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CASE REPORT

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A Rare Case Report: ICOS and WIPF1 Mutation Together in A Patient

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ABSTRACT

The inducible T-cell costimulator (ICOS) deficiency was first described in 2003. Autosomal re-cessive inherited ICOS deficiency is classified as combined immunodeficiency (CID) and has a wide clinical spectrum including hypogammaglobulinemia, recurrent infections, enteropathies, autoimmunity, lymphoproliferation, and malignancy. WAS/WASL Interacting Protein Family Member 1 (WIPF1) mutation causes WIP deficiency, characterized by thrombocytopenia, immu-nodeficiency, and eczema. Here, we aimed to present a patient with coexisting ICOS and WIP de-ficiency.

Keywords: ICOS, WIPF1, CVID, child

INTRODUCTION

The inducible T-cell costimulator (ICOS) is a member of the CD28/CTLA4 family that plays an important role in the regulation of T-cell-mediated immune responses as a secondary co-stimulatory signal transmitted as a result of T-cell receptor stimulation (1,2). Unlike CD28, *ICOS* is not constitutively expressed but is upregulated only in activated T cells. Co-stimulation through *ICOS* improves helper T cell functions important for differentiation and proliferation of lymphocyte subsets such as TH1, TH2, TH17, follicular T cell (TFH), and regulatory T (Treg) cells (3,4). Furthermore, *ICOS* mediates the interaction of T and B cells resulting in the formation of germinal centers and thus differentiates B cells into memory and long lasting plasma cells (3,5). Autosomal recessive inherited *ICOS* deficiency is classified as combined immunodeficiency (CID) and has a wide clinical spectrum including hypogammaglobulinemia, recurrent infections, enteropathies, autoimmunity, lymphoproliferation and malignancy (6).

The Wiskott-Aldrich syndrome-2 (WAS2) is an autosomal recessive immunological disease characterized by recurrent infections starting in infancy (7). It is characterized by thrombocytopenia and eczema with normal platelet volume. Laboratory studies show decreased CD8+ T cells, variably increased immunoglobulin levels (especially IgE), low B cells, abnormal function of T and NK cells, and impaired T cell migration. Cellular abnormalities are thought to result from defective F-actin polymerization (7). In our article, we aimed to present an interesting, previously unidentified case in which *ICOS* and *WIPF1* mutations, both of which are very rare, coexist.

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CASE

A 12-year-old female patient presented to our clinic with complaints of bloody diarrhea, weight loss, and swelling in both knees that had started two weeks ago. In her history, she started having convulsions at one month of age and used antiepileptic drugs, stayed in the hospital for 3 months due to peeling and bleeding of her skin at 6 months of age, started to have otitis at the age of 2 (20 attacks per year), had arthritis attacks in her arms and legs at the age of 6, and had frequent lung infections at the age of 8 (at least every month). It was learned that she started to have diarrhea 7-8 times a day and thrombocytopenia causing intracranial bleeding at the age of 9 years. In her family history, it was learned that her parents were cousins, her aunt had bowel disease, her two uncles had leukemia, and both her grandfathers had thrombocytopenia.

On physical examination, her height and weight were below the 3rd percentile, she had diffuse crepitant rales in her lungs, splenomegaly, arthritis in both knees and ankles, and clubbing. The patient was hospitalized and vancomycin and meropenem treatment was started. In her laboratory results, WBC: 3370 10^3/μL, ALC: 1610 (10^3 /μL), ANC: 1570 (10^3 /μL), Hb: 9.6 g/dL, Plt: 77000 (10^3/μL), MPV: 8 fl (9.2-12.2), CRP: 39.96 mg/L (0-5), and vitamin B12: 36 ng/L (180-914) were present. IgG (190 mg/dl) and Ig A (<60 mg/l) levels were low for her age (Table I); Ig M (110 mg/dl), CD3 (75%), CD4 (39%), CD8 (30%), CD19 (21%), and CD16/56 (7%) were in the age-appropriate range; and switched memory B cell: 1.38% (3.6-24%) and unswitched memory B cell: 0.65% (6.7-31.1%) were low for her age (Table II).

