All in the Family

Elizabeth Ann Misch, MD
Associate Professor
Division of Infectious Diseases, Department of Medicine
University of Wisconsin School of Medicine and Public Health

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN–MADISON

- 52-year old male, born in Laos with history of coronary artery disease, diabetes, and prior salmonella sepsis
- presented to ED in January 2022 with **left-sided chest pain, shortness of breath beginning that morning and rash on neck.** Also noted **cough.**
- Vitals: Temp 36.4C, pulse 72, RR 21, BP 110/69. O2 saturation: 96%, room air. Weight 77.1 kg, BMI 29.2
- **Exam:**
  - Tender over the left chest wall reproducing his symptoms.
  - Abdomen: soft and non-tender, no rebound or guarding

    ….

- Skin: Warm and pink. Erythematous, nontender, blanching, non-petechial rash extending from scalp down to neck and chest and mid abdomen, becoming scattered over arms and lower abdomen

---

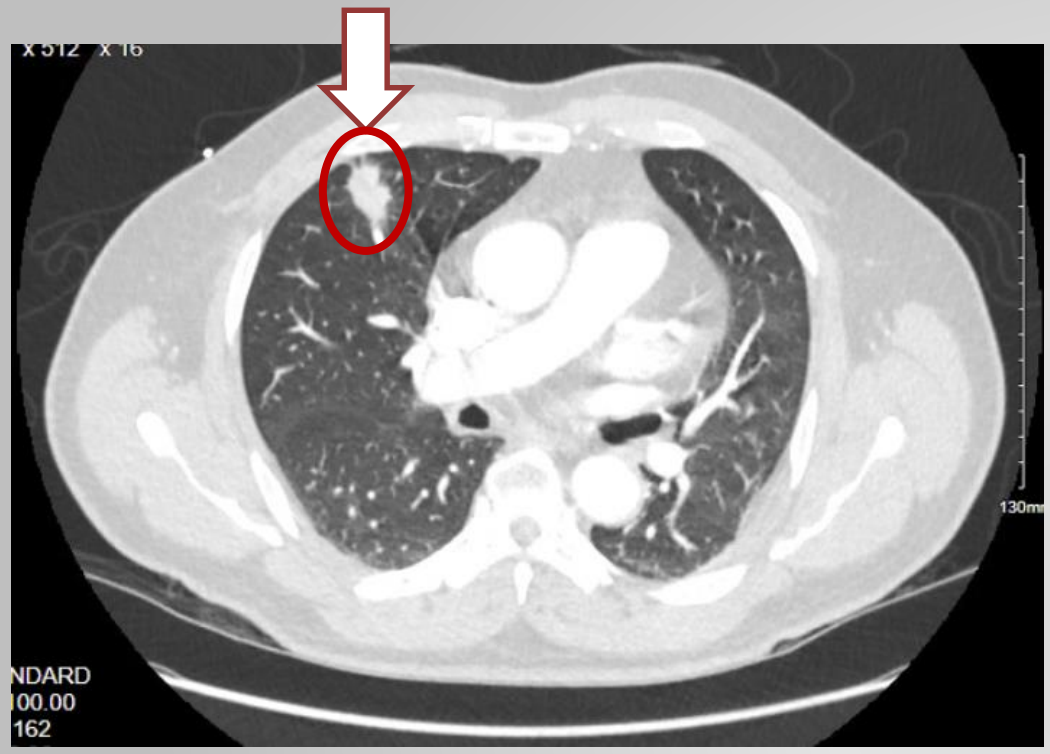
- WBC 22.0, hgb 11.9, plts 275K; alkaline phosphatase 290, ALT 54
- Procalcitonin: 0.31 ng/mL
- D-dimer: 2.11
- Swab positive for COVID-19 (PCR)
- U/A unremarkable, blood cultures obtained

