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# *Takayasu's arteritis as a cause of diagnostic difficulties in a 16-year-old girl*

Takayasu's arteritis (TA) is an idiopathic systemic inflammatory vasculitis, commonly seen in young women. It is a large vessel vasculitis, primarily affecting aorta, its major branches, but also proximal coronary, carotid, renal and pulmonary arteries. The presence of many organs insufficiency due to vascular occlusions or symptoms of systemic disease characterize the course of TA. The pulse deficit on upper and/or lower limbs, as a result of aorta and its main branches narrowing, is the most common symptom of TA (named "pulseless disease") (1). The histology of affected arteries is characterized as a granulomatous panarteritis with a presence of gigant cells infiltration (2, 3). The disease was firstly described by Japanese ophthalmologist Migito Takayasu in 1908. He presented the case of a young woman with characteristic fundal microaneurysm formations and arteriovenous anastomoses of the central vessels in the retina (4).

TA is more prevalent in Asians and the most frequent vasculitis is in Japan and South America. It is of very rare occurrence in West Europe, and has been sporadically diagnosed in Poland (5). There are few case reports in the Polish literature describing patients suffering from TA (6–8).

The aim of our report is to describe the clinical course of TA and draw physicians' attention to diagnostic difficulties of chronic inflammatory process due to such very rare systemic vasculitis. Large vessel vasculitis may have severe complications, so the early diagnosis is challenging.

The case emphasizes the importance of having a high index of suspicions for TA in children presenting with constitutional symptoms accompanied by high levels of acute phase reactants.

## CASE REPORT

We report a 16-year-old Caucasian girl that was hospitalized in the Gastroenterology Department of Pediatrics University Hospital, because of slightly elevated temperature, anemia, high levels of acute phase reactants and episodes of abdominal pain. In the past medical history she gave a 3 months' history of general malaise, fatigue, loss of appetite and weight loss (6 kg). She also complained of abdominal pain and extremity fatigue.

Two weeks before admission she was diagnosed in Outpatients' Clinic of Pediatrics Hematology and Oncology because of anemia and referred to Gastroenterology Dept. because of predominant abdominal symptoms. Initial laboratory tests showed high levels of acute phase reactants (ESR, C-reactive protein, hiper- alfa-1 and alfa-2 globulinaemia in serum protein electrophoresis);

hypergammaglobulinaeamia and microcytic anaemia with iron deficiency. Laboratory investigations revealed normal thyroid hormones, normal liver and renal function tests. The blood cultures were negative. The viral serological tests (hepatitis B, C virus, Epstein-Barr virus, Cytomegalovirus) were negative. The occult stool blood test was negative. The Mantoux test (RT23) was negative. A routine chest X-ray and abdominal ultrasound were normal. To exclude inflammatory bowel syndromes and other causes of gastrointestinal hemorrhage the panendoscopy of gastrointestinal tract was done (with mucose membrane biopsy for histopathological assessment) and revealed no abnormalities. The patient was examined by gynecologist and ophthalmologist.

The initial clinical picture was unclear. In default of unequivocal cause of observed symptoms the rheumatologic examination was performed. On physical examination her weight was 48 kg (between 10 and 25 percentile) and height was 160 cm (25 percentile for her age), her skin was pale, there were systolic bruits on auscultation over heart, at the interscapular area, and over abdominal aorta at epigastrium and middle gastrium. The heart rate was normal for age (75 per minute), the peripheral pulses were palpable, blood pressure was normal (right upper limb – 105/60 mmHg, left – 110/60 mmHg, right lower limb – 130/60 mmHg, left – 110/60 mmHg). There was no difference in systolic blood pressure between arms. In laboratory tests antinuclear antibodies were present (of titer 1:160 on Hep-2 cells substrate). Rheumatoid factor, p-ANCA and c-ANCA antibodies were not detectable.