Thorax CT showed diffuse cystic bronchiectasis and peribronchial wall thickening. Duodenoscopy was compatible with inflammatory bowel disease. 2 mg/kg methylprednisolone and sulfasalazine were started for gastrointestinal involvement. Intravenous immunoglobulin replacement treatment and sulfamethoxazole-trimethoprim prophylaxis were started due to severe hypogammaglobulinemia. In the immunodeficiency genetic panel studied with next-generation clinical sequencing, homozygous mutations in the *WIPF1*(c.310T>C) and *ICOS* (c.221_222delCA) genes were detected. There was a novel homozygous deletion in *ICOS* as c.221_222delCA, resulting in a frameshift mutation that led to affected protein features at the extracellular domain of ICOS (p.Thr74fs). A novel homozygous single base exchange in *WIPF1* as c.310T>C resulted in an amino acid sequence change (p.Phe104Leu). Both mutations had not been previously identified but had been reported to be pathogenic according to some genetic databases (ICOS; Mutation Taster, WIPF1; Mutation Taster, SIFT, PoolyPhen). Sanger sequencing confirmed segregation in keeping with autosomal recessive inheritance: both parents possessed one normal allele and one allele carrying the mutation, while the affected child was homozygous for both mutations. Two siblings were homozygous for *ICOS* (c.221_222delCA) and *WIPF1*(c.310T>C). It was learned that one of the siblings with the homozygous mutation was asymptomatic, and the 8-year-old brother had occasional joint pain. The patient presented again 5 months after she was discharged with the complaint of diarrhea 10 times a day. The patient, who seemed dehydrated and frail, was hospitalized. However, the patient was discharged because of the family's request without waiting for her complaints to fully subside. The necessary follow-up and treatment

Table I: Patient's immunoglobulin levels.

	Patient's immunoglobulin levels	Normal Range
Ig G mg/dl	**190**	639-1344
Ig M mg/dl	110	56-312
Ig A mg/dl	**<60**	0-312
Ig E IU/mL	7.7	

Ig: Immunoglobulin.

Table II: The patient's lymphocyte subsets.

Lymphocyte Subsets	%	Normal Range
$CD3^+$ T cells	73.6	57.8-86.2
$CD3^+$ $CD4^+$ T cells	36.25	27.3-46.7
$CD3^+$ $CD8^+$ T cells	32.17	16.5-39.4
$CD19^+$ B cells	21.06	5.1-21.9
$CD16^+$ $CD56^+$ NK cells	2.03	1.8-2.6
T cell subsets	**%**	**Normal Range**
$CD4^+CD45RA^+$	44.69	13-68.2
$CD4^+CD45RO^+$	55.48	28.2-67.6
$CD8^+CD45RA^+$	60.3	28-86.2
$CD8^+CD45RO^+$	40	12-66
B cell subsets	**%**	**Normal Range**
UCSM B	**1.38**	3.6-24.2
CSM B	**0.65**	6.7-31.1

UCSM B: Unswitched memory B cells, **CSM B:** Switched memory B cells.

recommendations were made to the patient. Unfortunately, it was learned that the patient did not go to a hospital for follow-up despite having recurrent diarrhea problems and died.

DISCUSSION

ICOS deficiency was defined as common variable immunodeficiency (CVID); however, by defining patients with opportunistic infections and expanding the clinical phenotype, it was switched from CVID to CID (6). There are 23 patients reported before our patient in the literature. Most of these patients presented with hypogammaglobulinemia accompanied by recurrent infections and autoimmunity (3,8,9). *ICOS* deficiency may affect the T and B cell compartments. Therefore, patients often have cellular and humoral immunodeficiencies that result in increased susceptibility to bacterial, viral, and opportunistic infections such as *Pneumocystis jirovecii* (3,5). *ICOS*-deficient T cells fail to express CXCR5, demonstrating the essential role of *ICOS* in the differentiation of CXCR5+CD4+T cells, which initiates germinal center formation and signals for maturation, differentiation, and survival of B cells (3). Therefore, patients with *ICOS* deficiency generally exhibited low B cells with a low memory component, as in our patient.

