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Case Study

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Severe pneumococcal pneumonia following Measles- Mumps- Rubella vaccination

Pneumonie pneumococică severă dezvoltată ca urmare a vaccinării Rujeolă-Oreion-Rubeolă

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Abstract

Hereby, we report a case of severe multi-lobular pneumococcal pneumonia with gangrene requiring pneumonectomy and accompanying septic shock that developed 1 day after a live-attenuated measles-mumps-rubella vaccination in a 58-year old kindergarten teacher.

Keywords: *severe pneumococcal pneumonia, Measles- Mumps- Rubella vaccination.*

Rezumat

Prezentăm un caz de pneumonie pneumococică multilobulară severă cu gangrenă şi şoc septic, necesitând pneumonectomie care s-a dezvoltat după o zi de la administrarea vaccinului viu-atenuat rujeola-oreion-rubeola la o educatoare de 58 de ani.

Cuvinte cheie: *pneumonie pneumococică severă,vaccinare Rujeolă-Oreion-Rubeolă.*

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Introduction

Measles is one of the most contagious viral diseases, which was a leading cause of death worldwide several decades ago. As it is a vaccine-preventable infectious disease, intensive arrangements and effective immunization programmes have been initiated in order to prevent measles infection and to reach the global elimination of the disease (1). Vaccination against measles is provided by the combined live attenuated measles-mumps-rubella vaccination (MMR), no single vaccine against measles is currently in clinical use. MMR has a good safety profile that is rarely associated with life-threatening complications or adverse events. To achieve and maintain high levels of population immunity, WHO developed strategies providing high vaccination coverage with two doses of MMR vaccine (2).

In accordance with the European Centre for Disease Prevention and Control (ECDC), the

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latest German national immunization schedule (August, 2013) recommends one dose of measles vaccine for adults aged 18 years and over and born from 1970 onward with no or uncertain vaccination history, with no vaccination history or with only one dose received during childhood. In addition, the German Standing Committee on Vaccination (STIKO) stresses the importance of measles vaccination in health care personnel and community health workers caring for patients with immunodeficiency disorders (www.stiko.de). Only one commercial type of MMR vaccine is available in Germany.

The recommendation of the Advisory Committee on Immunization Practices (ACIP) on MMR vaccination available in the United States is similar to the European guides except that persons born in 1957 or after should receive at least 1 dose of MMR vaccine if they do not have the evidence of immunity. For those adults who might be at increased risk for exposure or transmission of these diseases, students, health care personnel and international travelers 2 doses of MMR vaccine should be administered (3).

Naturally acquired measles causes transient immunosuppression leading to a temporary CD4 lymphocyte deficiency (4-6). In consequence, pneumonia is one of the most serious complications associated with measles, and at least 50% of measles-related pneumonias are due to bacterial superinfection and chronic suppurative lung disease is a typical complication after measles in non-vaccinated children (7-9). However, pneumonia after naturally acquired measles may also manifest due to direct viral invasion. Another important mechanism that predisposes to bacterial superinfections is that of direct damage to the respiratory tract through edema or loss of cilia by common viral pathogens, e.g. influenza, which proved to alter NK-cell response as well (10).

Streptococcus pneumoniae is the most frequent cause of community-acquired pneumonia (CAP). Pneumococcal disease develops suc-

