

Aortic involvement in ankylosing spondylitis

C. Palazzi¹, S. D'Angelo², E. Lubrano³, I. Olivieri²

¹Department of Internal Medicine, "Villa Pini" Clinic, Chieti; ²Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza; ³Rheumatology & Rehabilitation Research Unit, Mageri Foundation IRCCS, Research Institute for Rehabilitative Medicine, Telesse Terme, Italy.

This work should be attributed to the Rheumatology Department of Lucania San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Potenza, Italy.

Carlo Palazzi, MD, Senior Researcher; Salvatore D'Angelo, MD, Researcher; Ennio Lubrano, MD, PhD, Senior Researcher; Ignazio Olivieri, MD, Consultant, Director of Department.

Please address correspondence and reprint requests to: Dr. Ignazio Olivieri, Rheumatology Department of Lucania, San Carlo Hospital, Contrada Macchia Romana, Padiglione E, 85100 Potenza, Italy.

E-mail: ignazioolivieri@tiscalinet.it

Received on March 18, 2008; accepted in revised form on March 28, 2008.

Clin Exp Rheumatol 2008; 26 (Suppl. 49): S132-S135.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2008.

Key words: ankylosing spondylitis, aortic involvement, conduction abnormalities, retroperitoneal fibrosis.

ABSTRACT

Patients with ankylosing spondylitis (AS) may develop cardiovascular manifestations ranging from asymptomatic forms to life threatening conditions. The most important cardiovascular manifestation of AS is aortitis, which frequently involves the aortic root and the ascending aorta leading to valvular insufficiency. The extension of the subaortic fibrotic process into the interventricular septum may cause conduction abnormalities that represent the second common cardiovascular manifestations occurring in AS patients. More rarely, an involvement of coronary arteries and of thoracic and abdominal aorta could be present.

Rheumatologists managing AS patients should carefully consider, both in late and in early phases of the disease, the occurrence of an aortic involvement in order to promptly administer adequate treatment.

Introduction

Patients with ankylosing spondylitis (AS) and, less frequently, with the other spondyloarthropathies (SpA) may develop cardiovascular manifestations which may range from asymptomatic forms to life threatening conditions.

The most important cardiovascular manifestation of AS is aortitis, which frequently involves the aortic root and the ascending aorta leading to valvular insufficiency. Cardiac conduction abnormalities, caused by a subaortic fibrotic process extending into the interventricular septum, represent common cardiac complications occurring in AS patients. More rarely, an involvement of coronary arteries and of thoracic and abdominal aorta could be present.

Cardiovascular complications usually occur in late disease but in rare situations they may precede other features of AS.

1- Aortic valve and ascending aorta

The lone (i.e. without a concomitant stenotic lesion) aortic regurgitation (LAR) is characterized by annulus dilatation, thickening of the aortic cusps, and inward rolling of the free margins of the cusps (1-3). The advancement of the fibrotic process in the left atrium ("sub-aortic bump") can frequently damage the anterior leaflet of mitral valve inducing valvular regurgitation (4-5).

Usually, dilatation also involves the ascending aorta. Histopathologic findings of the aortic wall consist of: proliferation of the intima cells; focal inflammation of the media with destruction of elastic tissue and fibrosis; fibrous thickening of the adventitia (1-3). An important pathogenetic role is attributed to the inflammatory narrowing of the vasa vasorum that are surrounded by lymphocytes and plasma cells (1).

In the pre-echographic era the LAR was reported in less than 10% of AS patients (3,6). Since the 1980s, ultrasound examinations have expanded our knowledge on cardiac involvement in AS.

In 1982, Tucker *et al.* analysed 35 AS patients without clinically apparent cardiac involvement and 20 healthy control subjects, by using phased array two dimensional and sector-directed M mode echocardiography to determine the prevalence of aortic abnormalities. Two patients had aortic dimensions greater than 4.2 cm at the valve (normal 4.0 cm or less). Furthermore, 6 patients had slight areas of increased bright echoes below the left or noncoronary cusps suggestive of a subaortic "bump", and 2 of them had increased aortic cusp echoes suggestive of thickening or fibrosis, or both (7).

