Lymphadenitis with persistent pneumonia.

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The case

A 15-month-old Hispanic male who presented with right neck swelling which developed at about 1.5 months was admitted to the Scottish Rite Children Healthcare of Atlanta (CHOA). He was seen in the emergency department (ED) 1 month prior, tested positive for rhino/enterovirus and diagnosed with a viral infection then discharged home. Two weeks prior to admission, the neck swelling became red and bigger.

History and exam

On the day of admission, he had decreased oral intake and increased irritation so he was brought back to the ED. Patient did not have a fever, cough, or congestion. His neck did not have decreased range of movement. He did not have drooling, voice change, or drains.

In the ED, he was found to have a 6x4 cm area of erythema and swelling right sub mandible, with centralized fluctuance, and tenderness to palpation. Otherwise, his neck is supple; trachea is in midline; and the lungs clear to auscultation bilaterally. He received the blood test and he also had neck ultrasound. There was elevation of white blood cell count (WBC) (16.8 K/uL), C-reactive protein (CRP) (7.6 mg/dl), and erythrocyte sedimentation rate (95 mm/hr), microcytic anemia (Hb 8.5 g/dL, Hct 28.8 %, MCV 63 fL, MCH 19 pg, MCHC 31%) and abscess on imaging.

Patient received a dose of clindamycin and was admitted for incision and drain (I&D).

In addition, patient was admitted 2 months earlier for 2 days with left upper lobe (LUL) pneumonia diagnosis (**Figure 1**). He was treated with 1 dose of 50 mg/kg of ceftriaxone IV and was discharged on oral amoxicillin 100 mg/kg/day divided 3 times a day for 6 days. One month ago, he had a chest x-ray (CXR) at the first visit for the neck swelling complaint, which showed persistent opacification of the LUL. A CXR was repeated on this admission.

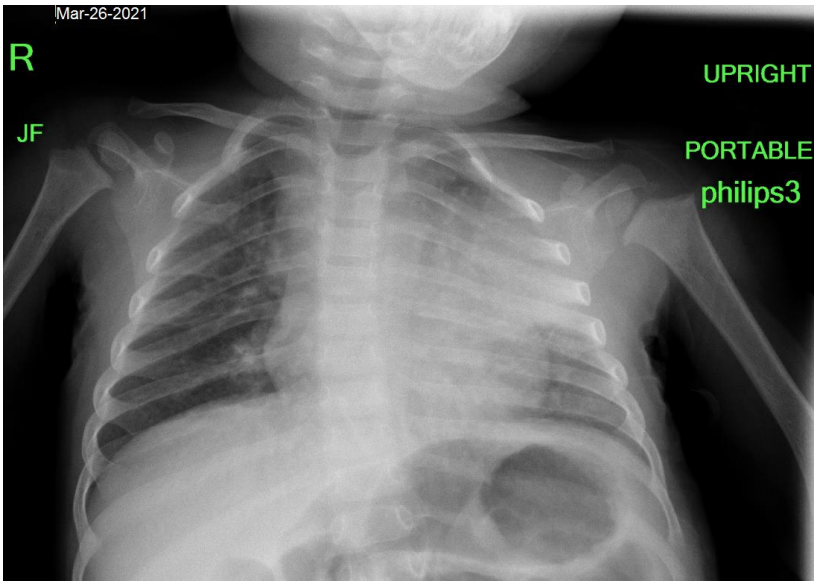


Figure 1: CXR 2 months prior to this admission.

The patient was up-to-date on vaccinations. He did not have allergies and lived with parents, 3 siblings (twin 6-year-old older sister and brother, and one younger brother), and maternal aunt. He stayed at home, and did not have cat exposure or travel in the past 6 months.

He crawled at around 6 months of age and was pulling to stand around 9 months of age. He recently refused to stand. Patient received formula as an infant then transitioned to whole milk. The family speaks Spanish. The hospital used an in-person interpreter for patient care.

Hospital course

Patient was diagnosed with abscess lymphadenitis, most likely *Staphylococcus* or *Streptococcus* infection. The differential diagnosis included tuberculosis (TB) or other mycobacterium infections based on the duration of swelling, lack of fever, and recent pneumonia. Other diagnoses to consider include infection of congenital abnormality such as brachial cyst.