A systolic bruit was the only indicative to perform cardiovascular diagnostic procedure. The doppler echocardiography revealed blood flow disturbances in descending aorta. The 64-row multidetector computed tomography (MDCT) was performed. There was evidence of thickening of thoracic (from level of Th 10) and abdominal aorta wall with abdominal aorta aneurysm (diameter – 27 mm). The aortic lumen dilatation spreads to the level of the renal arteries, and the periaortic infiltration to the level of L3 (above the level of the inferior mesenteric artery) (Fig. 1, 2). In addition, MDCT showed coeliac truncus involvement with its occlusion and superior mesenteric artery stenosis with poststenotical dilatation and collateral circulation to coeliac truncus (Fig. 3). In our patient an inflammatory infiltration involves the descending thoracic aorta, abdomen aorta to the level of renal arteries without their stenosis. MDCT revealed aortic diameter proximally to inflamed aortic wall – 17 mm, of descending aorta – 20 mm, and of aorta above the level of the renal arteries – 28 mm. Below the ostium of the superior mesenteric artery the aortic lumen was narrowed and at the level of the inferior mesenteric artery made – 13 mm with normal aortic wall. The diagnosis of Takayasu's arteritis – with abdominal aorta and its main branches involvement was established.

The patient was treated with prednisone (60 mg per day), cyclophosphamide (1 g i.v. per month) and nadroparine (2850 units s.c. per day). Vascular surgery or angioplasty procedures was not possible. From the technical point of view, there was no way for surgical bypass for the stenosis. Angioplasty carried high risk of complications.

After immunosuppressive treatment the absence of constitutional symptoms and partial normalization of acute phase reactants indicated low grade inflammatory disease activity. Decreased activity of the disease was verified with MDCT repeated after 3 and 6 months of the immunosuppressive therapy and did not reveal progression of vasculitis.

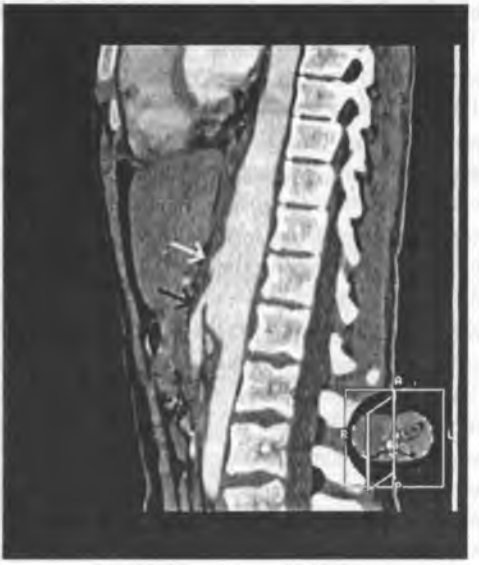

Fig. 1. The 64-row multidetector computed tomography (MDCT). Sagittal view. There is an aortic lumen dilatation and the periaortic infiltration. The black dart shows the proximal mesenteric artery stenosis with poststenotical dilatation. The white dart shows the anatomical point where coeliac truncus ought to be present (occlusion of coeliac truncus)

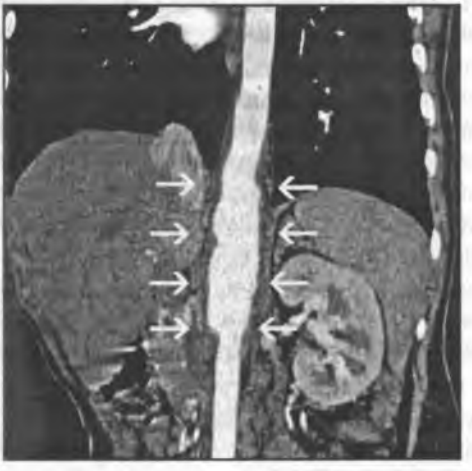

Fig. 2. Coronal view (the renal artery plane). The aortic lumen dilatation spreads to the level of the renal arteries

