

# World Journal of *Clinical Cases*

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## Efficacy of abatacept treatment in a patient with enteropathy carrying a variant of unsignificance in *CTLA4* gene: A case report

Ugur Musabak, Tuba Erdoğan, Serdar Ceylaner, Emre Özbek, Nuretdin Suna, Binnaz Handan Özdemir

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### Abstract

#### BACKGROUND

Cytotoxic T Lymphocyte Antigen-4 (CTLA4) deficiency is a genetic defect that causes a common variable immunodeficiency (CVID) clinical phenotype. Several studies have reported an association between CTLA mutations or variants and various autoimmune diseases. Targeted therapy models, which have become increasingly popular in recent years, have been successful in treating CTLA4 deficiency. In this article, we discuss the clinical outcomes of abatacept treatment in a patient with CTLA4 and lipopolysaccharide-responsive beige-like anchor (LRBA) variants that was previously diagnosed with CVID.

#### CASE SUMMARY

A 25-year-old female patient, who was visibly cachectic, visited our clinic over the course of five years, complaining of diarrhea. The patient was diagnosed with ulcerative colitis in the centers she had visited previously, and various treatments were administered; however, clinical improvement could not be achieved. Severe hypokalemia was detected during an examination. Her serum immunoglobulin levels, CD19<sup>+</sup> B-cell percentage, and CD4/CD8 ratio were low. An endoscopic

examination revealed erosive gastritis, nodular duodenitis, and pancolitis. Histopathological findings supported the presence of immune mediated enteropathy. When the patient was examined carefully, she was diagnosed with CVID, and intravenous immunoglobulin treatment was initiated. Peroral and rectal therapeutic drugs including steroid therapy episodes were administered to treat the immune mediated enteropathy. Strict follow-ups and treatment were performed due to the hypokalemia. After conducting genetic analyses, the *CTLA4* and *LRBA* variants were identified and abatacept treatment was initiated. With targeted therapy, the patient's clinical and laboratory findings rapidly regressed, and there was an increase in weight.

## CONCLUSION

The heterozygous *CTLA4* variant identified in the patient has been previously shown to be associated with various autoimmune diseases. The successful clinical outcome of abatacept treatment in this patient supports the idea that this variant plays a role in the immunopathogenesis of the disease. In the presence of severe disease, abatacept therapy should be considered until further testing can be conducted.

**Key Words:** Common variable immunodeficiency; Abatacept; *CTLA4* antigen; Case report

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**Core Tip:** In this article, a 25-year-old female patient who applied to our outpatient clinic with the complaints of severe diarrhea and weight loss is presented. As a result of the clinical examination, laboratory tests and histopathological examinations, the patient was diagnosed with common variable immunodeficiency with severe enteropathy. Variants of uncertain significance were detected in 1 cytotoxic T lymphocyte antigen-4 (*CTLA4*) gene region and 2 lipopolysaccharide-responsive beige-like anchor gene regions in the patient who underwent Whole Exome Sequencing test. Although these polymorphisms have been listed as non-pathogenic in the variant database, their association with some autoimmune diseases had been shown in the literature before. *CTLA4*-Ig fusion protein, which had been shown to be effective in these autoimmune diseases, was administered to our patient without delay and a dramatic improvement was achieved in clinical findings.

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## INTRODUCTION

Cytotoxic T lymphocyte antigen-4 (*CTLA4*) deficiency is an autosomal dominant primary immunodeficiency disease, in which both parental copies of the related gene must be healthy for adequate expression[1]. This disorder is also referred to as *CTLA4* haploinsufficiency. This molecule, which has an inhibitory function, is constitutively expressed in activated conventional and regulatory T cells (Tregs). The main function of *CTLA4* is to compete with the CD28 molecule for binding to CD80/86, which is expressed on antigen-presenting cell (APC) surfaces. T cell activation induced by the CD28 molecule is controlled by *CTLA4*; therefore, unpreventable T cell activation and autoimmunity may occur during *CTLA4* deficiency. Hence, this molecule is an essential regulator of T cell immunity.

*CTLA4* deficiency affects many systems and causes dysfunction in some organs due to T lymphocyte accumulation[2]. The main organs affected by lymphocytic infiltration are the lungs, liver, intestine, bone marrow, lymph nodes, and spleen. Consequently, signs and symptoms appear depending on the organ affected by the disease. These patients are prone to autoimmune diseases and are at high risk of developing lymphoma.

