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TAKAYASU'S ARTERITIS IN A PATIENT WITH RHEUMATOID ARTHRITIS- A CASE REPORT AND REVIEW OF LITERATURE.

Internal Medicine

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ABSTRACT

We describe a young female diagnosed with Rheumatoid Arthritis (RA) treated with Disease Modifying Anti-Rheumatologic Drug (DMARD) developing Takayasu's Arteritis (TA) few years later. Even though literature exists mainly as case reports describing the coexistence or concurrent occurrence of RA and TA, the exact mechanism behind this phenomenon is not clear. The development of non-specific systemic inflammatory response in the presence of a hereditary or epidemiological background predisposing to both the disease offers a possible explanation for this observation but further understanding of the relation between Takayasu arteritis and Rheumatoid arthritis is required.

KEYWORDS

Takayasu arteritis, Rheumatoid arthritis

INTRODUCTION

Takayasu's Arteritis is a rare form of large vessel vasculitis characterized by chronic, segmental and necrotizing inflammation affecting the aorta and its proximal branches [1], commonly seen in females of reproductive age[2], onset usually between 10 to 40 years[3] and common among Asian women. The aetiopathogenesis still remains tenebrous but sensitisation to infectious agents and resultant molecular mimicry has been postulated in TA development in addition to genetic predilection and environmental factors. Similar mechanisms are advanced in the development of several other autoimmune conditions and reported in association with TA. Observational studies in Takayasu arteritis patients describe a positive Rheumatoid Factor (RF) in some patients. [1][4]

Rheumatoid arthritis is a chronic, symmetrical, polyarthritis involving small joints with a wide variety of extra-articular manifestations.[5] Rheumatoid vasculitis, a rare manifestation, occurs in <1 to 5% of RA patients involves the small and medium sized vessels is responsible for many of the extra-articular manifestations.[6]Case reports on RA and TA co-existence have increased yet the relationship between the two has not been clearly established. Here we describe a young women with Rheumatoid arthritis who later developed Takayasu's arteritis, elaborated her clinical presentation and management.

Case Report

A 27-year-old female patient visited the rheumatology outpatient department of our institution with painful tender small joints of the hand, wrist and knee of both sides for past three months. Her serology for Rheumatoid factor was negative and had a raised Erythrocyte sedimentation rate (ESR), diagnosed as Rheumatoid arthritis (2019). She was admitted for swelling of face and painful joints at 11 years of age and had a blood transfusion at 20 years of age during vaginal delivery of her second child and there was no other past medical history. The patient was started on Methotrexate 10mg/week, Folate 1mg/day, Prednisolone 80mg/day and Omeprazole 20mg BD which improved her symptoms and steroid dose was tapered to 40mg/day. The patient lost to follow-up on resolution of her arthritis and discontinued medications after 2 years of therapy.

She then presented to the Emergency department after 3 years of diagnosis of Rheumatoid arthritis (RA) with complaints of acute onset breathlessness for past three days, grade 3 to 4 MMRC, not relieved by rest, no history of orthopnea or paroxysmal nocturnal dyspnea with a similar episode 1 month back. She also complained of cough with minimal whitish mucoid expectoration tinged with blood for past three days. She is married for 10 years, has two children birthed by normal vaginal delivery, puerperal sterilization done and her menstrual cycles are regular with normal flow. She had no symptoms suggestive of arthritis during this admission.

Recording for her vital signs resulted in identifying that neither pulse nor blood pressure could be measured in both her upper limbs. Palpation for other peripheral pulses revealed feeble carotid and subclavian artery pulsation with absent brachial, radial and ulnar artery pulsations. The lower limb peripheral pulsations were normally felt on both limbs. Lower limb blood pressure was 140/80mmHg and oxygen saturation was 83% in room air which improved to 98% with 6 L/min Oxygen flow in face mask. General examination revealed pallor, normal jugular venous pressure and no peripheral oedema, gangrene or ulcer. Carotid bruit heard and thrill palpable over left common carotid and fundus examination was normal.

Her investigations revealed a microcytic hypochromic anemia with a hemoglobin of 9.9g/dL, mean corpuscular volume 79fL, total count of 10,900 cells/mm3, platelet count of 3.8 lakhs/dL , ESR 24 mm in 30 minutes and 40mm/hr, C-reactive protein was 48 mg/L, Rheumatoid factor level was 9 IU/mL (<10 normal) and D-dimer was 483.3ng/mL. The blood glucose (118mg/dL), urea (21mg/dL), creatinine (0.7mg/dL), serum sodium, potassium, bilirubin, liver enzymes, total protein (6.6g/dL), albumin levels and urinalysis were normal. Immunological profile for Anti-Nuclear antibody (ANA), Anti-Cyclic Citrullinated peptide (Anti-CCP), Extractable Nuclear Antigen (ENA) panel, perinuclear pattern Anti Neutrophil cytoplasmic antibodies (p ANCA) and cytoplasmic pattern (c ANCA) were negative. Patient was started on intravenous antibiotic (ceftriaxone 2g OD), furosemide, Metoprolol 25mg OD, Azithromycin 500mg OD and Atorvastatin 40mg HS.

