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Case Report

Takayasu's Arteritis in Mexican Monozygotic Twins: Analysis of Human Leukocyte Antigens (HLA) Haplotypes

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Takayasu's arteritis (TA) is an idiopathic great vessel vasculitis that affects the aorta and its branches. This entity is associated with the major histocompatibility complex (MHC) genes. We studied DNA sequences of human leukocyte antigens (HLA) haplotypes in one pair of Mexican monozygotic twins affected by TA. HLA alleles were determined by sequence-specific priming. Genetic testing of the HLA haplotypes in both sisters were A*02 B*39 DRB1*04 DQB1*03:02/A*24 B*35 DRB1*16 DQB1*03:01. These results confirm that within the MHC are genes that determine genetic susceptibility to develop TA and sustain genetic heterogeneity of this disease among populations.

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Introduction

Takayasu's arteritis (TA) is a rare, systemic, and inflammatory large vessel vasculitis of unknown etiology that may lead to dilation or occlusion of the arteries in various degrees, mainly affecting the aorta and its major branches. This entity is more frequent in Asian and Latin American individuals than in other ethnic groups, and its clinical spectrum ranges from asymptomatic disease to catastrophic. In general, patients show heterogeneous responses to the treatment with glucocorticoids and cytotoxic agents.[1)] The major histocompatibility complex (MHC) has been associated with genetic susceptibility in the development of this condition. Then, the HLA-B52 haplotype is associated with this disease in the Asian population[2)] while HLA-DRB1*1602 and DRB1*1001 have been reported as markers of Amerindian ancestry in the Americas.[3)] Cases of TA affecting siblings are sporadic, and there are only four cases of monozygotic (MZ) twins affected by TA in the English literature—three occurred in Japanese siblings and one in twin sisters of Bangladeshi origin.[4)]

Case Report

Here, we introduce one case of Mexican MZ twins with the diagnosis of TA based on the American College of Rheumatology criteria[5)] (**Table 1**). In addition, we briefly analyze their clinical presentation, management, and immunogenetic studies.

Subject 1

A 26-year-old female without significant past medical history was sent to our institution for evaluation with new onset of bilateral lower extremity pain elicited after

Table 1 Takayasu's arteritis diagnostic criteria according to the American College of Rheumatology.[5]

- Age at disease onset <40 years.
- Claudication of the extremities.
- Decreased pulsation of one or both brachial arteries.
- Difference of at least 10 mmHg in systolic blood pressure between the arms.
- Bruit audible on auscultation over at least one or both subclavian arteries or the abdominal aorta.
- Arteriographic narrowing or occlusion of the entire aorta, its primary branches of large arteries in the proximal upper or lower extremities not because of arteriosclerosis, fibromuscular dysplasia, or other causes.

A patient shall be said to have Takayasu's arteritis if more than three of the above five criteria are present.

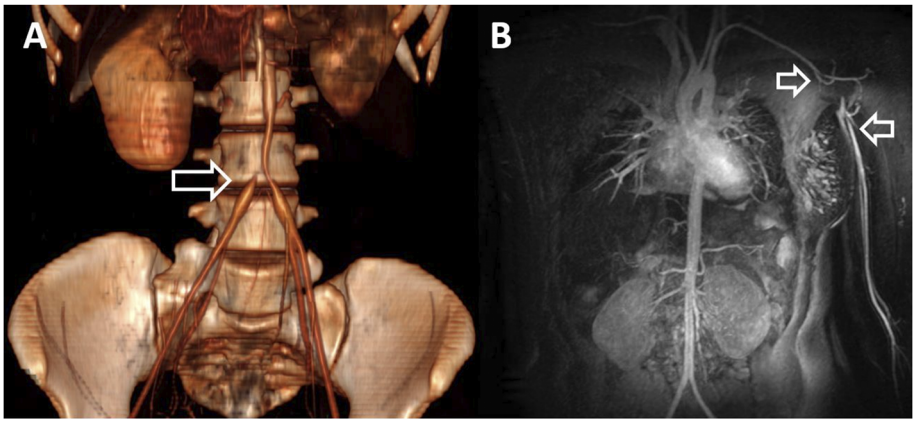

Fig. 1 Computed tomography angiography three-dimensional reconstruction that reveals a stenotic lesion distal aorta, extending to the proximal common iliac arteries bilaterally with a total occlusive lesion at the origin of the right common iliac artery (white hollow arrow) (**A**). A magnetic resonance angiography assessed the entire aorta and its branches and revealed 3 cm occluded segment in the left axillary artery (between two black hollow arrows) (**B**). Permission to reproduce **Fig. 1B** was granted by Elsevier. Hinojosa CA, Anaya-Ayala JE, Gomez-Arcive Z, et al. Eur J Vasc Endovasc Surg 2017; 54(3): 397–404.

