

Cooper Citywide Case 1 Encephalitis in a Returning Traveler 5/28/2019

Presented by
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History of the Present Illness

- 26 AAF presents as transfer to CUH on 1/23 for evaluation of encephalopathy and concern for peritoneal carcinomatosis.
- PMH inclusive for IBS and HTN
- Past Social History- US born, from New Jersey, Student, Single, No drugs or alcohol
- Allergies – NKDA
- Medications – None
- Family history – Sister has aggressive breast cancer. Mother had colon cancer.

History of the Present Illness

- On arrival – patient minimally verbal – laying under blankets only stating “I am numb” and “I am cold.”
- History obtained from patient’s mother and limited medical records from China
- Went to China for 14 months (7/17-9/18) on study abroad/teaching English program.
- Health assessment prior to departure was normal
- Prior to this (according to mother, who did not live with her) exhibited bizarre behavior (ex: talking in tongues, religious obsession, “cult-like” behaviors, poor hygiene); impulsive decision to go to China.

History of the Present Illness

- While in China became increasingly paranoid: reporting that her roommate had poisoned her, also reporting that she had been “assaulted”.
- Loosing weight, complaining of abdominal pain
- Towards end of stay in China, locked herself in her room x 5 days (thought someone was trying to assault her), authorities broke door down and transferred her to hospital.
- Diagnosed with a partial bowel obstruction. Concern for malignancy. Surgery recommended, but family brought her home.

脊柱 Spine	normal	四肢 Extremities	normal	神经系统 Nervous system	normal
其它所见 Other abnormal findings					
胸部 X 线检查 Chest X-ray exam.		PPD negative, So no need for CXR		心电图 ECG	N/A
化验室检查 (包括艾滋病、 梅毒血清学诊断) Laboratory exam.		HIV neg Hep C neg RPR neg CBC, chemistries - neg			

身高 Height	5'8"	体重 Weight	220 lbs	血压 Blood pressure	128/90
发育情况 Development	normal	营养情况 Nourishment	normal	颈部 Neck	supple
视力 Vision	左 L 右 R	矫正视力 Corrected vision	左 L 20/20 右 R 20/20	眼 Eyes	no lesions
辨色力 Colour sense	normal	皮肤 Skin	no rashes	淋巴结 Lymph nodes	no lymph nodes
耳 Ears	normal	鼻 Nose	normal	扁桃体 Tonsils	normal
心 Heart	RR & M	肺 Lungs	CXA BL	腹部 Abdomen	soft NT.

History of the Present Illness

- Upon return to US in 9/2018, moved back with father
- Experienced ongoing physical and cognitive decline
- Take to local ED in 11/2018 for increased fatigue, lethargy, significant weight loss, nausea, vomiting, and back pain. Limited evaluation done, discharged from ED.
- Symptoms progressed to include
 - Lower extremity weakness and swelling resulting in being bedbound
 - Ongoing abdominal pain with distention
 - Fevers – symptom that resulted in re-evaluation at ER in January

History of the Present Illness

- On presentation to her local hospital on 1/22/19 she was huddled under blankets, mumbling, and oriented only to person and place.
- On limited exam, **Temp 102° F, HR 110, distended abdomen, 1+ bilateral LE edema. Weight 143 lbs** (~220 lb prior to China)
- Labs done prior to transfer:
 - WBC 6.4, **Hg 10.7**, Plt 322
 - Na 139, K 3.9, Cl 101, HCO 26, BUN 13, Cr 0.4, Ca 8.9
 - Albumin 3.7, AlkP 83, Total Bili: 1.1, **AST 82**, ALT 43, Amylase 64, **Lipase 240, Lactate 2.1** (fell to 1.1 after hydration)
 - HCG neg, Trop <0.012, CK 37, IRN 1.36, Influenza A/B neg
- **CT Chest/Abd/Pelvis:** L > R pleural effusion, Right lung opacities, extensive mediastinal LN, diffuse peritoneal thickening

Exam on Arrival to CUH

- Vitals: BP 128/90, **HR: 145, Temp: 102.4F**, RR: 19, SpO2 99%,
 - Gen App: Well developed AAF, no acute distress, comfortable in bed.
 - Skin: No skin lesions
 - HEENT: Anicteric sclera, OP clear, Moist oral mucosa
 - Neck: supple
 - CV: **Tachycardic**, regular rhythm, no murmur.
 - Resp: **Coarse breath sounds bilaterally**, symmetric chest rise
 - GI: **Diminished bowel sounds, soft, moderately distended**, non-tender.
 - Extremities: **1-2 + bilateral edema.**

