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Case Report

Necrotizing Enterocolitis Due to Respiratory Syncytial Virus in a Newborn Baby

Yenidoğan Bebekte Respiratuvar Sinsitiyal Virüse Bağlı Nekrotizan Enterokolit

Mahli Batuhan Özdoğar[1], Dilem Eriş[2], Özgür Olukman[3]

[1]Bakırçay University, Çiğli Training and Research Hospital, Clinic of Pediatrics, İzmir, Turkey
[2]Bakırçay University, Çiğli Training and Research Hospital, Clinic of Neonatology, İzmir, Turkey
[3]Bakırçay University Faculty of Medicine, Department of Pediatrics, Division of Neonatology, İzmir, Turkey

ABSTRACT

Although rare, respiratory syncytial virus (RSV) infections can cause life-threatening extrapulmonary complications in otherwise healthy neonates. In this report, we describe a term infant who was admitted to the neonatal intensive care unit with transient tachypnea of the newborn but developed respiratory failure due to RSV bronchiolitis on follow-up which was complicated with necrotizing enterocolitis (NEC) and intestinal perforation. We want to draw attention to the development of NEC in a previously healthy term newborn infant with severe RSV disease, even in the absence of traditional risk factors. We hypothesize that the dysregulated pro-inflammatory response associated with severe RSV disease may alter intestinal blood flow and normal healthy microbial flora compromising mucosal epithelial cell barrier against bacterial translocation. Enteral feeding intolerance and septic ileus may represent important clinical outcomes in these patients.

Keywords: Respiratory syncytial viruses, necrotizing enterocolitis, bronchiolitis

ÖZ

Her ne kadar nadir olsa da, solunum sinsityal virüsü (RSV) enfeksiyonları, sağlıklı yenidoğanlarda yaşamı tehdit edebilecek akciğer dışı komplikasyonlara neden olabilir. Bu olguda, doğumdan sonra geçici takipne (TTN) tanısıyla yenidoğan yoğun bakım ünitesine (YYBÜ) yatırılan, ancak takip sürecinde RSV bronşiolitine bağlı solunum yetmezliği gelişen ve bu durumun nekrotizan enterokolit (NEK) ile bağırsak perforasyonu gibi komplikasyonlara yol açtığı bir zamanında doğmuş yenidoğan olgu sunulmuştur. Bu olgu ile, geleneksel risk faktörleri olmaksızın, daha önce tamamen sağlıklı olan zamanında doğmuş bir yenidoğanda ciddi RSV hastalığı sonrasında NEK gelişebileceğine dikkat çekmek istiyoruz. Hipotezimize göre, ciddi RSV hastalığı ile ilişkili düzensizleşmiş pro-enflamatuvar yanıt, bağırsak kan akımını ve sağlıklı mikrobiyotayı değiştirebilir; bu da mukozal epitel hücre bariyerinin bakteriyel translokasyona karşı direncini zayıflatabilir. Bu hastalarda enteral beslenme intoleransı ve septik ileus, önemli klinik sonuçlar olarak ortaya çıkabilir.

Anahtar kelimeler: Solunum sinsityal virüsleri, nekrotizan enterokolit, bronşiolit

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Corresponding Author
Mahli Batuhan Özdoğar,
Bakırçay University Çiğli Training and Research Hospital, Clinic of Pediatrics, İzmir, Turkey
E-mail: ozdogarbatuhan@gmail.com
ORCID: 0000-0003-3307-2863

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INTRODUCTION

Respiratory syncytial virus (RSV) is the leading infectious agent causing lower respiratory tract infections (LRTIs) and hospitalizations in infants, particularly those under one year of age[1]. The global RSV hospitalization rate for children under five years of age is 0.4% per year, highest among infants under six months (2%) and preterm infants under one year (6%)[2]. While RSV bronchiolitis is usually self-limiting, severe cases are more common in high-risk groups, including preterm infants, those with chronic lung or heart disease, immunodeficiencies, or daycare exposure[3]. Predicting the risk of serious complications of RSV infection is challenging. Gastrointestinal (GI) complications are rare, and necrotizing enterocolitis (NEC) has only been reported in a few cases[4]. NEC primarily affects preterm infants due to their immature intestines, but its pathogenesis in term infants is often linked to poor mesenteric oxygenation and underlying conditions like perinatal asphyxia, congenital heart disease, or sepsis. NEC in healthy term infants without risk factors is exceptionally rare[5]. This report presents a term newborn who developed NEC due to RSV-related late-onset nosocomial sepsis. Recognizing this rare but

