Headache and Fever Turns into Confusion

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Initial Presentation:

- 16 yo F with SLE and ESKD travelled from South America for tertiary care
  - Symptoms: blurry vision, facial rash, fevers, headache and hemoptysis
  - Multisystem disease: renal failure, pulmonary disease with vasculitis, cardiac dysfunction, hypertension, anemia, vaso-occlusive retinopathy, left retinal detachment, reduced cerebral volume and microhemorrhage on MR brain
  - Infectious Workup: negative for HIV, hepatitis, tuberculosis, histoplasma, malaria. Negative CSF studies

Initial Clinical Course:

- When infectious workup was reassuring, she was started on immunosuppression for her SLE with:
  - Cyclophosphamide with monthly infusions
  - Rituximab
  - Pulse steroids followed by oral steroids
- She developed several infectious complications including:
  - COVID-19 infection requiring ICU admission for respiratory support
  - Pan-uveitis with bacterial endophthalmitis; vitreous culture grew bacillus species
  - ESBL Klebsiella UTI

Headache and Fever

- About 4 months after her arrival to the US, patient presented for routine outpatient rheumatology follow up where she was found to have fever, significant fatigue, tremors, and headache

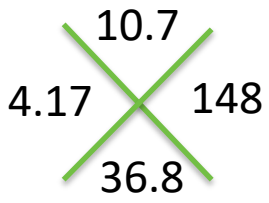
Vital Signs:

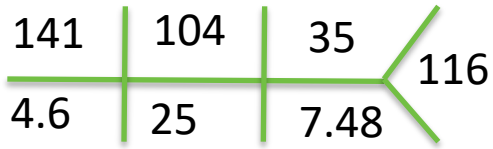
- HR 125
- BP 100/47
- Temp 39 C
- RR 18

Pertinent Physical Exam:

- Alert and oriented
- Normal speech and behavior
- Tachycardia with good peripheral perfusion
- Pain with neck flexion
- Bilateral arm tremor on outstretched hands
- Oral thrush
- L eye opacification (chronic), R pupil reactive

Laboratory studies / workup:





Mg: 2.1
Phos: 3.4
Calcium: 8.4

Neutrophils: 73%
Lymphocytes: 13%
Bands: 7%
Atypical Lymphocytes: 2%
Monocytes: 2%
Eosinophils: 1%
Metamyelocytes: 2%

TSH: 0.24 (low)
Free T4 (normal)

ESR: 7
CRP 0.1
Ferritin: 5968

UA:
SG: 1.018
100 protein
Neg LE
Neg nitrites
5 RBC
3 WBC

AST: 15
ALT: 8
Ammonia 27
Alk Phos: 52
Albumin: 3.3
Bilirubin: 0.4
Fibrinogen: 268

Respiratory PCR: negative

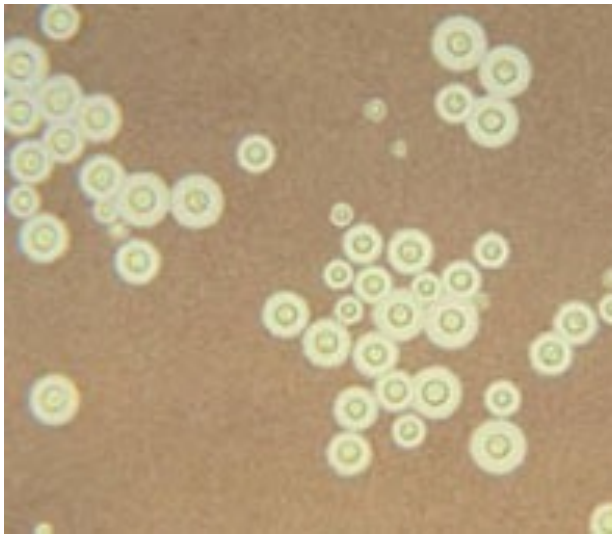
Laboratory studies / workup:

Head CT:

- No new acute intracranial abnormality.

CSF:

- Opening pressure: 16 cmH2O (normal)
- WBC: **99** [0-5]
  - Seg 77%, Lymph 19%, Mono/macrophage: 4%
- RBC: 3 [0-10]
- Protein: **182** [12-36]
- Glucose: **31** [40-70]
- Gram stain: **yeast present**
- Meningitis PCR: **cryptococcus neoformans/gatti**



Hospital Course:

- On admission she was started on empiric vancomycin, ceftriaxone, and acyclovir
- Her vital signs were stable and she had normal mental status
- With results of CSF studies and with the input of infectious disease team, she was started on:
  - Liposomal amphotericin B (5 mg/kg IV)
  - Flucytosine (25 mg/kg PO)

Confusion:

- About 48 hours after initial presentation to rheumatology clinic and shortly after starting antifungal therapy, the patient developed acute altered mental status with:
  - Confusion
  - Auditory hallucinations
  - Vertigo
  - Worsening tremor
  - Inability to follow commands

What is the differential diagnosis for this patient with SLE, cryptococcal meningitis, and altered mental status?

