

45/Male with Fever, LN and EN lesions

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History

August 2022

- 45-year-male from Bhavnagar, peon in office p/w
 - Fever without chills, high grade since 5 weeks
 - Inguinal swellings on both sides since 5 weeks
 - Skin lesions, painful, red, bump like swellings over both legs > arms since 3 weeks
 - Both feet swelling with decreased sensation
 - Decreased appetite and weight loss of 6 kgs
- No DM/HTN/IHD/TB
- P/H/O Spine surgery before 20 years, with residual right > Left foot drop

History

Feb 2022

- Before 6 months to this presentation, admitted to trust hospital in Bhavnagar for
 - Fever
 - Both ankle swelling with discharge from right ankle
 - Both inguinal swelling
- Treatment:
 - Pip-Tazo (4)
 - Meropenem (10), Metrogyl (10)
 - Levoflox (14), Linezolid (14)
- Afebrile for 3 months

History

July 2022

- Again developed inguinal swelling and fever
- USG was s/o right inguinal enlarged LN with abscess formation
- Needle biopsy – Necrotic granulomatous inflammation
- GeneXpert not ordered
- Empirical AKT
 - HERZ (Forecox 2 OD)
- No clinical improvement

Examination

- Looking sick
- Temp- raised
- Tachycardia+ (126/min)
- BP- 130/70 mmHg
- Systemic exam- unremarkable except sensory-motor neuropathy in both feet
- Multiple Erythematous tender nodules over legs and forearms- Erythema Nodosum
- B/L Inguinal and Axillary LNs
- Pallor+, B/L feet edema pitting+



Investigations

	18/02/22	23/02/22	28/02/22	06/07/22	01/08/22	03/08/22	06/08/22	11/08/22
HB	13.3	11.5	10.3	12.7	10.6	10.8	10.1	9.6
TC	13890	13190	19390	13480	16820	12580	13030	18090
DC				80/16		84/12	86/8.5	
PC	481000	555000	615000	5470000	507000	699000	862000	1099000
ESR				120		53	109	
CRP		196	237	77.2		194.3	132.7	
Urine	NAD	Protein +	NAD			NAD	NAD	
PT/INR							11.8/10.6/1.1	
RBS	108	120				153	122	
Urea		21	15				8	
Creatinine		0.7	1.11		1.08		0.6	0.62
Uric Acid			2.4		6.35			
Na			126				133	
K+			3.4				4.8	
SGPT		14	56		37	75.3	62	
STSH			3.47		Cpk 271			
S protine		7.7				7		
Alb		3.8				3.3		
Glob		3.9				3.6		

Ultrasonography

- Few pathological nodes are seen in bilateral femoral triangles, Largest LN of 42 x 14 mm on right side and on left side measures 35 x 12 mm with loss of fatty hilum, heterogenous echotexture and internal necrosis seen.
- Few pathological nodes seen in bilateral axillary regions, largest on right side of 22 x 10 mm and largest on left side of 31 x 10 mm on left side.
- Mild amount of free fluid seen in both ankle joints, fluid volume measuring 4-5 cc, no septations or solid nodule seen.
- Mild synovial thickening noted in both ankle joints, however no evidence of nodular thickening or periosteal abscess noted.
- No evidence of pathological nodes seen in neck on either side.
- No evidence of splenic infiltration or abdominal lymphadenopathy noted.