Lipopolysaccharide-responsive beige-like anchor (*LRBA*) deficiency is inherited from both parents in an autosomal recessive pattern[1]. This molecule has a protective role against the degradation of *CTLA4* in lysosomes. In addition, *LRBA* recycles *CTLA4*-containing vesicles in the plasma membrane. Thus, *LRBA* deficiency disrupts the trafficking of *CTLA4*-containing vesicles through cells and their expression on the cell surface. Consequently, the disease phenotype of *LRBA* deficiency is similar to that of *CTLA4* deficiency. The risks of autoimmunity, lymphoproliferation, and malignancy increase in the absence of molecules involved in the same pathway.

Abatacept comprises the extracellular domain of *CTLA4* and the Fc portion of IgG1 (a *CTLA4*-Ig fusion protein)[3]. Abatacept terminates T cell activation by binding to the co-stimulatory molecules, CD80 and CD86, on APCs. Thus, this agent blocks activation signals by interfering with the interaction between CD28 and these co-stimulatory molecules. Recently, considerable success has been achieved with abatacept, which is a targeted therapeutic agent, for the treatment of *CTLA4* and *LRBA* deficiencies[4].

Common variable immunodeficiency (CVID) is a multifactorial disease characterized by antibody deficiency, recurrent infections, autoimmunity, and malignancy[5]. High-resolution genetic analyses, especially in cases of CVID complicated by inflammatory bowel disease, have revealed that the underlying genetic defects are often *CTLA4* haploinsufficiency and *LRBA* deficiency[5,6]. Most patients with these genetic defects experience diarrhea and weight loss. Here, we report a



patient with severe immune-mediated enteropathy carrying a variant of uncertain significance in the *CTLA4* gene, whose clinical findings improved almost completely after abatacept therapy.

## CASE PRESENTATION

### Chief complaints

Five years prior to this report, a 25-year-old female patient visited our outpatient clinic complaining of watery stools at least 15 times a day. Accompanying complaints included abdominal pain, bloating, nausea, and appetite loss. The patient stated that the consistency of her stool increased from time to time; however, in most cases, it smelled poorly and had an oily appearance, and was bloody and contained mucus.

### History of present illness

The patient stated that she had been experiencing these symptoms for five years and had been diagnosed with infectious diarrhea or ulcerative colitis at various centers. The patient had received treatment; however, did not benefit from the treatment and the symptoms remained, resulting in dramatic weight loss.

### History of past illness

The patient's past history was unremarkable.

### Personal and family history

There was no family history of these symptoms. There was also no consanguinity between parents.

### Physical examination

Upon physical examination, the patient appeared cachectic. She was 168 cm tall and weighed 46 kg [Body mass index (BMI): 16.3]. She presented with pale skin and conjunctiva, dry skin and tongue, and a post-nasal purulent discharge was also observed. Auscultation revealed a 2/6 systolic murmur without radiation in the mitral focus and wheezing in the middle and lower zones of both lungs. Dullness was detected in the Traube area using percussion. Neither rebound nor defense was detected in the abdominal quadrants. Hypoactive bowel sounds were observed when listening through a stethoscope. Numerous painless and mobile lymphadenopathies were observed in the cervical, axillary, and inguinal regions, the largest of which was less than 1 cm in diameter.

### Laboratory examinations

Upon the patient's first admission, the results of the blood tests were as follows (the values measured outside the reference range are given in bold, and the reference ranges are given in parentheses).

A complete blood count with differential was performed; white blood cells:  $5.72 \times 10^3/\mu\text{L}$  (4.5–11), neutrophils:  $3.84 \times 10^3/\mu\text{L}$  (2–7.8), lymphocytes:  $1.37 \times 10^3/\mu\text{L}$  (1–4), monocytes: 0 (0–1), eosinophils: 0 (0–1), basophils:  $0.042 \times 10^3/\mu\text{L}$  (0–0.2), hemoglobin: 9.9 gr/dL (12–16), hematocrit: 60.51% (35–46), and platelet count:  $209 \times 10^3/\mu\text{L}$  (150–400).

All routine biochemical parameters measured in the venous blood were within normal limits, with the exception of the albumin level [2.78 g/L (3.5–5)], the total calcium level [7.5 mg/dL (8.4–10.2)], the potassium level [2.5 mmol/L (3.5–5.2)] and the phosphorus level [1.9 mg/dL (2.3–4.7)]. The C-reactive protein level was 28 mg/L (0–5), and the erythrocyte sedimentation rate (ESR) was 54 mm/hr (0–15). The fecal calprotectin level was  $> 1800 \mu\text{g/g}$  stool ( $< 50$ ).