Altered Mental Status: Differential Diagnosis

- Cryptococcal meningoencephalitis
  - *AMS in cryptococcal meningitis is more common with high opening pressure on LP, hydrocephalus, and abnormal brain imaging*
- Brain abscess
- Cerebral edema
- Stroke / cerebrovascular event
- Seizure
- PRES or hypertensive encephalopathy
- Medication side effect
- Hepatic encephalopathy
- Hyperammonemia
- Primary psychiatric illness

Clinical Course

- Repeat Labs:
  - Electrolytes unremarkable
  - Glucose: 109
  - Hemoglobin: 10.4
  - BUN: 54
  - Ammonia: 29
  - AST: 16, ALT: 11

Clinical Course

- Repeat Head CT:
  - No acute intracranial abnormality identified.
- MRI Brain, MRA, MRV:
  - Stable right periatrial T2 hyperintensity without restricted diffusion.
  - Stable cerebral atrophy with ventricular and sulcal prominence.
  - Stable apparent microhemorrhage
  - Normal MRA of the head.
  - Normal MRV of the head.
  - No evidence of optic neuritis.
  - Small, deformed left globe with apparent retinal detachment again seen.
- CTA Head and Neck:
  - No arterial abnormality in the head or neck.

Clinical Course

- EEG:
  - Consistent with **diffuse cerebral dysfunction**. There were no seizures or events of concern.

- Patient was transferred to the PICU for close neurological monitoring with continued altered mental status

- Repeat EEG obtained due to worsening confusion:
  - Consistent with triphasic waves and **moderate diffuse cerebral dysfunction**. This can be seen in the setting of significant renal impairment and medication toxicity, as well as in encephalitis

Clinical Course

- While in the PICU, patient received an additional 3 hour session of hemodialysis with her standard script which included blood flow of 300 mL/min
- Within 10 hours of hemodialysis, patient mental status returned to baseline: she no longer had confusion or hallucinations and she was alert and oriented

Why did this patient have improvement in mental status with hemodialysis?

Dialysis Effects

- Altered mental status treated with dialysis:
  - Ingestion / poisoning
  - Medication effect
  - Uremic encephalopathy
  - Hyperammonemia

Dialysis Effects

- Altered mental status treated with dialysis:
  - Ingestion / poisoning – less likely, occurred during hospitalization
  - **Medication effect**
  - Uremic encephalopathy – inconsistent with labs
  - Hyperammonemia – inconsistent with labs

Clinical Course

- For her cryptococcal meningitis, the patient received **flucytosine**, which has rare CNS side effects including:
  - ataxia, confusion, fatigue, hallucination, headache, paresthesia, parkinsonian-like syndrome, peripheral neuropathy, psychosis, sedation, seizure, vertigo

Clinical Course

- Flucytosine was discontinued and patient started on fluconazole (inferior medication); amphotericin B was continued
- Patient did not have recurrence of altered mental status
- She required prolonged hospitalization for cryptococcal meningitis induction therapy and **clinically improved**

Flucytosine

- Mechanism of action: inhibits fungal DNA, RNA, and protein synthesis
- More than 90% excreted by kidney with prolonged half life in ESKD
- Very little protein binding (3-4%)
- Molecular weight: 129.09 Da
- Volume of distribution: 0.6 L/kg
- Shown to be readily removed with hemodialysis in prior pharmacokinetic studies
- Therapeutic drug monitoring is recommended if available, especially in renal impairment

Principles of Medications Removed by Dialysis

Low molecular weight

Low degree of protein binding

High water solubility

Low volume of distribution

Principles of Medications Removed by Dialysis

- For hemodialysis to be an effective treatment for medication toxicity or overdose, the clearance by dialysis should be higher than the endogenous clearance for that patient
- Hemodialysis is generally more efficient than CRRT at clearing medications, but CRRT can be effective in patients who are not able to receive hemodialysis (ie hemodynamically unstable)

Medication Dosing for Dialysis

- Patients with ESKD are at risk for medication toxicity due to impaired renal function leading to impaired medication clearance
- Medications cleared by hemodialysis require close attention to dosing to maintain optimal drug levels on dialysis and non-dialysis days

Key Points

- The differential for altered mental status in a patient with SLE is broad - workup should include infectious studies and head imaging
- Children with kidney failure are at risk for medication toxicity
- Hemodialysis can be an effective treatment for medication toxicity, poisoning, or overdose and effectiveness depends on multiple characteristics of the medication

Acknowledgements

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Thank You!