Table1: Radiological Investigations Done For Further Evaluation.

Imaging	Findings
July/2021	
Echocardiography	Normal LV function, No regional wall motion abnormalities, EF-60%
CT Chest	Diffuse ground glass opacities noted in bilateral lung fields suggestive of interstitial lung disease.
Arterial Doppler	Carotid four vessel –Right common carotid and right internal carotid artery complete occlusion. Left common carotid reduced flow and increased peak systolic velocity in Left internal carotid, left vertebral (55% stenosis) and bilateral subclavian arteries indicating severe stenosis. Bilateral upper limb arteries- monophasic flow noted indicating vascular compromise.
CECT Aortogram of Upper limb	Diffuse circumferential wall thickening noted on the arch of aorta, bilateral common carotid, subclavian and axillary arteries. Right common carotid shows near total occlusion. Coeliac artery shows severe narrowing at its origin. Segmental narrowing noted in bilateral brachial,

	proximal radial and ulnar arteries. Imp: Vasculitis possibly takayasu arteritis.
Multislice CT angiogram of bilateral upper limb	Diffuse circumferential wall thickening noted in the ascending aorta, arch of aorta and descending aorta. Circumferential wall thickening noted, in brachiocephalic trunk, right proximal subclavian, left axillary artery, thickening with thin flow of contrast noted in left common carotid and right subclavian, with complete occlusion of right common carotid. Discontinuous circumferential wall thickening in left subclavian artery. Distal brachial, radial and ulnar arteries appear normal. Features suggestive of Takaysu aortoarteritis.
June 2022	
MRI Brain	Absent flow in bilateral ICA with distal reformation of MCA, ACA from circle of willis.

Based on the radiological investigations patient was diagnosed with Takayasu arteritis and insterstitial lung disease, Injection Methylprednisolone 60mg IV OD converted to oral prednisolone 60mg OD, Aspirin 150mg OD, Methotrexate 10mg/week, Folate 1mg/day and Omeprazole 20 mg BD were started.

Patient was again admitted the next year (June 2022) with complaints of giddiness and blurring of vision for one day, low grade fever for 1 week and similar complaints of breathlessness and cough with expectoration. Her investigations were negative for Widal test, IgM leptospirosis and scrub typhus. Her MRI brain was consistent with previous findings, EEG and fundoscopy was normal, discharged with same drugs as her previous admission.

On serial follow-up after 6 months her ESR is 22mm/hr, with raised total count 19,600, differential count 68%, hemoglobin of 11g/dl and normal renal and liver function test. She had complaints of weight gain, abdominal striae and puffiness of face and her steroid dose was tapered to 40mg/day.

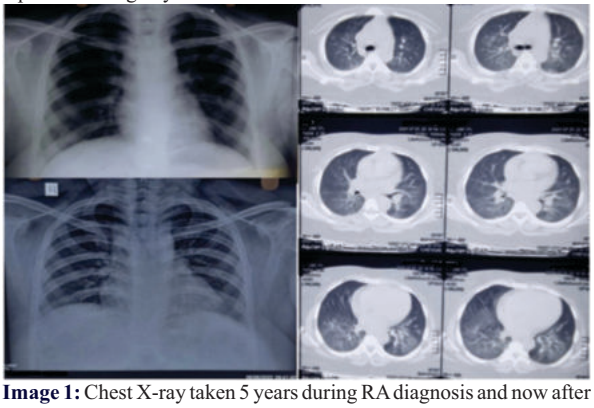

Image 1: Chest X-ray taken 5 years during RA diagnosis and now after ILD

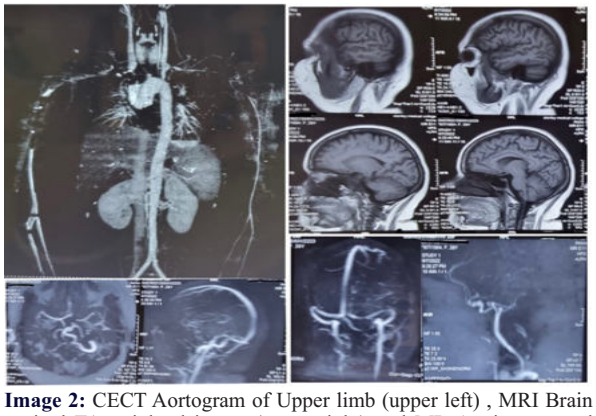

Image 2: CECT Aortogram of Upper limb (upper left) , MRI Brain sagittal T1 weighted image (upper right) and MR Angiogram and Venogram

DISCUSSION

Takayasu arteritis is a panarteritis of large and medium sized arteries[7] results in vessel wall thickening, thrombosis, fibrosis, stenosis or saccular aneurysm. The person presents with non- specific symptoms related to systemic inflammation such as fever, malaise, easy fatigability, weight loss, anorexia, arthralgia or stenosis related symptoms like hypertension, claudication, giddiness, headache, chest pain, and blood pressure variation between both limbs or absent pulse.[8]

