CASE REPORT

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Relapse of Takayasu arteritis as a cause of suicidal poisoning and subsequent major ischemic stroke successfully treated with thrombolytic therapy

Pogoršanje Takayasu arteritisa sa suicidnim trovanjem i ishemijskim moždanim udarom uspešno lečenim trombolitičkom terapijom

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Abstract

Introduction. Takayasu arteritis (TA) is a rare large vessel arteritis, affecting primarily aorta and its major branches. Its clinical manifestations can vary significantly – from asymptomatic to serious vascular events. Acute neurological complications are frequent at the onset of the disease and in relapses. Anxiety and depression are more frequent in TA patients than in general population as well as during relapses. Prevalence of transient ischemic attack or ischemic stroke in TA patients is approximately 10–20%. **Case report.** We presented a patient with TA that began with a depressive episode resulting in attempted suicide by bromazepame poisoning. This was subsequently followed by major ischemic stroke caused by thrombosis of the left middle cerebral artery (probably due to aortic arch embolism) successfully treated with intravenous thrombolysis. **Conclusion.** Intravenous thrombolysis appears to be safe and effective in patients with TA and stroke.

Key words:
takayasu arteritis; recurrence; poisoning; suicide, attempted; thrombosis; middle cerebral artery; tissue plasminogen activator; treatment outcome; depression.

Apstrakt

Uvod. Takayasu arteritis (TA) je redak arteritis velikih krvnih sudova, koji prvenstveno zahvata aortu i njene velike grane. Njegove kliničke manifestacije mogu znatno varirati, od asimptomatskih do ozbiljnih vaskularnih događaja. Akutne neurološke komplikacije su česte na početku bolesti i tokom relapsa. Anksioznost i depresija su češće kod bolesnika sa TA nego u opštoj populaciji i češće su tokom relapsa. Prevalencija tranzitornog ishemijskog ataka i ishemijskog moždanog udara kod bolesnika sa TA je približno 10–20%. **Prikaz bolesnika.** Prikazana je bolesnica čija je aktivna faza TA počela depresivnom epizodom koja je dovela do pokušaja samoubistva trovanjem bromazepamom. Sledio je *major* ishemijski moždani udar izazvan trombozom srednje moždane arterije (verovatno usled embolije poreklom aortnog luka), koji je uspešno lečen intravenskom trombolizom. **Zaključak.** Intravenska tromboliza je bezbedna i efektivna kod bolesnika sa TA i moždanim udarom.

Ključne reči:
takajasu arteritis; recidiv; trovanje; samoubistvo, pokušaj; tromboza; a. cerebri media; plazminogen, aktivator, tkivni; lečenje, ishod; depresija.

Introduction

Takayasu arteritis (TA) is a large vessel arteritis, affecting primarily aorta and its major branches. Its clinical manifestations can vary significantly – from asymptomatic to serious vascular events, occurring both at the beginning of the disease and during relapses (i.e. active phase). In the presented case, relapse of the disease began with a depressive episode resulting in attempted suicide by bromazepame poisoning. Ischemic stroke occurred subsequently, also in the active phase of the disease, and was successfully treated with intravenous thrombolysis.

To the best of our knowledge, this is the first report of TA relapse manifesting with depression and attempted suicide, followed by ischemic stroke and successful intravenous thrombolysis.

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Case report

A 61-year old female was found in a state of unconsciousness, on the floor of her home with a scalp laceration. The patient was in a shallow coma, Glasgow Coma Scale (GCS) score 7 with otherwise unremarkable neurological examination, subfebrile (37.2°C) and hypotensive (80/60 mmHg) with ECG showing regular sinus rhythm at a rate of 68/min. She was initially examined in the local hospital, intravenous dopamine and normal saline were administered, and head laceration was sutured. Multislice computed tomography (MSCT) of the head was done at local hospital and no signs of ischemia, hemorrhage, or other brain lesions were noted.

