LETTERS

# Treatment of mesenteric angina with prolonged anticoagulation in a patient with antiphospholipid (Hughes) syndrome and coeliac artery stenosis

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Antiphospholipid (Hughes) syndrome (APS) is a prothrombotic disorder associated with venous and arterial thrombosis. Arterial stenosis, particularly affecting the renal, coeliac and intracerebral arteries, has been observed. Anticoagulation with international normalised ratio ⩾3 may be able to improve hypertension and the renal function. We report a patient with APS and abdominal angina due to coeliac artery stenosis, whose condition improved on prolonged anticoagulation treatment.

A 39-year-old Caucasian woman was diagnosed with systemic lupus erythematosus and secondary Sjögren's syndrome in 1999. Her lupus anticoagulant tests (dilute Russell viper venom test) were positive more than once. However, no previous thrombosis or pregnancy loss was reported. She was treated with hydroxychloroquine 200 mg once daily and aspirin 75 mg/day. In December 2003, the patient had epigastric pain that was worse on eating, especially large meals, and a weight loss of about 6 kg. Clinically, an epigastric bruit was noted. Gastrointestinal endoscopy and colonoscopy were normal. Mesenteric angina was suspected and magnetic resonance angiography (MRA) showed a very tight stenosis of the coeliac artery of >90% (fig 1). Both renal arteries, superior mesenteric artery and the abdominal aorta were normal. Investigations for classical causes of mesenteric angina—hypertension, hypercholesterolaemia and diabetes—were negative; body mass index was normal; the patient did not smoke; and no cardiac arrhythmia was noted. Treatment with warfarin was begun, with a target international normalised ratio (INR) of 3.0–4.0. The median INR was maintained at >3.0. Ten months later, the abdominal pain had improved, the patient's weight remained stable and repeat MRA showed no change in the coeliac artery stenosis. Twenty two months after the diagnosis of coeliac artery stenosis, the abdominal pain completely disappeared and the patient's weight returned to normal. It will be interesting to note the changes in the stenotic lesion on high-intensity anticoagulation when the patient is seen at follow-up next year.

Atherosclerotic coeliac artery stenosis usually occurs in elderly patients, smokers or patients with cardiac arythmia. Our patient did not have any of these risk factors. We avoided false-positive coeliac artery stenosis secondary to arcuate ligament syndrome, as our patient was investigated by MRA in suspended inspiration.[1] Antiphospholipid syndrome (APS) has recently been recognised in association with arterial stenosis[2–5] of the renal,[3] intracranial,[4] and coeliac or mesenteric[5] arteries. The arterial lesions seen in APS consist of smooth, well-delineated narrowing at the proximal segment, distinct from atherosclerosis and fibromuscular dysplasia lesions.[3] The underlying pathology and mechanism for these stenotic lesions are unknown, but may include thrombosis, accelerated atherosclerosis or proliferation of smooth muscle.[3] Our recent reports suggest that anticoagulation with high INR (>3.0) may reverse the renal artery stenosis, with subsequent improvement of hypertension and renal function.[2] These data suggested that thrombosis may be the basis for the development of coeliac artery stenosis in patients with APS. Although our patient never had any thrombosis, given her symptoms, positive lupus anticoagulant and coeliac artery stenosis, a consensus opinion about anticoagulation

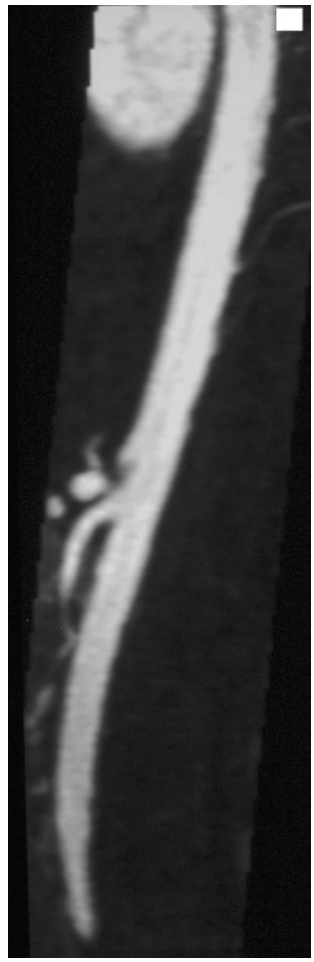

**Figure 1** Magnetic resonance angiography showing coeliac artery stenosis in a patient with antiphospholipid syndrome the arrow indicates celiac arrery stenasis.

