

Takayasu arteritis in Crohn's disease

Report of three cases

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Abstract. *Takayasu arteritis is a chronic vasculitis of unknown aetiology, which primordially affects the aorta and its primary branches. Current observations have revealed a high prevalence of other inflammatory diseases in patients with Takayasu arteritis and thus raised the possibility that Takayasu arteritis may be associated with abnormality of the immune system activated by other inflammatory disorders such as inflammatory bowel disease (Crohn's disease, ulcerative colitis). The association of Takayasu arteritis and ulcerative colitis has occasionally been reported, however the simultaneous occurrence of Takayasu arteritis and Crohn's disease is rare. We report three additional cases of adult female patients with Crohn's disease and subsequent clinical manifestation of Takayasu arteritis.*

Key words: *Takayasu arteritis, Crohn's disease, ulcerative colitis, inflammatory bowel disease, plasmapheresis*

Kloudová M, Tomš J, Chovanec V, Vodňanský P, Eliáš P, Rejchrt S, Bradna P, Bureš J. Takayasuova arteritida u Crohnovy choroby. Popis tří případů. Folia Gastroenterol Hepatol 2005; 3 (3): 92 – 98.

Souhrn. *Takayasuova arteritida je chronická vaskulitida neznámé etiologie, která postihuje především aortu a její primární větve. U nemocných s Takayasuovou arteritidou je vyšší prevalence jiných zánětlivých chorob, je tedy možné, že Takayasuova arteritida je spojena s abnormalitami imunitního systému aktivovaného chronickým zánětlivým onemocněním, například idiopatickými střevními záněty (Crohnova choroba, ulcerózní kolitida). Spojení Takayasuovy arteritidy a ulcerózní kolitidy bývá příležitostně pozorováno, současný výskyt Crohnovy choroby a Takayasuovy arteritidy je vzácný. V této práci jsou popsány tři případy dospělých žen s Crohnovou chorobou, u kterých se následně manifestovala Takayasuova arteritida.*

Klíčová slova: *Takayasuova arteritida, Crohnova choroba, ulcerózní kolitida, idiopatické střevní záněty, plasmafereza*

Takayasu arteritis is a chronic vasculitis of unknown origin. Its incidence is low in the United States and Europe (1 to 3 new cases per year per million population) (9,17,28). Sporadically, association between Takayasu arteritis and inflammatory bowel disease has been described, both in Crohn's disease (5-7, 13, 15,17,19,23,29,31,32,38,40,41,43,50,52,54) and ulcerative colitis (1,3,4,8,14,22,25,26,34,36,39,42,45). We report three additional cases of adult female pati-

ents with Crohn's disease and subsequent clinical manifestation of Takayasu arteritis.

CASE REPORTS

Case 1

A 20-year-old woman had been followed up for Crohn's disease for previous year elsewhere. Onset of the disease was associated with the erythema nodo-

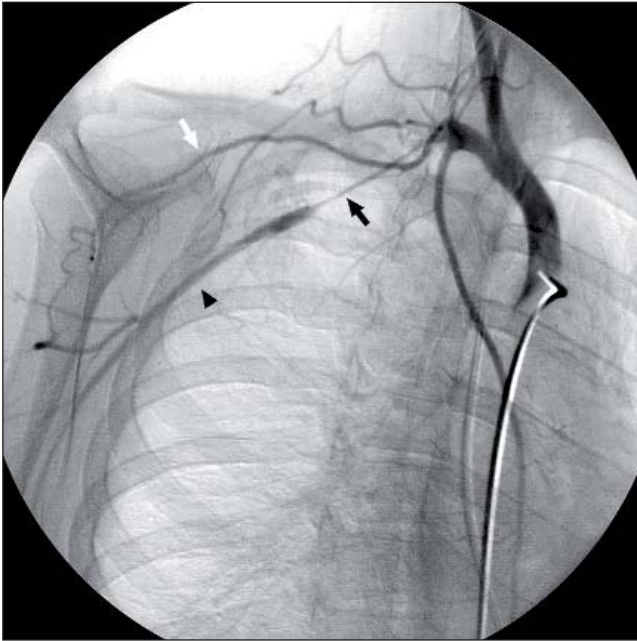


Figure 1
Arteriography of the first patient discovered extensive significant stenoses of the right subclavian artery (black arrow) and normal width of the right axillary artery (arrowhead). There are evident extensive collateral vessels (white arrow), which supply the right upper extremity with blood.

