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Case report

Imported human rabies in Switzerland, 2012: A diagnostic conundrum

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ABSTRACT

Human rabies is rare in Western Europe. It is not easily recognized in the absence of a history of exposure. We describe the clinical course, diagnosis and follow-up of an imported human rabies case in Switzerland. The patient, a U.S. citizen, presented at an outpatient clinic in Iraq with pain in his right shoulder on July 5, 2012. On July 8 he was transferred to a hospital in the United Arab Emirates, where he exhibited progressive encephalitis with coma. On July 29, he was transferred to a hospital in Switzerland, where he died on July 31, 2012. The autopsy showed severe encephalitis. Rabies was diagnosed by the rapid fluorescent focus inhibition test (RFFIT) and confirmed by fluorescence antibody testing (FAT) in brain smears and immunohistochemistry on paraffin-embedded brain sections. The viral strain was characterized by RT-PCR followed by sequencing and phylogenetic analysis as an American bat rabies strain associated with *Tadarida brasiliensis*. Close contacts and exposed health care workers received postexposure prophylaxis (PEP).

1. Why this case is important?

The last three indigenous human rabies cases in Switzerland due to the fox rabies epidemic were recorded in 1977.[1–3] Also in North America, either indigenously acquired, bat-derived rabies or imported rabies cases in humans are rare events.[4–7] Therefore, rabies as a differential diagnosis in patients exhibiting progressive encephalitis with unknown etiology might be considered with delay or missed. In the present case numerous differential diagnoses were considered along with rabies as a remote possibility. Timely consideration and diagnosis of rabies is important to implement barrier measures to minimize possible exposures followed by rabies postexposure prophylaxis (PEP) of close contact persons.

2. Case description

2.1. Clinical course

On July 5, 2012, the 34 year old patient, a U.S. citizen, returning to his job in Basra, Iraq, presented at an outpatient clinic with pain in his right arm and shoulder which had increasingly troubled him since June 25. Therefore, the patient's estimated infectious period began on June 11. He lived in California, USA, from January 2012 until May 2012 visiting family members for the last time from June 14 to 18, 2012. Subsequently, he spent one week of holiday in Bangkok and one week in Koh Samui, Thailand. While on holiday in Koh Samui, the patient first experienced symptoms of right arm pain and exhaustion. He did not report any biting incident. Since his condition deteriorated over subsequent days, he traveled by air to the City Hospital in Dubai on July 8, where he was transferred to the intensive care unit and intubated soon after due to generalized rigor, delirium, myoclonic seizures and suspected encephalitis. The patient was given analgesics and sedatives but remained in a persistent coma after sedation was stopped. Cerebrospinal fluid (CSF) taken on July 13 was inconspicuous (no pleocytosis, protein concentration 488 mg/l). A toxicology screen in urine, serological analysis for salmonella, malaria, HSV-1,2, CMV, HIV, HAV, HBV, HCV, EBV and PCR for M. tuberculosis all yielded negative results. Malignant neuroleptic syndrome was considered as principal differential diagnosis with indication of brain death. The patient was transferred to a hospital in Switzerland on July 29, 2012. On arrival, methicillin-resistant *Staphylococcus aureus* (MRSA) was excluded. An EEG showed no background activity and no reactivity to exteroceptive stimuli. Brain MRI showed global hypoxic brain ischemia with laminar hemorrhagic cortical necrosis with emphasis in the

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temporal lobes, but also in the frontal and parietal lobes, a massive up- and downward herniation and the circle of Willis was perfused insufficiently. Clinical examination of the patient, who was under pressure controlled ventilation, revealed a deeply comatose state in absence of sedatives. He exhibited bilateral mydriasis without pupillary light reaction. Corneal reflex and oculovestibular reflexes were absent and an apnea test showed minimal respiratory drive. Muscle tone was flaccid and deep tendon reflexes were not triggerable. A serum sample was collected on July 29 for the detection of antibodies to Japanese encephalitis virus, West-Nile virus and rabies virus, as another remote differential diagnoses. With the consent of the family, in view of the irreversible state, therapeutic measures were discontinued on July 31. The patient died on the same day. Based on the vaccination record, the patient was vaccinated against HAV, HBV and salmonella typhus, but not against rabies.

2.2. Autopsy

Autopsy was performed on August 2 and was restricted to the brain. Several fresh samples were taken from both cerebral hemispheres, including hippocampus and cerebellum, and stored frozen at -80 °C. The brain was fixed in formol for 3.5 weeks and then processed for detailed neuropathological analysis. Grossly, the brain was severely enlarged, edematous and autolytic indicating a brain death state. There was upper and lower brain stem herniation with fresh hemorrhages. Histology showed severe encephalitis with widespread and prominent neuronal loss and moderate inflammation in brain parenchyma as microglial nodules or more diffuse infiltrates, accompanied by moderate perivascular lymphocytic cuffing. There were occasionally some indistinct cytoplasmic structures in H & E stained slides, particularly in Purkinje, suggestive of rare Negri bodies.