Exam on Arrival to CUH

- Neuropsychiatric:
 - Flat affect. Awake, alert, oriented to self and year only. Reported that Barack Obama is the president. Unable to recall recent or remote events. Speech slow, but not dysarthric.
 - Vertical and horizontal nystagmus present
 - Strength: 4/5 upper extremities, 1/5 in lower extremities bilaterally.
 - Reflexes: Symmetric, 2+ b/l upper extremities and 1+ bilateral lower extremities.
 - Sensory exam: Reported decreased sensation in bilateral lower extremities, no sensory level.
 - Coordination: +Dysmetria in bilateral upper extremities. Gait could not be assessed due to lower extremity weakness.

Summary of Presentation to CUH

- 26 year old US born woman returns from 14 months in China, with encephalopathy of ? duration, 80 lb weight loss ?, new onset of fevers, diffuse weakness worse in her legs, and imaging revealing L > R pleural effusion, peritoneal thickening and some ascites, possible brain calcifications

Concerns of Admitting Team/ Differential Diagnosis

Infectious

- Neurosyphilis
- HIV infection
- Tuberculosis
- Cryptococcus
- Toxoplasmosis

vs.

Non-infectious

- Psychiatric diagnosis
- Sarcoidosis
- Malignancy
- Neoplastic syndrome
- Rheumatological disorder

What Next?

Hospital Course

- Started on broad spectrum antibiotics vancomycin, metronidazole, and cefepime – despite this, patient remained febrile for the first 3 days of hospitalization and blood and urine cultures negative .
- Consults placed to Psychiatry, Neurology, Pulmonary, Hematology/Oncology, and Infectious Diseases.
- Request made for imaging of brain, spine, chest, Lumbar puncture, Quantiferon TB gold-Plus
- Placed in airborne isolation, AFB sputum samples ordered

Initial Lab studies

WBC 6.15, **Hg/Hct 9.5/30.7**, Plt 321

Differential: 83.5% PMN, **13.5 bands**, **2.5% lymphs**.

BMP Na 137, K 3.8, Cl 98, CO2 24, BUN 4, Cr 0.33, Ca 8.2.

Mg 1.8

Phos 2.4

Liver Panel – Protein: 7.6, **Albumin 3.1** , Total Bili 0.7, Direct Bili 0.2,
ALT 33, **AST 72**

Lactate – 4.9

PT-INR – 17.4/1.5

HIV 1/2 Ag-Ab assay – Non-reactive

Influenza A+B PCR – Not detected

Additional Lab Studies

Pregnancy test – Negative

Drugs of abuse - Negative

Urinalysis – no abnormalities

TSH 0.20 Free T4 1.2 Free T3 0.9

Ca 6.4 (low) Intact PTH – 157.8 (elevated)

RF factor – negative

CCP Ab IgG – negative

Tumor Markers:

CEA 3.8 (normal)

