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ТРУДНОСТИ ДИАГНОСТИКИ И ВЕДЕНИЯ БОЛЬНЫХ С АРТЕРИИТОМ ТАКАЯСУ: ОПИСАНИЕ 5-ЛЕТНЕГО КЛИНИЧЕСКОГО НАБЛЮДЕНИЯ

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Difficulties in the Diagnosis and Management of Patients with Takayasu's Arteritis: A Description of a 5-Year Clinical Follow-Up

Резюме

Артериит Такаясу (неспецифический аортоартериит) — гранулематозное воспаление аорты и ее основных ветвей с прогрессирующим течением и развитием тяжелых ишемических нарушений. Трудность диагностики и возможности применения различных методов патогенетического антивоспалительного лечения артериита Такаясу обуславливает целесообразность изучения клинического случая.

Проведен анализ клинического случая больной артериитом Такаясу с манифестацией заболевания в виде общего воспалительного синдрома и проявлений тяжелой ишемии головного мозга в связи с двусторонним стенозирующим поражением сонных артерий. Наблюдение пациентки проводится с сентября 2017 года до настоящего времени, в ее терапии использовались различные методы фармакотерапии и хирургической коррекции. Проведен анализ динамики клинической симптоматики артериита Такаясу и клинических результатов ступенчатой терапии с применением высоких доз метилпреднизолона, болюсного введения циклофосфана с последующим длительным применением циклофосфана внутрь. В процессе лечения больной проведена ангиопластика сонных артерий. В связи с нестойким эффектом проводимой терапии больной были назначены внутривенные инфузии блокатора ИЛ-6 тоцилизумаба, что привело к наступлению ремиссии заболевания. Представленный клинический случай демонстрирует важное диагностическое значение применения методов визуализации сосудов в ранней диагностике и контроле за течением заболевания и эффективность применения ингибиторов ИЛ-6 в достижении и поддержании ремиссии артериита Такаясу.

Ключевые слова: *артериит Такаясу, ангиография, циклофосфан, тоцилизумаб*

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Abstract

Takayasu's disease (nonspecific aortoarteritis) is a granulomatous inflammation of the aorta and its main branches with a progressive course and development of severe ischemic disorders. The difficulty of diagnosis and the possibility of applying various methods of pathogenetic anti-inflammatory treatment of Takayasu's arteritis make it expedient to study a clinical case. The analysis of a clinical case of a patient with Takayasu's arteritis with manifestation of the disease in the form of general inflammatory syndrome and manifestations of severe cerebral ischemia due to bilateral stenotic carotid artery lesion was performed.

The patient has been under observation since September 2017 up to the present time, various methods of pharmacotherapy and surgical correction were used in her therapy. The dynamics of clinical symptomatology of Takayasu's arteritis and clinical results of step therapy with high doses of methylprednisolone, bolus administration of cyclophosphan followed by long-term oral cyclophosphan administration were analyzed. In the course of treatment, the patient underwent carotid angioplasty. Due to the unstable effect of the therapy, the patient was administered intravenous infusions of IL-6 blocker tocilizumab, which led to remission of the disease.

The presented clinical case demonstrates the important diagnostic value of vascular imaging methods in early diagnosis and control of the disease course and the effectiveness of IL-6 inhibitors in achieving and maintaining remission of Takayasu's arteritis.

Key words: *Takayasu's arteritis, angiography, cyclophosphamide, tocilizumab*

Conflict of interests

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TA — Takayasu arteriitis, CS — corticosteroids, IL-6 — interleukin 6, CRP — C-reactive protein

Introduction

Takayasu arteriitis (TA), or non-specific aortoarteriitis (NAA), is a rare autoimmune disorder, which is more typical for patients under 50 years of age and characterized by granulomatous inflammation of the aorta and major arteries [1, 2]. Multiple segmental lesions of the aorta and its branches with stenoses, occlusions, and aneurysms are typical for non-specific aortoarteriitis [1, 2, 4]. Arterial inflammation is the disease hallmark, which is associated with systemic acute-phase response to a variable extent. Inflammatory lesions are characterized by arterial wall thickening, which often leads to arterial lumen remodeling after myofibroblast proliferation. In the majority of cases, 90 % of patients develop arterial stenoses, while up to 25 % of patients suffer from aneurysms [5].