Incision and drainage procedure was done by otolaryngology with empiric clindamycin and acetaminophen, ibuprofen for pain control. The purulent discharge was collected for aerobic and anaerobic culture, fungal culture, and acid-fast bacillus (AFB) testing.

He also received an oral iron supplement (ferrous sulfate 6 mg/kg/day) for 3 months for anemia likely iron deficiency.

At admission, CXR was ordered to follow up on persistent LUL opacity. Radiology revealed LUL consolidation (**Figures 2 and 3**).

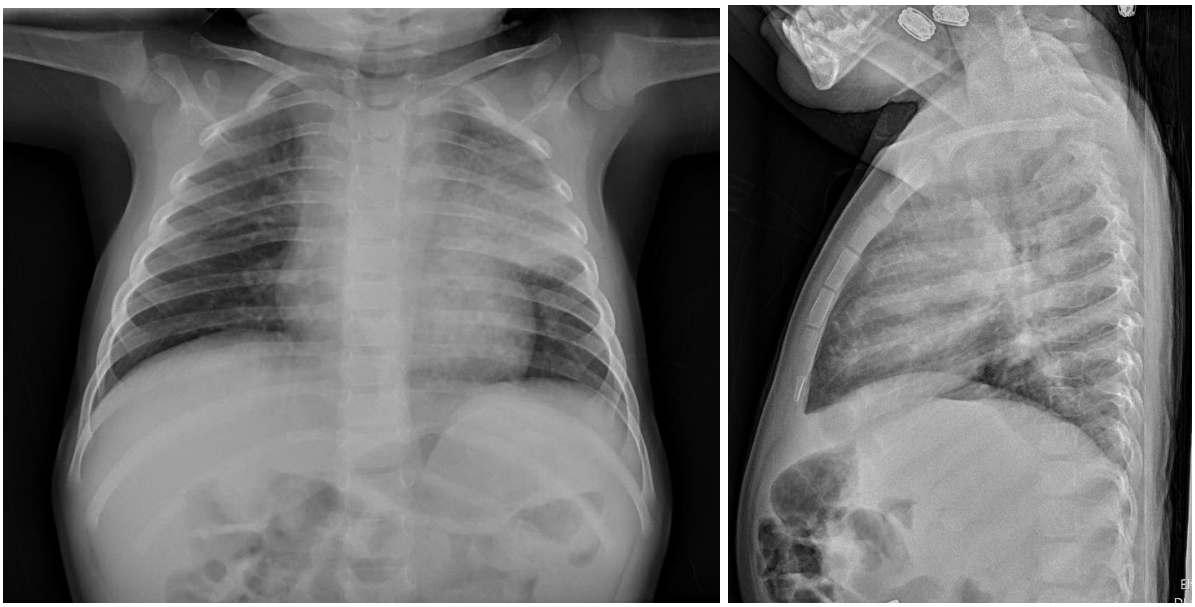


Figure 2 and 3: CXR at the admission

Diagnosis

Given the persistent upper lung infiltrate, differential diagnosis included tuberculosis, congenital pulmonary malformation, foreign body aspiration, or malignancy. We consulted a pulmonologist who recommended a chest computed tomography (CT) scan as it was uncommon for community pneumonia to persist over 2 months.

A chest CT scan was highly concerning for tuberculosis with calcifications in lung parenchyma and media sternal lymphadenopathy (**Figures 4-7**). With tuberculosis suspicion**,** infectious disease (ID) was consulted for to assist with work up and antimicrobial management.

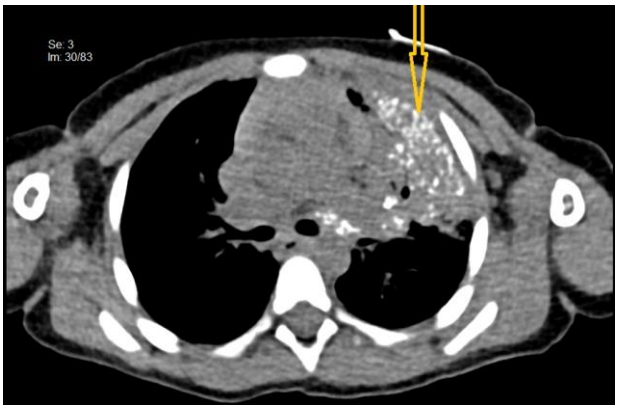


Figure 4: Military calcifications in the LUL and lingual.