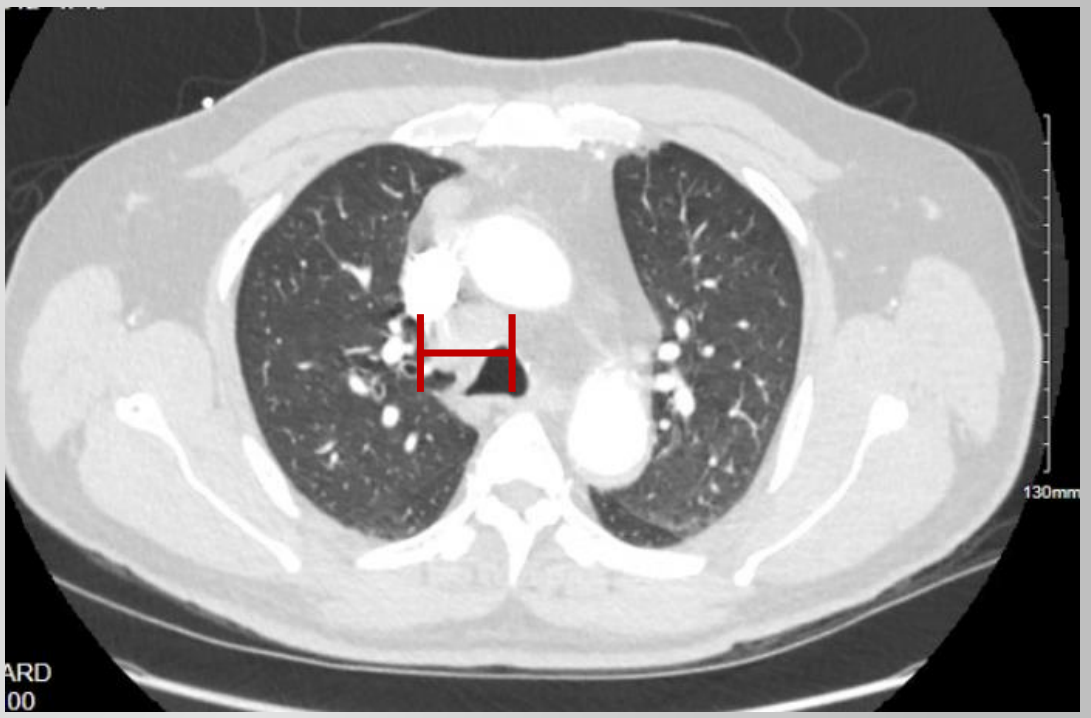
- CT of chest to rule out pulmonary embolus:
  - no Pulmonary embolus
  - spiculated right upper lobe mass and mediastinal lymphadenopathy
  - compatible with primary lung cancer

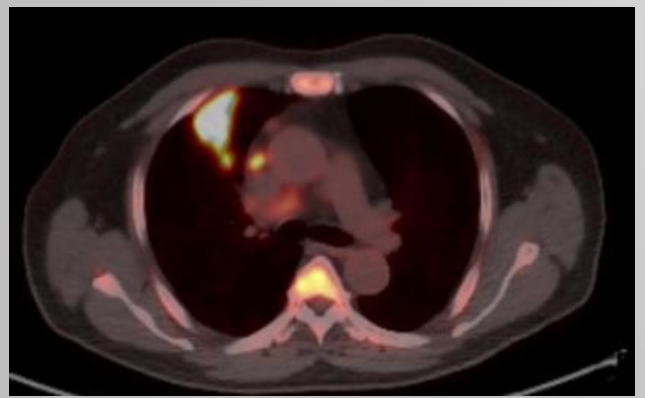
- 01/17/2022 CT abdomen pelvis showed retroperitoneal lymphadenopathy along with small soft tissue implants within splenic hilum measuring up to 1.4 cm.

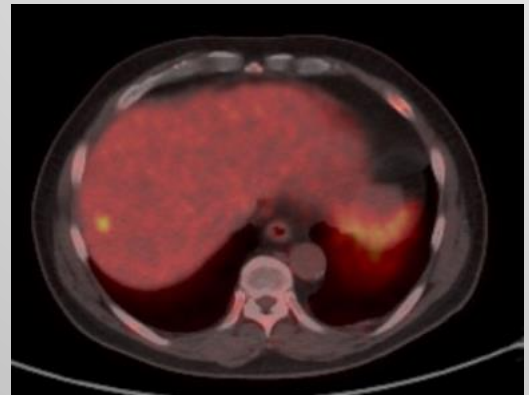
- Discharged home and referred to oncology for presumed underlying lymphoproliferative disorder

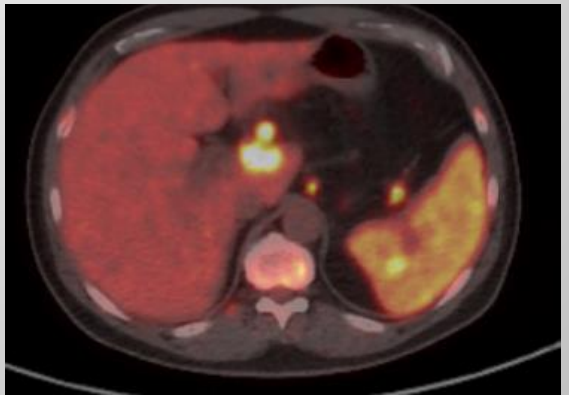
- **PET CT 3.5 weeks later:**
  - **intense uptake within the spiculated right upper lobe mass** suspicious for malignancy.
  - **uptake in R neck, mediastinal, right axillary, liver, spleen, bones, and abdominal/pelvic lymph nodes** suggestive of malignancy (nodal metastases from lung cancer and/or lymphoproliferative disorder like lymphoma.

