Case report

Powassan virus encephalitis, severe babesiosis and lyme carditis in a single patient

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Accepted 22 October 2019

SUMMARY

Ixodes scapularis is responsible for transmission of *Borrelia burgdorferi*, *B. miyamotoi*, *Babesia microti*, *Anaplasma phagocytophilum* and Powassan virus to humans. We present a case of an 87-year-old man who presented with fever and altered mental status. Initial workup revealed haemolytic anaemia, thrombocytopenia, mild hepatitis and acute kidney injury. Patient tested positive for *B. burgdorferi* and *Babesia microti*, and was started on doxycycline, atovaquone and azithromycin. He also underwent exchange transfusion twice. After some initial improvement, patient had acute deterioration of mental status and appearance of neurological findings like myoclonus and tremors. Therefore, testing for arboviruses was done and results were positive for Powassan virus. During a protracted course of hospitalisation, patient required intubation for respiratory failure and temporary pacemaker for unstable arrhythmias from Lyme carditis. Patient developed permanent neurological deficits even after recovery from the acute illness.

BACKGROUND

Ixodes scapularis or black-legged tick is responsible for transmission of *Borrelia burgdorferi*, *B. miyamotoi*, *Babesia microti*, *Anaplasma phagocytophilum* and the exceedingly rare *Flavivirus*, Powassan virus, to humans.¹ Coexistence of dual pathogens (two out of three from *Borrelia*, *Babesia* and *Anaplasma*) occurs in up to 28% and 13% of *Ixodes* ticks in Lyme disease endemic areas in USA and Europe respectively.^{2,3} The identification of co-infections is important since these diseases have different pathogenesis, clinical manifestations, complications and treatment modalities.⁴ Powassan virus infection, however, is very uncommon, under-reported and mostly a subject of isolated case reports.

Here we present a case of Powassan virus encephalitis resulting in residual neurological sequelae, severe babesiosis warranting exchange transfusion and Lyme carditis requiring temporary pacemaker in a single patient. To the best of our research, this is the first case report describing co-infection with these three pathogens.

INITIAL PRESENTATION

Patient is an 87-year-old man with medical history of hypertension, dementia (baseline memory impairment) and chronic kidney disease stage 3. He

presented to the emergency department with 1-day history of fever up to 103 °F (39.4°C) with rigors and chills, vomiting and drowsiness, in the background of 2 weeks of worsening fatigue, malaise, intermittent lightheadedness and mild abdominal pain. On presentation, patient was somnolent, responsive to pain but not to voice, febrile to 101 °F but haemodynamically stable. Patient lived at a farm in Saratoga county, Upstate New York, with very frequent outdoor exposure to ticks.

INVESTIGATIONS

Initial workup revealed:

- ▶ Haemolytic anaemia (haemoglobin 109 g/L (normal range 136–167 g/L), hematocrit 30% (40%–49%), reticulocyte percentage 11.1% (0.4%–2%), lactate dehydrogenase (LDH) 1200 units/L (90–225 IU/L), haptoglobin <10 mg/dL (25–234 mg/dL), indirect bilirubin 2.6 mg/dL and total bilirubin 3.4 mg/dL (0.1–1.2 mg/dL))
- ▶ Thrombocytopenia (44 000/μL (150 000 to 400 000/μL))
- ▶ Leukocytosis (13 000/μL (4000–9000/μL)) with raised inflammatory markers (erythrocyte sedimentation rate (ESR) 70 mm/hr (0–15 mm/hr), CRP 210 mg/L (<8 mg/L))
- ▶ Lactic acidosis (lactic acid 5.6 mmol/L (0.5–1 mmol/L), bicarbonate 18 mEq/L (21–30 mEq/L))
- ▶ Hepatitis (alanine transaminase (ALT) 134 units/L (5–60 units/L), aspartate transaminase (AST) 309 units/L (5–45 units/L))
- ▶ Non-ST elevation myocardial infarction type II (troponin 0.06 ng/ml (normal <0.03 ng/mL), normal EKG, most likely demand ischaemia in the state of acute illness)
- ▶ Acute kidney injury (creatinine 1.8 mg/dL (0.8–1.40 mg/dL) up from baseline of 1.3 mg/dL, blood urea nitrogen 45 mg/dL (7–22 mg/dL))
- ▶ Possible urinary tract infection: urinalysis with positive leucocyte esterase and negative nitrite, microscopy showed 20 WBC/hpf, 4–6 RBC/hpf and 2+ bacteria
- ▶ Chest X-ray was normal

