



# Case report of Usutu virus infection in an immunocompromised patient in Italy, 2022

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## Abstract

Usutu virus (USUV) is an arthropod-borne flavivirus emerged in Africa in 1950s and in Europe in 1990s causing a massive number of birds' deaths. The role of USUV as human pathogen has been only recently hypothesized and cases of USUV infection in humans remain limited and often related to immunocompromised subjects. Herein, we report a case of USUV meningoencephalitis infection in an immunocompromised patient with no history of previous flavivirus infection. The infection due to USUV evolved rapidly since hospital admission thus resulting fatal in few days after symptoms onset and, although not proven, a suspected bacteria co-infection has been hypothesized. Based on these findings, we suggested that when USUV meningoencephalitis is suspected in countries endemic, careful attention should be applied to neurological syndromes during summer months especially among immunocompromised patients.

**Keywords** Arbovirus · Flavivirus · Endemic · Italy · Human case

## Introduction

Usutu virus (USUV) is an arthropod-borne flavivirus belonging to the *Flaviviridae* family closely related to other important flavivirus belonging to the Japanese encephalitis virus (JEV) antigenic complex (Ashraf et al. 2015). Since the first discovery in South Africa in the middle of twentieth century, USUV widespread worldwide, thus becoming endemic in different countries (Vilibic-Cavlek et al. 2020).

Similarly to other members of the JEV serogroup complex, USUV is maintained in the environment through a bird-to-mosquito life cycle and humans are occasionally infected (Roesch et al. 2019). Herein, we report a case of USUV meningitis infection in an older patient, during summer 2022, in Italy.

## Case report

On 20th August 2022, an 80 year-old man presented in Reggio-Emilia Hospital with complaints of fever and asthenia. His past medical history included hypertension, past infiltrating prostate adenocarcinoma, psoriasis, and SARS-CoV-2 infection 6 months before. Since chest X-ray showed only peribronchovascular interstitial thickening and blood chemistry tests revealed only elevated levels of D-dimer (1376 ng/ml, range 10–500 ng/ml) and C-reactive protein (CRP, 3.87 mg/dl, range 0–0.5 mg/dl), he was discharged with oral antibiotic therapy (amoxicillin-clavulanate 875 mg/125 mg three times/day). However, on 21st August, he was readmitted to the Emergency Department for dyspnea and ataxia. Vital signs revealed body temperature (BT) 37.4 °C, blood pressure (BP)

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100/55 mmHg, heart rate (HR) 102 beats per minute (bpm), and SpO<sub>2</sub> 90% on room air: oxygen therapy with Venturi Mask FiO<sub>2</sub> 40% was administered, with achievement of SpO<sub>2</sub> 95%. Electrocardiogram (ECG) documented sinus rhythm, right bundle branch, and either left anterior fascicular block. He was admitted to the infectious diseases unit: saline solution and empiric antibiotic therapy with piperacillin/tazobactam (2.5 g four times/day as renal dosage adjustment) and azithromycin (500 mg/day) was administered. Molecular swab for SARS-CoV-2, blood and urine culture, was collected before starting antibiotic therapy.

On 22nd August, the patient became soporous, anuric, with high BT (39.2 °C), hypotension (90/55 mmHg), metabolic acidosis, and respiratory failure, presenting clinical features of septic shock and multi organ failure. He was transferred to high care medicine unit, where piperacillin/tazobactam was replaced by meropenem (loading dose of 1 g, then 500 mg three times/day); volemic expansion, diuretic therapy, and continuous positive airway pressure were administered. Blood exams revealed normal leukocyte count, relative neutrophilia, and severe lymphocytopenia (leukocytes 7600/ul, neutrophils 99%, lymphocytes 1%), renal failure (high levels of creatinine 3.27 mg/dl, low glomerular filtration rate, eGFR 18.3 ml/min/1.73 m<sup>2</sup>), rhabdomyolysis (high levels of creatine phosphokinase 1323U/l, range 32–294U/l, and myoglobine 8843 ng/ml, range 0–110 ng/ml), hepatic cytolysis (high levels of aspartate transaminase 3880U/l, range 2–40U/l, and alanine transaminase 1414U/l, range 4–49U/l), cardiac damage (high levels of creatine kinase MB, CK-MB, 14.80 ng/ml, range 0–2.37 ng/ml, and troponine 4895.3 ng/l, range 0–57.3 ng/l), confirmed by the increased repeated cardiac enzymes (CK-MB 18.28 ng/ml and troponine 6809 ng/ml); ECG reported atrial fibrillation, rapid ventricular response, non-sustained ventricular tachycardia, and previous inferior myocardial infarction: digossine was administered. At the same time, an increase of CRP (40 mg/dl) and PCT (738 ng/ml) was observed: on 23rd August, clindamycin (900 mg three times/day) was added to meropenem, while on 24th August, doxycycline was administered, in order to extend the antimicrobial spectrum to gram-positive, intracellular, and anaerobic bacteria.

