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Original article

Major postmortem pulmonary histopathological findings in preterm infants in Ethiopia

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Abstract

Background: *Respiratory disorders are the leading cause of death in preterm infants. Postmortem lung histological findings may help to confirm or exclude a clinical diagnosis. This study aims to describe the common postmortem pulmonary histological findings and their potential contributions to preterm neonatal mortality in Ethiopia.*

Methods : *A prospective, multicenter, and cross-sectional clinical study of preterm infants was conducted in five hospitals in three regions of Ethiopia. A total of 4,919 preterm infants were enrolled, and of these, 3,852 were admitted to neonatal intensive care units (NICUs). Within 28 days of postnatal age, 1,109 or 29% of those admitted to the NICU died. Consent was requested from all parents for a complete diagnostic autopsy (CDA) and was obtained in 441 of the preterm neonates who died. A histopathological examination of representative lung tissues was performed .*

Results*: On histopathologic examination of the lungs of these deceased preterm neonates, the major abnormal histological changes observed were hyaline membrane disease (HMD) in 81.6%, pneumonia in 44.7%, pulmonary hemorrhage or diffuse alveolar hemorrhage (DAH) in 39%, and*

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meconium aspiration syndrome (MAS) in 5.9%. A combination of histopathological findings, two or more, were also observed in > 30% of the preterm lungs.

Conclusion : *HMD was the most common pulmonary finding in extremely and moderately preterm infants. The highly prevalent pneumonia and pulmonary hemorrhage, with the frequently observed HMD, might have significantly contributed to their deaths. Histopathological findings, beyond confirming a clinical suspicion, can be used as input in the refinement of clinical and radiological diagnostic parameters to identify respiratory pathologies, particularly pneumonia, in preterm infants.*

Keywords: Postmortem, autopsy, histopathology, pulmonary, preterm

Background

Respiratory disorders are the leading cause of death in preterm infants (1). The major pulmonary pathological findings described in preterm neonates include hyaline membrane disease (HMD), pneumothorax, pneumonia, pulmonary hemorrhage/diffuse alveolar hemorrhage (DAH), meconium aspiration syndrome (MAS), and chronic lung disease (1-5). In some instances, extrapulmonary conditions result in respiratory distress, making it difficult to distinguish them from primary pulmonary pathologies. Moreover, overlapping morphologic features can be seen in different types of primary pulmonary pathologies (6).

HMD, also described as diffuse alveolar damage (DAD), is the most frequently presenting pathology in the lungs of preterm neonates. The risk of HMD is inversely proportional to gestational age (3,5). HMD is histologically characterized by the deposition of pinkish homogenous proteinaceous material along the alveolar lining with associated alveolar collapse and capillary edema. Usually, it is exacerbated by oxygen toxicity-induced epithelial necrosis. HMD is considered an existing phenomenon rather than a primary cause of respiratory failure, but it can determine the course of the illness and both short- and long-term outcomes. HMD can be complicated by pneumonia, pulmonary hypertension, and pulmonary hemorrhage (5, 7).

Pulmonary hemorrhage is difficult to detect while the neonate is alive but is a common postmortem finding in preterm neonates. Pulmonary hemorrhage is considered severe when at least one lobe of the lungs is involved based on gross or histologic examination (8).

Pneumonia is a significant cause of respiratory distress in preterm infants. It is classified as early-onset when it presents before 7 days or late-onset when it presents at or after 7 days of age (1). Clinically, pneumonia may not be easily diagnosed in preterm infants, particularly for cases with congenital pneumonia, where most of the deaths are misdiagnosed as respiratory distress syndrome (RDS) (9). The mortality rate due to pneumonia is inversely

proportional to gestational age (GA) and birth weight (BW) (10). Histomorphologically, pneumonia can present as a patchy or lobular involvement pattern where a conspicuous number of intra-alveolar and/or interstitial acute inflammatory infiltrates associated with edema, fibrin and vascular congestion are present (11).

MAS is not commonly seen in preterm infants except in preterm infants with listeriosis (12). The histologic features of MAS include tiny keratotic squames, lanugo, meconium bodies, and mucus in the bronchi and alveoli to a variable extent. Massive aspiration can be a lethal condition when it is complicated with bronchopneumonia (13,14).

The purpose of this study was to describe the major postmortem histopathological findings of primary pulmonary diseases in preterm infants who were admitted to the neonatal intensive care units of five hospitals in Ethiopia and died.

Methods

Study setting and design

The study was conducted as part of a project entitled "A Prospective Study of Causes of Illness and Death in Preterm Infants in Ethiopia" (SIP) (15,16). This was a prospective multicenter observational study conducted in five hospitals (Tikur Anbessa Hospital, Gandhi Memorial Hospital and St Paul Hospital in Addis Ababa, Gondar University Hospital in the north of Ethiopia, and Jimma University Hospital in southwest Ethiopia) from July 1, 2016 to May 31, 2018.

