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CASE REPORT

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Prospective study of a systemic sclerosis/dermatomyositis overlap patient presenting with anti-Ku and anti-Ki antibodies

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Abstract A 60-year-old woman visited the Keigu Clinic in January 1998 complaining of morning stiffness and flexion contracture of the distal interphalangeal joint. Blood tests showed the presence of antinuclear antibody at a 1:40 dilution with speckled staining. She was suspected of having Heberden's node. Nine months later, she developed Raynaud's phenomenon, sclerodactyly, and Gottron's sign, and was diagnosed with systemic sclerosis/dermatomyositis (SSc/DM) overlap. Blood tests revealed the presence of antinuclear antibody at a 1:5120 dilution, along with high titer of anti-Ku and anti-Ki antibodies. Subsequently, the patient developed interstitial pneumonia in January 2000. It is thought that the appearance of antinuclear antibody and development of other immunological events played an important role in determining this patient's limited SSc/DM overlap.

Key words Anti-Ku antibody · Immunoprecipitation · Prospective study · Systemic sclerosis/dermatomyositis (SSc/DM) overlap

Introduction

Anti-Ku antibody was initially reported by Mimori et al.[1] as a marker antibody in patients with an overlap syndrome of systemic sclerosis and dermatomyositis (SSc/DM). This antibody has also been found in approximately 10% of patients in the USA with systemic lupus erythematosus (SLE).[2] Ku antigen itself is a heterodimer composed of 70-kDa and 80-kDa subunits that bind to the ends of double-stranded DNA through its leucine zipper structure,[3] and moves along the DNA to repair damaged regions.[4,5] Recently, it has been demonstrated that the Ku antigen is an activation factor for DNA-dependent protein kinase, and is involved in DNA repair and V(D)J recombination.

Recently, we followed a patient prospectively, who went on to develop anti-Ku antibody during the course of an illness, and we report on our findings.

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Case report

A 60-year-old woman visited the Keigu Clinic in January 1998 with bilateral swelling, flexion contracture of the index finger distal interphalangeal (DIP) joint, and morning stiffness. Blood biochemistry and peripheral blood tests were all normal. Rheumatoid factor was negative. However, antinuclear antibody (ANA) was positive at a 1:40 dilution with a speckled staining pattern, and her erythrocyte sedimentation rate (ESR) at 31 mm/h and CRP at 0.7 mg/dl were both slightly elevated. A tentative identification of Heberden's node was made at that time. In October 1998, the patient again came to the clinic with complaints of general fatigue, Raynaud's phenomenon, and sclerodactyly with flexion contracture of the proximal interphalangeal (PIP) joint of all fingers. Her ANA became positive at a 1:5120 dilution with a speckled staining pattern, and she was suspected of having systemic sclerosis. Therefore, it was decided to further analyze her ANA. Subsequently, anti-Ku antibody was found to be positive at a 1:64 dilution, and anti-Ki antibody was found to be positive at a 1:256 dilution as determined by double immunodiffusion. This patient was having difficulty getting out of bed, and in June 1999 she was referred to Yokohama Municipal Hospital for further evaluation of a possible SSc/DM overlap. Her height