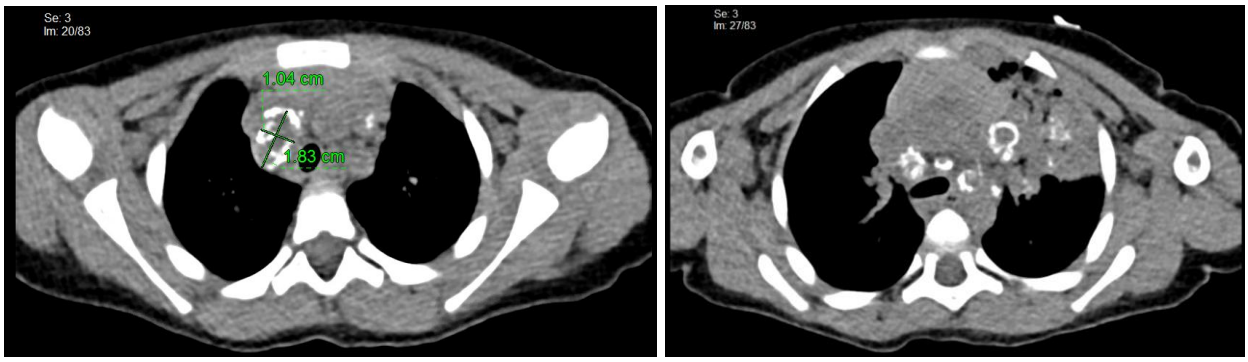


Figure 5, 6: Multiple rim calcified lymph nodes in the mediastinum and hilum

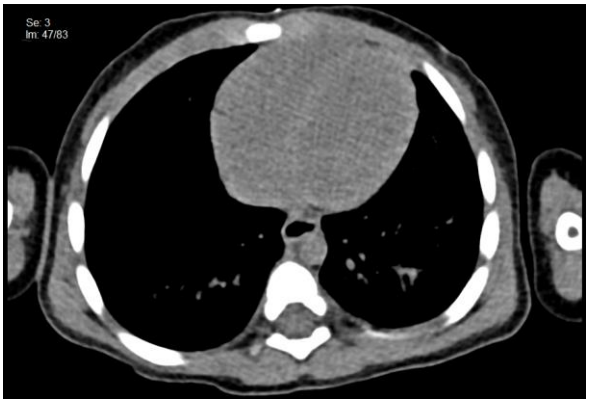


Figure 7: Diffuse soft tissue density nodules seen throughout the lung parenchyma.

An ID specialist was consulted. The differential diagnosis was most concerning for TB or nontuberculous mycobacteria that can cause pulmonary disease resembling tuberculosis, lymphadenitis, skin disease, or disseminated disease. Other considerations, although less likely given overall duration of symptoms and lack of fevers, were thought such as Cat Scratch Disease, persistent/partially treated Group A Streptococcus infection or *Staphylococcus aureus* infection, or Kikuchi disease.

Given that TB was highest on differential list in patient's age, the ID team recommended a complete work up (**Table 1**) and isolation was placed with airborne precautions.

