

Reviewer 1.

Thank you very much for the detailed comments. The authors have revised the manuscript as recommended.

Abstract

1. DNA-typing of HLA-B is common in Japan. Is it common in the Republic of Korea to measure only certain HLAs, such as HLA B51 and HLA B27? If comprehensive HLA-B DNA-typing is performed instead of measuring certain HLAs, the conclusion here does not hold.

☞ Thank you for your question. Yes, it is common in Korea to measure HLA containing only HLA B51 or HLA B27 using conventional PCR. Our patients underwent conventional PCR for HLA B27 and HLA B51 when medical examination was initially performed, and comprehensive HLA B DNA typing was performed only for experimental purposes. Thus, the sentence “In regions where conventional PCR for HLA typing is available for antigens such as HLA B27 or HLA B51, it is common to perform the HLA B27 test for evaluation of AS” has been added to the background section of the abstract.

Introduction

1. Please present the proportion of HLA B27-positive patients among those with ankylosing spondylitis.

☞ According to Jung et al., the proportion of HLA B27 positivity among Korean AS patients was 80%, and in a Korean population study, the HLA B27 positivity rate in Korean AS patients was 83.3% compared to a rate of 4.0% in healthy controls. This statistic has been added to page 4, lines 18-21.

Case Report

1. The style of presentation of such items as chief complaints and history of present illness of Case 1 and Case 2 in an alternating manner makes it difficult to identify individual cases. Please change the order of presentation: For Case 1, chief complaints, history of present illness, ...; then, please follow the same order for Case 2.

☞ The order of presentation has been changed as recommended.

2. Please specify the blood pressure, pulse rate, and respiratory rate at the time of presentation.

☞ The vital signs at the time of presentation have been added to page 5 lines 18-21 for case 1 and page 7 lines 20-21.

3. Please specify any physical findings suggestive of or ruling out arthritic symptoms at sites other than the spine, Achilles enthesitis, iridocyclitis, inflammatory bowel disease, aortic valve insufficiency, and mitral valve insufficiency.

► Physical findings of arthritic symptoms or extrarticular signs are also described. For case 1, articular symptoms and symptoms suggestive of inflammatory bowel disease are described on page 5, lines 11-14. Results of ophthalmologic examination are described on page 5 lines 24 and echocardiography on page 6 lines 10-11. For case 2, arthritic symptoms or extrarticular signs are described on page 7 lines 9-11 and line 22-23.

4. Please present test results of blood specimens for WBC, CRP, sedimentation rate, antinuclear antibodies, and rheumatoid factors.

☞ Blood test for WBC, CRP, ESR, ANA and rheumatoid factors have been presented as recommended. They have been added to page 6 lines 1-4 for case 1 and page 8 lines 4-7 for case 2.

5. In "Fig. 3. In the pedigree of the family," please identify the persons who correspond to Case 1 and Case 2.

☞ The pedigree of the family has been revised as recommended and the patients in

cases 1 and 2 have been identified.

6. Please also provide a diagnosis for each person whose HLAs are shown (such as a person with ankylosing spondylitis and a person only with sacroiliitis).

☞ The pedigree of the family has been revised as recommended.

Discussion

1. Please emphasize that the proportions of HLA B51-positive individuals in literature 11 is a statistic for Korea. The proportion varies depending on race. I cannot understand the flow of logic in the sentence, "Thus, the strong association between AS and HLA B27 suggests that significance of HLA B51 testing in SpA could be restricted to the cases without HLA B27 haplotype." A more detailed explanation is needed for the reader to understand this better.

☞ The proportion of HLA prevalence in other countries in HLA-prevalent regions have been added and the importance of HLA B27 testing in the HLA-prevalent regions is described on page 10. In the HLA B51-positive region, HLA B51 positivity increased by more than 10% in healthy controls. Usually, sacroiliitis is found in fewer than 10% of normal controls, but in this family, sacroiliitis developed in 60% of daughters, and all daughters who had sacroiliitis were positive for HLA B51. Thus, if HLA B27 testing is negative, HLA B51 could be tested to facilitate the diagnosis of AS/SpA.

2. Has Case 1's wife been tested for HLA? Are HLA 40:01 (B60) and HLAB51:01 shown for the fourth daughter who developed Grade 1 sacroiliitis correct? If correct, Case 1's wife has HLA 40:01 (B60) or HLAB51:01. Please mention this.

☞ The wife of the patient in case 1 passed away years before this study and HLA genotyping could not be performed. We hypothesized that she would be positive for HLA B40 and HLA B58 (added to page 10 lines 23-25).

3. If comprehensive HLA-B DNA typing is performed instead of measuring certain HLAs, the conclusion, "it is advisable to check for HLA B51 positivity in patients with

HLA B27-negative AS or SpA, even in the absence of clinical signs of Behcet's disease," is doubtful. On the other hand, the conclusion is understandable if HLA is measured in clinical practice when SpA is suspected. An argument in the core tip, "Thus, it is advised to perform HLA B51 testing as a genetic marker for HLA B27 negative AS/Spondyloarthropathy regardless of clinical symptoms of Behcet's disease" also does not hold if comprehensive HLA-B DNA typing is performed.

☞ In clinical practice, testing of certain HLA typing is usually carried out as HLA B27 for evaluation of AS and HLA B51 for evaluation of BD. If a patient suspected of having SpA is negative for HLA B27, additional testing of HLA B51 could facilitate the diagnosis of SpA even if the patient does not have clinical features of BD (added to page 11 lines 23-28).

Reviewer 2.

Thank you very much for the comments.

1. The authors identified and presented an HLAB51 positive family without Behcet disease. The English of the article should be reviewed by a native speaker.

☞ This manuscript has been reviewed by a native English editor from Editage.

2. Ages of family members should be added to the pedigree. Genital and eye examination results of the family should be mentioned. Have family members been tested for pathergy?

☞ As recommended, the ages of family members have been added to the pedigree.

Family members other than patients in cases 1 and 2 did not undergo genital and eye examinations. However, we enquired about symptoms or previous history of genital ulcer or blurred vision, and they reported no abnormality in the genitalia and eye. Family members were not tested for pathergy.

Re-reviewer:

Comment: I'm satisfied with responses to my original recommendations and accept

the revisions.

Answer: Thanks for your comments.