physical exertion and intermittent febrile episodes over a period of two weeks. Her femoral and pedis artery pulses were diminished bilaterally on physical exam. Although the C-reactive protein was within normal limits, her laboratory data were notable for the elevation of erythrocyte sedimentation rate (ESR) (32 mm/hr). A full workup that included Anti-DNA, P-ANCA, C-ANCA, and Rheumatoid factor was negative. A computed tomography angiography revealed a narrowing of the distal aorta and proximal bilateral iliac arteries. She met the criteria for TA and then was started on Prednisone and Methotrexate therapy with an improvement in symptomatology. After 14 months, she was sent to our vascular surgery clinic with progressive and worsening bilateral lower extremity intermittent claudication, resistant to maximum immunomodulatory treatment the prior year. She did not have evidence of reactivation of the disease. Her worsening ischemic symptoms were the result of progressive stenosis of the distal aorta (**Fig. 1A**). Given her young age and following discussions about open versus endovascular reconstruction, the decision was to perform an aortoiliac bypass grafting using 18 millimeters (mm) by 9 mm Dacron graft during the "late phase" of the disease. The patient recovered well from the surgery, and at eight years of follow-up of the procedure, she remains symptom-free. The surgical aspects of this case have been previously described.[6]

Subject 2

Her twin sister presented to our institution a year later with new onset of left upper extremity numbness and pain associated with physical activity and febrile episodes. She had no previous significant medical history like her twin sister and lived with their parents, with similar lifestyles in the same environment. On exam, her left arm showed no signs of acute ischemia, and the brachial, radial, and ulnar pulses were diminished in that extremity with a pale and cold hand. Her ESR was 30 mm/hr, and a thoracic, abdominal, and pelvic magnetic resonance angiography (**Fig. 1B**) evaluated the entire aorta and its branches. This study revealed 3 cm occluded segment in the left axillary artery. She was taken to the operating room for arterial reconstruction, following initial immunosuppressive therapy by the rheumatology service and during the "late or inactive phase" of the disease. We used a 7 mm expanded

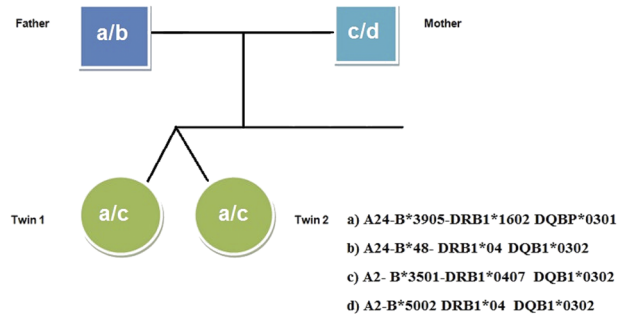

Fig. 2 Flow diagram of human leukocyte antigens (HLA) typing and sequences of the twin sisters and their parents.

polytetrafluoroethylene graft for the bypass. Postoperatively, the patient recovered well, and at seven years, she is doing well. We studied DNA sequences of human leukocyte antigens (HLA) haplotypes in the MZ twins. HLA alleles were determined by sequence-specific priming after DNA amplification of each locus and genetic testing of HLA haplotypes demonstrated in both sisters: A*02 B*39 DRB1*04 DQB1*03:02/A*24 B*35 DRB1*16 DQB1*03:01. In addition, we completed the HLA typing of their parents (**Fig. 2**).

