Case Report

Takayasu Arteritis and Thyroid Dysfunction : Just a coincidence?

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ABSTRACT

Takayasu's arteritis is a chronic, progressive, granulomatous vasculitis involving large arteries especially aorta and its branches, common in Southeast Asia region, usually affecting females in 2nd-4th decade. A 52 year old female patient presented at the General Medicine Outdoor of a tertiary-care hospital with progressive generalized body swelling and breathlessness on exertion since two month and decreased level of alertness since two days. Her laboratory reports were suggestive of hypothyroidism. On physical examination, she had no pulses in upper limbs, CT angiography of aorta and its branches suggestive of Takayasu's arteritis. This existence of Takayasu's arteritis and hypothyroidism may not be just fortuitous. An underlying autoimmune mechanism might be a possible explanation.

Case :

A 52 year old, 72 kg Indian female patient was brought by relatives with complaints of excessive weight gain in past one year with snoring and increased daytime sleep and tiredness, progressive generalized body swelling and breathlessness on exertion since two month and decreased level of alertness since two days. Patient was a known case of Systemic hypertension and Ischemic Stroke in 1996. There was no history of DM/IHD/CKD or decreased urine output. In past history, Patient was COVID-19 positive 6 month back, had no history of hospitalisation / desaturation, was on home isolation then. Patient had gone to a local practitioner who advised a cardiologist opinion for exertional dyspnea. She visited a cardiologist and her 2D-Echo on the day of admission, was suggestive of no RWMA, LVEF 60%, RA/RV dilated with D-shaped LV Cavity, Severe TR, Severe PAH (PASP by TR Jet-74 mmHg). With this report and complaints patient presented to OPD. On examination patient was morbidly obese (BMI of 32) with generalised anasarca, was drowsy, afebrile, RR of 16/min, JVP was raised, bilateral upper limbs pulses were non-palpable with non recordable Blood Pressure. Lower limb peripheral pulses were well felt on both sides, with a BP in lower limbs of 140/90 mmHg. SpO2 was 95% on 6 lit O2 as measured in the toes. There was no Cyanosis or Clubbing, On CVS examination, a Grade 4 Pansystolic murmur in tricuspid area was present. On respiratory examination, bilateral basal crepitations were present. Her abdomen was distended, soft, with tender hepatomegaly. On CNS examination, patient was drowsy, Asterixis present, right sided pupil was normal reacting to light (left eye had phthisis bulbi). RBS-101 mgm/dl, ECG was suggestive of normal sinus rhythm with rate of 80/min, with S wave in Lead1 and inverted T wave in Lead 3. D-Dimer was 3000 mcg/lit. ABG analysis was s/o Chronic Respiratory Acidosis (pH-7.33, pCO2-61 mmHg, HCO3-31.7). Patient was started on heparin drip. Patient's baseline S. Creatinine was 0.43 mgm%. CT Pulmonary Angiography was provisionally suggested of no evidence of Pulmonary embolism. Serum Albumin was 3.5 gm/dl. Thyroid Function test showed a TSH of 50 microIU/ml, Free T3-2.58 pg/dl (N=130-450 pg/dl), FreeT4-0.29 ng/dl (N=0.8-1.8 ng/dl). On eye examination right sided Fundus was Normal. Patient was kept on BiPaP (NIV) support for CO2 retention and was given loading doses of thyroxine f/b maintenance dose. Ultrasonography abdomen was suggestive of thick subcutaneous edema along with congestive hepatomegaly. Inj lasix at 5mg per hour drip was started in view of Anasarca. Patient's General condition started improving over next 24 hours, urine output was adequate and patient became conscious and oriented. Detailed history was taken

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and she had a history of intermittent Claudication in bilateral upper limb. CT-PA was reviewed which was suggestive of - Pulmonary artery dilated with reversal of aorta-pulmonary ratio s/o pulmonary hypertension.

