A Postmenopausal Patient with Tangier Disease Developing Sjögren's Syndrome

To the Editor:

Tangier disease is a rare hereditary disease presenting with a deficiency of high density lipoprotein (HDL) and accumulation of cholesterol ester in the reticular endothelial tissues. Tangier disease was found to be caused by a homozygous mutation of the ATP-binding cassette transporter protein A1 (ABCA1) in 1999[1]. It is possible to identify the precise mutation site by genetic sequence analysis. We describe the possible association of Tangier disease with Sjogren's syndrome (SS) in a postmenopausal patient with anticentromere antibody (ACA) and a newly identified anti-inositol 1,4,5-trisphosphate receptors (IP_3R) antibody[2].

The patient initially presented with a low level of serum cholesterol in 1990 at age 35 years. She developed Raynaud's phenomenon in January 2005, and began complaining of severe fatigue. Apolipoprotein (apo) analysis showed an extremely low level of apo A-I, 1 mg/dl. Lipoprotein analysis indicated that she was deficient in fast- and slow-migrating HDL subfractions, and extremely low in levels of slow-migrating LDL[3]. There were 3 unusual aspects regarding this case, as follows.

First, she continued having Raynaud's phenomenon in the winter and even occasionally in the summer. However, skin manifestations such as sclerodactyly, generalized skin sclerosis, pigmentation, and depigmentation were not observed. Thus, she was not diagnosed as having systemic sclerosis. However, early-stage SS was suspected because of her dry mouth and eyes[4]. In addition to the ACA, anti-IP_3R antibodies were identified, for the first time. There are 3 types of IP_3R (anti-IP_3R1, anti-IP_3R2, and anti-IP_3R3), and the levels of all 3 were elevated to 146.7, 60.8, and 106.6 densimetric units, respectively, significantly higher than the normal averages of 75.8, 49.0, and 51.0[2]. These anti-IP_3R antibodies are often found in SS. Although our patient refused sialography examinations and lip biopsy, other serological and noninvasive procedures such as Schirmer and Saxon tests supported a diagnosis of SS[4].

Second, bilateral cystic ovarium and uteric myoma were removed from the patient in 1996 at the age of 43 years. She began to experience severe fatigue and widespread pain and could not leave the house by age 52 years. Although fibromyalgia (FM) could not be ruled out, postmenopausal impairment was strongly suspected because of the low estrogen level (14.1 pg/ml) and relatively high score (48 points) on the simplified menopausal index (SMI)[5]. Following estrogen replacement therapy, her SMI decreased to 30 points. Her postmenopausal symptoms improved so dramatically within 2 months that she was able to work as a saleswoman. She was found not to have any tender points among 18 areas and hormone replacement therapy (HRT) relieved her complaint of depression. Thus, she was diagnosed as having not FM, but rather postmenopausal depression[6].

Regarding the third unusual aspect, extremely low levels of HDL-C led to a tentative diagnosis of apo A-I-deficient disease and Tangier disease. Genetic analyses revealed a homozygotic mutation in ABCA1 at the 913 amino acid position, where K(AAG) was converted into a stop codon (TAG). The ABCA1 gene contains 2 transmembrane domains and 2