TA diagnosis remains a difficult task due to primary-chronic course of the disease and multiple non-specific symptoms; due to this, more than 12 months pass in the majority of patients (75 %) from the moment of the first symptoms emerging to the final diagnosis [3].

In 2022, new classification criteria for Takayasu arteriitis were published by the American College of Rheumatology. These are based on mandatory criteria (age at disease onset <60 years, vasculitis confirmed by imaging), as well as the sum of specific clinical signs and imaging features of the aorta and its branches, with each item having a corresponding point weight:

- female sex (1),
- angina (2),
- intermittent claudication in extremities (2),
- auscultation of arterial bruits (2),
- decreased pulse strength on radial arteries (2),
- decreased pulsation and tenderness upon the carotid artery palpation (2),
- difference between blood pressure in arms over 20 mm Hg (1),
- organic changes in various arterial regions (1 point for each region, up to 3 points in total),
- bilateral paired involvement of arteries (1),
- simultaneous involvement of the abdominal aorta and renal or mesenteric arteries (3)

5 or more points in total allow to establish the diagnosis of TA. The sensitivity of updated criteria is 93.8 %, while their specificity is 99.2 % [6].

Laboratory markers of systemic inflammation and immunological markers of autoimmune disorders (for differential diagnosis) are important in the diagnosis of TA. Acute TA is characterized by increased C-reactive protein (CRP) levels; IgA, IgM, IgG, C3 complement, anticardiolipin and anti-b2 glycoprotein antibodies may increase as well; rheumatoid factor (RF), antinuclear

factor (ANF), anti-cyclic citrullinated peptide antibodies (ACPA), anti-double stranded DNA, anti-neutrophil cytoplasmic antibodies (ANCA) are usually negative. Standard medical imaging methods usually include ultrasound duplex scanning, CT/MR angiography or contrast-enhanced angiography, which help in determining the location and extent of arterial lesions. One should note that the use of contrast-enhanced angiography is currently limited — this method is mainly used prior to elective surgeries. Based on the scarce and non-specific clinical signs in TA, several authors recommend screening duplex scanning of the aortic arch branches and abdominal aorta for all people below 50 years of age with increased erythrocyte sedimentation rate and/or CRP that cannot be explained with any other causes [1, 3].

Standard treatment with corticosteroids (CS) and cytostatic agents (predominantly methotrexate (MT)) based on the results of retrospective observational studies may be not sufficient to achieve complete stable TA remission [9]. Such refractory cases are treated with timely administration of biological agents, namely interleukin 6 (IL-6) inhibitors and TNF-alpha blockers [7, 8]. In cases of significant arterial stenotic lesions, surgical reconstructive surgeries are applied [3, 10]. Surgical treatment is applied in patients with clinically significant circulatory disorders: angioplasty and/or stenting is used in critical arterial stenotic lesions; prolonged stenosis with significant periarterial fibrosis or occlusion require bypass interventions or other reconstructive surgeries. With that, patients should not undergo vascular surgical interventions in the active TA phase [9].

Tumor necrosis factor (TNF) inhibitors and interleukin 6 blockers (anti-IL-6) are more commonly used in patients with Takayasu arteriitis not responding to treatment with CS and cytostatic agents [8].

Several studies have shown that the serum IL-6 level in patients with Takayasu arteriitis is significantly higher than that in the control group and is positively associated with the disease activity. Moreover, high IL-6 expression has been demonstrated in the vascular wall of patients with Takayasu arteriitis. Thus, IL-6 is a key factor participating in the immune and inflammatory reaction in Takayasu arteriitis. Tocilizumab is a recombinant humanized monoclonal antibody which binds to the IL-6 receptor and blocks its biological effects, inhibiting TA activity and progression. According to the European League Against Rheumatism (EULAR) guidelines, tocilizumab can be administered in cases of relapsing or refractory Takayasu arteriitis [7].

Remote treatment results concerning the prevention of occlusive or aneurysmatic pathological changes of major arteries depend on early diagnosis and rate of achieving the disease remission or low inflammation activity.