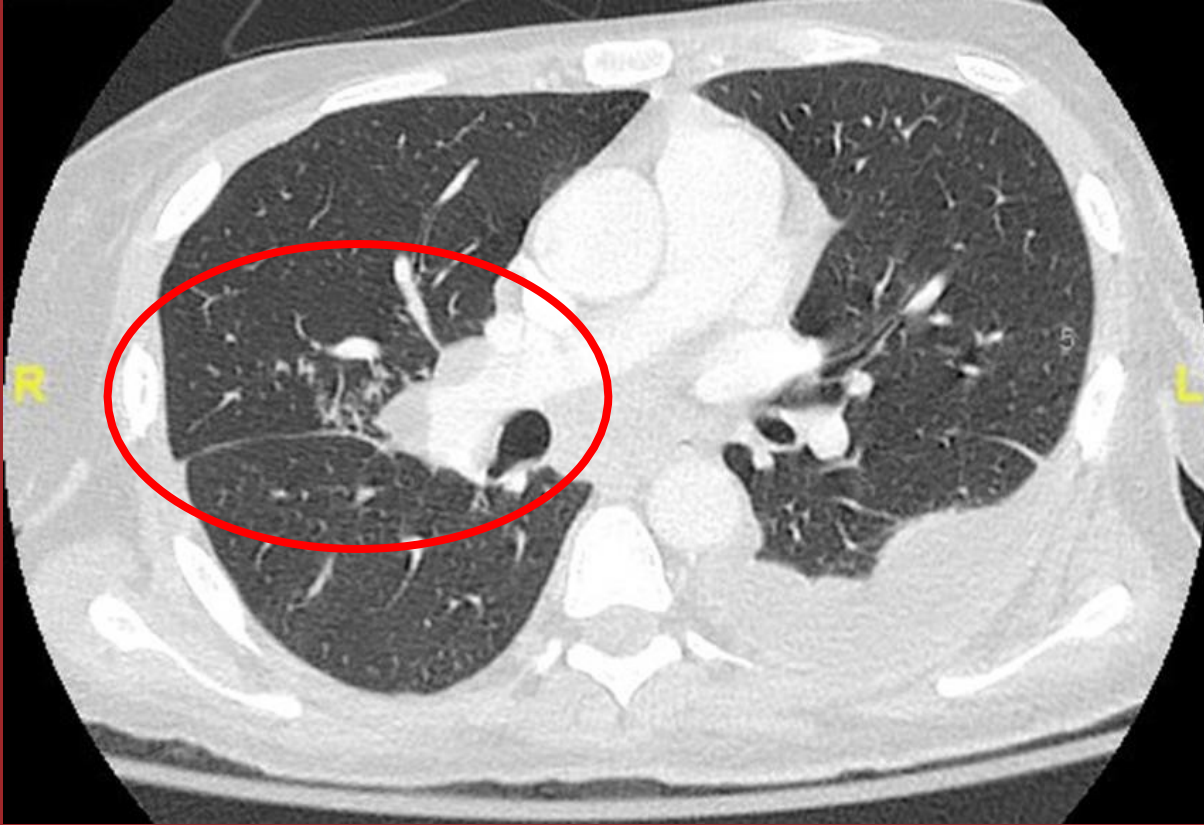
CA 19-9 – 18 (normal)

Quantiferon Gold – “Negative”

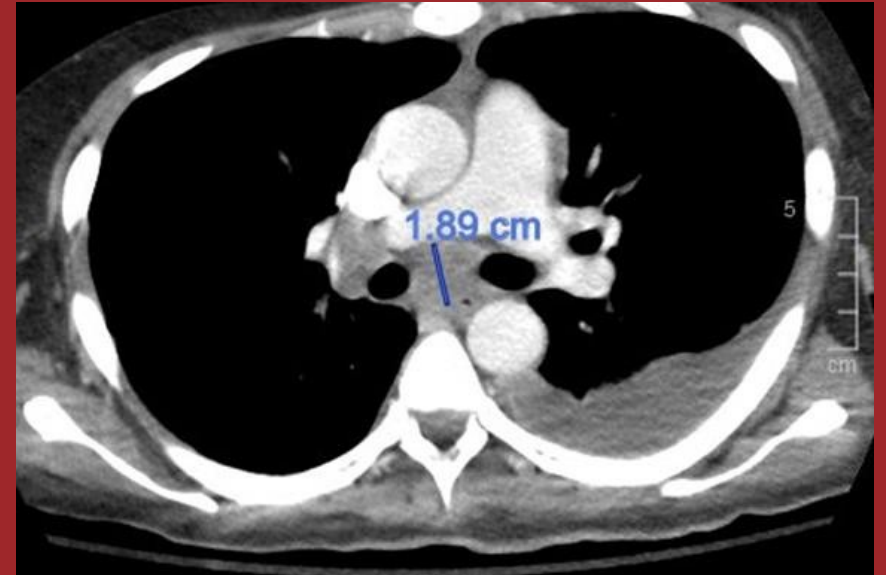
Serum Angiotensin Converting Enzyme 179 (ULN < 50)

Quantiferon - TB	Ref Range & Units NEGATIVE	1/24/19 0718 NEGATIVE
Comment: (NOTE) Negative test result. M. tuberculosis complex infection unlikely.		
NIL	[IU]/mL	1.82
MITOGEN NIL	[IU]/mL	2.23
TB1-NIL	[IU]/mL	0.12
TB2-NIL	SEE COMMENT [IU]/mL	0.22