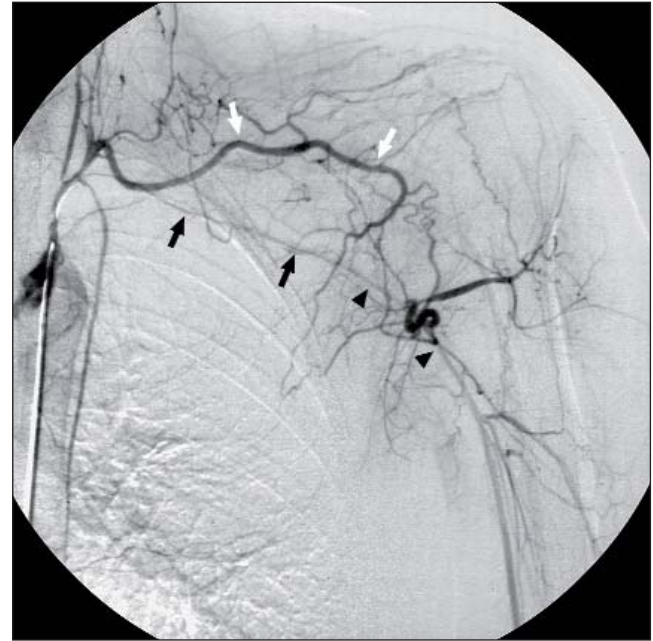


Figure 2
Arteriography of the first patient also revealed extensive significant stenoses the left subclavian artery (black arrows) and left axillary artery (arrowheads). Several extensive collaterals are also seen (white arrows), supplying the left upper extremity with blood. The costocervical trunk is markedly filled.

sum eruption. Initial immunosuppressive treatment by azathioprine was complicated by bone marrow suppression, acute pancreatitis and disseminated intravascular coagulation. She was referred to our Department. Subtotal colectomy and resection of the terminal ileum were done because of severe diffuse stenosing involvement. One year later she was operated for intractable enterovaginal fistulas. At the age of 24, she started to suffer from severe headaches and from pain in her upper extremities during exertion, especially exercising in an elevated position (e.g. brushing her hair etc.). Her digits became cold and pale. Arterial pulses in the arms diminished and blood pressure in both arms was not measurable. There was a vascular bruit over the subclavian arteries. Doppler ultrasonography and arteriography revealed significant stenosis of both subclavian arteries and the left axillary artery (Figs 1 and 2). The patient fulfilled six of six diagnostic criteria for Takayasu arteritis according to the American College of Rheumatology (3). Initial treatment was started with five infusions of 125 mg methylprednisolone every other day followed by oral prednisone (30 mg per day) and by daily infusions of alprostadil. Because of further deterioration, i.v. infusion of 50 g immunoglobulin was administered. No improvement was achieved either. That is why a series of five plasmaphereses was decided on. Despite

accurate volume, albumin and mineral replacement, the patient tolerated this treatment poorly, including malaise, vomiting and severe hypertensive reaction. However, substantial clinical improvement of both Takayasu arteritis and Crohn's disease was achieved. The treatment continued with methotrexate (20 mg weekly up to cumulative dose of 1,000 mg) and prednisone (10 to 20 mg per day, with a few breaks; estimated cumulative dose was 26 g within a nine-year period). At the age of 25, she aborted at the fifth week of pregnancy. One year later she gave birth to her first healthy baby. At the age of 29, full clinical remission of both Takayasu arteritis and Crohn's disease was achieved. Arterial pulses became palpable on both radial arteries and blood pressure measurable again. In the same year, she successfully delivered her second healthy infant. Both deliveries were possible owing to caesarean section.

Case 2

A 24-year-old woman had a history of the Henoch-Schönlein purpura at six. Crohn's disease was diagnosed when she was sixteen and two surgical resections (ileo-coecal resection first and resection of the stenotic neo-terminal ileum subsequently). At the age of 24 she was referred to our Department because of two inflammatory stenoses of the ileum. In the

same year she began to complain about exertion pain in her left upper extremity. Arterial pulse was not palpable on the left radial artery and blood pressure was not measurable on her upper limb. There was a vascular bruit over the left subclavian artery. Doppler ultrasonography and arteriography showed a 95% stenosis of the left subclavian artery. The patient fulfilled six of six diagnostic criteria for Takayasu arteritis according to the American College of Rheumatology (3). Successful angioplasty with balloon dilatation was performed followed by maintenance therapy with prednisone (20 mg daily for three months) and long-term azathioprine (2.5 mg per kg per day) and ticlopidine (500 mg daily). Complete remission of both Crohn's disease and Takayasu arteritis was achieved. At the age of 27 she moved and since that time she has been followed up elsewhere.

