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CASE REPORT

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HLA-B52-positive vasculo-Behçet disease: usefulness of magnetic resonance angiography, ultrasound study, and computed tomographic angiography for the early evaluation of multiarterial lesions

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Abstract We report a case of HLA-B52-positive Behçet disease accompanied by multiarterial lesions. A 24-year-old woman was suffering from sporadic high fever and recurrent oral and genital ulcers, and laboratory data revealed severe inflammation. A diagnosis of Behçet disease was made. Magnetic resonance angiography, ultrasound study, and computed tomographic angiography demonstrated multiarterial lesions that had caused no symptoms. These noninvasive examinations were extremely useful in evaluating asymptomatic early vascular lesions.

Key words Behçet disease (BD) · Computed tomographic angiography (CTA) · HLA-B52 · Magnetic resonance angiography (MRA) · Ultrasound (US)

Introduction

Behçet disease (BD) is a syndrome of unknown etiology that contains some distinctive symptoms such as recurrent oral ulcers, genital ulcers, skin lesions, and ocular lesions. The close association of BD and HLA-B51 has been widely recognized. In the Japanese population, HLA-B51-positive BD patients comprise approximately 50% of all BD patients.[1] Consequently, positive HLA-B51 has been generally considered as a helpful marker for the diagnosis of BD. Meanwhile the significantly high frequency of positive HLA-B52 in the population of Takayasu arteritis has also been recognized.[2,3]

By contrast, several specific subtypes of BD have been described, namely entero-BD, neuro-BD, and vasculo-BD. Extensive therapies are often required for these special types of BD because of the severe and life-threatening symptoms of these types. Vasculo-BD in particular has been reported to cause arterial occlusion/stenosis and pseudoaneurysms in the aorta and its main branches.[4–9] Arterial occlusion/stenosis and pseudoaneurysms often cause ischemic organ diseases such as brain infarction[10] and life-threatening rupture,[11,12] respectively. Therefore, these arterial lesions should be detected and evaluated as soon as possible.

The usefulness of magnetic resonance angiography (MRA), ultrasound study (US), and computed tomographic angiography (CTA) with multiple detector-row computed tomography (MDCT) has already been reported for the evaluation of vasculitic arterial lesions, such as Takayasu arteritis.[13] Furthermore, these methods of evaluation are noninvasive, valuable techniques for the estimation of arterial lesions.[14]

In this report we describe an HLA-B51-negative but HLA-B52-positive BD patient who developed multiarterial lesions. The interpretation of arterial lesions in BD patients and the expediency of MRA, US, and CTA with MDCT for early evaluation of arterial lesions are discussed.

Case report

A 24-year-old woman had suffered from sporadic high fever over 38°C and sore throat since mid-December 2002. Approximately 2 weeks before pyrexia first appeared, she had given birth to a son. She was diagnosed with acute pharyngitis by a local physician and hospitalized for 4 days from December 27, 2002. Antibiotics were administered intravenously and her symptoms ameliorated. After discharge from the hospital the symptoms did not recur.

Around mid-August 2003, she began to suffer from high fever again. General fatigue and appetite loss also appeared at this time. The patient was brought to the same hospital for examination. Blood examination demonstrated no abnormal findings except for a high C-reactive protein (CRP)

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level, over 10 mg/dl (normal values <0.3 mg/dl). Sputum, urine, and stool culture revealed normal flora. Evidence of tuberculosis infection was not apparent. Immunological fecal occult blood test was not performed. Upper gastrointestinal endoscopic examination revealed mild nonspecific gastritis and abdominal US demonstrated mild splenomegaly without lymph node swelling. She was examined by otorhinologists, neurosurgeons, and ophthalmologists; however, no abnormal findings were detected. Around the beginning of September her symptoms gradually ameliorated without special treatment and she was discharged in mid-September 2003.

At the beginning of October 2003, painful open genital ulcers appeared. Genital herpes was suspected by the patient's gynecologists and she underwent treatment. Approximately 2 weeks later the ulcers had completely closed and she did not complain of any symptoms. In mid-January 2004, the high fever appeared again and she was hospitalized. Blood examination demonstrated almost exactly the same findings as the previous time; a high level of CRP, 13.8 mg/dl. At the beginning of February 2004, the pyrexia improved slightly; nevertheless, the genital ulcers worsened and polyarthralgia, especially of the bilateral knee joints, and painful oral ulcers appeared. She was referred and admitted to our division on April 8, 2004.

