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TAKAYASU ARTERITIS AS A CAUSE OF ACUTE MYOCARDIAL INFARCTION (literature review)

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Background. Takayasu arteritis (TAK) is a rare autoimmune vasculitis that primarily affects the aorta and its main branches, particularly the coronary arteries, which can significantly worsen a patient's prognosis. Undiagnosed TAK is common in young women and can lead to acute myocardial infarction (AMI), a potentially life-threatening condition.

Aim. The aim of this review was to analyse current data on the incidence, clinical course, diagnosis, treatment and prognosis of patients with TAK and AMI. Increasing the awareness of general practitioners, cardiologists and rheumatologists about the importance of early recognition and treatment of patients with TAK and AMI will improve the prognosis of patients.

Materials and methods. We performed the online literature search using PubMed and Scopus to collect articles on AMI in TAK published from 2013 to 2024 that were available in open access. The combinations of the following keywords "coronary angiography", "myocardial infarction", "myocardial revascularization", "percutaneous coronary intervention", and "Takayasu arteritis" were used. Two reviewers received and evaluated all articles independently. After excluding duplicates, all articles were checked for relevance. Articles without related content, studies on pediatric patients, in vitro studies, and experimental models were rejected as exclusion criteria.

Results. TAK is a significant cause of AMI in young patients, particularly women, with an incidence of 3,4-34,0 %. Coronary artery lesions in TAK can result in sudden death, and AMI can be the first manifestation of TAK. The condition is characterized by lesions in the ostia and proximal segments of the coronary arteries. Early diagnosis and treatment, especially in young individuals with anginal pain and systemic inflammation, are essential to reduce morbidity and mortality.

Conclusion. AMI can occur in young patients as a sight of systemic vasculitis, including TAK. TAK is a more frequent reason of AMI than recognized before, especially in young women. Coronary vasculitis, as an unrecognized sign of TAK, can be life-threatening. Early diagnosis and appropriate treatment, including immunosuppressive therapy, can prevent significant morbidity and mortality.

Keywords: coronary angiography, myocardial infarction, myocardial revascularization, percutaneous coronary intervention, Takayasu arteritis.

Background. Takayasu arteritis (TAK) is a rare autoimmune vasculitis that primarily affects the aorta and its main branches, particularly the coronary arteries [1]. TAK has long been considered a rare disease mostly affecting the Far Eastern population. However, recent studies show that it occurs in all ethnic groups worldwide with increasing prevalence rates [2]. The annual incidence was 0.8 per million and the prevalence was 7,5 per million according to the results of an open retrospective matched cohort study using a UK primary care database (IQVIA Medical Research Data) [3]. The average annual incidence of TAK in the nationwide population-based study in Korea was 0,24 per 105 people and the prevalence was 2,82 per 105 people. [4]. The study by Watanabe et al. demonstrated that TAK developed at the age of 18-40 years [5], and young women are more likely to be affected [5, 6], especially those of Asian descent, and the ratio of women to men was 1:5 [5].

The etiopathogenesis of the inflammatory process in TAK remains largely undefined [7]. Inflammation of the arteries leads to thickening of their walls, fibrosis and stenosis or occlusion [8, 9], thrombosis [9], and destruction of the elastic and muscular layers may occur, which causes aneurysm formation and dissection [9]. Ucar et al. found a strong association of TAK with accelerated atherosclerosis [10]. Endothelial dysfunction [11] and platelet activation [12] have been detected in patients with TAK. Literature data suggest that arterial stenosis is more common than arterial aneurysms in TAK [13].

Clinical manifestations of TAK are diverse and depend on the localization of the affected arteries and the degree of their damage [7, 14, 15]. The first symptoms of TAK are nonspecific. Early diagnosis requires clinical awareness and high suspicion of this disease [6]. Vascular lesions are challenging to detect on initial presentation, making the TAK diagnosis rather complex [15]. According to the recommendations of the European Alliance of Associations for Rheumatology (EULAR), key symptoms such as new onset or worsening of limb claudication, weight loss >2 kg, subfebrile temperature, fatigue, night sweats, myalgias, arthralgias, arthritis, severe abdominal pain, stroke seizures (non-hypertensive), fainting, dizziness, limb paresis, AMI, angina, acute visual symptoms (amaurosis fugax or diplopia), and essential clinical examination findings (hypertension, new pulse loss, different pulse, bruits, carotidynia) indicate TAK activity [16].