Quantiferon TB Gold

Tuberculin Skin Test (TST)

Place nasogastric tube to obtain 3 gastric aspirates for AFB culture and at least one for Mycobacterium tuberculosis (MTB) PCR (ideally early morning when patient is still asleep, at least 6 hours from last meal)

To rule out central nervous system (CNS) TB given age
- Brain MRI under general anesthesia
- Lumbar puncture with craniospinal fluid (CSF) cell counts, protein/glucose and AFB culture

To concern of TB dissemination
- MRI whole body

To rule out bone TB given patient could not bear weight
- Spine and pelvic XR

To rule out immunodeficiency in a disseminated TB
- HIV Screen

Table 1: Diagnostic TB test for the patient

In addition to a tuberculosis-diagnosis test, complete blood count and CRP were repeated to monitor his lymphadenitis treatment. Both WBC and CRP improved. His hemoglobin slightly increased. Below is comparison chart based on hospital day (HD) (**Table 2**)

Component	HD1	HD4	Unit
WBC	15.75	10.86	K/uL
HGB	8.5*	8.7*	g/dL
HCT	28.8*	29.8*	%
MCV	61.0*	62.2*	fL
PLATELET COUNT	655*	513*	K/uL
AUTOMATED ABS NEUT	7.66	3.39	K/uL
C-REACTIVE PROTEIN	7.6*	2.5*	Mg/dL

Table 2: Comparison chart based on hospital day for CBC, CRP

Result of his HIV and CSF test are listed following (Table 3).

	Value	Ref Range
HIV-1 p24 Ag with HIV-1,2 Ab	Non-reactive	Non-reactive
CSF Cell Count/Diff		
Appearance CSF	Clear	
Color CSF	Colorless	
Xanthochromia	Negative	Negative
WBC CSF	1	0 - 20 /UL
RBC CSF	0	0 - 10 /UL
Glucose CSF	52	40 - 70 mg/dL
Protein CSF	24	15 - 45 mg/dL

Table 3: Lab results (HIV and CSF)

MRI Brain revealed tuberculous pachymeningitis/ leptomeningitis (Figure 8-11)

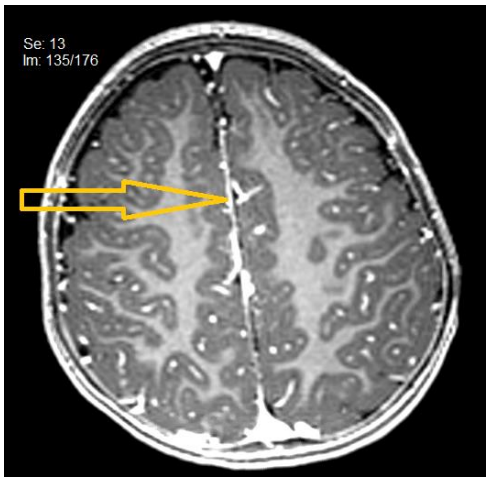


Figure 8:
Multifocal nodular thickening and enhancement involving the falx cerebri.

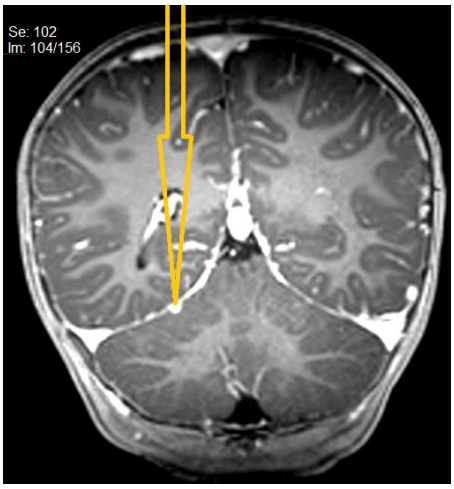


Figure 9:
Bilateral cerebellar, tentorial leaflets.

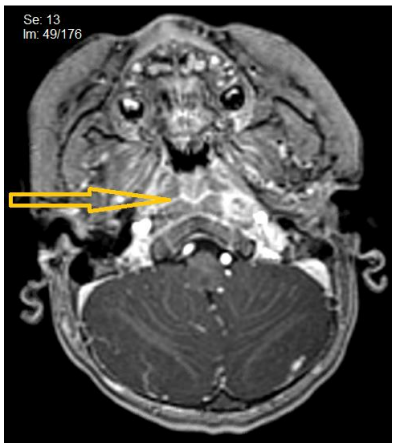


Figure 10: Left posterolateral cerebellar hemisphere folia.

