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CASE BASED REVIEW

Childhood-onset Takayasu arteritis and immunodeficiency: case-based review

Seher Sener[1] · Ozge Basaran[1] · Ezgi Deniz Batu[1] · Erdal Atalay[1] · Saliha Esenboga[2] · Deniz Cagdas[2] · Bulent Baris Kuskonmaz[3] · Yelda Bilginer[1] · Fatih Ozaltin[4] · Berna Oguz[5] · Ali Duzova[4] · Ilhan Tezcan[2] · Seza Ozen[1]

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Abstract

Takayasu arteritis (TAK) has been rarely reported in patients with immunodeficiency. In this review, we present two cases with childhood-onset TAK (c-TAK) and primary immunodeficiency while reviewing similar cases in the literature. We reviewed the data for our two pediatric patients with c-TAK and primary immunodeficiency. We also reviewed the literature for patients with c-TAK and immunodeficiency from the inceptions of the databases up to November 2021. A 14-year-old patient had lipopolysaccharide-sensitive beige-like anchor (LRBA) deficiency, and a 16-year-old had X-linked severe combined immunodeficiency (X-linked SCID). During the follow-up, they developed findings suggestive of vasculitides such as hypertension, elevation in acute phase reactants, weakness, and weight loss. Thoracoabdominal computed tomography angiography revealed findings consistent with vasculitis involving the aorta and its major branches. Patients were diagnosed with c-TAK, and corticosteroids were given to both patients in the treatment. We identified 11 articles describing 17 TAK patients with immunodeficiency in our literature search. Two of the patients with c-TAK were infected with human immunodeficiency virus (HIV), another patient had Wiskott-Aldrich syndrome, and the other had idiopathic CD4 + T lymphocytopenia. Nine adult patients with TAK were infected with HIV, three patients had common variable immunodeficiency disorder (CVID), and the other had STAT1 gain-of-function mutation. Clinicians should consider that immunodeficiencies may be accompanied by vasculitic conditions such as TAK. Hypertension, increased inflammatory markers, and constitutional symptoms may be red flags for the development of TAK.

Keywords Childhood-onset · Immunodeficiency · Takayasu arteritis · Vasculitis

Introduction

Childhood-onset Takayasu arteritis (c-TAK) is a vasculitis of unknown etiology characterized by intramural granulomatous inflammation of the aorta, the proximal portion of its major branches, and the pulmonary arteries [1, 2]. Vascular inflammation primarily causes wall thickening, followed by stenosis and thrombus formation, leading to organ dysfunction secondary to ischemia [3–5].

Inflammation is a central feature in the pathogenesis of TAK. The inflammation may be localized to a portion of the thoracic or abdominal aorta and branches or involve the entire vessel [6]. The immunohistopathologic examination has shown that the infiltrating cells in aortic tissue mainly consist of cytotoxic lymphocytes, especially gamma delta T lymphocytes [7]. The inflammatory process within the vessel can lead to narrowing, occlusion, or dilation of involved portions of the arteries in which causes a wide variety of symptoms.

Various infectious agents, genetic factors, and cellular immunity are thought to play a role in the development of TAK [8, 9]. Vasculitis has been reported in patients with various forms of primary immunodeficiency in case reports in the literature, albeit rare [10–12]. Although the cause of the coexistence of immunodeficiency and vasculitis is not fully understood, it is speculated that immune dysregulation predisposes to inflammatory vasculitides [13]. Vasculitis complicating immunodeficiency can represent a challenging confounder and mimic of serious infections. Clinicians caring for patients with primary immunodeficiency need to be aware that vasculitis may be a rare manifestation associated with immunodeficiencies.

✉ Seza Ozen
sezaozen@hacettepe.edu.tr

Extended author information available on the last page of the article

This report presents two cases in which c-TAK with primary immunodeficiency and analyses previously published cases of TAK and immunodeficiency.

Search strategy for systematic literature review

We screened PubMed/MEDLINE and Scopus. We used the keywords of "Takayasu arteritis," "large vessel vasculitis," and "immunodeficiency" and searched all literature from the inceptions of the databases to June 20th, 2022. The search was restricted to English articles. Case reports/series, original research articles, editorials, and review articles about TAK patients with immunodeficiency were analyzed. The articles, including data about TAK patients with immunodeficiency, have been included in the final analysis. Two authors (OB and SS) independently screened titles, abstracts, and full texts of all relevant articles. Gender, age at disease onset, age at diagnosis, signs, symptoms, laboratory findings, radiologic findings, treatments, and outcomes of the patients were evaluated.