Three years later, LaBresh *et al.* studied with a two-dimensional echocardiography 25 AS patients, 9 with Reiter's syndrome and 2 with inflammatory bowel

Competing interests: none declared.

disease-associated spondylitis (8). Sub-aortic fibrous ridging or marked leaflet thickening was disclosed in 30.5% of the cases. Interestingly, patients with aortic valve abnormalities had significantly longer disease duration. A correlation between the disease duration and the prevalence of the aortic damage was confirmed by other authors (9, 10). In particular, Khan observed that the prevalence of the aortic valve disease was 4% and 10% in patients with disease duration less than 5 years and more than 30 years, respectively (10). In a recent study from Turkey, in which 88 AS patients were evaluated by echocardiography, a moderate/mild aortic regurgitation was found in 4 (4.6%) cases (11). Very recently, Lange *et al.* from Germany examined 77 patients with AS by echocardiography and found abnormalities (*e.g.*, aortic and mitral insufficiency) in 20 patients (12). In this series, patients with cardiac abnormalities were older and had a longer disease duration when compared to non-affected patients. In 2006, Brunner and co-workers from Switzerland, using echocardiography, studied 100 male subjects with AS and a disease duration of more than 15 years (13). No increased prevalence of mitral and aortic valve regurgitation and arrhythmia was found in comparison with the normal population. These authors argued that cardiac disorders in AS have been overestimated in the past. At present, there are no reasonable hypotheses to explain why the results reported by Brunner are in contrast with those of the other studies.

Transesophageal echocardiography, a method that allows a better visualization of the valve structures, was used by Roldan *et al.* to examine 44 AS patients and 30 healthy volunteers (4). Twenty-five of the 44 AS patients underwent clinical and echocardiographic follow-up about 40 months later. Aortic root and valve abnormalities were found in 82% of patients and in 27% of controls ($p < 0.001$). Aortic root thickening, increased stiffness and dilatation were seen in 61%, 61% and 25% of AS subjects, respectively. Valve thickening (41% for the aortic and 34% for the mitral valve) consisted

mainly (74%) of nodularities of the aortic cusps and basal thickening of the anterior mitral leaflet, forming the characteristic subaortic bump. More than 50% of cases showed valve regurgitation. Aortic root and valve abnormalities were related to the disease duration but not to the activity, severity or therapy of AS. During follow-up of 25 patients, new aortic root or valve alterations were detected in 24%, previous valve insufficiency worsened significantly in 12% and aortic disorders disappeared in 20%. Twenty percent of patients developed heart failure, underwent valve replacement, had a stroke or died, as compared with 3% of control subjects.

Recently Demiralp and co-workers analysed 35 AS patients without cardiovascular disorders and 30 healthy subjects (14). Aortic strain, distensibility index and stiffness index beta were calculated from aortic diameters measured by echocardiography and blood pressures simultaneously measured by sphygmomanometry. They observed that in AS patients aortic elasticity was diminished and this reduction did not correlate with the duration of AS.

The relationship between LAR and HLA B27 has been analyzed in 2 studies. Bergfeldt and co-workers indicated a possible causal association HLA B27/valvular disease, in 15 to 20% of 91 consecutive patients with LAR of different degrees of severity (2). In a group of 100 subjects suffering from LAR, Qaiyumi *et al.* found 7 cases of HLA B27-positive spondyloarthropathies (4 AS, 3 Reiter's syndrome) (15). Moreover, it is possible that HLA B27 positive patients with LAR or conduction abnormalities had not previously received a diagnosis of SpA. Thus, the notion regarding the occurrence of cardiovascular complications in long-standing SpA does not always seem to be valid.

Aortitis can range from chronic, haemodynamically irrelevant fibrosis to acute aortic insufficiency with rapid deterioration of cardiac function. However, aortitis usually causes a gradual dilatation of the aorta with a slow progression of the aortic insufficiency. In fact, a diastolic murmur is audible for several years before dyspnea develops.

As with all valvular regurgitation, endocarditis prophylaxis is advisable. Valvular surgery has been successfully carried out in these patients.

2- Cardiac conduction abnormalities

The second most common cardiac diseases in AS are conduction disturbances usually characterized by high degree atrioventricular blocks.