On admission, the patient exhibited a low-grade fever of 37.3°C, a few oral ulcers, and polyarthralgia in both knees without swelling and redness. No signs of Raynaud's phenomenon, facial erythema, cutaneous hypersensitivity and other skin lesions, swelling of the lymph nodes, or alopecia were observed. Heart sounds were clear with regular sinus rhythm, a pulse rate of 72 beats/min, and a blood pressure of 88/62 mmHg. Both radial arterial pulses were palpable with no laterality. No differences in the blood pressure were observed in the bilateral upper extremities. Bruits were audible in the bilateral cervixes, left subclavian portion, and the center of the upper abdomen. No rales were audible in the lung fields. She did not complain of ocular symptoms, claudication of the extremities, or central nervous system symptoms. The genital ulcers were completely cicatrized with no pain.

Laboratory data on admission were as follows: increased level of CRP, 12.0 mg/dl (normal values <0.3) and erythrocyte sedimentation rate, 97 mm/h (normal, 3–15); white blood cells, 9700/mm^3 (normal, 2800–8800), neutrophils, 7275/mm^3; lymphocytes, 1552/mm^3; hemoglobin, 9.8 g/dl (normal, 11.6–14); platelets, 51.6×10^4/mm^3 (normal, 17.4–37.1×10^4); coagulation tests within normal range; aspartate aminotransferase, 16 IU/l (normal, 13–33); alanine aminotransferase, 33 IU/l (normal, <6–27); total bilirubin, 0.2 mg/dl (normal, <1.0); lactate dehydrogenase, 100 IU/l (normal, 119–229); alkaline phosphatase, 740 IU/l (normal, 115–359); blood urea nitrogen, 7 mg/dl (normal, <9–20); creatinine, 0.5 mg/dl (normal, 0.5–1.0); serum iron, 11 μg/dl (normal, 45–145); ferritin, 152 ng/ml (normal, 8–120); immunoglobulin G, 1760 mg/dl (normal, 870–1700); immunoglobulin A and M within normal range; hemolytic complement (CH_{50}), 67.6 IU/ml (normal, 30–50); antinuclear antibodies, 160× (normal, less than 40×). No rheumatoid factor, anti-DNA, anti-RNP, anti-Sm, anti-Ro, anti-La, or anti-Scl-70 antibodies were detected using routine commercial enzyme-linked immunosorbent assay kits. Neither antineutrophil cytoplasmic antibody for proteinase-3 (PR3-ANCA) nor antineutrophil cytoplasmic antibody for myeloperoxidase (MPO-ANCA) was detected. Antimitochondria antibodies were not detected. Thyroid functions were normal. Urinalysis revealed no abnormalities. HLA loci determined by a conventional serological method were A2, A24, B35, B52, and DR15. Immunological fecal occult blood test was weakly positive.

Utilizing the diagnostic criteria from the Behçet Disease Research Committee of Japan (1987 revision), the patient's condition was diagnosed as possible BD. The high CRP level was considered to support the diagnosis of BD. Ophthalmologic examination revealed no abnormal findings, including iridocyclitis and chorioretinitis.

To confirm the diagnosis, gastrointestinal examinations were performed. Upper gastrointestinal endoscopy demonstrated only mild chronic gastritis without aphthoid ulceration and tumors. Total colonoscopy performed on April 9, 2004 demonstrated multiple nonhemorrhagic erosions in the cecum (Fig. 1) and whole ascending colon. The pathohistology of biopsied specimens demonstrated nonspecific inflammation. No open ulcer or Bauhin's valve deformity were observed, and the terminal ileum mucosa was intact. Abdominal CT performed on April 14 revealed colonic wall thickness in the same portions (Fig. 2A) and thickened wall of abdominal aorta (maximum 4 mm) in the lower portion of the celiac artery (Fig. 2B). Whole-body gallium scintigraphy performed on April 19 revealed a hot spot in the lower right abdomen that was considered as the cecum (Fig. 3).