Case 1

A 14-year-old boy, who was followed up with the diagnosis of lipopolysaccharide-sensitive beige-like anchor (LRBA) deficiency, suffered from biopsy-proven drug or infection-associated tubulointerstitial nephritis (TIN); creatinine values returned to normal values following discontinuation of

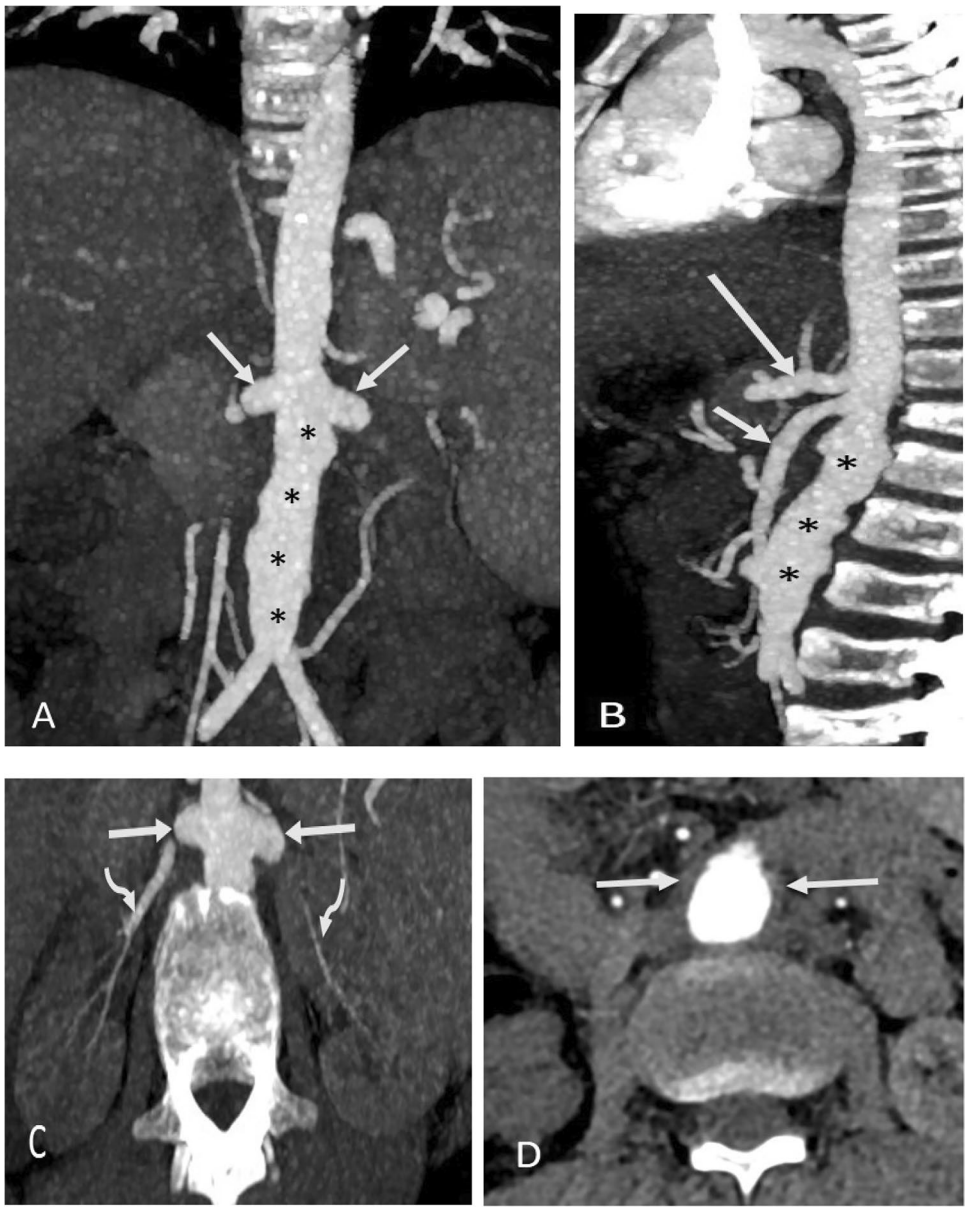

Fig. 1 Takayasu arteritis **(case 1)** involving the abdominal aorta and bilateral renal artery. (**A**, B) Coronal **(A)** and sagittal **(B)** maximum intensity projection CT angiography images show focal dilatations of the abdominal aorta with contour irregularities from the level of the renal artery origin to the aortic bifurcation *(asterisks)*. (**A**) Aneurysmatic enlargement followed by total occlusion is observed at the right and left renal artery origins *(arrows)*. (**B**) Diameter of the celiac trunk *(long arrow)* and superior mesenteric artery *(short arrow)* are normal. (**C**) Axial maximum intensity projection CT angiography image shows aneurysmatic enlargement of the right and left renal artery origins followed by total occlusion *(arrows)*. Contrast filling of both renal arteries *(curved arrows)* develops through collateral vessels. (**D**) Axial CT angiography image shows irregular wall thickening of the abdominal aorta *(arrows)*

potential drugs. About 2 months later, the patient's hypertensive values were detected and he had an episode of posterior reversible encephalopathy syndrome.