Case 3

A 37-year-old woman underwent urgent surgery for inflammatory obstruction of the large bowel (ileo-caecal resection was done). This was the first manifestation of Crohn's disease. After surgery she was put on 5-aminosalicylates and was symptom-free. However, there were several inflammatory markers in laboratory blood tests (ESR 84/100; leukocytes 12.10⁹/l; thrombocytes 557.10⁹/l; C-reactive protein 119 mg/L). These findings could not be explained by Crohn's disease, control endoscopy was quite normal. Two years later a vascular bruit occurred over the left subclavian artery and both common carotid arteries.

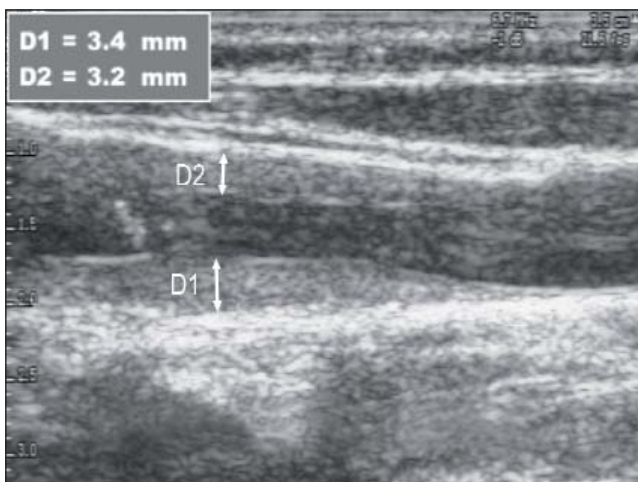


Figure 3
Ultrasonography of the third patient displays the thickening of the wall of the common carotid artery at 3.5 mm, which corresponds to 60% stenosis. Normal width of the arterial wall is 1.5 mm.

There was a marked difference of the blood pressure between the arms. Doppler ultrasonography (Fig. 3) and arteriography revealed extensive stenoses of primary branches of the aorta: 60% stenosis of both common carotid arteries, 50% stenosis of the left subclavian artery, 50% stenoses of both renal arteries, 70% stenosis of the truncus coeliacus, 50% stenosis of the superior mesentery artery and 50% stenosis of the subrenal aorta. At age of 39, the diagnosis of Takayasu arteritis was established based on five of six diagnostic criteria for Takayasu arteritis by American College of Rheumatology (3). This patient only did not have exertion pain. Methylprednisolone (estimated cumulative dose of 10 g within a 21-month period) and azathioprine (2.5 mg per kg daily) have been administered as her long-term therapy. Nowadays, being forty, the patient has reached full remission of both diseases.

Discussion

Takayasu arteritis is a chronic vasculitis, in which initially the aorta and its primary branches are affected (18). Although there is a considerable variability in disease manifestation, the initial vascular lesion frequently occurs in the left middle or proximal subclavian artery. As the disease progresses, the left common carotid, vertebral, brachiocephalic, right middle or proximal subclavian artery, right carotid and vertebral arteries and the aorta may also be involved. The abdominal aorta and pulmonary arteries are affected in approximately 50 percent of patients. All our three patients have had involvement of the left subclavian artery at presentation. In 80 – 90 % cases young women are affected (18,30), mostly between 10 and 40 years. Our case reports are consistent with these data, Takayasu arteritis occurred at 24, 24 and 37 years of age in our patients.

There is a higher incidence of the disease in Asia (150 per 1 million inhabitants) than in Europe (1 – 3 per 1 million population) (9,17,28). The aetiology of Takayasu arteritis is unknown. Also the pathogenesis is poorly understood. HLA-Bw52 and HLA-B39 have been found in increased frequency in some studies, thus suggesting a possible immunogenetic association (47).