	Patient	Normal
pANCA	Negative	-
cANCA	Negative	-
SAR-COV-2 IgG Antibody	13.54 AU/ml	< 12 AU/ml
CRP	99 mg/lit	< 6 mg/lit
ESR	45 mm/1hr	-
Anti-TPO Antibody	350 U/ml	<34U/ml

CT Aortography was done, s/o

- Long segment circumferential mural wall thickening with significant luminal narrowing seen involving **right brachiocephalic artery, left subclavian artery,** and **left common carotid artery** just after its origin from arch of aorta throughout its entire visualised course and also involving **right CCA** and **right subclavian artery** with significant enhancement.
- Right subclavian artery not visualised and replaced by multiple collaterals.
- Prominent collaterals noted arising from intercostal and internal thoracic arteries on both sides.
- **Multiple collateral channels** seen in posterior cervical region, neck, axilla and posterolateral chest wall.
- **f/s/o Large Vessel Arteritis - Takayasu arteritis (Type 1).**

Patient was given thyroid hormone replacements, steroids and azathioprine was started and the patient's general condition improved and was discharged.

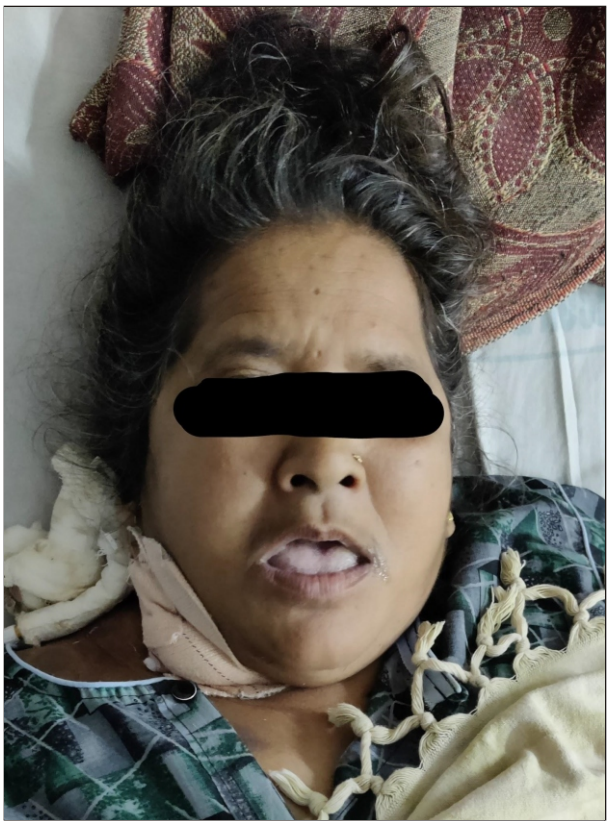