He had stage II hypertension (between 150/100 and 170/110 mm Hg) despite multiple antihypertensive drugs [beta-blocker, angiotensin-converting enzyme [14] inhibitor, anti-aldosterone agent, calcium channel blocker, and alpha-adrenoreceptor antagonist]. He also had intermittent headaches. Physical examination revealed no significant difference in blood pressure between the four extremities, no loss of pulse/weakness, nor any murmurs. Moreover, although the patient did not have any signs of an active infection, the acute phase reactants were consistently high. C-reactive protein (CRP) was 17 mg/L (range = 0–8), while erythrocyte sedimentation rate (ESR) was 38 mm/h (range = 0–20) Additional laboratory tests, including complete blood cell count, urinalysis, and kidney and liver function tests, were normal. Findings from the remaining vasculitis and autoimmune workup were negative, including the antinuclear antibody and antineutrophil cytoplasmic antibodies screen.

Computed tomography (CT) angiography of the thoracoabdominal aorta was performed for the vascular assessment. CT angiography images revealed prominent contour irregularities, wall thickness, and focal dilatation of the abdominal aorta from the level of the renal artery origin to the aortic bifurcation and also focal enlargement at the level of both renal artery origins, followed by complete occlusion (Fig. 1). The patient was diagnosed with TAK. After three days of pulse methylprednisolone (15 mg/kg/day) therapy, oral prednisolone was continued at 1 mg/kg/day and gradually

