Hospital of the University of Pennsylvania

Citywide Infectious Disease Conference
25 September 2018

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Presentation

60’s year old woman initially presented to an OSH with diarrhea and vomiting x 5 days

• Loose, liquid, nonbloody stools, denies fever
• Vitals: 177/86, HR 69, RR 18, 100% on RA, Temp? “afebrile”
• NAD, nontoxic appearing
• Initial labs significant for:
  • WBC 15.5, (88% PMNs, 8% lymphs, 4% monos)
  • Na 127, Glu 181, Cl 90, Cr 0.7
  • Normal LFTs
  • Enteric pathogen panel neg
At the OSH

Day #2
Continued diarrhea, vomiting, put on liquid diet, not tolerating PO
Confusing words: “she was calling her cat, Teddy, a puppy”
  • Hyponatremia 127 to 118 → fluid restriction, salt tablets, 3% saline
  • Cr 0.7 → 1.7
  • K 2.8
  • WBC 15 → 20

Day #3, fever to 102.3
Became progressively lethargic → intubated
  • Developed bradycardia to 40s and hypotension.
  • TTE: mild MR and AI, sinus rhythm 71
Started on Vancomycin and Meropenem
OSH course

HD # 3, MRI head:
• “Nonspecific left parietal calvarial enhancing lesion, which could reflect a hemangioma, although given the history of prior malignancy calvarial metastasis is difficult to fully exclude. Would consider bone scan as clinically warranted.”

CT abd/pelvis:
• No acute abnormalities
OSH course continued

• Day #3, LP: 0 WBC, 0 RBCs, normal protein, normal glucose
  • HSV 1,2 neg
  • CrAG neg
  • Gram stain neg

• Respiratory viral panel neg

• HIV neg

• Blood cultures day 1, 3, 4, 9 → no growth

• C. diff neg
PMH

• Cystosarcoma phyllodes of left breast s/p mastectomy 2009
• Subsequent metastatic disease to the pelvis – 2012

Surgical History:
• Splenectomy
• left nephrectomy
• Hysterectomy
• appendectomy
Social history (obtained from cousin)

• Lives alone
• Not married, no partner, no kids
• Reportedly a “hoarder,” family hadn’t been in house for a while
• 10-12 outdoor cats, maybe one indoor cat
• Works at Dollar Store
• Lives in a rural area of Kent County, Delaware
• No known international travel

• Prior notes indicate no tobacco, drugs, alcohol
At OSH:

• Team orders Bartonella serologies
• Starts Doxycycline and Rifampin on day #8
• Discontinues Vancomycin and Meropenem
Transferred to HUP Neuro ICU day #9

• T 93.3, HR 54, BP 80/52, placed on Bair hugger
• Multiple episodes of asystole between 5-8 seconds, transcutaneous pacemaker placed
• Exam:
  • Intubated, poor dentition, withdraws to painful stimuli
  • +corneal reflex, no gag or cough
  • Bradycardic
• Na 165 on arrival, WBC 20 (88% PMNs)
• EEG showing generalized seizure activity
• Unable to obtain LP initially
Repeat MRI head and LP:

MRI: “FLAIR signal abnormality and gyral swelling in the bilateral medial temporal lobes. No signal abnormality in the deep gray nuclei. Pattern would be most consistent with HSV encephalitis. Additional considerations include limbic encephalitis given history of malignancy, however considered less likely given interval increase in signal abnormality since 7/28/2018”

LP: day #12 (day 3 after HUP transfer)
• WBC 13 (17% PMN, 31% Lymph, 52% monos), 6 RBCs
• Protein 285, Glucose 51
Differential?
Diagnostic studies:

- HIV
- Lyme serologies
- Ehrlichia/Anaplasma
- Quantiferon

Additional CSF studies

- HSV I, II
- Arbovirus panel (WNV, EEV, WEV, California Encephalitis, St. Louis)
- Bartonella
- Powassan
- Paraneoplastic panel
- NMDAR ab
- RT-QUIC, 14-3-3
- Enterovirus 71
- HHV6
Case, continued