Fig. 1 : **Hypothyroid facies**

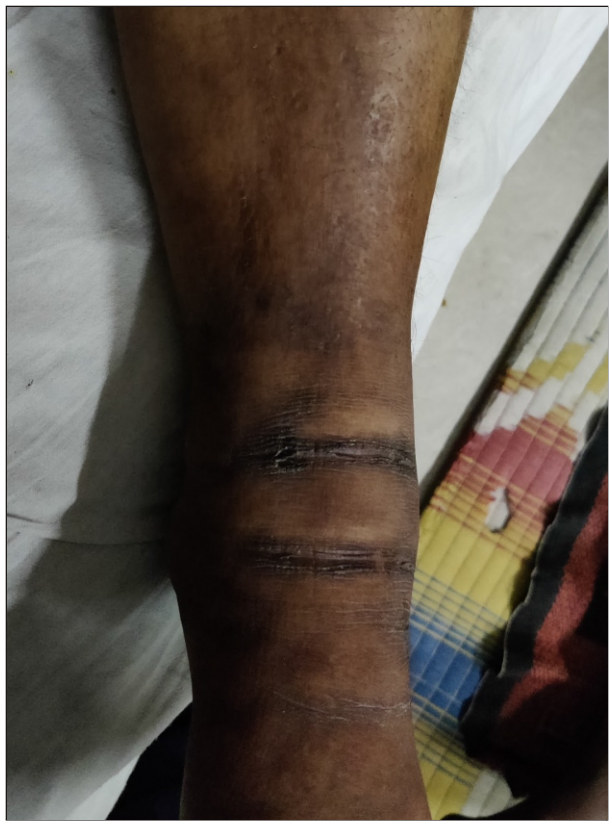

Fig. 2 : **Left lower limb showing chronic skin changes**

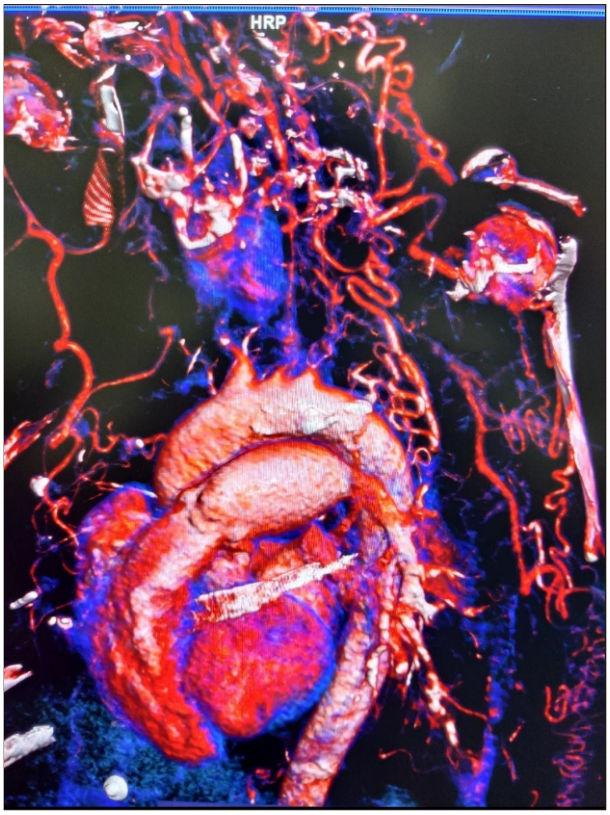

Fig. 3 : **CT Aortography of the patient showing narrowing of major vessels at the origin**

Discussion :

According to the American College of Rheumatology Classification Criteria, 1990 for Takayasu's Arteritis, our patient fulfils three out of the six criteria mentioned. The criteria includes the following

1. Age at disease onset < 40 years : Development of symptoms or findings related to Takayasu arteritis at age < 40 years.
2. Claudication of extremities : Development and worsening of fatigue and discomfort in muscles of 1 or more extremities while in use, especially the upper extremities.
3. Decreased brachial artery pulse : Decreased pulsation of 1 or both brachial arteries.
4. Blood pressure difference > 10 mmHg : Difference of > 10 mmHg in systolic blood pressure between arms.

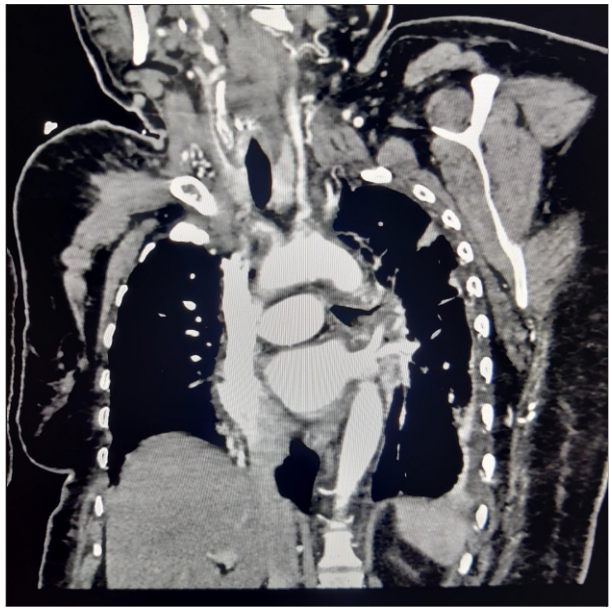

Fig. 4 : **CT Aortography showing narrowing of left internal carotid caliber at origin and throughout the course**

