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Case report

Hantavirus cardiopulmonary syndrome due to Puumala virus in Germany

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ABSTRACT

In Germany Puumala virus (PUUV), known to cause mild forms of hemorrhagic fever with renal syndrome (HFRS), is the predominating endemic hantavirus. We herein describe an unusually severe case of a PUUV infection that occurred in summer 2015 in South Eastern Germany in a region known to be endemic for PUUV since over ten years. A 54-year-old female gardener was admitted to hospital with fever, cough and dyspnea. Within 48 hours the patient developed a rapid progressive adult respiratory distress syndrome (ARDS) with circulatory failure and required ECMO (extracorporeal membrane oxygenation) treatment. Serological and molecular biological examinations of serum samples confirmed an infection with PUUV. Partial sequences of the S- and M-segment clustered to a strain previously described in South Eastern Germany. Our reported case highlights, that in rare incidents PUUV can cause hantavirus cardiopulmonary syndrome, a syndrome that is usually found after infections with New World hantaviruses, and neurological symptoms.

1. Why is this case important?

In Central Europe a mild hemorrhagic fever with renal syndrome, known as nephropathia epidemica, is the typical clinical entity of infections caused by Puumala virus (PUUV; hantavirus) [1]. In Germany areas in the federal states of Baden-Württemberg, Bavaria, Lower Saxony, North Rhine-Westphalia, Hesse and Thuringia are considered as endemic for PUUV. Since 2001 over 10.000 clinically apparent PUUV-infections were reported with outbreaks in 2005, 2007, 2010, 2012, and 2014, with a tendency to increasing caseloads. Comparatively, in 2015 an unusually high number (n = 757) of PUUV infections occurred in Germany [2].

In this report we describe a severe life-threatening manifestation of a PUUV infection acquired in South Eastern Germany clinically resembling a hantavirus cardiopulmonary syndrome (HCPS) that is usually caused by hantaviruses endemic in the Americas [3]. In the context of increasing numbers of Hantavirus cases in Germany, clinicians and microbiologists should therefore take hantaviruses into consideration in cases of severe pulmonary infections in endemic regions.

2. Case description

In July 2015 a 53-year-old woman with severe headache, radiating into the neck, chills, fatigue and vomiting was admitted to a county hospital in South Eastern Germany. At the time of hospitalization the symptoms existed for three days. Prior to her illness, the patient had extensively worked in her private garden during a warm and dry period. Medical history revealed no pre-existing conditions other than longterm inhalative nicotine abuse.

Besides the prominent headache, the body temperature was 37.7 °C on first clinical examination. Suspicious laboratory findings were low thrombocytes ($100 \times 10^3/\mu l$), impaired glomerular filtration rate (GFR, 48 ml/min), mild elevated transaminases and a significant elevated C-reactive protein (CRP), 162 mg/l). An antimicrobial therapy with aciclovir and ceftriaxone was initiated. However, a viral meningitis could be excluded as there were no pathological findings in the liquor. On the second day of admis-

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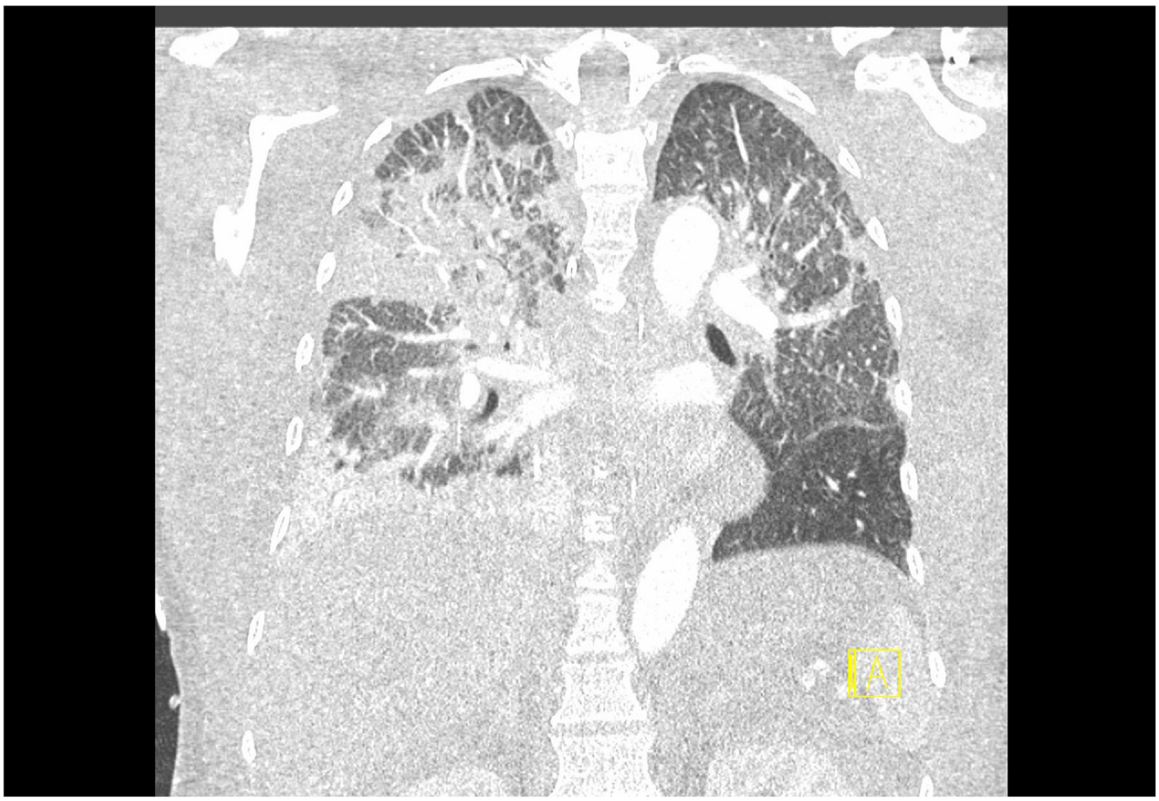