The inflammatory processes cause thickening of the walls of the affected arteries. Narrowing, occlusion or dilation of involved portions of the arteries in varying extent result in a wide variety of symptoms

(12). Active inflammation is indicated by the presence of mononuclear cells, predominantly lymphocytes, histiocytes, macrophages and plasma cells (37). Giant cells and granulomatous inflammation are typically found in the media (46). Destruction of the elastic lamina and the muscular media can lead to aneurysmal dilation of the affected vessel. Alternatively, progressive inflammation and dense scarring may proceed from the adventitia leading to a compromise of the vascular lumen. Intimal proliferation may also contribute to the development of stenotic arterial lesion. Immunohistopathologic examination has shown that the infiltrating cells in aortic tissue mainly consist of killer cells especially CD8+ T lymphocytes and γ/δ T lymphocytes (11). The release of these cells may cause vascular injury by releasing large amounts of the cytolytic compound perforin. There may also be a role for antiendothelial antibodies in this disorder. In one study with 19 patients with diagnosis of Takayasu arteritis a 20 times higher titre of these antibodies was found than is the normal level in 18 of the patients. No other autoantibodies associated with other forms of vascular injury such as antinuclear, antineutrophilic cytoplasmic, anti-DNA or antiphospholipid antibodies were found (27). We did not prove any of these antibodies, which are routinely examined in our laboratory.

In most cases the diagnosis is based upon suggestive clinical features and imaging of the arterial tree by MRI, CT or angiography that demonstrates smoothly tapered luminal narrowing or occlusion that is accompanied by thickening of the wall of the vessel. In all our three patients we used ultrasonography examination first, which supported clinical suspicion of Takayasu arteritis and the diagnosis was confirmed by angiography. The angiography estimates the phase of stenoses more precisely.

The diagnostic criteria were established by the American College of Rheumatology in 1990 (3): a) first symptoms before forty years, b) laborious pain in extremity; c) lower pulsation at affected arteries; d) difference in systolic pressure of extremity over 10 mmHg; e) bruit above the affected artery; and f) arteriography assay narrowing or occlusion of the aorta or its primary branches, disagree for atherosclerosis or fibromuscular dysplasia. The diagnosis is established, when three of these six diagnostic criteria are fulfilled. The sensitivity is 90.5 % and specificity 97.8 % (3). The first and the second of our patients fulfilled

all these six criteria. The third one fulfilled only five of six criteria. She did not have the laborious pain in upper extremities, although she had a 60% stenosis of both common carotid arteries and 50% stenosis of the left subclavian artery. The diagnostic signs appeared subsequently within two years.

Arteriography may define the location and appearance of the arterial lesion and also makes therapeutic intervention possible at the same session. Percutaneous endovascular biopsy to obtain histological confirmation of the diagnosis would need further studies to evaluate its benefit and complication rates. In our second case, angiography was used to solve the 95% stenosis on the left subclavian artery with prompt relief from the patient's symptoms. There are two prognostic factors associated with this disease: the incidence of complications and the presence of a progressive course (24). The skin complication could be erythema nodosum and pyoderma gangrenosum. The involvement of the pulmonary arteries leads to pulmonary hypertension and with connected dyspnoea and haemoptysis. The involvement of mesenteric arteries causes abdominal pain and gastrointestinal bleeding. The involvement of coronary arteries causes ischaemic heart disease in all its forms. Involvement of carotid and vertebral arteries could cause vertigo, syncope, orthostasis, headache and dementia. The late manifestation due to cerebral ischaemia is visual impairment. Only our first patient had erythema nodosum five years before manifestation of the Takayasu arteritis and she suffered from headache, vertigo and syncope with convulsions three years before laborious pain in her extremities.

The mainstay of therapy for Takayasu arteritis is corticosteroids. Angioplasty or bypass grafts are reserved for irreversible arterial stenosis. An initial daily dose is 45 to 60 mg of prednisolone or its equivalent dose. The corticosteroid dose can be gradually reduced when the symptoms and laboratory tests related to the inflammatory process have improved (20). Approximately one-half of all patients with Takayasu arteritis have chronic active disease for which glucocorticoid therapy alone does not provide sustained remissions (51). The combination of azathioprine with glucocorticoids has been assessed in an uncontrolled series of 15 young women in India. All remitted within 12 weeks during treatment with prednisolone (1 mg per kg daily) and azathioprine (2 mg per kg daily). The prednisolone was gradually tapered