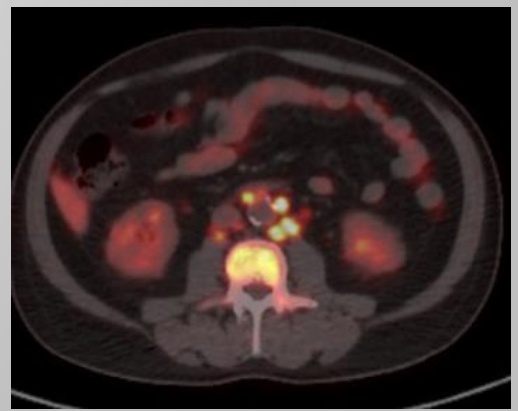

130mm


130mm









Past medical history

- Salmonella septicemia
- acalculous cholecystitis
- renal failure, on hemodialysis
- Alcoholic liver disease
- Congestive heart failure
- Hyerlipidemia
- Type 2 diabetes
- Latent TB infection, INH in 1990s

Cont’d

- hypertension
- Gout
- Gout
- Former smoker
- Cholecystitis
- CAD/ST elevation MI, s/p stentsplaced August of 2014
- Knee surgery

Biopsy of supraclavicular lymph node 7 days later

- Pathology of LN biopsy
  - **no malignancy**
  - **non-necrotizing granulomas with many** AFB+ organisms
  - *"consistent with mycobacterial lymphadenitis"*
  - no AFB culture done (entire sample dropped in formalin)

Admitted for Lung biopsy 13 days later

Evolution of Systems:

- Poor appetite since having COVID-19
- 30-lb unintentional weight loss
- Fatigue
- Cough productive of brown-to-red sputum
- Dyspnea on exertion
- Chest pain
- Fevers
- Headache and back pain

Family History

- Daughter: asthma
- Mother: DM2
- Father: gout, stroke
- Brother (s): lung cancer, diabetes, liver and kidney problems

Social History

- Born in Laos
- quit smoking about 7 years ago; 13.00 pack-year smoking history.
- alcohol use
- No particular exposures
- no recent travel to Laos or elsewhere

Physical exam

Temp 36.3 C (97.4F), Resp 18, Pulse 101, BP 114/74, SpO2 97%

- non-toxic appearance.
- normal exam

Labs

- WBC 19,000 (neutrophils: 16K), platelets 60,000
- Creat 1.5. Alkaline Phosphatase 574. ALT 49.
- Quantiferon gold: indeterminate
- HIV testing: negative
- CSF: 121 wbc (95% lymphs), 0 rbc, protein 28, glucose 48.

Peripheral blood, bone marrow aspirate, and biopsy:

- Peripheral blood: anemia, thrombocytopenia and neutrophilia.
- **Bone marrow aspirate and biopsy**: Hypercellular marrow showing trilineage hematopoiesis with **scattered granulomas**, AFB negative. No evidence of metastasis or lymphoproliferative disorder.

Lung biopsy

- **AFB** smear **positive.**
- PCR negative for M. tuberculosis.
- PCR positive for **Mycobacterium avium**

- **Pathology: Granulomatous inflammation containing numerous acid fast bacilli.** *numerous acid-fast mycobacterial organisms within histiocytes.*

AFB cultures of various tissue compartments

1. **Bone marrow**: *Mycobacterium avium* (AFB neg)
2. **Bronchoalveolar** lavage: *Mycobacterium avium* (AFB+)
3. **Lung** biopsy: *Mycobacterium avium* (AFB+)
4. **Blood**: *Mycobacterium avium*
5. Urine: *Mycobacterium avium*
6. **CSF:** negative

DIAGNOSIS

1. **Disseminated *Mycobacterium avium* complex** (“MAC”)
2. **Ostensibly immune competent host** ***… or NOT??***

Broad immunodeficiency workup:

1. Absolute CD4: 244 L (430 - 1800 cells/uL)
2. HIV 4th gen assay: neg
3. Immunoglobulins: nml

ABSOLUTE LYMPHOCYTES	**647**	LOW	**1000 - 3500 /uL**
CD3+ PERIPHERAL T CELL	**53**	LOW	**56 - 84 %**
CD3+CD4+ T HELPER CELL	**34**	normal	**31 - 64 %**
CD3+CD8+ T CYTOTOXIC/SUPRESSOR CELL	**18**	normal	**9 - 39 %**
ABSOLUTE CD3+	**345**	LOW	**840 - 2669 /uL**
ABSOLUTE CD4+	**219**	LOW	**488 - 1734 /uL**
ABSOLUTE CD8+	**115**	LOW	**154 - 1097 /uL**