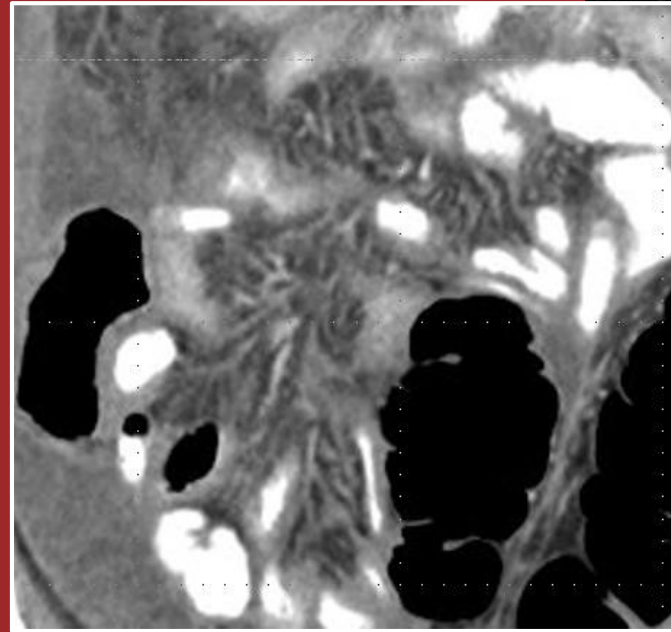
Chest CT Scan with Contrast 1/23



1. Mediastinal lymphadenopathy. Predominantly right sided bronchiolitis including tree-in-bud pattern .
2. Small left partially loculated pleural effusion.



