BioMed Research Journal
BMRJ, 4(1): 173-181
www.scitcentral.com

ISSN: 2578-8892

Case Report: Open Access

A Shock and a Surprise! An Unusual Presentation of Tuberculosis

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Received September 11, 2019; Accepted September 18, 2019; Published April 25, 2020

ABSTRACT

We report an uncommon case of multiple-site aorto-arteritis (Takayasu/NSAA) with active tuberculosis in an adolescent Indian girl. Her initial presentation of brief fever and breathlessness along with barely recordable peripheral pulses and BP was baffling. The clinical course was complicated by symptomatic hypocalcaemia and hypo-vitaminosis D. CECT scan of chest showed extensive necrotizing mediastinal lymphadenitis, compressing large airways. Bronchoscopic lymph-node biopsy confirmed tuberculosis. Both CT and MR angiography revealed multiple sites of arterial narrowing. This case provides evidence to strengthen the association of tuberculosis with Takayasu's aorto-arteritis. Further review of literature suggests a relationship of hypovitaminosis-D with both, an increased proneness to tuberculosis and Takayasu arteritis.

Keywords: Non-specific aorto-arteritis, Tubercular arteritis, Takayasu's aorto-arteritis, Hypovitaminosis-D, MR angiography

Abbreviations: NSAA: Non-Specific Aorto-Arteritis; TA: Takayasu's Aorto-Arteritis; 3D-MIP and VR: 3-Dimensional Maximum Intensity Projection (MIP) and Volume Rendering (VR); ATT: Anti-Tubercular Therapy; cQT: corrected QT Interval; CECT scan: Contrast Enhanced CT scan

INITIAL CASE PRESENTATION

A 16 years old girl was brought to the ER on New-Year's Eve, with increasing breathlessness over few hours, following 2 days of low-grade fever. She had attended school regularly until the same morning. There was no history of cough, sputum, haemoptysis, rash, seizure, syncope, palpitations or chest pain. No vomiting, aspiration, exposure to fumes; insect bites, unusual food intake or medication was reported. There was no weight loss, diarrhea, dysuria or recent stressors. Not sexually active, she'd recently had a normal period.

Clinical examination showed an averagely built adolescent, breathless but comfortable lying down. Respiratory rate was 36/min, oxygen saturation was 92%. There was no cyanosis, stridor or audible wheeze. Bilaterally radial pulses were imperceptible, femorals were feeble and carotids were well felt. Cardiac monitor showed normal rhythm of 90 beats/min. Arm BP was unrecordable bilaterally. She was warm but not febrile. Moderate pallor and sweating were observed. No urticarial-rashes, angioedema, lymphadenopathy, edema or icterus were noted. Trachea was central; chest expansion and resonant percussion-note were equal on both sides. Cardiac and liver dullness were preserved. Breath sounds were normal. Apex beat and heart sounds were normal. Abdominal and neurological examinations were unremarkable. Capillary blood glucose was 76 mg/dl and blood gases showed mild hypoxemia.

With a provisional diagnosis of warm-shock (anaphylactoid/toxin-mediated/sepsis-related), emergency management was initiated. Oxygen was given by face-mask; crystalloids were administered rapidly (500 ml/h initially); and bladder was catheterized to monitor urine output. Hydrocortisone 200 mg was given straightaway and 100 mg repeated 6 hourly. Empiric treatment for community-acquired sepsis was instituted (third-generation cephalosporins and vancomycin). Anti-histaminic were added. Despite adequate hydration and urine output there was no improvement in BP for 2 h; therefore, ionotropic support was initiated. Breathlessness resolved and oxygen saturation improved within 6 h.

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Citation: Khati C & Sony AK. (2020) A Shock and a Surprise! An Unusual Presentation of Tuberculosis. BioMed Res J, 4(1): 173-181.

INVESTIGATIONS AND CLINICAL COURSE

Initial investigations **(Table 1)** showed moderate dimorphic-anemia, no leucocytosis, relative-lymphocytosis, normal platelets, moderately elevated ESR; normal CRP, urinalysis, blood biochemistry, pH and blood gases. X-ray chest showed mild hilar prominence. Resting ECG was normal.

