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Cardiovascular imaging

A patient with Takayasu arteritis presenting with malignant hypertension: a case report

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Background Takayasu arteritis (TA) is a rare large-vessel vasculitis primarily affecting the aorta and its proximal branches. The manifestation of TA is variable, ranging from asymptomatic cases to severe organ dysfunction secondary to vascular damage, which often delays diagnosis.

Case summary Here, we present a 37-year-old male patient suffering from visual impairment and malignant hypertension. Emergency fundoscopy showed large left subretinal bleeding and bilateral signs of hypertensive retinopathy. Echocardiographic and magnetic resonance imaging showed mildly reduced left ventricular ejection fraction and signs of hypertensive cardiomyopathy. Evaluation for secondary causes of arterial hypertension did not reveal an underlying disease, and the patient was discharged with optimal medical therapy. He was re-admitted after 11 days with fever of unknown origin, fatigue, and elevated inflammatory markers. The diagnosis of TA was finally established using ^{18}F-fluorodeoxyglucose positron emission computed tomography scan and sonography of carotid and subclavian arteries. Anti-inflammatory combination therapy for active, severe TA with ophthalmologic involvement was initiated using high-dose glucocorticoids and the tumour necrosis factor alpha inhibitor adalimumab to minimize drug-related risks. The patient was scheduled for multidisciplinary follow-up appointments, including specialist consultation in rheumatology, angiology, cardiology, diabetology, and ophthalmology.

Discussion This case highlights the diversity of initial symptoms, the challenges of TA diagnosis, and the importance of comprehensive evaluation for rare secondary causes of arterial hypertension. Individualized acute and long-term care necessitates multidisciplinary management of immunosuppressive therapy, secondary organ involvement, and concomitant diseases.

Keywords Takayasu arteritis • Vasculitis • Secondary hypertension • Cardiovascular disease • Case report

ESC curriculum 2.1 Imaging modalities • 3.1 Coronary artery disease • 6.5 Cardiomyopathy • 9.1 Aortic disease

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Learning points

- Initial symptoms and organ manifestations of Takayasu arteritis (TA) are diverse and may require extensive medical workup and advanced imaging for timely diagnosis.
- Screening for rare secondary causes of arterial hypertension should be considered in patients with other findings suggestive of vasculitis.
- Visual symptoms should be recognized as a red flag of potential secondary retinal involvement in TA patients.
- Immediate anti-inflammatory therapy relies on high-dose glucocorticoids to stop vascular inflammation. Long-term immunosuppressive strategy should, however, include glucocorticoid-sparing partners, such as tumour necrosis factor (TNF) alpha inhibitors.
- Acute care as well as long-term follow-up should be coordinated in multidisciplinary teams including rheumatologists, angiologists, ophthalmologists, cardiologists, and other specialists, based on the individual disease phenotype.

Introduction

Takayasu arteritis (TA) is a large-vessel vasculitis commonly affecting the aorta, its proximal branches, and pulmonary arteries.[1] The incidence in Europe ranges from 0.4 to 3.4 per 1 000 000 persons per year with a female predominance.[2–4] The typical onset of symptoms occurs between 10 and 45 years of age.[2,4] The pathophysiology is not fully understood but involves T-cell dominated infiltration of the arterial wall tissue leading to vascular damage, stenosis, and even aneurysmatic dilatation.[2,3] Depending on the quality and location of lesions, the disease may manifest with a wide variety of symptoms, laboratory findings, and organ involvement, including myocardial ischaemia and kidney dysfunction.[5,6] Here, we report a patient initially presenting with visual impairment and malignant hypertension, who was subsequently diagnosed with TA. This case highlights the diversity of clinical manifestations of TA, the importance of comprehensive evaluation for causes of secondary hypertension, and the challenges of individualized immunosuppressive therapy for this rare disease.

Case presentation

A 37-year-old male patient presented to the emergency department with visual impairment and photophobia. He had noticed a black line in the visual field of his left eye 3 days ago. Physical examination was otherwise unremarkable. The patient had a body mass index (BMI) of 37 and a 31 pack-year smoking history. He was previously diagnosed with arterial hypertension and started taking candesartan 8 mg b.i.d. approximately 5 years prior without attending any regular check-ups. On admission, his blood pressure was 243/149 mmHg, which was lowered immediately using amlodipine and intravenous urapidil. Other vital signs were within normal ranges, and the patient denied further neurological or cardiovascular symptoms. Examination of the heart, lungs, abdomen, and fluid status was unremarkable. Emergency fundoscopy showed a large subretinal bleeding near the left macula and bilateral Roth and cotton wool spots consistent with hypertensive retinopathy. The patient was admitted to the cardiology department for further evaluation and management of malignant hypertension.

