ABSTRACT

The first cases of Yellow Hyaline Membrane Disease (YHMD) were seen in USA in the beginning of 1965, coinciding with the start of an active intensive care unit for premature infants and the era of prolonged survival of severe cases of respiratory distress syndrome in newborns. The lungs of newborns with YHMD can often be identified grossly by slight yellow discoloration. The yellow color is permanent and does not fade when the lungs are exposed to air, light, or prolonged refrigeration. Microscopically, the bright yellow color is found to be due to myriads of homogeneous, sharply delineated, intensely yellow membranes, most of which are lining the luminal aspects of pink-staining “conventional” hyaline membranes.

The most extensive clinical morphological study on YHMD clarified that the more of premature infants survived longer, the more frequent YHMD was diagnosed. Comparison of the population characteristics of the infants in the pink and yellow groups revealed several differences: YHMD newborns were found to be more premature, had smaller autopsy weight and survived longer.

The authors reviewed the literature on clinical, morphological and biochemical aspects of YHMD from the first article in 1976 to the last systematic research in 1983. The last cases seen by one of the authors were in 1998 when the economic crisis in Bulgaria led to shortage of surfactant medication in the hospitals. Hopefully, YHMD would remain a condition that is not seen in the practice nowadays and would be discussed only as a phenomenon with historical significance.

Key words: yellow hyaline membrane disease, histology, premature newborns.

In March of 1973, Marie Valdés-Dapena (St. Christopher’s Hospital for Children, Philadelphia) observed, for the first time in her experience, what appeared to be a variant of pulmonary hyaline membrane disease in a 6-day-old, prematurely born male infant, transported to the hospital because of respiratory distress. At autopsy the external and cut surfaces of the lungs were bright yellow. Microscopically the yellow color was found to be due to myriads of homogeneous, rather sharply delineated, intensely yellow membranes, most of which lined the luminal aspects of pink-staining “conventional” hyaline membranes. Within the next few months, five similarly affected infants were encountered in that hospital and ten other infants in three nearby institutions. Other pediatric pathologists have observed similar yellow hyaline membranes since 1965 and have referred to them as “bilirubin membranes” or “icterus of pulmonary hyaline membranes”. These facts are described in the article by Valdés-Dapena et al. from 1976 (1, Fig. 1A). The authors earnestly noted that brief mention was made of the entity in two North American publications from 1969; a Spanish atlas of pediatric pathology, published in 1974, included a photomicrograph of yellow membranes without any particular discussion (Fig. 1B).
Fig. 1. Facsimile of the first (A) and last pages (B) of the Valdés-Dapena et al. article in J Pediatr, 1976 (1).

In the Commentary of Valdés-Dapena et al.’s article William Blanc (Dept. of Pathology, College of Physicians and Surgeons of Columbia University) wrote (2):

“The first cases in Babies Hospital were seen in December, 1964, and the beginning of 1965, coinciding with the start of an active intensive care unit for premature infants and of the prolonged survival of severe cases of respiratory distress syndrome. The icteric hyaline membranes was given one paragraph and one picture in the report of a 1968 National Institute of Child Health and Human Development conference and buried. We should be indebted to Dr. Valdes-Dapena and her collaborators for bringing up the subject and inducing pathologists to reconsider questions unanswered at the time and still unanswered at the close of their paper.”

Although in 1976 Cho & Sastre described two cases with YHMD and intrahepatic cholestasis (3), Valdés-Dapena et al. conducted and published in the same year the first systematic study of 16 infants with YHMD in comparison to a control group of 68 infants with conventional HMD. It was established that length of life of the YHMD group cases was statistically significant longer than the control group: 142 hours vs. 30 hours. Serum concentration of bilirubin was not markedly elevated in most of the 16 patients and was predominantly of the unconjugated type.

Yellow staining of hyaline membranes was noted by Colby et al. (4) during an extensive study of bronchopulmonary dysplasia amongst the newborns died with the clinical diagnosis of respiratory distress syndrome and ventilated for at least 24 hours. For the studied 12 year period (1962-1973) the authors investigated 299 cases and found 51 with YHMD in Stanford University Hospital, first of which was observed in 1964. For the period 1964-1968 there were 1-3 cases per year and 8-10 cases yearly for the period 1969-1973, representing 38 to 82% of the examined infants for the studied years.

The most extensive morphological study on YHMD was published by Turkel & Mapp in 1983 and performed in the Los Angeles County-University of Southern California Medical Center from 1970 to 1980 (5). They reported a total of 667 cases with HMD, 499 of which with pink and 168 with yellow membranes. It was found that as more of the premature infants survived longer, YHMD was a more frequent finding, increasing from 7% of all newborns having HMD at autopsy in 1970 to 50% in 1980. Comparison of the population characteristics of the infants in the pink and yellow groups revealed several differences: YHMD newborns

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2. Driscoll S: Personal communication.
4. Favara B: Personal communication.
were found to be more premature and had smaller autopsy weight. The most marked difference seemed to be in length of survival: the mean length of survival for all 667 infants was 4.21 days; the mean for pink group was 3.54 days, and the mean value for yellow group was 6.20 days (P< .00001).