Table 1. Summary of lab investigations.

Inv/Ref Range	Day 1	Day 2	Day 4	Day 7	Week 2	Week 3	Week 4	Month 2	Month 6
Hb (g/dl)	10.7	10.5	10.2	9.2	9.4	10.0	10.4	12.0	12.4
Hematocrit (%)	38.6	35.2	33.5	31.8	30.8	32	32	38	38.2
MCV (Fl)	96.3	96.2	98.7	98.0	98.2	94	90	82	85
RDW	18	17	19	16	16	15	13	14	14
TLC (cumm)	8000	8000	7000	5800	3900	4850	6200	6500	7,300
Neutrophils (%)	34	30	28	25	22	32	40	45	56
Lymphocytes (%)	62	65	65	68	74	67	56	50	40
Platelets ($\times 10^5$)	3.8	3.5	2.6	2.8	1.9	2.9	3.0	2.8	3.1
ESR (mm in 1 h)	-	48	-	60	46	-	-	32	15
Peripheral smear	Dimorphic anemia, relative lymphocytosis		Normocytic normochromic RBCs						
CRP mg/L (N: 0-6)	-	1.18	-	-	-	-	-	-	-
Procalcitonin micro g/l (cut off <0.2)	-	-	-	-	<0.05	-	-	-	-
LDH mg/dl (N<90)	-	-	-	-	433	-	-	104	-
Random blood glucose mg/dl	76	120	136	120	140			115	126
Bilirubin (mg/dl) 0.8-1.0	0.5	0.4	0.6	0.6	0.8	-	1.0	0.8	0.6
SGOT (IU/L)	33	24	18	25	45	-	60	75	60
SGPT(IU/L)	28	20	16	20	60	-	74	86	82
Alk Phosphatase IU/L (42 to 98)	125	98	130	200	178	-	111	124	130
Total protein g/L (6.0-8.3)	6.0	-	-	6.0	6.1	-	6.5	6.8	7.2

Albumin g/dl (3.4-5.4)	3.2	-	-	3.1	3.2	-	3.5	3.8	4.3
INR	0.8	-	-	-	-	-	-	-	-
Urea mg/dl (10-50)	19	12	15	25	13	-	-	-	20
Creatinine mg/dl (0.5-1.8)	0.6	0.6	0.8	0.6	0.8	-	-	-	0.6
Na^+ m eq/L (135-145)	135	142	130	138	132	-	-	-	-
K^+ m eq/L (3.5-5.1)	4.5	4.8	3.5	2.1	4.0	-	-	-	-
cCa mg/dl (8.7 to 10)	8.2	8.3	7.2	6.5	8.5				9.4
24 h Urine Ca mg/24 h (100 to 300)	-	-	-	-	23	-	-	-	-
Urine spot Na meq/L (>20)	-	-	-	60.7	-	-	-	-	-
Urine K m eq/L (25-125)	-	-	-	6.2	-	-	-	-	-
B12 level pg/ml (100 to 350)				23.6					482
Folate level ng/ml (5 to 15)				1.3					20
Ferritin ng/ml (30 to 300)				564.7					45
Vitamin D3 ng/ml (>20)				4.0					32
TSH IU/ml (0.3 to 5)				0.33					1.4
Lipid profile					Normal				Mild⇧TGs
HIV I and II			Negative						
Mantoux test					<5 mm				

X-ray chest showed mild hilar prominence. Resting ECG was normal.

At 48 h, although improved breathing was sustained, BP in all 4 limbs remained low- around 60/40 mm Hg with feeble radial, femoral and popliteal pulses. Surprisingly, carotids and dorsalis-pedis were well felt bilaterally. She was sitting-

up and standing without hemodynamic instability. Weight was 42 kg. Urine output and repeat blood-tests showed no deterioration despite apparent hypotension. Inotropes were therefore tapered off and urinary catheter removed.