Resting electrocardiogram showed normal sinus rhythm with left anterior fascicular block and t-wave inversions in I, aVL, V5, and V6. There were no signs of intracranial bleeding or stroke on computed tomography scan of the brain. Laboratory testing revealed hyperlipidaemia [low-density lipoprotein 177 mg/dL (normal range <115 mg/dL)], elevated HbA1c (6.7%) (normal range <5.5%), and leucocytosis (12.9 G/L) (normal range 3.9–10.2 G/L) (*Table 1*). Inpatient 24 h blood pressure monitoring values were still substantially increased (24 h mean 181/128 mmHg, reverse dipping profile, no side difference) (*Figure 1A*). Transthoracic echocardiography showed a mildly reduced left ventricular (LV) ejection fraction without regional wall motion abnormalities and LV hypertrophy (interventricular septum thickness 20 mm, posterior LV wall thickness 23 mm) without obstruction of the LV outflow tract or systolic anterior movement phenomenon, in summary consistent with hypertensive cardiomyopathy. Contrast-enhanced cardiac magnetic resonance imaging confirmed these findings but showed no signs of myocardial oedema, infiltrative cardiomyopathy, or specific distribution of late gadolinium enhancement (*Figure 1B* and *C*).

Based on the patient's age, severely elevated blood pressure, and presence of hypertension-mediated organ damage, evaluation of common causes of secondary hypertension was initiated according to the current European Society of Cardiology/European Society of Hypertension guidelines.[7] Renal artery duplex sonography did not show signs of relevant renovascular disease. Regular serum creatinine, plasma metanephrine, and 24 h urinary cortisol excluded parenchymal kidney disease, phaeochromocytoma, and Cushing's disease, respectively. Plasma aldosterone–renin ratio, plasma parathyroid hormone levels, and thyroid function were normal, as well. The patient was discharged with optimized anti-hypertensive and heart failure medication including candesartan (16 mg b.i.d.), amlodipine (5 mg b.i.d.), bisoprolol (2.5 mg b.i.d.), doxazosin (4 mg b.i.d.), and spironolactone (25 mg q.d.), as well as metformin (500 mg q.d.) and atorvastatin (40 mg q.d.) (*Table 2*). He was advised for smoking cessation, life-style modification, and ambulatory polygraphy for evaluation of obstructive sleep apnoea.

Table 1 Initial laboratory values and diagnostic tests for secondary causes of arterial hypertension

Parameter	Result	Normal range
Leucocytes	12.3 G/L	3.9–10.2 G/L
Hemoglobin	14.8 g/dL	13.5–17.5 g/dL
Thrombocytes	328 G/L	146–328 G/L
Sodium	141 mmol/L	135–145 mmol/L
Potassium	4.0 mmol/L	3.5–5.1 mmol/L
C-reactive protein	1.0 mg/dL	<0.5 mg/dL
Procalcitonin	<0.1 µg/L	<0.1 µg/L
Low-density lipoprotein	177 mg/dL	<115 mg/dL
HbA1c	6.7%	<5.5%
Serum creatinine	1.2 mg/dL	0.7–1.2 mg/dL
Glomerular filtration rate	77 mL/min	>60 mL/min
Thyroid stimulating hormone	1.72 mU/L	0.27–4.20 mU/L
Free triiodothyronine	2.9 ng/L	1.71–3.71 ng/L
Free thyroxine	1.4 ng/L	1.71–3.71 ng/L
Plasma metanephrines	42 ng/L	<90 ng/L
24 h urinary cortisol	1.7 µg/dL	4.2–60 µg/dL
Aldosterone–renin ratio	4.7	<20