and azathioprine was continued for one year. No new arterial lesions were found and no worsening of the previously noted stenoses or aneurysms (21). The use of methotrexate was evaluated in an open label study of 18 such patients that were followed for a mean of almost three years. Weekly administration of methotrexate (constant dose 17 mg) plus glucocorticoids resulted in remissions in 13 of 16 patients (51). An uncontrolled series of 15 patients who required high dosage of glucocorticoids to maintain remission and who relapsed while treated with other agents were treated with anti-TNF agents. Improvement was noted in 14 of 15 patients, sustained remission was achieved in 10 patients (35). Another possible drug is cyclophosphamide, but there is very limited experience (10). Benefits have been also reported in three patients treated with mycophenolate mofetil (16) and one patient treated with leflunomide (44). In our three patients the remission of the Takayasu arteritis was achieved by therapy with azathioprine and glucocorticoids in two patients. This therapy controlled the Crohn's disease, too. In our first patient we had to choose another therapy, because she had serious complications on previous treatment with azathioprine for Crohn's disease. Plasmapheresis was a crucial turning point in the inauspicious course of the disease. Afterwards long-term therapy with glucocorticoids and methotrexate was used. This treatment was successful in maintenance of remission of both Takayasu arteritis and Crohn's disease.

Inflammatory bowel disease is frequently associated with extraintestinal and systemic complications. They may affect almost all organs and systems and significantly influence both morbidity and mortality. The pathogenesis of the most common extraintestinal manifestation is immunologically mediated and appears to be mainly due to an autoimmunoaltered process that is associated with the production of various cytokines (49). Mechanisms of injury at extracolonic sites may involve a number of autoimmune responses including tissue damage with resulting of sequestered antigens, increased expression of major histocompatibility antigens, ectopic expression of molecules, redistribution of intracellular molecules to the cell surface and dysregulation of cytokine production (2,53).

The parallel appearance of the inflammatory bowel disease and Takayasu vasculitis is rare. The coexistence of two immune-mediated diseases in the same subject is unusual as they are generally consi-

dered to be independent. Hypotheses concerning their possible inter-relationship are advancing. The immunohistopathological mechanisms are similar, which support the previous supposition about inter-relationship.

The association of the Takayasu arteritis and ulcerative colitis has occasionally been reported. To the best of our knowledge, about fifty such cases have been reported in world literature to date (1,3,4,8,14,22,25,26,34,36, 39,42,45). In the literature available, twenty-four cases of coincidence of Crohn's disease and Takayasu arteritis (5-7, 13, 15, 17, 19, 23,29,31,32,38,40,41, 43,50,52,54) were described. In nearly 90 % of cases the diagnosis of Takayasu arteritis is simultaneous or subsequent after the diagnosis of Crohn's disease (50). In all our cases, Takayasu arteritis was presented only after Crohn's disease (five, eight or one year later). Distribution of vascular involvement by parallel course of Crohn's disease and Takayasu arteritis does not vary from sole Takayasu arteritis. In two of 24 published cases of parallel coincidence of both diseases, Takayasu arteritis was diagnosed post mortem. Both of these patients, a 33-year-old man (15) and a 33-year-old woman (40) died suddenly from heart attacks. The involvement of coronary arteries in Takayasu arteritis was revealed by necropsy.

Two studies reported three patients who developed Takayasu arteritis after total proctocolectomy for ulcerative colitis (3,34). In all our three cases, previous bowel resection was carried out for Crohn's disease.

The other important issue of these diseases discussed is pregnancy. Pregnancy should be planned because of combined immunosuppressive therapy, especially if methotrexate or anti-TNF-alfa therapy is used. It is difficult to predetermine the course of both diseases as they may improve or worsen during pregnancy. Nevertheless, both maternal and foetal prognosis is favourable in general (6,48). In our first case, after initial early abortion the patient gave birth to two healthy children. Vaginal delivery is possible (48) but we recommended caesarean section in our case because of previous repeated abdominal and vaginal surgery.

Ulcerative colitis or Crohn's disease and Takayasu arteritis are serious, potentially fatal conditions affecting young people. In most cases, they can be controlled by balanced immunosuppressive therapy. The reasons for parallel coincidence of inflammatory

bowel disease and Takayasu arteritis remain to be answered.

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