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Short Communication

CTLA-4 gene mutation and multiple sclerosis: A case report and literature review

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Abstract We reported a patient with autoimmunity (multiple sclerosis), immunodeficiency (hypogammaglobulinemia with severe infections), enteropathy (diarrhea with intestinal inflammation), splenomegaly, lymphadenopathy and lymphocytic infiltration of non-lymphoid organs (lung, gut and brain). The patient was found to have a heterozygous mutation in cytotoxic T lymphocyte antigen-4, and had excellent response to abatacept.

Introduction

Immunodeficiency disorders are a group of diseases of variable genetic etiologies. With the advance of genetic technologies, more genetic mutations of immune dysregulation have recently been identified. The protein cytotoxic T lymphocyte antigen-4 (CTLA-4) is a negative immune regulator essential for the function of regulatory T cells (Tregs), which are responsible for the suppression of T cell proliferation and differentiation.[1] Heterozygous CTLA-4 mutations have been recognized to result in diverse clinical phenotypes, including various organ-specific autoimmune diseases, hypogammaglobulinemia, recurrent infections, and malignancies.[2] However, the natural history of this condition is largely unknown, and the responses to a wide range of therapies are unpredictable.[3] Here, we described a patient with multiple sclerosis and immune dysregulation,

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who was subsequently found to have a heterozygous mutation in CTLA-4, and had excellent response to abatacept.

Case presentation

The 14-year-old girl was well until she visited our hospital in 2007 because of recurrent fever, diarrhea, headache, and intermittent chest discomfort off and on for 2 years. There was no relevant family history. An episode of generalized tonic-clonic seizure occurred 3 days before admission. During admission, physical examination revealed multiple neck lymphadenopathy and splenomegaly. There was no evidence of infectious causes of lymphadenopathy, including negative cytomegalovirus, Epstein—Barr virus, human immunodeficiency virus, human T-lymphocyte virus, *Mycobacterium tuberculosis* and cryptococcus infection. Brain magnetic resonance imaging (MRI) showed multiple nodular lesions over brain parenchyma, with high signal intensity on T2 weighted image, which indicated inflammation rather than tumor metastasis (Fig. 1a). Chest computed tomography (CT) and Gallium-67 whole body scan also found diffuse intrapulmonary nodules and multifocal gallium-avid lesions (Figure S1). The pathological examination of lymph nodes of lung, neck and abdomen revealed lymphoid hyperplasia, instead of sarcoidosis or malignancy. Upper and lower gastrointestinal endoscopic studies showed lymphoid tissue hyperplasia grossly and lymphoplasma infiltration histologically. Considering the possibility of autoimmune diseases, we arranged serial tests which showed normal C3 (93.6 mg/dl), low C4 level (<5.7 mg/dl), and negative antinuclear antibodies. A marked reduction in naive $CD4^+$ T cell (13.5%) and increase in memory $CD4^+$ T cell (44.8%) were noted by flow cytometry. Total IgG (619 mg/dl) and IgA (32 mg/dl) were low, while IgM (32 mg/dl) and IgE (25 mg/dl) were normal. About her family history, her father died from brain lymphoma when she was a toddler.

Autoimmune disorder was considered first after all the initial assessment. Her symptoms were controlled under the treatment of systemic corticosteroid but relapsed after tapering corticosteroid. Brain MRI showed newly appeared multiple focal lesions (Fig. 1b). The pathological findings within brain lesions showed tumefactive demyelinating change and reactive inflammatory infiltration with macrophages and T cells predominantly, which suggested multiple sclerosis (MS). She received intravenous immunoglobulin (IVIg) replacement and long-term prednisolone, and remained free of serious neurologic symptoms or infection in the following 4 years. Subsequent image studies showed decreasing extent of brain lesions and generalized lymphadenopathy.

However, between 2012 and 2014, she had been hospitalized several times for severe pneumonia, and osteoporosis with humeral and femoral fractures. Neurologic symptoms, including back pain, diplopia, involuntary lower legs movement progressed in year 2014. Brain MRI found multiple new T2-enhanced lesions (Fig. 1c). In the following 4 years, she received treatment for MS, including IVIg, mycophenolate mofetil, azathioprine and interferon-beta with a partial response. The symptoms flared up 4 times between 2016 and 2018, manifested with dysarthria, facial palsy, seizure, limbs numbness and weakness, tinnitus, and vertigo.