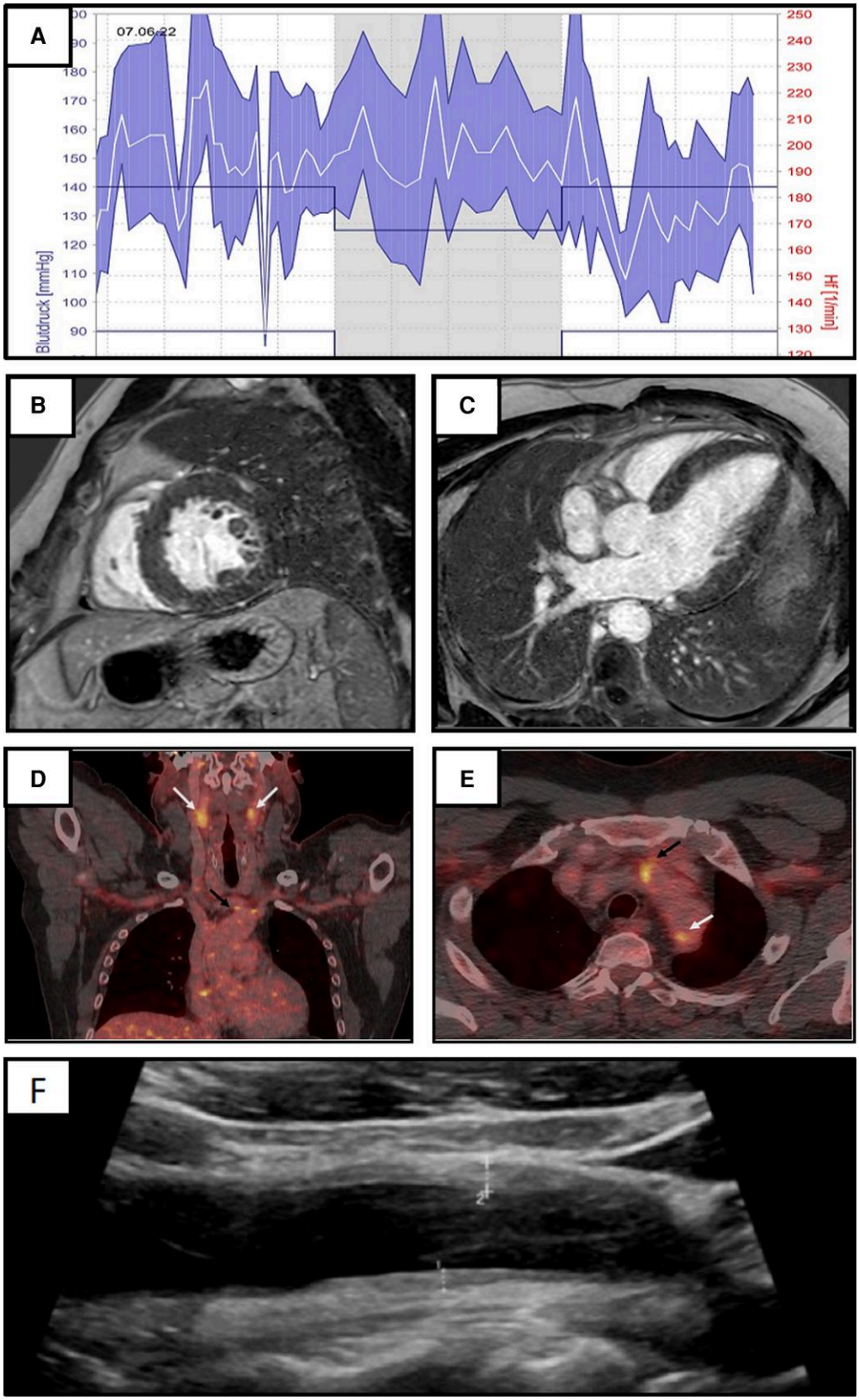

Figure 1 (*A*) 24 h blood pressure monitoring showing substantially increased values and reverse dipping profile. (*B*,*C*) Contrast-enhanced cardiac magnetic resonance imaging showing left ventricular hypertrophy without signs of late gadolinium enhancement or left ventricular outflow tract obstruction. (*D*) ^{18}F-fluorodeoxyglucose positron emission computed tomography scan showing increased uptake at the origin of the brachiocephalic trunk (black arrow) and the carotid arteries (white arrows). (*E*) Increased tracer uptake at the origin of the brachiocephalic trunk (black arrow) and left subclavian artery (white arrow). (*F*) Vascular sonography of the carotid arteries showing typical homogeneous and hyperechoic wall thickening of the left carotid (2.6 mm) ('macaroni sign').

Table 2 Initial medical treatment for arterial hypertension, heart failure, and diabetes mellitus

Medication	Dose
Bisoprolol	2.5 mg b.i.d.
Candesartan	16 mg b.i.d.
Amlodipine	5 mg b.i.d.
Spironolactone	25 mg q.d.
Doxazosin	4 mg b.i.d.
Metformin	500 mg q.d.
Atorvastatin	40 mg q.d.