Clinical Case Report

The female patient Z., 30 years old, visited the general practitioner in September 2017 complaining of periodic retrosternal pain irradiating to the interscapular region and left shoulder, not related to physical exertion and resolving spontaneously. The patient also suffered from dizziness, fatigue attacks and dark spots in the vision, tachycardia, palpitations, and moderate dyspnea of mixed origin on physical exertion. According to the patient, the disease started in April 2017, when after an episode of hypothermia for the first time she developed retrosternal pain, transient numbness in the arms (more on the left side), fever up to 38 °C. Subsequently, she developed drowsiness, headaches and dizziness, episodic hypotension with BP decrease to 80/40 mm Hg presenting with general weakness, dizziness, transient sweating against the background of persisting retrosternal pain. Laboratory data revealed ESR increase to 42 mm/hour, anemia (96 g/L), and thrombocytosis over 600,000. Patient's life history: no infectious diseases (tuberculosis, viral hepatitides, malaria, HIV infection), allergic reactions (including to medications), blood transfusions were reported. No occupational hazards were detected; the patient underwent no surgeries. The general practitioner suspected the systemic connective tissue disorder, and the patient was referred to the rheumatologist. The following pathological changes were revealed during the physical examination by rheumatologist in the polyclinics: pale skin, livedo reticularis on the thighs, mild edema in the lower third of both legs, tachycardia (HR 93/min), asymmetrical blood pressure (BP could not be measured on the right arm, 80/50 mm Hg in the left arm). Cardiac tones were muffled and rhythmic during auscultation; the systolic murmur irradiating to the neck vessels was auscultated at the aorta. Changes in the laboratory tests were as follows: ESR increased to 30 mm/h, anemia (hemoglobin 98 g/L, red blood cells 3.72×10^{12}/L), thrombocytosis 625×10^{9}/L, CRP increased to 36 mg/L (0–5 mg/L). No significant changes were detected in the biochemistry panel. Antinuclear factor (HEp-2 cell line) was mildly positive (1:160 titer). The immunoblotting test did not reveal increased titers of antinuclear antibodies, anti-double stranded DNA antibodies, antibodies to chromatin, ribosomal chromatin, centromere B, SS-A, SS-B, Sm, Sm/RNP, RNP, Scl-70, Jo-1. Anti-neutrophil antibodies were not detected. No laboratory data confirmed the systemic infections in the patient (hepatitis B, C, D, E; HIV infection; syphilis). Accounting for the patient's age (below 50 years), fever, increased laboratory acute-phase systemic inflammation parameters, angina with signs of heart failure (dyspnea on physical exertion), pain in the neck vessel region (carotodynia), bruit auscultated on subclavian arteries, significant difference in BP values between arms, the diagnosis of Takayasu

arteriitis was detected. The patient was referred to the ultrasound of extra- and intracranial vessels, as well as echocardiography with subsequent hospitalization to the rheumatology department of the Republican hospital. However, the patient refused the hospitalization to the specialized department due to family circumstances.

At night on October 9, 2017, the patient's condition drastically deteriorated — an ischemic stroke developed in the territory of the right middle cerebral artery, which was confirmed by the computed tomography of the brain. The patient was hospitalized to the regional vascular center, where she was again examined by the counseling rheumatologist. Based on the clinical data, ultrasound signs (thickened walls of the right carotid artery with complete occlusion and significant local thickening of the left carotid artery walls up to 4.5–5 mm along 2.5–3 cm), computed tomography data (complete occlusion of the right carotid artery, hemodynamically significant stenosis of the left carotid artery), the diagnosis of Takayasu arteriitis was confirmed for the patient. After the neurological status was stabilized, on October 26, 2022 the patient was transferred to the rheumatology department of the State Budget Health Institution of the Crimea Republic "N.A. Semashko Republican Clinical Hospital". She was administered the following treatment: pulse-therapy (methylprednisolone 1000 mg for 3 consecutive days, cyclophosphamide 800 mg once) with subsequent switching to oral methylprednisolone (Medrol) 16 mg/day and oral cyclophosphamide 50 mg/day. Positive changes were noted with the treatment administered: retrosternal pain decreased in intensity, dyspnea and pain along neck vessels resolved, ESR and CRP levels dropped to normal values. In January 2018, the patient was counseled in the A.N. Bakulev Scientific Center of Cardiovascular Surgery. The diagnosis of TA was confirmed; it was recommended to postpone conservative treatment and repeat the counseling 6 months later to decide on surgical correction of detected arterial stenoses. In March 2018, a single episode of loss of consciousness (7–10 minutes) developed in a patient, without signs of recurrent stroke based on brain computed tomography data. From March 2018 to October 2019 the patient continued oral methylprednisolone in the dose of 12–8 mg/day and cyclophosphamide 50 mg/day. During this period, no more syncope episodes were observed; hypotension (~80/40 mm Hg) persisted, with moderate systemic inflammation signs (CRP level 5.6–12.3 mg/L; ESR 10–22 mm/h). In January 2019, the patient was hospitalized for surgical treatment to FSBI V.A. Almazov National Medical Research Center, Ministry of Health of Russia (Saint-Petersburg), where CT angiography was performed with the following results: thickened walls of the aorta and major neck arteries in proximal regions, occlusion of the right common carotid artery, stenosis of the left common carotid artery (64.3 % in diameter/84.2 % area), hypoplastic left vertebral artery, no contrast enhancement of the 6th segment of the vertebral artery along approximately 24 mm (occlusion? subocclusion?) — these changes confirmed Type I TA (Figure 1).

