

Dissection of the Ascending Aorta in a Patient with HLA-B27 Associated Ankylosing Spondylitis

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ABSTRACT. We describe a 38-year-old patient with ankylosing spondylitis complicated by a non-traumatic dissection of the ascending aorta without concomitant Marfan's syndrome. (First Release Mar 15 2008; *J Rheumatol* 2008;35:713–6)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS

DISSECTION OF THE AORTA

HLA-B27

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with a wide clinical spectrum of articular and extraarticular features that occurs in genetically predisposed persons and is triggered by environmental factors¹. Cardiovascular involvement in HLA-B27 related spondyloarthropathies is widely described²⁻³. The most common findings include conduction abnormalities and aortic root and aortic valve disease²⁻⁵. Only 2 patients with AS have been reported to present a non-traumatic dissection of the ascending aorta^{6,7} and both of them were HLA-B27 negative. Several authors⁸⁻¹³ have highlighted the clinical and pathogenic similarities between AS and Marfan's syndrome (MS), suggesting that there could be a common tissue susceptibility factor. There are cases of both MS and AS in the same patient. The clinical similarities of both entities are described in Table 1. We present a new description of this vascular event in a patient with AS positive for HLA-B27 in whom MS was not present.

CASE REPORT

A 38-year-old patient with a recent non-traumatic dissection of the ascending aorta was sent to our rheumatology unit for investigation of recurrent anterior uveitis. His cardiovascular risk factors included obesity, with a body mass index of 31.35 kg/m², and recent hypertension. Four months earlier, he presented an acute aortic dissection complicating an 8 cm-diameter aneurysm of the ascending aorta, extending from the right coronary sinus to both iliac arteries. We performed emergency surgery by replacing the aortic root (Bentall procedure), ascending aorta, and aortic arch with a

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Table 1. Clinical points of comparison between ankylosing spondylitis (AS) and Marfan's syndrome (MS).

	AS	MS
Articular	Dorso-lumbar spondylitis, sacroiliitis hip and knee arthritis, enthesitis ¹ , caudal root sheath ectasia, acetabular osteitis ⁸	Scoliosis, joint laxity overgrowth of long bones, acetabular osteitis ¹⁴ , caudal root sheath ectasia ¹⁵
Ocular	Anterior uveitis	Ectopia lentis
Cardiovascular	Aortitis	Aortic root dilatation
Pulmonar	Apical lung fibrosis	Apical bullae, spontaneous pneumothorax
Retroperitoneal	Retroperitoneal fibrosis ¹⁶	Retroperitoneal fibrosis ¹⁷

Dacron graft (Figure 1). Pathological findings showed fibrinoid necrosis of the middle media with an intense acute neutrophil polymorphonuclear infiltrate. No other pathological finding was seen in the rest of the aorta and aortic valve.

Our patient did not present a phenotype suggestive of MS, but interestingly, his father had died at the age of 33 due to an unspecified cardiovascular problem. At the examination our patient was asymptomatic, but he had a history of inflammatory back pain and stiffness in early adulthood (from 18 to 25 years old) and recurrent unilateral anterior uveitis (2-3 episodes per year) in the previous 3 years that had responded well to topical treatment.

On physical examination, our patient appeared healthy, with a normal intelligence quotient. Vital signs were normal; height: 175 cm, weight: 96 kg. No joint laxity was observed. He presented a severe limitation of the lumbar spine with Schober test result of 2 cm. Sacroiliac stress tests were negative, and no neurological findings were seen.

Laboratory findings revealed the presence of HLA-B27, an allele of the major histocompatibility complex class I, erythrocyte sedimentation rate: 26 mm/h (reference range: 0-20) and C-reactive protein: 4.7 mg/dl (0–0.8). Antinuclear antibodies, syphilis serology, and plasma levels of cystine and homocysteine were negative. No mutations were detected for exons 1 to 65 of the fibrillin 1 gene. Radiography of the pelvis revealed grade III bilateral sacroiliitis (Figure 2).

We diagnosed AS with related extraarticular features (recurrent unilateral anterior uveitis and dissection of the ascending aorta) according to the modified NY criteria of 1984¹⁸.