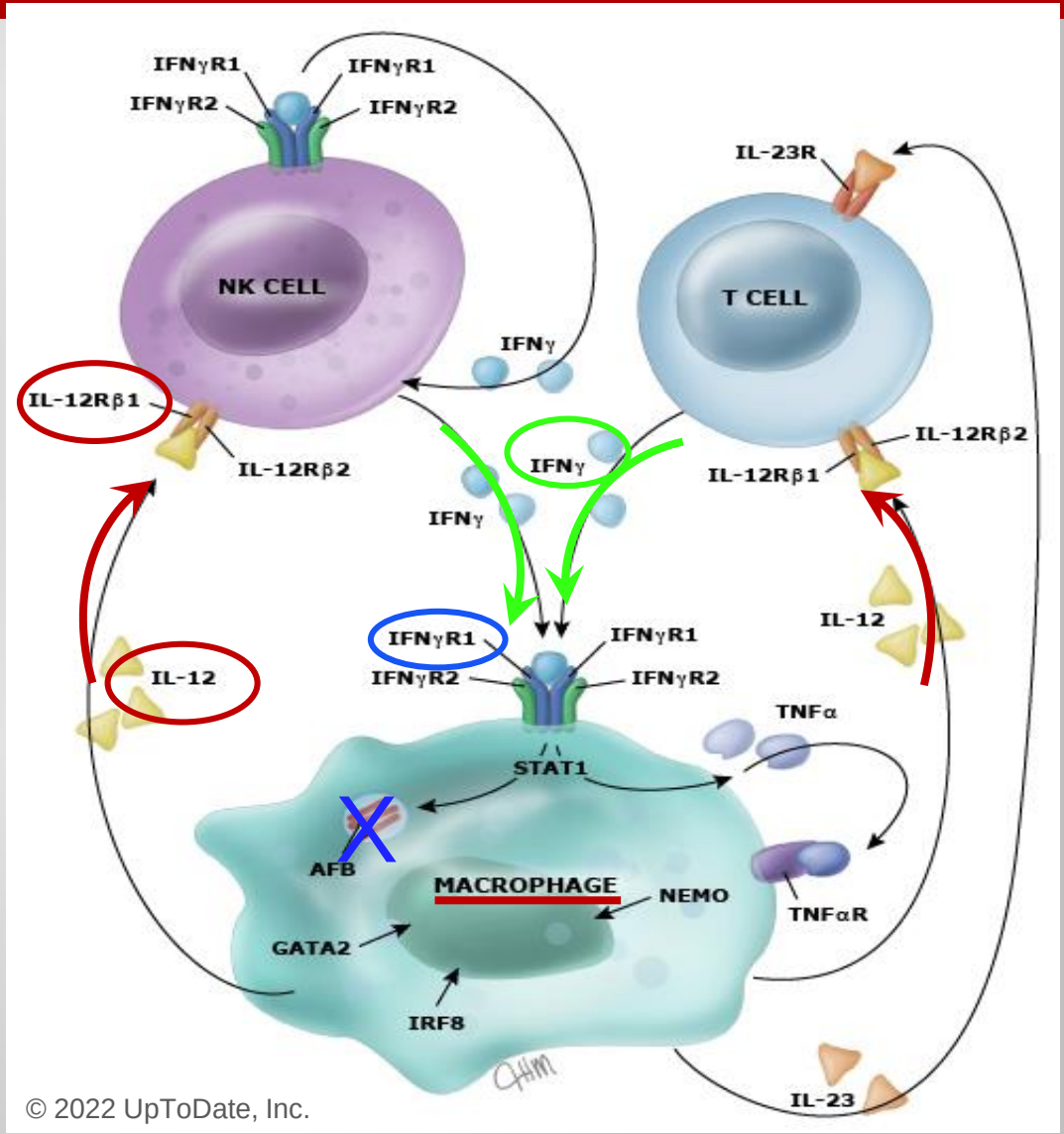
Should patients with NTM infection be worked up for underlying immunodeficiency?