After 11 days, the patient's clinical condition worsened. He reported daily episodes of fever up to 38.0°C, night sweats, and fatigue and was re-admitted. The patient denied dyspnoea, chest pain, or symptoms of infection. Inflammatory markers were elevated [C-reactive protein 8.2 mg/dL (normal range <0.5 mg/dL), erythrocyte sedimentation rate 88 mm/h (normal range <15 mm/h), and leucocytes 12.3 G/L (normal range 3.9–10.2 G/L)]. Transoesophageal echocardiography was performed, which did not show evidence of vegetation formation. Blood culture samples remained sterile. Laboratory screening showed negative anti-nuclear antibodies, anti-neutrophil cytoplasmatic antibodies, and rheumatoid factor. An ^{18}F-fluorodeoxyglucose positron emission computed tomography (^{18}F-FDG PET-CT) scan was performed, which identified areas of abnormal tracer uptake in both common carotid arteries [target-to-blood pool ratio (TBR): 1.3] as well as the brachiocephalic trunk (TBR: 1.3) and subclavian arteries (*Figure 1D* and *E*). There was no relevant involvement of the pulmonary artery or the aorta itself other than areas adjacent to the origins of affected supra-aortic vessels (*Figure 1D* and *E*). There were no signs of active coronary lesions. The diagnosis of TA was substantiated using vascular sonography, which showed typical homogenous hyperechoic wall thickening of the left carotid (2.6 mm) (*Figure 1F*) and left subclavian artery (2.4 mm).[8] Furthermore, extended ophthalmological evaluation showed ocular manifestations consistent with Takayasu retinopathy. Conclusively, the patient fulfilled three major and three minor criteria according to the 1995 diagnostic algorithm by Sharma *et al.*[9]

Table 3 Takayasu arteritis anti-inflammatory medication plan

Timeline	Dose of prednisolone
Days 1–3	1000 mg/d intravenous
Days 4–7	250 mg/d intravenous
Weeks 2–3	100 mg/d per os
Week 4	80 mg/d per os
Week 5	60 mg/d per os
Week 6	40 mg/d per os
Week 7	30 mg/d per os
Week 8	20 mg/d per os
Week 9	15 mg/d per os
Week 10	10 mg/d per os
Week 11	40 mg/d (due to temporary C-reactive protein elevation)
Week 12	30 mg/d per os
Week 13	20 mg/d per os
Week 14	15 mg/d per os
Week 15	10 mg/d per os
Timeline	**Dose of adalimumab**
Since week 2	40 mg subcutaneous injection every 14 days

We began treatment of active severe TA with retinal involvement using 1000 mg intravenous methylprednisolone q.d. for 3 days, following 250 mg q.d. for 4 days, and switched to oral application with 100 mg q.d. for another 14 days[10] (*Table 3*). The patient temporarily required additional insulin treatment for blood glucose control [max 346 mg/dL (normal range <100 mg/dL)], which was terminated after steroid dose adjustment. Dual-energy X-ray absorptiometry (DEXA) scan yielded a minimal *T*-value of −1.4, indicating osteopenia. We decided to start glucocorticoid-sparing therapy using adalimumab 40 mg every 14 days. This allowed for gradual reduction of prednisolone dose to 10 mg per day, followed by further tapering. The patient's discharge medication otherwise included candesartan (16 mg b.i.d.), amlodipine (5 mg b.i.d.), bisoprolol (2.5 mg b.i.d.), doxazosin (8 mg b.i.d.), eplerenone (25 mg q.d.), pantoprazole (40 mg q.d.), metformin (1000 mg b.i.d.), cholecalciferol (1000 units q.d.), and atorvastatin (40 mg q.d.).

Eight weeks after discharge, the patient reported feeling overall well. His blood pressure had stabilized allowing for discontinuation of doxazosin. He was cleared for ophthalmic surgery and underwent pars plana vitrectomy and pan-retinal endolaser photocoagulation of his left eye, which significantly improved his vision. The patient was scheduled for multidisciplinary follow-up appointments, including specialist consultation in rheumatology, cardiology, diabetology, angiology, and ophthalmology.

Discussion

Early clinical signs of TA typically reflect a general inflammatory state, while advanced stages are characterized by findings related to vascular damage, such as neurological symptoms, peripheral pulselessness, claudication, or blood pressure discrepancies.[2] Standard laboratory markers of systemic inflammation as well as specific parameters for autoinflammatory diseases do not correlate with disease status in TA patients and have therefore limited usefulness for the diagnostic process if vasculitis is suspected.[11] Diagnostic algorithms consequently rely on imaging of the aorta and its major branches when epidemiological, clinical, and laboratory information implies the possibility for TA. The selection of imaging modalities depends on local expertise and availability; however, screening for an unknown origin of fever may justify the early use of functional imaging instead of magnetic resonance or computed tomography angiography. ^{18}F-fluorodeoxyglucose positron emission computed tomography scans offer a powerful combination of whole-body imaging and mapping of inflammatory activity and have therefore been used more extensively to provide imaging support for the diagnosis of TA despite higher radiation exposure.[2] In a recent meta-analysis, Soussan and colleagues estimated the pooled sensitivity and specificity at 87 and 73%, respectively.[12] Especially for follow-up purposes, (contrast-enhanced) arterial sonography offers the possibility of radiation-free and time-effective monitoring of vascular changes, including haemodynamic information.[13] If the affected vessels are accessible, sonography could therefore be considered for initial diagnostics.