Drug overdose was suspected since empty packages of prescribed medications were found in her vicinity and she was transported to the Military Medical Academy for toxicology screening. Upon admission to emergency room, benzodiazepine antagonist – flumazenil (0.2 mg *iv*) was administered with partial improvement of consciousness. She was admitted to the Toxicology Clinic in a soporous state (GCS 9), with slurred speech and unresponsive, miotic pupils. Bromazepame plasma concentration was 1.02 mg/L (levels above 0.3 mg/L are considered toxic, coma is virtually invariable above 1.0 mg/L) with serum positive for 3-OH-bromazepame metabolite (this suggests even higher blood levels of bromazepame than those detected). Toxicology screening for ramipril and amlodipine (concomitant therapy, also suspected in overdose) were negative. Laboratory analyses at this time showed marked leukocytosis of $22.1*10^9$ (normal values: $4–11*10^9$/L) and very high creatine kinase levels of 4,390 (normal 26–200 U/L). Leukocytes remained elevated throughout the course of treatment ($> 20*10^9$/L). Acute phase reactants – erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) values at that time were unavailable. The patient was treated with flumazenil in the total dose of 2.3 mg during three days, rehydrated, intubated with continuous cardiorespiratory support and had good recovery further on. From day four she was fully alert and responsive, with unremarkable neurological exam. There was no record in personal medical history regarding depressive disorder or previous suicide attempts. The patient and her family denied any psychiatric symptoms prior to this. According to the patient, an argument with her daughter provoked her to act in this manner. Psychiatric exam found her to be suffering from an anxious-depressive disorder without current suicidal tendencies, and she was prescribed with trazadone 50 mg/day and lorazepame 3 mg/day. The personal history revealed that she was diagnosed with TA, at the age of 59, according to the current criteria [1]. The disease was presented a few months prior to diagnosis, with general weakness, malaise, arthralgia and low-grade fever. During hospitalization at that time, significantly elevated acute phase reactants were noted, while cardiac ultrasound showed only mild aortal sclerosis. However, position emission tomography (PET) scan showed increased accumulation of fluorine-18 fluorodeoxyglucose (18F-FDG) in the projection of all of the major aortic branches (brachiocephalic trunk, carotid and subclavian arteries) and MSCT aortography showed aortal wall thickening (4.5 mm) from descendent part to iliac arteries. Corticosteroid and azathioprine therapy was introduced as regular long lasting treatment.

Several months prior to attempted suicide, the patient on her own stoped taking recommended therapy. Besides this, she was treated with ipratropium bromide /fenoterolhydrobromide for chronic obstructive pulmonary disease, and was taking medium doses of ramipril, hydrochlorothiazide and nifedipine for arterial hypertension. The personal history also revealed the presence of fatty liver, gallbladder calculosis and chronic gastritis.

On the ninth day after admission, while still not taking immunosuppressive drugs, acute neurological impairment occurred, manifested as sensorimotor aphasia and severe right-sided weakness. National Institute of Health Stroke Scale (NIHSS) score was 13. She was normotensive, ECG showed regular sinus rhythm. MSCT of the brain showed discrete zone of subcortical hypodensity in the left operculum (Figure 1), while MSCT brain angiography showed left medial cerebral artery (MCA) occlusion (Figure 2). Besides this, a few chronic ischemic lesions in the left lentiform and caudate nucleus and right subcortical frontal regions were observed (Figure 1).

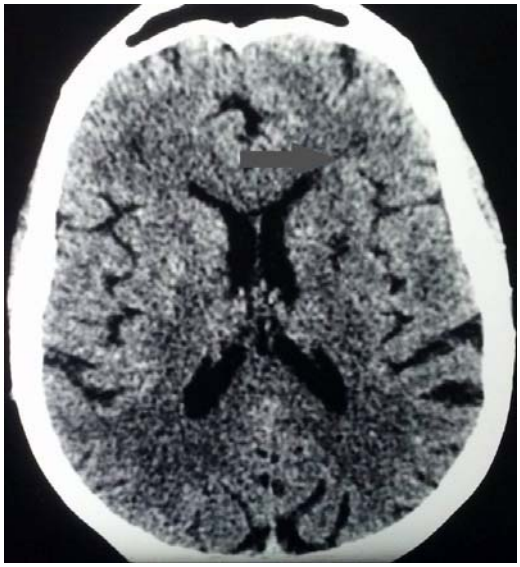

Fig. 1 – Multislice computed tomography (MSCT) axial noncontrast head scan shows left opercular hypodense lesion corresponding ischemia.

Since the patient was in therapeutic window for thrombolysis, 1 hour from symptoms onset, intravenous recombinant tissue plasminogen activator (rTPA) was administered according to standardized protocol [2, 3]. During the first 24-hour observation period, a significant clinical improvement was noted, primarily improvement of speech (minor dysphasia) and of right hand limb strength, NIHSS being 7. Control brain MSCT with angiography 24 hours after thrombolysis showed M2 and M3 segments patent, presumably through collaterals and M1 occluded. No radiological signs of acute ischemia were noted. Thrombolytic therapy was without brain hemorrhage or any other medical complication (Figure 3).