severe complication with manifestations distinct from typical RSV respiratory symptoms can help clinicians identify at-risk infants at an early stage of the disease, enhance clinical suspicion, and initiate timely, life-saving interventions.

CASE REPORT

A male infant, born from a gravida 3, para 1 29-year-old mother via C-section at 38^{+1} weeks gestation, weighing 3035 g showed signs and symptoms of respiratory distress requiring nasal application of continuous positive airway pressure (nCPAP) after the initial postnatal stabilization steps in the delivery room. He was then transferred to the neonatal intensive care unit (NICU) for advanced respiratory support with the diagnosis of transient tachypnea of the newborn (TTN). Apgar scores at the first and fifth postnatal minutes were 9 and 10 points, respectively. He was provided with non-invasive ventilation support via nasal application of intermittent positive pressure ventilation (nIPPV). Initial physical examination revealed symptoms and signs of tachypnea, tachycardia, grunting, and intercostal retractions. The peripheral oxygen saturation (SpO_2) was between 90% and 95% under 25% oxygen support. Arterial blood gas analysis, chest X-ray and transfontanel ultrasound were normal. Cardiac echocardiogram revealed a small perimembranous inlet ventricular septal defect with a mild-moderate shunt and secundum atrial septal defect (ASDII) which did not cause any hemodynamic instability. Normal chest X-ray, complete blood count ,peripheral blood smear findings, as well as negative acute phase reactants and blood culture ruled out presence of early-onset neonatal sepsis and congenital pneumonia.

After application of non-invasive mechanical ventilation support for one day, the infant was transitioned to room air. His nutritional support was provided with total parenteral nutrition (TPN) on the first day of life. On day 2, minimal enteral feeding with a volume of 20 mL/kg was started with breast milk and increased gradually, reaching full feeds by day 3. From postnatal day 2, he was brought to his mother who provided kangaroo care for her infant

On postnatal day 6, the infant developed lethargy, feeding intolerance with emesis and abdominal distension, tachypnea, and grunting. Laboratory tests for late-onset nosocomial neonatal sepsis revealed leukocytosis, thrombocytopenia, elevated C-reactive protein and procalcitonin. Blood gas analysis was compatible with respiratory acidosis. Chest X-ray findings included prominent bilateral bronchovascular markings, air trapping, and patchy densities in the right lung. Abdominal X-ray showed an abnormal gas pattern with dilated and edematous bowel loops, consistent with septic ileus. However, there were no signs of pneumatosis intestinalis, portal venous gas, or spontaneous intestinal perforation. Oral feeding was discontinued, and TPN as well as empiric combination antibiotherapy with broad-spectrum antibacterials (vancomycin + meropenem) was initiated after taking blood, urine and cerebrospinal fluid cultures. Gastric decompression using intermittent nasogastric suction was performed. Non-invasive ventilation support was provided with nIPPV. Abdominal ultrasound revealed free fluid between the bowel loops, bowel wall thickening and edema with increased echogenicity. The infant was started on pentoxifylline and intravenous immunoglobulin as adjunctive therapies for sepsis. A nasopharyngeal swab was sent for differential diagnosis of respiratory viruses including severe acute respiratory syndrome-coronavirus-2 after learning that his mother had mild symptoms like runny nose and sore throat suggestive of acute upper respiratory tract infection during her visit to the NICU. The polymerase chain reaction (PCR) test was found to be positive for RSV. The stool PCR test for enteric pathogens as well as blood, urine and cerebrospinal fluid cultures were all negative. On follow-up, the infant developed mixed acidosis and circulatory compromise requiring vasopressor support, endotracheal intubation, and invasive mechanical ventilation. Replacement therapy with appropriate blood products was administered for the management of anemia and thrombocytopenia. On postnatal 8^{th} day, abdominal distension worsened significantly, and additional physical signs suggesting further clinical deterioration such as abdominal wall erythema, crepitus, and induration were observed. The diagnosis of bowel perforation was confirmed by the abdominal radiography that revealed free air under the diaphragm consistent with the diagnosis of pneumoperitoneum. Due to intestinal perforation, the infant underwent exploratory laparotomy with resection of the affected intestinal region and end-to-end anastomosis without the need for ileostomy or colostomy. Postoperatively, he received ongoing medical management, including supportive care and antibiotherapy.

