Methotrexate Neurotoxicity: An Uncommon Cause of Encephalopathy and Stroke-Like Symptoms in the Pediatric Population

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CASE REPORT
- 13 year old right handed girl with recently diagnosed non-metastatic osteosarcoma of the right femur admitted for high dose methotrexate with leucovorin rescue
- Day 1: received high dose methotrexate- no intrathecal administration
- Day 2: Fever to 39.9 and started on ceftriaxone, delayed methotrexate clearance so fluid rate increased
- Day 3:
  - Persistently febrile, switched to cefepime
  - RRT for fever, tachycardia, tachypnea → diagnosed with non-occlusive pulmonary embolism and started on therapeutic heparin
  - Lower extremity ultrasound showed no DVTs
  - Evening: unstable when walking; “didn’t know what was going on”
- Day 4:
  - Making strange noises “ee”, appeared confused and not understanding what was going on around her
  - Head CT in the morning unremarkable
  - Evening: favoring left hand; grabbing onto rail with left hand, giving high five only with left hand; making strange facial expressions (grimacing, smiling); couldn’t recall who various family members in the room were
  - Developed tachypnea, high fever, hypertension with SBP 135, and hypoxia requiring nasal cannula and then non-rebreather
  - Had delayed methotrexate clearance
  - Exam on evening of Day 4: rarely following commands, exam limited by poor cooperation, unable to name objects or state name or location, no cranial nerve abnormalities, no focal weakness

TREATMENT & OUTCOMES
- No standard therapy other than supportive care
- Dexamethasone (DM), NMDA antagonist
  - In study of 18 patients with sudden onset of neurological impairments after receiving methotrexate
    - Typical dose 1 mg/kg BID for 1-7 days
    - Group A: 8/18 patients received DM >24 hr after symptom onset
    - Group B: 10/18 patients received DM >24 hr from symptom onset

NEUROIMAGING (DWI)
- Symmetric regions of restricted diffusion involving the centrum semiovale, deep white matter, and corpus callosum, with minimal associated T2/FLAIR

Methotrexate Neurotoxicity and Leukoencephalopathy
- Incidence (in patients with ALL) 9%-53%
- Signs/symptoms:
  - Headache
  - Seizures
  - Aphasias
  - Hemiparesis
- Risk factors:
  - High-dose treatment
  - Intrathecal treatment
  - Young age
  - Association with cranial radiation
  - NO relation to 42 hour MTX level as it relates to leucovorin dose
- Onset: 2-14 days after intrathecal, high-dose, or prolonged low-dose methotrexate
- Imaging:
  - T2 hyperintensities in the periventricular white matter, particularly in the centrum semiovale

PROPOSED PATHOGENESIS
- 1) Increased adenosine accumulation
- 2) Elevated homocysteine → excitatory effect on NMDA receptor
- 3) Alterations of biotin metabolism
- 4) Direct neurotoxic effect of methotrexate on cell
- Germine polymorphisms can contribute to methotrexate-induced leukoencephalopathy and neurotoxicity: J. GSTP1, MTHFR, SHMT1

QUESTIONS
- Will she be re-challenged with high dose methotrexate as part of her chemotherapy regimen in the future should it be indicated?
  - No clear contraindications

REFERENCES