Since mild bruit was audible in multiple regions, US was performed on April 13, 2004. Ultrasound revealed arterial

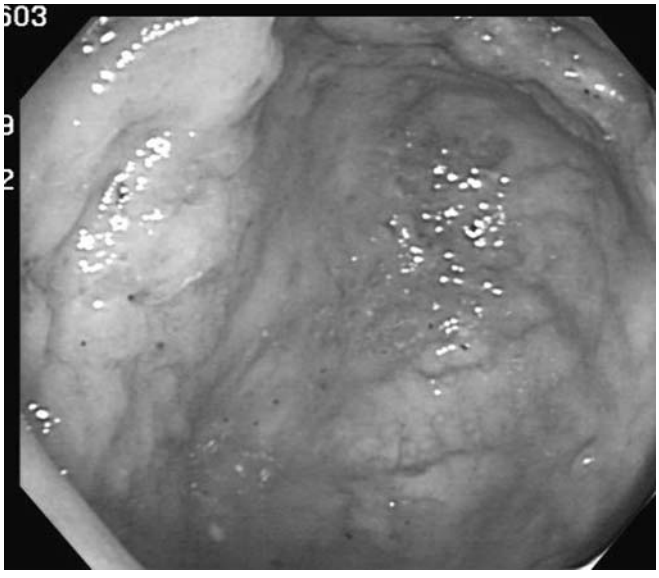

Fig. 1. Total colonoscopy performed on April 12 revealed multiple erosions of cecum without hemorrhage and ulceration

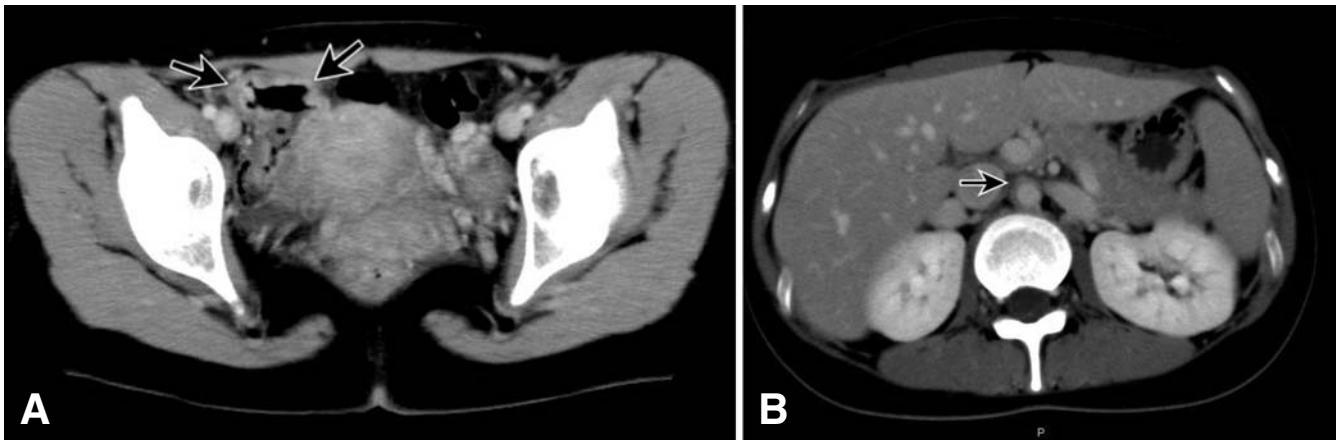

Fig. 2A,B. Abdominal computed tomography performed on April 14. **A** Colonic wall thickness in the cecum and whole ascending colon (*arrows*). **B** Thickened wall of abdominal aorta (maximum 4 mm) in the lower portion of the celiac artery (*arrow*)

