
Takayasu arteritis: clinical features in 110 Mexican Mestizo patients and cardiovascular impact on survival and prognosis

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ABSTRACT

Objective. Takayasu Arteritis (TA) is a rare disease that mainly affects large elastic arteries. It is more frequently seen in Asia, the Mediterranean basin, South Africa and Latin America. We have characterized its clinical manifestations and identified the cardiovascular mortality predictors in a cohort of 110 Mexican Mestizo patients.

Material and methods. Retrospective review of 110 charts of TA patients complying with the American College of Rheumatology (ACR) criteria, seen in a single hospital between 1976 and 2003. Demographic, clinical, and radiological characteristics were described. With the use of actuarial table analysis at 2, 5, and 10 years, and Kaplan Meier methods applying t function for probability, plus Cox regression analysis, the following factors were identified as mortality predictors: systemic arterial hypertension, coronary heart disease and aortic valve regurgitation. Informed consent and approval from the institutional Internal Review Board (IRB) were obtained.

Results. We observed a slowly progressive widespread obstructive arterial disease with cardiovascular (48%), neuro-ophthalmic (36%), and skin morbidity (13%). Systemic hypertension and heart disease were significant mortality predictors. Twenty-six percent of cases died due to myocardial infarction, chronic renal failure, stroke, or surgical complications.

Conclusion. TA in Mexican Mestizos shows a clinical pattern similar to the one recognized in the Far East. Management strategies must be directed at reducing the identified mortality risk factors.

Introduction

The term Takayasu arteritis (TA) was coined in 1952 by Caccamise and Whitman (5). However, cases of the disease have been documented since the 18th

and 19th centuries. In 1908, Japanese ophthalmologists reported the case of a young woman with peculiar retinal neovascularization and absent pulses in the upper limbs. The first case-series were published in 1951 (1-7). Classification criteria for this primary vasculitis were proposed in 1990, stressing aorta and its main branches (and sometimes pulmonary arteries) involvement (8). Although TA is distributed worldwide, it predominates in certain populations (9) In Mexico, TA was first observed in 1946, and some case-series from our centre have been reported (10-13). On this occasion we updated the clinical features seen in the last 30 years and have sought for factors predicting mortality.

Material and methods

We identified 119 clinical charts in which arteritis was cited as diagnosis. Of those seen between 1976 and 2003, 110 fulfilled ≥ 4 TA ACR classification criteria (8). Demographic and clinical data at diagnosis and follow-up were retrieved.

The definition of Mexican Mestizo was based on the following: being born in Mexico with both parents and grandparents of Mexican ancestry, having black lank hair, dark skin, high cheekbones and shovel incisive teeth as Native American Indians usually do. Blood group was O⁺ in two thirds of patients, similar to the distribution reported in the general Mexican Mestizo population. These phenotypic characteristics identify a population sharing genetic imprints (14-15).

We analyzed hospital admissions applying Bayesian Theorem to establish by inference yearly incidence.

Laboratory data included complete blood count and erythrocyte sedimentation rate (ESR), fibrinogen (Fb), C-reactive protein (CRP), fasting blood sugar, urea, creatinine, total cholesterol, triglycerides, Venereal Disease Research Laboratory slide test (VDRL),

Competing interests: none declared.

Table I. Takayasu's arteritis proposed score to indicate clinical activity.

3 points	2 points	1 points
<ul style="list-style-type: none"> • Carotodynia/angiodynia • Major ischemic event 	<ul style="list-style-type: none"> • Subcutaneous nodules (Erythema nodosum-like) • Absence or loss of previously present peripheral pulse • New murmur 	<ul style="list-style-type: none"> • Fever/low grade-fever • Weight loss • Malaise • Arthralgia/arthritis

Only 1 clinical item can be chosen in every column. Clinical points are not cumulative. Laboratory features are cumulable, each one has a value of 0.5 point: anemia, leucocytosis, thrombocytosis, erythrocyte sedimentation rate (ESR) hyperfibrinogenemia, raised C reactive protein.

Clinical Activity: ≥ 5 This suggests that inflammation may be the main damage mechanism (16).

antinuclear antibodies (ANA), rheumatoid factor (RF), total serum proteins, prothrombin/partial thromboplastin time (PT/PTT) and isotopic renograms. The reported Mantoux test was performed with 5 International Units of old tuberculin, purified protein derivate (PPD) (Connaught-Aventis Pasteur Ltd TM).