Abdominal ultrasound showed liver size 14.5 cm, spleen 11 cm, kidneys 10 cm length, normal texture and no free fluid. Few retroperitoneal lymph-nodes were present. Doppler-study on renal arteries showed normal flow. CECT scan of chest **(Figure 1)** showed a large, conglomerate, lobulated and necrotic, mediastinal lymph-node mass, possibly of tubercular etiology; causing compression of the large airways. Abdominal CT scan **(Figure 2)** showed few enlarged mesenteric lymph nodes, the largest measuring 12 × 6 mm.

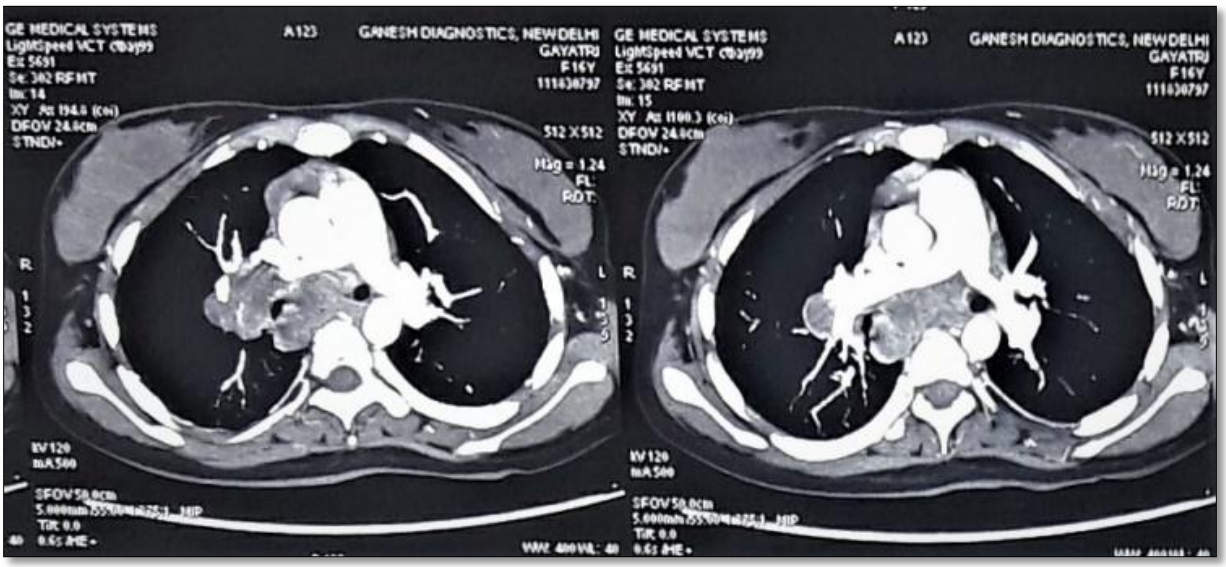

Figure 1. CECT scan of chest showing a lobulated conglomerate mediastinal mass measuring 75(AP) X76 (TR X70 (CC) mm, with extensive areas of necrosis, causing compression of trachea, both main bronchi and moderate stenosis of right main bronchus. The mass was extending to post carinal region, pushing the trachea anteriorly. Diffuse bilateral air trapping with pleural thickening around right posterior and lateral basal segments were seen. Features were suggestive of a large, conglomerate, lobulated and necrotic, mediastinal lymph-node mass of tubercular etiology causing compression of the large airways.

