Anticardiolipin Antibodies in Crohn's Disease Associated with Diabetes Mellitus

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We present a 58-year-old man with hyperglycemic subcoma. His blood glucose level was 1,163 mg/100 ml on admission and the data of the coagulate system revealed abnormalities in the prothrombin time, fibrinogen and serum fibrin degradation products. Continuous intravenous insulin infusion therapy (CIH) was performed, and a satisfactory recovery of consciousness level and blood glucose level were obtained. Further examination revealed the patient had Crohn's disease (CD) associated with IgG and IgM anticardiolipin antibodies (aCLs). The patient was treated with corticosteroid hormones and salazosulfapyridine, and the abnormalities in the coagulate system returned to the normal range and aCLs eventually disappeared. It was speculated that in such a case, anticardiolipin antibody may play a role in the pathogenesis of CD. (Internal Medicine 35: 866–870, 1996)

Key words: hyperglycemic subcoma, coagulate system, thrombosis

Introduction

While the pathogenesis of Crohn's disease (CD) remains unknown, certain features of this disease have been suggested (1), and thromboembolic complications have reported to be frequent in CD (2–12). On the other hand, anticardiolipin antibody (aCL), which is a direct antibody against anionic phospholipids (2), was first detected in a case of systemic lupus erythematosus (SLE) with thrombosis (13); thereafter aCL was described in patients with CD (3, 11). Here, we report a case of CD, in which the patient's first symptom was hyperglycemic subcoma associated with aCLs, which disappeared following excellent clinical improvement by treatment with corticosteroid hormones and salazosulfapyridine.

Case Report

A 58-year-old Japanese man was admitted to our hospital with hyperglycemic subcoma on September 20, 1994. The patient's and his family's medical histories were not contributive to diabetic subcoma. From September 14, 1994, he had suffered from a high fever of 38°C, and polyuria and polydipsia appeared day by day. The patient had no history of abdominal pain, diarrhea or bloody stools before admission. Initial examination showed blood pressure of 124/80 mmHg and a regular pulse rate of 100/min. His body temperature was 37.8°C, and

consciousness level was 10 on the Japanese coma scale (14). Lung and heart sounds were clear. Anemia and icterus were not revealed on palpebral and bulbar conjunctiva. A hard fist-sized mass was palpable in the right lower abdomen with no spontaneous pain or tenderness. The laboratory data on admission were as follows (Table 1): white blood cell count, 20,500/mm³; red blood cell count, 495 × 10⁴/mm³; hemoglobin level, 15.2 g/100 ml; platelet count, 33.0 × 10⁴/mm³; serum sodium, 122 mEq/l; serum potassium, 6.9 mEq/l; serum chloride, 81 mEq/l; blood glucose, 1,163 mg/100 ml; and HbA1c, 7.4%. Urinalysis revealed glycosuria and ketonuria. C-reactive protein was 10.3 mg/100 ml. The arterial blood gas data were pH 6.996, HCO₃⁻ 3.1 mmol/l, and BE -28.4 mmol/l. The data of the blood coagulate system as follows: prothrombin time, 36%; activated partial thromboplastin time, 40 second; fibrinogen, 558 mg/100 ml; and serum fibrin degradation products, 30.1 µg/ml. Examination of eye fundus revealed no abnormalities.

Ketotic diabetic subcoma was diagnosed, and CIH treatment was started. Following the start of treatment, the patient's consciousness level and blood glucose level immediately improved, as shown in Fig. 1. A plain abdominal roentgenogram showed enlargement of the sigmoid colon (Fig. 2). A computed tomographic scan of the pelvic region showed enlargement of the colon (Fig. 3). A barium enema of the colon revealed serrated mucosa, a cobblestone appearance and a longitudinal ulcer in the sigmoid colon, and no involvement in rectum (Fig.

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Table 1. Laboratory Data on Admission

Hematology		Blood glucose	1,163 mg/100 ml
White blood cell	20,500/mm ³	Hemoglobin A1c	7.4%
Band neutrophil	13%	Serum osmolality	371 mOsm/kg
Segmented neutrophil	65%		
Red blood cell	495 × 10 ⁴ /mm ³	Urinalysis	
Hemoglobin	15.2 g/100 ml	Protein	(±)
Hematocrit	50.7%	Glucose	(4+)
Platelets	33.0 × 10 ⁴ /mm ³	Ketone body	(2+)
Erythrocyte sedimentation rate	22 mm/h	Occult blood	(3+)
		Serology	
Blood chemistry		C-reactive protein	10.3 mg/100 ml
Total protein	6.6 g/100 ml	Arterial blood gas	
Albumin	4.24 g/100 ml	pH	6.996
Blood urea nitrogen	65.8 mg/100 ml	PaCO ₂	12.6 mmHg
Creatinine	2.1 mg/100 ml	PaO ₂	135 mmHg
Blood uric acid	11.9 mg/100 ml	HCO ₃ ⁻	3.1 mmol/l
Total bilirubin	0.4 mg/100 ml	BE	-28.4 mmol/l
Aspartate aminotransferase	45 KU	Others	
Alanine aminotransferase	49 KU	Urine C-peptide	6.1 µg/day
Lactate dehydrogenase	388 WU	Coagulation test	
Alkaline phosphatase	14.3 KA	Prothrombin time	36%
γ-glutamyltransferase	42 IU/l	Activated partial prothrombin time	40 sec
Sodium	122 mEq/l	Fibrinogen	558 mg/100 ml
Potassium	6.9 mEq/l	Serum fibrin degradation products	30.1 µg/ml
Chloride	81 mEq/l		
Calcium	4.8 mEq/l		
Inorganic phosphate	10.1 mg/100 ml

Figure 1. The change of blood glucose. BG: blood glucose, CIII: continuous intravenous insulin infusion therapy, CI: conventional insulin therapy, ○: BG level was 1,163 mg/100 ml on admission.