To assess disease activity, a clinical score which combines simple clinical and laboratory data was applied (Table I). More than 5 points were considered necessary to identify active disease (16).

One hundred and seven cases had a diagnostic panaortogram (Seldinger technique) (17-18) some also had a coronariography, right heart catheterization or cerebral angiographies. Panaortograms and others studies were classified according to Hata (19). Three patients had an MRI instead of an aortogram, due to known adverse reaction to iodine contrast media.

Echocardiographic data in M mode, two-dimensional and Doppler techniques using Hewlett-Packard 100 and 5500 machines with electronic transducers of 3.5 MHz, were also analysed (20).

To identify survival predictors we used age, time of diagnosis, presence or absence of systemic arterial hypertension, left ventricle concentric hypertrophy, aortic valve regurgitation and acute myocardial infarction as variables.

In order to analyze this long time observation, we divided it into two periods 1976-1990, and 1991-2003 to reduce differences in diagnostic work up and treatment modalities to diminished bias attributable to the long observation period in this retrospective study.

Statistics

Demographic and clinical characteristics are expressed as frequencies and percentages for categorical variables, means and standard deviation for Gaussian distributed continuous variables. Those with non Gaussian distribution were analyzed by non-parametric χ^2 or Fisher's exact test. Survival at 2, 5 and 10 years was analyzed using an actuarial table. To identify mortality predictive factors we used the Kaplan Meier method. Linear combination of these variables was analyzed by Cox regression using SPSS and EPI-Info software.

Bioethics

This is a retrospective, descriptive, observational study approved by institutional Internal Review Board (IRB). Informed consent was obtained and confidentiality kept.

Results

Demographics

A total of 94 patients (85%) were women and 16 (15%) men, with a female: male ratio of 5.8:1. Mean age was 26 ± 9 years at the time of diagnosis. One hundred and one patients (91%) were under 40 years old at time of diagnosis.

Mean follow-up was 75 ± 83 months (0-453). Twenty-seven cumulative incidence global mean was 9/10000/year admissions, a monotonic increase since 1990 with a predicted annual incidence of 3 new patients/year were identified by Bayesian Probability (Table II).

Clinical features

In this series, the so-called pre pulseless stage of TA was identified only in four young females aged 12, 18, 32 and 34 years, who sought attention due to systemic disease with low fever ($< 38.5^\circ\text{C}$), malaise, myalgia, headache, skin nodules, cervical bruits, and systemic arterial hypertension with normal or slightly reduced peripheral pulses. The presence of angiodynia prompted a panaortogram showing characteristic arterial occlusive disease.

Clinical manifestations in the chronic stage include headache, upper limb claudication, dizziness, dyspnea, palpitations, syncope, malaise, and ocular manifestations such as mono or binocular amaurosis fugax in 25 cases. (Table III)

Ocular signs at the anterior eye segment, included cataracts in 8 patients

Table II. Takayasu's arteritis patients 1976-2003. Age-related incidence rate.

Year	10-19	20-29	30-39	40-49	AT cases	Annual Hospitalization	Incidence rate/10,000/year
1976-1979	1	1	2	-	4	14499	2.7
1980-1984	2	6	3	1	12	11649	10.3
1985-1989	8	14	8	1	31	24537	12.6
1990-1994	9	12	1	4	26	23127	11.2
1995-1999	6	5	8	1	20	20940	9.5
2000-2003	4	5	6	2	17	24186	7
Total						118938	9/10,000/year

Table III. Clinical manifestations in Takayasu arteritis, total and gender proportion.