Investigations

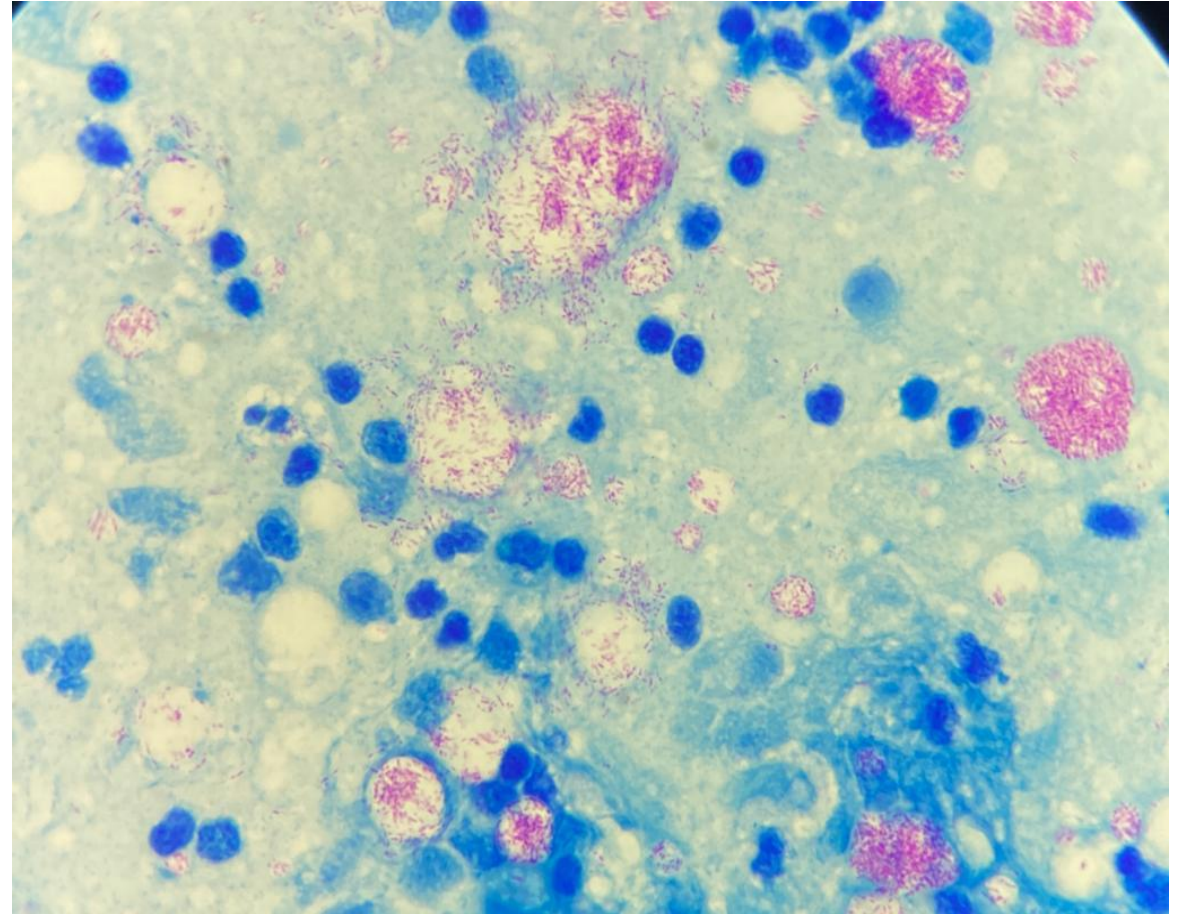
- Anemia
- Neutrophilic leukocytosis
- Thrombocytosis
- Elevated ESR, CRP, Ferritin
- Elevated SGPT
- HIV, HBsAg, HCV- Negative
- Hyperglobulinemia without M-band
- Brucella serology- Negative
- Radio-imaging: Multiple bilateral inguinal and axillary lymphadenopathy. No abdominal or mediastinal LN

Differentials

- Tuberculosis
- Leprosy
- Disseminated NTM inf
- Disseminated Fungal inf
- Vasculitis
- Sarcoidosis
- Lymphoma

- ANA, ANCA, RF- Negative
- Syphilis Ab- Negative
- Blood cultures (Aerobic/MycoF)- sterile
- ACE level- 50 (<62)

- Left axillary LN excision – necrotic tissue with pus
 - Direct microscopy- plenty of AFB
 - GeneXpert- Negative
 - Bacterial culture- Negative
 - TB culture- sent
 - HPE- Necrotising granulomatous lymphadenitis