5. Bruit over subclavian arteries or aorta : Bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta.
6. Arteriogram abnormality : Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not caused by arteriosclerosis, fibro muscular dysplasia, or similar causes; changes usually focal or segmental.

Takayasu arteritis can be divided into the following six types based on angiographic involvement :

Type I - Branches of the aortic arch

Type IIa - Ascending aorta, aortic arch, and its branches

Type IIb - Type IIa region plus thoracic descending aorta

Type III - Thoracic descending aorta, abdominal aorta, renal arteries, or a combination

Type IV - Abdominal aorta, renal arteries, or both

Type V - Entire aorta and its branches

Also examination findings and laboratory evaluation was suggestive of hypothyroidism.

Several isolated observations of Thyroid involvement with Takayasu Disease have been reported. Hashimoto's thyroiditis in combination with TD was reported by *Adler S et al.* in a 25-year-old woman, by *Shimokawa H et al.* in a 51-year-old woman, by *Shih G, et al.* in a 54-year-old woman and by *Lee ML et al.* in a 16-year-old girl. *Kettaneh A et al.* reported the association of autoimmune hyperthyroidism with TD in two patients aged 34 and 49; both of them had underlying Crohn's disease, *Ahmed M et al.* reported an autoimmune hyperthyroidism associated with TD in a 52-year-old patient, Xu AJ et al. reported the association of TD with Hashimoto's thyroiditis in a 12-year-old girl. *Bouomrani S et al* proposed two major mechanisms; Direct - the specific thyroid localization of Takayasu vasculitis and Indirect - the association of two dysimmune / autoimmune diseases.

Indirect Mechanism -

The association of TD with several alleles of human leukocyte antigens (HLA) is reported by several authors without individualizing a particularly dominant association. This hypothesis is reinforced by the association of TD with several autoimmune / dys-immune disorders at the same time : TD with autoimmune hepatitis, autoimmune thyroiditis, and chronic sialadenitis in the observation of *Suzuki H et al.,* TD with autoimmune hepatitis, Hashimoto thyroiditis, and pustular dermatitis of the scalp in the observation of *Watanabe S et al.* The observation of several immunological abnormalities concerning both innate and acquired immunity and so humoral and cellular immunity

- *Tamura N, et al.* reported significantly higher levels of TNF-α and interleukin-6 (II-6) in TD compared to the general population with a positive correlation with the disease activity
- The presence of a large polyclonal hypergammaglobulinemia in both the active and inactive forms of TD
- A significantly higher rate of Th17-type T-cells compared to the general population : odds ratio at 2.1 versus 0.75 ($p < 0.0001$)
- Interleukin 17 (Il-17) and interleukin-23 (Il-23) levels significantly higher than the general population : odds ratio at 6.2 versus 3.9 and 15 versus an undetectable level respectively, $p < 0.001$.

Thus, these so-called "unusual" associations of Takayasu's arteritis with autoimmune thyroiditis, in particular that of Hashimoto, reasonably suggest the possibility of a physio-pathological association between them; Cell-mediated immunological mechanisms play an important role in both diseases. Proinflammatory cytokines such as tumor necrosis factor (TNF-α), interleukins 6, 8, 12 and 18 are common to both conditions amplifying the inflammatory process and causing disease in genetically predisposed subjects.

