Fatal rare case of measles complicated by bilateral pulmonary embolism: a case report and short literature review

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Abstract
Different endemic outbreaks of measles have been diagnosed worldwide during the last several years. Some have had severe and fatal complications, possibly because of decreasing vaccination rates. The present case report describes an unvaccinated boy aged 2 years 11 months who was diagnosed with severe measles complicated by pulmonary embolism (PE). Clinical examination revealed a maculopapular rash, hyperemic pharynx, Koplik’s spots, upper respiratory airway obstruction, and tachycardia with no meningeal signs of irritation. Laboratory investigations showed leukocytosis, anemia, normal liver enzyme levels, a moderately high C-reactive protein level (26 mg/L), a high erythrocyte sedimentation rate (65 mm/h), and immunoglobulin M positivity for measles. The patient was treated with antibiotic therapy (meropenem at 20 mg/kg every 8 hours) and supportive measures (anti-inflammatory drugs and intravenous rehydration). On the fourth day of hospitalization, the patient’s general condition became profoundly altered; although cardiorespiratory resuscitation maneuvers were initiated, the child died. Autopsy revealed bilateral pleural effusion with serous citrine fluid, acute purulent bronchopneumonia, bilateral hilar adenopathy, and bilateral PE. Additional research is needed to establish optimal care for pediatric patients with measles, especially when complicated by PE.

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Introduction
The incidence of measles virus infection in childhood has dramatically increased during the last several years. This increase has been associated with more complications of the disease and even increased mortality. Pulmonary embolism (PE) remains a rare complication of measles. Although it was first described many decades ago by von Löschner, our understanding of pediatric PE remains unclear. This could be due to the neglect or rarity of pediatric PE diagnosis, limiting the development of a standardized approach to its management. Therefore, the incidence of undiagnosed PE as a complication in children with various infectious diseases might be underestimated, resulting in increased morbidity and especially mortality of measles.

We herein report a case of a child with confirmed measles complicated by PE who was admitted to a hospital specializing in infectious diseases. The patient’s parents provided informed consent, and the ethics committee of Constanta Clinical Infectious Diseases Hospital approved the publication of this case report.

Case report
A boy aged 2 years 11 months was admitted to the Pediatric Department of Constanta Clinical Infectious Diseases Hospital in Romania. The child had been symptomatic for the last several days and was referred from the emergency unit to our hospital by ambulance because of an altered general condition. The child presented with a fever (38.8°C), loss of appetite, dry tongue, generalized rash, mucopurulent rhinorrhea, cough, dyspnea with intercostal retraction, fine crackles, rhonchus, rhythmic heart sounds, a supple and mobile abdomen with respiratory movements, gurgling, accelerated intestinal transit, four watery stools per day, and normal urination. Additionally, a maculopapular rash on the face, upper limbs, and trunk had been observed by his parents during the last 48 hours. At admission, general clinical examination revealed a hyperemic pharynx, Koplik’s pathognomonic spots, an extended maculopapular rash, dry cough, dyspnea, intercostal and subcostal retractions, fatigue, fine crackles, rhonchus at lung auscultation, tachycardia (155 beats/minute), and a Glasgow score of 15 with no meningeal signs of irritation. The child’s epidemiological history revealed the absence of any previous vaccination, including vaccination to measles.

Laboratory tests indicated positive serology for measles (i.e., immunoglobulin M), leukocytosis (27.3×10⁹ cells/L; reference range, 6–17×10⁹ cells/L), anemia, a moderately high C-reactive protein level (26 mg/L; reference range, 0–5 mg/L), and high erythrocyte sedimentation rate (65 mm/hour; reference range, 3–9 mm/hour). The levels of liver enzymes (alanine aminotransferase and aspartate aminotransferase) and creatinine were normal. Other laboratory investigations revealed a negative stool culture, the presence of Staphylococcus epidermidis in both right and left conjunctival secretions, and no Gram-positive or -negative cocci in the pharyngeal exudate. During hospitalization, the child’s altered clinical condition persisted, with a decrease in the arterial oxygen saturation from 97% to 90%,
crackles, tachycardia, and diuresis; his stools remained normal. Treatment included antipyretic, analgesic, anti-inflammatory, and antitussive drugs; intravenous rehydration with electrolyte rebalancing and energy support; antibiotic and antifungal therapy; immunoglobulin to stimulate the immune system and prevent severe complications; and supplemental oxygen therapy. Given the leukocytosis and elevated C-reactive protein level, a bacterial superinfection with probable pulmonary involvement was considered, and meropenem was recommended as a broad-spectrum antibiotic. The patient thus received meropenem at 20 mg/kg every 8 hours. Despite slow improvement during the first 3 days of hospitalization with only slightly low arterial oxygen saturation (around 92%), the patient subsequently developed bradycardia (65 beats/minute) with more frequent episodes of oxygen desaturation under continuous oxygen supplementation. During the fourth day of hospitalization, the child developed sudden-onset cardiopulmonary gasping with metabolic acidosis and severe bradycardia (40 beats/minute). Cardiorespiratory resuscitation maneuvers were initiated for more than 1 hour, including patient repositioning, secretion aspiration, continuous-flow oxygen, corticosteroids, adrenaline, and external cardiac massage; however, the child died.