It is not unusual for TA patients to present with end-organ pathologies secondary to vasculitis. Functional stenosis of the affected arteries can lead to ischaemia-driven symptoms of the respective downstream organ, i.e. chest pain, gastrointestinal, respiratory, or neurological symptoms. Ocular ischaemia occurs more rarely, but vision impairment was reported by 30%,[14] and retinopathy detected in 4% in French

multicentre analysis of 318 patients.[4] Importantly, visual symptoms are also seen in patients with giant cell arteritis, even though this large-vessel vasculitis primarily affects older individuals.[2] Takayasu arteritis retinopathy commonly features dilation or malformation of small arteries, but also bleeding and neovascularization indicating ischaemia.[15] Extensive ophthalmologic screening for vasculitis may be sensible based on suggestive general and visual symptoms. Besides, laser application, intravitreal injection of anti-vascular endothelial growth factor agents, anti-platelet therapy, and other therapeutic options potentially control concomitant ocular disease, which emphasizes the need for close cooperation between ophthalmologic and medical specialists.

The patient reported in this article primarily suffered from malignant hypertension with hypertensive retinopathy, which triggered evaluation for secondary causes of arterial hypertension. In a retrospective analysis of 381 TA patients, 57.5% initially presented with hypertension, which is consistent with previously published data from other Asian populations, but higher compared to the European cohort reported by Comarmond *et al.*[4,16,17] This overlap may result both from renal artery involvement or blood pressure dysregulation based on arteritis affecting the aorta and its branches.[16] In the absence of clinical cues for arteritis, the standard search for secondary causes of hypertension does not include TA.[7] Considering that the diagnosis of TA is often established months after the first symptoms occur,[4] a focused clinical examination including blood pressure measurement on all extremities, auscultation for arterial bruits, and extensive arterial palpation in younger patients with hypertension could potentially accelerate diagnosis and treatment initiation.

Without specific treatment, TA patients with severe hypertension are at higher risk of death or major events.[18] Male sex and elevated C-reactive protein levels are predictive of relapse, but on the contrary, smoking history is associated with event-free survival.[4] It has also been shown that retinopathy is an independent predictor of complication-free survival and vascular complications, which makes ophthalmologic assessment essential for estimating individual risk.[4] The presence of hypertension-related cardiac and visual impairment in this case underlines the importance of early treatment for both the underlying arteritis and its complications. Considering the high relapse rate, most patients require long-term immunosuppressive therapy.[4] Today, various disease-modifying anti-rheumatic agents are available to moderate side effects related to highly dosed systemic glucocorticoid therapy, which is usually initiated as first-line therapy for acute TA.[10,19] Timely consideration of these agents is therefore recommended as part of contemporary TA management.[10,19] Although data from prospective clinical trials is not available, the use of tumour necrosis factor (TNF) inhibitors, such as adalimumab, has shown promising results compared to methotrexate and azathioprine.[20,21] In the present case, early TNF inhibitor treatment and reduction of glucocorticoid dose improved blood glucose control and led to clinical stabilization and adequate complication management.

Conclusion

Due to the knowledge gaps regarding TA pathogenesis, the lack of biomarkers, and the variety of symptoms, the diagnosis of this rare disease is an ongoing challenge. This case report highlights the importance of a comprehensive evaluation for secondary causes of arterial hypertension including TA and the value of functional imaging for pinpointing the diagnosis. The growing number of advanced imaging modalities and disease-modifying anti-inflammatory drugs raises important questions concerning individualized long-term care and therefore requires prospective clinical trials to optimize outcomes.

Lead author biography

Laura Villegas Sierra graduated from the University of Antioquia in Medellín, Colombia, in 2019. After internships on different heart centres in Germany, the Netherlands, and France and practising in Colombia, she is currently working as a cardiology resident at LMU Klinikum in Munich, Germany. Her scientific interest is in electrophysiology and cardiovascular risk reduction.

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Data availability

The dataset analysed during the current case report is available from the corresponding author on reasonable request. The data are not publicly available due to ethical restrictions and legal constraints. Readers may contact Dr. Lüsebrink for reasonable requests for the data.

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