Abdominal Imaging: Ultrasound and CT Scan

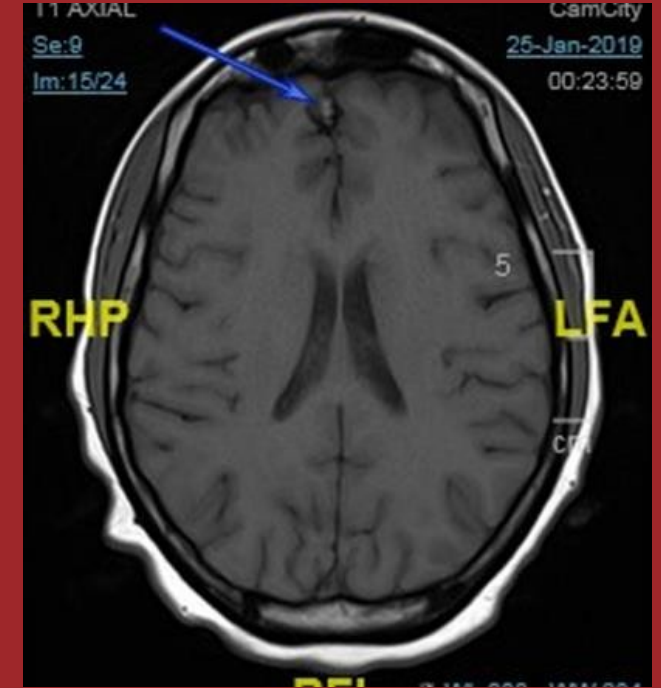
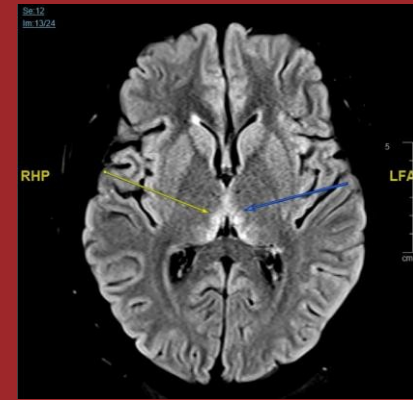
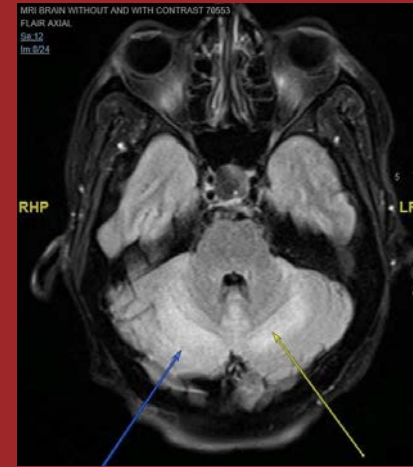
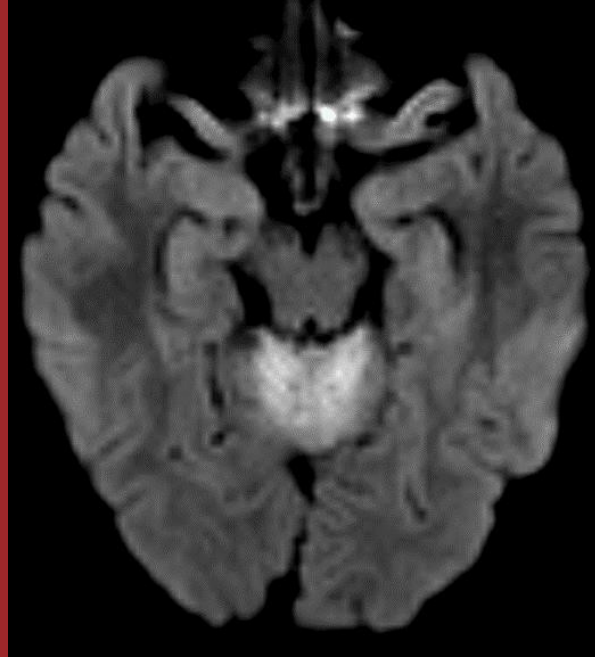
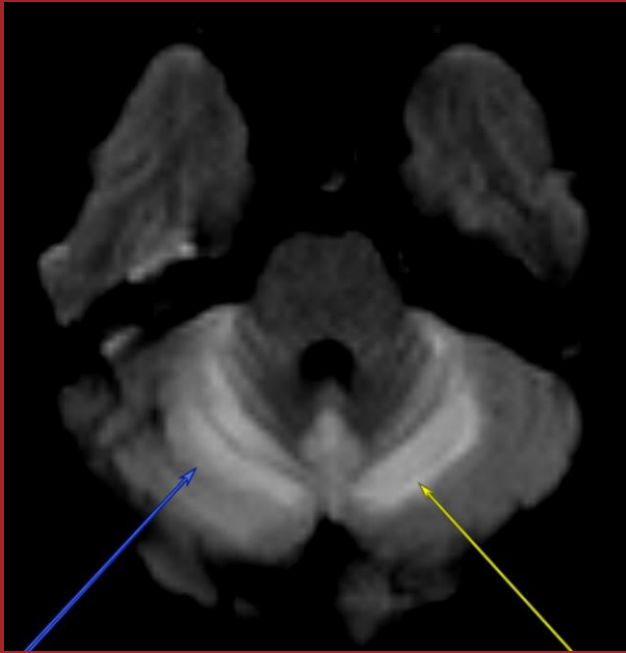


Portable abdominal/pelvic ultrasound
complex ascites with solid-appearing debris or masses

CT Abdomen and Pelvis with IV and PO contrast

1. Hepatomegaly and steatosis.
2. Peritoneal enhancement and complex loculated ascites.

MRI of brain and spine (day 3 1/25)



Diffusion studies

“Consistent with edema in the cerebellum and medial thalami with patchy enhancement of the cerebellar folia and possibly within the internal auditory canals.”

“Two parafalcine lesions without enhancement.” MRI imaging of spine normal.

Lumbar Puncture (day 3 1/25)

SPINAL FLUID, OTHER		
CSF TUBE NUMBER	1 st	4 th
CSF APPEARANCE	CLEAR AND COLO... st	CLEAR AND COLO... st
PROTEIN CSF	31	
CORRECTED NUCLEATE...	2 nd	2 nd
CSF NUCLEATED CELLS	2 nd	2 nd
CSF RBC	7 th ▲	4 th ▲
CSF GLUCOSE	48	

CSF glucose 48, protein 31

CSF Cytology – negative

CSF Angiotensin Converting Enzyme – 6 (normal)

CSF flow cytometry– too few lymphocytes to characterize

CSF bacterial culture – No Growth to date

CSF Fungal culture – No Growth to date

CSF AFB Culture – No Growth to date

CSF MTB PCR: Negative

Paracentesis

Fluid:

HEMATOLOGY/CELLS, ...	
FLUID NUCLEATED CELLS	<i>551</i>
SEG FLUID	<i>1</i>
LYMPHS FLUID	<i>98</i>
OTHER CELLS FLUID	<i>0</i>
NRBC FLUID	<i>0</i>
MESOTHELIAL FLUID	<i>0</i>
MONO/MACROPHAGE FLUID	<i>1</i>
RBC FLUID	<i>35</i>

amylase: 30, protein: 3.8.