TAKs have a high morbidity and mortality rate in young patients, especially from ischaemic complications [17]. In patients with TAK, cardiac pathology is the major cause of morbidity and mortality [3, 4]. Coronary artery lesions (CAL) are the cause of poor prognosis and high mortality [18]. TAK can lead to fatal events, including those caused by CAL [7], even in infants [19]. CAL is typical in patients with TAK and occurs in 4,6 to 58,2 % of cases [13, 20-24]. Comarmond et al. showed that although the risk of cardiovascular events was similar between TAK patients and controls, the prevalence of myocardial ischemia was over five times higher among TAK patients (p=0,002) [25].

Undiagnosed TAK is often found in young women and it can be the cause of acute coronary syndrome (ACS) [26, 27]. Meta-analysis of 35 studies (3262 patients with TAK) found that the average delay in diagnosis of TAK from the onset of symptoms ranged from 2 months to 7,6 years [17]. Timely diagnosis of TAK and appropriate treatment are essential to prevent severe complications and improve prognosis [6, 27, 28].

Aim: to analyze current data on the incidence, clinical course, diagnosis, treatment, and prognosis of patients with TAK and AMI. Increasing the awareness of general practitioners, cardiologists, and rheumatologists about the importance of early detection and treatment of patients with TAK and AMI, will improve the prognosis of patients.

MATERIALS AND METHODS

The review was performed as a literature search using PubMed and Scopus to collect articles on acute myocardial infarction in TAK published from 2013 to 2024 that were available in open access. The combinations of the following keywords "coronary angiography", "myocardial infarction", "myocardial revascularization", "percutaneous coronary intervention", and "Takayasu arteritis" were used. Only articles investigating TAK with at

least one severe ischemic complication were considered for inclusion. We included case reports, original papers and review articles investigating TAK that were available in open access. We excluded articles (i.e., studies and case reports) on other vacuities and other types of articles such as notes, conference papers, letters, animal studies, short surveys, editorials, and author responses. Two reviewers received and evaluated all articles independently. After excluding duplicates, all articles were checked for relevance. Articles without related content, studies on pediatric patients, in vitro studies, and experimental models were rejected as exclusion criteria.

RESULTS

AMI is rare in young women, but TAK can be one of the reasons for its development. In young females with chest pain typical for ACS, systemic vasculitis, including TAK, should be considered [29]. Timely diagnosis and prompt treatment may improve long-term prognosis. [16, 18]. Patients with TAK have an increased risk of severe ischemic complications, such as stroke and AMI [17]. TAK cohort rates of AMI and stroke were 3,4 % and 11,4 %, respectively, and total major ischaemic complications were 13,8 % [30]. The incidence of AMI in TAK according to literature data is 3,4-34,0 % [17, 20, 30-33] (Table 1). Careful monitoring and proactive management are required given the significant burden of major ischemic complications of TAK [30].

Table 1

Incidence of acute myocardial infarction in Takayasu arteritis

Authors, years	Country	Study	Number of patients, n	The mean age (years ± SD)	Female, %	Incidence of AMI, %
Sun et al., 2013 [20]	China	Retrospective	587	The average age at the onset of cardiac symptoms was 43,5±13,5	80,0	24,4; previous AMI – 8,9 (out of 45 patients)
Furuta et al., 2015 [31]	United Kingdom	Retrospective observational	23	Age at diagnosis – 29,2 (age range 6,9-64,1)	78,0	13,0
Kim et al., 2018 [17]	Canada	Meta-analysis	3262	Mean age at symptom onset or diagnosis ranged from 10 to 49 years	>70,0	3,4
Yuan et al., 2020 [21]	China	Retrospective	141	35,7±16,9	77,3	12,1
Khan et al., 2022 [32]	Pakistan	Retrospective cross-sectional analysis	18	35,94±2,7	72,0	16,7 (patients with ACS)
Huo et al., 2022 [33]	China	Retrospective	1580	36,5±12,3 (the mean age at symptom onset), 38,8±12,3 (the mean age of onset of cardiac ischemia)	85,1	34,0 (out of 94 patients)
Lu et al., 2023 [30]	China	Single-center, large cohort	703	37 (age range 26-47)	83,93	3,4