Direct Mechnism :

More rarely, thyroid involvement during TD could result (at least theoretically) from a direct vasculitic mechanism (thyroid specific location of Takayasu arteritis), especially that the thyroid gland is richly vascularized and the involvement of small vessels has been objectified during TD [23]. This hypothesis could explain the cases in which the thyroid dysfunction is not immunological (negative antithyroid antibodies) and where the thyroid imaging shows an enlarged thyroid with local vascular abnormalities suggestive of granulomatous thyroid vasculitis specific for TD.

Prevalence- Patients with GCA have the lowest age and sex-adjusted risk of hypothyroidism while patients with GPA and MPA had the highest risk. Possible explanations for these findings include differences in genetic susceptibilities, immune responses, or treatment exposures between the forms of vasculitis. The interplay of thyroid disease and vasculitis warrants further investigation.

Variable	GCA N=427	TAK N=225	PAN N=108	GPA N=873	MPA N=170	EGPA N=285
Mean age±(SD), years	72 (8.5)	38.4 (12.7)	48.6 (16.2)	50.7 (16.3)	59.7(14.5)	53.3 (13.8)
Female sex, N (%)	300 (70)	209 (93)	60 (55)	467 (54)	107 (63)	159 (56)
Ethnicity, N (%)						
White	413 (97)	182 (81)	92 (85)	800 (92)	151 (89)	248 (87)
African American	5 (1)	10 (4)	5 (5)	15 (2)	4 (2)	6 (5)
Asian	4 (1)	28 (12)	6 (6)	39 (5)	5 (3)	16 (6)
Other	5 (1)	5 (2)	5 (5)	19 (2)	10 (6)	15 (5)
Any thyroid disease, N (%)	55 (23)	20 (9)	7 (7)	107 (12)	31 (18)	26 (9)
Hypothyroidism, N (%)	51 (12)	14 (6)	6 (6)	93 (11)	30 (18)	23 (8)
Hyperthyroidism, N (%)	4 (1)	6 (3)	1 (1)	14 (2)	1 (1)	3 (1)
Any thyroid disease, OR* (95% CI)	0.58 (0.40, 0.85)	0.72 (0.43, 1.20)	0.60 (0.27, 1.32)	1.54 (1.16, 2.05)	1.70 (1.12, 2.59)	0.77 (.050, 1.20)
Hypothyroidism, OR* (95% CI)	0.61 (0.41, 0.90)	0.57 (0.31, 1.03)	0.59 (0.25, 1.38)	1.51 (1.12, 2.05)	1.81 (1.18, 2.80)	0.82 (0.52, 1.30)
Hyperthyroidism, OR* (95% CI)	0.40 (0.13, 1.30)	1.80 (0.65, 4.97)	0.69 (0.09, 5.16)	1.52 (0.72, 3.21)	0.78 (0.18, 3.33)	0.76 (0.23, 2.52)

GCA=giant cell arteritis, TAK=Takayasu arteritis, PAN=polyarteritis nodosa, GPA=granulomatosis with polyangiitis, MPA=microscopic polyangiitis, EGPA=eosinophilic granulomatosis with polyangiitis, N=number of patients, SD=standard deviation, OR=odds ratio, CI=confidence intervals

* age- and sex-adjusted

Table : **Prevalence of Thyroid dysfunction in various types of vasculitis**

Also, our patient had type 2 respiratory failure, which can also be attributed to severe hypothyroidism, possible mechanisms being

(1) Impaired central ventilator responses to hypoxia and hypercapnia;

(2) Hypoventilation caused by respiratory muscle dysfunction; and

(3) Obstructive sleep apnea syndrome (OSAS), likely from pharyngeal narrowing due to soft tissue infiltration by mucopolysaccharides and protein.

Conclusion :

As discussed above, our case having both, thyroid dysfunction and Vasculitis together, is more than mere coincidence. There are many mechanisms proposed, immune-dysregulation being the most logical explanation So, we should have relatively high degree of suspicion in patient with arteritis to screen for thyroid dysfunction, so that timely treatment can be started at an early stage of disease, improving patient's quality of life.

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