It was first described in 1856 by Savory yet the etiology of the disease remains elusive.[2] Autoimmune reactions have been postulated to worsen the vasculitis by cytotoxic T lymphocyte infiltration and pro-inflammatory cytokine production, namely Tumor Necrosis Factor alpha(TNFα) which plays a pivotal role in the pathogenesis of various other autoimmune conditions such as psoriatic arthritis, inflammatory bowel disease, psoriasis, axial spondyloarthropathies, juvenile idiopathic arthritis, non-infectious uveitis and Systemic lupus erythematosus.[9][10]

The environmental factors that trigger these reactions include infectious agents particularly Mycobacterium tuberculosis by two mechanism firstly immune cross reactivity between mycobacterial heat shock proteins (HSPs) and human HSPs or other proteins like HLA class II molecules, cartilage proteoglycan, adventitial layer of large arteries, and sites of increase turbulence. Secondly activation of T cell populations that react with human HSPs, thus implied in the pathogenesis of both TA and RA and a possible link between them.[11]

Table 2: Clinical Profile Of Takayasu Arteritis With Rheumatoid Arthritis Described In Literature

Type of involvement										
Case	**Age/ sex**	**RA Age at onset; yr**	**TA Age at diagnosis; yr**	**RF**	**Nodule**	**Erosion**	**HLA**	**Arteriography**	**Necropsy**	**Reference**
1	63/F	40	63	+	NR	NR	NR	I		[14]
2	65/F	55	65	+	+	NR	NR	I		[14]
3	16/F	16	20	-	-	+	NR	I		[14]
4	49/F	44	49	+	+	NR	NR		III	[14]
5	37/F	37	26	+	+	+	DR4	III		[14]
6	53/F	50	53	-	-	-	NR	I		[14]
7	50/F	48	50	+	NR	NR	NR		III	[14]
8	61/F	50	61	+	+	NR	NR		I	[14]
9	82/F	74	82	-	-	NR	NR		I	[14]
10	68/M	47	68	+	+	NR	NR		III	[14]
11	61/F	58	61	+	+	NR	NR		I	[14]
12	52/F	26	52	+	+	NR	NR		I	[14]
13	69/M	68	69	+	+	NR	NR		Aortic root	[14]
14	60/M	48	60	+	+	NR	NR		?	[14]
15	46/M	37	46	+	+	NR	NR		II	[14]
16	67/M	65	67	+	+	NR	NR		III	[14]
17	64/F	61	64	+	+	NR	NR		III	[14]
18	44/M	?	44	+	+	+	NR	Aortic root		[14]
19	64/F	60	64	+	NR	+	DR 2,12,5	III		[14]
20	36/F	34	36	+	-	+	DR4,1	I		[14]
21	30/F	28	24	+	+	+	NR	NR	NR	[1]
22	50/F	46	39	+	NR	NR	NR		I	[1]
23	49/F	48	49	-	NR	NR	NR	I		[3]
24	45/F	31	39	+	+	+	NR	III		[1]
25	43/F	38	43	+	NR	+	NR	I		[7]
26	40/F	20	28	-	NR	+	NR	II		[8]
27	27/F	24	27	-	-	+	NR	I		Our case

It has been described in association with various other autoimmune conditions such as Crohns disease (less rare)[8] systemic lupus erythematosus, rheumatoid arthritis, sero-negative spondyloarthropathies, inflammatory bowel disease, anterior uveitis, Wegener's granulomatosis, sarcoidosis, amyloidosis, Sweet syndrome, and even some immunodeficiency syndromes.[12]

In the first case series reporting this association suggested an etiological connection to explain the "rheumatic symptoms". The systemic inflammation in RA results in extraarticular manifestations mainly via medium and small vessel vasculitis but inflammation of aortic root has also been reported.[1][2]

Analysis of the 27 cases reports (Table 2) show female predilection (21 females, 6 males), with an average age of diagnosis for RA was 44.3 years and TA was 50 years. In majority of the patients RA was diagnosed first except case reported by Rush et al.[13] The average duration between diagnosis of TA and RA was 7.38 years, but this period is variable as in 6 patients it exceeded 10 years (more than 20 years in three patients).

Six patients were seronegative RA, as described by Abdelghani et al seven deaths in reported in literature were complications of TA which determines the prognosis.[8]

Mariani et al reported a patient (case 25) who developed TA during treatment with TNF alpha inhibitors indicating the presence of other pathophysiologic mechanisms in the development of TA in a subgroup of patients.[7]

With the increasing number of observations on the co-existence of RA and TA it could not be excluded as occurrence by chance. Authors have suggested an immunologic reaction common to both diseases in the background of predisposing genetic factors as a possible explantion but further studies are required to examine this observation.

CONCLUSION

The possibility of Takayasu arteritis should be regarded in a Rheumatoid arthritis patients when patient develops systemic hypertension or symptoms of ischemia.

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