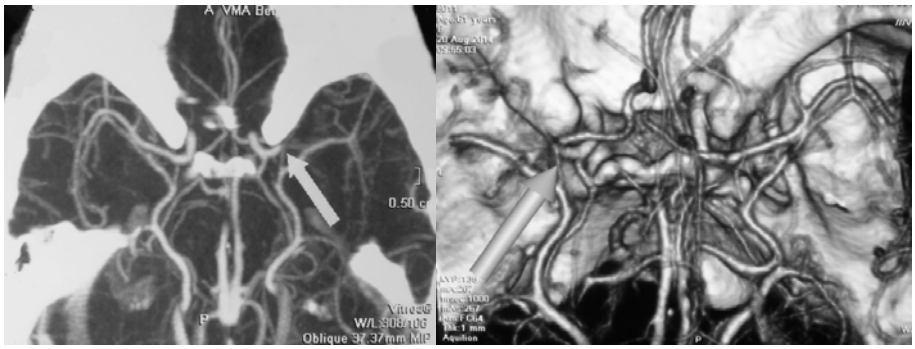

Fig. 2 – Multislice computed tomography (MSCT) brain angiography prior to *iv* thrombolysis shows occlusion of the left medial cerebral artery (MCA).

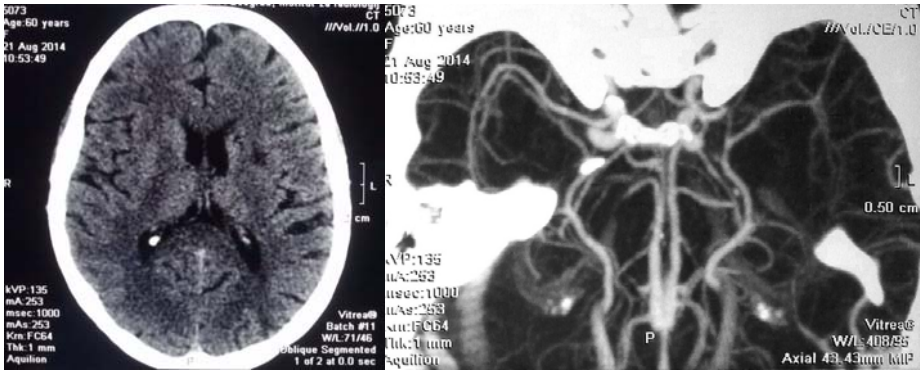

Fig. 3 – Repeated multislice computed tomography (MSCT) and MSCT angiography showing M2 and M3 postcontrast opacification of left medial cerebral artery (MCA).

A marked leukocytosis ($26.8*10^9$/L) with elevated acute phase reactants – ESR 86/h (normal value < 10/h) and CRP 195 (normal value < 3.0 mg/L), mild elevation of liver enzymes [AST 55 U/L (normal value < 37 U/L), ALT 100 U/L (normal value 7–49 U/L), LDH of 1.350 U/L (normal value 120–246 U/L)] were present in the following days. Protein C and S and antiphospholipid antibodies were negative. Serial ECGs showed sinus rhytm, with heart rates between 70 and 80/min. Polymerase chain reaction (PCR) for the most common thrombophilias-Factor V Leiden, prothrombin variance, methylenetetrahydrofolate reductase (MTHFR) and plasminogen activator inhibitor-1 (PAI-1) were negative. Carotid and vertebral Doppler sonography showed double angulation of left internal carotid artery (ICA), tortuous vertebral arteries and bilateral external carotid artery (ECA) stenosis of 20 to 25% with stable fibrolipid plaques and no other structural, nor hemodynamical significant findings. Contrast enhanced transcranial Doppler sonography showed no signs of right-to-left shunting and no microembolic signals. Transthoracic echocardiography (TTE) showed normal dimensions of atria and ventricles, preserved global and segmental kinetics, with normal blood flow and pericardium. Ejection fraction was 65%. Transesophageal echocardiography (TEE) findings were consistent with TTE findings, without additional pathology. MSCT aortography showed slight aortic arch atheromatosis with thickening (3–4 mm) of thoracic aorta wall (Figure 4).

The patient was released from hospital ten days after ischemic stroke (18 days from the attempted suicide). NIHSS upon release was 2 – a discrete right facial paresis and a minimal right hand paresis. She was advised to take aspirin 100 mg/day, atorvastatin 40 mg/day, methylprednisolone 20 mg/day for two weeks, then 15 mg/day, trazadone 50 mg/day and lorazepame 3 mg/day proscribed by psychiatrist and her usual bronchodilatative and antihypertensive therapy.