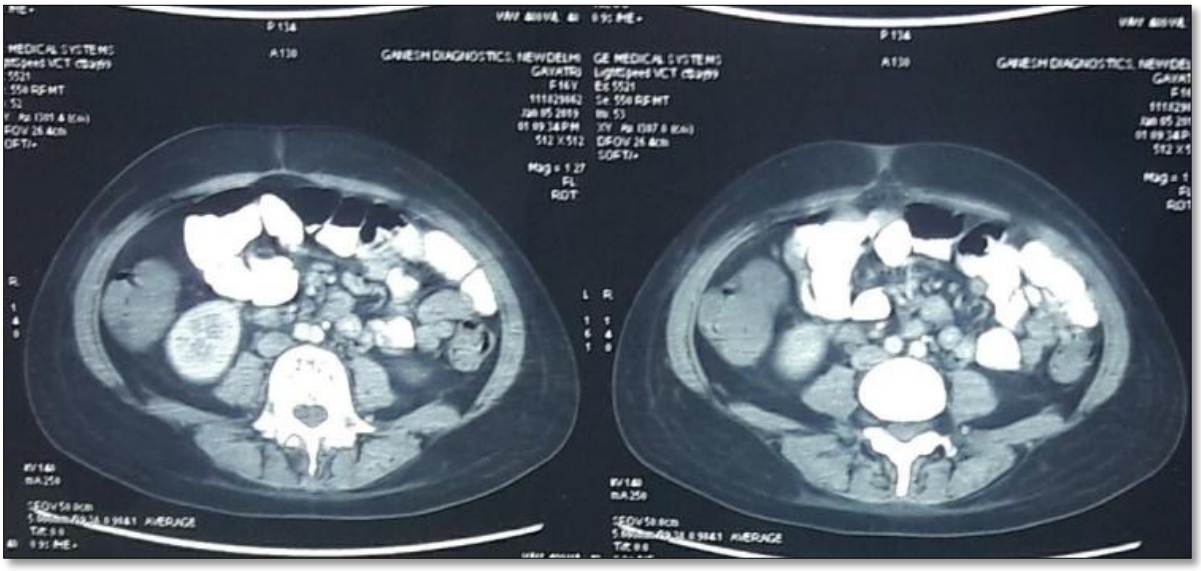

Figure 2. CT scan of the abdomen showing few enlarged mesenteric lymph nodes, the largest measuring 12 × 6 mm. With no history of TB in the patient or her contacts, first-line ATT (rifampicin, isoniazid, pyrazinamide and ethambutol) was initiated. Other antimicrobials were stopped. Oral steroids (1 mg/kg/day) were continued in view of recent large-airway compression.

On day 4, in the light of feeble peripheral pulses and a previous history of claudication in both calf muscles 2 months earlier; contrast-enhanced helical CT scan of aorta and its branches was performed in angiographic mode **(Figure 3)**. 3D-MIP and VR reconstructions were obtained. Bilateral severe luminal narrowing of sub clavian and axillary arteries and circumscribed infra-renal aortic narrowing for a 49 mm segment were seen. Fundoscopy was normal. ATT and oral prednisolone were continued.