All preterm infants admitted to the study hospitals with a gestational age of less than 37 completed weeks were enrolled. Three methods of gestational age assessment, ultrasound, last menstrual period (15), and physical examination using the new Ballard score, were used. All deliveries where an induced abortion was performed and for which the gestational age could not be reliably determined using the three GA assessment methods were excluded from the study. The analysis for this paper only included those cases for which a complete diagnostic autopsy (CDA) was performed.

A panel of experts decided on primary and contributory causes of death using the histopathological findings as well as other clinical and investigational parameters. In some cases, the panel might have decided to use other parameters to decide primary and contributory causes of death. Therefore, the numbers may not tally. The details of the findings are published elsewhere (16). This study focused only on analyzing the major histological findings in the lung but not on the causes of death.

CDA Procedures

CDA was performed according to the hospital protocol and guidelines of the involved institutions within 6-12 hours after death in all cases. After dissection of the lungs, liver, brain, and kidneys, representative lung samples from both lungs were taken and fixed in 10% neutral buffered formalin for 24 hours. Paraffin sections were prepared from the fixed tissues and stained with hematoxylin and eosin as per standard procedures.

Data collection, entry, and analysis:

The CDA results were reported using a standardized data reporting format prepared for this study(15). The format included a checklist of major preterm problems and expected histological features of each case, and the pathologist summarized the major findings in the format. All CDAs and histologic slide reviews were performed by experienced pathologists of the respective institutions. Representative histological pictures of major findings were taken using an Infinity HD Lumenera camera fitted on an Olympus BX43F microscope.

Results

The total number of preterm deaths with a CDA was 441 [Figure 1]. Most preterm deaths in the study were between the gestational ages of 28-34 weeks (78.7%).

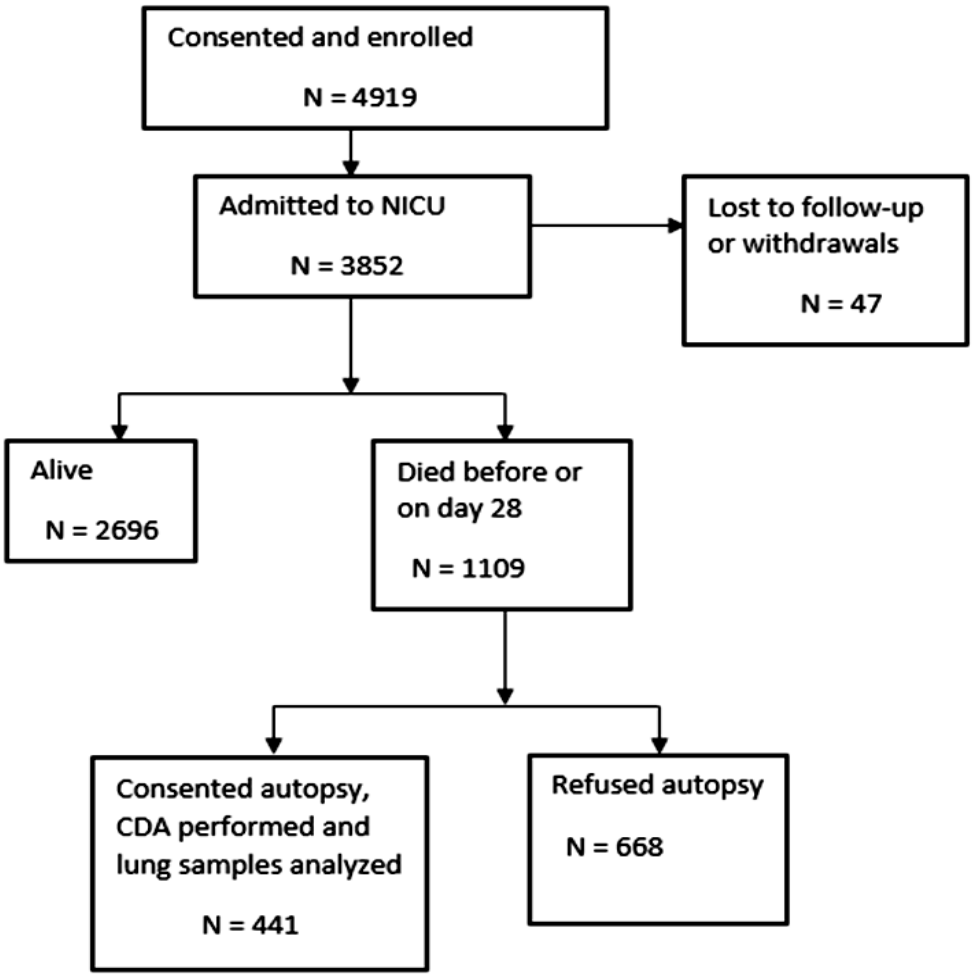

Figure 1: Enrollment flow chart

(NICU-neonatal care unit, CDA-complete diagnostic autopsy)