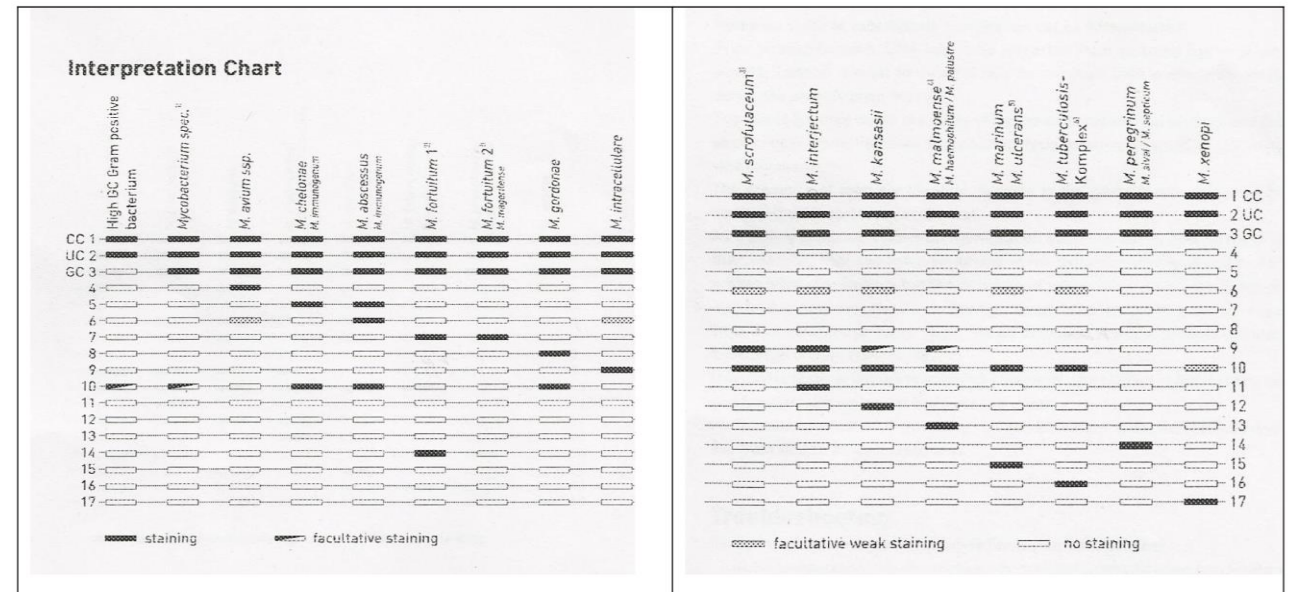
NTM speciation by LPA

- Presence of band no 5 and 10- mycobacterium Chelonae
- Very light band no 13- ?mixed NTM population ?NTM not in the scope of test

Specimen: Tissue

Method:

The technology is based on reverse-phase hybridization (Line probe assay) aimed at revealing an amplification product of a proprietary fragment (Mycobacteria sp.) of approximately 230 bp within the 23S rRNA gene.



Result: LPA NTMCM shows clear presence of band no. 05 and 10 along with a very light band of 13

Interpretation: The test indicates presence of *Mycobacterium chelonae*

Summary

- Multifocal lymphadenopathy and erythema nodosum due to disseminated *M. Chelonae* infection in an apparently healthy adult male
- Antimicrobial treatment started
 - Inj. Amikacin 1gm IV OD
 - Tab Clarithromycin 500mg 1 BID
 - Tab Moxifloxacin 400mg 1 OD

- Against our expectation, patient continued to have persistent fever and constitutional symptoms.
- New skin lesions continued to erupt even with antimicrobial treatment of 2 weeks
- Dermatologist reference was sought and ear lobe biopsy was done which was negative for leprosy.
- Due to cost constraint, patient was discharged and Linezolid was added

Follow up

- Follow up at 2 weeks
 - Decreased fever intensity but still persisted
 - EN lesions and constitutional symptoms remained same
 - Developed severe glossitis- Linezolid discontinued
 - Patient refused to take injectable antibiotic- lack of understanding/ cost issue
- Antibiotics revised:
 - Tab Clarithromycin 500mg 1 BID
 - Tab Moxifloxacin 400mg 1 OD
 - Cap. Clofazimine 100mg 1 BD

Underlying immune deficiency

- Primary CD4 cytopenia
- Adult onset immune deficiency

CD4 Count: 721 (39%)

CD8 Count: 277 (15%)

Adult Onset Immune-Deficiency (AOID)

- Anti-IFN-gamma autoantibody syndrome
- First case reported in 2004, >600 cases till now
- South-east Asia: Thailand, Taiwan, Japan and South China, Philippines, Vietnam, Cambodia, Singapore, and Malaysia¹
- Age of onset: 30-50 years
- Polymorphism in HLA DRB1 and DQB1
- Only one case of anti-IFN γ Ab syndrome in a patient of Indian origin has been reported from Australia²
- May be under-recognized in India

1. Pithukpakorn M, et al. HLA-DRB1 and HLA-DQB1 are associated with adult-onset immunodeficiency with acquired anti-interferon-gamma autoantibodies. PLoS ONE. 2015;10(5): e0128481.
2. Arvind Yerramilli, et al Disseminated Nontuberculous Mycobacterial Infection Associated With Acquired Immunodeficiency Due to Anti-Interferon γ Autoantibodies, *Open Forum Infectious Diseases*, Volume 6, Issue 4, April 2019, ofz131, <https://doi.org/10.1093/ofid/ofz131>

Isolated Organisms in 97 Patients with Opportunistic Infections.

- Infections associated with AOID
 - Non-tuberculous mycobacteria
 - Non-typhoidal salmonella
 - Dimorphic mold (*P. marneffeii*)
 - Varicella zoster infection
 - CMV

IFN-gamma auto-antibodies were detectable in over 80% of patients suffering from disseminated NTM without previously known risk factors

Variable	Group 1 (N=52)	Group 2 (N=45)
Organisms isolated (no./patient)		
Median	1	2
Range	1–4	1–5
Mycobacteria (no. of patients)		
Rapidly growing	36	39
Slowly growing	15	8
Nontuberculous mycobacteria, not specified	5	2
<i>Mycobacterium tuberculosis</i>	4*	10†
Total	60	59
Bacteria (no. of patients)		
Salmonella species		25
<i>Burkholderia pseudomallei</i>		4
Other		9
Fungi (no. of patients)		
<i>Cryptococcus neoformans</i>		10
<i>Histoplasma capsulatum</i>		7
<i>Penicillium marneffeii</i>		7
Varicella–zoster virus (no. of patients)		
Disseminated		3
Local	5	10
Parasites (no. of patients)		
<i>Strongyloides stercoralis</i>		1