The patient underwent balloon angioplasty with left common carotid artery stenting. The patient continued supportive anti-inflammatory treatment (methylprednisolone 8 mg/day, azathioprine 100 mg/day); laboratory signs of inflammatory activity persisted minimally (CRP 3.2–5.5 mg/L; ESR (Westergren) 12–18 mm/h).

However, in September 2019, brain symptoms worsened again, and the patient was hospitalized to the Republican vascular center with complaints of short-term loss of consciousness, BP decrease to 70/30 mm Hg, and worsened signs of left-sided hemiparesis; recurrent ischemic stroke in the territory of the right middle cerebral artery was suspected. Computed tomography revealed the following changes: a cystic & gliotic lesion sized 55x37 mm was detected in the right frontotemporal region, involving the basal ganglia, midline brain structures were shifted 3 mm to the right, no signs of acute cerebrovascular accident were detected (Figure 2); condition after left common carotid artery stenting, occlusion of the right common carotid artery, proximal region of the left vertebral artery, narrowing of the left internal carotid artery, subocclusion in the lower third of the left common carotid artery, stenosis in the middle third of the left common carotid artery (ostium diameter 5.0–5.3 mm, with significant narrowing of the contrasted lumen in the proximal region up to 2.3 mm; the stent is visualized distally in its lumen, the contrasted lumen in the middle third is narrowed approximately to 50 %).

Accounting for the changes detected after the remote counseling, in October 2019 the patient was transferred to the Cardiovascular Surgery Department of FSBI V.A. Almazov National Medical Research Center, Ministry of Health of Russia (Saint-Petersburg), where the repeated balloon angioplasty of the left common carotid artery (CCA) with stenting was performed on October 11, 2019. The following conservative treatment was recommended: biological therapy with the drug Tocilizumab (Actemra) 680 mg (IV drip) once every 4 weeks; subcutaneous methotrexate 15 mg SC weekly; folic acid 5 mg/week; methylprednisolone continued in the dose of 16 mg/day. The first tocilizumab infusion in the defined dose was administered in November 2019 in the biological therapy ward of the State Budget Health Institution of the Crimea Republic "N.A. Semashko Republican Clinical Hospital"; however, after that the drug was administered irregularly (the regular infusion was skipped in December 2019) due to drug availability issues.

In February 2020, the patient's condition significantly deteriorated — syncope recurred, and acute-phase