Of the 441 preterm deaths, a total of 1002 major histopathologic findings were reported. Of these, 758 (75.8%) were found to be primary pulmonary pathologies. (supplemental table)

The major lung primary pulmonary histopathological findings included 360 (81.6%) with HMD, 197 (44.7%) with pneumonia, 172 (39%) with pulmonary hemorrhage, and 26 (5.9%) with MAS. Additionally, diffuse non-exudative alveolar edema with a conspicuous number of hemosiderin-laden macrophages was observed in three cases. Multiple histopathologic findings were observed as HMD with pneumonia in 170 cases (38%), HMD with pulmonary hemorrhage in 152 cases (34%), and pneumonia with pulmonary hemorrhage in 120 cases (27%).

HMD was observed across all gestational age groups with no significant difference in the proportions. HMD was the most prevalent pulmonary pathology finding across all gestational age categories. Although not statistically significant, 87.3% of preterm infants between gestational ages of 32 and 34 weeks had HMD, followed by those <28 weeks, where 82.6% showed pathological findings consistent with HMD. There was no significant difference by sex or birth weight.

Table 1: Gestational age, sex, and birth weight distribution related to the major primary pulmonary pathologies

Pulmonary findings			**HMD**			**Pneumonia**			**DAH**			**MAS**		
Variables	Categories	N	%	OR	P-value	%	OR	P-value	%	OR	P-value	%	OR	p-value
	<28	35	82.60	1.234	0.704	40	0.644	0.309	64.30	0.185	0.002	12.80	0.318	0.305
	28-31	213	78.40	0.927	0.835	44.60	0.778	0.395	34.30	0.577	0.065	4.20	0.476	0.2
	32-34	134	87.30	1.757	0.174	43.30	0.738	0.332	49.20	1.075	0.818	8.20	0.966	0.951
	35 - <37	59	79.70	Ref.	Ref.	50.80	Ref.	Ref.	47.50	Ref.	Ref.	8.50	Ref.	Ref.
Sex	Male	243	79.80	0.758	0.273	44.40	0.795	0.895	38.30	0.975	0.9002	6.90	1.538	0.31
	Female	193	83.90	Ref	Ref.	45.10	Ref.	Ref.	38.90	Ref.	Ref.	4.70	Ref.	Ref.
Birth weight	<1000	59	89.80	1.767	0.326	47.50	0.982	0.962	37.30	0.764	0.498	6.80	0.625	0.503
	1000-1500	201	77.10	0.674	0.35	45.30	0.899	0.741	32.80	0.629	0.156	4.50	0.403	0.119
	1500 -2000	122	83.60	1.02	0.966	41.80	0.781	0.47	47.50	1.165	0.656	6.60	0.604	0.398
	>= 2000	48	83.30	Ref	Ref.	47.90	Ref.	Ref.	43.70	Ref.	Ref.	10.40	Ref.	Ref.

Hyaline membrane disease (HMD), pneumonia, diffuse alveolar hemorrhage (DAH), and meconium aspiration syndrome (MAS)

Pneumonia was documented across all gestational age groups, with the highest rate in infants with a GA of 35 to <37 weeks (30/59, 50.8%). However, this result was not statistically significant. A relatively high occurrence was documented in infants with a birth weight <1000 gm (28/59, 47.5%) and >=2000 gm (23/48, 47.9%), which was also not significantly different.

Pulmonary hemorrhage was observed in all gestational age categories. However, it was a rare finding among the <28 weeks gestational age group (14.3% only, p<0.005). There were only 5 cases in this gestational age group.

MAS was largely observed in infants of GA 32 to <37 weeks 16/26 (61.5%). There were no sex differences in the occurrence of HMD, pneumonia, or DAH. However, MAS occurred more frequently in males with an M:F ratio of 2:1.

HMD was predominantly found in preterm infants who died between 24 and 72 hours after birth. Pneumonia was observed in neonates who died between 24 hours and 7 days (132/197, 67%). DAH was commonly observed in infants who died between 24-72 hours postnatal age. MAS was documented in 5 of the 26 neonates who died within 24 hours of birth.

(HMD-hyaline membrane disease, DAH-diffuse alveolar hemorrhage, MAS- Meconium aspiration syndrome)

Histological analysis

Histological analysis was performed for the two most common conditions, i.e., HMD and pneumonia. Waxy-appearing layers of a hyaline membrane composed of fibrin, cellular debris, and red blood cells mostly covered extensive areas of the lungs [Figure 2A], and only in a few cases was a patchy hyaline membrane seen in the organizing phase with hyperplasia of type 2 pneumocytes. [Figure 2B].