Clinical findings	Total 110 n (%)	Female n=94	Male n=16	<i>P</i>
Malaise	33 (30)	28 (30)	5 (31)	NS
Fever	22 (20)	21 (22)	1 (6)	NS
Anorexia	16 (15)	15 (16)	1 (6)	NS
Weight loss	20 (18)	17 (18)	3 (19)	NS
<i>Central nervous system and eye manifestations</i>				
Stroke	10 (9)	5 (5)	5 (31)	< 0.004
Headache	77 (70)	69 (73)	8 (50)	NS
Dizziness	61 (55)	56 (59)	4 (25)	< 0.02
Syncope	39 (35)	33 (35)	6 (38)	NS
Seizures	22 (20)	17 (18)	5 (31)	NS
Blurred vision	39 (35)	37 (39)	6 (38)	NS
Amaurosis	25 (22)	23 (25)	2 (13)	NS
Uveitis	6 (5)	5 (5)	1 (6)	NS
Cataract	8 (7)	8 (9)	0	NS
<i>Cardiovascular manifestations</i>				
Dyspnea	60 (55)	49 (52)	11 (69)	NS
Hypertension	58 (53)	43 (46)	15 (94)	< 0.001
Diastolic >110	15 (14)	9 (10)	6 (37)	
Diastolic <110		85 (90)	10 (63)	
Palpitation	39 (35)	37 (39)	6 (38)	NS
Chest pain	35 (32)	31 (33)	4 (25)	NS
Carotodynia	23 (21)	21 (22)	2 (13)	NS
Cough	17 (15)	16 (17)	1 (6)	NS
<i>Cutaneous manifestations</i>				
Erythema nodosum	21 (19)	17 (18)	4 (25)	NS
<i>Others</i>				
Arthralgias	82 (75)	70 (75)	12 (75)	NS
Active disease ¹⁶	35 (32)	31 (33)	4 (25)	NS

(7%) and uveitis in 6 (5%); main findings in the posterior pole were mainly due to systemic arterial hypertension. Ischemic eye disease was present bilaterally in 10 patients with low intraocular pressure (IOP) (<11 mm), in 9 monocular low IOP was seen. Takayasu's retinopathy of both eyes was present in 23 patients.

Reduced bilateral visual acuity, with or without refractive correction was present in 9 patients affecting both eyes. Monocular legal-blindness (<20/200) with normal vision in the opposite eye was present in 11 patients. Two patients were bilaterally blind.

Fourteen patients with unilateral or bilateral carotid involvement had bilateral visual claudication related to physical work or positional head change.

Thrill, carotid, and supraclavicular bruits were frequent findings. Left side body vessels were affected in 64 patients (58%), carotodynia was present in 23 (21%). Thoracic, abdominal or peripheral bruits were found in 51 cases (46%).

High systemic blood pressure measured at any limb was found in 58 patients (53%). Twenty-three patients showed uncontrolled hypertension; some of them developed transient hypertensive encephalopathy.

Thirty-three patients were hospitalized because of complicated systemic hypertension. Heart failure in 11 (10%), mild azotemia in 31 (28%) and stroke sequel in 10 (9%) were identified among these cases, including more than 2 abnormalities in some of them. Most patients improved after medical treatment.

Neurological manifestations predominated in patients with arterial disease involving neck vessels (Type I, IIa, b, V). These were: generalized dull headache in 77 (70%), postural dizziness in 61 (55%), syncope in 39 (35%), grand mal seizures in 22 (20%), and stroke in 10 (9%). In 21 patients, skin lesions mimicking erythema nodosum were present.

Gender differences were sought in relation to clinical presentation; although significant differences in hypertension,

stroke and dizziness were found, wide confidence limits can not predict risk accurately due to the small size of the two groups.

Laboratory findings

The most common laboratory abnormality was high ESR in 58 cases (53%), normocytic normochromic anemia in 51 (47%), neutrophilia in 21% and hyperfibrinogenemia in 18%. Raised CRP was also common (30%)

As a possible relationship between tuberculosis and TA has been hypothesized, we looked for related data. No single case of active tuberculosis was documented although 2 patients had lung tuberculosis in the past, which was optimally treated. Twenty-seven patients (24%) had potential exposure to mycobacteria as they had diseased relatives. The Mantoux intradermal test (PPD 5 IU), carried out on 61 subjects, was positive in 53 (82%) (>10mm induration/48hrs).

Disease activity

At diagnosis, clinical activity was found in 35 (32%) patients. The most frequent signs or symptoms were: angiodynia/carotidynia in 20/35, (57%), stroke or new bruits (n=3, 9%), and/or constitutional manifestations such as low fever (n=10, 29%), malaise (n=9, 26%), arthralgias (n=13, 37%) or weight loss (n=8, 23%).