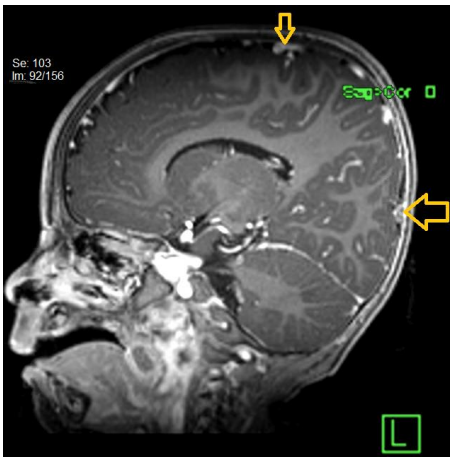


Figure 11: Bilateral pachymeninges /leptomeninges.

Spine and pelvis XR suspicious for sacroiliitis.

A magnetic resonance imaging scan (MRI) of the whole body revealed necrotic bilateral cervical adenopathy and upper mediastinum; right sacroiliitis with abscess formation and regional myositis; and splenomegaly.

Quantiferon (IGRA) result is listed in **Table 4.**

Component	Result	Ref. Range
QuantiFERON TB Gold Plus	Positive (A)	Negative
QuantiFERON TB1 minus NIL	1.14 (H)	0.00 - 0.34 IU/mL
QuantiFERON TB2 minus NIL	1.37 (H)	0.00 - 0.34 IU/mL
QuantiFERON Mitogen minus NIL	1.66	IU/mL
QuantiFERON NIL	0.21	IU/mL

Table 4: Quantiferon result

Tuberculin skin testing (TST) induration was 15 mm (**Figure 12**). The result (Table 4) was positive because of the induration > 5 mm in a patient who had close contact with known contagious people with TB disease (his maternal aunt; findings on CXR consistent with active or previous TB disease; and clinical evidence of TB disease (lymphadenitis, pneumonia). [1]

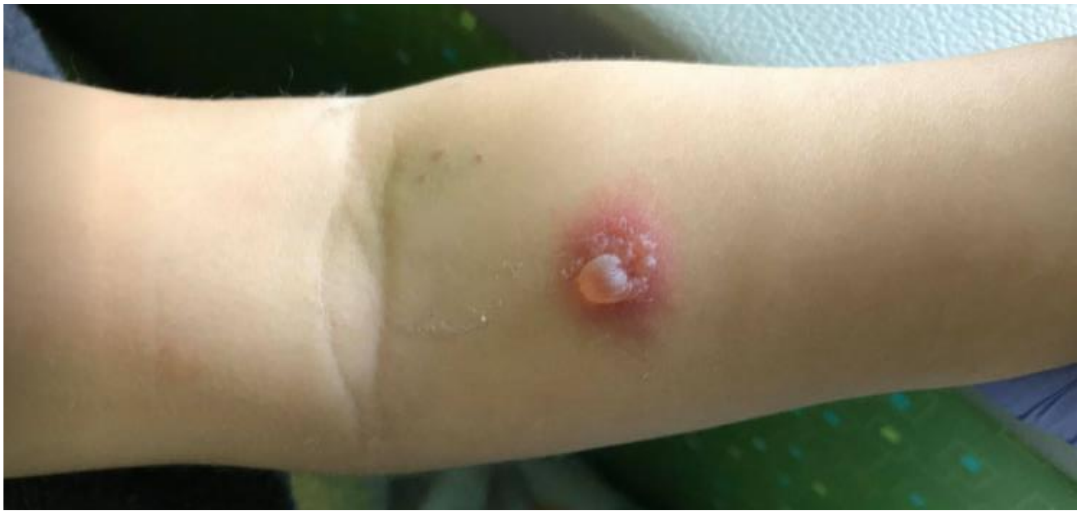


Figure 12: TST at 48 hour, 15 mm duration (not measure erythema or blister)

On hospital day 5

A detailed family and exposure history was obtained again with a Spanish interpreter.

The mother and her sister were born in Guatemala and moved to the United States 5 years ago. When mom moved to the United States, she had a negative test for TB. The mother had recently visited Guatemala 2 years ago before the patient's birth with her twin children. The father was born in the United States, but his family is historically from Guatemala. The patient was born and has stayed in the United States.