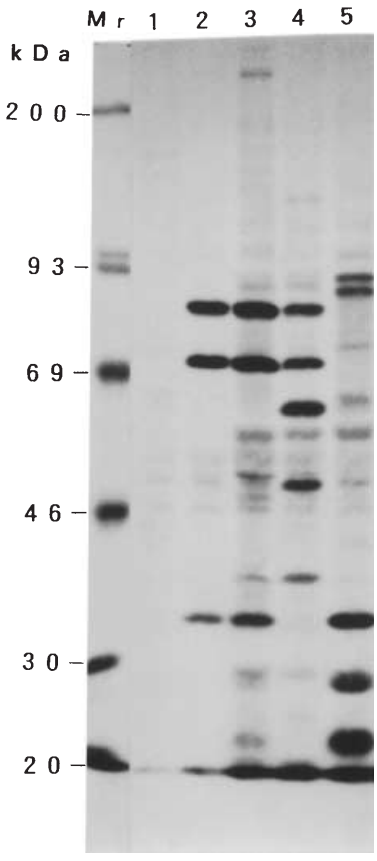

Fig. 1. Immunoprecipitation of anti-Ku antibodies reacting with ^{35}S methionine-labeled HeLa cell extracts. The patient's serum in lane 2 and the other two systemic lupus erythematosus (SLE) sera containing anti-Ku antibodies in lanes 3 and 4 immunoprecipitated 80/70-kDa doublet proteins. Bands at 34 kDa in lanes 2 and 3 were precipitated from anti-Ki antibodies. Bands at 90/86 kDa and other bands in lane 5 were precipitated from anti-NOR 90 and anti-U1 RNA antibodies used as molecular weight controls

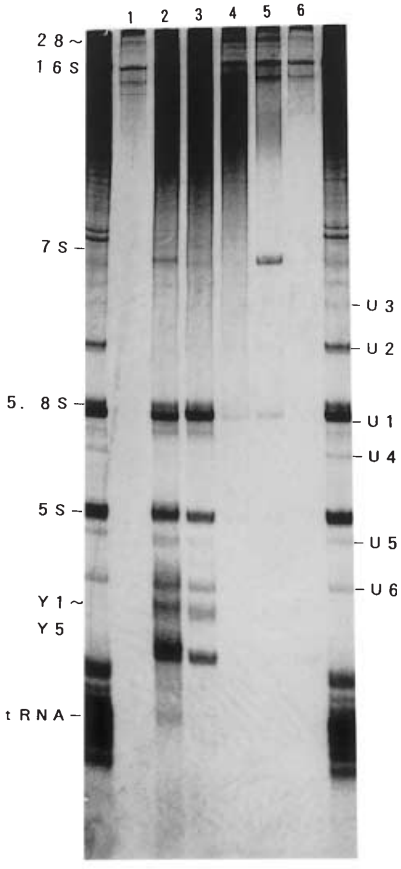

Fig. 2. Immunoprecipitation of anti-Ku antibodies reacting with unlabeled nucleic acid. The patient's serum in lane 4 did not immunoprecipitate significant RNA bands, but instead yielded a high molecular weight nucleic acid smear. Two SLE sera containing anti-Ku antibodies in lanes 2 and 3 immunoprecipitated significant RNA bands corresponding to anti-SS-A/Ro and ant-SS-B/La. A serum containing antinucleolar antibody was placed in lane 5

(162 cm) and weight (56 kg) were within normal limits. Her face was tight and shiny, and resembled a mask. Anemia and icterus were not observed. Her heart and breathing sounds were within normal limits. Her abdomen was slightly distended, and a scar from an earlier appendectomy was observed on the lower right abdomen. Flexion contracture of the PIP joints and sclerodactyly up to the PIP joints were prominent, and Gottron's sign over the knuckled area was suspected. Pigmentation and depigmentation of her forearm were also observed. A slight muscle atrophy of the limb girdle area was seen.

At the time of admission, 5 mg prednisolone was administered. A muscle biopsy was not performed since it was judged that there was sufficient muscle strength remaining, and more critically, because consent could not be obtained. Immuno-precipitation using ^{35}S methionine-labeled Hela cells was used to evaluate autoantibody (Fig. 1). The patient serum placed in lane 2 immunoprecipitated 80/70-kDa doublet proteins, which were suspected of being the Ku antigen, and a 34-kDa protein which was suspected of being the Ki antigen. SLE sera known to possess anti-Ku antibody were placed in lanes 3 and 4, and they immunoprecipitated the same doublet proteins. Normal serum was placed in lane 1.