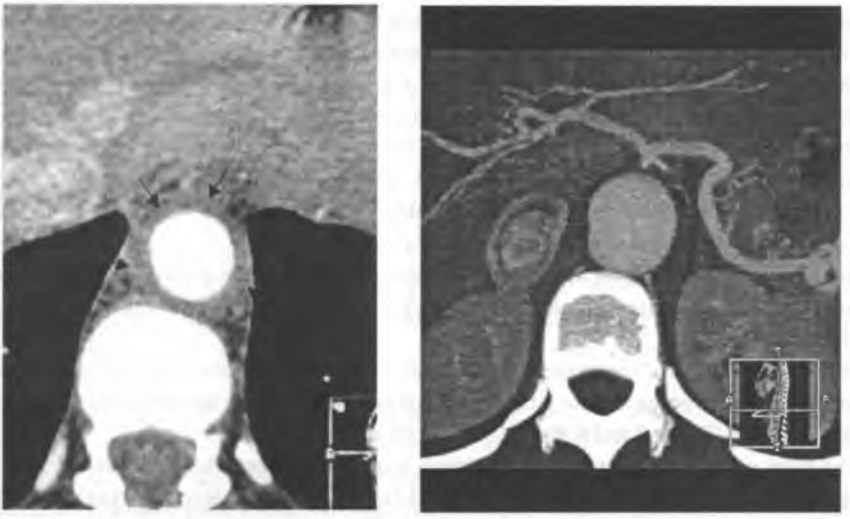

Fig. 3. 3D volume rendering reconstruction. Proximal coeliac truncus occlusion
a – on the level of thoracoabdominal aorta. b – collateral circulation to hepatic and splenic arteries

## DISCUSSION

In 80–90% cases Takayasu's arteritis affects young women, mostly between 10 and 40 years of age. The female/male ratio is about 8:1 in adults and from 4:1 to 2:1 in children (5).

Our patient, three months before admission, manifested general malaise and weight loss. The episode of acute abdominal pain and nonspecific general symptoms were the main cause to admit the patient to the hospital. The loud systolic bruit over interscapular area was the only symptom that supported the proper diagnosis. A study of 104 Italian patients suffering from TA showed that 70% of patients experienced nonspecific musculoskeletal signs and constitutional symptoms at the disease onset. The most common clinical finding at diagnosis was a bruit (90%) (9).

In our case MDCT revealed the inflammatory process involving thoracoabdominal aorta to the level of renal arteries but without their involvement.

The most common type of TA changes involves the entire aorta and its branches both above and below the diaphragm (5, 10, 11). This pattern of aortic involvement, seen in our patient, is less commonly observed. Both hypertension and typically seen lack of pulse and the blood pressure difference on upper and lower limbs were not observed in our case.

In 1990, the American College of Rheumatology proposed criteria for clinical diagnosis of TA (12): 1) age at the disease onset < 40 years; 2) claudication of extremities; 3) decreased bronchial artery pulse; 4) blood pressure difference >10 mmHg on upper limbs; 5) bruit over subclavian arteries or aorta; and 6) characteristic arteriogram abnormalities. The presence of at least three of the six criteria is required to diagnose TA. This classification is easy to use, but it does not recognize other clinical features that are often seen in the course of disease (13). In 1995 Sharma et al. proposed modified criteria for clinical diagnosis of TA (14). The criteria are divided into two groups: major and minor criteria. The major criteria include: 1) left midsubclavian artery lesion; 2) right midsubclavian artery lesion; and 3) the presence of at least 1 month of characteristic signs and symptoms: limb claudication, pulselessness or blood pressure differential > 10 mmHg in arms, exercise ischaemia, neck pain, fever, amaurosis fugax, syncope, dyspnoe, palpitations, blurred vision. Ten minor criteria: high ESR (> 20 mm/h), carotodynia, hypertension (persistent blood pressure > 140/90 mmHg brachial

or > 160/90 mmHg popliteal), aortic regurgitation or anuloaortic ectasia, pulmonary artery lesion, left mid common carotid lesion, distal brachiocephalic trunk lesion, descending thoracic aorta lesion, abdominal aorta lesion and coronary artery lesion. The presence of two major or one major and two minor criteria or four minor criteria suggests a high probability of TA.