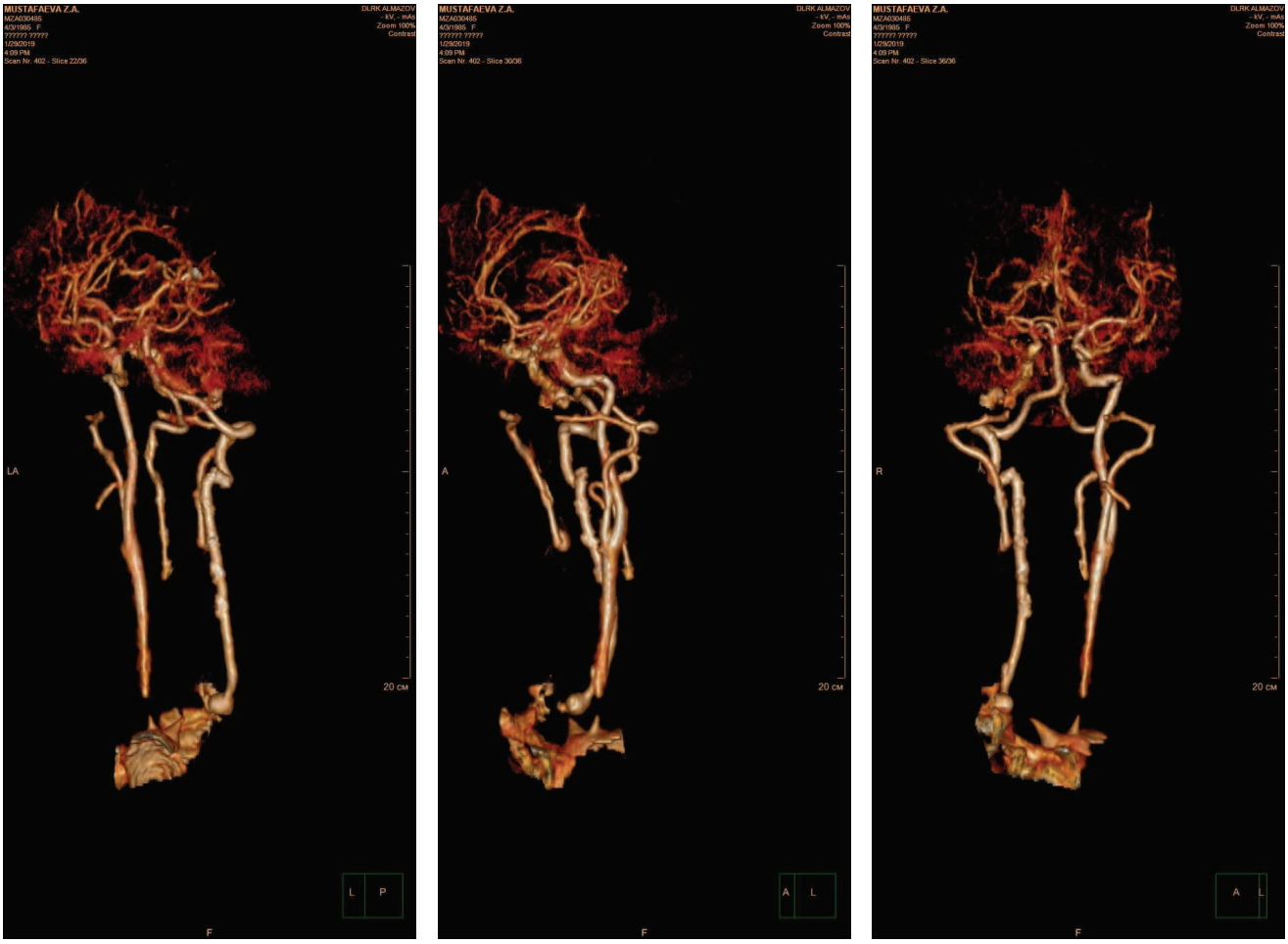

Figure 1. *Multislice computed tomography. Thickening of the walls of the aorta and the main arteries of the neck in the proximal sections, occlusion of the right common carotid artery, stenosis of the left common carotid artery*