- Initially started on Doxycycline and Ceftriaxone
- Started on high dose steroids, plasma exchange for autoimmune encephalitis
- Primary team adds Ampicillin and Acyclovir
Case, continued

• HUP day #7
  • Attempted brain biopsy, but patient became hypotensive, aborted
  • Started RIPE
  • Sent rabies samples to CDC
  • CSF next-generation metagenomic sequencing sent to UCSF

• HUP day #12:
  • Called OSH: Bartonella IgG returned positive, titer 1:128
  • Restarted on Doxycycline and Rifampin
Case, continued

• CDC calls back: rejects rabies sample as inadequate, please re-send

HUP day #14

• Rabies studies resent to CDC on HUP day #14
• Although nuchal biopsy accidentally gets dipped in formalin for a few seconds
• Does the five second rule apply?
Case, continued

HUP day #17

• Rabies serum IgG positive, IgM negative
  • RRFIT titer: 1:200
• Rabies CSF IgG and IgM positive
• Saliva PCR negative
• Nuchal biopsy – PCR negative
Case, continued

HUP day #19
• Repeat MRI → worsening T2 signal abnormality
• Repeat serum sent for rabies testing, nuchal biopsy
  • Nuchal biopsy - PCR negative
  • RRFIT titer: 1:210
• Hospital Day #23
  • Family meeting with cousin and family, decides to withdraw care
Postmortem

- Human brain tissue positive for rabies virus antigen by DFA

- Sequencing indicate eastern raccoon rabies virus variant
What about the Milwaukee Protocol?

2004 – 15F from Wisconsin p/w fever, ataxia, obtundation, dysarthria
Bat bite one month prior
• Midazolam + Ketamine, Ribavirin + Amantadine
• Released 76 days later, regained full function, except with residual choreoathetosis and ballismus

• At least 26 subsequent case reports of patients treated with Milwaukee protocol have subsequently died
• Routine use no longer recommended
Rabies in the United States

• Average of 3 cases a year (23 cases between 2008 and Sept 2017)
• Leading source are bats
• Transplant-related
  • 2004, four recipients from a donor who died of encephalitis in Texas
• No cases of human to human transmission
Cases of Rabies in humans in the US and Puerto Rico from 2011 to 2017

<table>
<thead>
<tr>
<th>Date of onset</th>
<th>Date of death</th>
<th>Reporting state</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Exposure*</th>
<th>Rabies virus variant†</th>
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<tr>
<td>5-May-17</td>
<td>21-May-17</td>
<td>VA</td>
<td>65</td>
<td>F</td>
<td>Bite</td>
<td>Dog, India</td>
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<td>25-Nov-15</td>
<td>1-Dec-15</td>
<td>PR</td>
<td>54</td>
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<td>3-Oct-15</td>
<td>WY</td>
<td>77</td>
<td>F</td>
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<td>Bat, Ln</td>
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<td>24-Aug-15</td>
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<td>65</td>
<td>M</td>
<td>Bite, Philippines</td>
<td>Dog, Philippines</td>
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<td>26-Sep-14</td>
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<td>28</td>
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<td>31-Jan-13</td>
<td>27-Feb-13</td>
<td>MD</td>
<td>49</td>
<td>M</td>
<td>Kidney transplant</td>
<td>Raccoon, eastern United States</td>
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<td>Bite</td>
<td>Bat,Tb</td>
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<td>MA</td>
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<td>Bat,Tb</td>
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<td>MA</td>
<td>40</td>
<td>M</td>
<td>Contact, Brazil</td>
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<td>21-Aug-11</td>
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<td>NC</td>
<td>20</td>
<td>M</td>
<td>Unknown (organ donor)§</td>
<td>Raccoon, eastern United States</td>
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<tr>
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Rabies worldwide – disease of poverty

Worldwide burden:

- 55,000 reported human cases, but vastly underreported
- Large burden in low- and middle-income countries
- Mostly stray dogs
  - About 20,000 cases in India each year
  - About 10,000 cases in China each year, grossly under-reported