Patients with *ICOS* deficiency have chronic diarrhea due to enteropathy. Most of the patients with enteropathy exhibited mild symptoms without growth retardation (3,5). However, a male patient with severe enteropathy who was dependent on total parenteral nutrition and required hematopoietic stem cell transplantation (HSCT) to relieve the symptoms was reported (10). Our patient also had chronic diarrhea and growth retardation. Findings in *ICOS* deficiency may manifest as various disorders such as autoimmunity, autoimmune cytopenia, inflammatory bowel disease, interstitial pneumonia, psoriasis, rheumatoid arthritis, hepatitis, and granulomatous lesions (3,5). These autoimmune manifestations include high IL-12 expression, which causes TH1 cell dominance, and decreased CTLA4 expression and may be associated with impaired IL-10 production. It was thought that Abatacept could be used for the decreased CTLA4 expression (5), Abatacept treatment in patient with *ICOS* deficiency has not been reported in the literature.

Although the Kaplan-Meier 55-year survival rate of ICOS deficiency is estimated to be 81% (CI 0.72–1.0), mortality was higher in those with the enteropathy phenotype, but not statistically significant (5). Disease severity varied in two patients who shared the same homozygous-missense mutation, suggesting that this wide variety of clinical presentations was the result of other modifying factors (5). One female patient, was reported to be asymptomatic although she had a homozygous mutation but intravenous immunoglobulin treatment was administered to this patient (3).

In a study in which 15 *ICOS* deficiency patients were followed up for 14 years, it was reported that 40% of the patients used systemic steroids due to immune thrombocytopenia and neutropenia, inflammatory bowel disease, rheumatoid arthritis, and herpes keratitis, and two patients needed to use immunosuppressant agents such as cyclosporine for neutropenia and methotrexate for rheumatoid arthritis in addition to this treatment (3). Corticosteroid was started for immune dysregulation findings and sulfasalazine was started for inflammatory bowel disease in our patient's first hospitalization, and corticosteroid treatment was discontinued when her symptoms were under control.

The Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency disease characterized by immunodeficiency, thrombocytopenia and eczema. The gene responsible for X-linked WAS encodes the Wiskott-Aldrich syndrome protein (WASP) (11). WASP is expressed in hematopoietic cells and has many functions in the immune system. WASP interacting protein (WIP) forms a structural complex with WASP. The primary function of WIP is to stabilize WASP and prevent its degradation (12). The *WIPF1* mutation causes the autosomal recessive Wiskott-Aldrich Syndrome Type2, characterized by thrombocytopenia, immunodeficiency, and eczema. Mutations in *WIPF1* are extremely rare and have so far been reported in only the three kindreds of 6 patients (13). Senthil et al. (14) reported the clinical features of the seventh case of WAS2 related to WIP deficiency and they extended the phenotype of WIP to include transient, juvenile myelomonocytic leukemia (JMML), which has previously been described a rare presentation of WAS but never in WAS2.

In *WIPF1* deficiency, PI3K signaling, which is one of the main signaling pathways regulating B cell homeostasis, survival, differentiation, and class change recombination is reduced. Class shifting of B cells is also impaired in *ICOS* deficiency, and we think that the combination of two mutations played a role in the severe clinical course of

our patient.

CONCLUSION

HSCT can be a life-saving and curative therapy for patients with a severe disease course in both mutations. However, our patient did not come for follow-up and died before he had the chance to receive this curative treatment. For regions where consanguineous marriages are common, it should not be a surprise that both rare genetic diseases are seen in the same patient.

Conflict of Interest

The authors declare no conflict of interest.

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Institutional Review Board Statement

The study was granted exemption from requiring ethics approval because written informed consent was obtained from the parents.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Author Contributions

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