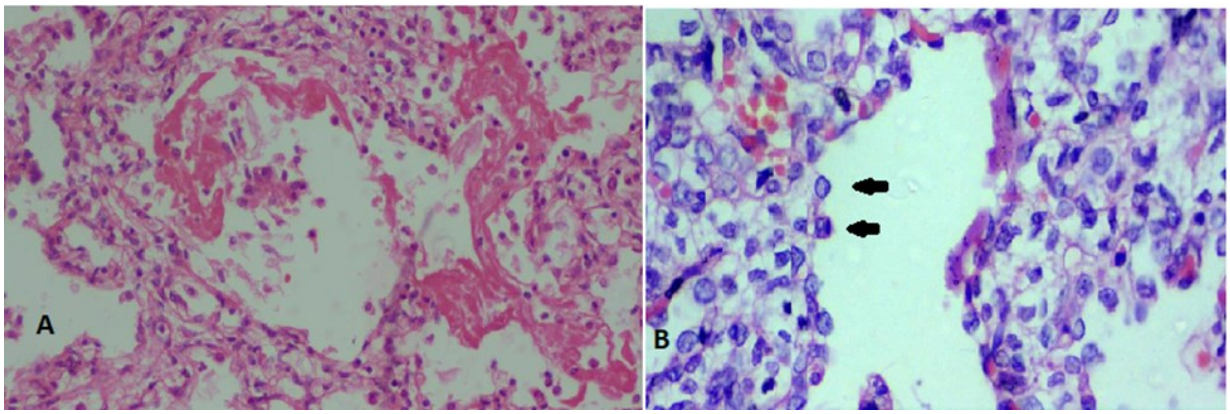

Figure 2. (A) A hyaline membrane in an early phase of HMD in association with epithelial disruption (10x objective). (B) A hyaline membrane in the organizing phase of HMD with a prominence of type 2 pneumocytes (arrows) (20x objective).

Intra-alveolar or interstitial hemorrhage was considered significant or diffuse when it involved a large area of a lobe or more lobes with or without intra-alveolar fibrin or capillaritis [Figure 3 (A)].

Histologically, pneumonia was considered present when a significant exudate with neutrophilic infiltrates and an increase in foamy macrophages were seen in the alveolar spaces, intrabronchiolar, intrabronchial, and interstitium associated with capillary congestion and,at times,an extension of polymorphs into the sinusoids of parabronchial lymph nodes [Figure 3(B)].

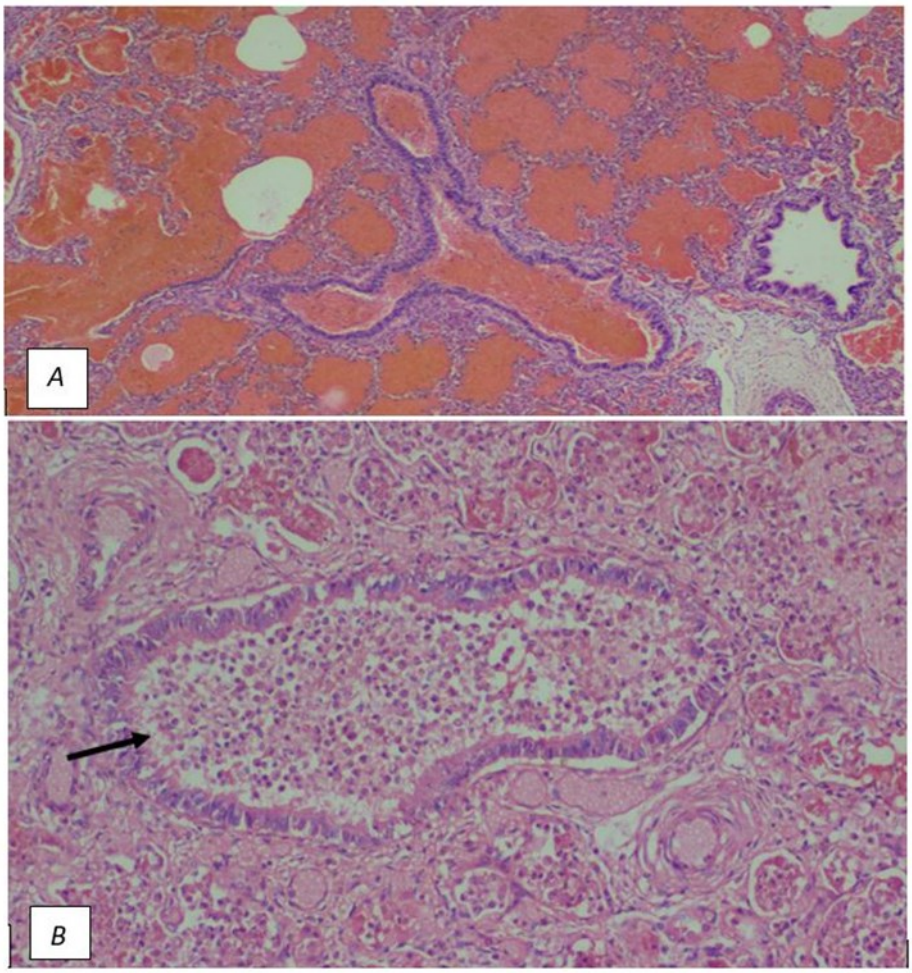

Figure 3: (A) Diffuse intra-alveolar and intrabronchial hemorrhage (10x objective). (B) Classical pneumonia with intra-alveolar and intrabronchiolar neutrophilic exudate (arrow) (10x objective)

