

Takayasu Arteritis: Diverse Aspects of a Rare Disease

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Takayasu arteritis is a rare vasculitis affecting the aorta, its large branches, and proximal portions of renal, coronary and pulmonary arteries. Early in the pathology, mononuclear cells and granulomas with Langerhans cells are predominant in the adventitia and media; in the late phase, disruption of the elastin layer and medial and intimal fibrosis are prominent [1]. The disease has a chronic course with a monophasic (20–30%) or relapsing-remitting profile (70–80%) and a serious and occasionally fatal prognosis. The incidence of TA is estimated to be 0.8–2.6/1,000,000/year with the highest rates in Japan and South America. TA mainly affects young females.

The diagnosis of TA is based on the presence of three or more American College of Rheumatology TA classification criteria [Table 1] [2]. Classification of vascular occlusion in TA has prognostic implementation [3]. While the etiology

TA = Takayasu arteritis

Table 1. American College of Rheumatology Criteria for Takayasu arteritis

Age at disease onset < 40 years
Claudication of the extremities
Decreased brachial artery pulse
Blood pressure difference > 10 mmHg between arms
Bruit over subclavian arteries or aorta
Arteriogram abnormality, not related to arteriosclerosis or fibromuscular dysplasia

of TA is unknown, genetic predisposition to TA is linked to HLA-52, HLA-39, HLA-67, mainly in Japan. In TA pathogenesis, activated T cells, macrophages, dendritic, natural killer, and γ/δ cells play a pivotal role [4]. B cell activation and accumulation of CD19+/CD20-/CD27 antibody-secreting B lymphocytes in the adventitia was found to correlate with TA activity and inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein [5].

In the active phase of TA, patients manifest general symptoms, such as fever, fatigue, weight loss and arthralgia. Absent or diminished pulses, vascular bruits, extremity pain and claudication, hypertension, neck pain and carotidynia, visual disturbances, abdominal and chest pain, dyspnea, and hemoptysis are the main clinical signs. Reno-vascular hypertension, stroke, myocardial infarction, limb ischemia, pulmonary hypertension, and pulmonary embolism are life-threatening complications of TA [6,7]. Inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease, are relatively common in TA patients. Coexistence with sarcoidosis, uveitis, familial Mediterranean fever, pyoderma gangrenosum, relapsing polychondritis, systemic lupus erythematosus and rheumatoid arthritis has also been reported.

There are no specific laboratory tests for the diagnosis of TA. Among imaging modalities, conventional angiography, magnetic resonance angiography (especially gadolinium-enhanced), computed tomography-angiography, Doppler ultrasound and positron emission tomography are widely used for the diagnosis and monitoring of TA. Diffuse thickening of the vessel wall, narrowing, stenosis, post-stenotic dilatation and arterial aneurysms

are the most common type of vascular lesions [7].

The goal of therapy in TA is to suppress the inflammation and prevent irreversible vessel damage. High dose corticosteroids are the mainstay of treatment, but a high rate of relapse has been reported with tapering of corticosteroids. Early introduction of disease-modifying anti-rheumatic drugs is the standard of care; these include methotrexate, azathioprine, cyclosporine A, micophenolate mofetyle, cyclophosphamide and leflunomide [8,9]. High rates of DMARD failure have been observed in corticosteroid-resistant TA patients. The addition of low doses of aspirin significantly reduced the incidence of cranial ischemic complications in patients with giant cell arteritis. In a multivariate model, anti-platelet therapy resulted in fewer ischemic events in 48 TA patients [10]. In patients with a critical thrombotic event (e.g., pulmonary emboli) anticoagulants are used. Critical arterial stenosis accompanied by cerebral, cardiac or limb ischemia, uncontrolled reno-vascular or pulmonary hypertension, large aortic aneurysm and severe aortic regurgitation may demand endovascular intervention. A high early restenosis rate was observed in TA patients who underwent endovascular procedures during the active phase of the disease.

Tumor necrosis factor-alpha blockade has become a target therapy in difficult-to-treat TA. The addition of anti-TNF therapy resulted in clinical improvement and sustained remission in the majority of TA patients, with halting of radiological progression and discontinuation of corticosteroids [11,12]. In most patients

DMARDs = disease modifying anti-rheumatic drugs
TNF = tumor necrosis factor

only high infliximab doses (5 mg/kg) with narrow infusion interval allowed TA control [13,14]. The granulomatous nature of TA justified the preference for choosing monoclonal antibodies to TNF, infliximab and adalimumab, compared to the soluble TNF-receptor etanercept. In about 20% of TA patients, treatment with anti-TNF agents was followed by adverse events (serious infections, including tuberculosis) and the need to discontinue the treatment [14]. The long-term use of anti-TNF agents without warning signals has been addressed in several reports [11,12].

In the current *IMAJ* issue, two reports present patients with TA. Killinger et al. [15] describe the case of TA in a young woman with cervical arteries and aortic stenosis. Laczik and co-authors [16] report a 24 year old man with uncontrolled hypertension and recurrent MI with coronary and renal artery stenosis and aortic stenosis [16]. Both patients had signs of late TA complications at the time of TA diagnosis. Every physician who has ever encountered a patient with TA will admit how challenging it is to recognize TA. There are numerous reasons for this: the rarity of TA, the low index of suspicion, non-specific clinical signs of systemic disease along with symptoms of regional ischemia, absence of specific tests such as autoantibodies or tissue biopsies, and dependence on imaging techniques. A delay in the diagnosis of TA will result in irreversible vascular stenosis and ischemia. In both reported cases, high doses of corticosteroids did not control the course of TA and there was a need for DMARDs as well as endovascular procedures. An endovascular procedure may be advocated in the active phase of TA only if the ischemia is life threatening. Every attempt should be made at maximal TA control before undertaking such a procedure because of the risk of restenosis. Finally, in both cases, post-procedure immune suppression controlled TA and prevented post-procedure restenosis. In the patient described by Killinger et al. [15] the stan-