Intraoperative findings revealed a segmental necrosis and perforation of the distal ileum. Approximately 5 cm of the affected bowel was resected, followed by a primary end-to-end anastomosis. Any signs of diffuse peritonitis, abscess or additional pathology were not observed in the remaining bowel segments. A pelvic drain was

placed at the conclusion of the surgery. Post-operative care included continued TPN and antibiotherapy. On post-operative day 5, a contrast enema was performed to assess anastomotic integrity and rule out stricture and any post-operative complications were not observed. Enteral feeding was initiated on postoperative day 10 at a dose of 10-20 mL/kg TPN and its dose was gradually increased based on the patient's tolerance. By postoperative day 17, full enteral feeding was achieved. The infant was discharged in good health on postnatal day 30.

Written informed consent was obtained from the infant's parents for publication of this case report.

DISCUSSION

NEC is one of the most common GI emergencies with devastating results in the newborn. Most cases occur in very low birth weight (VLBW) preterm infants (birth weight <1500 g) born at <32 weeks of gestation, however approximately 10% of cases occur in term infants[5]. Term infants who develop NEC typically have preexisting illnesses such as perinatal asphyxia, intrauterine growth restriction, congenital heart disease, sepsis, hypotension, gestational diabetes, polycythemia, history of blood transfusions, or maternal drug use[5]. The case we present here is a full-term male infant who did not have any of the traditional risk factors for NEC. The infant was delivered via C-section, with high Apgar scores and without any need for resuscitation. He was admitted to the NICU for TTN. Non-invasive ventilation was used briefly at minimal settings for 24 hours, after which he was transitioned to room air. No signs of congenital pneumonia or early-onset neonatal sepsis were observed. He exclusively received breast milk, which is known to reduce NEC risk by promoting gut health through its prebiotic and probiotic components. Enteral feeds were introduced minimally on day one and gradually increased to full feeds.

RSV infections in infants usually present as upper respiratory symptoms progressing to bronchiolitis. Extrapulmonary manifestations of RSV are quite uncommon[4]. Severe cases, particularly affecting preterm or immunocompromised infants, may cause apnea, respiratory failure, myocarditis, arrhythmias, encephalopathy, seizures, jaundice, or GI complications like gastroenteritis. However, RSV-related NEC is exceptionally rare[6]. Although NEC is most frequently seen in preterm infants, there are only a few reported cases linking RSV to NEC in term neonates. For instance, Eisenhut[4] described extrapulmonary complications of RSV, including NEC, but most cases occurred in premature infants[4]. Lambert et al.[5] and Abbo et al.[7] also reviewed cases of NEC in full-term neonates, yet a causal relationship between their cases with NEC, and RSV was not explicitly confirmed.

Arias et al.[8], described 4 previously healthy, term and late-preterm infants in all hospitalized with respiratory failure due to RSV bronchiolitis and developed NEC on follow-up. This article is striking in terms of demonstrating the devastating results of RSV. Indeed, although 3 infants presented in this article were discharged from the hospital without further complications; 1 infant died of septic shock. These findings underscore the importance of recognizing RSV as a potential but underreported trigger for NEC in term infants.