Discussion

The incidence of TA worldwide is estimated at 2.6 cases per million annually.[7] This entity is considered an inflammatory multifactorial vascular disease with both genetic and immunologic mechanisms involved.[2] Possibly, antigens stimulate the arterial tissue, leading to the expression of heat shock protein-65, which induces MHC class I-related chain A (MICA). Subsequently, natural killer (NK) cells and gamma-delta T cells express NKG2D receptors, and these may recognize MICA in vascular smooth muscle cells, leading to an acute inflammatory process. Pro-inflammatory cytokines are released from the NK and T cells, inducing the production of matrix metalloproteinases and amplifying the inflammatory response. This event would induce more MHC antigens and stimulate molecule expression on vascular cells, recruiting more mononuclear cells.[8] As mentioned above, the HLA-B52 is associated with this disease in Asia. In the Mexican population, studies have demonstrated an association with HLA-DRB1*1301 alleles, and a high frequency of HLA-B39 has been also observed.[9] Sequencing HLA-B39 alleles in Mexican patients demonstrated that these alleles share residues with Asian alleles (B51, B52, and B39) associated with this disease. Interestingly, we confirm the presence of haplotypes previously reported by Salazar in Colombian patients with TA in our study subjects.[2] In the case of abdominal aortic aneurysms, lesions that can occur secondary to TA, recently, we reported increased frequencies of the alleles HLA-DRB1*01 and HLA-DRB1*16 in Mexican Mestizo patients with degenerative aneurysms and associations with MHC genes, suggesting a possible relationship with this vasculitis.[10] As regards non-MHC genes, authors, including Terao,[2] have found and reported evidence of associations with TA as the one located in the IL12B region. In the twin sisters presented in this article, we did not investigate non-MHC haplotypes, but this is an area that deserves further research to increase our understanding of the pathogenesis of TA and identify those individuals genetically susceptible.

In this report, the presence of this inflammatory disease in genetically homogenous individuals exposed to the same environment reinforces the relevance of environmental and genetic triggers of TA.

Conclusion

In summary, the immunogenetics results obtained in the Mexican MZ twin sisters described in this article suggest that MHC antigens (e.g., HLA genes) might contain genetic traits within the 3.5 megabases of deoxyribonucleotide acid (DNA) that not only determine genetic susceptibility to develop this disease but also sustain the genetic heterogeneity and the disease different clinical patterns among populations.

To our knowledge, this is one of the few cases of TA affecting MZ twins that includes an MHC haplotype autochthonous of populations in the Americas.

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Informed Consent

Obtained by the two participants.

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Author's Contributions

Study conception: CH, JAA, JG
Data collection: RB, JG, JAA
Analysis: RB, JG, JAA, JMQ
Investigation: JAA, LMH,
Manuscript preparation: JAA, JMQ

Critical review and revision: all authors
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References

1) Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. Ann Intern Med 1994; **120**: 919-29.
2) Terao C. Revisited HLA and non-HLA genetics of Takayasu arteritis—where are we? J Hum Genet 2016; **61**: 27-32.
3) Salazar M, Varela A, Ramirez LA, et al. Association of HLA-DRB1*1602 and DRB1*1001 with Takayasu arteritis in Colombian mestizos as markers of Amerindian ancestry. Int J Cardiol 2000; **75 Suppl 1**: S113-6.
4) Numano F, Isohisa I, Kishi U, et al. Takayasu's disease in twin sisters. Possible genetic factors. Circulation 1978; **58**: 173-7.
5) Arend WP, Michel BA, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum 1990; **33**: 1129-34.
6) Hinojosa CA, Anaya-Ayala JE, Torres-Machorro A, et al. Middle aortic syndrome in Takayasu's Arteritis: report of two surgical cases. Ann Vasc Surg 2016; **34**: 270.e13-7.
7) Numano F, Kobayashi Y. Takayasu arteritis—beyond pulselessness. Intern Med 1999; **38**: 226-32.
8) Arnaud L, Haroche J, Mathian A, et al. Pathogenesis of Takayasu's arteritis: a 2011 update. Autoimmun Rev 2011; **11**: 61-7.
9) Girona E, Yamamoto-Furusho JK, Cutino T, et al. HLA DR6 (possibly DRB1*1301) is associated with the susceptibility to Takayasu arteritis in Mexicans. Heart Vessels 1996; **11**: 277-80.
10) Anaya-Ayala JE, Hernandez-Doño S, Escamilla-Tilch M, et al. Genetic polymorphism of HLA-DRB1 alleles in Mexican mestizo patients with abdominal aortic aneurysms. BMC Med Genet 2019; **20**: 102.