Discussion

Respiratory disorders are the most frequent causes of admission to a neonatal ICU and the leading cause of early neonatal mortality in preterm infants (1). Primary pulmonary pathologies are the most common causes of respiratory distress when compared to other secondary causes, such as cardiac anomalies (17,18). In our study, pulmonary pathologies were found to be 3 times more common than non-pulmonary pathologies. The top pulmonary pathologies were HMD, pneumonia, DAH and MAS. There were no significant differences in the frequencies between gestational age groups, sex, and birthweight. However, DAH occurred significantly less often in those infants at <28 Wk gestational age. Out of the observed HMDs among preterm deaths, 86.9% fall in the <35 weeks gestational age categories. This was also observed in a related clinical study (19).

Pneumonia was recorded in nearly half (44.7%) of our cases. This high occurrence is consistent with other studies since preterm neonates are susceptible to infections (20-22). Most of our

cases were early-onset pneumonia, and their occurrence was inversely proportional to GA, which is similar to reports elsewhere (23). The occurrence of pneumonia in 55.8% of neonates at <72 hrs of age suggests congenital pneumonia (11,23,24). A high chance of underdiagnosis of congenital pneumonia has been described in the literature (25).

Patchy or diffuse alveolar hemorrhage was consistently seen in association with HMD and pneumonia in most of the cases and was found in a higher proportion among early to mid-preterm infants. DAH alone occurred only in 8/441 (1.8%) of the cases. Interestingly, DAH occurred at a significantly lower frequency in extremely preterm neonates, which is in sharp contrast to the described literature (26).

Consistent with similar studies, MAS was seen in a minority of the cases (26, 5.9%) (27). However, one might consider this as higher than expected in preterm infants (28,29). MAS occurred in equal proportion in all GA groups in contrast to the expected concentration at later preterm gestational ages (28). MAS is fatal only if meconium is massively aspirated. In all our cases, MAS was seen as a patchy finding, and we presume that it is less likely to be the direct cause of death. However, it is argued in some literature that the amount aspirated may not correlate with severity (29).

This study aims primarily to characterize the major pulmonary histopathologic changes. However, we also found unexpected histologic features that we believe are diagnostically important. However, the major pneumonia histologic findings are classical with extensive fibrinopurulent exudate. In some cases, even with associated pleuritis, the exudate was localized, suggesting focal pneumonia [figure 4] – a situation that can easily be missed, ignored clinically, or called something else.