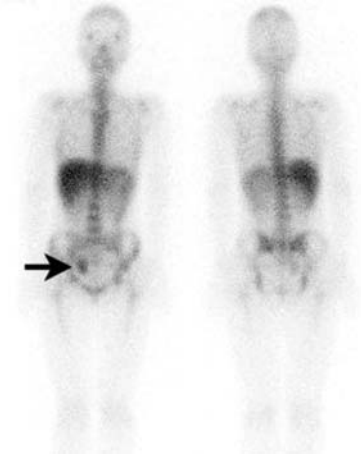

Fig. 3. Whole-body gallium scintigraphy performed on April 19 revealed a hot spot in lower right abdomen that was considered to be the cecum (*arrow*)

wall thickness and lumen irregularities in the bilateral common carotid artery, especially the left common carotid artery (Fig. 4A), and abdominal aorta, especially around the portion of the celiac artery (Fig. 4B). The celiac and superior mesenteric arteries were intact on US. On color Doppler US, a mild mosaic pattern figure was observed in the same regions. Magnetic resonance angiography performed on the same day from the aortic arch to the common carotid and vertebral arteries also revealed irregular thickness and stenosis in the bilateral common carotid arteries, and partial narrowing in the left subclavian artery (Fig. 5). Although abdominal MRA was performed, the images obtained were poor and worthless for evaluating the abnormality of the abdominal aorta. Computed tomographic angiography with MDCT performed on May 5 showed these arterial lesions more evidently (Fig. 6).

As a result of the aforementioned inspection, we diagnosed the patient to have incomplete type BD with characteristic positive symptoms – oral ulcers, genital ulcer, polyarthralgia, colonic erosions, and vascular lesions. Because the patient had colonic lesions and conspicuous multiarterial lesions, we concluded that more aggressive treatment was essential. Therefore, 20 mg/day of prednisolone and 1500 mg/day of mesalazine were administered orally, in addition to 1 mg/day of colchicine. Anticoagulation therapy was also performed with warfarin and aspirin. The therapy was successful and sporadic high fever was no longer evident. C-reactive protein levels decreased rapidly and turned negative, approximately 2 weeks after the treatment started. The oral ulcers disappeared. The genital ulcers did not deteriorate and ocular attack was not observed. By contrast, the bruit was audible in the patient's cervix and abdomen to the same extent as prior to treatment.

Discussion

The present case exhibited incomplete BD accompanied with colonic and arterial lesions. Expressly the arterial lesions were very impressive in this case because they were widespread in the left subclavian artery, abdominal aorta, and bilateral carotid arteries. The carotid arteries, in particular, are relatively less damaged in BD.[15,16] It has been reported that in the Japanese population, BD patients who have large vascular lesions comprise approximately 4% of all BD patients.[15] The arteries are damaged in about half of these cases.[15] However, the rate of mainly affected vessels differs with the various reports. Kabbaj et al. reported that 85% of the vascular involvements occurred in the venous circulation.[17] By contrast, Ko et al. reported an almost equal incidence of venous, arterial, and combined arterial and venous involvement.[16] It is plausible that any blood vessels may be affected in BD patients.

In the present case, intensive early examinations revealed conspicuous arterial lesions that were as yet asymptomatic. These lesions were very similar to those observed