DIFFERENTIAL DIAGNOSIS

Since Upstate New York is an endemic area for tick-borne illnesses and patient had frequent exposure to ticks, differential diagnosis included Lyme disease, babesiosis and anaplasmosis. There was also a concern for thrombotic microangiopathy,

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To cite: Khan AM, Shahzad SR, Ashraf MF, et al. *BMJ Case Rep* 2019;**12**:e231645. doi:10.1136/bcr-2019-231645

but peripheral smear did not reveal any schistocytes, ADAMSTS activity also came out to be normal later. Sepsis secondary to urinary tract infection was also a consideration.

INITIAL TREATMENT AND FURTHER PROGRESSION

Patient was empirically started on intravenous fluids, piperacillin/tazobactam for coverage of possible urinary tract infection, doxycycline for Lyme, and atovaquone and azithromycin for babesiosis.

Subsequently, patient's peripheral smear showed red cell inclusions consistent with *Babesia* species. *Babesia* PCR and serology returned positive as well, and parasitemia was estimated at 11.9%. C6 Lyme ELISA was positive followed by positive IgM and IgG antibodies against *B. burgdorferi* on Western blot. Doxycycline, atovaquone and azithromycin were continued. Urine and blood cultures were negative, therefore piperacillin/tazobactam was discontinued.

Given the high-grade parasitemia ($\geq 10\%$), haemolytic anaemia and hepatic and renal impairment, patient underwent exchange transfusions twice within the first week of presentation. Patient showed signs of improvement gradually during the first week. Fever and chills resolved, mental status improved, *Babesia* parasitemia markedly decreased to 0.2% and there was a significant reduction in creatinine, ALT, AST, bilirubin and markers of haemolysis.

However, on day 9 of admission, patient had rapid worsening of mental status with severe agitation followed by progressive lethargy. Neurological examination was significant for tremors of hands and feet, generalised myoclonic jerking and upgoing plantar reflex. Patient became obtunded and developed acute hypoxic respiratory failure necessitating intubation (arterial blood gas showing pH 7.33 (7.33–7.45), pCO₂ 42 mm Hg (34–45 mm Hg), pO₂ 29 mm Hg (83–108 mm Hg), Bicarbonate 21 mEq/L (22–26 mEq/L) on 6 L oxygen per nasal cannula).

CT head and MRI brain were negative for any acute findings of bleeding, ischaemic changes or encephalitis. Electroencephalography (EEG) demonstrated generalised background slowing which can be seen in encephalitis but no epileptic foci. Given the rapid neurological deterioration, neuroborreliosis was a consideration so lumbar puncture was done. Cerebrospinal fluid (CSF) analysis showed WBCs $0.02 \times 10^9/L$ (normal $0-5 \times 10^9/L$), RBCs $0.00022 \times 10^{12}/L$, 96% lymphocytes, 4% monocytes, 0% neutrophils, glucose 60 mg/dL (45–80 mg/dL), protein 48 mg/dL (20–40 mg/dL). Doxycycline was switched to intravenous Ceftriaxone to empirically treat neuroborreliosis. Levetiracetam was added for myoclonus.