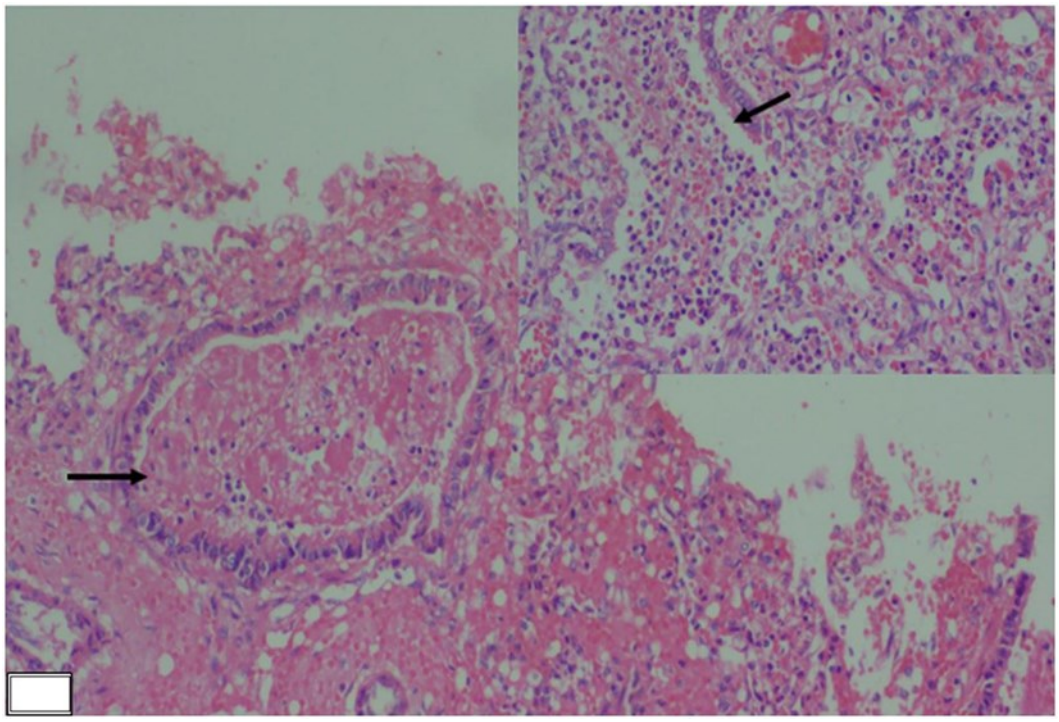

Figure 4. Patchy pneumonia with intrabronchiolar fibrin and neutrophils (arrows, 20x objective)

Additionally, intra-alveolar and intrabronchiolar 'fibrin balls' or fibrin plugs with patchy areas of organization, also described as acute fibrinous and organized pneumonia (AFOP), were consistently seen in the classical pneumonia cases with or without combined features of HMD and DAH but not in isolated cases of HMD [Figure 5]. This histologic pattern of acute lung involvement with largely unknown clinical significance is documented as a distinct clinical entity and is also observed in connective tissue diseases involving the lungs, drug-induced pneumonia, and virus-associated cases of pneumonia such as COVID-19 with good corticosteroid response (30-32). However, we found it to be difficult to put it as a separate disease entity in preterm infants. Rather, we speculate that these features may add to the radiographical clues that can be helpful in differentiating pneumonia from HMD.

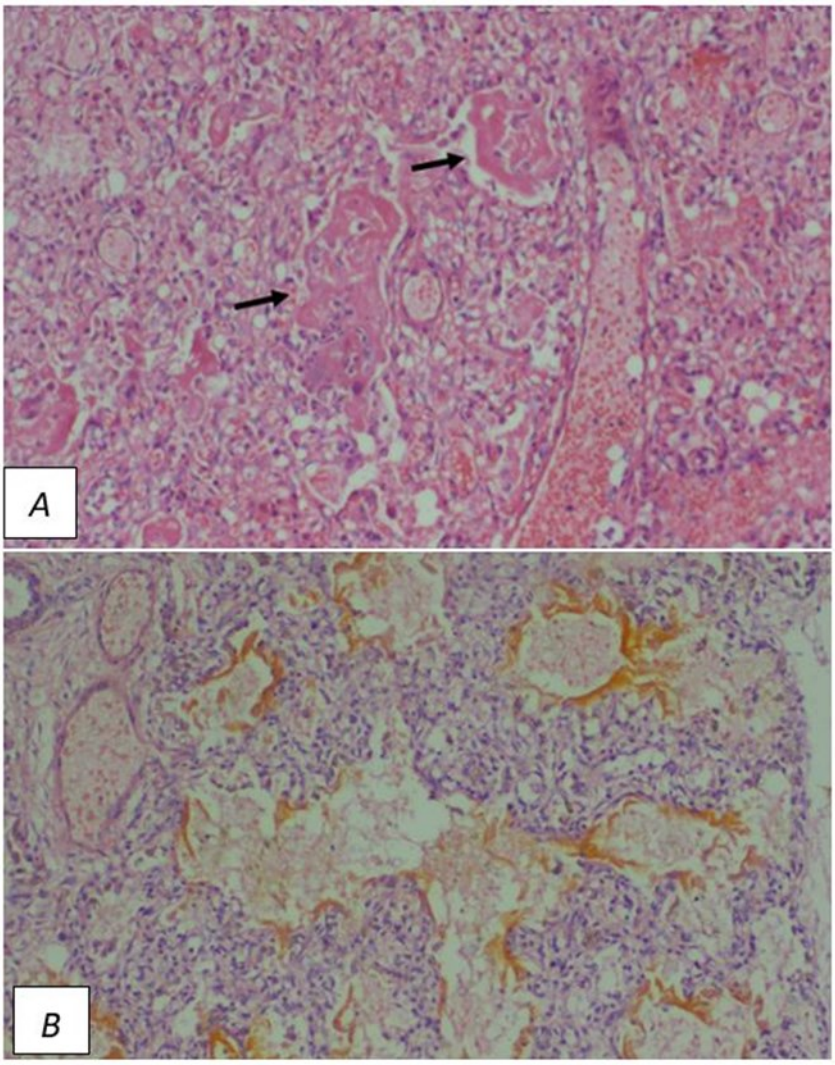

Figure 5. (A) case of pneumonia with fibrin balls (arrow) (20x objective), (B) Yellow/bilirubin-tinged hyaline membrane (10x objective)

The presence of yellow-stained membranes in a few of our cases [Figure 5] may suggest bilirubin-stained hyaline membranes, and we speculate that this may lead to the persistence of HMD, leading to poor respiratory outcomes in these neonates.