As reported by Bergfeldt, atrio-ventricular (AV) conduction blocks have been detected in AS patients since the 1940s (3). The prevalence of conduction disorders was estimated by Khan in 3% of patients with disease duration less than 15 years and in 9% for subjects with longer disease (10), although other authors described prevalences up to 48% (16-18). First, 2nd and 3rd degree AV blocks have been reported. Conduction blocks can not only be AV (mainly localized in the suprahisian region) (19) but also intra-ventricular and they can show an intermittent nature (6, 17). Bradycardia or pauses due to sinus node dysfunction have also been described (16, 19). Bergfeldt observed that a high percentage (12.6%) of 223 patients with permanently implanted pacemakers for severe bradyarrhythmias had HLA B27-related SpA (20). But the role played by HLA B27 in the pathogenesis of arrhythmias cannot be exclusive because cases of HLA B27-negative AS with severe conduction disturbances have also been reported (20, 21).

In countertendency, the study of Moller (22) and the very recent study of Brunner *et al.* (13) did not confirm the increased frequency of cardiac conduction disturbances in AS. As a consequence, Brunner *et al.* (13) suggested that a cardiological evaluation should not be routinely recommended in patients suffering from AS.

What are the AS-related anatomic heart alterations that could be involved in the pathogenesis of conduction disorders? The inflammatory and, later, fibrotic lesions extending from the aorta to the interventricular septum (1, 4) and the obliterative intimal proliferation in the sinus node artery and in the atrioventricular node artery (3) are the more probable causative factors. The

intermittent AV blocks are most likely associated to a reversible inflammatory process rather than to a permanent fibrotic scar (3).

Clinical manifestations may range from asymptomatic patients, for first-grade atrioventricular blocks or presence of an adequate escape rhythm, to complete heart block causing Stokes-Adam's attacks and requiring urgent hospitalisation.

There is no specific therapy for conduction disturbances. However, in the presence of symptoms, pacemaker implantation is needed.

3- Coronary arteries involvement

Recently Huffer and Furgerson described a case of aortic root dilatation with sinus of Valsalva and coronary aneurisms associated with AS (23). As previously seen in aortic lesions, histopathologic findings showed an inflammatory nature and consisted of perivascular lymphocytic and polymorphonuclear infiltrate with scattered fibrosis. No significant atherosclerotic damages were present. Furthermore, a patient with focal coronary aneurismal dilatation was also recently reported by Worthley and Curtis (24).

4- Thoracic and abdominal aorta

Aneurysmatic dilatations of thoracic (25-27) or abdominal (28) aorta have rarely been described in AS patients. In the abdominal case, pathologic examination of the aneurysmal wall revealed hyalinization of the connective tissue, with several lymphocytic infiltrates, conspicuous calcification, and absence of elastic fibers. The original structure of the arterial wall was not recognized (29). These findings are similar to those previously reported in AS ascending aortitis (1).

The Italian group of Afeltra and co-workers (30) described a case of retroperitoneal fibrosis (RPF) associated with AS and reviewed other 18 cases reported in the literature. A local immune response to atheromatous plaque in the context of a systemic inflammatory disorder such as AS was hypothesized as a possible cause (30). Although RPF has been reported in several patients with systemic autoimmune diseases (31),

the relationship with AS seems to be stronger. In fact, in 2002 LeBlanc *et al.* suggested to consider RPF as an extra-articular manifestation of AS (32).

The HLA-B27 antigen may cause susceptibility to RPF. In this regard, Littlejohn and Keystone (33) described HLA-B27 positive patients suffering from RPF but without AS. On the other hand, Afeltra *et al.* found that the 43% of patients with concomitant RPF and SpA were HLA-B27 negative (30).

5- Aortic involvement in HLA B27-related juvenile arthritis

Aortic valve involvement was also described in patients with HLA B27-related juvenile arthritis (B27-JA). Huppertz *et al.* examined 40 subjects suffering from this kind of arthritis by echocardiography and compared them with an age- and sex-matched control group negative for HLA B27 (34). Four patients with B27-JA, and none in the control group, had inflammatory aortic regurgitation. Jiménez-Balderas *et al.* analysed the cardiac abnormalities in 20 patients with juvenile onset ankylosing spondylitis (JOAS), 31 with adult onset ankylosing spondylitis (AOAS) and in 20 healthy controls without cardiopulmonary symptoms (35). Ninety percent of JOAS and 51% of AOAS patients were HLA B27-positive. Abnormal aortic ring reflectance was shown in 19% of AOAS vs. 0% abnormalities in JOAS and controls ($p=0.01$). The aortic root diameter was increased in 58% of AOAS, 30% of JOAS, and 0% of controls ($p=0.001$). Despite the higher prevalence of HLA B27, JOAS had a lower frequency of aortic alterations than AOAS.