**Abbreviations:** APS, antiphospholipid syndrome; INR, international normalised ratio; MRA, magnetic resonance angiography

was reached among treating doctors, consulting surgeon and the patient.

Treatment of chronic abdominal angina in patients with atherosclerotic vascular disease classically relies on revascularisation.[6] No effective medical treatment exists. Our observations constitute the first report on the clinical efficacy of prolonged anticoagulation in a patient with abdominal angina and coeliac artery stenosis. Although coeliac artery stenosis was still present 10 months after the introduction of anticoagulation, clinical signs improved and completely resolved 2 years later. As in renal artery stenosis, warfarin with a target INR of 3.0–4.0 may be considered in patients with coeliac artery stenosis and APS.

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# Evaluation of allele frequencies in the *PADI4* gene and anti-cyclic citrullinated peptide antibodies of patients with rheumatoid arthritis in a Japanese population

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A case–control linkage disequilibrium study in a Japanese population showed that the peptidyl arginine deiminase type 4 (*PADI4*) is a susceptibility locus for rheumatoid arthritis ($p<0.05$).[1] Ikari *et al*[2] also showed an association of the *PADI4* haplotype with rheumatoid arthritis in an independent Japanese study, but the relationship between the level of anti-cyclic citrullinated peptide (anti-CCP) antibodies and the haplotype has not been shown. Barton *et al*[3 4] and Caponi *et al*[5] could not validate the association in the UK or Caucasian French populations. The purpose of this study was to ascertain the relationship between levels of anti-CCP antibodies and *PADI4* allele frequencies in a Japanese population.

Of the 122 patients with rheumatoid arthritis, most were women (78.9%), the mean patient age was 56 (range 19–83 years) and 77.1% were positive for rheumatoid factor. The allele frequencies of four exonic single-nucleotide polymorphisms (SNPs; padi4_89*G/A, padi4_90*T/C, padi4_92*G/C and padi4_104*T/C) and one intronic SNP (padi_94*T/C) were investigated. The serum levels of anti-CCP antibodies were measured in these patients. The associations between anti-CCP antibodies and the five SNPs were tested using the $\chi^2$ test. One-way analysis of variance and the Bartlett test were used to determine statistical differences in levels of anti-CCP antibodies between intronic and exonic genotypes.

Anti-CCP antibodies were positive in 99 (81.2%) patients. The five SNPs were not associated with the presence of anti-CCP antibodies. The mean levels of anti-CCP antibodies were between 249.5 and 485.8 U/ml in each SNP. No association between levels of anti-CCP antibody and the five SNPs was seen. Similarly, the five SNPs were not associated with the presence of rheumatoid factor (table 1).

The allele frequencies of patients were comparable to those in a UK population.[3 4] Mori *et al*[6] showed that SNPs in *PADI4* had similar allele frequency among Caucasian, African-descent and Japanese populations. Suzuki *et al*[1] reported that a functional haplotype affects the stability of transcripts of *PADI4* and is associated with the presence of anti-CCP antibodies in 123 patients. However, they could not show an association of the susceptible allele frequencies with the levels of anti-CCP antibodies in 122 cases. The result was consistent with the UK study.[3 4] The discrepancy between our study and the previous Japanese studies[1 2] may be a result of the distribution of patients. In Japan, doctors and orthopaedic surgeons treat patients with rheumatoid arthritis in outpatient clinics. Patients with severe symptoms are often treated in the department of internal medicine rather than in the department of orthopaedic surgery, which may cause a bias in the Japanese studies. In our study, showing an association of the *PADI4* haplotype with rheumatoid arthritis, but without levels of anti-CCP in a Japanese population, other genes near *PADI4* may have an association with rheumatoid arthritis.

Patients with severe symptoms may show an association with a susceptibility haplotype on further investigation. The mechanism of collaboration between *PADI4* and other genes may be elucidated in the pathogenesis of rheumatoid arthritis.

**Abbreviations:** CCP, cyclic citrullinated peptide; PADI4, peptidyl arginine deaminase type 4; SNP, single-nucleotide polymorphism