Paracentesis cytology – negative for malignant cells, fibrinous material with **mature lymphocytes and scattered histiocytes and mesothelial cells.**

Bronchoscopy 1/25

- Vocal cords normal. No endobronchial lesions seen. Bronchial mucosa appeared normal.
- BAL cloudy, pink fluid along with mucus plugs.

BAL Resp. culture – Acinetobacter calc./Baumannii Complex, few S. aureus
BAL AFB and Fungal Stains negative, Culture NGTD

Lymph Node Culture – Many Acinteobacter, 2 morphologies of S. aureus
Lymph Node AFB and Fungal Stains negative, Culture NGTD

Cytology of LN biopsy – negative for malignant cells, **portion of a single caseating granuloma, special stains for AFB and fungus negative,** immunostain for pancytokeratin negative, CD68 highlights epithelioid histiocytes in the granuloma

Hospital Course (Days 1-7)

- Persistent fevers to 101-102 F despite broad spectrum antibiotics
- Some increasing hypoxia – CT imaging revealed progressive bilateral opacities with stable effusions and lymphadenopathy
- Intermittently following some commands and answering simple questions -> non verbal and exhibited periods of catatonia.
- EEG: no seizure activity, pattern c/wtoxic/metabolic disease
- Not able to eat, Dobhof tube inserted
- Becoming pancytopenic: WBC 1.5, platelets ~80k, Hg 8
- Neurology concerned for paraneoplastic or other autoimmune encephalitis, wants to start pulse steroids/IVIG.

Management Questions at this time:

- What is wrong with this patient?
 - **High possibility of disseminated TB**
- Would you do any other tests or collect other specimens?
 - **Peritoneal biopsy if possible**
- Would you adjust antimicrobial therapy and if so, to what?
 - **On day 8, ID started RIPE plus steroids**
- Would you let neurology start treatment for possible autoimmune encephalitis? (High dose pulse steroids + IVIG or Plasmapheresis)
 - **Yes as we don't feel that full constellation of symptoms can be explained by TB alone**

Clinical Course

- Within 24 hrs, pt experiences improvement in symptoms.
- Over next few days, starts to say more words, answer more questions, exhibit emotion (happy), and coordination also improving.
- Completes course of Pulse steroids, then changed to Dexamethasone initially 8 mg q 6 hrs
- Repeat brain MRI day 4 of TB and steroid therapy:
 - Mild persistent signal abnormality in the cerebellar hemispheres and thalami with **decreasing** enhancement. No new abnormalities seen.

Hospital Course Continued

Bronch BAL LUL TB Xpert® MTB/Rif (resulted hospital Day 11)

<u>Procedure</u>	<u>Result</u>
MTBRIF Source	BAL LUL f
Mycobacterium Tuberculosis by PCR	Not Detected
MTB Rifampin by PCR	Not Applicable
MTB Cmplx Interpretation	Not Detected

Bronch LN Specimin Xpert® MTB/Rif: (resulted hospital Day 11)

<u>Procedure</u>	<u>Result</u>
MTBRIF Source	Lymph Node Asp f
Mycobacterium Tuberculosis by PCR	Detected *
MTB Rifampin by PCR	Not Detected
MTB Cmplx Interpretation	Detected C

Additional Laboratory Studies

- Rheumatologic/Immunologic
- Studies

- ANA screen – negative
- Complement C3, C4 – normal
- ANCA – negative
- Myeloperoxidase Ab < 1.0
- Proteinase 3 Ab < 1.0
- SSA/SSB Ab – Negative
- IGG Subclass 4 normal
- DS DNA Ab negative IgA
- Normal

Cancer Markers

CA-125 elevated at 125 (ULN 35)

**Paraneoplastic Antibody studies
from Serum and CSF**
All Negative except....

VGCC TYPE P/Q AB	<30	<30 pmol/L
VOLTAGE GATED POTASSIUM CHANNEL (VGKC) AB	207 H	<80 pmol/L

Repeat CAT Scans of Chest and Abdomen, Day 15 (Day 9 of steroids/TB therapy)



1. Resolving peritoneal enhancement and infiltration since 1/26/2019. No ascites.
2. Near complete resolution of inflammatory pulmonary opacities and left pleural effusion.
3. Stable mediastinal lymphadenopathy.

