am J Hematol* 2022;97:666–7.
22 Keshavarz P, Yazdanpanah F, Rafiee F, *et al*. Lymphadenopathy following COVID-19 vaccination: imaging findings review. *Academic Radiology* 2021;28:1058–71.
23 Patil A, Swerdlow SH, Lossos IS, *et al*. Atypical follicular hyperplasia with light chain-restricted germinal centers after COVID-19 booster: a diagnostic pitfall. *Virchows Arch* 2023;482:905–10.
24 Wang XJ, Moore EM, Swerdlow SH, *et al*. Light chain-restricted plasmacytoid cells in hyperplastic germinal centers: a clinicopathologic investigation. *Am J Clin Pathol* 2021;156:871–85.
25 Soub HA, Ibrahim W, Maslamani MA, *et al*. Kikuchi-Fujimoto disease following SARS CoV2 vaccination: case report. *IDCases* 2021;25:e01253.
26 Tan HM, Hue S-S, Wee A, *et al*. Kikuchi-Fujimoto disease post COVID-19 vaccination: case report and review of literature. *Vaccines (Basel)* 2021;9:1251.
27 Fan BE. Hematologic parameters in patients with COVID-19 infection: a reply. *Am J Hematol* 2020;95:E215.
28 Henry BM, de Oliveira MHS, Benoit S, *et al*. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med* 2020;58:1021–8.
29 McGonagle D, Sharif K, O'Regan A, *et al*. The role of cytokines including Interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev* 2020;19:102537.
30 Chomarat P, Banchereau J, Davoust J, *et al*. IL-6 switches the differentiation of monocytes from dendritic cells to Macrophages. *Nat Immunol* 2000;1:510–4.
31 Foote JR, Patel AA, Yona S, *et al*. Variations in the phagosomal environment of human neutrophils and mononuclear phagocyte Subsets. *Front Immunol* 2019;10:188.
32 Elsoukkary SS, Mostyka M, Dillard A, *et al*. Autopsy findings in 32 patients with COVID-19: a single-institution experience. *Pathobiology* 2021;88:56–68.
33 Yang Z, Hu Q, Huang F, *et al*. The prognostic value of the SOFA score in patients with COVID-19: a retrospective, observational study. *Medicine (Baltimore)* 2021;100:e26900.