- yes, for disseminated disease
- no, in general, for pulmonary disease

Haworth CS et al. Thorax 2017;72:iii1–ii64. doi:10.1136/thoraxjnl-2017-210927;
British Thoracic Society guidelines, 2017

IFN- γ / IL-12 signaling pathway is critical to defense against mycobacteria

- present with disseminated NTM infection, ***not*** pulmonary disease
- mutations in the IL-12/IL-23/ IFN-γ signaling pathway
- at least 25 mutations in 17 different genes to date
- may also be susceptible to salmonella and some fungal and viral infections

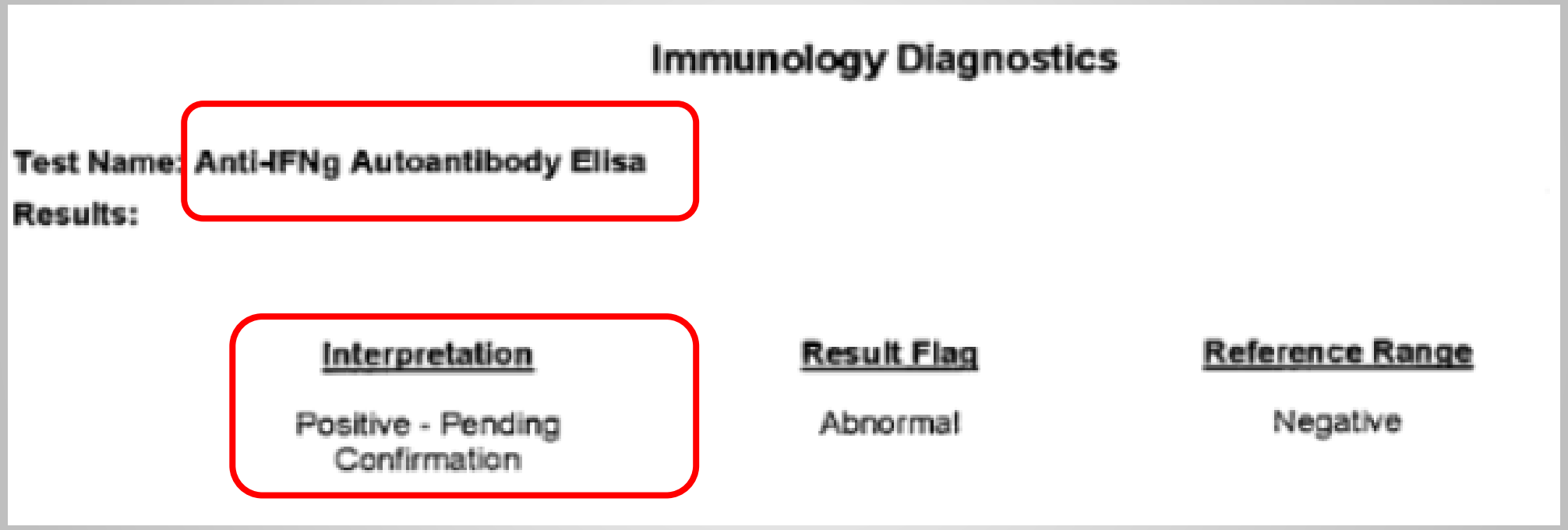


Wu U-I. Lancet Infect Dis. 2015 15:968-80

Late Onset Susceptibility to Mycobacteria

Defect	Inheritance	Presentation	Features
GATA2 deficiency	AD (MSMD)	Late childhood/adulthood	Monocytopenia or other cytopenia; erythema nodosum; lymphedema; pulmonary alveolar proteinosis
Anti-interferon-γ antibodies	-- / (Acquired)	Early to late adulthood	Asian females; ↑ risk of meliodosis, fungal and herpes virus infections