Associated Non-infectious conditions

Associated conditions at presentation	Thailand (n = 74)	United States (n = 23)
Total number (%) of patients	48 (65%)	9 (39%)
Sweet syndrome	28 (38%)	2 (9%)
Lymphatic obstruction	11 (15%)	1 (4%)
Erythema pustulosis	12 (16%)	
Chronic pain	6 (8%)	4 (17%)
Hypercalcemia	6 (8%)	
Erythema nodosum	4 (5%)	1 (4%)
Pustular psoriasis	2 (3%)	
Neuropathy	2 (3%)	2 (9%)

Gloria H Hong, et al Natural History and Evolution of Anti-Interferon- γ Autoantibody-Associated Immunodeficiency Syndrome in Thailand and the United States, *Clinical Infectious Diseases*, Volume 71, Issue 1, 1 July 2020, Pages 53–62, <https://doi.org/10.1093/cid/ciz786>

Diagnosis of AOID

- Detection of anti-IFN γ Ab and demonstration of its neutralizing capacity
- Case reports and studies have shown utility of QuantiFERON-TB Gold as screening test

Use of QuantiFERON-TB Gold In-tube assay in screening for neutralizing anti-interferon- γ autoantibodies in patients with disseminated nontuberculous mycobacterial infection

- **Objective:** to determine whether QuantiFERON-TB Gold In-tube (QFT-GIT), a commercialized IFN- γ release assay, could be used to screen for neutralizing anti-IFN- γ Abs among previously healthy adults with DNTM
- **Methods:** plasma concentration of anti-IFN- γ Abs and their neutralizing capacity through ELISA and flow cytometry were measured in non-HIV patients with dNTM infection. correlation between QFT-GIT results and the presence of neutralizing anti-IFN- γ Abs among patients with and without previously recognized immunosuppression were analyzed
- **Results:** Irrespective of the autoantibody concentration or disease activity, **all patients with neutralizing anti-IFN- γ Abs (100%, 30/30) had indeterminate QFT-GIT results** because of extremely low or undetectable IFN- γ levels in the mitogen tubes. **None of the four DNTM patients who were previously healthy and tested negative of anti-IFN- γ Abs had an indeterminate QFT-GIT result**
- **Conclusion:** An indeterminate QFT-GIT result because of undetectable or extremely low IFN- γ level in the mitogen tube suggests the presence of neutralizing anti-IFN- γ Abs in a previously healthy patient with DNTM infection.

TB-Gold Plus in our patient

Reg Date and Time	: 08-Aug-2022 05:27	Sample Type	: Heparin Whole Blood - Li	Mobile No.	:
Sample Date and Time	: 08-Aug-2022 05:27	Sample Coll. By	: non	Ref Id1	: IPD 20692
Report Date and Time	: 10-Aug-2022 16:17	Acc. Remarks		Ref Id2	: 301 C

TEST	RESULTS	UNIT	BIOLOGICAL REF RANGE	REMARKS
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QuantiFERON-TB Gold Plus (QFT-Plus) assay

IFN Level Of Nil <i>ELISA</i>	0.04	IU/mL
Difference Of TBAg1 -Nil <i>Calculated</i>	0.05	IU/mL
Difference Of TBAg2 -Nil <i>Calculated</i>	0.06	IU/mL
Difference Of Mitogen-Nil <i>Calculated</i>	0.08	IU/mL
Interpretation Of Tb-Gold Plus	Indeterminate	

Treatment for AOID

- Unique challenge
- No published guideline
- Intravenous immunoglobulin, subcutaneous IFN-gamma, plasmapheresis, steroids, cyclophosphamide and rituximab- case reports and series
- We started steroids (Prednisolone 15mg/day) as patient was not ready for plasmapheresis, IVIG, or rituximab

Continuation

- Follow up at 1 months
 - Afebrile
 - Complete resolution of EN like lesions
 - No antibiotics related side effects
 - Prednisolone reduced to 10mg/day
 - AFB culture remained sterile



Continuation

- Follow up at 2 months
 - Remained afebrile, complete resolution of skin lesions and constitutional symptoms
 - Weight gain 2 kg
 - No drug related side effect except skin discoloration due to clofazimine
 - Repeat USG: Decreased size of LN with resolution of internal necrosis and no loss of fatty hila



Unanswered questions

- Mycobacterial culture remained sterile
- How long to continue antimicrobials?
- How long to continue steroids? Dose?
- Use of other treatment modality?
- How to monitor for immunity status? Unavailability of anti-IFN γ Ab levels
- Prognosis ?

Thank You