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Review Article

CTLA-4 Deficiency: Pathophysiology, Clinical Manifestations, and Immunological Findings

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Abstract

Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) deficiency is a primary immune regulatory disorder caused by heterozygous germline loss-of-function variants in the *CTLA4* gene. CTLA-4 is expressed mainly on activated T cells and regulatory T cells that plays a key role in maintaining immune tolerance by limiting T-cell activation. Also, CTLA-4 has recently become a key target in immune checkpoint-based therapeutics, particularly in cancer treatment via the use of monoclonal antibodies against this molecule. Loss of CTLA-4 function leads to uncontrolled T-cell activation and impaired Treg-mediated immune regulation. Consequently, this immune dysregulation underlies the coexistence of autoimmunity and immune deficiency. Hypogammaglobulinemia is one of the most common immunologic findings in CTLA-4 deficiency and may resemble common variable immunodeficiency. However, CTLA-4 deficiency is a multisystem disorder. Clinical manifestations are highly variable and may include recurrent respiratory infections, bronchiectasis, chronic diarrhea, malabsorption, autoimmune cytopenia, lymphadenopathy, splenomegaly, and organ infiltration. Laboratory findings commonly include lymphopenia, reduced naïve $CD4^+$ T cells, increased activated T cells, impaired regulatory T-cell function, reduced $CD19^+$ B cells, decreased class-switched memory B cells, expanded CD21-low B cells, reduced natural killer cells, and low serum immunoglobulin levels. Recognition of these clinical and laboratory features is essential for early diagnosis, appropriate management, and improved long-term outcomes in patients with CTLA-4 deficiency. This study reviews the pathophysiology, clinical manifestations and laboratory findings in patients with CTLA-4 deficiency.

Keywords: Autoimmunity; CTLA-4 Deficiency; Hypogammaglobulinemia; Immune Dysregulation; Lymphoproliferation

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Introduction

Primary immunodeficiency disorders (PIDs) are a heterogeneous group of disorders characterized by impaired development or function of the immune system, resulting in recurrent or severe infections, immune dysregulation, autoimmunity, and malignancy (1). Among these disorders, CTLA-4 deficiency has recently been recognized as an important cause of autoimmunity, immune dysregulation, and hypogammaglobulinemia (2). Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) is a T-lymphocyte surface protein that serves as a critical immune checkpoint and is expressed primarily on activated conventional T cells and regulatory T cells (Tregs). It negatively regulates T-cell activation and prevents autoimmunity (3). CTLA-4 deficiency is caused by heterozygous germline loss-of-function variants in the *CTLA4* gene located on chromosome 2q33.2, resulting in uncontrolled T-cell activation and impaired regulatory T-cell suppression. Consequently, this immune dysregulation underlies autoimmune disease, lymphoproliferation, and recurrent infections (4, 5).

The most common immunologic finding observed in CTLA-4 deficiency is hypogammaglobulinemia, and the condition may clinically resemble common variable immunodeficiency (CVID). However, CTLA-4 deficiency affects multiple organ systems and can cause organ dysfunction due to the accumulation of T lymphocytes. Moreover, it is often associated with additional manifestations such as autoimmune cytopenia, interstitial lung disease, enteropathy, and lymphoid organ enlargement(6, 7).

The aim of this study is to review the pathophysiology, clinical manifestations and laboratory findings in patients with CTLA-4 deficiency.

Immune Regulatory Functions of CTLA-4

The activation of naïve T cells requires both T-cell receptor (TCR) engagement and antigen-presenting cell (APC)-derived costimulatory signaling; without this secondary signal, T cells become anergic. This represents an important mechanism for the maintenance of immune tolerance (8). The interaction between the cell-surface molecule CD28, the principal T-cell costimulatory receptor, and its ligands B7-1 (CD80) and B7-2 (CD86) mediates the principal costimulatory pathway required for naïve T-cell activation (9, 10).