Although the parents denied any family history of TB multiple times, we called and found information from the State Department of Health (DOH) that 6 months prior to patient's admission, the aunt was diagnosed with active TB and she had finished 3

months of treatment. The parents did not understand this was a TB infection. At that time, the whole family were tested for TB. The mother had positive interferon-gamma release assay (IGRA), negative CXR. She was pregnant with the patient's younger brother at the time and was recommended to have TB treatment postpartum. However, the mother has not received treatment yet. The father had a negative IGRA. The older sister had a negative IGRA and negative CXR. The older brother had a diagnosis of latent TB and completed 3-month treatment. The patient had a negative IGRA, negative TST, but a CXR with a large dense opacity in the left middle lobe, which was concerning for an enlarged thymus. He was asymptomatic at the time. The DOH were not informed of the patient's pneumonia diagnosis from 2 months prior.

This time, the DOH recommended tests for the family again. The mother had a repeat CXR. The father received another IGRA and repeated CXR. The older sister was retested for IGRA and was given a repeat CXR. The older brother and the aunt did not need require any testing unless they had any symptoms.

Discussion

TB disease is caused by the organisms of the *Mycobacterium tuberculosis* complex[1]. The discussion focuses on the diagnosis test for TB in children and adolescence in the United States.

Almost 80% of childhood TB disease in the United States is associated with some form of foreign contact for the child, parent, or other ousehold member[1]. This patient lived with Spanish-speaking family members who had recently immigrated to the United States. His presumed infectious source was his aunt. Two months ago, TB-exposure information was missed which led to diagnose of community pneumonia, in part because CXR findings are rarely specific for TB.[1] In this admission, initially, lymphadenitis was considered due to common pathogen (*streptococcus* or *staphylococcus*). The missing information might cause by parents understanding about TB and language barriers. I believe this language barrier could happen in many TB cases as more than 87% of reported TB cases in the United States occur in Hispanic and non-White people.[1] Luckily, the TB control system of DOH has traced cases and reported clinicians.

Below is indication for TB diagnosis test (TST or IGRA) in infants, children, and adolescents in the United States (Table 5) [1, 3]

Children for whom **immediate TST or IGRA** is indicated (such as patient and his siblings)

- Contacts of people with confirmed or suspected contagious tuberculosis
- Children with radiographic or clinical findings suggesting tuberculosis disease
- Children immigrating from countries with endemic infection
- Children with history of significant travel to countries with endemic infection who have substantial contact with the resident population