At autopsy, a macroscopic anatomical pathological examination revealed cerebral edema, internal hydrocephalus, hemorrhage of the choroid plexuses, and enlargement of the cerebral tonsils (Figure 1). We also observed polyserositis with acute pericarditis.

**Figure 1.** (a) Disseminated bronchopneumonia: focus of inflammatory condensation surrounding bronchioles with intraluminal suppurative exudate and bronchiolitis [hematoxylin–eosin (HE) stain, ×10]. (b) Inflammatory condensation surrounding a bronchiole with intraluminal suppurative exudate and vascular congestion (HE stain, ×10). (c) Leukocytic alveolitis with vascular and septal congestion; partial disruption of bronchiole walls by inflammation (HE stain, ×20). (d) Focus of inflammatory condensation surrounding a bronchiole with intraluminal suppurative exudate (HE stain, ×40).
bilateral peritonitis and pleural effusion with serous citrine fluid, acute purulent bronchopneumonia, hilar adenopathy, and bilateral pulmonary thromboembolism (Figures 2 and 3) as well as stasis at the level of the liver, spleen, and kidney.

**Discussion**

The measles virus is an RNA virus that belongs to the Paramyxoviridae family. Its incubation period ranges from 10 to 12 days. Affected patients initially develop signs of an upper respiratory tract infection lasting about 2 to 4 days, followed by pathognomonic Koplik’s spots and a generalized maculopapular rash.5,6 The measles virus is contagious, and its transmission rate is high (90%).7,8 In contrast, in populations with higher vaccination rates, acute measles infection is most often caused by infections acquired abroad.9

An embolus is a “travelling clot,” and PE is usually a complication of deep vein thrombosis. In children, PE is a very rare and unrecognized condition, but it is usually fatal.10 In autopsy examinations of children with PE, the intravitam diagnosis could not be established.11 Although many physicians consider PE to be silent in children, symptoms and signs are seen but ignored by clinicians in some cases, leading to a misdiagnosis of pneumonia, malignancy, or exacerbation of heart failure.12,13

Aspirin is used to prevent PE in adults, but this advantage is lacking in children.

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**Figure 2.** (a) Inflammatory condensation surrounding a bronchiole with intraluminal suppurative exudate and vascular congestion [hematoxylin–eosin (HE) stain, ×10]. (b) Exudative bronchiolitis and intravascular red thrombi (HE stain, ×10). (c) Exudative bronchitis and intra-arterial red thrombus (HE stain, ×10). (d) Intra-arterial mixed thrombus (HE stain, ×10).
Aspirin is not usually used to treat fever in children because it has been associated with a high risk of Reye syndrome in the presence of certain viral illnesses. One study showed that thromboembolic events can be a common cause of mortality in hospitalized children without surgical interventions. Because our patient’s respiratory condition continuously deteriorated, rapid diagnosis was crucial for survival. Complications of measles usually occur in children aged <5 years and adults aged >20 years.

PE in children may have classic symptomatology, unlike in adults, however, its onset is more silent. Delayed diagnosis of PE may result from misdiagnosis or confusion with pneumonia or exacerbation of heart failure. In many cases, only autopsy revealed the PE; no antemortem diagnosis of PE had been made. Leukocytosis in a child with a viral infection, as in our patient (17.4 × 10⁹ cells/L; reference range, 6–12 × 10⁹ cells/L), can be a surrogate biomarker of acute PE. Thus, maintaining a high index of suspicion for PE in children is mandatory if symptoms such as chest pain, hemoptysis, fever, or even syncope are present. Moreover, tachycardia and edema due to deep vein thrombosis may be present. Therefore, many medical conditions and infections can mask the diagnosis of PE, leading to delayed diagnosis or misdiagnosis of PE with development of subsequent complications.

Figure 3. (a) Lymph node with marked vascular congestion and lymphocyte depletion [hematoxylin–eosin (HE) stain, ×10]. (b) Heart with minimal vascular congestion and interstitial edema (HE stain, ×10). (c) Liver with portal and sinusoidal congestion (HE stain, ×20). (d) Kidney with vascular, peritubular capillary, and glomerular congestion (HE stain, ×10).
example, our patient did not exhibit tachycardia but instead showed bradycardia, which was related to the presence of pericarditis. However, many epidemiological studies are based on autopsy findings mostly in children who are already known to have PE.\textsuperscript{20} In another review of 3600 pediatric autopsies, Buck et al.\textsuperscript{21} reported a 3.7\% incidence of massive PE; among these patients, 31\% died.

Most importantly, every physician must be aware of the beneficial effects of a strict vaccination policy, which is mandatory to prevent further infections and eliminate sporadic cases or epidemics of measles in the future.\textsuperscript{7} Based on these observations, we further recommend prospective clinical trials specifically based on the risk categorization of pediatric PE.

The most common adverse reactions observed after measles vaccination are fever and rash.\textsuperscript{22} Severe adverse effects, the frequency of which is unknown, include subacute sclerosing panencephalitis, febrile seizures, acute encephalitis, Guillain–Barré syndrome, and Stevens–Johnson syndrome, but not PE.\textsuperscript{22}

In conclusion, children with measles should be considered to be at risk of PE. Although PE in children is a rare medical condition and may often go unrecognized, it can potentially be fatal. Therefore, additional research is needed to establish optimal management of measles in children, especially when complicated by PE.

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