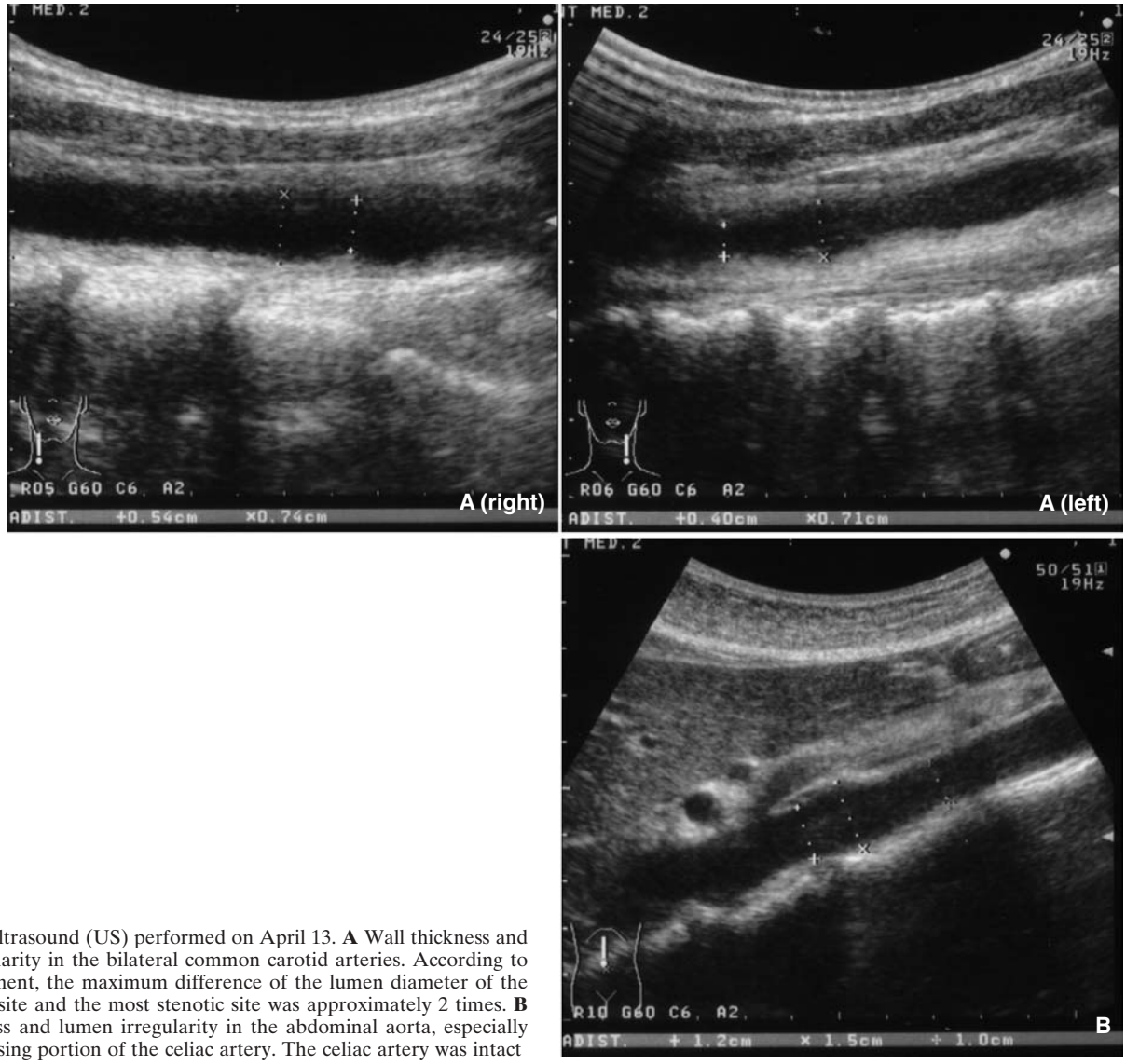

Fig. 4A,B. Ultrasound (US) performed on April 13. **A** Wall thickness and lumen irregularity in the bilateral common carotid arteries. According to US measurement, the maximum difference of the lumen diameter of the most dilated site and the most stenotic site was approximately 2 times. **B** Wall thickness and lumen irregularity in the abdominal aorta, especially around the rising portion of the celiac artery. The celiac artery was intact

in Takayasu arteritis regarding their distribution. The negative HLA-B51 and positive HLA-B52 seemed to support the diagnosis of Takayasu arteritis.[2,3] However, we diagnosed this patient's illness as vasculo-BD. The recurrent oral aphthoid lesions and genital ulcers were more plausible with the diagnosis of BD than Takayasu arteritis. Furthermore, a case of Takayasu arteritis complicated with oral lesions, genital ulcers, and colonic lesions has never been reported to our knowledge. Nakamura et al. described an HLA-B51-negative young BD female with multiarterial lesions that were very similar to Takayasu arteritis.[18] Recently, Sugimoto et al. reported the genetic association of positive HLA-B52 and abdominal aortic aneurysms that were not caused by Takayasu arteritis.[19] In our patient, the positive HLA-B52 might have played a role in the development of Takayasu arteritis-like lesions. Matsumoto et al. reported that histological granulomatous aortitis similar to Takayasu arteritis was observed in one vasculo-BD case.[20] Generally, pathological examination of the affected artery is not easy and even if it is carried out, the differential pathological diagnosis may be difficult. Although Seo et al. reported that the granulomatous reaction and the plasma cell infiltration were more pronounced in Takayasu arteritis compared with vasculo-BD, they also described that the aortic lesions based on the different diseases had the similar histologic features indistinguishable in terms of the clinical disease association.[21]