Conclusion

Aortic involvement is a rare but potentially life threatening complication which may occur both in late and, more rarely, in early AS. Rheumatologists managing AS patients should carefully consider the occurrence of aortic insufficiency, cardiac conduction abnormalities and, more rarely, arteritis of thoracic and abdominal aorta and coronary arteries so that an adequate treatment could be promptly carried out.

References

1. BULKLEY BH, ROBERTS WC: Ankylosing spondylitis and aortic regurgitation. Description of the characteristic cardiovascular lesion from study of eight necropsy patients. *Circulation* 1973; 48: 1014-27.
2. BERGFELDT L, INSULANDER P, LINDBLOM D, MÖLLER E, EDHAG O: HLA-B27: an important genetic risk factor for lone aortic regurgitation and severe conduction system abnormalities. *Am J Med* 1988; 85: 12-8.
3. BERGFELDT L: HLA-B27-associated cardiac disease. *Ann Intern Med* 1997; 127: 621-9.
4. ROLDAN CA, CHAVEZ J, WIEST PW, QUALLS CR, CRAWFORD MH: Aortic root disease and valve disease associated with ankylosing spondylitis. *J Am Coll Cardiol* 1998; 32: 1397-404.
5. SHAH A: Echocardiographic features of mitral regurgitation due to ankylosing spondylitis. *Am J Med* 1987; 82: 353-6.
6. KINSELLA TD, JOHNSON LG, IAN R: Cardiovascular manifestations of ankylosing spondylitis. *Can Med Assoc J* 1974; 111: 1309-11.
7. TUCKER CR, FOWLES RE, CALIN A, POPPRL: Aortitis in ankylosing spondylitis: early detection of aortic root abnormalities with two dimensional echocardiography. *Am J Cardiol* 1982; 49: 680-6.
8. LABRESH KA, LALLY EV, SHARMA SC, HO G JR: Two-dimensional echocardiographic detection of preclinical aortic root abnormalities in rheumatoid variant diseases. *Am J Med* 1985; 78: 908-12.
9. O'NEILL TW, KING G, GRAHAM IM, MOLONY J, BRESNIHAN B: Echocardiographic abnormalities in ankylosing spondylitis. *Ann Rheum Dis* 1992; 51: 652-4.
10. KHAN MA: Ankylosing spondylitis: clinical features. In KLIPPEL JH and DIEPPE PA (Eds.): *Rheumatology*, 2nd ed., Mosby, London, 1998: 6.16.1-6.16.10.
11. YILDIRIR A, AKSOYK S, CALGUNERI M, OTO A, KES S: Echocardiographic evidence of cardiac involvement in ankylosing spondylitis. *Clin Rheumatol* 2002; 21: 129-34.
12. LANGE U, STAPFER G, DITTING T *et al.*: Pathologic alterations of the heart and the kidney in patients with ankylosing spondylitis. *Eur J Med Res* 2007; 12: 573-81.
13. BRUNNER F, KUNZ A, WEBER U, KISSLING R: Ankylosing spondylitis and heart abnormalities: do cardiac conduction disorders, valve regurgitation and diastolic dysfunction occur more often in male patients with diagnosed ankylosing spondylitis for over 15 years than in the normal population? *Clin Rheumatol* 2006; 25: 24-9.
14. DEMIRALP E, KARDESOGU E, KIRALP MZ *et al.*: Aortic elasticity in patients with ankylosing spondylitis. *Acta Cardiol* 2004; 59: 630-4.
15. QAIYUMI S, HASSAN ZU, TOONE E: Seronegative spondyloarthropathies in lone aortic insufficiency. *Arch Intern Med* 1985; 145: 822-4.
16. NITTER-HAUGE S, OTTERSTAD JE: Characteristics of atrioventricular conduction disturbances in ankylosing spondylitis (Mb. Bechterew). *Acta Med Scand* 1981; 210: 197-200.

