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

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 recurrent histological patterns associated with clinical and laboratory parameters. Increased macrophages were identified in the bone marrow tissues and 36% of cases demonstrated 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 on haemophagocytic macrophages. In this study, we aimed to characterise the histological evidence of HLH in the BM.

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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 <100×10^9/L, neutrophils <1.0×10^9/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.

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 clinico-pathological 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, y^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 V4.0.4 using the R packages base, dplyr, psych, ggplot2, and power Mediation.

### 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 varied from 20% to 50%, with a mean (range) 42% (10–76%). In addition, there were increased BM macrophages expressing MUM1 in 24 cases (96%) 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...
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 interfolicular dysplasia (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.

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 µL, 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 µL, 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).
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 morbids 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%). 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-threatening inflammatory condition that can be associated with infection, malignancy or genetic predisposition.

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. 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), 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 fulfill criteria for an HLH diagnosis. 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. 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. 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 plasmacytosis. In a different study of 20 COVID-19 autopsies, Haslbauer et al identified mild to moderate

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.

More globally, general leukocytosis has been associated with patient demise across multiple studies.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Lymph node plasma cell analysis for MUM1, CD138 and Kappa:Lambda ratio</th>
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<tbody>
<tr>
<td>Marker</td>
<td>Frequency</td>
</tr>
<tr>
<td>MUM1</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>2+</td>
<td>21 (84%)</td>
</tr>
<tr>
<td>1+</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>CD138</td>
<td></td>
</tr>
<tr>
<td>0 (Predominantly negative)</td>
<td>14 (56%)</td>
</tr>
<tr>
<td>1+</td>
<td>11 (44%)</td>
</tr>
<tr>
<td>Kappa:lambda</td>
<td></td>
</tr>
<tr>
<td>Polytpeic</td>
<td>4 (16%)</td>
</tr>
<tr>
<td>&gt;3:1; kappa excess</td>
<td>18 (72%)</td>
</tr>
<tr>
<td>&lt;1:2; lambda excess</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Too few to assess</td>
<td>2 (8%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Factors associated with BM haemophagocytic macrophages</th>
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<tbody>
<tr>
<td>BM haemophagocytic macrophages</td>
<td>Wilcoxon rank-sum test</td>
</tr>
<tr>
<td>BM plasmacytosis (m-score)</td>
<td>Yes (n=9)</td>
</tr>
<tr>
<td>AST last (nl: 10--50 U/L)</td>
<td>34*</td>
</tr>
<tr>
<td>Ferritin last (nl: 30–400 μg/L)</td>
<td>612*</td>
</tr>
<tr>
<td>LN follicular hyperplasia (m-score)</td>
<td>5</td>
</tr>
<tr>
<td>Hospitalisation (days)</td>
<td>20*</td>
</tr>
</tbody>
</table>

*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.
LN plasmacytosis in all cases with plasmablast activation. These plasmablasts demonstrated heterogeneous positivity CD138 and MUM1. 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. 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. 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. 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. Another histological pattern of necrotising lymphadenitis in patients after COVID-19 vaccine has not been seen in this study.

LN plasmacytosis was most highly associated with low monocye 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. It has been hypothesised that this is due to recruitment of the monocyte/macrophage cells to sites of inflammation. 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. 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. 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.

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.

**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>
<thead>
<tr>
<th>Table 4</th>
<th>Factors associated with LN plasmacytosis</th>
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<tbody>
<tr>
<td></td>
<td>LN plasmacytosis</td>
</tr>
<tr>
<td></td>
<td>Yes (n=20)</td>
</tr>
<tr>
<td>Monocyte count first (nl: 0.16–1.10x10⁶/µL)</td>
<td>0.25*</td>
</tr>
<tr>
<td>AST last (nl: 10–50 U/L)</td>
<td>44.5*</td>
</tr>
<tr>
<td>WBC count last (nl: 4.00–10.00x10⁶/µL)</td>
<td>11.06*</td>
</tr>
<tr>
<td>Neutrophil count last (nl: 1.92–7.60x10⁹/µL)</td>
<td>7.62*</td>
</tr>
<tr>
<td>Ferritin last (nl: 30–400 µg/L)</td>
<td>662*</td>
</tr>
</tbody>
</table>

*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.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>SOFA score analysis with BM and LN patterns</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BM haemophagocytic pattern</td>
</tr>
<tr>
<td></td>
<td>Present (n=9)</td>
</tr>
<tr>
<td>SOFA Score (≥9), predictive of poor prognosis (n=25)*</td>
<td>22</td>
</tr>
</tbody>
</table>

*P values determined by χ² analysis. All other analyses performed by Student’s t-test.

BN, bone marrow; LN, lymph node; SOFA, Sequential Organ Failure Assessment.
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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. GFP 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.

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Competing interests None declared.

Patient consent for publication Not applicable.

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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 basis are not protected to provide the privacy of the individuals.

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