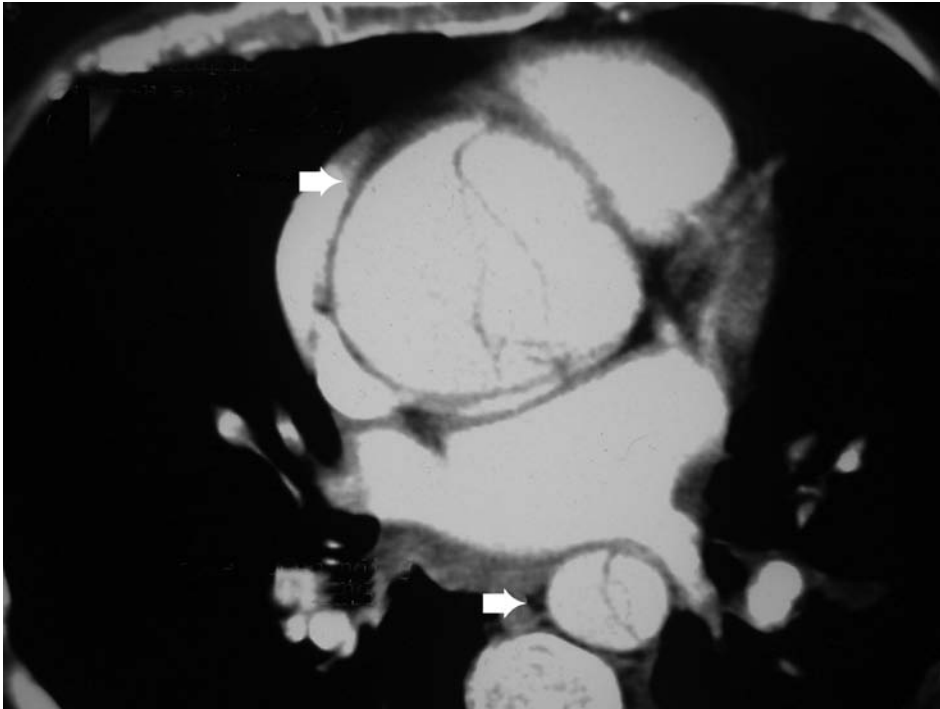


Figure 1. Spiral computed tomography (CT) showed a dilated aortic root (8 cm, arrow at top; intimal flap inside) and dissected descending thoracic aorta (arrow at bottom).



Figure 2. Plain anteroposterior view of the pelvis showed grade III bilateral sacroiliitis.

DISCUSSION

There are different possible cardiovascular complications in AS. The most common are aortic disease (both root and valve) and conduction defects²⁻⁵. A prevalence of aortic lesions in AS of 82% using transesophageal echocardiography has been reported⁵. Conduction defects cause the most frequent cardiac symptoms in AS². Both these complications are related to HLA-B27^{2,19} even without articular symptoms. HLA-B27-associated cardiac syndrome was shown to consist of severe cardiac conduction system abnormalities and lone aortic regurgitation without concomitant arthritis, with HLA-B27 results positive in 66 to 88% of male patients². Another reported cardiac manifestation is myocardial failure, which is mostly a left ventricular dysfunction^{3,20}. There are reports of aneurysm of the aorta related to AS, located in the ascending, descending, or entire thoracic aorta,²¹⁻²⁴ and even in the abdominal aorta. Aortic elasticity decreases²⁵ even without cardiac involvement, and only 2 reports have described a dissection of the ascending aorta^{6,7}. Interestingly, and unlike our patient, both reported patients were HLA-B27 negative. Even though HLA-B27 have been present in other AS patients with aortitis and aneurysm^{21,23}, its importance in aortic dissections still needs to be fully confirmed. Aortic rupture after minor trauma is possible and is probably related to the firm adherence of the aorta to the anterior longitudinal ligament²⁶. All of these events are important because cardiovascular events are the leading cause of death in AS patients, with a rate of 35%²⁷.

MS is a multisystem connective tissue disorder of autosomal dominant inheritance that affects one out of every 5000 individuals²⁸. Clinical diagnosis depends on a combination of major and minor criteria defined in the revised 1996 Ghent criteria²⁹ and the gene for MS is localized to chromosome 15q21 and encodes the microfibrillar protein fibrillin-1³⁰⁻³¹. Although the presence of a dissection of the aorta in a young patient requires us to rule out MS, considered as a major criterion²⁹, other entities such as spondyloarthropathies should also be considered; moreso when we take into account the clinical and pathological similarities between AS and MS⁸⁻¹⁷ and their possible coexistence¹⁰⁻¹³.