In our patients: sex, age, systolic bruit over interascapular area on ascultation, limb fatigue, abdominal pain supported TA diagnosis. MDCT demonstrated a wide-spread inflammation of arteries. Laboratory tests showed high ESR and CRP. Upon the presence of both, ACR and Sharma modified criteria, the diagnosis of TA was established.

In the following studies, in many presented series of patients, the time between the onset and diagnosis was very long – approximately 15 months (15, 16). In our case the diagnosis was established after three months.

We started a combined immunosuppressive treatment with prednisone and monthly administrated cyclophosphamide stopping disease progression, that was confirmed by normalization of acute phase reactants and MDCT after 3 and 6 months after treatment.

The main goal of TA treatment is to achieve clinical remission. Than, if there are anatomical capabilities the surgical operations can be performed. Only 50% of patients respond to glucocorticoids, that is why cytotoxic treatment with cyclophosphamide, azathioprine or methotrexate is proposed. Approximately 20% of all patients are resistant to any kind of therapy (15). Recently, patients resistant to glucocorticoids and other immunosuppressive agents, have been treated with mycophenolate mofetil and anti-tumour necrosis factor alfa inhibitors (17–19).

Surgery is recommended when patient is in clinical remission of disease to minimalize operative risk and avoid complications due to inflammation such as restenosis, anastomotic failure, thrombosis, haemorrhage and infection. The cumulative survival rate in the groups of patients undergoing endovascular treatment (bypass grafts) was 81.4% and 73.5% at 10 and 20 years, respectively (20, 21). Unfortunately, about 20–30% interventions require revascularization, and after percutaneous transluminar angioplasty even 44% of patients undergo reoperations after short time (after 12–24 months) (15, 22).

Kieffer et al. (23) presented the results of operative treatment on 33 patients with descending thoracic or thoracoabdominal aortic aneurysm in association with Takayasu's disease. The extension of aneurysmal lesions and involvement of visceral and supraaortic vessel are main risk factors of long-term outcome after surgery. Despite severe complications (3/33 patients died of multiple organ failure, 3/33 patients developed paraplegia, 2/33 patients required reoperation, for hematoma in one case and bowel necrosis in one, 4/33 patients developed respiratory complications requiring artificial ventilation), the authors concluded the outcome of surgery as satisfactory.

The etiopathogenesis of Takayasu's arteritis is still unexplained. In the group of TA patients there is an association with the HLA-Bw52 and HLA-B39 that indicates immunogenetic background of this disorder. Recently, *Mycobacterium tuberculosis*, its 65 kDa heat shock protein, has been implicated as one of trigger factors of immunological reaction (24). A cell-mediated and humoral immunity are involved in autoimmunological process in TA. The presence of hypergammaglobulinaemia, immune complexes, anti-endothelial cells antibodies, anticardiolipin antibodies express the disturbances in humoral immunological response. A depletion of CD4+ , an elevation of CD8+ in sera of patients and type of histopathological assessment express the cell-mediated immune mechanism. Active inflammation is characterized by the presence of mononuclear cells, predominantly lymphocytes T ($\gamma/\delta$ and $\alpha/\beta$ T lymphocytes), and killer cells (NK). A perforin is expressed in infiltrating lymphocytes (NK activity marker). Antigens HLA class I and II and ICAM-1 are overexpressed at the side of inflammation. There is no reliable index of disease activity in TA. Recently, Matsuyama et al. have presented preliminary results analyzing levels of metalloproteinases (MMP)-2,-3,-9 in acute phase and in

remission of TA. MMP-3 and MMP-9 were only elevated in patients with active disease in comparison with control. MMPs might have been markers of active inflammation in TA (25–28).

Although Takayasu's arteritis is a very rare disease that appears in Polish population, it is important to include it in differential diagnosis in patients with constitutional symptoms of unclear origin.