In 2018, taking her complicated history and the suboptimal therapeutic response of MS, whole exome sequence (WES) was performed to explore the possible underlying genetic cause. Broad genetic panel screening followed by Sanger confirmation identified the heterozygous CTLA-4 mutation (c.208C > T, p.Arg70Trp), while her mother and

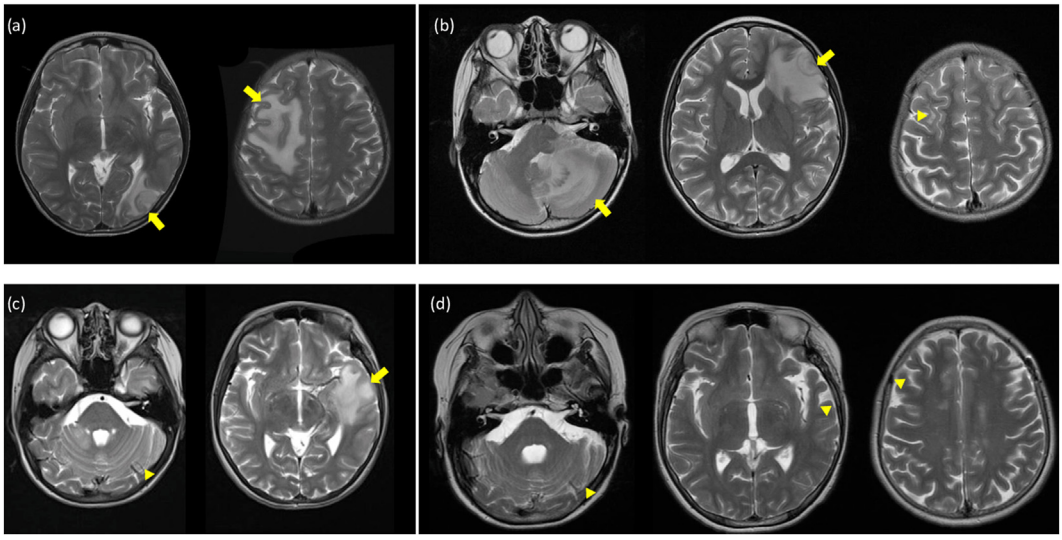

Figure 1. Serial brain MRI T2 weighted images. (a) (May, 2007): multiple T2-hyperintense nodular lesions over brain parenchyma (arrow); (b) (March, 2008): newly appearing multiple T2-hyperintense focal lesions (arrow), previous brain lesions had diminished under systemic corticosteroid (arrow head); (c) (April, 2014): newly appearing multiple T2-hyperintense focal lesions (arrow), previous brain lesions had diminished (arrow head); (d) (Feb, 2020) no definite abnormal enhancing lesion in brain parenchyma, and previous brain lesions had diminished (arrow head).

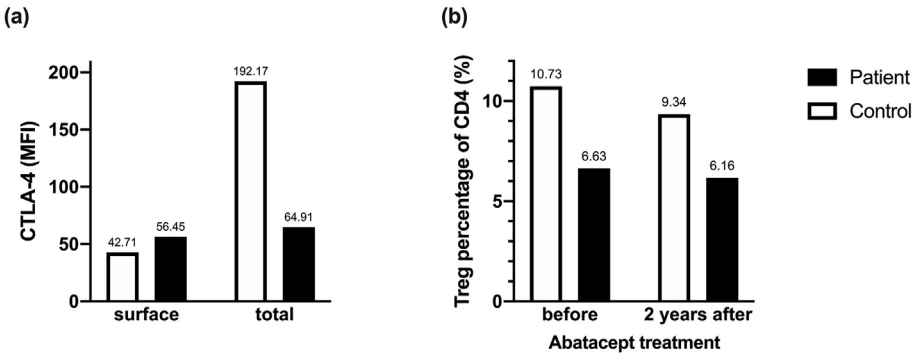

Figure 2. CTLA-4 and regulatory T cell amount. (a) $CD3^+$ T cells was stimulated with phytohemagglutinin (PHA) 1 μg/mL for 4 days and then CTLA-4 amount was analyzed by surface and intracellular staining with flow cytometry. (b) Regulatory T cell ($CD3^+CD4^+CD25^{high}CD127^{low}$ cell) was analyzed by flow cytometry before and 2 years after abatacept treatment.

brother were normal. Lower amount of CTLA-4 and Treg were noted by flow cytometry (Fig. 2). Therefore, in addition to mycophenolate mofetil and monthly IVIg, the patient received abatacept since March 2018 at the dosage of 500 mg every 4 weeks (as recommended for weight range), with excellent response. The diarrhea, neurologic symptoms improved, and seizure was well controlled under levetiracetam. Follow-up brain MRI in Feb, 2020 showed no definite abnormal enhancing lesion in brain parenchyma (Fig. 1d). Less IVIg supplement with higher trough IgG level was noted. The total CTLA-4 expression increased to the control's level, while the Treg numbers were similar to those before treatment (Fig. 2, S2, S3).