Children who should have **annual TST or IGRA**

- Children living with HIV infection

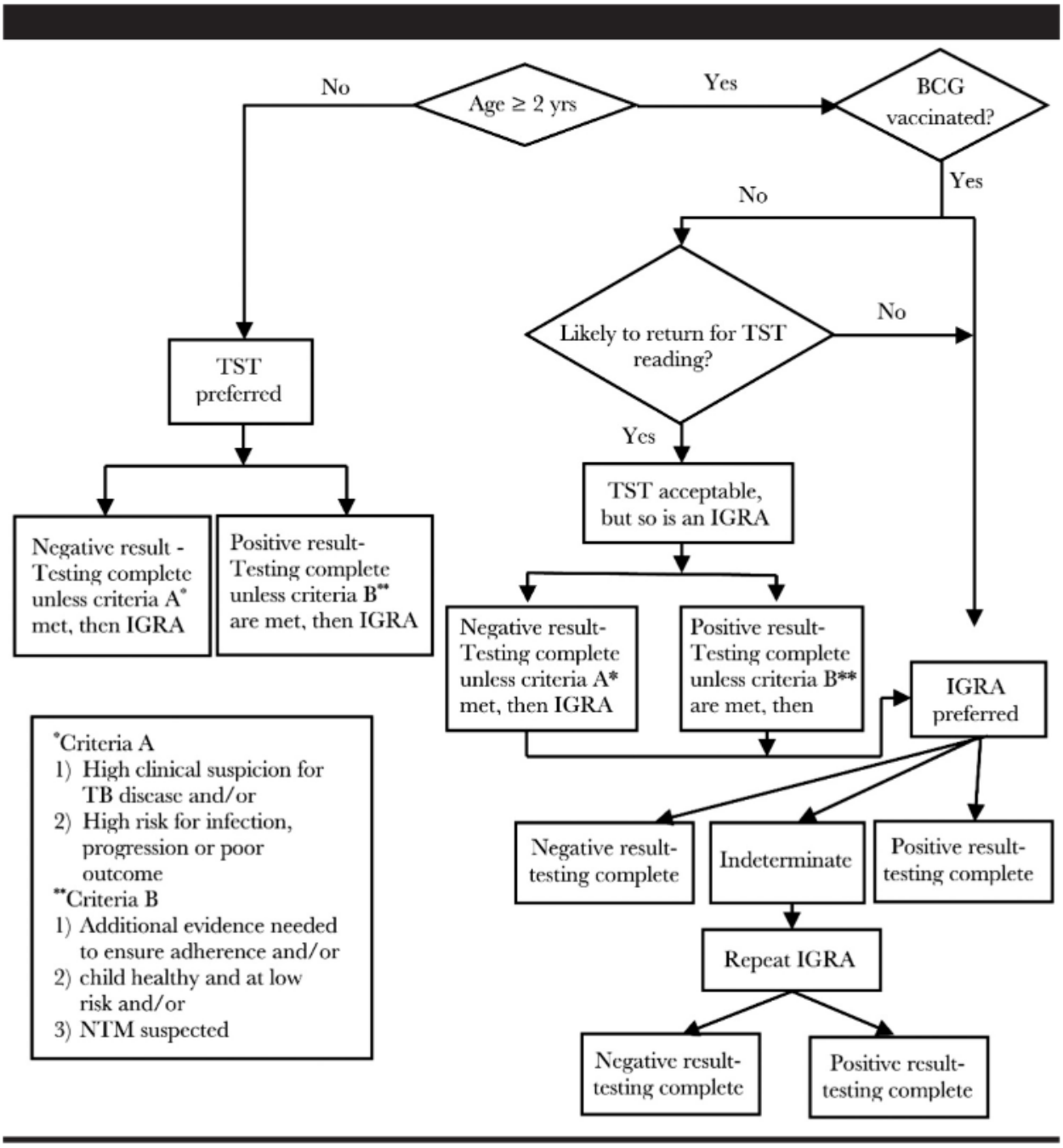
Children at increased risk of progression of TBI to TB disease

- Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immunodeficiency, and children receiving tumor necrosis factor (TNF) antagonists, deserve special consideration.

Table 5: Diagnosis test (TST or IGRA) is recommended for Infants, Children, and Adolescents in the US

Choosing TST or IGRA depends on the patient's age (younger or older than 2 years of age, BCG vaccinated status and ability to return for TST reading). Depending on the results (positive or negative) of TST or IGRA, further steps will be needed to confirm TB. Below is the guideline for use of TST and IGRA (Figure 13).

Figure 13: Guidance on strategy for use of TST and IGRA for diagnosis of TBI in children with at least 1 risk factor, by age and BCG immunization status of Red Book – AAP [1]



Laboratory Confirmation of M tuberculosis[1,2,3]

Specimen of sputum, gastric aspirate, bronchial washing, pleural fluid, cerebrospinal fluid (CSF), urine, or other body fluid or a tissue biopsy specimen will culture for *M tuberculosis*. Positive results from nucleic acid amplification tests (NAATs) are considered confirmatory, but culture isolation of the organism is still required, especially for detection of drug-resistant genes. Because *M tuberculosis* complex organisms are

slow growing, detection of these organisms may take as long as 6 weeks using liquid media.

Laboratory for disseminated TB[1,2,3]
This depends on symptoms to guide further tests to find disseminated locations. This patient initially had CXR and a chest CT scan based on his primary lesion. Lungs are the most common lesion location of TB.[3] He also had a brain MRI, whole body MRI, and pelvic and hip x-ray to find disseminated TB. The result showed TB had occurred in the central nervous system (pachymeningitis, leptomeningitis), joints (sacroiliitis), and muscles (myositis).