According to Cavalli et al, in young women under 40, presenting to the emergency department with acute ischemic heart disease, the following causes were identified: coronary atherosclerosis in 60 %, TAK in 10 %, vasospasm in 7,5 %, sympathomimetic drug abuse in 7,5 %, coronary artery dissection in 5 %, and Takotsubo cardiomyopathy in 2,5 %. The proportion of patients with TAK was higher than with more well-known causes, namely, vasospasm [26]. Most CALs are localized in the ostia or proximal segments of the coronary arteries [22, 24, 33], and increase the risk of cardiac death due to arrhythmias and myocardial ischaemia [7]. Rarely, AMI can present as the first manifestation of TAK (Table 2) [27, 34-38]. Wilson et al. described three cases of chest pain in adolescent girls due to the development of acute myocardial ischemia as a result of TAK and CAL with different disease courses, resulting in different treatments, including heart transplantation. TAK is rare in childhood and should be considered in any adolescent girl with systemic inflammation and chest pain typical of AMI [35].

The development of cardiogenic shock resulting from CAL (99 % ostial obstruction in the left main coronary artery, LMCA) as the first manifestation of TAK was reported [39]. The case of a 29-year-old man with inferior wall AMI secondary to triple vessel coronary artery dissection (left anterior descending artery, LAD; left circumflex artery, LCX, and right coronary artery, RCA) was published by Tahtouh R. et al. During further examination, the patient was diagnosed with TAK [40].

Hlavaty et al. noted that CALs in the ostium or proximal segments of the coronary arteries were the main risk factors for sudden death due to arrhythmias. The authors describe the case of the sudden cardiac death of a 15-year-old girl who sought medical care after an episode of syncope shortly before death. The autopsy revealed that three major coronary arteries had multiple lesions of the proximal segments, corresponding

Table 2

Cases of acute myocardial infarction as the first manifestation of Takayasu arteritis

Author, years	Gender patient' s, age	ECG changes	Diagnosi S	Coronary artery imaging data with visualization	Treatment	Outcome s
Allaoui, 2017 [27]	Female, 30 years	ST-segment depression by 2-3 mm in V_1-V_6 leads, T-wave inversion in V_5-V_6 leads	AMI without ST-segment elevation, complica ted by cardioge nic shock, and clinical death	70-90 % LMCA stenosis of 16-20 mm in length	CABG, aspirin, clopidogrel, enoxaparin, furosemide, ACEi, beta-blockers, prednisone, methotrexate	NA
Zhang et al., 2019 [34]	Female, 34 years	ST-segment elevation in V_1-V_5 leads	AMI complica ted by pulmona ry edema	Middle segments occlusion of the LAD and middle segments of the LCX	Primary PCI LAD, prednisone, methotrexate, clopidogrel, aspirin, atorvastatin	In 12 weeks, the patient had no chest pain

Wilson et al., 2021 [35]	Female, 13 years	ST-segment elevation in leads III, aVF	ACS of the LV inferior wall	1. RCA ostium severe stenosis. 2. Restenos is of the proximal RCA	1. PTCA and DES implantation. Pulse therapy with GC, cyclophosphamid e. After 4 months the treatment was changed: infliximab, GC, and methotrexate. 2. PTCA	No progressi on of the disease
	Female, 14 years	ST-segment depression in inferior leads	AMI	Extensive fusiform aneurysmal dilation of LAD and LCX with proximal narrowing of the RCA and bilobed fusiform aneurysmal dilation extending distally	Cyclophosphamid e, GC, tocilizumab, mycophenolate	At the age of 16, a heart transplant was performed, as an ischemic cardiomyopathy developed
Zhou et al., 2021 [36]	Female, 22 Years	ST-segment elevation in aVR, ST-segment depression in other leads	AMI	1. CAG and IVUS showed that the RCA was occluded with collateral circulation and that there was severe negative remodeling at the ostium of LMCA. 2. IVUS demonstrated progressive external elastic membrane enlargement of the LMCA ostium at 3 and 15 months post-initial PTCA	1. Primary PTCA in the LMCA. Aspirin, clopidogrel, heparin, atorvastatin, prednisone, methotrexate. 2. After 3 months, RCA stenting was implantation	No symptoms or inflammation