The lungs of newborns with YHMD can often be characterised grossly by a slight yellow coloration. This yellow color is permanent and does not fade when the lungs are exposed to air, light, or prolonged refrigeration. On microscopic examination of stained or unstained fresh frozen or paraffin-embedded fixed sections, the YHMs are clearly visible as a permanent bright yellow pigment which does not fade with time and is unaffected by conventional hematoxylin and eosin staining. The yellow pigment is seen lining the alveolar surface of the pink membrane, diffusely within hyaline membranes, free in alveolar/bronchiolar lumen or within macrophages, depending upon the stage of the disease.

Valdés-Dapena et al. examined the histochemical nature of the pigment in YHMD and observed that Hall’s stain indicated the presence of bilirubin, at least within the luminal aspect of the yellow membranes. By electron microscopy the yellow membranes were seen to contain innumerable needlelike, slightly curved slender structures varying in length from 2.500 Å to 5.000 Å and in width from 250 Å to 400 Å; these were interpreted as either bilirubin-protein or bilirubin-lipoprotein complexes (1). Morgenster et al. investigated homogenates of lungs with YHMs and usual hyaline membranes, using scanning spectrophotometer, and established unique absorption shoulder at 454 nm in the former (6). This shoulder corresponded to the absorbance of unconjugated bilirubin and could be reproduced by adding purified unconjugated bilirubin to non-YHM lung homogenate prior to extraction. Thin layer chromatography of the extracted YHM material produced two unique spots identical to those of chemically pure bilirubin. When exposed to ultraviolet light, these two spots fluoresced orange-red. This was considered significant because ultraviolet microscopy of YHMD lung sections revealed similar orange-red fluorescence heterogeneously embedded within the YHMs.

The properties of the bilirubin in YHMD differ in two important ways from those seen in other diseases usually attributed to bilirubin deposition, such as scleral icterus and kernicterus. Primarily, the presence of the YHMs does not correlate with increased peak level of serum bilirubin. Secondly, unlike the coloration of kernicterus which disappears upon exposure to room air, the yellow color of YHMD is permanent, and neither changes nor fades on prolonged exposure to air or light. The explanation, given by Morgenster et al., was based on the presence in the neonatal lungs of unelucidated substance capable of binding bilirubin. The authors investigated polymyxin B as a potential candidate for bilirubin binding agent, used for endotracheal washings. Despite promising results from in vitro study, the conducted double-blind clinical study at Magee-Women’s Hospital rejected the presence of polymyxin as a contributing factor to the etiology of YHMD (6).

A variety of theories have been offered to explain the pathological mechanism for the occurrence of YHMD. Most accepted hypothesis states that prolonged survival, mild hyperbilirubinemia, hypoproteinemia, coupled with decreased bilirubin binding to albumin could result in increased tissue deposition of unconjugated bilirubin by diffusion through alveolar walls damaged by prolonged shock. This type of pigment would secondarily stain the already formed intra-alveolar membranes (5). Such mechanism is responsible for development of kernicterus in neonates: damage to the blood-brain barrier and subsequent leakage of protein and bilirubin into the brain parenchyma. Doshi et al. in 1980 (7) and Turkel & Mapp in 1983 (5) observed significant association between the pulmonary yellow membranes and kernicterus. In 1983 Doshi et al. (8) proposed clinical diagnosis of YHMD by tracheal aspiration cytology as useful method in identifying infants at risk for kernicterus.
Interesting fact – as early as 1976 Blanc noted in a clinical observation that some ventilated babies after physiotherapy had expectorated puzzling bright yellow debris (2).

The last systematic researches concerning YHMD in scientific literature were published in 1983 (5, 8). Later, YHMD is credited 1-2 sentences and a few references in specialized books and reviews for lung and pediatric pathology (9-11). It might be speculated that the problem has been clarified or the number of dead newborns with HMD has been significantly decreasing due to successful use of surfactant. The last 2 cases seen by one of the authors (V. Ivanova) were in 1998 when economic crisis in Bulgaria led to shortage of surfactant medication throughout the healthcare system (Fig. 2 A, B), (12). Nowadays, medical community believes that YHMD should remain locked between the pages of books and will be referred to in the future as an entity from the past.

**Fig. A, B. Lung tissue with YHME, H&E staining.**
*Courtesy of the author (V. Ivanova).*

**REFERENCES:**