Our Patient



Immunology Diagnostics

Test Name: Anti-IFNg Autoantibody Elisa

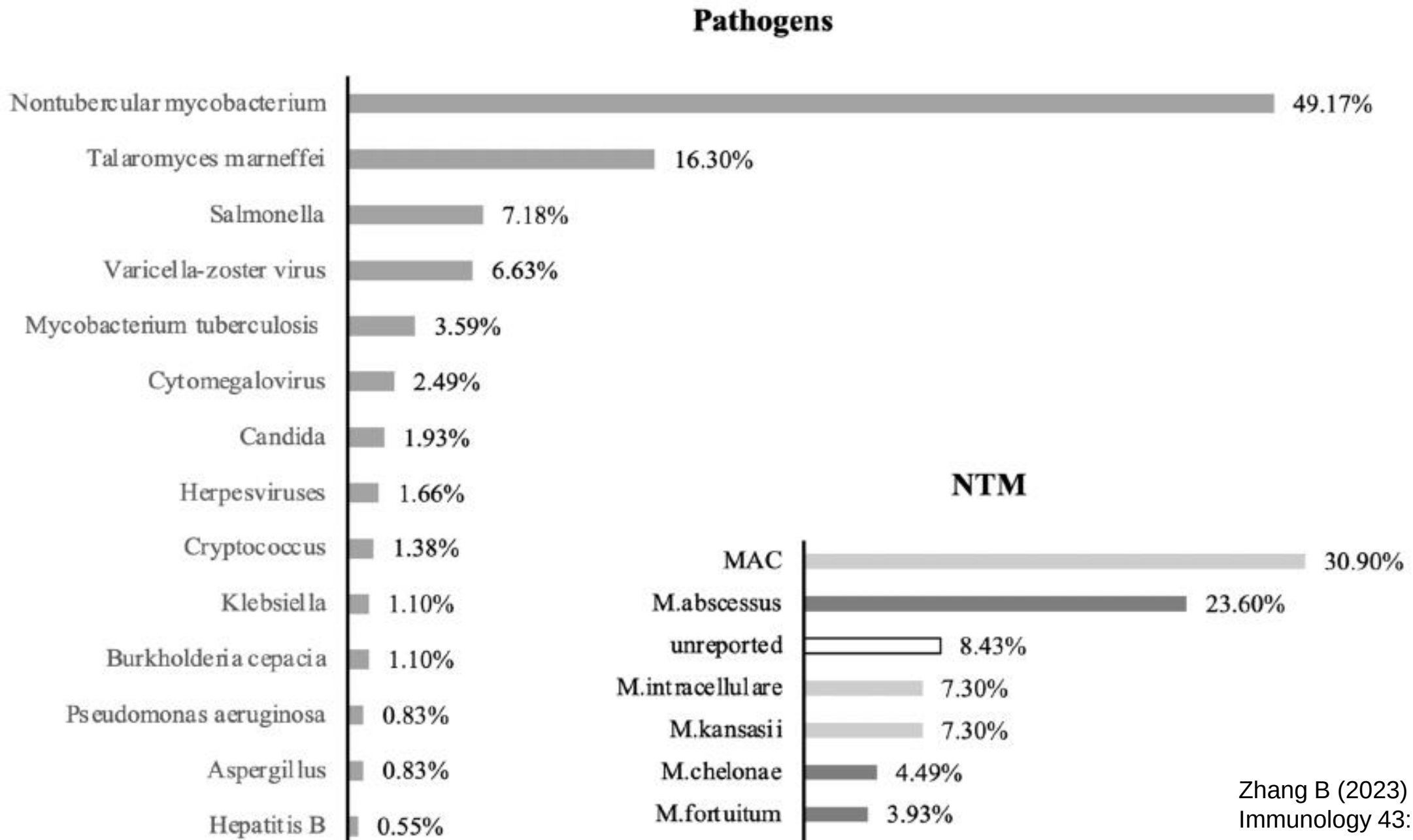
Results:

Interpretation	Result Flag	Reference Range
Positive - Pending Confirmation	Abnormal	Negative

Auto-antibodies to Interferon-gamma (AIGA)

- High titers of serum Antibody able to neutralize IFNg in functional assays
- In U.S., >90% of cases reported in Asian Immigrants, suggesting genetic basis
- Appears to be associated with several HLA alleles
- adult onset
- Increased risk of infections due to mycobacteria –TB and NTM, *salmonella*, *Talaromyces marneffei* [fungus endemic in SE Asia, esp Vietnam]