RNA determination was made by immunoprecipitation of unlabeled cells followed by silver staining (Fig. 2). The patient's serum placed in lane 4 did not immunoprecipitate any distinct RNA bands, but a high molecular weight smear of degraded DNA, which is characteristic of anti-Ku, was seen. Sera from two anti-Ku-positive SLE patients placed in lanes 2 and 3 precipitated 7S, 5.8S, and 5S RNA, which are thought to represent SS-B antigen, and hY1–hY5 RNA, which is thought to represent SS-A antigen, along with a high molecular weight nucleic acid smear. Normal sera were placed in lanes 1 and 6.

The patient caught a cold in December 1999 and medication was prescribed. However, her condition did not improve, and a chest X-ray showed an elevation of the bilateral diaphragm and a faint linear shadow in the bilateral lower lung field. Interstitial pneumonia was suspected. Her levels of KL6 fluctuated between 919 and 960 U/ml. The patient had denied sicca symptoms, severe muscle weakness, or dyspnea upon exertion until recently (Fig. 3).

Discussion

We do not know exactly when this patient developed the SSc/DM overlap. However, judging by the elevation of aspartate aminotransferase (AST) (GOT) levels, we think it occurred sometime after July 1998. Her ANA was not tested on a continuous basis during this period. Typical SSc/DM overlap symptoms, including Raynaud's phenomenon, sclerodactyly, and Gottron's signs were observed, along with a high titer of anti-Ku in October 1998, on her fourth visit to the clinic. It should be noted that because we could

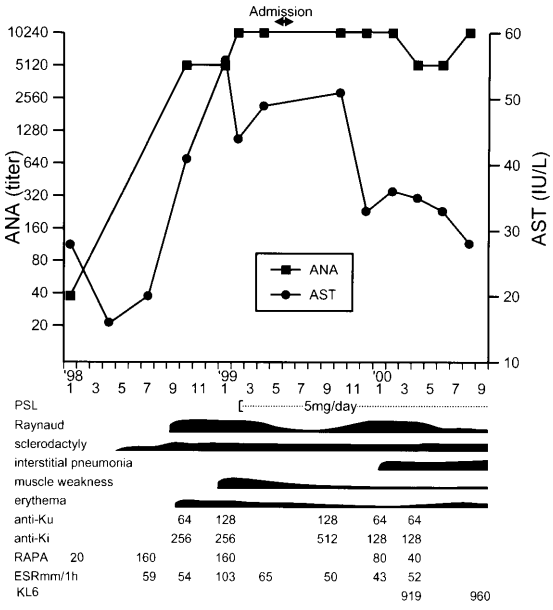

Fig. 3. Clinical course of the patient, who presented with anti-Ku and anti-Ki antibodies. Titers were determined by double immunodiffusion. *AST*, asparate aminotransferase; *ANA*, antinuclear antibody; *PSL*, prednisolone; *ESR*, erythrocyte sedimentation rate; RAPA, rheumatoid arthritis particle agglutination

not obtain the patient's consent, not all of Bohan's diagnostic criteria for DM[6] were fulfilled, and as a result our diagnosis of SSc/DM has to be described as tentative. However, we think we have accumulated enough circumstantial evidence to make this highly probable. We hypothesize that the appearance of ANA and other immunological events played an important role in determining the clinical manifestations in such a short period of time. Anti-Ku antibodies have been observed in patients with such syndromes as SSc/DM overlap. As for this particular patient, she also had anti-Ki antibody, which is found in a small percentage of patients with SLE and Sjögren's syndrome.[7,8] We believe that an overlap with SLE or Sjögren's syndrome can be ruled out in this case since the patient had no clinical nor laboratory findings of SLE, and since her sialography and lip biopsy results were both negative.

Unfortunately, sera from this patient's first three visits to the clinic were not kept. It is therefore impossible to determine the immunological progression of her disease retrospectively.

The functions of Ku antigen have recently been established. Ku antigen can bind to the ends of dsDNA in conjunction with a DNA-dependent protein kinase (DNA–PK),[9] and play a role in the repair of damaged DNA and V(D)J recombination in B and T cell activation.[10] However, many of the complicated functions of Ku antigen remain to be determined, and this must be done before a complete clinical interpretation of the significance of anti-Ku antibody can be made.

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