Case Report
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Congenital Analbuminemia in a Korean Male Diagnosed with Single Nucleotide Polymorphism in the ALB Gene: The First Case Reported in Korea

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Congenital analbuminemia (CAA) is an autosomal recessive disease characterized by extremely low serum levels of albumin. CAA is caused by various homozygous or heterozygous mutations of the *ALB* gene. Patients often exhibit no clinical symptoms, aside from rare accompanying conditions, such as fatigue, ankle edema, and hypotension. This case report describes the case of a 28-year-old asymptomatic Korean male referred to our center with hypocalcemia, vitamin D deficiency, and hypoalbuminemia who was diagnosed with CAA. To determine the cause of hypoalbuminemia in the patient, laboratory tests, radiological examination, and DNA sequencing were performed. The patient was confirmed to not exhibit any other clinical conditions that can induce hypoalbuminemia and was diagnosed with CAA using DNA sequencing. The present case of CAA is the first to be reported in Korea.

Key Words: Hypoalbuminemia; hypocalcemia; vitamin D deficiency; sequence analysis, DNA

INTRODUCTION

Congenital analbuminemia (CAA) is an autosomal recessive disease characterized by extremely low levels of serum albumin without specific causes that can induce hypoalbuminemia (i.e., reduced protein synthesis due to hepatic dysfunction or re-distribution of protein aside from loss of protein from blood vessels in the kidneys or gastrointestinal tract). Since the absence of key serum proteins in adults can be partially offset by increased synthesis of other serum proteins, this condition is usually considered to be benign. Therefore, patients with CAA typically only exhibit very mild clinical symptoms, such as fatigue, ankle edema, and hypotension.[1-4]

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CAA diagnosis relies on the elimination of other clinical conditions that can lead to hypoalbuminemia and sequencing of the *ALB* gene to detect mutations. In all reported cases, a mutation in *ALB* located on chromosome 4 (4q11-13) has been identified as a driver of CAA and is induced by homozygous or heterozygous DNA deficiency.[5]

CASE REPORT

In January 2018, a 28-year-old Korean male visited Department of Endocrinology, Seoul National University Bundang Hospital because of hypoalbuminemia, hypoproteinemia, hypocalcemia, and vitamin D deficiency that had been detected during a health check-up. The patient had not been experiencing physical discomfort. There was no relevant personal or family medical history. Height and weight were 170 cm and 63 kg. Physical examination revealed a blood pressure of 107/70 mm Hg, pulse rate of 70 per minute, respiration of 18 per minute, and body temperature of 36.8°C. Cardiovascular, respiratory, abdominal, and neurological assessments produced normal outcomes.

Blood test outcomes indicated normal complete blood

counts and electrolytes. In addition, liver function test and thyroid function test outcomes were normal. Blood abnormalities were hypoproteinemia, hypoalbuminemia, moderate hypocalcemia, vitamin D deficiency, and elevated parathyroid hormone (PTH) and alkaline phosphatase (ALP) levels.

We performed kidney function, complement, spot urine, and albuminuria tests to eliminate the possibility of nephrotic syndrome, and the outcomes were normal. All laboratory test outcomes are summarized in Table 1. A kidney ultrasound examination revealed kidneys of normal size with normal parenchyma. Esophagogastroduodenoscopy outcomes were normal, and the patient did not exhibit suspicious symptoms of protein loss (e.g., diarrhea). The patient showed elevated PTH levels and underwent a parathyroid scan, which proved normal. Dual energy X-ray absorptiometry confirmed a normal level of bone density: Z-scores were -1.0 [bone mineral density (BMD) 0.703 g/cm^2] on the left femoral and -0.8 (BMD 0.858 g/cm^2) on the spine (Fig. 1).

Serum protein electrophoresis was performed to detect low albumin concentrations and compensatory increases of non-albumin proteins, especially α1 and α2 globulin fractions (Table 1). To confirm the diagnosis of CAA at the molecular level, we performed *ALB* mutation analysis. DNA sequencing revealed a novel mutation of heterozygous single nucleotide polymorphism (SNP) causing C>T transition at position c.1668 C>T, p.Leu556= in the *ALB* gene (Fig. 2).