Diffuse non-exudative alveolar edema with hemosiderin-laden macrophages was observed in three cases, perhaps the result of underlying cardiac anomalies.

Although this paper presents the largest autopsy series describing pulmonary pathologies in Ethiopia, it has some limitations. The lung pathologies were not correlated with corresponding placenta findings as described in perinatal autopsy guidelines, and the low consent rate may bias the findings.

In conclusion, an autopsy is instrumental in establishing a diagnosis and identifying new findings. This study has demonstrated the high occurrence of pneumonia in preterm infants in a low-resource settings such as Ethiopia. The classic histologic evidence with extensive involvement of lung parts may dictate pneumonia

as a strong contributory factor or perhaps the most important cause of death in the 44.7% of preterm neonates in this study. Therefore, we strongly recommend consideration of infectious conditions such as pneumonia as a contributor to death, in addition to HMD in this setting.

List of abbreviations

HMD	Hyaline Membrane Disease
NICU	Neonatal Intensive Care Unit
DAH	Diffuse alveolar hemorrhage a.k.a. Pulmonary hemorrhage.
MAS	Meconium Aspiration Syndrome
RDS	Respiratory Distress Syndrome
GA	Gestational age
BW	Birth Weight
SIP	Study of causes of illness and death in preterm infants
CDA	Complete Diagnostic Autopsy
OR	Odds Ratio

Declarations

Ethical approvals

The study was approved by the institutional review board of each hospital and at the College of Health Sciences of Addis Ababa University. All clinical procedures were conducted per the hospital protocol. In addition to the consent taken for the main study, separate parental consent was obtained for the CDA.

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Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

MAT - Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy

RPP- Contributed to the design, analysis, and interpretation and critically revised the manuscript. RP agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AKN - Contributed to the design, analysis, and interpretation and critically revised the manuscript; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

RHA - Contributed to the design, analysis, and interpretation and critically revised the manuscript and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

TDB - Contributed to design, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

MBM - Contributed to conception and design; contributed to acquisition, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

TBG - Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AAG - Contributed to the design, analysis, and interpretation and critically revised the manuscript. AA agrees to be accountable for all aspects of work ensuring integrity and accuracy.

YGS - Contributed to design, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

YB - Contributed to design, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

MAG - Critically revised the manuscript, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

BAE - Critically revised the manuscript, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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BW - Contributed to the design, analysis, and interpretation & critically revised the manuscript and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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ZTK - Critically revised the manuscript, agrees to be accountable for all aspects of work ensuring integrity and accuracy.

EMM - Contributed to the design, analysis, and interpretation and critically revised the manuscript and agrees to be accountable for all aspects of work ensuring integrity and accuracy.

RLG - Contributed to the design, analysis, and interpretation and critically revised the manuscript. RLG agrees to be accountable for all aspects of work ensuring integrity and accuracy.

LMM - Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

References

1. Sweet LR, Keech C, Klein NP, Marshall HS, Tagbo BN, Quine D, et al. Respiratory distress in the neonate: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. Vaccine. 2017;35(48 Pt A):6506-17.
2. Nese N, Bulbul Y. Diagnostic value of perinatal autopsies: analysis of 486 cases. J Perinat Med. 2018;46(2):175-81.
3. Kumar P, Angst DB, Taxy J, Mangurten HH. Neonatal autopsies: a 10-year experience. Arch Pediatr Adolesc Med. 2000;154 (1):38-42.
4. Gallacher DJ, Hart K, Kotecha S. Common respiratory conditions of the newborn. Breathe (Sheff). 2016;12(1):30-42.
5. Lidia Grappone1 FM. Hyaline membrane disease or respiratory distress syndrome? A new approach for an old disease. Journal of Pediatric and Neonatal Individualized Medicine 2014;3(2):e030263.
6. Wigglesworth JS. Pathology of the lung in the fetus and neonate, with particular reference to problems of growth and maturation. Histopathology. 1987;11(7):671-89.
7. Locci Giorgia FV, Gerosa Clara, Faa Gavino. Hyaline membrane disease (HMD): the role of the perinatal pathologist. Journal of Pediatric and Neonatal Individualized Medicine. 2014;3(2):e030255.
8. van Houten J, Long W, Mullett M, Finer N, Derleth D, McMurray B, et al. Pulmonary hemorrhage in premature infants after treatment with synthetic surfactant: an autopsy evaluation. The American Exosurf Neonatal Study Group I, and the Canadian Exosurf Neonatal Study Group. J Pediatr. 1992;120(2 Pt 2):S40-4.
9. Feria-Kaiser C, Furuya ME, Vargas MH, Rodriguez A, Cantu MA. Main diagnosis and cause of death in a neonatal intensive care unit: do clinicians and pathologists agree? Acta pediatrica (Oslo, Norway : 1992). 2002;91(4):453-8.
10. Reiterer F. Neonatal Pneumonia. In: Neonatal Bacterial Infection. IntechOpen; 2013. doi:10.5772/54310
11. Duke T. Neonatal pneumonia in developing countries. Arch Dis Child Fetal Neonatal Ed. 2005;90(3):F211-9.
12. Lamont RF, Sobel J, Mazaki-Tovi S, Kusanovic JP, Vaisbuch E, Kim SK, et al. Listeriosis in human pregnancy: a systematic review. J Perinat Med. 2011;39(3):227-36.
13. Yurdakok M. Meconium aspiration syndrome: do we know? The Turkish journal of pediatrics. 2011;53(2):121-9.
14. Vora H, Nair S. Study of Meconium Aspiration Syndrome in Neonates. GCSMC Journal of Medical Sciences. 2014;3(1): 64-6.
15. Muhe LM, McClure EM, Mekasha A, Worku B, Worku A, Dimtse A, et al. A Prospective Study of Causes of Illness and Death in Preterm Infants in Ethiopia: The SIP Study Protocol. Reprod Health. 2018;15(1):116.