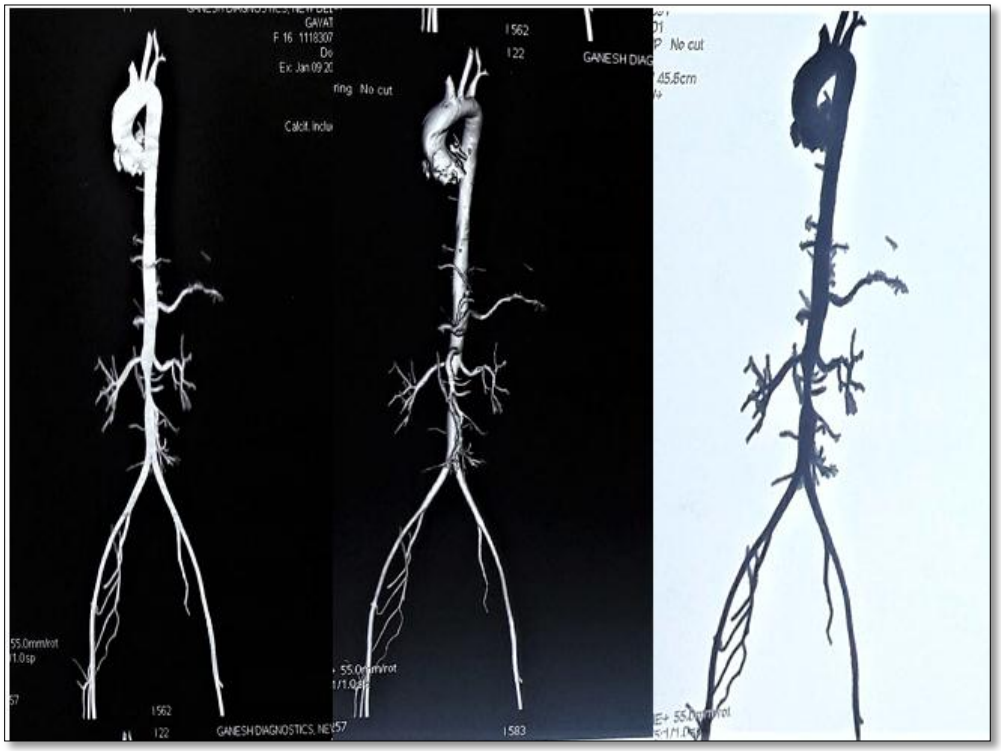

Figure 3. Helical CT scan of aorta and its branches in angiographic mode and 3D-MIP and VR reconstructions. Circumscribed hypodensities involving bilateral sub clavian and axillary arteries were noted causing severe luminal narrowing and distal attenuated flow, suggestive of arteritis. Circumscribed hypodensity was also noted of infra-renal aorta involving a segment of approximately 49 mm, causing moderate luminal narrowing. Bilateral renal arteries and coeliac artery showed normal take-off and branching. Mesenteric arteries showed normal arcading. Normal bifurcation of common iliac arteries with branching into internal and external iliac arteries was seen. No aneurysm, wall thickening, calcification or irregularity was noted.

On day 7, she developed symptomatic hypocalcaemia in the form of carpopedal spasms and positive Trousseau's sign. Severe hypovitaminosis D, hypocalcaemia and hypokalemia along with low urinary potassium and calcium were detected **(Table 1)**. ECG showed a prolonged cQT interval of 510 ms. Symptoms did not recur after replacement therapy and cQT interval normalized in 2 days. Other micronutrient supplements were added in view of deficient iron, folate and B12 **(Table 1)**, along with a high-protein diet. Mantoux and HIV testing were negative.

With a diagnosis of tubercular mediastinal-lymphadenitis and non-specific aorto-arteritis (NSAA), she was referred to a higher centre. There she underwent bronchoscopic lymph-node biopsy and cardiovascular MR imaging and angiography. The lymph-node biopsy showed epithelioid granulomata, caseation and occasional acid-fast bacilli. GeneXpert-test (molecular detection of mycobacteria and rifampicin resistance), was negative. The MR imaging and angiography was suggestive of NSAA with active tuberculosis **(Table 2)**. Salient features were enlarged, necrotic and conglomerate lymph-nodes in right para-tracheal, sub-carinal, hilar and supra-clavicular locations with nodular lesions in right lower-lobe. Angiographic narrowing of infra-renal aorta; occlusion of superior mesenteric artery and both sub-clavians with distal reformation; and diffuse disease of bilateral anterior tibial and left peroneal arteries.

Table 2. Report of cardiovascular MRI.