At follow-up visits, after one and six months, inflammation parameters (ESR and CRP, as well as complete blood count) were within normal range, the patient did not have new neurological, psychiatric nor any other symptoms, and overall recovery was good.

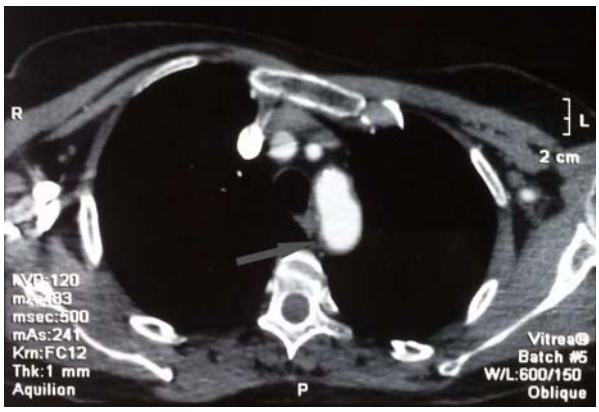

Fig. 4 – Multislice computed tomography (MSCT) aortography shows slight aortic arch atheromatiosis with thickening of the thoracic aorta wall.

Discussion

In the presented patient, relapse of TA was initially manifested as severe depression and attempted suicide with

subsequent development of major ischemic stroke, severe neurological impairment and successful thrombolytic treatment. Elevated parameters of systemic inflammation confirmed TA relapse [3]. Disease activity affects quality of life and mental and functional status in TA patients. Anxiety was found to be significantly higher in TA patients than in healthy controls [4]. Depression is twice more common in TA patients [5]. However, anxiety and depression have significantly higher incidences in active disease than in remission [5]. There are no published papers assessing incidence and prevalence of suicide attempts and suicides in patients with TA. To the best of our knowledge, this is the first published case of suicide attempt as principal manifestation of TA relapse.

Takayasu arteritis is a relatively rare systemic vasculitis with estimated incidence of 2.6 *per* million [5]. Spectrum of TA symptoms is wide, ranging from asymptomatic to serious, often psychiatric and neurological manifestations [6, 7]. Natural course is virtually unpredictable regarding initial presentation, onset of disease activity and symptom severity [8]. Asymptomatic progression is not uncommon [6–9]. The first symptoms of TA in our patient appeared at 59 years, which is rather late considering the second and the third decade of life as the usual time of TA clinical presentation [6]. Most frequent neurological symptoms are headache, dizziness, visual disturbance, transitory ischemic attacks and ischemic stroke [6, 7, 9].

Literature data regarding ischemic stroke due to TA is sparse and consists mostly of case reports and case series [10–18]. There are only few, mostly retrospective studies currently available assessing stroke in the setting of TA [9]. The prevalence of ischemic stroke in patients with TA is found to be, depending on study, between 5% and 15%, especially at the onset of the disease and during the relapses [11–16]. Etiology of ischemic stroke in patients with TA is various: artery-to-artery embolism – from aortic arch and its major branches, carotid stump syndrome, hypercoagulable state, or cardiogenic emboli due to aortic regurgitation [9]. Thrombosis of the left middle cerebral artery was the cause of major ischemic stroke in our patient, probably due to aortic arch embolism. Other possible causes of stroke were excluded – cardiogenic embolism, carotid artery embolism, thrombophilias, hypertension and atrial fibrillation.

The presence of TA is not regarded as contraindication for intravenous thrombolysis in patients with stroke according to present guidelines for acute ischemic stroke treatment [2]. Reported cases of rTPA use in TA patients with acute ischemic stroke are extremely rare and in the available literature there is only one published paper [10]. Furthermore, there are no randomized clinical trials regarding therapy of neurologic complications in TA. R-TPA application in presented case resulted in the complete recovery without complications.

Therapeutic approach in TA is oriented in general to diminishing disease activity with corticosteroids and immunosuppressants [19]. The presented patient did not take recommended corticosteroid and immunosuppressant therapy, which was a probable cause of TA relapse. Treatment of arterial hypertension and other secondary manifestations is also advised in order to decrease the incidence of end-vessel pathology [8]. Low dose aspirin use could be associated with lower frequency of repeated ischemic events in patients with TA [20], and this was our therapeutic choice as secondary prevention.