However, 50 (45%) patients had a 3 to 4.5 points score, suggestive of clinical activity with our previously reported scale. Most of these cases had abnormal laboratory data rather than clinical findings, suggesting inflammation without clinical findings.

Panaortogram and angiographic findings

Generalized aortic disease according to Hata's classification (Type V) was found in 76 (69%) patients. Type I disease was present in 21 (19%), type IIa was present in 3 (3%) while type IIb in 4 (4%); type III was also found in 4 cases (4%) and Type IV in 2 (2%). (Fig. 1) Frequently affected arteries were subclavian artery in 72 patients (65%), the left in 68, both arteries in 32. The primary carotid arteries were affected

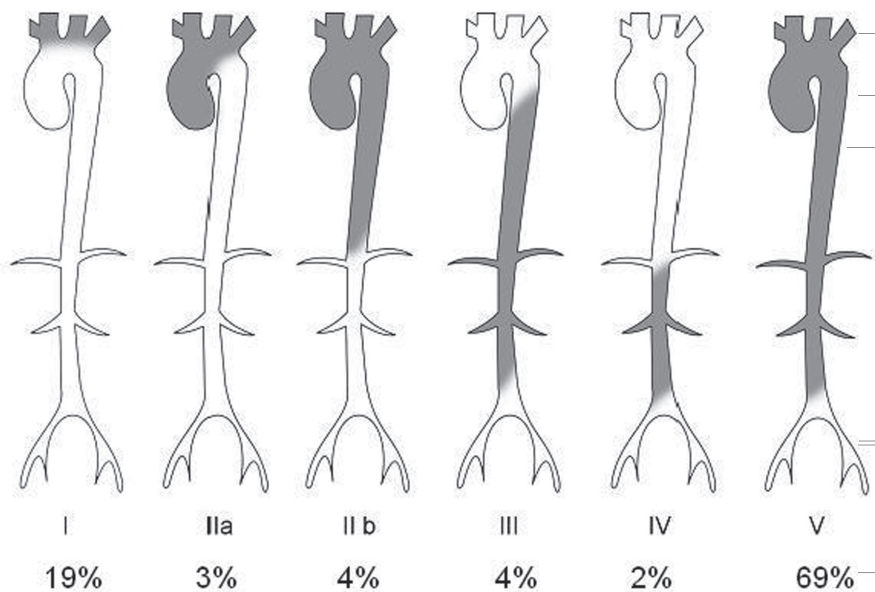


Fig. 1. Current classification of arterial involvement in Takayasu arteritis based on angiographic findings (19).

in 53 (48%), the vertebral in 24 (22%). The abdominal aorta in 39 (35%), renal arteries were partially or totally occluded in 52 (47%), the upper mesenteric artery in 19 (17%), the lower in 11 (10%), and proximal iliac arteries in 24 (22%). Long segmental stenosis was the characteristic lesion, irregular lumen, "bumpy" aorta, was also present. Aneurysms were scarce (10%).

Heart involvement

Sixteen asymptomatic patients had abnormal auscultatory findings. Seventy-six cases were studied by echocardiogram, 31/76 cases (41%) had organic aortic regurgitation; in addition 19 had subclinical mitral or tricuspid regurgitation. In eight patients, the echocardiogram showed mild pulmonary hypertension.

Eight patients (11%) developed heart failure with dilated hypokinetic left ventricle (mean ejection fraction $35 \pm 7\%$), five of them had regurgitant valve disease, four aortic and one mitral-aortic regurgitation. All these cases died from cardiac complications.

On follow-up, fifteen cases (14%) had acute myocardial infarction; fourteen had a coronary angiography performed. In five it showed involvement of the anterior descending coronary or circumflex artery, four had both arteries affected, and five had right coronary artery occlusion. Eleven were under 40

years old. Nine had no traditional risk factors associated with ischemic heart disease.

Secondary systemic hypertension due to renal arteries stenosis was identified in 41 (75%) cases of which 50% had left ventricular hypertrophy.

Treatment

Treatment was instituted by the treating physicians. No established treatment protocol was followed. Pentoxifyllin, 800 to 1200 mg qd was prescribed to 20 patients (18%) as vasodilator and because it is thought to modify macrophage activation and inflammation (21-22).