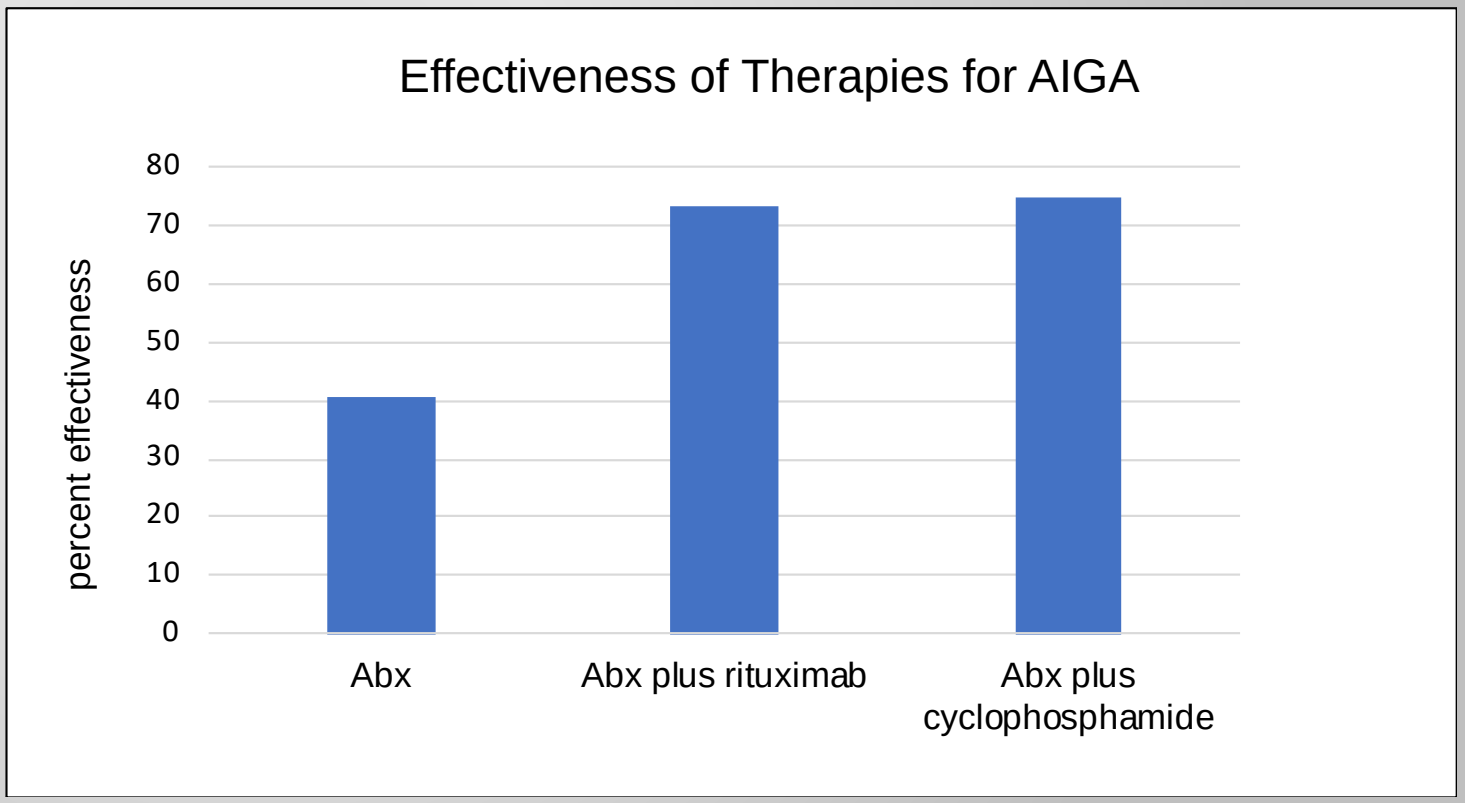
Zhang B Journal of Clinical Immunology (2023) 43:1660–1670



Zhang B (2023) Jl Clin Immunology 43:1660–1670

Auto-antibodies to Interferon-gamma (AIGA)

- recurrence rate up to 56.0%.
- Treatment: anti-infective therapy and immune suppression
- Unknowns
  1. **How long to treat**
     - with anti-infectives
     - with rituximab
  2. **Do Ab levels predict recurrence?**



Zhang B (2023) Jl Clin Immunology 43:1660–1670

Additional family history

- Sister with mycobacterial lymphadenitis, being treated at NIH
- Brother with *Talaromyces marneffi* infection, preceded by *Listeria* infection

- Started on antibiotic regimen: **Azithromycin, Ethambutol, Rifampin** (>rifabutin)**, and Moxifloxacin**
- **Readmitted two months later** with more weight loss (total now 50 lbs) and depression, ongoing low blood counts, fatigue, chest pain, hip pain, dysphagia, rash, hypotension and tachycardia due to poor oral intake
- *Sputum AFB smear +.* AFB cultures sputum, urine, stool, CSF, blood all negative

- Moxifloxacin stopped
- **IV amikacin started**
- **Skin rash biopsy:**
- "*mixed suppurative and granulomatous inflammation."* AFB smear and culture negative.
- *IV rituximab started*

Update 1 yr, 8 months into therapy:

- **MAC treatment Regimen:**
  - **Rifabutin daily** (previously, rifampin)
  - **Ethambutol daily**
  - **Azithromycin daily**
  - Clofazimine daily x 13 months
  - IV Amikacin x 1 month early on; stopped 2nd to kidney injury later attributed to hypercalcemia)
  - Moxifloxacin daily for two months
- Sputum AFB smears remained positive through 6 months after treatment initiation; AFB cultures converted two months into treatment

Weight gain: 56.2 kg (124 lbs)→77.6 kg (170 lbs)

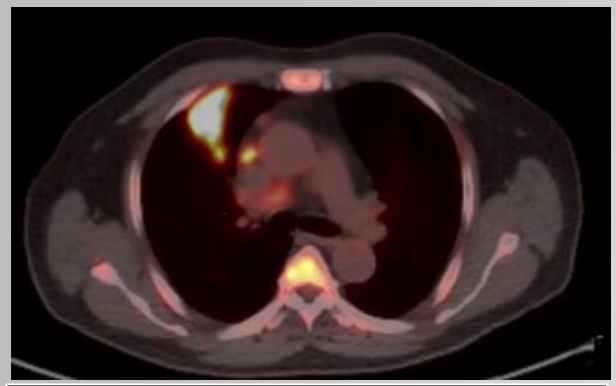
Rituximab infusions: 8 over 18-month period