Clinical Course

- Completes 5 day course of IVIG
- Receives a second course of methylprednisolone 1 gram daily x 5 days
- Steroids then decreased to Dexamethasone 0.3 mg/kg
- Further improvement in neurologic status, more verbal and interactive, memory remains poor, behavioral outbursts
- Passes swallowing study and able to eat
- Discharged to rehab facility with follow-up in Regional TB Clinic

Updated Microbiology Results

- BAL: AFB positive at 4 weeks for MAC
- LN AFB: Positive for MTB at 4 weeks
- CSF AFB: Finalized negative
- Ascitic Fluid AFB: Positive for MTB at 5 weeks

Discussion

- TB remains the leading infectious cause of death globally though diagnosis remains challenging.
- Gold standard for diagnosis is either isolation of MTB in culture OR detection of MTB-Specific nucleic acids by rapid molecular methods
 - Culture is time-consuming (taking several weeks to months to turn positive)
 - Rapid molecular may not be readily available on site in many hospitals
- Sputum smear microscopy (developed > 100 yrs ago) has low sensitivity ($\leq 50\%$) but remains common practice.
 - Costs less and easy to do.

Discussion

- Based on our patient's risk factors (recent travel to a TB-endemic area and radiological findings) TB was on the differential early.
- While the majority of active TB occurs from reactivation of latent TB, a small portion of patients can experience **primary progressive TB**
 - Our patient's PPD and health assessment prior to departure were negative
 - Risk factors for primary progressive TB include immunosuppression, malnutrition, prolonged steroid usage, and young age.
- In 2017, extrapulmonary TB (EPTB) accounted for less than a quarter of TB cases globally
- Of EPTB manifestations, the most severe is CNS involvement (TB meningitis, intracranial tuberculoma) which accounts for 5 to 10 % of all EPTB and approximately 1% of all TB cases

Discussion

- Could all have this been TB?
 - Investigation was unrevealing for underlying malignancy
- Neurology identified possibility of limbic encephalitis based on patient's neuropsychological exam and MRI findings of edema/hyperintensity in the cerebellum and medial thalami
 - Paraneoplastic panel revealed elevated serum anti voltage-gated potassium channel antibody – suggesting presence of anti-voltage-gated potassium channel autoimmune encephalitis.
 - As a cause of encephalitis, autoimmune causes are uncommon however they show a good response to immune-modulatory treatments such as high-dose steroids, IVIG, plasma exchange, or Rituximab

Discussion

- Could the patient's TB have initiated an autoimmune process?
 - Autoimmune phenomena have been encountered in the TB populations
 - Ability to detect antibodies against granulomatosis with polyangiitis and SLE in TB patients
 - Poncet's disease and uveitis in TB patients, Optic neuritis (Devic's disease)
 - TB and sarcoidosis also appear to be in the same disease spectrum as both are granulomatous diseases.
 - Large cohort study from Taiwan revealed that TB patients had an 8-Fold higher risk of developing sarcoidosis than non-TB subjects – conversely patients with sarcoidosis had a 1.85 fold higher risk of developing TB than non-sarcoid patients.

Take Home Points

- This case emphasizes the importance of having and acting on a high suspicion when dealing with MTB as objective tests are limited by sensitivity and turn-around time and early initiation of empiric therapy is crucial to decreasing mortality and morbidity.
- TB is associated with other autoimmune diseases – must be cognizant of this.
- Our literature review revealed only **three** other published cases of concomitant presentations of TB with autoimmune encephalitis
- No way to tell which one happened first for our patient though
- As diagnosis was made soon after arrival and patient was started on appropriate therapy – her clinical condition improved rapidly – at last outpatient eval on 5/8 - she was walking unassisted and her overall clinical condition continues to improve – may not have happened if treatment was further delayed.

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THANK YOU