Following T-cell activation, CTLA-4 is rapidly upregulated and negatively regulates T-cell activation by competing with CD28 for binding to the costimulatory molecules CD80 and CD86 on APCs. This occurs due to its higher binding avidity and affinity compared with CD28. In addition, CTLA-4 removes CD80 and CD86 ligands via transendocytosis (11, 12), thereby limiting costimulatory signaling and reducing T-cell activation. Through this mechanism, CTLA-4 inhibits T-cell proliferation, suppresses IL-2 production, and prevents excessive immune responses (13).

In addition to competing with CD28 for ligand binding, Engagement of CTLA-4 can directly suppress T-cell activation by attenuating TCR-mediated signaling pathways. Through recruitment of phosphatases such as protein phosphatase 2A (PP2A) and tyrosine phosphatase SHP-2, which then dephosphorylates several kinases, including AKT, MEK, ERK, and JNK, resulting in limiting T-Cell activation (14-16). CTLA-4 also increases the threshold required for T-cell activation, particularly when antigen presentation or costimulatory signals are weak. Consequently, CTLA-4 plays a crucial role in maintaining peripheral tolerance and preventing inappropriate immune responses against self-antigens (17).

CTLA-4 has recently become a key target in immune checkpoint-based therapeutics, particularly in cancer treatment via the use of monoclonal antibodies against this molecule. Evidence from preclinical models and clinical studies indicates that blockade of CTLA 4, promotes antitumor T-Cell activity and some individuals exhibit clinical tumor regression (18). Following the efficacy of CTLA 4 blockade in animal models anti CTLA 4 antibodies were subsequently developed for clinical interventions. Ipilimumab, a recombinant human immunoglobulin (Ig) G1 monoclonal antibody with FDA approval, blocks the interaction between CTLA 4 and its ligands via binding to the MYPPPY motif. Tremelimumab, is a human IgG2 monoclonal antibody. Both Ipilimumab and tremelimumab have been trialed in several advanced cancers, including melanoma, prostate cancer, ovarian cancer, non-small cell

lung cancer, mesothelioma, and urothelial cancer. Evidence has shown their efficacy (19-27).

Pathophysiology of CTLA 4 Deficiency

CTLA-4 is constitutively expressed by $Foxp3^+$ $CD4^+$ regulatory T cells (Tregs) and plays an essential role in maintaining immune homeostasis. Kojo et al. used a mouse model with Treg-specific deletion of CTLA-4 and demonstrated that loss of CTLA-4 in Tregs alone is sufficient to cause severe, fatal immune dysregulation. These mice developed systemic lymphoproliferation, multi-organ inflammatory disease (including myocarditis, gastritis, and tissue infiltration in multiple organs), elevated levels of IgE and IgG, and strong T-cell–mediated autoimmunity. This finding emphasizes the essential role of CTLA-4 in Treg-mediated immune regulation (28).

Dysregulated T-cell activation in CTLA-4 deficiency disrupts normal B-cell maturation and compromises humoral immunity. Affected patients typically show reduced follicular B cells and class-switched memory B cells, together with an expansion of late transitional B cells and activated atypical B-cell populations. These abnormalities impair effective antibody production and contribute to hypogammaglobulinemia. Overall, dysregulated interactions between T and B lymphocytes help explain the coexistence of humoral immunodeficiency and autoimmune manifestations in CTLA-4 deficiency (29).

Clinical Manifestations

CTLA-4 insufficiency is characterized by a highly variable clinical phenotype, with a phenotypic spectrum ranging from asymptomatic carrier status to fatal autoimmunity and considerable heterogeneity in presenting symptoms, and organ involvement. Initial manifestations may include autoimmune cytopenia, recurrent respiratory infections, enteropathy, diabetes mellitus type 1, neurological symptoms, thyroid disease, arthritis, bone marrow failure, splenic sequestration, growth failure, fever or night sweats, atopic dermatitis, alopecia, and, less frequently, primary biliary cirrhosis, Addison's disease, and impaired wound healing (30, 31).