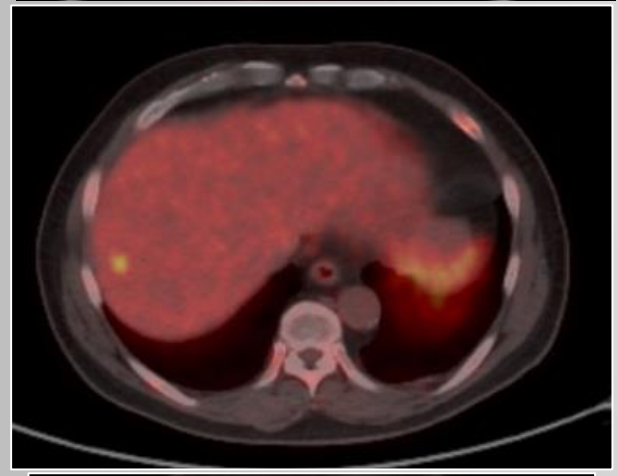
Plan to stop antibiotic therapy after approx. two years completed

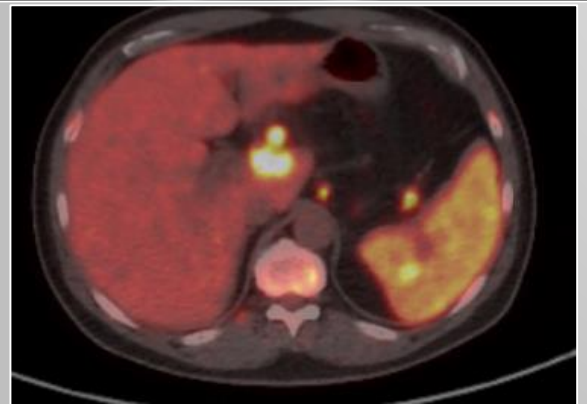
Repeat PET (1 year, 8 months into therapy)

- interval resolution of the numerous foci of intense uptake previously detailed on prior PET CT
- mild increased activity throughout the bone marrow is likely mildly reactive and greatly improved from prior.

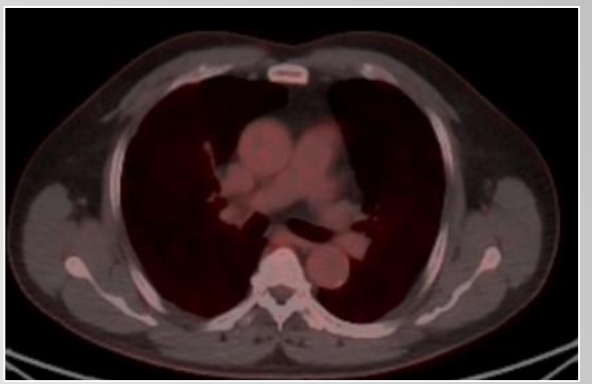
BEFORE

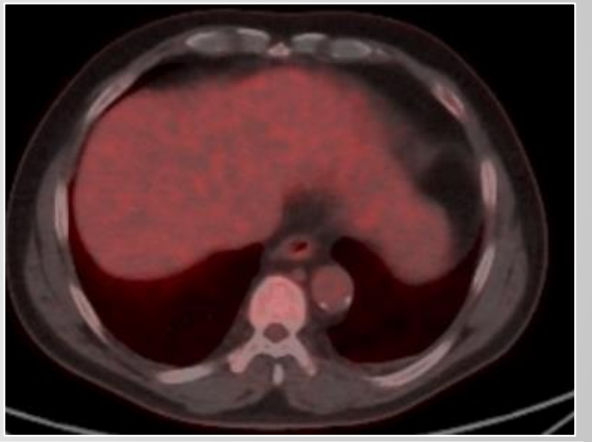


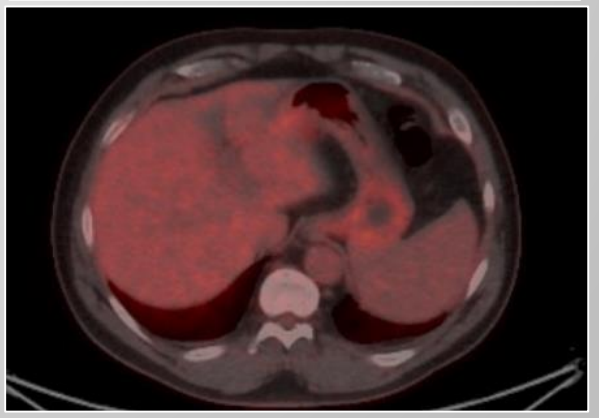




AFTER







Thank you

Questions?