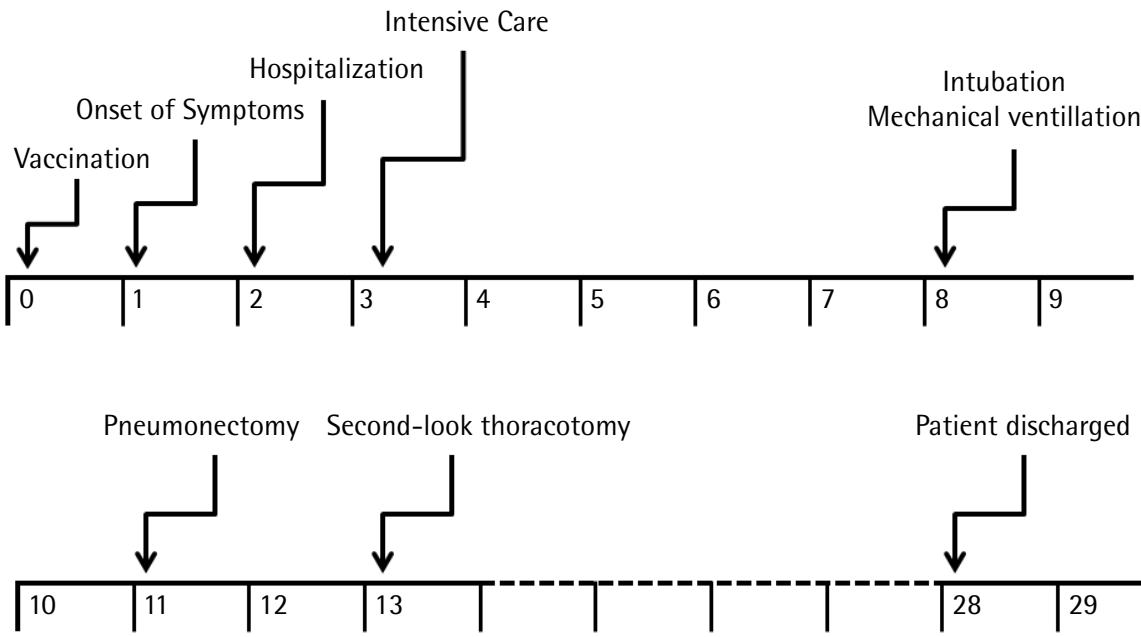

Figure 1. Time course of events after vaccination

ceeding nasopharyngeal colonization with the homologous strain (11). Several studies show that the highest frequency of pneumococcal colonization is found in young children, this risk group is thought to be responsible for horizontal dissemination of pneumococcal strains within the community (12).

The clinical case

In June 2014, a 58-year-old female kindergarten teacher underwent an MMR vaccination.

Vaccination had been recommended due to her occupation with increased risk for exposure to measles, rubella, or mumps. The patient and also her only son had never acquired measles and had never been vaccinated before.

Twenty-four hours after vaccination, the patient developed fever and malaise. Because of worsening symptoms, the patient presented to the emergency room of the local hospital on the following day and was immediately hospitalized because of worsening general health condition, fever, weakness, and confusion. Chest computed tomography scan confirmed the diagnosis of CAP and revealed consolidation in the right upper, middle, and lower lobes suggestive for pneumococcal pneumonia. According to the CURB severity index, the patient exhibited severe CAP with 3 (confusion, respiratory rate > 30/min, urea > 1.1 mmol/l) out of 4 criteria. She was immediately transferred to the ICU and treatment with clarithromycin (500 mg, bid) and cefazolin (2 g, tid) was initiated. After 2 days, because of worsening conditions, she was transferred to the ICU of the University Hospital of Jena.

On admission bronchoscopy with bronchoalveolar lavage was performed in order to identify the etiologic pathogens. Based on the results of the antibiotic susceptibility testing cefazolin was replaced by ceftriaxone on the 3rd day (2 g, od). Further molecular diagnostic tests found no evidence of recent infection by other respiratory pathogens.

Due to worsening respiratory insufficiency and non-decreasing CRP (306.8 mg/l), ciprofloxacin (400 mg, tid) was added on the 6th day to cover possible superinfection by nosocomial Gram-negative pathogens. On the same day, the patient developed severe hyponatremia (115 mmol/l) requiring treatment with fludrocortison.

On the 8th day, respiratory failure required invasive mechanical ventilation. A repeated chest CT scan revealed complete consolidation of the right upper and middle lobes, furthermore, concomitant pneumothorax with pleural effusion were demonstrated, requiring insertion of chest tubes.

On the 11th day, because of the evolving massive pleural empyema and the increasing CRP values, ceftriaxone was replaced by piperacillin-tazobactam (13.5 g per day, continuous infusion) and a thoracotomy was performed revealing abscesses and necrosis of the entire right lung requiring total pneumectomy.

On the 13th day a second look thoracotomy was performed in order to remove the intrathoracal drains and tampons and invasive mechanical ventilation was discontinued on the 15th day. The antibiotic therapy was changed to orally administered moxifloxacin 400 mg, od. The subsequent postoperative evolution of the patient was satisfactory with no further signs of infection or relapse during a follow-up period of 4 weeks. An immunodeficiency disorder was suspected in the light of the fulminant and severe manifestation of the disease, therefore, immunological assessment was performed and preventive 10 g polyvalent Immunoglobulin substitution was administered.

On the 28th day post vaccination, the patient was transferred to the regular ward and discharged to a rehabilitation center on the 37th day.