The pituitary and sex hormone levels were low in the luteal period of the cycle LH: 0.3 mIU/mL (5–20), FSH: 1.72 mIU/mL (2–10), Estradiol: 26.5 pg/mL (29–318), Progesterone: 0.7 ng/mL (3–20). Other hormone levels; ACTH: 5 pg/mL (9–56), Cortisol (morning): 0.8  $\mu\text{g/dL}$  (4–22), free T3: 1.2 pg/mL (1.71–3.71), free T4: 0.63 ng/dL (0.7–1.48), TSH: 0.273 mIU/mL (0.4–4.8).

### Immunological examinations

The serum levels of all major immunoglobulin isotypes were low during outpatient clinic admission. IgG: 4.15 g/L (6.52–16.31), IgA: 0.29 g/L (0.65–4.21), IgM: 0.23 g/L (0.33–2.93), and total IgE:  $< 1 \text{ IU/mL}$  ( $< 87$ ). The serum levels of the IgG subgroups were below the normal limits: IgG1: 3.05 g/L (4.05–10.11), IgG2: 1.73 g/L (1.69–7.86), IgG3: 0.62 g/L (0.11–0.85) and IgG4: 0.17 g/L (0.03–2.81). After retrospectively examining the laboratory results of the patient, it was found that the levels of the major serum immunoglobulins 4 mo prior were similar to the most recent measurements. The patient's blood group was Rh + A, and the anti-B antibody titer was positive (+ + + +). The anti-hepatitis B antibody level was 511.3 U/L ( $< 10 \text{ U/L}$ ). The percentages of CD4<sup>+</sup> T cells 18.2% (24.2–54.4), CD19<sup>+</sup> B cells 3.3% (6.5–20.6), and the CD4/CD8 ratio 0.25% (0.7–3.6) were lower than the normal limits, while the percentages of CD3<sup>+</sup> T cells 71.8% (51.3–83.5) and CD3<sup>+</sup>CD16<sup>+</sup>CD56<sup>+</sup> NK cells 21.9% (3.7–28.5) were found within reference ranges. The percentage of CD8<sup>+</sup> T cells 55.2% (12.8–40.2) was higher than the reference limits.

All auto-antibodies (anti-dsDNA, anti-histon, anti-RNP, anti-Sm, anti-SSA, anti-SSB, anti-Scl-70, anti-PM/Scl, anti-Jo1, anti-CENP-B, anti-PCNA, anti-nucleozom, anti-Rib-P-protein, anti-DFS70, anti-tissue transglutaminase, anti-endomysial, anti-gliadin) investigated using indirect immunofluorescence or immunoblot methods were negative. It should be kept in mind that in case of deficiencies of IgG and/or IgA, the autoantibodies can be observed as negative.

### Microbiological examinations

In the sputum culture, *Pseudomonas Aeruginosa* growth was observed, and antibiotic treatment as oral levofloxacin 500 mg daily dose was administered to clear the infection. No bacteria, viruses, parasites, or parasitic eggs were detected in the stool tests.

### Imaging examinations

Splenomegaly and enlargement of the para-aortic lymph nodes were detected using whole abdominopelvic ultrasonography and computed tomography. Peribronchiolar reticular and ground-glass infiltrations consistent with acute bronchiolitis were observed in the lower lobe of the right lung and the basal segments of the right middle lobe using high-resolution chest computed tomography.

No pathological observations were made from the radiological images of the pituitary and adrenal glands.

### Endoscopic examinations

Upper and lower gastrointestinal tract endoscopies were performed due to the persistent diarrhea and treatment-resistant hypokalemia (Figure 1). An endoscopic examination revealed erosive gastritis, nodular duodenitis, and pancolitis.

### Histopathological examinations

Histopathological examination of the duodenal biopsy specimen revealed features of active chronic duodenitis, characterized by villous blunting and expansion of the lamina propria due to mononuclear inflammation. In addition, an increase in the number of intraepithelial lymphocytes was observed. A colon biopsy revealed significant nodular lymphoid hyperplasia and a Graft-versus-Host Disease-like pattern with increased crypt epithelial apoptosis throughout the mucosa (Figure 2). These histopathological features indicated immune-mediated enteropathy.