2.3. Diagnosis

The first distinct indication for rabies diagnosis was released on August 8, as the patient had a rabies neutralizing titer of 1: 497 corresponding to 11.2 I.U./ml in RFFIT.[8,9] Anamnestic follow-up of the patient's vaccination history revealed the absence of pre-exposure rabies vaccination, thus confirming the diagnosis of rabies. Rabies was then also confirmed by FAT[10] using the frozen native brain samples of cerebellum and both cerebral hemispheres on August 22. Immunohistochemistry using the monoclonal mouse antibody HAM[11] directed against rabies nucleocapsid protein performed on paraffin sections of the brain demonstrated prominent immunoreactivity with large Negri bodies in neuronal somata in addition to smaller granular bodies and immunolabeled cell processes. This was demonstrable only focally in a few blocks from frontal and temporal cortices bilaterally and hippocampus (Fig. 1). RT-PCR[12] using brain suspension revealed a strongly positive result on August 24. Phylogenetic analysis of the sequence of the 543 bp nucleotide fragment showed its close relationship to classical Rabies virus strains circulating in *Tadarida brasiliensis* insectivorous bats in the Americas (Fig. 2).

2.4. Public health investigation

Exposure criteria were defined as open wound or mucous membrane exposure to the patient's saliva, tears, CSF or neural tissue during the presumed infectious period starting on June 11, 2012. For the investigation of contacts abroad, the employer, hospitals and the transport company, which transferred the patient to Switzerland, were notified. CDC, along with local and international partners, revealed 39 potentially exposed contacts in USA, Thailand and Iraq, 7 of whom received PEP due to concern about contact

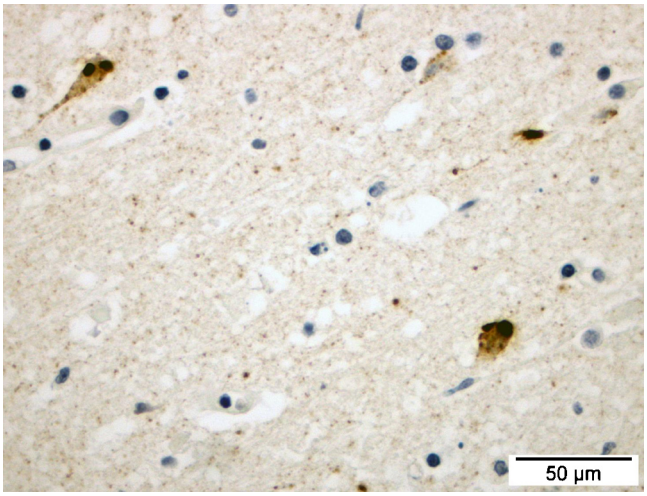

Fig. 1. IHC of paraffin section of temporal cortex labeled with a monoclonal mouse anti-nucleocapsid antibody using hematoxylin as counterstain (200-fold magnification). Several large Negri bodies are present in the soma of neurons, in addition to small granular immunoreactivities.

with potentially infectious saliva or tears.[13] Personal interviews with family members and staff at the Swiss hospital, external laboratories involved and the funeral home with possible exposure revealed 4 persons, 2 of whom were family members, who met the criteria for PEP in Switzerland (1× extubation, 2× close familial contact, 1× handling of nervous tissue). Three unvaccinated persons received a full course of PEP including passive immunization with 20 I.U./kg body weight of human rabies immunoglobulin (HRIG) applied to the anterolateral aspect of the thigh.[14] One person with pre-exposure vaccination received 2 boosters on days 0 and 3. 13 contact persons, though not meeting the criteria for PEP were also offered a simple course of PEP without HRIG or 2 doses at days 0 and 3 in case of pre-exposure vaccination (3 persons) due to personal concern. The success of all PEPs was confirmed serologically on day 21 or 14 in the case of persons without or with pre-exposure rabies vaccination, respectively.[15]

3. Other similar and contrasting cases in the literature

Rabies is not always suspected in human cases and particularly its paralytic form is considered as a diagnostic challenge.[16] In a recent clinical study in India, 34 patients exhibited paralytic symptoms, six encephalitic and 7 primarily psychiatric manifestations. The authors pointed out, that the diagnostic dilemma was raised by clinical features resembling psychiatric disorders.[17] Paralytic rabies was also observed in humans due to bat exposure.[18,19] Other CNS pathogens can be the source of misdiagnosis.[20,21] As a consequence of unrecognized clinical rabies, a total of 16 fatal rabies cases have been observed in the context of organ and tissue transplantations, out of which 9 cases followed cornea transplantation.[4,22] In the case of organ transplantations, both donors experienced a rapid course of encephalitis and prompt brain death. The donors' use of drugs like cocaine and marijuana was a major misleading element to diagnosis in both cases.[23,24]

4. Discussion

Human rabies is rare in regions without endemic canine rabies like Western Europe, North America, Australia, New-Zealand or Japan. Accordingly, it may not be considered as a differential diagnosis. As in the present case, transmission of rabies virus can occur