Protocol	Cine: SA 4CH T1W, T2 FS-4 CH, SA T1 Scout LGE Sequences Pre and post contrast T1 mapping and T2 mapping Contrast MRA for thoraco-abdominal aorta Non-contrast MRA (QUISS) for lower limb arteries Post-contrast T1 SPACE-axial, sagittal	
Gross findings	1. Situs solitus, levocardia, AV-VA concordance. No cardiac chamber dilatation. No RWMA. 2. Valves not thickened. No abnormal myocardial S1 on T2. LV myocardium shows normal T1 and T2 mapping values. No LGE seen. No pericardial thickening or enhancement seen. LV functions absolute normalized. 3. Multiple enlarged, necrotic, conglomerate mediastinal lymph nodes in right para-tracheal, sub-carinal, hilar and right supra-clavicular locations. Largest one in para-tracheal location. Measures 26 mm in SAD. 4. Nodular lesion (granuloma) in right lower lobe. 5. No pleural or pericardial effusions.	
Cardiac measurements	EF: 56.44 (56-78%); EDV: 86.62 (52-141) ml; EDV: 31.74 (13-51) ml; SV 48.89 (33-97) ml; CO 5.52 (2.65-5.98)L/min; CI: 4.12 (1.75- 3.80) L/min/m^2	
MR Angiogram	Findings	
Ascending aorta	No significant disease	
Arch of aorta	No significant disease	
Innominate artery (IA)	No significant disease	
Common carotid (CCA)	Right	Left
	No significant disease	Mild proximal disease. No significant stenosis
Sub clavian artery (SCA)	Long segment tight stenosis/occlusion in SCA beyond VA origin for the length of 5.0 cm with reformation of axillary artery through collaterals	Long segment tight stenosis/occlusion in SCA beyond VA origin for the length of 4.6 cm with reformation of axillary artery through collaterals
Impression: 1. Diffuse circumferential disease involving upper infrarenal aorta for the length of 3.6 cm causing 50 to 60% stenosis. Lower infra-renal aorta and aortic bifurcation are spared. 2. Occlusion of 2nd and 3rd parts of bilateral SCAs with distal reformation. 3. Tight ostio-proximal SMA stenosis. 4. Diffuse significant disease of bilateral ATAs and left peroneal A. 5. Multiple necrotic mediastinal lymphadenopathy and granuloma in right lung lower lobe. 6. No features to suggest any specific myocardial pathology. Features suggestive of Non-Specific Aorto-Arteritis (NSAA) with active tuberculosis. Advise: Following the assessment of NSAA disease activity, DSA with or without angioplasty maybe		

PRESENT CONDITION AND FUTURE PLAN

Decision for angioplasty was deferred since her NSAA was active and widespread. Adequate collaterals had already formed and no vital organ was at immediate risk. Under close follow-up, presently she has completed 8 of the planned 9 months of ATT. She is still on 5 mg prednisolone, which was gradually tapered after 4 months. No other immunosuppressant or anti-platelet agent has been introduced due to steady improvement. Having gained 8 kg weight, she has no limb-claudication, Raynaud's phenomena, cough, breathlessness, pain chest/abdomen or syncope. There is steroid-induced acne but no significant hyperglycemia or dyslipidemia. All micronutrient deficiencies are corrected. Peripheral pulses remain feeble, although volume has improved. BP in both upper limbs is 70/40 mm Hg. In the lower limbs it is 96/50 mm Hg (right) and 84/44 mm Hg (left). Faint bruits are heard over the left anterior tibial artery and abdominal aorta.

If these gains continue, MR angiography will be repeated annually. She will remain under long-term follow-up. ECG, echocardiography and fundoscopy will be used to assess masked hypertension.

DISCUSSION

Takayasu arteritis (TA) was named after the Japanese ophthalmologist who first described its fundoscopic findings in 1905 [1]. Over 500 publications were reviewed for this case-report. Of these, a few representative publications between 2000 to 2019 have been cited to keep the discussion contemporary. The latest reference-books in cardiology [1,2] and rheumatology [3] have not unequivocally attributed pathogenesis of TA to TB. Genetic predisposition, inflammatory/autoimmune processes and other factors including infections are implicated in its perpetuation. In fact, TA, tubercular, infective and syphilitic arteritides are listed as distinct entities [1]. Despite this several similarities between tubercular arteritis and TA exist. Both are large-vessel granulomatous arteritis, characterized by comparable involvement of the aorta and its major branches; and are prone to relapses/disease progression. Tuberculous arteritis, usually secondary to the dissemination of *Mycobacterium tuberculosis* infection from the mediastinum and/or lung to the adjacent aorta; mimics TA clinically [4-6], as seems to be the case in our patient.