Golubović et al., 2022 [37]	Female, 51 years	–	ST-elevated AMI of the anterior wall LV	The narrowing of the ostial segment of the LAD	DES implantation in the LAD. Cyclophosphamide, GC	Good general condition, with regression of all the previously mentioned problems
Wang et al., 2023 [38]	Female, 16 years	ST-segment elevation in the aVR lead and ST-segment depression in leads I, II, III, aVF, aVL, and V_1-V_6.	Non-ST segment elevation AMI	1. 99 % stenosis in the ostium of LMCA. 2. Within 1 year, recurrent pain and shortness of breath developed, a repeat CAG revealed 90 % stenosis of the LMCA stent	1. DES implantation in the LMCA. GC and folate reductase inhibitor therapy. 2. PTCA was performed, and treatment was initiated with an interleukin-6 receptor inhibitor	NA

Note: ACEi – angiotensin-converting enzyme inhibitor; BMS – bare metal stent; CABG – coronary artery bypass graft; CAG – coronary angiography; DES – drug-eluting stent; GC – glucocorticoids; IVUS – intravenous ultrasound; LAD – left anterior descending artery; LCX – left circumflex artery; LMCA – left main coronary artery; LV – left ventricle; NA – available; PCI – percutaneous coronary intervention; PTCA – percutaneous transluminal coronary angioplasty. RCA – right coronary artery

microscopically to TAK [7]. Notably, TAK can be a life-threatening disease, including in infants. Wang E.L. et al reported the sudden death of an 8-month-old girl due to bilateral ostial stenosis of the coronary arteries [19].

A case of TAK in a 26-year-old patient with severe refractory CAL, causing two ACS and multiple recurrent angina episodes was described by Cobilinschi C.O. et al. Despite being on full immunosuppressive therapy, the patient has undergone two aortic-bifurcated carotid bypasses, multiple interventional procedures with stent placement, balloon angioplasty, and up to ten recurrent in-stent restenoses requiring repeat interventions [41].

It is important to note that isolated coronary TAK is very rare. Clemmensen et al. described a case of TAK in a previously healthy 22-year-old woman with AMI complicated by cardiogenic shock requiring temporary mechanical support and, subsequently, urgent heart transplantation. Signs typical of TAK were found in the histomorphologic examination of the explanted heart in the left coronary artery [42]. Tokunaga C. et al reported about localized TAK in a 19-year-old woman who was admitted with ventricular fibrillation to the emergency room. She underwent percutaneous coronary intervention (PCI) as emergency CAG detected ostia stenosis of the LMCA up to 99 %. Since the patient was diagnosed with ischemic cardiomyopathy that developed after AMI, she was implanted with an extracorporeal left ventricular assist device. After confirming the absence of systemic inflammation, it was replaced with a Jervik 2000 as a bridging device for transplantation. After 39 months, orthotropic heart transplantation was performed [43].

Diagnosis. Physicians should consider TAK in the differential diagnosis of chest pain in young women [39]. Early diagnosis of TAK can be difficult due to the lack of specificity of systemic inflammatory manifestations at the onset of the disease and the asymptomatic course before devel-

oping ischemic complications [44]. The 2018 EULAR guidelines state that in case of suspected TAK, the patient should be referred to an experienced center for an examination that includes large-diameter vessel imaging [16]. American College of Rheumatology/EULAR 2022 classification criteria are used to diagnose TAK [45].

Patients with TAK often have elevated levels of acute phase reagents, particularly erythrocyte sedimentation rate and C-reactive protein [20]. According to the findings of Li J. et al. the level of high-sensitivity C-reactive protein was higher in the group with TAK and heart disease compared to the group of patients with TAK without heart involvement (p = 0,017) [24].