In large studies, symptomatic *CTLA4* mutation carriers have been reported to present with diverse predominant clinical diagnoses. The most common include autoimmune cytopenia, common variable immunodeficiency (CVID), severe gastrointestinal inflammation such as enteropathy or inflammatory bowel disease (IBD), and respiratory disease. Pulmonary manifestations may include recurrent infections, bronchiectasis, asthma, and granulomatous-lymphocytic interstitial lung disease (GLILD). Other major diagnoses include lymphoma, endocrinopathies, inflammatory central nervous system disease, and autoimmune lymphoproliferative syndrome (ALPS)-like or immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)-like phenotypes. Thus, CTLA-4 insufficiency frequently overlaps clinically with other primary immune regulatory disorders and antibody deficiencies (4, 7, 30-34).

Non-malignant lymphoproliferation is particularly common and may present as splenomegaly, chronic lymphadenopathy, hepatomegaly, or lymphocytic infiltration of target organs, including the lungs, gastrointestinal tract, brain, bone marrow, kidney, and retroperitoneal tissues.

Respiratory disease is also a major component of the clinical manifestations and includes recurrent upper and lower respiratory tract infections, pneumonia, sinusitis, otitis media, bronchiectasis, lymphocytic pneumonitis, and GLILD (4, 31, 32, 35).

Autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), diabetes type 1, autoimmune thyroid disease, and myasthenia gravis (MG) have been associated with CTLA-4 deficiency (36-44).

Gastrointestinal involvement is frequent and may be severe. Patients can present with chronic diarrhea, malabsorption, and weight loss. Reported gastrointestinal disorders include Crohn's disease, atrophic gastritis, coeliac disease, acute pancreatitis, pancreatic insufficiency, and CVID-like gastroenteropathy. In some patients, long-standing gastrointestinal inflammation has been associated with gastric cancer (4, 30, 33, 45, 46).

Autoimmune cytopenias represent another prominent and sometimes life-threatening manifestation, including immune thrombocytopenia purpura, autoimmune hemolytic anemia, autoimmune neutropenia, pure red cell aplasia (PRCA), Evans syndrome, and multilineage cyto-

penias. Autoimmune cytopenias are often treatment-resistant and are a common indication for allogeneic hematopoietic stem cell transplantation (alloHSCT) (30, 31).

Neurological involvement, although less common than hematologic, pulmonary, or gastrointestinal manifestations, contributes significantly to morbidity. Also, it may be underestimated due to prominent extra-neurologic features. Reported manifestations include autoimmune encephalitis, encephalomyelitis, hypophysitis, hydrocephaly cerebral perivascular lymphocytic infiltration leading to headache, vomiting, paraplegia with bladder dysfunction, seizures, aphasia, demyelinating disease, optic neuritis, visual impairment, cranial nerve palsies, ventriculomegaly, cognitive dysfunction, and neurological complications secondary to hematologic disorders or systemic autoimmune disorders for example, hydrocephaly as a symptom of SLE (30, 46-51).

Malignancy is an important complication of CTLA-4 insufficiency, particularly lymphomas, including Hodgkin lymphoma, diffuse large B-cell lymphoma, and Burkitt lymphoma. Several cases of lymphoma have been associated with Epstein–Barr virus infection. Gastric adenocarcinoma has also been reported. Indeed, a large longitudinal study reported gastric adenocarcinoma and lymphoma represented the most common malignancy (52).

Overall, CTLA-4 insufficiency should be considered a multisystem immune dysregulation syndrome in which antibody deficiency, autoimmunity, lymphoproliferation, tissue infiltration, recurrent infections, and malignancy risk coexist (30, 53). The common clinical manifestations reported in patients with CTLA 4 deficiency is summarized in **Table 1**.

Immunological Findings

CTLA-4 deficiency is associated with abnormalities affecting both cellular and humoral immunity. Previous studies have reported the following immunological findings:

1. T-cell abnormalities

Patients commonly exhibit lymphopenia, with reduced numbers of $CD3^+$ T cells and $CD4^+$ helper T-cells, mainly due to a loss of naïve $CD4^+$ T-cells, indicating impaired T-cell homeostasis. In addition, many T-cells show evidence of chronic activation, reflected by increased expression of activation markers such as HLA-DR. Although the number of $CD4^+$ $FoxP3^+$ Tregs is often increased, their suppressive function is impaired because of the underlying CTLA-4 defect. Elevated double-negative T-cells further support the presence of immune dysregulation and autoimmune or inflammatory manifestations (2, 30, 54).