Fibrillinopathies represent a wide group of connective tissue disorder groups where mutations of fibrillin or transforming growth factor- β (TGF- β) share a clinical spectrum, predominantly in the skeleton, the aorta, and the eyes³². A better understanding of fibrillin biochemistry, a 350 kDa glycoprotein, and the role of TGF- β has led us to consider that fibrillinopathies (especially MS) and AS, could be more closely linked than previously thought⁸⁻¹³. Fibrillin-1 is found in the extracellular matrix of tendons, ligaments, periosteum, skin, heart valves, aorta, and ocular lenses and confers biomechanical properties in connecting and maintaining tissues and organs³¹. It also regulates the TGF- β , latent TGF- β binding proteins (LTBP), which hold TGF- β in an inactive complex and bone morphogenetic protein sig-

nalling. TGF- β regulates the proliferation, differentiation, and migration of many cell types, and therefore has an important role in morphogenesis, organogenesis, tissue maintenance, and scarring^{32,33}. Overproduction of TGF- β due to a dysregulation of fibrillin-1 could be one important step in pathology. The mutation or reduction of fibrillin-1 is thought to be secondary to a congenital defect in MS^{28,29} and in AS, and could be due to an inflammation target in connective tissue exposed to repetitive biomechanical stress^{8,9}. Another point is that fibrillin-1 is rich in cysteine. Even though our patient had normal plasma levels of cysteine, it is thought that a deficiency of cysteine impairs fibrillin-1 deposition³⁴. Takagi recently described a patient with AS with aortic dissection and low levels of cysteine in plasma⁷. Further studies are required.

Cardiac involvement in AS patients reveals a tissue-specific modulation towards fibrosis at the sites subjected to stress, such as the ascending aorta. Histological findings reveal adventitial scarring, intimal proliferation, and fibrous thickening of the aortic wall³⁵ compatible with overproduction of TGF- β . The finding of TGF- β in sacroiliac biopsies³⁶ and in the anterior chamber of the eye³⁷ supports the hypothesis. Chronic periaortitis is a group that involves inflammatory aneurysm of the abdominal aorta, idiopathic retroperitoneal fibrosis as described in both MS¹⁷ and AS¹⁶, and perianeurysmal retroperitoneal fibrosis³⁸. Aortitis in AS has been related to aneurysm formation²¹⁻²⁴ and has been described without it⁴. This is in consonance with the aortic specimen of our patient that showed fibrinoid necrosis of the middle media with an intense acute neutrophil polymorphonuclear infiltrate, being different from the other cases with aortic dissection described by Takagi, *et al*^{6,7} that revealed neither aortitis nor cystic medial necrosis.

In summary, different cardiovascular complications in AS are possible. We describe the first case of non-traumatic dissection of the aorta in a young patient with HLA-B27 positive AS. After surgery pathology studies showed features of acute aortitis that may have been related to aneurysm formation.

REFERENCES

1. Khan MA. Update in spondyloarthropathies. *Ann Intern Med* 2002;136:896-907.
2. Bergfeldt L. HLA-B27-associated cardiac disease. *Ann Intern Med* 1997;127:621-9.
3. Lautermann D, Braun J. Ankylosing spondylitis — cardiac manifestations. *Clin Exp Rheumatol* 2002;20 Suppl 28:11-15.
4. Ansell BM, Bywaters EGL, Doniach I. The aortic lesion of ankylosing spondylitis. *Br Heart J* 1958;20:507-15.
5. 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.
6. Takagi H, Kato T, Matsuno Y, Umeda Y, Fukumoto Y, Mori Y, Hirose H. Aortic dissection without Marfan's syndrome in ankylosing spondylitis. *J Thorac Cardiovasc Surg* 2004;127:600-2.
7. Takagi H, Sekino S, Umamoto T. Aortic dissection and ankylosing