On 24th August, the patient was soporous, poorly responsive, presenting proximal tetraparesis and cyanosis of head and upper limbs. Total body computed-tomography was unremarkable, except for 2 cm bilateral pleural effusion and atelectasic thickening of the adjacent lung. Metabolic acidosis (pH 7.26) and anuria persisted: haemodialysis was performed, without volemic subtraction because of haemodynamic instability (BP 80/40 mmHg, HR 130 bpm); noradrenaline was administered. The patient died on 26th August.

## Microbiological analysis

On August 25th, a serum plasma and urine specimens were sent to the Regional Reference Centre for Microbiological Emergencies of the Clinical Microbiology Unit of the University Hospital in Bologna (IRCCS Azienda Ospedaliera Universitaria di Bologna) for diagnosis of infection due to West Nile virus (WNV), Toscana virus (TOSV), and USUV following the regional guidelines for arbovirus infection in the Emilia-Romagna region (available at: <https://bur.regione.emilia-romagna.it/bur/area-bollettini/bollettini-in-lavorazione/n-105-del-14-04-2022-parte-seconda.2022-04-13.6916747152/approvazione-del-piano-regionale-di-sorveglianza-e-controllo-delle-arbovirosi-anno-2022/allegato-1-piano-regionale-arb.2022-04-13.1649851706>). Samples were tested by molecular and serological assays (Cavrini et al. 2011; Gaibani et al. 2012): serum, plasma, and urine specimens were extracted from 500 ul and eluted in 55 ul, then tested by multiplex real time PCR. Serological assays for WNV and TOSV were performed by commercial kit (Euroimmun, Germany). Test gave positive results for USUV by real time PCR, while gave negative molecular results for WNV and TOSV. Deeper analysis of positive results showed that USUV RNA was present in high detectable level in both serum, plasma, and urine with a cycle threshold (Ct) respectively of 24, 25, and 17. At the same time, serological assay gave negative results for WNV and TOSV by commercial diagnostic tests at time of the diagnosis of USUV infection. Serological assays have been not performed due to the unavailability of patient samples.

## Conclusion

Although several studies hypothesized the role of USUV as human pathogen, the paucity of infections in human posed several doubts on its role as pathogen (Gaibani and Rossini 2017). The limited availability of specific USUV diagnostic tests and the elevated cross-reactivity to other closely related flavivirus contributed to under-identify infections. In the last years, different cases of human infections, concomitantly with increased virus circulation in different European countries, have been reported (Gaibani and Rossini 2017), renewing interest for USUV as human pathogen (Clé et al. 2019). USUV infection may occur in a wide range of symptoms ranging from totally asymptomatic to moderate (e.g. fever, headache, and rash) or severe signs of infection (e.g. neurological diseases).

In this case, meningoencephalitis infection due to USUV evolved rapidly since hospital admission thus

resulting fatal in few days after symptoms onset. Although a suspected bacteria co-infection has been hypothesized, bacteria culture gave negative results in all samples tested also considering previous antimicrobial exposition. Previous studies showed that subjects with infection due to USUV exhibited a wide symptoms including fever and headache, including influenza-like illness (ILI) and neurological disorders (Gaibani and Rossini 2017; Pacenti et al. 2019). Similarly, symptoms associated to USUV infection in this case included respiratory distress syndrome, infarction, and encephalitis.

In conclusion, here, we described a fatal case of USUV infection in human occurred during the late summer 2022. Based on these findings, an active surveillance for WNV and USUV should be constantly applied to monitor the circulation of both virus in endemic area and to rapidly identified human cases presenting severe neurological diseases. Further studies are necessary to clarify the role of USUV in human disease and clarify its role as human pathogen.

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## Declarations

**Conflict of interest** The authors declare no competing interests.

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