On day 10 of hospitalisation, patient developed various cardiac arrhythmias most prominently sinus bradycardia down to 20 beats/min, frequent pauses on electrocardiogram (EKG) and accelerated idioventricular rhythm secondary to atrioventricular (AV block). The most likely explanation was Lyme carditis. Temporary transvenous pacemaker was placed for control of heart rate and rhythm.

Meanwhile, CSF gram stain and culture, CSF serology and PCR for *B. burgdorferi* and other *Borrelia* species returned negative, thereby making neuroborreliosis less likely. At this point, rare causes of encephalitis were probed and arbovirus testing returned positive for 'Powassan Virus' with a reactive Powassan E polyvalent microsphere immunofluorescence assay (MIFA). Repeat Powassan MIFA after 1 week was reactive again. IgM ELISA and Plaque Reduction Neutralisation Test (PRNT 90) for Powassan virus were negative. However, positive Powassan immunofluorescence assay even on repeat testing, clinical

evidence of neuro-invasive disease and lower sensitivity of PRNT 90 made the diagnosis of Powassan virus infection most likely. Serology for Western Equine, Eastern Equine, California and St. Louis Encephalitis Viruses was negative. Paraneoplastic neurological antibodies anti-Hu, Yo, and Ri were negative.

Patient was continued on supportive management (including mechanical ventilation, tube feeding and intravenous fluids), ceftriaxone for Lyme carditis, and completed azithromycin and atovaquone course for babesiosis.

OUTCOME AND FOLLOW-UP

Patient had some gradual clinical improvement. On day 18, he started to open his eyes and obey commands, hence he was extubated. The transvenous pacemaker was retrieved. However, patient demonstrated persistent residual neurological deficits including vocal cord dysfunction, dysphonia, dysphagia and showed very high risk of aspiration on Video-fluoroscopic Swallow Evaluation precluding any oral intake. He was fed via a nasogastric tube and needed frequent suctioning of secretions.

On day 28 of admission, patient was discharged to a nursing facility. Patient will be evaluated for a gastrostomy tube placement for feeding purpose given the persistent dysphagia.

DISCUSSION

Powassan virus can cause potentially fatal neuro-invasive disease in human beings. Since the diagnosis of its first case in 1958, less than 200 cases have been reported in the USA. The number of cases has increased in the recent years because of improved detection modalities.⁵ As per United States Centre of Disease Control and Prevention (CDC), 33 cases were detected in USA in 2017 (21 in New York state), the highest incidence compared with prior 10 years.⁶ Powassan virus has an incubation period of 1–5 weeks. Clinical course usually has a febrile prodromal phase with non-specific symptoms like headache, sore throat, malaise and lethargy. It can be followed by central nervous system (CNS) involvement with aseptic meningitis, encephalitis or meningoencephalitis. Neurological manifestations may be protean including headaches, altered mental status, aphasia, seizures, ocular symptoms like nystagmus or ophthalmoplegia, paralysis, gait disturbances and respiratory failure.^{5 7–9} Permanent neurological sequelae including headaches, hemiplegia, muscle wasting and memory disturbances can be seen in as much as 50% of the patients and up to 10%–15% cases are fatal.^{5 10 11} As per United States Centre of Disease Control and Prevention (CDC) definition, diagnosis of Powassan virus and other arboviruses is based on clinical criteria (which classifies the disease as neuroinvasive or non-neuroinvasive) plus laboratory criteria (based on detection of virus or its antibody in the serum or CSF).¹² Diagnosis is primarily through the health departments in the endemic areas since commercial assays are very limited. It relies on measurement of virus-specific IgM antibodies in serum or CSF through ELISA, immunofluorescence assay or microsphere immunoassay, followed by PRNT for confirmation. PRNT 50 is more sensitive but compromises specificity and PRNT 90 has high specificity at the cost of sensitivity. Sensitivity of RT-PCR to detect viral RNA in CSF specimens or tissues is unknown hence this method should not be used to rule out the diagnosis.^{7 10 13 14} Treatment is mostly supportive, aimed at respiratory support, fluid resuscitation and alleviation of cerebral oedema. High dose corticosteroids and intravenous immunoglobulin (IVIG) have been used in some cases with questionable efficacy. Use of antivirals is also not substantiated.⁷