17. BERGFELDT L, EDHAG O, VALLIN H: Cardiac conduction disturbances, an underestimated manifestation in ankylosing spondylitis. A 25-year follow-up study of 68 patients. *Acta Med Scand* 1982; 212: 217-23.
18. THOMSEN NH, HØRSLEV-PETERSEN K, BEYER JM: Ambulatory 24-hour continuous electrocardiographic monitoring in 54 patients with ankylosing spondylitis. *Eur Heart J* 1986; 7: 240-6.
19. BERGFELDT L, VALLIN H, EDHAG O: Complete heart block in HLA B27 associated disease. Electrophysiological and clinical characteristics. *Br Heart J* 1984; 51: 184-8.
20. BERGFELDT L: HLA B27-associated rheumatic diseases with severe cardiac bradyarrhythmias. Clinical features and prevalence in 223 men with permanent pacemakers. *Am J Med* 1983; 75: 210-5.
21. PEETERS AJ, TEN WOLDE S, SEDNEY MI, DE VRIES RR, DIJKMANS BA: Heart conduction disturbance: an HLA-B27 associated disease. *Ann Rheum Dis* 1991; 50: 348-50.
22. MØLLER P: Atrioventricular conduction time in ankylosing spondylitis. Distribution of P-R intervals in patients and their relatives. *Acta Med Scand* 1985; 217: 85-8.
23. HUFFER LL, FURGERSON JL: Aortic root dilatation with sinus of Valsalva and coronary artery aneurysms associated with ankylosing spondylitis. *Tex Heart Inst J* 2006; 33: 70-3.
24. WORTHLEY MI, CURTIS MJ: Coronary aneurysms and ankylosing spondylitis: what stenting option is truly optimal? *Int J Cardiol* 2006; 106: 422-3.
25. KAWASUJIM, HETZER R, OELERT H, STAUCH G, BORST HG: Aortic valve replacement and ascending aorta replacement in ankylosing spondylitis: report of three surgical cases and review of the literature. *Thorac Cardiovasc Surg* 1982; 30: 310-4.
26. SEO JW, PARK IA, YOON DH *et al.*: Thoracic aortic aneurysm associated with aortitis: case reports and histological review. *J Korean Med Sci* 1991; 6: 75-82.
27. STAMP L, LAMBIE N, O'DONNELL J: HLA-B27 associated spondyloarthropathy and severe ascending aortitis. *J Rheumatol* 2000; 27: 2038-40.
28. TAKAGI H, MORI Y, UMEDA Y *et al.*: Abdominal aortic aneurysm with arteritis in ankylosing spondylitis. *Vasc Surg* 2003; 38: 613-6.
29. SLOBODIN G, NASCHITZ JE, ZUCKERMAN E *et al.*: Aortic involvement in rheumatic diseases. *Clin Exp Rheumatol* 2006; 24 (Suppl. 41): S41-7.
30. AFELTRA A, GENTILUCCI UV, RABITTI C *et al.*: Retroperitoneal fibrosis and ankylosing spondylitis: which links? *Semin Arthritis Rheum* 2005; 35: 43-8.
31. VAGLIO A, SALVARANI C, BUZIO C: Retroperitoneal fibrosis. *Lancet* 2006; 367: 241-51.
32. LEBLANC CM, INMAN RD, DENT P, SMITH C, BABYN P, LAXER RM: Retroperitoneal fibrosis: an extraarticular manifestation of ankylosing spondylitis. *Arthritis Rheum* 2002; 47: 210-4.
33. LITTLEJOHN GO, KEYSTONE EC: The association of retroperitoneal fibrosis with systemic vasculitis and HLA-B27: a case report and review of the literature. *J Rheumatol* 1981; 8: 665-9.
34. HUPPERTZ H, VOIGT I, MÜLLER-SCHOLDEN J, SANDHAGE K: Cardiac manifestations in patients with HLA B27-associated juvenile arthritis. *Pediatr Cardiol* 2000; 21: 141-77.
35. JIMÉNEZ-BALDERAS FJ, GARCÍA-RUBI D, PÉREZ-HINOJOSA S *et al.*: Two-dimensional echo Doppler findings in juvenile and adult onset ankylosing spondylitis with long-term disease. *Angiology* 2001; 52: 543-8.