2. B-cell abnormalities

B-cell abnormalities are also prominent in CTLA-4 deficiency. Patients frequently have reduced total $CD19^+$ B-cell counts, a marked decrease in class-switched memory B-cells, and an increased proportion of naïve B-cells, suggesting impaired B-cell maturation and differentiation. CD21-low B-cells, a subset associated with chronic immune activation and autoimmunity, are consistently expanded. These cells exhibit features of B-cell exhaustion, including reduced immunoglobulin production in vitro. In some patients, B-cells may be almost completely absent. Also, Hypogammaglobulinemia is one of the most common immunological findings in CTLA-4 deficiency and is characterized by reduced levels of one or more immunoglobulin isotypes (IgG, IgA, and/or IgM). This contributes to recurrent infections and impaired antibody responses. In addition, natural killer (NK) cell numbers are often reduced (4, 7, 30, 33). The common immunological findings reported in patients with CTLA 4 deficiency are summarized in **Table 1**.

Conclusion

CTLA-4 deficiency is a complex immune dysregulation disorder with variable clinical and immunological manifestations. Although hypogammaglobulinemia and recurrent infections are common findings, many patients also develop autoimmunity, lymphoproliferation, organ infiltration, and other inflammatory complications. In addition, hypogammaglobulinemia may mimic phonetically more common immunodeficiency disorders such as CVID. The underlying defect in CTLA-4-mediated immune regulation results in abnormalities affecting both T-cell and B-cell function, indicating the coexistence of immune deficiency and autoimmunity. Recognition of these characteristic clinical and immunological

Table 1. Common Clinical and Immunological Findings in CTLA-4 Deficiency

Category	Findings
Clinical Manifestations	
Recurrent infections	Recurrent upper and lower respiratory tract infections, pneumonia, sinusitis, otitis media
Pulmonary involvement	Bronchiectasis, asthma, lymphocytic pneumonitis granulomatous-lymphocytic interstitial lung disease (GLILD)
Gastrointestinal disease	Chronic diarrhea, malabsorption, weight loss, enteropathy, Crohn's disease, coeliac disease, atrophic gastritis, pancreatitis, pancreatic insufficiency
Autoimmune manifestations	Autoimmune cytopenias (immune thrombocytopenia purpura, autoimmune hemolytic anemia, autoimmune neutropenia), Evans syndrome, pure red cell aplasia, type 1 diabetes mellitus, autoimmune thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, myasthenia gravis
Lymphoproliferation	Splenomegaly, lymphadenopathy, hepatomegaly, lymphocytic infiltration of organs
Neurological manifestations	Autoimmune encephalitis, encephalomyelitis, optic neuritis, seizures, demyelinating disease, cranial nerve palsies, cognitive dysfunction, hypophysitis, hydrocephaly, aphasia, visual impairment,
Malignancy	Hodgkin lymphoma, diffuse large B-cell lymphoma, Burkitt lymphoma, gastric adenocarcinoma
Other features	Growth failure, fever, night sweats, atopic dermatitis, alopecia
Immunological Findings	
T-cell abnormalities	Lymphopenia; reduced $CD3^+$ and $CD4^+$ T cells; decreased naïve $CD4^+$ T cells; increased activated T cells ($HLA\text{-}DR^+$); impaired regulatory T-cell suppressive function; increased double-negative T cells
B-cell abnormalities	Reduced $CD19^+$ B cells; decreased class-switched memory B cells; increased naïve B cells; expansion of CD21-low B cells
Humoral abnormalities	Hypogammaglobulinemia (reduced IgG, IgA, and/or IgM); impaired antibody responses
Other immune abnormalities	Reduced natural killer (NK) cell numbers

features is essential for early diagnosis, appropriate treatment, and improved long-term outcomes in affected patients.

Conflicts of Interest

The authors declare no conflicts of interest.

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