Daily oral consumption of calcium 500 mg and vitamin D 1000 IU was commenced to treat hypocalcemia and vitamin D deficiency. At an outpatient follow-up visit after 3 months, the physical examination outcomes were still normal. Blood 25(OH)D levels had increased from 2.4 to 19.3 ng/mL. PTH levels had decreased from 234 to 141 pg/mL, and ALP levels had decreased from 116 to 104 IU/L. Throughout five outpatient follow-up visits, serum albumin concentrations remained below 2.2 g/dL, and no specific clinical symptoms or signs were evident.

This study was approved for exemption of subject consent by Seoul National University Bundang Hospital Institutional Review Board (IRB No. B-1905/538-701).

Table 1. Laboratory Findings

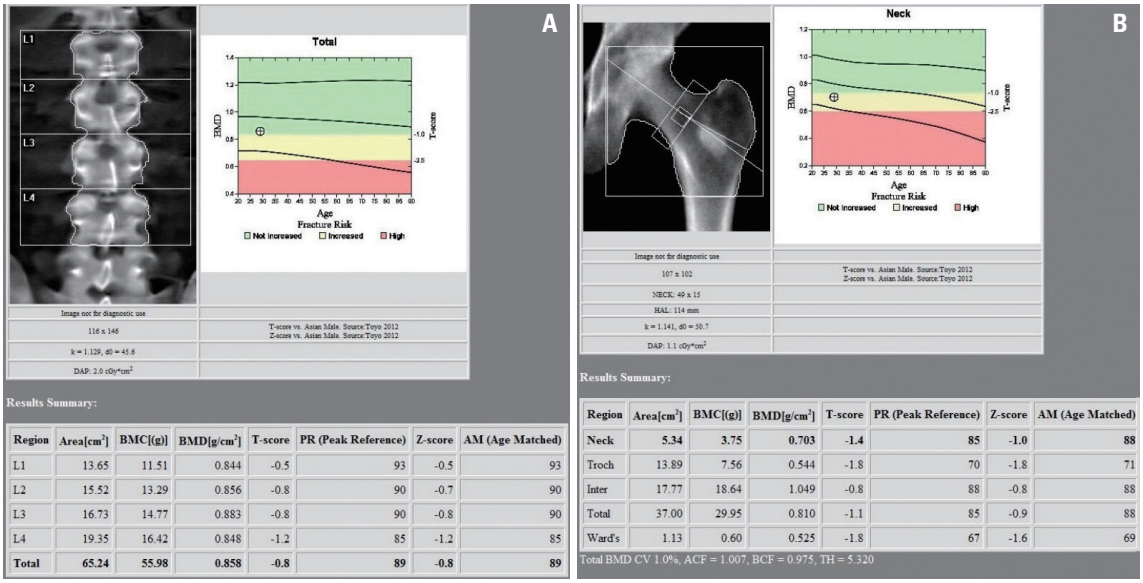
Analyte	Results	Normal reference range
Hemoglobin (g/dL)	15.7	13–17
White blood cells (1000/μL)	3.6	4.0–10.0
Platelets (1000/μL)	142	130–400
Blood urea nitrogen (mg/dL)	10.0	10–26
Creatinine (mg/dL)	0.69	0.7–1.4
Na/K (mmol/L)	143/4.4	135–145/3.5–5.5
Serum total protein (g/dL)	3.6	6.0–8.0
Serum albumin (g/dL)	2.2	3.3–5.2
α1 globulin (relative) (%)	2.4–4.4	9.7
α2 globulin (relative) (%)	6.0–10.7	20.4
β1 globulin (relative) (%)	4.6–6.7	6.4
β2 globulin (relative) (%)	3.3–6.3	5.0
γ globulin (relative) (%)	12.6–22.2	8.6
Total bilirubin (mg/dL)	0.37	0.2–1.20
AST (IU/L)	38	0–40
ALT (IU/L)	15	0–40
Total cholesterol (mg/dL)	140	0–200
LDL cholesterol (mg/dL)	77	55–155
HDL cholesterol (mg/dL)	37	35–55
Triglycerides (mg/dL)	62	0–150
Calcium (mg/dL)	6.5	8.8–10.5
Ionized calcium (mmol/L)	1.015	1.05–1.35
Phosphate (mg/dL)	3.5	2.5–4.5
ALP (IU/L)	116	30–115
25(OH)D (ng/mL)	2.4	>20
IgG (mg/dL)	248	700–1700
IgA (mg/dL)	54	90–400
IgM (mg/dL)	71.9	45–230
Lactate dehydrogenase (IU/L)	185	100–225
C3 (mg/dL)	85	70–150
C4 (mg/dL)	28	10–35
Urine ACR (mg/g)	<1.46	<30
Urine microalbumin (mg/dL)	<0.3	<15
Urine protein (mg/dL)	74	1–114
PTH (intact) (pg/mL)	234	8–76
fT4 (ng/dL)	1.05	0.93–1.70
TSH (μIU/mL)	3.07	0.27–4.20