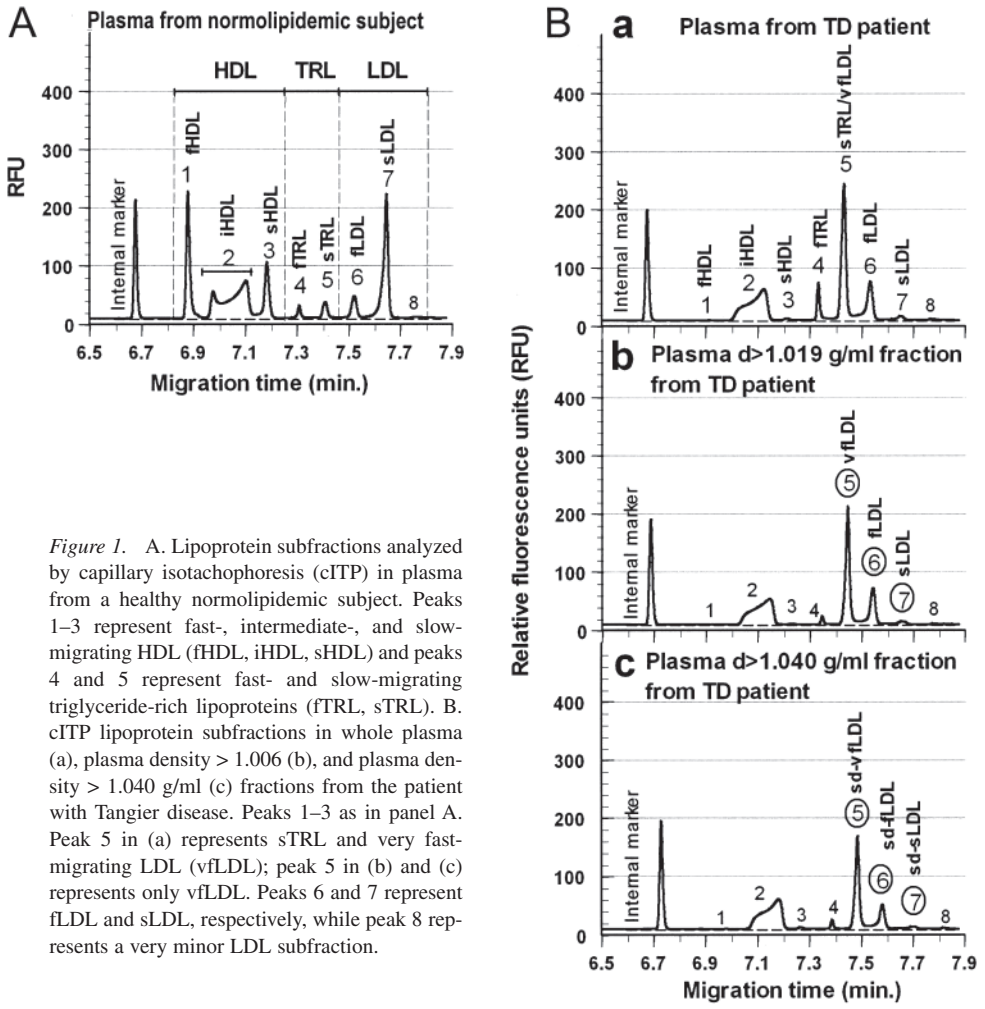

Figure 1. A. Lipoprotein subfractions analyzed by capillary isotachophoresis (cITP) in plasma from a healthy normolipidemic subject. Peaks 1–3 represent fast-, intermediate-, and slow-migrating HDL (fHDL, iHDL, sHDL) and peaks 4 and 5 represent fast- and slow-migrating triglyceride-rich lipoproteins (fTRL, sTRL). B. cITP lipoprotein subfractions in whole plasma (a), plasma density > 1.006 (b), and plasma density > 1.040 g/ml (c) fractions from the patient with Tangier disease. Peaks 1–3 as in panel A. Peak 5 in (a) represents sTRL and very fast-migrating LDL (vfLDL); peak 5 in (b) and (c) represents only vfLDL. Peaks 6 and 7 represent fLDL and sLDL, respectively, while peak 8 represents a very minor LDL subfraction.

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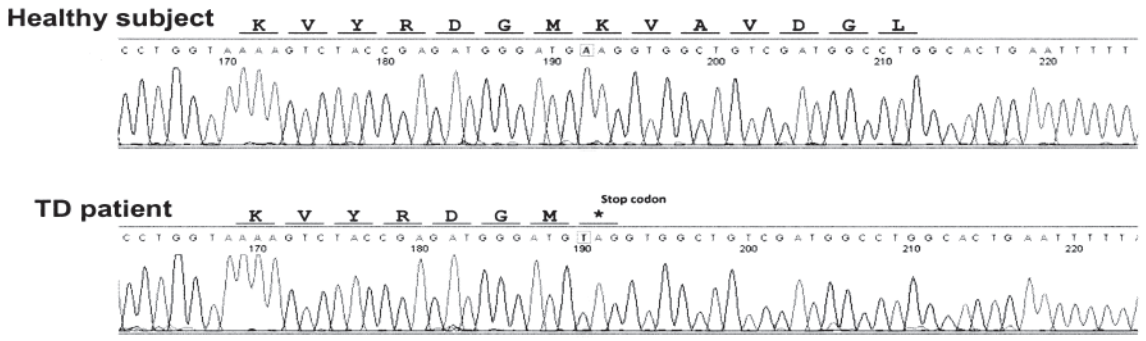

Figure 2. All 50 exons of the ABCA1 gene were analyzed. A novel homozygous A>T non-sense point mutation was identified at nucleotide 2737 in Exon 19, resulting in the introduction of a stop codon in place of amino acid K at position 913 on the ABCA1 position.

nucleotide-binding fold (NBF) domains[7]. This homotype gene anomaly causes severe dysfunction following deletion of the 2 NBF domains and one transmembrane domain. A variety of non-sense and mis-sense abnormalities in ABCA1 have been reported in the extracellular loop and 2 NBF[8]. Recent studies suggest that amino acid abnormalities in the C-terminal are more critical for ABCA1 dysfunction[9].

Our patient had never had a history of shortness of breath or chest pain, and her electrocardiogram, ultrasound cardiogram, and ultrasound survey of carotid artery showed no evidence of abnormalities. However, diminished HDL-C, apo B/apo A-I ratio > 95, atherogenic charge-modified LDL and small dense LDL, and relatively high titers of anti-IP_3R suggested a risk of developing coronary heart disease in the future. Recently, we reported a case of localized cutaneous systemic sclerosis (lc-SSc) in a female smoker having very high titers of anti-IP_3R antibodies subsequently developing acute myocardial infarction[10]. We suspected that endothelial cells might be so injured by heavy smoking that anti-IP_3R antibodies could access IP_3R on the surface of the endoplasmic reticulum. HRT had been administered, but because it is a known risk factor for coronary heart disease and breast cancer after the age of 63 years[11] it was decided to terminate its use before the patient turned 60.

Finally, there have been 31 cases of Tangier disease reported in Japan, but this is only the second such case developing connective tissue disease. This association is thought to be more than merely incidental. Further studies are needed to elucidate this mechanism.

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