Based on the 2018 EULAR guidelines, magnetic resonance imaging is the first-line tool for TAK diagnosis, while alternative methods include computed tomography or positron emission tomography and ultrasound. For the diagnosis of TAK, conventional angiography is not suggested. It has been replaced by the above-mentioned vascular imaging techniques [46]. The main indication for conventional angiography in large vessel vasculitis is interventions such as angioplasty or stenting [47].

Liu et al. retrospectively analyzed the clinical and angiographic data of 6 patients with TAK manifested by AMI. LMCA lesions were detected in 83,33 % of cases, LAD – in 33,33 %, LCX – in16,67 %, and RCA – in 66,67 % [48]. Cardiac magnetic resonance imaging with late gadolinium enhancement detected coronary artery disease in 25,9 % and AMI in 22,2 % of patients with TAK [25].

Treatment. The management of patients with ACS should follow the recommendations of the European Society of Cardiology (2023) [49]. Without appropriate control of systemic inflammation with immunosuppressive drugs, however, disease progression is inevitable, regardless of interventional or surgical treatment [35].

GC is the core of therapy to induce and maintain remission of TAK, and non-biologic disease-modifying agents in combination with GC should be given in all patients with TAK. Tocilizumab or tumor necrosis factor inhibitors may be considered in case of relapse or refractory disease despite treatment with conventional disease-modifying antirheumatic drugs. It is recommended that adjunctive therapy with conventional immunosuppressive drugs need to be considered when TAK is diagnosed. The patient's comorbidities or contraindications should determine the choice of a specific immunosuppressive agent [16].

It is essential to focus on evidence of the impact of immunosuppressive treatment on CAL in TAK. The literature reports a decrease in coronary ostial stenosis four months after starting combined therapy with GC and tocilizumab [28]. Zhou et al. also noted that negative remodeling might be reversible in patients with TAK through percutaneous transluminal coronary angioplasty (PTCA) and long-term immunosuppressive medication [36].

Endovascular and surgical interventions. The best myocardial revascularization strategy for patients with TAK and AMI is debated [36]. The updated EULAR guidelines state that elective endovascular interventions or reconstructive surgery should be performed during sustained remission. However, arterial dissection or critical vascular ischemia needs an emergency surgical intervention [16].

Interventional procedures are recommended in the inactive stage, as the presence of inflammation in patients with TAK can lead to stent restenosis and require repeated procedures [21]. The incidence of MACE was higher in TAK with CAL in the active disease in comparison with the stable inactive one [50].

Liu et al. emphasize that in AMI, urgent PCI is the primary treatment which is highly effective and safe and is the first option for management in case of hemodynamic instability. However, the risk of acute reocclusion and long-term target vessel restenosis is significant with PTCA alone. The long-term restenosis incidence is also high after bare-metal stent (BMS) implantation. The placement of a drug-eluting stent (DES) can inhibit intimal proliferation and the advancement of vessel wall fibrosis so that the restenosis rate is substantially lower compared to PTCA and BMS implantation [48].

Coronary artery bypass grafting (CABG) is the preferred method of myocardial revascularisation compared with interventional therapy, which has been linked to a significantly increased re-intervention rate in CAL [21].

Wang et al. showed that during a median follow-up period of 4,5 years, 42,1 % of patients with TAK and significant coronary stenosis experienced at least one of the MACEs defined as a composite of cardiac death, myocardial infarction, and coronary revascularization. The long-term incidence of MACE and re-vascularisation was significantly more frequent in the patients with PCI in comparison to the CABG and medical therapy groups. The CABG and medical therapy groups had similar cumulative rates of MACEs and subsequent revascularization. Independent predictors of MACEs were active disease at initial examination and PCI [51]. Although, Zhang et al. highlighted that primary PCI was an essential and effective method of revascularization in AMI and TAK, and appropriate immunosuppressive treatment improves long-term outcomes [34].