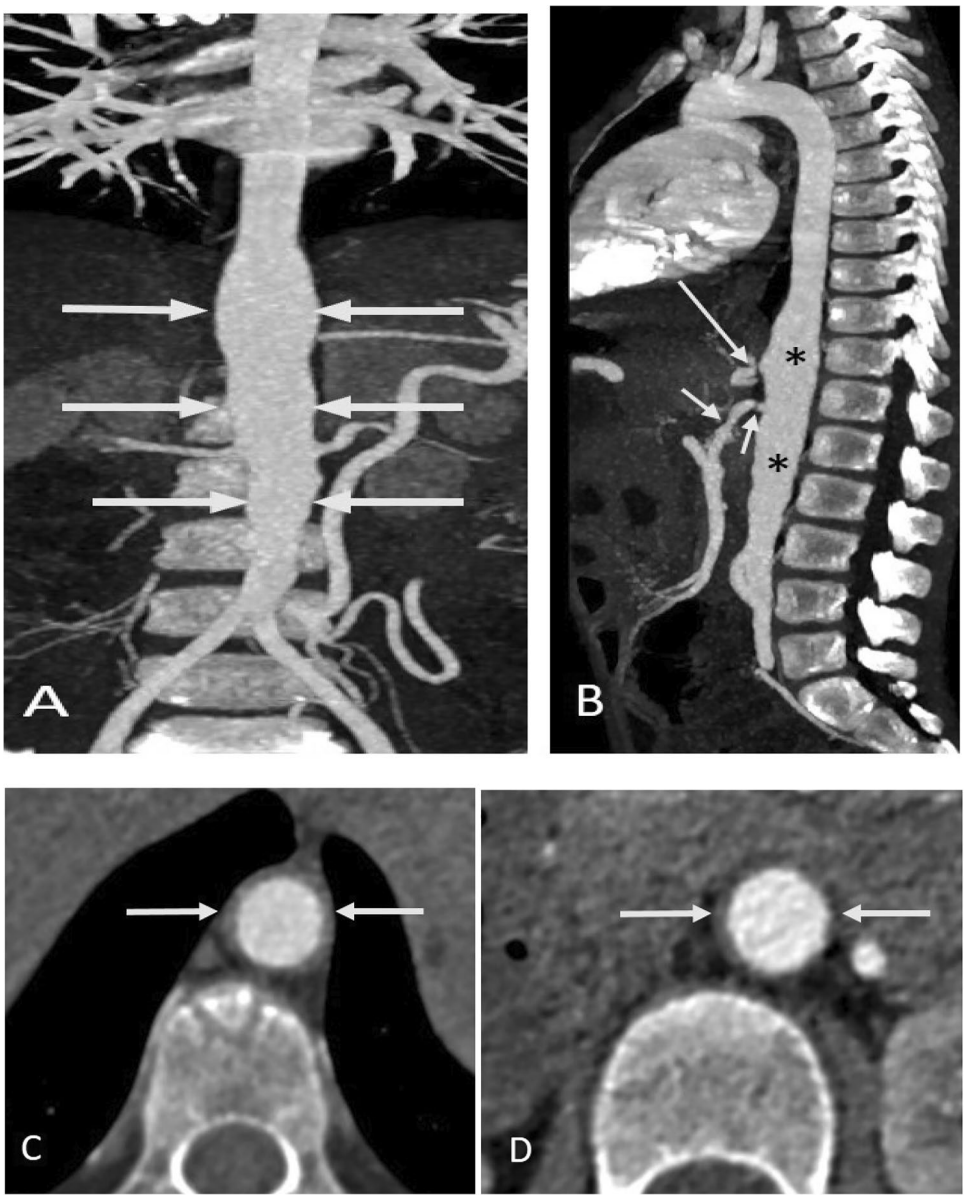

Fig. 2 Takayasu arteritis **(case 2)** involving distal part of descending thoracic aorta, abdominal aorta, celiac trunk, and superior mesenteric artery. (**A**) Coronal maximum intensity projection CT angiography image shows dilatation (aneurysm formation) and luminal irregularity of the terminal part of descending thoracic aorta and abdominal aorta *(arrows).* (**B**) Sagittal maximum intensity projection CT angiography image shows subtotal occlusion at the origin of the celiac trunk *(long arrow) and* stenosis at the origin and proximal segment of the superior mesenteric artery *(short arrows)* besides the dilatation of distal descending thoracic aorta and abdominal aorta *(asterisk).* (**C**) Axial CT angiography image shows concentric diffuse wall thickening of the thoracic aorta *(arrows).* (**D**) Axial CT angiography image shows concentric diffuse wall thickening of the abdominal aorta *(arrows)*

decreased to 5 mg/day. Blood pressure control was achieved (< 90th percentile for age, gender, and height) with antihypertensive drugs, and the bone marrow transplant (BMT) was performed in the follow-up. Three months after BMT, his physical exam is normal and he continues to be followed up with low-dose corticosteroid therapy.

Case 2

A 16-year-old boy with a history of recurrent respiratory infection was diagnosed with X-linked severe combined immunodeficiency (X-linked SCID), due to a genetic defect in the interleukin-2 receptor gamma common chain and bronchiectasis for ten years, presented with cough, weakness, and weight loss. He was on regular monthly intravenous immunoglobulin (IVIG) therapy for the underlying immunodeficiency. His blood pressure was 155/108 mm Hg at admission. On physical examination, the patient had bilateral rales in the lower zones of the lungs, and his pulse was weak in the lower extremities. His laboratory findings revealed an elevated CRP level (37 mg/L) and an elevated ESR (53 mm/h). Other laboratory tests were normal except for hemoglobin, which was 9.4 g/dL. Chest CT revealed mild bronchiectasis and peribronchial thickenings in all lobes of the bilateral lung, linear atelectasis, and also significant enlargement in the diameter of the distal descending thoracic aorta and abdominal aorta. These findings were evaluated by the radiologist as significant in terms of vasculitis. Thereupon, the patient underwent thoracoabdominal aorta CT angiography. CT angiography showed fusiform aneurysmatic enlargement in the section starting from the terminal part of the descending aorta and extending to the infrarenal aorta, aortic wall thickening and irregularity, subtotal occlusion at the origin of the celiac trunk, and severe segmental stenosis of the superior mesenteric artery (Fig. 2).

Thus, the patient was diagnosed with TAK. After three-day pulse methylprednisolone (15 mg/kg/day), treatment was continued with oral prednisolone 1 mg/kg/day, and also adalimumab (25 mg/m^2/twice a week) was started. BMT was planned for the patient, but the family did not give consent. In the follow-up, the patient had severe hypertensive values under low-dose prednisolone (5 mg/day), adalimumab, and two antihypertensive drugs treatment (beta-blocker and ACE