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALP, alkaline phosphatase; 25(OH)D, 25-hydroxy vitamin D; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; C3, complement component 3; C4, complement component 4; urine ACR, urine albumin to creatinine ratio; PTH (intact), intact parathyroid hormone; fT4, free thyroxine; TSH, thyroid stimulating hormone.

DISCUSSION

The diagnosis of CAA is typically based on hematological indices, serum protein electrophoresis, and genetic analysis. Serum albumin concentrations can vary from 1 to 10 g/dL.[1] CAA is extremely rare, with approximately 70 cases reported worldwide. The cases are constantly being updated in the albuminemia registry.[5] Thus far, all molecular level studies on CAA have indicated that a mutation in the *ALB* gene near the centromere of chromosome 4 (4q11-13, 74269972–74287129) is the driver of this disease. The *ALB* gene is located on chromosome 4 and is divided into 15 exons by 14 introns.[6] Identification of various mutations causing the onset of CAA suggests that the disease is genetically heterogeneous.[5,6]

CAA is a risk factor of high morbidity and mortality during pregnancy and infancy, indicating that albumin plays a critical role in the prenatal and perinatal periods.[7,8] However, since a low level of serum albumin can be partially supplemented by increased levels of other serum proteins, CAA in adults does



Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
L1	13.65	11.51	0.844	-0.5	93	-0.5	93
L2	15.52	13.29	0.856	-0.8	90	-0.7	90
L3	16.73	14.77	0.883	-0.8	90	-0.8	90
L4	19.35	16.42	0.848	-1.2	85	-1.2	85
Total	**65.24**	**55.98**	**0.858**	**-0.8**	**89**	**-0.8**	**89**

Region	Area[cm²]	BMC[(g)]	BMD[g/cm²]	T-score	PR (Peak Reference)	Z-score	AM (Age Matched)
Neck	**5.34**	**3.75**	**0.703**	**-1.4**	**85**	**-1.0**	**88**
Troch	13.89	7.56	0.544	-1.8	70	-1.8	71
Inter	17.77	18.64	1.049	-0.8	88	-0.8	88
Total	37.00	29.95	0.810	-1.1	85	-0.9	88
Ward's	1.13	0.60	0.525	-1.8	67	-1.6	69

Total BMD CV 1.0%, ACF = 1.007, BCF = 0.975, TH = 5.320

Fig. 1. Bone mineral density (BMD) in the patient with congenital analbuminemia at the lumbar spine (A) and left femur (B). L1, lumbar spine 1; L2, lumbar spine 2; L3, Lumbar spine 3; L4, Lumbar spine 4; DAP, dose area product; HAL, hip axis length; BMC, bone mineral content; Troch, trochanter; Inter, intertrochanter; Ward's, Ward's triangle; CV, coefficient of variation; ACF, autocorrelation function; BCF, bias correction; TH, total hip.