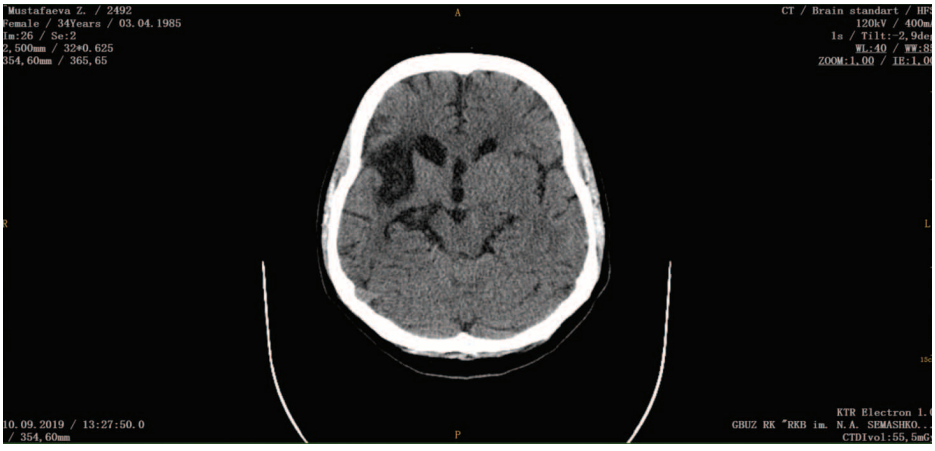

Figure 2. *Computed tomography of the head without contrast: cystic-glial changes in the frontal and temporal lobes on the right*

parameters increased (ESR 34 mm/h, CRP 27.8 mg/L). The ultrasound examination of neck vessels (March 3, 2020) revealed negative changes: condition after left CCA stenting, the stent function was not impaired in the ostium; a hypoechogenic concentric narrowing was detected in the lower third of the stent, 12 mm long, with the local hemodynamic difference, blood flow increase to 290 cm/sec, stenosis degree of 80 %, with moderate blood flow deficit in the left middle cerebral artery (MCA) territory due to insufficient collateral compensation. Narrowed lumen was detected in proximal regions of the left common carotid artery stent, 17 mm long, with the blood flow of 5.9 m/sec — this was counted as >90 % restenosis. The patient was hospitalized to the rheumatological department, where she was administered combined pulse therapy (methylprednisolone 1000 mg IV drip for 3 days + cyclophosphamide 1000 mg once); methylprednisolone dose was also increased to 24 mg/day.

After discharge (in May 2020), tocilizumab treatment was resumed in the dose of 600 mg IV drip once every 4 weeks, while continuing subcutaneous methotrexate 15 mg/week. After 6 months of continuous tocilizumab treatment, the body temperature normalized, retrosternal pain, dyspnea, numbness of both arms decreased, no syncope were detected; laboratory tests revealed ESR decrease to 10–12 mm/h, hemoglobin increase to 118 g/L, platelet count decrease to 411×10^9/L, CRP 3.8–4.2 mg/L; no negative changes were detected during the ultrasound examination of major vessels. Methylprednisolone dose was decreased to 8 mg/day. For the next two years the patient continued methylprednisolone in the dose of 8 mg/day, subcutaneous methotrexate 15 mg weekly (discontinued in November 2020), folic acid 5 mg/week, rivaroxaban 15 mg/day, atorvastatin 20 mg/day, clopidogrel 75 mg/day, and tocilizumab (Actemra) 600 mg (IV drip) once every 4 weeks until May 2021, then in subcutaneous injections 162 mg weekly. Within the previous two years, the patient's clinical condition is stable; no episodes of acute cerebrovascular accident or loss of consciousness were detected; the functional neurological status did not demonstrate negative changes, no retrosternal pain has been observed. CRP values fluctuated a little (2.8–3.4–5.9 mg/L), ESR was within normal limits, the hemoglobin level was 112–117 g/L. During tocilizumab treatment, single increases of ALT and AST values were observed (84 and 72 U/L, respectively), which did not lead to therapy discontinuation. The patient was not infected with the novel coronavirus infection. The ultrasound examination of extra- and intracranial vessels (June 4, 2022): condition after left common carotid artery stenting, the stent function was not impaired in the ostium; a hypoechogenic concentric narrowing was detected in the lower third of the stent, 11 mm long, with the local hemodynamic difference, blood flow increase to 270 cm/sec, stenosis degree of 78 %, with moderate blood flow deficit in the left middle cerebral artery territory due to insufficient collateral compensation. The occlusion of the right common carotid artery was also detected, with systemic blood flow deficit in the right MCA territory due to insufficient collateral and functional compensation (signs of collateralization via anterior and posterior communicating arteries on the right side). Brachiocephalic trunk stenosis (70 %). Stenosis of the right subclavian artery (60 %), stenosis of the right vertebral artery ostium (60–65 %). Occlusion of the 1st segment of the left vertebral artery. Hypoplasia of the left renal artery with occlusion in the ostial region.