Classic TA frequently occurs in Asian countries with high TB burden, strangely affecting young females 9 times more often than males. Similar aortitis is also encountered in people of different ethnicities [1-3]. Both may either be incidentally detected, or may present with vaso-occlusive phenomena in vital circulations and rarely as aneurysm formations [7-9]. Association of TA with latent, past or active tuberculosis is widely published [10-17], mainly as case-reports. Jansson et al. [4] have reviewed 18 cases of co-occurring TA and TB, where all patients were below 25 years, over half had lymph-node TB, all received ATT, 90% received steroids; and 2 cases relapsed needing additional immunosuppressants. Lim et al. [5] studied 267 patients of TA between 1994 to 2014, with and without TB. Cases were diagnosed according to the 1990 American College of Rheumatology criteria [18]. A total 94 (35.2%) patients had past or concomitant TB. Clinical features and angiographic findings in TA were not different in the presence or absence of concomitant TB. Previous similar studies also report no significant difference between TA and TB arteritis, except the absence of proven tuberculosis by available methods. Soto et al. [14] processed 181 aortic tissues for gene-sequences indicating TB. The *IS6110* sequence identified the *M tuberculosis* complex and the *HupB* established differences between *M. tuberculosis* and *M. bovis*. They identified a higher frequency of *IS6110* and *HupB* genes in aortic tissues of TA patients suggesting that arterial damage could occur due to previous infection *with M. tuberculosis*. One report was found that refuted the presence of *M tuberculosis* in arterial lesions from 10 patients with Takayasu's arteritis [19]. Biopsies were assessed by acid-fast and auramine-fluorochrome stains, mycobacterial cultures and direct-amplification test.

Whether TA or NSAA; ESR, CRP and procalcitonin have been used as markers of inflammation during active disease and for detection of relapses with varying reliability. Imaging by Doppler and ultrafast-ultrasound fails to pick up active inflammation. Cardiovascular MR is superior to CT angiography in active disease and during follow-ups for relapses. DSA and FDG-PET scans additionally are able to detect vessel-wall oedema and are marginally superior in active disease [7-9,20,21]. Additional tests to screen for tuberculosis include X-rays, BCG, histopathology, microbiological processing and molecular-methods.

Improved treatment modalities, are associated with better outcomes in the present century compared to the previous [1-3,7-9]. The course of disease is variable. Remissions and relapses are both reported, therefore there is a need for long-term follow-up. Steroids (mainstay), other immune-suppressants and biologic-response-modulators have all been included in recommended treatment options with comparable results [1-3]. Most data comes from open-labelled trials, observational-studies and individual series. Sample-sizes are generally small and histopathological evidence is difficult to gather from living patients.

The 'surprise' as indicated in the title of this report, actually came from an unexpected development. Our patient had hypo-calcemic tetany and cQT prolongation on day 7 of presentation. High-dose steroids probably precipitated the derangement in the background of severe vitamin-D deficiency **(Table 1)**. Growing evidence suggests that vitamin D deficiency might be implicated in the development of active TB. Literature review showed considerable data on the association of hypovitaminosis-D

with (a) proneness to tuberculosis from insufficient vitamin-D dependent defensins [22-25] and (b) an indolent course of the disease [26-28]. Interleukin (IL)-15 and IL-32 play roles in the vitamin-D mediated TB defense mechanisms. We also found credible reports of an association of vitamin-D deficiency with tubercular and Takayasu arteritis [29,30].

Had it not been for sudden breathlessness from large airway obstruction and a dramatic 'shock-like' presentation; this girl's condition may have gone unnoticed for longer. Indolent course of disease was evinced by a short and mild febrile illness; insignificant rise in phase reactants (ESR, CRP and procalcitonin); and cutaneous anergy on Mantoux-testing; all in the presence of extensive conglomerate necrotising mediastinal and other lymphadenitis plus pulmonary TB. It may have been due to concurrent severe deficiency of micronutrients, especially vitamin-D3. In South-Asia, despite abundant sunlight, hypovitaminosis-D in females does occur. Traditionally the women are fully-clothed when outdoors, at all times. Perhaps, here lies a simple explanation for the gender-difference in incidence of TA and NSAA.

CONCLUSION

Indolent tubercular granulomatous inflammation of arterial walls, facilitated by lowered anti-tubercular defenses from vitamin D deficiency may actually play a significant role in the genesis of NSAA or TA. This case lends credence to the tubercular etiology of NSAA.

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