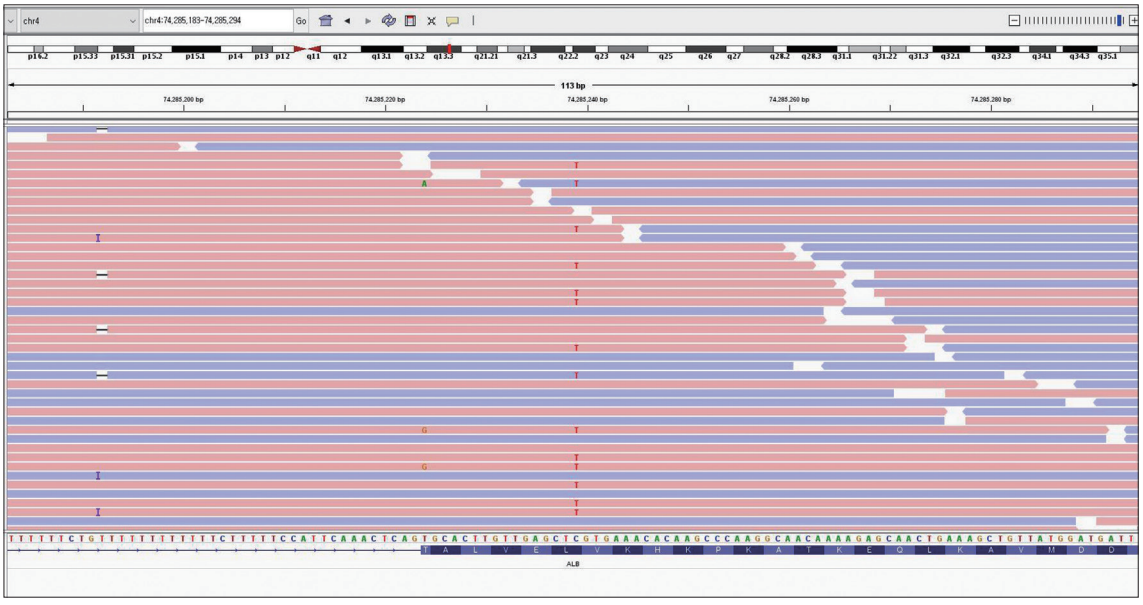


Fig. 2. *ALB* gene mutation analysis reveals NM_000477.5(*ALB*): c.1668C>T, p.Leu556=, heterozygote. chr4, chromosome 4; bp, base pair.

not result in clear symptoms and, thus, is considered a relatively benign disease. The benign features of CAA often lead to a misdiagnosis or delayed diagnosis of this rare condition.[9]

Serum albumin is a key transporter of serum calcium. Approximately 45% of circulating calcium is attached to serum albumin.[2] It is expected that a patient with low serum albumin concentrations will exhibit low levels of total serum calcium despite having normal levels of biologically active ionized calcium.[2] In addition, serum albumin acts as a transporter of vitamin D. The majority of 25(OH)D and 1,25-Dihydroxyvitamin D circulating in the bloodstream is tightly bound to the vitamin D binding protein, 10–15% is bound to albumin, and <1% of circulating vitamin D exists in an unbound form.[10] Therefore, hypoalbuminemia may have effects on vitamin D deficiency. Nonetheless, hypocalcemia and vitamin D deficiency are thought to rarely affect the bone density of healthy young males (as in this case report), although they may have more severe effects in different age groups.[7,8]

The only limitation of this study was that the medical history of family members could only be assessed via question-answer interviews. We could not confirm the history of hypoalbuminemia in the patient's family members, and the presence of ge-

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netic mutations could not be assessed.

The 28-year-old Korean male patient harbored a heterozygous SNP c.1668C>T, p.Leu556= in the *ALB* gene. The patient presented with hypoalbuminemia with accompanying hypocalcemia and vitamin D deficiency, but no other clinical symptoms. Continued interest in this rare disease and efforts in genetic diagnosis will contribute to uncovering the molecular genetic basis of CAA.

AUTHOR CONTRIBUTIONS

Conceptualization: Sung Hee Choi. Data curation: Youngji Kim. Formal analysis: Youngji Kim. Investigation: Sung Hee Choi. Methodology: Sung Hee Choi. Project administration: Sung Hee Choi. Resources: Ye Seul Yang, Cheol Min Shin, Man Jin Kim, and Sung Sup Park. Software: Youngji Kim and Sung Hee Choi. Supervision: Sung Hee Choi. Validation: Youngji Kim and Sung Hee Choi. Visualization: Sung Hee Choi. Writing the original draft: Youngji Kim and Sung Hee Choi. Manuscript review and editing: Sung Hee Choi. Gene analysis: Sung Sup Park.

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