One hypothesis linking RSV to NEC suggests that an immature immune system, especially in premature infants, struggles to control viral replication, leading to development of severe disease[9]. This case is notable because the infant was full-term and previously healthy yet developed a severe RSV infection triggering a systemic inflammatory response. Since he showed signs and symptoms of severe sepsis such as mixed acidosis, hypotension, bicytopenia, and coagulopathy soon after the onset of the diseas, he likely had a high viral load. Pro-inflammatory mediators have the potential to damage protective barriers in the gut, alter intestinal blood flow, and reduce the expression of tight junctions, leading to increased gut permeability and bacterial translocation[10]. RSV infection in our patient likely caused immune dysregulation and excessive pro-inflammatory cytokine production, compromising gut barrier integrity and promoting bacterial translocation. These mediators further aggravated intestinal injury, leading to bowel necrosis and perforation.

Another potential mechanism is RSV-induced hypoxia and hypoperfusion[11]. Although the infant was initially managed with non-invasive ventilation, he later required intubation due to mixed acidosis and hypotension. Although his blood gas analysis measurements were within normal range. and SpO_2 targets were reached with minimal ventilator settings, he might have experienced a transient hypoxic phase potentially impairing the integrity of the intestinal mucosal barrier and promoting perforation.

It has been demonstrated that the lung-gut microbiota axis plays an important role in the development, regulation, and maintenance of healthy immune responses. In their review, Marsland et al.[12] have

suggested the presence of a "vital cross-talk" between the mucosal tissues of our body by exemplifying intestinal complications developed during respiratory disease and vice versa[12]. Some respiratory viral infections like influenza are shown to accompany intestinal symptoms in the course of the disease due to alterations in intestinal microenvironment and induction of intestinal immune injury through microbiota-mediated inflammatory processes[13]. In our case, RSV may have caused intestinal mucosal injury via similar pathways resulting in intestinal perforation. Animal studies and *in vitro* models provide mechanistic support for this hypothesis. For example, Chiba et al.[14] demonstrated that RSV infection in mice alters the composition of gut microbiota and aggravates systemic inflammation, increasing intestinal permeability. Similarly, Groves et al.[15] reported that RSV can induce toll-like receptor signaling and cytokine dysregulation in intestinal epithelial cells, compromising mucosal integrity. These findings support the notion that RSV-induced dysbiosis and immune activation may contribute to NEC pathogenesis, even in the absence of traditional risk factors.

Our patient was a full-term healthy infant with no other comorbidities except mild TTN. All standard delivery room and neonatal intensive care interventions were appropriately applied, including non-invasive ventilation, early kangaroo care, and exclusive breastfeeding. Empiric antibiotherapy was avoided. Despite these optimal disease management strategies, high viral load with RSV led to an induction of exaggerated inflammatory response that ultimately resulted in intestinal perforation. In conclusion, severe RSV disease in newborns can result in NEC, even in the absence of traditional risk factors. Clinicians should consider the possibility of NEC in infants who develop feeding intolerance and abdominal distension during RSV infection and take appropriate precautions.

Given the potential for RSV to cause severe complications such as NEC even in term infants, implementation of preventive strategies carries crucial importance. In addition to maternal immunization during pregnancy, which facilitates the transplacental transfer of RSV-specific antibodies, the use of long-acting monoclonal antibodies like nirsevimab directly in newborns has also shown promise in protecting against severe RSV disease. The Centers for Disease Control and Prevention recommends RSV vaccination during 32-36 weeks of gestation and also supports the use of nirsevimab in infants born during or entering their first RSV season. These complementary approaches hold promise in mitigating not only common respiratory symptoms but also rare and life-threatening complications such as NEC in term neonates.

Ethics

Informed Consent: Written informed consent was obtained from the infant's parents for publication of this case report.

Footnotes

Author Contributions

Surgical and Medical Practices: M.B.Ö., Ö.O., Concept: M.B.Ö., D.E., Ö.O., Study Design: M.B.Ö., D.E., Ö.O., Data Collection or Processing: M.B.Ö., Ö.O., Analysis or Interpretation: M.B.Ö., D.E., Ö.O., Literature Search: M.B.Ö., D.E., Ö.O., Writing: M.B.Ö., Ö.O.

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