- spondylitis in hypocystinemia. *J Thorac Cardiovasc Surg* 2005;129:1198.
8. Simkin PA. Acetabular osteitis in ankylosing spondylitis: does fibrillin figure in its pathogenesis? *J Rheumatol* 2001;28:2663-6.
 9. Edwards JCW, Bowness P, Archer JR. Jekyll and Hyde: the transformation of HLA-B27. *Immunol Today* 2000;21:256-60.
 10. Fietta P, Manganelli P. Coexistent Marfan's syndrome and ankylosing spondylitis: a case report. *Clin Rheumatol* 2001;20:140-2.
 11. Fietta P, Manganelli P. Is fibrillin-1 the link between ankylosing spondylitis and Marfan's syndrome? [letter]. *J Rheumatol* 2002;29:8.
 12. Rovensky J, Zlnay D. Marfan's syndrome and ankylosing spondylitis [letter]. *Isr Med Assoc J* 2003;5:153.
 13. Kiss C, Jónap I, Gergely P, Poór G. Coexistent Marfan's syndrome and ankylosing spondylitis. *J Rheumatol* 2006;33:1199-200.
 14. Van de Velde S, Fillman R, Yandow S. Protrusion acetabuli in Marfan syndrome. History, diagnosis, and treatment. *J Bone Joint Surg Am* 2006;88:639-46.
 15. Ho NC, Hadley DW, Jain PK, Francomano CA. Dural ectasia associated with Marfan syndrome. *Radiology* 2001;223:767-771.
 16. Afeltra A, Gentilucci U, Rabitti C, Amoroso A, Caricato M, Vadacca M, Valeri S, Zardi EM, Coppola R, Picardi A. Retroperitoneal fibrosis and ankylosing spondylitis: which links? *Semin Arthritis Rheum* 2005;35:43-8.
 17. Chong WK, al-Kutoubi MA. Retroperitoneal fibrosis in Marfan's syndrome. *Clin Radiol* 1991;44:386-8.
 18. Van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis: a proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-7.
 19. 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.
 20. Gould BA, Turner J, Keeling DH, Hickling P, Marshall AJ. Myocardial dysfunction in ankylosing spondylitis. *Ann Rheum Dis* 1992;51:227-32.
 21. Stamp L, Lambie N, O'Donnell J. HLA B27 associated spondyloarthropathy and severe ascending aortitis. *J Rheumatol* 2000;27:2038-40.
 22. Kawasaki M, 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.
 23. Takagi H, Yoshio M, Yukio U, et al. Abdominal aortic aneurysm with arteritis in ankylosing spondylitis. *J Vasc Surg* 2003;38:613-6.
 24. Somer T, Siltanen P. Aneurysm of the descending thoracic aorta, amyloidosis and renal carcinoma in a patient with ankylosing spondylitis. *Am J Med* 1970;49:408-15.
 25. Demiralp E, Kardesoglu E, Kiralp MZ, et al. Aortic elasticity in patients with ankylosing spondylitis. *Acta Cardiol* 2004;59:630-4.
 26. Fazl M, Bilbao JM, Hudson AR. Laceration of the aorta complicating spinal fracture in ankylosing spondylitis. *Neurosurgery* 1991;8:732-4.
 27. Lehtinen K. Mortality and causes of death in 79 patients with ankylosing spondylitis. *Scand J Rheumatol* 1980;9:145-7.
 28. Ho NC, Tran JR, Bektas A. Marfan's syndrome. *Lancet* 2005;66:1978-81.
 29. De Paepe A, Devereux RB, Dietz HC, Hennekem RCM, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet* 1996;62:417-46.
 30. Dietz HC, Cutting GR, Pyeritz RE. Marfan syndrome caused by a recurrent de novo missense mutation in the fibrillin gene. *Nature* 1991;352:337-9.
 31. Maslen CL, Corson GM, Maddox BK, Glanville RW, Sakai LY. Partial sequence of a candidate gene for the Marfan syndrome. *Nature* 1991; 352:334-7.
 32. Gelb BD. Marfan's syndrome and related disorders — more tightly connected than we thought. *N Engl J Med* 2006;355:841-4.
 33. Robinson PN, Arteaga-Solis E, Baldock C, et al. The molecular genetics of Marfan syndrome and related disorders. *J Med Genet* 2006;43:769-87.
 34. Majors AK, Pyeritz RE. A deficiency of cysteine impairs fibrillin-1 deposition: implications for the pathogenesis of cystathionine B-synthase deficiency. *Mol Genet Metab* 2000;70:252-60.
 35. 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.
 36. Poole RA. The histopathology of ankylosing spondylitis: are there unifying hypotheses? *Am J Med Sci* 1998;316:228-33.
 37. Ma D, Niederkorn JY. Transforming growth factor-beta downregulates major histocompatibility complex class I antigen expression and increases the susceptibility of uveal melanoma cells to natural killer cell-mediated cytotoxicity. *Immunology* 1995; 83:263-9.
 38. Vaglio A, Corradi D, Manenti L, Ferretti S, Garini G, Buzio C. Evidence of autoimmunity in chronic periaortitis: a prospective study. *Am J Med* 2003;114:454-62.