### Genetic and flow cytometric analyses

Targeted sequencing using next-generation sequencing technology was used for molecular diagnosis. A custom panel including STAT1, STAT3, STAT5B, CTLA4, LRBA, IL2RA, and FOXP3 was used for analysis. Although heterozygous polymorphisms (A2692T and S2797L) were identified in exons 54 and 56 of LRBA, a heterozygous polymorphism (T17A) was found in exon 1 of CTLA4. Pathological results were analyzed using flow cytometry at the expression level. Accordingly, the level of CTLA4 expression in the patient's PHA-stimulated CD3<sup>+</sup> T cells was lower than that in healthy control (3.2 *vs* 16.6).

## FINAL DIAGNOSIS

Considering the 2014 ESID criteria, the patient was diagnosed with CVID.

## TREATMENT

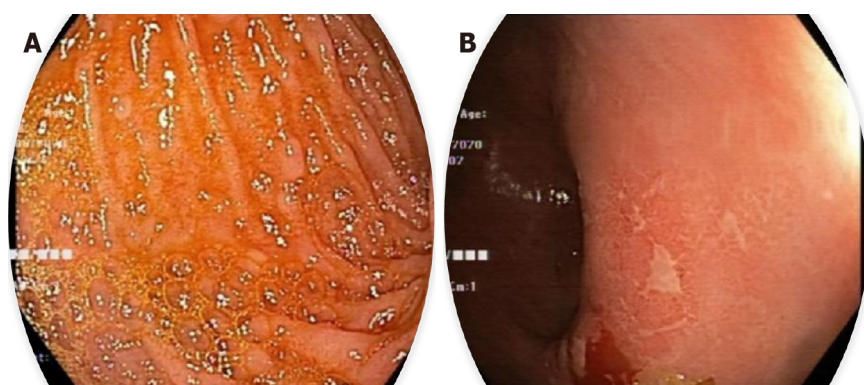
Intravenous immunoglobulin (IVIG) treatment was initiated at a dose of 600 mg/kg every three weeks. Peroral and rectal therapeutic agents (*i.e.*, methylprednisolone and mesalamine) were administered to treat the immune mediated bowel disease. Both intravenous and peroral potassium were used to treat life-threatening hypokalemia. After the genetic results were obtained, abatacept (CTLA-4-Ig fusion protein) treatment was started subcutaneously at a dose of 125 mg every two weeks. After a clinical response was observed in the third month of treatment, abatacept treatment was continued at the same dose once per month. At present, the patient is still being followed-up asymptotically with abatacept and IVIG treatment.

## OUTCOME AND FOLLOW-UP

Three months after initiating the abatacept treatment, the patient exhibited decreased stool frequency and an increase in appetite. In the sixth month of treatment, her endoscopic and histopathological findings had regressed, and she had gained 11 kg.

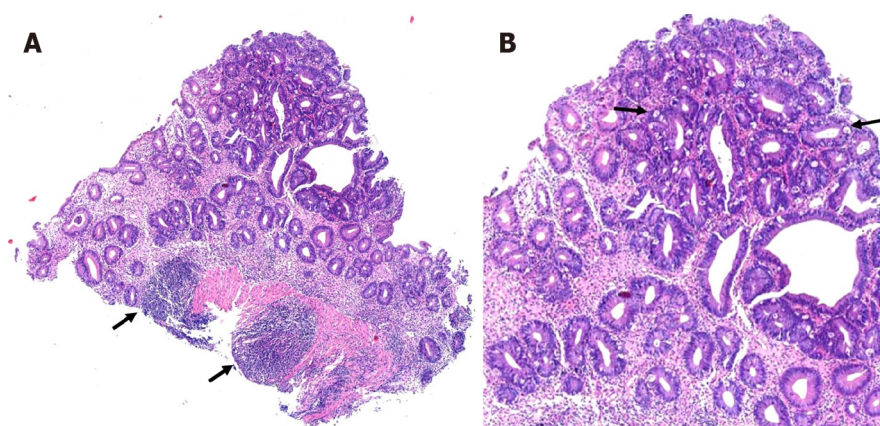
## DISCUSSION

In our case, the CTLA4 (T17A) and LRBA (A2692T, S2797L) variants were defined as benign in the ClinVar database (ClinVar). The A/G polymorphism at position 49 (codon 17) in exon 1 of CTLA4 results in a Thr17-to-Ala (T17A) substitution[7]. The +49 A/G polymorphism has been extensively studied in autoimmune diseases. In two consecutive meta-analyses, the +49 A/G polymorphism was found to be associated with susceptibility to systemic lupus erythematosus[8]. In addition, there are two reports that have suggested a relationship between the A allele of CTLA-4 +49 A/G and



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**Figure 1 Endoscopic examinations.** A: After performing a gastroduodenoscopy, erosive gastritis was observed. The mucosa in the bulbous and 2<sup>nd</sup> part of the duodenum was edematous and nodular; B: After performing a colonoscopy, we found that the severity was variable, the mucosa in all colon segments, including the rectum, was edematous and hyperemic, the vascular structure was lost, it was sensitive to the touch, and erosion and ulceration had occurred in places. The ulcers were millimeter in size, superficial and covered with exudate.