The patient currently continues her follow-up in the biological therapy ward of the counseling polyclinics of the State Budget Health Institution of the Crimea Republic "N.A. Semashko Republican Clinical Hospital"; she continues tocilizumab treatment as supportive therapy for TA with signs of unstable clinical & laboratory remission, without significant progression of stenosis in major neck arteries during the previous two years.

Discussion

The current clinical report describes the case of severe Takayasu arteriitis characterized by the bilateral involvement of carotid arteries with quick progression of organic changes leading to cerebral blood flow deficit and formation of ischemic lesions in the brain tissue. The inflammatory process in major arteries of the observed patient was refractory to treatment with cytostatic agents combined with average CS doses. When CS dose was decreased, the inflammatory process "escaped" from the combined treatment control (with cyclophosphamide, azathioprine, and methotrexate used successively), which manifested with increased laboratory markers of systemic inflammation and worsening stenosis of common carotid arteries. Insufficient treatment efficacy may be related not only to the severe disease course, but also to late therapy onset, as the disease manifested already with stenoses formed. The treatment was overtly insufficient in the early period (insufficient oral methylprednisolone dose (16 mg/day), cyclophosphamide 50 mg/day orally in 2017–2019, irregular tocilizumab administration in the beginning due to the drug availability issues).

At the same time, one should note that the anti-inflammatory treatment used led to clinical improvement and low activity of the systemic inflammatory process — this enabled two reconstructive surgeries in major vessels stabilizing hemodynamic parameters in the brain.

CS are the mainstay of TA treatment; high CS doses in combination with cytostatic agents are effective for remission induction. However, inflammatory relapses in vessels are rather common — they lead to recurrent and prolonged CS treatment with a high risk of related adverse events [11]. Cumulative CS side effects is a serious problem in the treatment of TA patients, which is mainly associated with the long-term treatment required. As known, immunosuppressive agents are used in patients with severe signs, though they have some limitations. Due to this, IL-6 and TNF-α inhibitors play an important role both in maintaining inflammation remission and decreasing the CS dose with the rate of associated adverse events [12].

Administration of the IL-6 inhibitor tocilizumab somewhat became a breakthrough in the treatment of our patient — this was associated with stable TA remission achievement and maintenance, as well as no progression of organic changes in neck arteries. Currently tocilizumab is considered the inseparable part of standard TA treatment; it usually used with the inefficacy of methotrexate and other cytostatic agents [13]. Two

randomized clinical trials have demonstrated significant efficacy of tocilizumab compared to CS monotherapy [14, 15]. The steroid-sparing effect of tocilizumab (allowing for significant methylprednisolone dose) and satisfactory treatment tolerance with no increases in the adverse event rate were observed as well [16–18].

In 2018, the French Takayasu network published the retrospective multicenter trial including 46 patients with TA administered tocilizumab. Significant decrease in the median NIH scale and daily Prednisolone dose was observed with tocilizumab treatment. Besides, survival was significantly better in patients administered tocilizumab compared to the group of patients administered only disease-modifying antirheumatic drugs (DMARDs) [19].

Based on the data from the prospective multicenter Japanese trial evaluating the long-term (>2 years) efficacy and safety of tocilizumab used in the treatment of TA patients, the significant steroid-sparing effect was observed with tocilizumab treatment from Week 24 to Week 96 compared to CS. 70 % of patients with TA developed relapses when taking CS in the dose of less than 10 mg/day for 6 months [20]. The results of the Nakaoka Y. et al. trial showed that the majority of patients administered tocilizumab in the dose of 162 mg/week may decrease the CS dose to <0.2 mg/kg/day within more than 48 weeks [21].

The trial of Liao H. at el. also demonstrated that tocilizumab may be a more effective alternative to cyclophosphamide in TA treatment due to decreased requirement of higher CS doses, improvement of thickness of the subclavian artery wall with time, and superior safety profile with less side effects [7].

At the same time, several issues of long-term TA treatment with IL-6 inhibitors have to be solved: duration of treatment with IL-6 inhibitors when achieving persistent disease remission; safety and feasibility of their combination with methotrexate and other cytostatic agents; possibility of complete corticosteroid discontinuation with their long-term use. Accounting for rare TA cases and associated difficulties of organizing randomized clinical trials, the analysis of serial clinical cases presuming the use of these drugs in patients with different disease course is important for analyzing the aspects of IL-6 inhibitor use in clinical practice.

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