Discussion

We reported the identification of heterozygous CTLA-4 mutation in a patient with multiple sclerosis. The mutation was predicted to cause a quantitative defect in CTLA-4 expression associated with an altered phenotype of Tregs, and exhibited variable clinical penetrance and phenotype.[3] In our patient, CTLA-4 mutation resulted in a combined phenotype of autoimmunity (multiple sclerosis), immunodeficiency (hypogammaglobulinemia and severe infections), enteropathy (diarrhea with intestinal inflammation), splenomegaly, lymphadenopathy and lymphocytic infiltration of non-lymphoid organs (lung, gut and brain). Previous large cohort study had presented the common clinical manifestations of CTLA4 mutation carriers, including hypogammaglobulinemia, lymphoproliferation, respiratory-, gastrointestinal-, or neurological features, which were consistent with our patient's phenotype.[2]

The lymphoproliferative disorder is a hallmark of our patient, which distinguish our patient form typical multiple sclerosis. Previous study had reported that CTLA-4 haploinsufficiency results in characteristic lymphocytic infiltration in non-lymphoid organ.[4] Lymphoid tissue hyperplasia was found in the pathological examination of upper and lower gastrointestinal endoscopic studies, and lymph nodes from lung, neck, and abdomen. Although the white matter lesions in MS patients are composed of infiltrates of inflammatory cells, including lymphocytes and macrophage,[5] lymphoproliferative disorder was not usually found. Thus, explore the possible underlying genetic cause is presumed in our Case.

CTLA-4 is an inhibitory receptor highly expressed by Tregs, down-regulating effector T cell proliferation.[6] In health individuals, both CD25 and CTLA-4 molecules are critical for fully competent function of Tregs in regulating autoimmunity.[7] CTLA-4 signaling is also a critical regulator of resting memory CD4 T cells and inhibits memory CD4 T cell proliferation.[8] In our patient, CTLA-4 mutation resulted in lower CTLA-4 expression, lower number of Tregs and increased memory $CD4^+$ T cells, which likely conveyed a defect in Tregs suppressive function. An absence of Tregs predisposed to extensive autoimmune disease and immune dysregulation.[9]

MS, an idiopathic inflammatory demyelinating disorder of the central nervous system, are mediated by self-reactive T cells that have escaped the deletional mechanisms of central tolerance.[10] Our patient had been recognized and treated as MS based on the pathology of brain lesions. There are numbers of genes associated with MS. The strongest genetic association signal in MS resides within the major histocompatibility complex (*MHC*) in chromosome 6p21.3. The genome-wide association studies (GWAS) confirmed the association of MS and interleukin-7 receptor α (*IL7Rα*) gene, interleukin-2 receptor α (*IL2Rα*) gene, and tumor necrosis factor receptor superfamily member 14 (*TNFRSF14*) gene. After a decade of GWAS screenings in European populations, the MS genetic atlas currently includes 110 non-*MHC* risk variants belonging to 103 genetic loci.[3] A number of studies also demonstrated a linkage between CTLA-4 heterozygous mutation and MS.[11] Previous study reported a higher frequency of CTLA4 mutation among primary progressive MS than among bout-onset MS.[12] In the meantime, the treatment of anti-CTLA-4 in some pre-existing MS patients did result in the deterioration of MS.[13] Therefore, the lower or absence of CTLA-4 related function was associated with MS progression. The pathophysiology of CTLA-4 mutation-related enteropathy probably involved a hyperactive immune state in the setting of a T-cell regulatory defect, resulting in destruction of the enterocyte.[14]

In the workup of patients with immune dysregulation, genetic analysis has gained increasing importance. In our

patient, detection of heterozygous CTLA-4 mutation provided a new therapeutic option. Abatacept, a humanized CTLA4-IgG fusion protein that modulates T cells activity, has been successfully used in patients with CTLA4 haploinsufficiency by restoring the insufficient CTLA-4 activity.[15] Abatacept was also useful in autoimmune enteropathies refractory to conventional therapies.[14] Our patient had a great clinical response to abatacept, with improvement of hypogammaglobulinemia, enteropathy, lymphadenopathy and neurological symptoms.

In conclusion, precision medicine targeted to the specific genetic defect provides the better approach to treatment, comorbidity monitoring and care of patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmii.2021.10.009.