Twenty-seven patients out of the 35 active patients were treated with oral prednisone (1mg/kg/qd), most of them after the 1980s. In addition, since the 1990s, 18 received oral weekly methotrexate (7.5 mg), and two more received intravenous cyclophosphamide pulses, (750 mg/m² body surface) monthly up to 6 months with gradually steroid tapering. Constitutional symptoms improved easily, but ESR and/or CRP did not show a homogeneous response.

Sixty-five (58%) patients were not given steroids or immunosuppressive as they were judged inactive.

Invasive treatment

During follow-up, surgery or angioplasty/stenting had been occasionally

performed. The main indication for it was to alleviate vessel stenosis in chronically diseased patients with ischaemic symptoms. Kidney auto transplantation was performed successfully in 8 cases; in 4 additional cases surgical renal artery bypass achieved good results. Carotid-aorta, aorta-aorta and aorta-iliac arteries bypasses were performed successfully in 16 cases.

Coronary bypass procedures failed in 3 patients who developed acute myocardial infarction and died shortly after surgery. Only one young female survived this procedure.

Seven patients were treated with minimal invasive procedures. Angioplasty alone (2 cases) or angioplasty plus stenting were performed in 5 patients. However, reocclusion ensued within 6 months in all but two females, aged 15 and 16 years respectively. In them, vessel patency continues after 4 years.

Follow-up data and mortality

We lost 9 patients to follow-up. Of the remaining 101, 70 are still alive.

In general, cases diagnosed between 9 and 24 years old usually showed a waxing and waning course with constitutional manifestations. In contrast, cases diagnosed at 25 years old and over had cardiovascular or neuro-ophthalmological manifestations, mainly as sequelae.

Mortality: There were 30 (27%) deaths. Twenty-one hypertensive patients died from cardiovascular causes such as myocardial infarction, stroke, aortic dissection or peripheral occlusive arterial disease, surgical complications or pulmonary embolism. The cause of death in 9 patients could not be determined even after interviewing their relatives.

Survival

Survival at 2, 5 and 10 years after diagnosis was 92%, 81% and 73%, respectively. Actuarial table analysis identified that survival was linked to three major cardiovascular conditions, each linked to certain age groups: coronary disease developing between 10 and 19 years showed 50% survival at 2, 5, or 10 years after diagnosis. People aged between 20 and 39 years had a stable survival rate of 88%.

Aortic valve regurgitation also decreased survival in the younger age range of 10 to 29 years (OR 2.07, 95% CI 1.21-3.71). No effect of this variable was observed in people over 30 at diagnosis. Echocardiogram identified that aortic valve regurgitation (in 76 cases) reduced the 5-year survival to 40% (Log Rank $p=0.01$), while coronary heart disease lowered it to 44% (Log Rank $p=0.07$) (Fig. 2).

As for systemic arterial hypertension, there were differences according to age. Young patients with hypertension had a progressive decrease survival from 65% at 2 years, 57% at 5 and 48% at 10 years after diagnosis. For patients between 20 and 39 years old, survival was 87% at any time point, and for people aged 40 or more, hypertension did not influence survival.

The cumulative impact of these three predictors in the whole group is shown in Figure 3.

Discussion

Previous observations regarding the demography, geographic and ethnic background of our cases are confirmed (23). Our institution is a referral centre for cardiovascular disease in a country with 103 million persons. In this setting we estimate a cumulative incidence of 9/10000 admissions.

The mean age of our series was 26 years, similar to the reported in India, Japan, and other Asian countries, with only 8% of our cases aged 40 years at time of diagnosis.

The majority of cases were diagnosed when chronic clinical manifestations had been established with few seen in the so-called "pre-pulseless phase" of TA.

In relation to chronic disease, systemic arterial hypertension is a morbidity factor linked to nephrosclerosis, retinal abnormalities, stroke and left heart hypertrophy and failure. Arterial occlusion may explain secondary systemic arterial hypertension through abnormal baroreceptor regulation at the ascending aorta or by occlusive disease of renal arteries.