## CONCLUSION

The case emphasizes the importance of having a high index of suspicions for TA in children presenting with constitutionals symptoms accompanied by high levels of acute phase reactants.

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## SUMMARY

Takayasu's arteritis (TA), commonly seen in young women, is a large vessel vasculitis, primarily affecting aorta and its major branches. The presence of many organs insufficiency due to vascular occlusions or symptoms of systemic disease characterize the course of TA. The early diagnosis is challenging. The aim of our report is to describe diagnostic difficulties, clinical course and angiographic characteristics of TA in young girl. We report a 16-year-old girl that was hospitalized because of an episode of abdominal pain with a 3 months' history of malaise and weight loss. The laboratory tests showed high levels of acute phase reactants, hypergammaglobulinaeamia and microcytic anaemia. A systolic murmur on auscultation at the interscapular and abdomen area, was the only reason to start cardiovascular diagnostics. The doppler echocardiography revealed blood flow disturbances in descending aorta. On the 64-row multidetector computed tomography (MDCT) the evidence of thickening of thoracic and abdominal aorta wall with abdominal aorta aneurysm, coeliac truncus occlusion and superior mesenteric artery stenosis with collateral circulation were present. The diagnosis of TA was established. The patient was treated with prednisone, cyclophosphamide and nadroparine. Partial normalization of acute phase reactants was observed. From the technical point of view vascular surgery or angioplasty procedures were not possible and carried high risk of complications. The case emphasizes the importance of having a high index of suspicions for Takayasu's arteritis in patients presenting with constitutional symptoms accompanied by high levels of acute phase reactants.

Choroba Takayasu przyczyną trudności diagnostycznych u 16-letniej pacjentki

Choroba Takayasu (TA) to idiopatyczna układowa choroba zapalna naczyń, dotycząca najczęściej młodych kobiet, której istotą jest zapalenie dużych naczyń (aorty i jej odgałęzień). TA może przebiegać z dominującymi objawami ogólnoustrojowymi lub narządowymi, wynikającymi z niedokrwienia poszczególnych organów. Postawienie wczesnej prawidłowej diagnozy jest trudne. W pracy przedstawiamy trudności diagnostyczne, przebieg kliniczny i obraz angiograficzny naczyń u młodej pacjentki, u której ostatecznie rozpoznano TA. 16-letnia pacjentka była hospitalizowana w celu ustalenia przyczyny dolegliwości bólowych w jamie brzusznej. W trzymiesięcznym okresie poprzedzającym przyjęcie do szpitala pacjentka była osłabiona, zaobserwowała ubytek masy ciała. W badaniach laboratoryjnych stwierdzono wysokie wartości wykładników stanu zapalnego, hypergammaglobulinemię i niedokrwistość mikrocytarną. Szmer skurczowy w okolicy międzyłopatkowej i nad jamą brzuszną był powodem przeprowadzenia rozszerzonej diagnostyki układu sercowo-naczyniowego. Badanie ECHO wykazało zaburzony przepływ w aorcie zstępującej. Przy pomocy 64-rzędowej tomografii komputerowej (MDCT) stwierdzono pogrubienie ściany aorty piersiowej i brzusznej, z tętniakowatym poszerzeniem aorty brzusznej, z całkowitą niedrożnością pnia trzewnego i zwężeniem tętnicy krezkowej górnej oraz wytworzeniem krążenia obocznego. Rozpoznano TA. Pacjentkę leczono prednizonem, cyklofosfamidem oraz heparyną drobnocząsteczkową, uzyskując ograniczenie aktywności procesu zapalnego, wyrażone obniżeniem wykładników ostrej fazy. Z technicznego punktu widzenia nie istniały możliwości anatomiczne przeprowadzenia chirurgicznego zabiegu naczyniowego. Zabieg angioplastyki niósł ze sobą wysokie ryzyko powikłań. W przypadkach występowania u pacjenta niejasnych objawów ogólnoustrojowych przy obecności laboratoryjnych wykładników procesu zapalnego należy w diagnostyce różnicowej brać pod uwagę chorobę Takayasu.