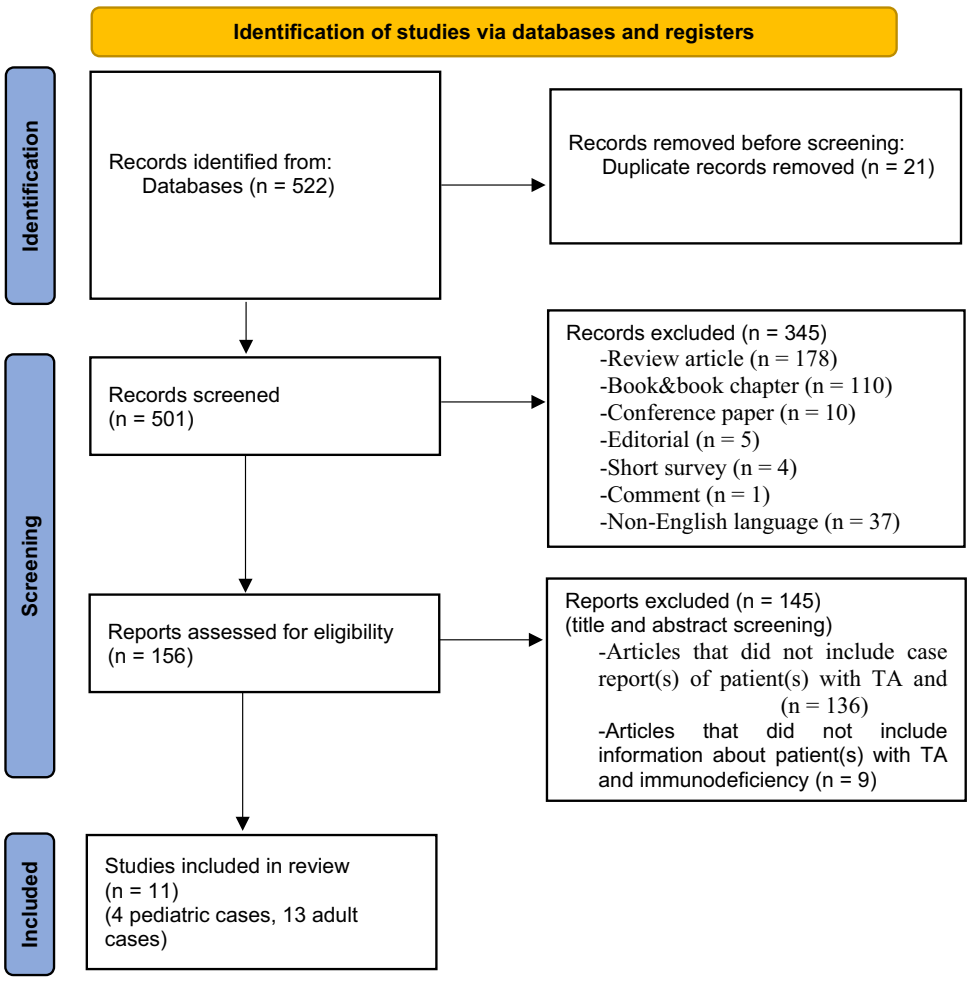

Fig. 3 The PRISMA flow diagram of literature screening

Table 1 The characteristics of previously reported four cases of childhood-onset Takayasu arteritis-associated immunodeficiency and our cases

First author, year (ref. #)	Age at diagnosis	Gender	Associated immunodeficiency	Clinical features at diagnosis of TAK	CRP, ESR	Radiologic findings	Treatment	Outcome
Lau, 1992 [18]	5.5 years	Male	Wiskott-Aldrich syndrome	Abdominal pain, twitching of limbs and face, hypertension	NA	On conventional aortogram: a saccular aneurysm with narrowing of the origin of the right renal artery and stenotic left renal artery, impairment of contrast flowing into the left renal artery with a delayed filling of the superior mesenteric artery, and an enlarged collateral artery was seen rising from the inferior mesenteric artery	Surgery	Exitus
Shingadia, 1999 [20]	16 years	Male	Infected with HIV	High-grade fever, malaise, absence of the left brachial and radial pulses	ESR: 55 mm/h	On CT: circumferential mural thickening of the aortic arch and the descending thoracoabdominal aorta consistent with aortitis On conventional aortogram: focal dilatation of the aortic arch and the thoracoabdominal aorta between the diaphragm and celiac trunk	Corticosteroid, antiretroviral and antituberculosis therapy	In remission
Kilic, 2002 [19]	9 years	Male	Idiopathic CD4 + T lymphocytopenia	Dyspnea, malaise, cough, hypertension, decreased left radial and brachial pulses, heart failure	ESR: 71 mm/h	On MRI: dilatation and irregular contour of the ascending and descending aorta, and narrowing of the abdominal aorta On conventional angiography: narrowing of the left subclavian artery, dilatation of the thoracic aorta, occlusion of the superior mesenteric and renal arteries	Corticosteroid	Exitus
Baruteau, 2011 [17]	11 years	Male	Infected with HIV	Fever, breathlessness, blood pressure asymmetry in the upper limbs, absence of the left radial pulse	NA	On CT scan: dilation of the left ventricle, occlusion of the proximal circumflex artery, and a giant coronary artery aneurysm located in the proximal left anterior descending artery On vascular Doppler US: vasculitis lesions of the vertebral, subclavian, and femoral arteries and the celiac trunk were occluded	Corticosteroid, antiretroviral and antituberculosis therapy, vitamin K antagonist, beta-blocker, ACE inhibitor, anti-aldosterone agent	In remission
Case-1	14 years	Male	LRBA deficiency	Headache, hypertension	CRP: 17 mg/L ESR:38 mm/h	On CT angiography: prominent contour irregularities, wall thickness and focal dilatation of the abdominal aorta from the level of the renal artery origin to the aortic bifurcation and also focal enlargement at the level of both renal artery origins, followed by complete occlusion	Corticosteroid, beta-blocker, ACE inhibitor, anti-aldosterone agent, calcium channel blocker and alpha-adrenoreceptor antagonist	In remission