The usefulness of US, MRA, and CTA with MDCT for the evaluation of vascular lesions has already been well established. These examinations are noninvasive and easily repeatable, if necessary. Ultrasound has been adapted to cardiac, ocular, and vascular manifestations in BD patients. Ultrasound exhibits the favorable ability to examine arteritis lesions, in comparison with conventional angiography.[22] Recently, US has been used to treat aneurysms in the radial artery by percutaneous intra-aneurysmal thrombin injection.[23] Many studies have described the ultrasonographic findings of arterial lesions seen in Takayasu arteritis. Never-

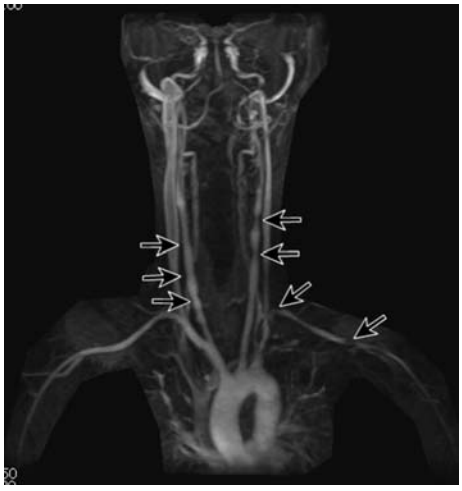

Fig. 5. Magnetic resonance angiography performed on April 13 revealed irregular dilatation and stenosis (*arrows*) in the bilateral common carotid arteries and partial narrowing in the left subclavian artery

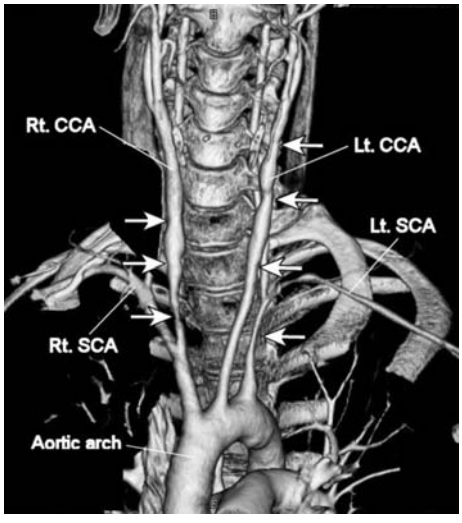

Fig. 6. Computed tomographic angiography with multiple detector-row computed tomography performed on May 5 showed evidence of arterial lesions; irregular dilatation and stenosis (*arrows*) in the bilateral common carotid arteries and diffuse narrowing in the left subclavian artery. *CCA*, common carotid artery; *SCA*, subclavian artery

theless, few studies to date have discussed the ultrasonographic findings of vascular lesions in vasculo-BD. The efficacy and advantages of MRA and MR imaging on vasculo-BD have been described in detail.[24,25] Magnetic resonance angiography usually reveals broad aspects of the arterial system, including deep arteries that US cannot reach, such as the pulmonary artery and intracranial arteries. To the best of our knowledge, no cases of vasculo-BD that were evaluated by three-dimensional (3D) reconstructed MRA have been reported. Recently, 3D-constructed multislice spiral CT has been used to assess vascular lesions, especially in the field of cardiology.[26–28] Recent reports have suggested that CTA with MDCT in the field of cardiology exhibits sufficiently high diagnostic capability compared with conventional angiography.[29,30] Therefore, CTA may be a helpful diagnostic tool in the field of rheumatology, such as in the diagnosis of vasculitic syndromes.

By contrast, general, conventional angiography requires special circumstances and techniques, as well as some risks such as unexpected hemorrhage and arterial wall injury. Magnetic resonance angiography, US, and CTA appear to be suitable for the detection and follow-up examination of vascular lesions in BD patients because of the low risk of iatrogenic complications. It is likely that conventional angiography may be superior to these noninvasive examinations in terms of precision and accuracy; however, we believe that the combination of these examination procedures involves a clinical usefulness equal to that of invasive angiography.

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