Conclusion

Acute psychiatric and neurological symptoms in patients with TA are more frequent than in general population, and tend to occur more often during relapses. This is, to the best of our knowledge, the first reported clinical case of suicide attempt caused by TA relapse, as well as one of the two reports of successful intravenous thrombolysis after ischemic stroke in a patient with TA. Intravenous thrombolysis with rtPA appears to be safe and effective in patients with TA and stroke.

REFERENCES

1. *Jennette JC, Falk RJ, Bacon PA.* 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthrit Rheumat 2013; 65(1):1–11.
2. *Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM* et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013; 44(3): 870−47.
3. *O'Connor TE, Carpenter HE, Bidari S, Waters MF, Hedna VS.* Role of inflammatory markers in Takayasu arteritis disease monitoring. BMC Neurology 2014; 14: 62.
4. *Yilmaz N, Can M, Oner FA, Kalfa M, Emmungil H, Karadag O.* Impaired quality of life, disability and mental health in Takayasu's arteritis. Rheumatology 2013; 52(10): 1898−904.
5. *Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M* et al. Takayasu arteritis. Ann Intern Med 1994; 120(11): 919–29.
6. *Ringleb PA, Strittmatter EI, Loewer M, Hartmann M, Fiebach JB, Lichy C*, et al. Cerebrovascular manifestations of Takayasu arteritis in Europe. Rheumatology 2005; 44(8): 1012–5.
7. *Li-xin Z, Jun N, Shan G, Bin P, Li-ying C.* Neurological manifestations of Takayasu arteritis. Chin Med Sci J 2011; 26(4): 227−30.
8. *Chatterjee S, Flamm SD, Tan CD, Rodriguez ER.* Clinical Diagnosis and Management of Large Vessel Vasculitis: Takayasu Arteritis. Curr Cardiol Rep 2014; 16(7): 499.
9. *De Paula LE, De Mont Alverne AR, Shinjo SK.* Clinical and vascular features of Takayasu arteritis at the time of ischemic stroke. Acta Reumatol Port 2013; 38: 248−51.
10. *Hedna VS, Patel A, Bidari S, Elder M, Hoh BL, Yachnis A,* et al. Takayasu's arteritis: Is it a reversible disease? Case Report and Literature Review. Surg Neurol Int 2012; 3: 132.
11. *Gao S, Wang R.* Takayasu arteritis presenting with massive cerebral ischemic infarction in a 35-year-old woman: a case report. J Med Case Rep 2013; 7: 179.
12. *Sikaroodi H, Motamedi M, Kahnooji H, Gholamrezanezhad A, Yousefi N.* Stroke as the first manifestation of the Takayasu arteritis. Acta Neurol Belg 2007; 107(1): 18−21.

13. *Kato Y, Dembo T, Takeda H, Fukuoka T, Nagoya H, Deguchi I,* et al. Stroke as a Manifestation of Takayasu's Arteritis Likely due to Distal Carotid Stump Embolism. Inter Med 2010; 49(7): 695−9.
14. *Deyu Z, Dijun F, Lisheng L.* Takayasu arteritis in China. A report of 530 cases. Heart Vessels 1997; 7(Suppl): 32−6.
15. *Vanoli M, Daina E, Salvarani C, Sabbadini MG, Rossi C, Bacchiani G,* et al. Takayasu arteritis: a study of 104 Italian patients. Arthritis Rheum 2005; 53(1): 100−7.
16. *Park MC, Lee SW, Park YB, Chung NS, Lee SK.* Clinical characteristics and outcomes of Takayasu arteritis: analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification. Scand J Rheumatol 2005; 34(4): 284−92.
17. *Arnaud L, Haroche J, Limal N, Toledano D, Gambotti L, Costedoat Chalumeau N,* et al. Takayasu arteritis in France: a single-center retrospective study of 82 cases comparing white, North African, and black patients. Medicine (Baltimore) 2010; 89(1): 1−17.
18. *Sato EI, Hatta FS, Levy-Neto M, Fernandes S.* Demographic, clinical, and angiographic data of patients with Takayasu arteritis in Brazil. Int J Cardiol 1998; 66(Suppl 1): S67−S70.
19. *Keser G, Direskeneli H, Aksu K.* Management of Takayasu arteritis: a systematic review. Rheumatology (Oxford) 2014; 53(5): 793−801.
20. *De Souza AW, Machado NP, Pereira VM, ArraesAE, Reis Neto ET, Mariz HA*, et al. Antiplatelet therapy for the prevention of arterial ischemic events in Takayasu arteritis. Circ J 2010; 74(6): 1236–41.

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