Table 1 (continued)

First author, year (ref. #)	Age at diagnosis	Gender	Associated immunodeficiency	Clinical features at diagnosis of TAK	CRP, ESR	Radiologic findings	Treatment	Outcome
Case-2	16 years	Male	X-linked severe combined immunodeficiency (a genetic defect in the interleukin-2 receptor gamma common chain)	Cough, weakness, weight loss, hypertension and weak lower limb pulses	CRP: 37 mg/L ESR: 53 mm/h	On CT angiography: fusiform aneurysmatic enlargement in the section starting from the terminal part of the descending aorta and extending to the infrarenal aorta, aortic wall thickening and irregularity, subtotal occlusion at the origin of the celiac trunk, and severe segmental stenosis of the superior mesenteric artery	Corticosteroid,adalimumab, tocilizumab, beta-blocker, ACE inhibitor	In remission

ACE, angiotensin-converting enzyme; *CT*, computed tomography; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *HIV*, human immunodeficiency virus; *MRI*, magnetic resonance imaging; *NA*, not assessed; *LRBA*, lipopolysaccharide responsive beige-like anchor; *US*, ultrasonography; *TAK*, Takayasu arteritis

inhibitor), and the acute phase reactants remained high. Adalimumab treatment was discontinued, and tocilizumab (8 mg/kg/once a month) was started because magnetic resonance [15] angiography showed progression of the vasculitis (a new aneurysmatic lesion distal to the thoracic aorta). The monthly IVIG treatment was continued. At the last follow-up visit, he had no complaints and blood pressure was normal (< 90th percentile for age, gender, and height) without any antihypertensive drug.

Takayasu arteritis patients with immunodeficiency in the literature

This systematic literature review was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 statement [16]. The overview of the systematic literature review process is shown in Fig. 3. We identified 11 articles describing 17 TAK patients with immunodeficiency during the literature search [10, 12, 17–25].

Four of 17 TAK patients were children [17–20], and the characteristics of them are summarized in Table 1. Except for one, the others were relatively older. Two of the patients were infected with human immunodeficiency virus (HIV) [17, 20], another patient had Wiskott-Aldrich syndrome [18], and the other had idiopathic CD4 + T lymphocytopenia [19]. Corticosteroids were used in the treatment of TAK in all but one. Two of these patients were in remission, while the other two died.

Thirteen of 17 TAK patients were adult [10, 12, 21–25], and the characteristics of four patients from them are summarized in Table 2. Nine adult patients with TAK were infected with HIV [21–23], three patients had common variable immunodeficiency disorder (CVID) [10, 12, 25], and the other had STAT1 gain-of-function mutation [24]. Corticosteroid was the most frequently used immunosuppressive agent in adult patients ($n = 6$). Other agents included methotrexate ($n = 3$), azathioprine ($n = 2$), tacrolimus ($n = 1$), cyclosporine ($n = 1$), rituximab ($n = 1$), infliximab ($n = 1$), cyclosporine ($n = 1$), and abatacept ($n = 1$). Four of these patients were in remission, three died, and four had stable disease.

Apart from the studies we mentioned, some studies in the literature have also reported cases of immunodeficiency and large vessel vasculitis [26–29]. However, these studies were not included in our literature review since the diagnosis of TAK in the patients in these studies was not certain.

Discussion

Rheumatic diseases and rarely vasculitic disorders may accompany immune deficiencies [12]. However, TAK in immunocompromised patients is very rare. There had been

Table 2 The characteristics of previously reported cases of adult Takayasu arteritis-associated immunodeficiency