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**Figure 2 Panoramic view of colonic mucosa.** A: Arrows point to the enlarged and increased number of lymphoid follicles (lymphoid hyperplasia) (HE, 2 $\times$ ). No atypia of lymphoid cells was noted. The lamina propria expanded with the infiltration of immune cells, such as lymphocytes, plasma cells, and macrophages. The number of crypts diminished focally (HE, 20 $\times$ ); B: The arrows point to the increased crypt epithelial apoptosis in a Graft-versus-Host Disease-like pattern. The lamina propria expanded with predominantly mononuclear inflammatory cell infiltration (HE, 200 $\times$ ).

susceptibility to celiac disease[9,10]. In one of these studies, this polymorphism was found to predispose patients to celiac disease, independent of HLA[9]. Another autoimmune disease that was found to be associated with the *CTLA4* +49 A/G polymorphism is rheumatoid arthritis[11].

Abatacept, which is a *CTLA4*-Ig fusion protein, is a biologic agent that has been approved by the Food and Drug Administration for the treatment of rheumatoid arthritis[4]. Accordingly, we initiated abatacept treatment after genetic analyses were performed. Dramatic regression was observed in the clinical and laboratory findings shortly after abatacept treatment, with a 25% increase in weight within six months. Previous studies have also reported the successful use of this biological agent in LRBA deficiency and *CTLA-4* haploinsufficiency[1,4].

Collen *et al*[4] reported two patients with *CTLA-4* deficiency who were successfully treated with abatacept. Both patients were diagnosed with celiac disease prior to genetic diagnosis. Heterozygous mutations, c.457+2T>C and c71\_72del (in exon 1), in the *CTLA4* gene of the patients were identified using DNA sequencing. Despite following a gluten-free diet and undergoing various immunosuppressive treatments, the clinical course of these patients was severe. However, after abatacept treatment, the clinical findings of the patients were controlled.

As for the LRBA deficiency, Boz *et al*[12] reported a boy with early-onset refractory autoimmune gastritis with a biallelic mutation (c.C6415T p.R2139X in exon 42 and c.C7315T p.R2439X in exon 49) in the LRBA gene (chr 4; NM\_006726; NP\_006717) with whom long-term clinical remission had been achieved after abatacept treatment. In another report, Maggiore *et al*[13] presented a case of LRBA deficiency due to a homozygous mutation (c.1963C>T) in LRBA and unusual late-onset enteropathy. This patient had an atypical onset of LRBA deficiency with persistent fever, giant cervical lymphadenopathy, hepatosplenomegaly, and hypertransaminemia. Despite the use of high-dose intravenous immunoglobulins and various immunosuppressive drugs, treatment was unsuccessful. When abatacept treatment was initiated after genetic diagnosis, the clinical findings regressed and the effectiveness of the immunosuppressive drugs increased. In a multi-center study conducted by Kiykim *et al*[14], the long-term efficacy of abatacept was investigated in 22 patients

with LRBA deficiency, and a superior clinical response was obtained in most patients when compared to previous therapies.

The LRBA polymorphisms detected in our patient were not associated with any particular disease in the genetic databases. Therefore, we concluded that the success achieved with abatacept treatment was not related to this variant. However, it has been reported that abatacept treatment provides improvement in patients with autoimmune diseases and immunodeficiencies due to LRBA deficiency[14].

## CONCLUSION

The rapid recovery of our patient after abatacept treatment suggests that the polymorphic variant that we detected may be pathogenic. In adult patients with CVID and severe inflammatory complications of the gastrointestinal system, abatacept therapy should be considered as soon as CTLA4 variants are detected. However, further functional studies and intrafamilial segregation analyses are required to interpret the pathogenicity of these variants. These studies should be swiftly performed, as the results may help to better understand and define the pathophysiological and clinical consequences of the disease.

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## FOOTNOTES

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