Eye examination is critical to assess both hypertensive and ischemic eye disease. The eye often shows characteristic changes, retinal damage through

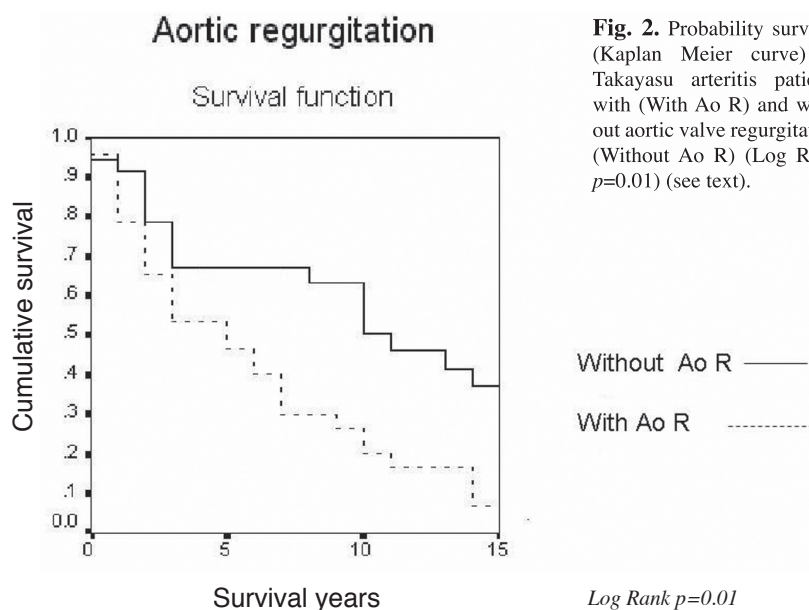


Fig. 2. Probability survival (Kaplan Meier curve) in Takayasu arteritis patients with (With Ao R) and without aortic valve regurgitation (Without Ao R) (Log Rank $p=0.01$) (see text).

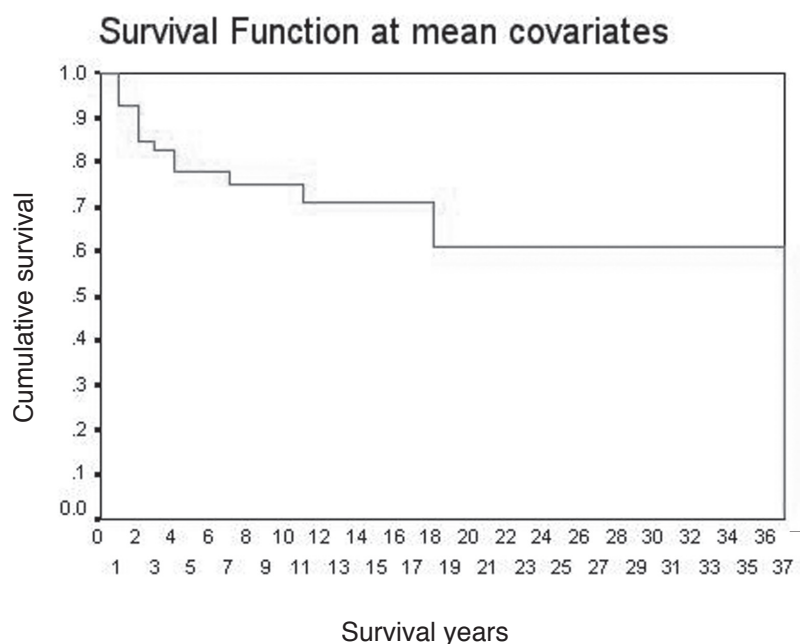


Fig. 3. Survival in Takayasu arteritis considering time and function as major covariates. Time related survival rate analysis includes aortic valve regurgitation, coronary heart disease and systemic arterial hypertension. Mortality started two years after diagnosis and stabilized at 17 years.

hypertension being more frequent than ischemic abnormalities such as the classical peripapillary arteriovenous shunts, overstressed for years as diagnostic cornerstone of TA. Eye anterior chamber may be involved because ischemic eye disease, and lens opacities or uveitis have been described before steroids use in some rare cases (24).

The central nervous system is a critical source of TA manifestations through brain circulatory changes or hypertensive complications (25).

Aortic regurgitation, a complication of TA has been reported between 7 to 16% of patients (26). It was common in our series and found to be linked to left ventricle hypertrophy and heart

failure, affecting the prognosis negatively.