Management

The patient received disseminated TB treatment with 4 antibiotics (RIP therapy: rifampin, INH- Isoniazid, pyrazinamide and amikacin) and steroids (Table 6). The patient had stable renal function (serum Creatinine 0.28 mg/dl), which allowed him to start on amikacin 20mg/kg/dose IV Q24h. The pharmacist monitored the pharmacokinetics of amikacin at 2h, 6h to monitor area under the curve, and calculated peak which both within desired range for treatment of tuberculosis. Clindamycin was stopped after a 5-day treatment.

Antibiotics:
Rifampin 20 mg/kg Q24h
Isoniazid 15 mg/kg Q24h
Pyrazinamide 35 mg/kg Q24h
Amikacin 20 mg/kg Q24h

TB Meningitis Management:
Prednisolone 2 mg/kg Q24h

Table 6: RIP therapy and amikacin, steroid.

The records of the aunt who was treated for active TB were obtained. If her patient cultures are negative, the drug susceptibility for isolates from her (presumed source) can guide decisions about his treatment.

Discharge

On HD 8, the patient was discharged. He received directly observed therapy (DOT) with local DOH. A prescription was prescribed for a 1 month supply (RIP, Prednisolone and Vitamin B6, iron supplement) as requested per DOH. The case manager applied for preauthorization and found a compound pharmacy to provide medication at home for the patient. The family received pharmacy education by pharmacist for RIP therapy

(reason for the medication, how to give it, when to give it and common side effects). Medical items were provided including syringes to give liquid medicine and a pill cutter to cut Vitamin B6. The parents were able to demonstrate the medication use. All information was translated to Spanish.

A discharge summary was faxed to the local DOH. A referral to physical therapy and Baby Can't Wait (the Georgia early intervention program) were provided for his motor delay.

Follow-up

The patient followed up with a primary care pediatrician (PCP) for anemia and an ID clinic for his TB. A sign-out call was given in detail to the patient's PCP. The ID team reached out to DOH to make sure he had follow-up in place.

His first follow-up 1 month after discharge with the ID team showed improvement. He was asymptomatic, gaining weight, and had no side effects from his medications.

Microbiology results showed in Table 7

MTB by PCR (gastric): detected. MTB Rifampin by PCR: not detected. MTB Complex Interp: detected. 1st, 2nd, 3RD gastric aspirate, and CSF: AFB Stain: No AFB seen. Culture: No AFB isolated at 6 weeks. Wound on Right Neck Tissue, Excision: - Necrotizing granulomatous inflammation - Focal, equivocal immune histochemical staining for mycobacteria

Table 7: Microbiology results returned after discharge

The family members were give follow-up screening tests, which found:

- The mother had a normal CXR and she remained asymptomatic.
- Father has a negative IGRA, normal CXR, and was asymptomatic.
- The older sister had a negative IGRA, negative CXR, and was asymptomatic.
- The 2-month-old younger brother was admitted for TB screening, including TST (negative), CXR (no signs of infiltration), Quantiferon TB (negative), nasogastric tube for gastric lavage x 3 days (all negative for AFB stain and culture). Due to close TB exposure, he received isoniazid prophylaxis for 6 months per DOH guidelines as most infections caused by *M tuberculosis* complex in children and adolescents are asymptomatic.[1] After 6 months of prophylaxis, he will repeat TST and Quantiferon.

Reference:

1. Kimberlin DW, Brady MT, Jackson MA, et al. *Tuberculosis*. In: Red Book: 2018 Report of the Committee of Infectious Disease. 31st ed. American Academy of Pediatrics; 2018:829-853.

2. Nolt D, Starke JR. Clinical report: tuberculosis infection in children and adolescents: testing and treatment. *Pediatrics.* 2021;148(6): e2021054663.doi.org/10.1542/peds.2021-054663

3. Centers for Disease Control and Prevention. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection—United States. Castro KG, Goldberg S, Jereb J, et al. Updated guidelines for using interferon gamma release assays to detect Mycobacterium tuberculosis infection—United States, 2010. In: *MMWR Recomm Rep*. 2010;59:1-26.