Figure 2. Abdominal plain X-ray film on admission showed the enlargement of sigmoid colon (◄).

Figure 4. The barium enema of the colon on November 2, 1994 showed serrated mucosa (◄), cobblestoned appearance (◄) and longitudinal ulcer (◄) of the sigmoid colon.

Figure 3. Pelvic CT on October 7, 1994. Enlarged colon was noted (◄).

Figure 5. The colonoscopic biopsy specimen obtained from the ulcer bed of the sigmoid colon. Non-caseating granuloma was recognized (HE stain, x200).

4). A barium enema of small bowel was not performed. Colonoscopy, performed on November 21, 1994, showed the sigmoid colon had a cobblestone appearance, with a longitudinal ulcer and severe stenosis, which was impossible to observe

further. Colonoscopic biopsy specimens from the sigmoid colon revealed non-caseating granuloma (Fig. 5). Immunological examination revealed no other abnormalities, except for positive results of IgG and IgM aCLs and histocompatibility

Table 2. Immunological Examination on October 18, 1994

CH50	40.4 CH50 U/ml
ANA	(-)
anti DNA antibody	<1.0 IU/ml
anti Sm antibody	(-)
anti RNP antibody	(-)
RA test	(-)
Lupus anticoagulant	(-)
IgG anticardiolipin antibody*	3.9
IgM anticardiolipin antibody*	6.6
anti Insulin antibody	5.7%
anti islet antibody	(-)
HLA • DR4	(+)

ANA: anti nuclear antibody, HLA: histocompatibility antigen, RA: rheumatoid arthritis, RNP: ribonucleo-protein. *: assay was done by the means of enzyme linked immunosorbent assay and it's normal range was under 1.0, (-): negative result, (+): positive result.

antigen (HLA) DR4 (Table 2). Based on the results of these examinations, the patient was diagnosed as diabetes mellitus (DM) with aCL-associated CD. Corticosteroid hormone treatment (900 mg/day intravenous infusion of hydrocortisone) was started on October 5. The abnormalities in the coagulate system returned to normal 5 days after the start of treatment. Salazosulfapyridine treatment was started on November 17, and his clinical course markedly improved and aCLs eventually changed to negative as shown in Fig. 6. Colonoscopy on January 23, 1995 showed almost normal mucosa in the lower sigmoid colon, although severe stenosis was still present. The patient was discharged on February 29, 1995.

Discussion

CD is very difficult to distinguish from ischemic colitis (15). In the present case, the patient had a high fever of unexplained origin with no bowel symptoms or extracolonic manifestations such as arthritis or liver disease antedating or overshadowing the bowel involvement (16), and a cobblestone appearance and a longitudinal ulcer were revealed by a barium enema and colonoscopy (16). Colonic mucosal biopsy also revealed granuloma (16). Based on these clinical and histological findings, we thought it may be reasonable to diagnose this case as CD.

Vianna et al were the first to report a case of CD associated with aCL (3). Later, Chamouard et al reported that the aCL was present in about 20% of CD cases (2). The presence of aCL is observed in the active or quiescent phase of CD (8), and the presence of aCL is not related to episodes of thrombotic events

(2). Although the inflammation process in CD can sometimes explain the increased thrombotic risk, it is thought that the presence of aCL may accelerate the thrombotic mechanism, because aCL is considered to reveal potentially thrombogenic cellular alterations (2). In the present case, the abnormalities in the coagulate system were decreased prothrombin time and increased serum fibrinogen, which is the most frequently reported hemostasis abnormality and an important risk factor for arterial thrombosis (11), and increased serum fibrin degradation products. Thromboembolic episodes were not observed. Although it has been reported that the presence of aCL may be associated with genetic factors, such as HLA DR7 or DRW53 (2), in the present case, only DR4 was recognized by the examination of HLA. On the other hand, Matake et al reported that DR4 is generally recognized in Japanese CD patients (17). It was also reported that DR4 and DR53 are more frequent in aCL-positive CD patients (18). The present case presented two interesting problems. The first is that DM and CD occurred at the same time. Although it is uncertain whether one was an accidental complication of the other, it may be speculated that the possibility of outcome of these two diseases at the same time, because the pathogenesis of one of these two diseases has been recognized as an abnormal immunological mechanism (1, 2) and these two diseases have the same hereditary factor, such as DR4 (18, 19). To the best of our knowledge, there are no case reports of both DM and CD occurring concurrently. The second problem is the change of aCL in the clinical course. It was reported that treatment with corticosteroid hormones seems to reduce the level of aCL (2). In the present case, aCL was positive in the active phase but following the clinical improvement by treatment with corticosteroid hormones and salazosulfapyridine, aCL became negative (Fig. 6). The abnormalities in the coagulate system in our case returned to normal following treatment with corticosteroid hormones. It was uncertain whether the abnormalities in the coagulate system in our case were due to DM or CD, as abnormalities in the coagulate system in DM have been reported (20). It has been demonstrating that CD granuloma often have a vascular origin, that intestinal microvessels could participate in the initiation of such lesions, and that microthrombotic episodes may play a role in the development of intestinal ulcerations (12). It was thus speculated that aCL, in our case, may play a role in the mechanism of vascular injury in CD.

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Figure 6. Clinical course. The improvement of body temperature, C-reactive protein and white blood cell were followed by the treatment. In this table, the dose of corticosteroid hormone was revealed as converted dosage of prednisolone, which maximum dose was 180 mg/day and maintenance dose 17.5 mg/day. aCL: anticardiolipin antibody, BT: body temperature, CRP: C-reactive protein, WBC: white blood cell.

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