Ischemic heart disease and heart failure at a young age and without traditional risk factors may occur in TA. To explain this condition it has been proposed the involvement of coronary ostium because of the arteritis process extending to the valve plane; abnormal coronaries because of atherosclerosis linked to arterial hypertension, and occasionally true coronaritis demonstrated only in necropsy cases (27).

The cause of TA is unknown. It is interesting to notice that in some countries with a high frequency of the disease, tuberculosis is also highly prevalent, as in Mexico. In this regard, we observed a positive skin test in over 80% of patients, which is at least twice the reported in general population. However, no tuberculosis flares were registered when patients took oral steroids or immunosuppressive drugs. This observation deserves further studies to explore the relationship between mycobacterial infection, host immunity, and development of TA (28-33).

Angiographically, the main arterial involvement seen was classified as types V, I, IIa and II b. Compromise of aortic arch and thoracic aorta has been reported mainly in Japan. Type III disease, involving the thoracic and abdominal aorta sparing the ascending aorta and its arch, carotids and subclavian arteries, is less common. Isolated disease on abdominal aorta, Type IV, is relatively common in India and Thailand (34, 35) but not in other countries such as Japan, Korea or China. Therefore, our cases resembled the Far East topography disease pattern, and it is known that type V disease is linked to systemic hypertension, cardiovascular morbidity and late mortality in TA patients.

Panaortography and other angiographic procedures are risky and require important amounts of contrast. Also, more than one procedure is often required to demonstrate coronary arteries, pulmonary or brain circulation involvement, increasing renal risk due to radiographic contrast. Certain patients have limiting conditions such as kidney dysfunction which contraindicate the use of contrast compounds. Newer imaging techniques

are safer. Computed axial or helically computed tomography (CT), vascular ultrasonography, magnetic resonance imaging and angiography (MRI and MRA) may replace or complement conventional aortography as diagnostic procedures in TA (36-39).

This review covered a long period and radiographic studies dominate the image evaluation in most of our cases. Recently we had the opportunity to expand our image capabilities and some experiences have been published elsewhere (40).

Evaluation of activity in TA is a difficult issue. So far, there is no validated nor worldwide accepted tool to measure it, especially in the setting of long-lasting disease. Since pathologically proven wall vessel inflammation has been reported in cases considered clinically inactive under glucocorticoid treatment (41) it is important to develop such indices, preferably in multicentric studies and compare them in different ethnic groups. We have proposed a set of clinical and laboratory data to assess activity (16). With its use, we identified activity in 32% of patients with a score of 5 or more points. However, an important proportion of patients had borderline values 3 to 4.5 points in where there might exist controversy regarding active disease.

Another controversial issue is medical treatment. Glucocorticoids produce quick response of constitutional symptoms and improvement on peripheral pulses (42). However, experience has shown that some cases require immunosuppressive agents. We observed that most of our cases in whom oral weekly methotrexate or cyclophosphamide pulses were used, had improvement. Invasive treatment, either interventional cardiology procedures or traditional surgery was done in certain individuals. Our review, as other published case series, has shown that the presence of active disease at the time of interventional treatment had a negative impact on its outcome, as opposed to performing such procedures when patients have inactive disease (43, 44).

To establish survival and prognostic factors in our cases was paramount in this work.

Patients with TA have a long survival unless heart involvement and systemic arterial hypertension are present (45). These figures are reduced by approximately 20% in 10 years in our series. Bad prognosis is linked to Type V widespread disease, systemic arterial hypertension, and concentric left ventricle hypertrophy; myocardial infarction in youngsters, regurgitating aortic valve disease and blindness, which usually occur in Type V cases. This situation justifies both, current anti-inflammatory treatment accepting limitations already mentioned and intensive use of cardiovascular drugs to attain arterial hypertension and heart failure control and, when necessary, invasive approaches to correct faulty valves or circulatory regional deficit.

Recently, a paper pointed out clinical characteristics in Korean TA patients; results were comparable to our experience (46). Multicenter protocols may answer many important questions regarding diagnostic approach, activity evaluation and treatment strategies, mainly as TA is a rare disease everywhere.

Finally, TA is a risk factor for cardiovascular disease and since cardiovascular disease remains the most common cause of death and increased morbidity, it is necessary to improve diagnostic skills of TA and search for subclinical cardiovascular disease in recently detected cases.

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