Diagnosis of babesiosis relies on identification of intraerythrocytic *Babesia* parasites by microscopic examination of a peripheral blood smear, or positive *Babesia* PCR, or isolation of *Babesia* parasites from a whole blood specimen by animal inoculation in a reference laboratory (a method rarely employed). Serology is not a part of the diagnostic criteria and should only be used as an adjunct.^{13 15 16} As per Infectious Diseases Society of America guidelines of 2006, mild-moderate babesiosis should be treated with azithromycin and atovaquone, and severe disease with quinine and clindamycin. However, based on a more recent retrospective study, atovaquone and azithromycin may have equal efficacy in severe disease.^{4 15 17} There are no prospective studies for comparison. Partial or complete exchange transfusion should be considered in patients with high-grade parasitemia ($\geq 10\%$), severe haemolysis, or pulmonary, renal, or hepatic compromise.^{4 15}

Lyme disease is diagnosed primarily by detection of diagnostic IgM or IgG antibodies in the serum. United States Centre of Disease Control and Prevention (CDC) recommends a two-step testing protocol. A negative first step obviates the need of further testing. However, if the first step is positive or indeterminate, the second step should be performed for confirmation. During the first few weeks of infection serology is less sensitive and classic erythema migrans rash may suffice for clinical diagnosis.^{4 13 15} The traditional two-tiered algorithm employs enzyme immunoassay (EIA) followed by Western blot. If the duration of illness is 4 weeks or less, separate IgM and IgG Western blot tests should be done. If duration is more than 4 weeks, IgG Western blot alone is recommended.^{4 15} Recently, CDC has approved a modified two-tiered strategy wherein a United States Food and Drug Administration (FDA) approved EIA may replace the Western Blot as the confirmatory second step.¹⁸ Lyme carditis encompasses the various cardiac abnormalities in patients with Lyme disease. It occurs in 4%–10% of the cases of Lyme disease.¹⁹ The most common conduction abnormality is heart block. Other aberrations may include atrial fibrillation, bundle branch block, intraventricular conduction delay, prolonged QTc interval, supraventricular tachycardia and ventricular tachycardia. Less frequently, myocarditis and pericarditis, and very rarely, acute heart failure and chronic dilated cardiomyopathy may occur.²⁰ Intravenous ceftriaxone is the first line treatment of Lyme carditis, though cefotaxime is an acceptable alternative. Temporary pacing may be warranted in many cases. However permanent pacemaker is only used in exceptional cases since conduction disorders are usually fully reversible within 6 weeks.^{15 19 20}

Learning points

- It is important to recognise co-infections of tick-borne illnesses as they often have different complications and principles of treatment
- In endemic areas, patients who fail to respond to optimal therapy for common tick borne illnesses, especially with the presence of neurological findings, testing for arboviruses like Powassan virus should be considered
- Powassan virus is associated with a high risk of permanent neurological deficits and long term rehabilitation is necessary even after resolution of acute illness
- More studies are needed to elucidate whether there is a difference between efficacy of azithromycin plus atovaquone and quinine plus clindamycin regimens in severe babesiosis
- Identification of arrhythmias in Lyme carditis and prompt treatment with medications or pacemaker could be life-saving

Contributors AMK, served as the primary author of this case report and worked on all the elements right from the introduction to the discussions. SRS was designated with the task of working on the case presentation as well as to find the relevant resources for the discussions. MFA worked on the discussion section with special reference to finding literature on the rare Powassan virus. UN also worked on case presentation and made sure the chronology of how the case progressed during the course of hospitalisation was accurate. All authors of this case report had important contributions that led to its final form.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Next of kin consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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