Fig. 1. CT scan day of admission at University Hospital Regensburg. Bilateral (right > left) inflammatory infiltrates and alveolar sept enlargement as a sign of heart failure.

sion the clinical condition of the patient rapidly deteriorated. The patient developed high fever at 40 °C, and worse, an acute respiratory failure, requiring intubation and mechanical ventilation, and falling into septic shock aggravated by a cardiomyopathy. A massively reduced left ventricular ejection fraction of 20% was revealed in transthoracic echocardiography and serum troponin levels were considerably elevated (6 ng/ml). Simultaneously electrocardiogram changes in terms of negative T-waves appeared as a hint for cardiomyopathy. Antibiotic therapy was changed to piperacillin/tazobactam, clarithromycin and aciclovir. Despite mechanical ventilation with Post-End-Expiratoric-Pressure (PEEP) of 12 mbar and a highest ventilation pressure of 30 mbar, on day three the patient required extracorporeal circulatory and pulmonary support using veno-arterial extracorporeal membrane oxygenation (ECMO)Therefore, the mobile ECMO team of the University Hospital Regensburg cannulated the patient for veno-arterial ECMO and transferred the patient to the medical ICU of the University Hospital Regensburg. Beyond low thrombocytes ($78 \times 10^3/\mu l$), impaired GFR (36 ml/min), mild elevated transaminases, an elevated CRP (105 mg/l) and ongoing leukocytosis ($30 \times 10^3/\mu l$), a high procalcitonin (PCT, 8.93 ng/ml) was found. As the respiratory situation continuously worsened another venous cannula was inserted and the ECMO changed to a veno-veno-arterial mode. On day 4 of admission the patient presented a severe ARDS, a severe sepsis with multiorgan failure, cardiomyopathy, acute kidney failure, requiring intermittent dialysis, disseminated intravascular coagulation, and a massive capillary leakage, requiring a highly positive fluidbalance. After another 3 days on high dose vasopressors the capillary leakage, cardiac-, and respiratory function improved, allowing the weaning of ECMO on day 12 of the patient's illness.

In the further course, the patient remained critically ill, with only minor improvement of the cardiopulmonary and kidney symptoms. Further, the patient developed an uveitis anterior and a secondary adrenocortical insufficiency. After 17 days of mechanical ventilation the patient was extubated for the first time. Unfortunately, four days after extubation the patient aspirated a huge amount of liquid food that lead to an acute respiratory insufficiency, requiring intubation and a therapeutic bronchoscopy a day later, which was complicated by an acute hypoxic bradycardia, leading to a short resuscitation. After recovery from the aspiration pneumonia the patient showed diminished cognitive capability e.g. prolonged diminished vigilance and diminished social interaction. Computer tomography (CT)-scan and magnet resonance imaging (MRI) of the central nerve system revealed no significant pathological findings except a bilateral calcification of the basal ganglia in terms of Morbus Fahr. At day 39 the patient was transferred to the general ward followed by a long-term rehabilitation in a neurological rehabilitation center. Table 1 summarizes the timeline of the symptoms and diagnosis of the hantavirus case.

Blood cultures, cerebrospinal fluid (CSF), urine and bronchoalveolar lavage (BAL), and serum samples were taken on the day of admission in Regensburg, six days after symptoms onset. Bacteriological cultures of BAL, urine and CSF (day 5 and day 15) remained sterile as well as several blood cultures. Acid-fast bacilli smears and cultures from all respiratory secretions and CSF were also negative. Pulmonary type of leptospirosis was excluded as no antibodies were detected in two serum samples (day 6, day 12) and PCR from urine tested negative. PCRs screening for the following respiratory pathogens in BAL (day 6): *Chlamydia* (C.). *pneumoniae*, *C. psittaci*, *Mycobacterium pneumoniae*, *Legionella* spp., *Coxiella burnetii*, *Pneumocystis jirovecii*, influenza-, parainfluenza-, respiratory syncytial-, herpes simplex-, adeno-, and cytomegalo virus, were all negative. Herpes simplex-, cytomegalo-, varicella zoster-, and Epstein Bar virus PCRs were also negative from CSF (day 6). Additionally, galactomannan in BAL and Legionella antigen in urine was negative. Hantavirus RNA was also not detectable in BAL and CSF taken at day 4 and day 24, respectively (Fig. 1).