16. Muhe LM, McClure EM, Nigussie AK, Mekasha A, Worku B, Worku A, et al. Major causes of death in preterm infants in selected hospitals in Ethiopia (SIP): a prospective, cross-sectional, observational study. The Lancet Global Health. 2019;7(8):e1130-e1138. doi:10.1016/S2214-109X(19)30220-7

17. Hermansen CL, Mahajan A. Newborn Respiratory Distress. Am Fam Physician. 2015;92(11):994-1002.

18. Dandekar CP, Mysorekar VV, Rao SG, Anupama V. Perinatal autopsy--a six-year study. Indian Pediatrics. 1998;35(6):545-8.

19. Nagendra K, Wilson C, Ravichander B, Sood S, Singh S. Incidence and etiology of respiratory distress in newborn. Medical Journal Armed Forces India. 1999;55(4):331-333. doi:10.1016/S0377-1237(17)30363-5

20. Gunville CF, Sontag MK, Stratton KA, Ranade DJ, Abman SH, Mourani PM. Scope and impact of early and late preterm infants admitted to the PICU with respiratory illness. J Pediatr. 2010;157(2):209-14 e1.

21. Agapitos E, Kouri E, Alexacos L, Bacoula C, Papacharalampous NX. Primary causes of perinatal death. An autopsy study of 556 cases in Greek infants. Pathology, research and practice. 1986;181(6):733-8.

22. Nakamura Y, Hosokawa Y, Yano H, Nakashima N, Nakashima T, Komatsu Y, et al. Primary causes of perinatal death. An autopsy study of 1000 cases in Japanese infants. Human pathology. 1982;13(1):54-61.

23. Webber S, Wilkinson AR, Lindsell D, Hope PL, Dobson SR, Isaacs D. Neonatal pneumonia. Archives of disease in childhood. 1990;65(2):207-11.

24. Nissen MD. Congenital and neonatal pneumonia. Pediatric respiratory reviews. 2007;8(3):195-203.

25. Barton L, Hodgman JE, Pavlova Z. Causes of death in the extremely low birth weight infant. Pediatrics. 1999;103(2):446-51.

26. Coffin CM, Schechtman K, Cole FS, Dehner LP. Neonatal and infantile pulmonary hemorrhage: an autopsy study with clinical correlation. Pediatric pathology. 1993;13(5):583-9.

27. Scott H, Walker M, Gruslin A. Significance of meconium-stained amniotic fluid in the preterm population. Journal of Perinatology: official journal of the California Perinatal Association. 2001;21(3):174-7.

28. Mazor M, Hershkovitz R, Bashiri A, Maymon E, Schreiber R, Dukler D, et al. Meconium-stained amniotic fluid in preterm delivery is an independent risk factor for perinatal complications. European journal of obstetrics, gynecology, and reproductive biology. 1998;81(1):9-13.

29. Hutton EK, Thorpe J. Consequences of meconium-stained amniotic fluid: what does the evidence tell us? Early human development. 2014;90(7):333-9.

30. Angeles Montero-Fernandez M, Pardo-Garcia R. Histopathology features of the lung in COVID-19 patients. Diagnostic histopathology (Oxford, England). 2021;27(3):123-7.

31. Dai JH, Li H, Shen W, Miao LY, Xiao YL, Huang M, et al. Clinical and Radiological Profile of Acute Fibrinous and Organizing Pneumonia: A Retrospective Study. Chinese medical journal. 2015;128(20):2701-6.

32. Onishi Y, Kawamura T, Higashino T, Mimura R, Tsukamoto H, Sasaki S. Clinical features of acute fibrinous and organizing pneumonia: An early histologic pattern of various acute inflammatory lung diseases. PloS one. 2021;16(4):e0249300.