First author, year (ref. #)	Number of patients	Age at diagnosis	Gender	Associated immunodeficiency	Clinical features at diagnosis of TAK	CRP, ESR	Radiologic findings	Treatment	Outcome
Maeshima, 2018 [24]	1	21 years	Female	PID (STAT1 gain-of-function mutation)	Pulseless right radial artery	NA	On CT angiography: damaged large vessels from neck to lower limbs and severe aortic regurgitation	Corticosteroid, tacrolimus, methotrexate, infliximab, cyclosporine, abatacept	Exitus
Tudela, 1990 [25]	1	42 years	Female	CVID	Hypertension, periumbilical systolic murmur	NA	On CT scan: aortic aneurysm A digital angiography: a large dilated abdominal aorta with bilateral stenosis of the renal arteries, multiple stenosis in the upper mesenteric artery and a complete abolished function of the left kidney	NA	NA
Knysz, 2010 [23]	1	18 years	Female	Infected with HIV	Hypertension, motor aphasia, stroke	NA	On MRI: dilatation and irregular contour of the ascending and descending aorta, and narrowing of the abdominal aorta On conventional angiography: narrowing of the left subclavian artery, dilatation of the thoracic aorta, occlusion of the superior mesenteric and renal arteries	Antiretroviral and anticoagulant therapy	NA
Ferfar, 2018 [21]	7	Median 38 (21–47)	Female ($n=5$), male ($n=2$)	Infected with HIV ($n=7$)	Arthralgias ($n=1$) fever ($n=1$), discrepancy in blood pressure ($n=2$), absent left radial pulse ($n=1$), back pain ($n=1$), hypertension ($n=1$), claudication ($n=1$), supraclavicular pulsatile mass ($n=1$)	High CRP ($n=2$)	On vascular imaging: Thoracoabdominal aortic aneurysms ($n=4$), popliteal ($n=1$) or superficial femoral artery ($n=1$) thrombosis, carotid ($n=2$) or subclavian artery ($n=1$) stenosis, carotid ($n=1$) or celiac coronary artery ($n=1$) aneurysms, subclavian artery occlusion ($n=3$) and aneurysms ($n=1$), renal artery occlusion ($n=2$), celiac artery stenosis ($n=1$), iliac and femoral artery occlusion ($n=1$), iliac artery aneurysm ($n=1$), aortic valve insufficiency ($n=1$), vertebral artery occlusion ($n=1$)	Corticosteroid ($n=3$), methotrexate ($n=1$), azathioprine ($n=1$), antiretroviral therapy ($n=6$), antiplatelet agent ($n=5$), statin ($n=1$), surgery ($n=6$)	Remission ($n=2$), stable disease ($n=4$), exitus ($n=1$)
Skeik, 2013 [12]	1	29 years	Male	CVID	Memory impairment, difficulty talking and understanding, blurry vision, facial droop, and upper extremity weakness	CRP: 6.9 mg/dL; ESR: 33 mm/h	On CT angiography: extensive aortic calcification in ascending, descending thoracic, and abdominal aorta, descending aortic aneurysm, celiac and superior mesenteric artery stenosis	Corticosteroid, azathioprine, methotrexate, rituximab, antiplatelet and anticoagulant agents, statin, surgery	In remission

Table 2 (continued)

First author, year (ref. #)	Number of patients	Age at diagnosis	Gender	Associated immunodeficiency	Clinical features at diagnosis of TAK	CRP, ESR	Radiologic findings	Treatment	Outcome
Jerschow, 2007 [10]	1	53 years	Female	CVID	Arm pain, claudication, weakness, numbness, blood pressure difference between the arms, absence of left radial pulse, diminished left carotid pulse and a left subclavian bruit	NA	On angiogram: narrowing of the proximal left subclavian artery, narrow left vertebral artery originating separately from the aortic arch	Corticosteroid,IVIG	In remission
Kalungi, 2004 [22]	1	23 years	Female	Infected with HIV	Fainting, weakness, headache, left facial palsy, hypotonia	ESR:8 mm/h	On Doppler US: no flow in the left common carotid artery (obliteration) and minimal flow in the left subclavian artery (stenosis)	None	Exitus

CT, computed tomography; *CRP*, C-reactive protein; *CVID*, common variable immunodeficiency disorder; *ESR*, erythrocyte sedimentation rate; *HIV*, human immunodeficiency virus; *IVIG*, intravenous immunoglobulin; *MRI*, magnetic resonance imaging; *NA*, not assessed; *PID*, primary immunodeficiency diseases; *US*, ultrasonography; *TAK*, Takayasu arteritis

only four c-TAK patients with immunodeficiency reported in the literature. Here, we present two patients with immunodeficiency who developed TAK during the follow-up.

Although uncertainties in the pathogenesis of TAK remain, cell-mediated inflammation is involved in the pathophysiology of vascular cell injury in TAK [30]. Immunohistochemical studies of the infiltrating cells in the aortic tissue of patients with TAK have shown that they mainly consisted of gamma–delta T-cells, natural killer (NK) cells, cytotoxic T-cells, T-helper cells, and macrophages, suggesting a role for these cells in the physiopathology of the disease [7]. A study of peripheral blood cells from patients with TAK detected an elevated ratio of CD4 + /CD8 + lymphocytes, and another one showed increased basal activity of protein kinase C and intracellular calcium levels [31], suggesting that these cells are in an activated state. A different study by Seko et al. [7] of the infiltrating cells in aortic tissue samples from patients with TAK showed that T-cells, NK cells, and cytotoxic T-cells played a critical role in vascular cell injury by expressing and releasing massive amounts of a membrane-disrupting protein known as perforin directly onto the surface of arterial vascular cells. These findings confirm that cell-mediated inflammation, especially T lymphocytes, plays an essential role in the pathogenesis of TAK. Therefore, the development of TAK is not unexpected, especially in patients with cellular immune dysregulation.