Laboratory findings

Microbiological analysis of the bronchial alveolar lavage sample from the right lower lobe obtained by bronchoscopy revealed *Streptococcus pneumoniae*. The isolate was completely susceptible to macrolides, penicillin and cephalosporines.

The laboratory diagnosis of viral and fungal respiratory tract infections was accomplished through multiplex real-time reverse transcriptase polymerase chain reaction (RT- PCR) assay.

Thirteen pathogenic respiratory agents, including ten respiratory viruses: influenza viruses A and B (Inf A and Inf B), respiratory syncytial virus (RSV), parainfluenza viruses 1-4 (PIV 1-4), human adenovirus (HAdV), varicella zoster virus (HHV-3) and cytomegalovirus (HHV-5) and three fungal species: *Candida, Aspergillus*, and *Cryptococcus* were screened using the multiplex protocol. None of these pathogens were detected in the patient's samples. Unfortunately, measles PCR or cell culture was not performed in this case.

Quantitative serum immunoglobulin tests were performed for the three major immunoglobulin classes (IgG, IgA and IgM) in order to assess the humoral immunity and this revealed a significant IgG2, IgG4 and IgA-deficiency.

Discussion

Measles virus (MV) has severe immunosuppressive effects, which make measles patients susceptible to secondary bacterial or viral infections. MV suppresses cell-mediated immunity by inhibition of $CD4^+$-T-cell cytokine production (4, 6). The ability of MV to suppress lymphocyte proliferation results in lymphopenia with decreased numbers of T cells and B cells in circulation (5, 12). Unfortunately, CD4 cell count was not measured during this hospitalization. However, an absolute lymphopenia (1.22 Gpt/l) was measured. We should also take into consideration the fact that pneumonia could also be caused by direct viral invasion or by direct damage to the respiratory tract, which predisposes patients to bacterial superinfections.

In this clinical case, a significant IgG2, IgG4 and IgA deficiency was detected. IgA deficiency predisposes to respiratory tract infections and is associated with impaired antibody responses to vaccination. Additionally, selective IgG2 and 4 subclass deficiency have been identified as a risk factor for infections by encapsulated bacteria like *S. pneumoniae* (14). According to the criteria of the European Society for Immunodeficiencies, a diagnosis of a common variable immunodeficiency (CVID) was suspected (15). However, the patient reported to have been always in "good health and had never taken antibiotics or was hospitalized for infections before the current event", despite frequent exposure to respiratory pathogens due to her occupational activity as kindergarten teacher. Therefore, one of the criteria of the revised diagnostic definition for "probable CVID" was missing (16). Although increasing evidence suggests that immunoglobulin deficiencies predispose patients to invasive bacterial infections (14), it remains a subject of debate if the patient's immune deficit could have been enough to trigger the pneumococcal infection even in the absence of MMR vaccination history.

Streptococcus pneumoniae is one of the most frequent pathogen causing bacterial infection in patients with measles (18), it is also proved to be the major bacterial pathogen in other cases of impaired cellular immune response, e.g. AIDS (16, 17). A recently published review summarized the role of impaired immune pathways in influenza virus infection, which induces susceptibility to secondary bacterial pneumonia (20). In this case, the presence of a viral or fungal respiratory tract coinfection was also supposed, but as presented earlier, the laboratory diagnosis revealed no viral pathogen.

Due to the sequential occurrence of MMR vaccination and severe pneumococcal pneumonia it can be assumed that the infection induced by the attenuated vaccination virus caused a temporary immunosuppression that was complicated by severe pneumococcal pneumonia. This may have been aggravated by the fact that the patient had no preexisting immunity against measles and the detected IgA, IgG2 and IgG4 deficiency, which increases the susceptibility for both measles and pneumococcal infection (14). A PubMed research revealed no results when searched for "CVID" and "Live vaccine" or "MMR" terms taken together.

The Vaccine Adverse Event Reporting System (VAERS) has summarized higher rates of severe adverse events only in patients over the age of 60 for the yellow fever vaccine, another live attenuated vaccine (20, 21).

Conclusion

Currently, there is no clinical experience with the use of MMR in elderly patients with CVID. This case report shows that attenuated live vaccines should be used with caution in these patients, particularly in patients with no preexisting immunity.

Furthermore, the age restriction issued by vaccination should be considered when vaccinating adults with MMR (i.e. born after 1970). In this individual case, the indication was seen because of the occupational activity and the obviously lacking immunity against measles. It would be a speculation whether prior vaccination with a pneumococcal polysaccharide vaccine had prevented or attenuated this severe pneumonia.

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