dard infliximab regimen failed and stable clinical remission was achieved only after shortening the infusion interval; importantly, there was a regression of arterial stenosis, inserted stents remained patent, and there were no new arterial lesions during 30 months follow-up. Laczik and colleagues [16] reported a dreadful disease course with recurring MI in a very young person without obvious risk factors. This combination of young age and multiple vascular events should be a warning alarm as it is highly suspicious for underlying systemic pathology such as vasculitis or thrombophilia, or both. Only a few cases of TA with positive antiphospholipid antibodies or the presence of lupus anticoagulants have been reported, with obvious APLS syndrome in some of them. In this situation, only the combined use of anticoagulation and immune suppression led to control of both conditions, TA and APLS.

In this same issue of *IMAJ*, de Jesús et al. [17] reported on 11 pregnancies in 9 women with TA. Since the majority of TA patients are women of reproductive age, several questions may arise: Could the pregnancy affect the course of TA? Could TA itself or TA treatment affect the pregnancy and fetal conditions? How does one cope with the similarity of major complications of TA and pregnancy, such as hypertension and preeclampsia? What kind of analgesia and what route of labor is preferable in women with TA? Several studies on pregnancy and TA have been published. Among 137 pregnancies in TA patients reported by Gasch et al. [18], hypertension or preeclampsia were registered in 39%, cesarean section in 23%, abortion and intrauterine death in 15%, prematurity in 8%, and intrauterine growth retardation and low birth weight in 15% of cases. There were no data supporting an exacerbation of TA during pregnancy. There is general agreement that the outcome of pregnancy would be better if the pregnancy occurred during TA remission. In the report of de Jesús et

al., women entered pregnancy in a state of TA remission that remained stable during the pregnancy and the early postpartum period, which probably contributed to the successful outcome [17]. The authors suggest that the increased intravascular volume characteristic of pregnancy is a major trigger for hypertension and preeclampsia; controlling blood pressure before conception correlated with better outcome. All patients except two (one with preeclampsia) were treated with low doses of aspirin that, in the authors' opinion, served both conditions: TA and prophylaxis of preeclampsia. In their report, there were no patients with pulmonary artery involvement or aortic dilatation, whereas in the literature, both complications are critical issues in the course of pregnancy in TA patients. The results of this report illustrate that a good pregnancy outcome in TA patients may be achieved when control of TA and hypertension, appropriate monitoring, and a clear plan for delivery managed by a multidisciplinary team are the standard of care.

Instead of progress in the treatment of TA there are still patients with difficult-to-treat TA because of TNF blocker failure. Recently, three patients with uncontrolled TA were successfully treated with rituximab, monoclonal antibodies to CD20+ B lymphocytes [5]. Several reports demonstrated control of severe TA with inhibitor of soluble receptor to interleukin-6, tocilizumab [19]. A patient with severe TA and inflammatory bowel disease was successfully treated with tocilizumab for more than 5 years; clinical remission was accompanied by improvement in arterial patency as well as by normalization of serum interleukin-6 and TNF α levels [20].

Three articles in the current issue of *IMAJ* draw attention to a rare disease, TA. Two case reports demonstrated a dreadful course of TA: one presented an unusual combination of TA and antiphospholipid syndrome and the other reported on the long-term efficacy of TNF blockade in corticosteroid- and DMARD-resistant TA [15]. Today, corticosteroids, DMARDs, TNF α blockers and

MI = myocardial infarction

APLS = antiphospholipid syndrome

endovascular procedures have changed the fate of TA, improving patient survival and prognosis. A number of reports suggested the efficacy of B cell targeting in TA. Patients and medical staff have to cope with this chronic condition for life. Patients' rehabilitation, psychological and social support, and education are important in light of the disease chronicity. As the majority of TA patients are young women, obstetric problems of the disease itself and treatment regimens are essential issues, and were discussed in the article by de Jesús and team [17]. It is obvious that a complicated condition such as TA demands a multidisciplinary approach with a highly qualified and experienced team. It seems advisable to concentrate patients with TA in tertiary centers that enable early diagnosis, appropriate assessment, and treatment.

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Capsule

A FOXO3-IRF7 gene regulatory circuit limits inflammatory sequelae of antiviral responses

Antiviral responses must be tightly regulated to defend rapidly against infection while minimizing inflammatory damage. Type 1 interferons (IFN-I) are crucial mediators of antiviral responses and their transcription is regulated by a variety of transcription factors; principal among these is the family of interferon regulatory factors (IRFs). The IRF gene regulatory networks are complex and contain multiple feedback loops. The tools of systems biology are well suited to elucidate the complex interactions that give rise to precise coordination of the interferon response. Litval et al. have used an unbiased systems approach to predict that a member of the forkhead family of transcription factors, FOXO3, is a negative regulator of a subset of antiviral genes.

This prediction was validated using macrophages isolated from *Foxo3*-null mice. Genome-wide location analysis combined with gene deletion studies identified the *Irf7* gene as a critical target of FOXO3. FOXO3 was identified as a negative regulator of *Irf7* transcription and the researchers have further demonstrated that FOXO3, IRF7 and IFN-I form a coherent feed-forward regulatory circuit. These data suggest that the FOXO3-IRF7 regulatory circuit represents a novel mechanism for establishing the requisite set points in the interferon pathway that balances the beneficial effects and deleterious sequelae of the antiviral response.

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Eitan Israeli

“A decent provision for the poor is the true test of civilization”

Samuel Johnson (1709-1784), English lexicographer