Among the separately reported four cases in the literature [17–20], two were HIV-infected, one patient had Wiskott-Aldrich syndrome, and the other had idiopathic CD4 + T lymphocytopenia [17–20].

One of the HIV-infected cases was additionally infected with Mycobacterium tuberculosis [17]. Although the evidence of tuberculosis was not definite in the other HIV-positive case, both were given antituberculosis therapy. The incidence of HIV-associated vasculitis in the literature is less than 1% [32, 33]. Vasculitis involving medium-sized vessels has been described in HIV-infected adults and children [32, 33]. In the reported cases, the authors concluded that a common inflammatory process, possibly triggered by tuberculosis or HIV, may underlie the etiology of TAK. Consequently, they suggested that large vessel arteritis such as TAK should be considered, especially in HIV-infected individuals.

In another case report, a patient with WAS who developed TAK was presented [18]. Patients with WAS have been reported to develop collagen-vascular diseases, although TAK has been reported in only one patient [34, 35]. Lau et al. [18] reported that immunodeficiency might predispose to persistent infection and chronic antigenic stimulation in this case, which may trigger harmful autoimmune processes that cause collagen-vascular disease.

Kilic et al. [19] reported a patient with idiopathic CD4 + T lymphocytopenia who developed TAK in their

report. Idiopathic CD4 + T lymphocytopenia is rare in the absence of immunodeficiency, most commonly infection with HIV [36]. The low CD4 + T lymphocyte counts may cause dysgammaglobulinaemia and inflammatory syndromes such as TAK [37].

Only a few cases of immunodeficiency with TAK have been reported in adults. In 1990, Tudela et al. [25] reported a 42-year-old Hispanic female patient with common variable immunodeficiency disorder (CVID) who developed hypertension during follow-up and was diagnosed with TAK based on the positive results of the vessel biopsy. A 53-year-old Hispanic woman with CVID who applied with complaints of chronic diarrhea, joint pain, weight loss, and depression and had been treated with IVIG for about 3 years was diagnosed with TAK by Jerschow et al. [10]. In another study, Ferfar et al. [21] presented 11 HIV-infected patients with large vessel vasculitis, and seven of them fulfilled international criteria for TAK.

This review has limitations. Most importantly, the number of pediatric patients included in the study and identified during the literature search was quite low. Based on this limited number, it is challenging to express clear ideas about the management and disease course of these patients.

Conclusion

In conclusion, our study emphasizes that vasculitic conditions such as TAK may accompany patients with immunodeficiency. In such patients, constitutional symptoms, hypertension, and increased inflammatory markers occurring during the follow-up should warn clinicians about a possible coexistence of vasculitis. Immune dysregulation may be a predisposing factor for the development of these inflammatory diseases.

Declarations

Consent to participate Consent was obtained from both parents and children for the publication of their data.

Disclosures None.

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Authors and Affiliations

Seher Sener[1] · Ozge Basaran[1] · Ezgi Deniz Batu[1] · Erdal Atalay[1] · Saliha Esenboga[2] · Deniz Cagdas[2] · Bulent Baris Kuskonmaz[3] · Yelda Bilginer[1] · Fatih Ozaltin[4] · Berna Oguz[5] · Ali Duzova[4] · Ilhan Tezcan[2] · Seza Ozen[1]

Seher Sener
kzl_seher@hotmail.com

Ozge Basaran
ozgesalor@yahoo.com

Ezgi Deniz Batu
ezgidenizbatu@yahoo.com

Erdal Atalay
drerdalatalay@hotmail.com

Saliha Esenboga
saliha.esenboga@hacettepe.edu.tr

Deniz Cagdas
deniz.ayvaz@hacettepe.edu.tr

Bulent Baris Kuskonmaz
bkuskon@hacettepe.edu.tr

Yelda Bilginer
yeldabilginer@yahoo.com

Fatih Ozaltin
fozaltin@hacettepe.edu.tr

Berna Oguz
oguzberna@yahoo.com

Ali Duzova
aduzova@hacettepe.edu.tr

Ilhan Tezcan
fetezcan@hacettepe.edu.tr

[1] Division of Pediatric Rheumatology, Department of Pediatrics, Hacettepe University, Ankara, Turkey

[2] Division of Pediatric Immunology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

[3] Division of Pediatric Hematology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

[4] Division of Pediatric Nephrology, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey

[5] Department of Radiology, Hacettepe University Faculty of Medicine, Ankara, Turkey