Prognosis. All-cause mortality was higher in patients with TAK in the analysis of survival during 15 years of follow-up. Multivariate analysis showed that TAK and coronary artery disease were associated with decreased survival [52]. According to the study by Egebjerg et al. in a Danish nationwide cohort study, mortality was statistically increased in TAK compared to the control during the first three years of follow-up, but not after more than three years. The risk for major cardiovascular events was significantly higher in patients with TAK in comparison with the general population, both for<3 years (HR 12,0, 95 % CI: 3,8-37,0) and >3 years (HR 7,6, 95 % CI: 2,8-21,0) [53]. Based on the study data, the survival rate of patients with TAK after 1, 2, 5, and 10 years was 97,34 %, 96,05 %, 93,93 % and 89,23 %, respectively. In most cases, the causes of death were cardiovascular diseases (heart failure, AMI, stroke) [54].

CONCLUSIONS

AMI can occur in young patients as a sight of systemic vasculitis, including TAK. TAK is a more frequent reason of AMI than recognized before, especially in young women. Coronary vasculitis, as an unrecognized sign of TAK, can be life-threatening. In patients with suspected TAK, the presence of nonspecific systemic symptoms, coupled with the absence of a palpable pulse or ischemic manifestations, should prompt further evaluation through imaging studies of large and medium-sized vessels to confirm the diagnosis. Early diagnosis and appropriate treatment, including immunosuppressive therapy, can prevent significant morbidity and mortality. It is important that conduct further investigations to optimize the management of patients with TAK and AMI to ensure a more beneficial prognosis.

Authors' contributions

HM, MD: study conception and design; HM, MD, TK: performed literature search and data extraction and analysis; HM, MD: wrote the first draft of the manuscript; writing of the paper; all authors have read and approved the of the work.

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АРТЕРІЇТ ТАКАЯСУ ЯК ПРИЧИНА ГОСТРОГО ІНФАРКТУ МІОКАРДА (огляд літератури)

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Актуальність. Артерііт Такаясу (АТК) – це рідкісний аутоімунний васкуліт, який вражає переважно аорту та її основні гілки, зокрема, коронарні артерії, що може значно погіршити прогноз пацієнтів. Недіагностований АТК нерідко зустрічається у молодих жінок і може бути причиною гострого інфаркту міокарда (ГІМ), потенційно небезпечного для життя стану.

Ціль: аналіз сучасних даних щодо поширеності, клінічного перебігу, діагностики, лікування та прогнозу пацієнтів із АТК та ГІМ. Підвищення обізнаності лікарів загальної практики, кардіологів та ревматологів щодо важливості ранньої діагностики та лікування пацієнтів із АТК та ГІМ сприятиме покращенню прогнозу пацієнтів.

Матеріали та методи. Проведено пошук літератури з використанням баз даних PubMed та Scopus для збору статей про ГІМ при АТК, опублікованих з 2013 р. по 2024 р., що були доступні у відкритому доступі. Використовували комбінації таких ключових слів: «коронарна ангіографія», «інфаркт міокарда», «реваскуляризація міокарда», «черезшкірне коронарне втручання» та «артерііт Такаясу». Два автори отримали та оцінили всі статті незалежно один від одного. Після виключення дублікатів, всі статті були перевірені на релевантність. Статті без спорідненого змісту, дослідження на дітях, дослідження in vitro та експериментальні моделі були відхилені як критерії виключення.

Результати. АТК є основною причиною ГІМ у молодих пацієнтів, особливо жінок, з частотою 3,4-34,0 %. Ураження коронарних артерій при АТК може бути причиною раптової смерті, а ГІМ може бути першим проявом АТК. Захворювання характеризується ураженням устя та проксимальних сегментів коронарних артерій. Рання діагностика та лікування АТК, особливо у молодих осіб з ангінозним болем та системним запаленням, є важливими для зниження захворюваності та смертності.

Висновки. ГІМ може виникати у молодих пацієнтів як прояв системного васкуліту, в тому числі АТК. АТК є більш частою причиною ГІМ, ніж визнавалося раніше, особливо у молодих жінок. Коронарний васкуліт, як недіагностований прояв АТК, може бути небезпечним для життя. Рання діагностика та відповідне лікування, включаючи імуносупресивну терапію, можуть запобігти значній захворюваності та смертності.

Ключові слова: коронарна ангіографія, інфаркт міокарда, реваскуляризація міокарда, черезшкірне коронарне втручання, артерііт Такаясу.

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