Case Report

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Autoimmune manifestations of CTLA-4 haploinsufficiency in two patients of Southeast Asian ethnicity

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ABSTRACT

We report 2 patients who first developed cutaneous manifestations, followed by autoimmune phenomena, infections, and hypogammaglobulinemia. They were initially diagnosed with common variable immunodeficiency; however, the diagnosis was revised to cytotoxic T-lymphocyte antigen 4 haploinsufficiency after genetic and functional testing.

Keywords: Common variable immunodeficiency; cytotoxic T-lymphocyte antigen 4 haploinsufficiency; hypogammaglobulinemia; inborn errors of immunity

1. Introduction

Cytotoxic T-lymphocyte antigen 4 haploinsufficiency (CTLA-4-H) is an autosomal dominant monogenetic disorder caused by a heterozygous CTLA-4 germline mutation [1]. Its diagnosis is complicated by a highly variable clinical phenotype, including an immune dysregulation syndrome with autoimmunity, lymphoproliferation, atopy, malignancy, as well as immunodeficiency with hypogammaglobulinemia and recurrent infections [2]. CTLA-4-H has been reported mainly in North America and Western Europe, while lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency is mainly in East Asia [3].

2. Case report

A 53-year-old Malay male first developed violaceous papules, plaques, and nodules on both legs and arms at the age of 44 years old (Fig. 1A). He later developed widespread lymphadenopathy, maxillary sinusitis, lung nodules, cholestatic hepatitis, splenomegaly, and thrombocytopenia over the course of the next 6 years. Biopsy of the skin, lymph nodes, and liver all demonstrated non-necrotizing granulomas and returned negative for mycobacterial studies and malignancy (Fig. 1B). Anti-nuclear antibody, anti-mitochondrial antibody, anti-liver antibody, anti-liver-kidney microsomal antibody, and anti-smooth-muscle antibody were negative. Serum angiotensin-converting enzyme levels were normal. He was diagnosed with sarcoidosis and started on moderate-dose corticosteroids and azathioprine. One month after initiation of prednisolone and azathioprine, he was discovered to have hypogammaglobulinemia IgG 5.4 g/L (8.5–18.0), IgA <0.4 g/L (1.2–4.4), and IgM 0.7 g/L (0.4–2.4) on a myeloma panel. There were no immunoglobulin levels performed before his diagnosis of sarcoidosis. He later developed listeria meningoencephalitis and 2 episodes of disseminated zoster, and his IgG levels further dropped to 3.3 g/L. He was diagnosed with presumed granulomatous common variable immunodeficiency (CVID) and given monthly intravenous immunoglobulin (IVIG) replacement. Investigations revealed mild leukopenia (lymphocytes 856 cells/uL [1000–3500]), slightly low levels of CD4 177 cells/uL (280–1430), normal levels of CD8, CD19, natural killer cells, and switched memory B cells (CD19+CD27+IgD-) of 0.68%. There was a blunted response to pneumococcal and 2 doses of Moderna coronavirus-19 vaccination. Targeted next-generation sequencing primary immunodeficiency disorder (PID) panel identified a heterozygous missense variant of uncertain significance c.506C>A (p.Ala169Glu) in the CTLA-4 gene which replaces alanine (neutral and nonpolar) with glutamic acid (acidic and polar). This variant is not present in the population database. Surfacing staining for CTLA-4 showed reduced expression of CTLA-4 on both unstimulated and stimulated Foxp3+T cells by flow cytometry (Fig. 2). Further history from the patient revealed that 4 of his 12 siblings developed early-onset gastrointestinal and breast malignancy in their forties. His parents and siblings did not have recurrent infections or autoimmune disease and they declined genetic testing. He is currently treated with regular replacement IVIG, prednisolone, and ciclosporin. Since the initiation of monthly IVIG, he has not experienced any serious or major infections.

The second patient is a 28-year-old Chinese male with a prior history of atopic dermatitis diagnosed at 13 years old. He developed recurrent sinusitis at 18 years old, followed by 3 episodes of pneumonia over the course of 2 years. He was found to have chronic rhinosinusitis, bronchiectasis, hypogammaglobulinemia (IgG 4.3, IgM 0.4, and IgA 0.5 g/L), and blunted postvaccination responses to pneumococcus and tetanus. He does not have any family history of recurrent infections, malignancy, or autoimmune diseases. He was initially treated for presumed CVID with regular

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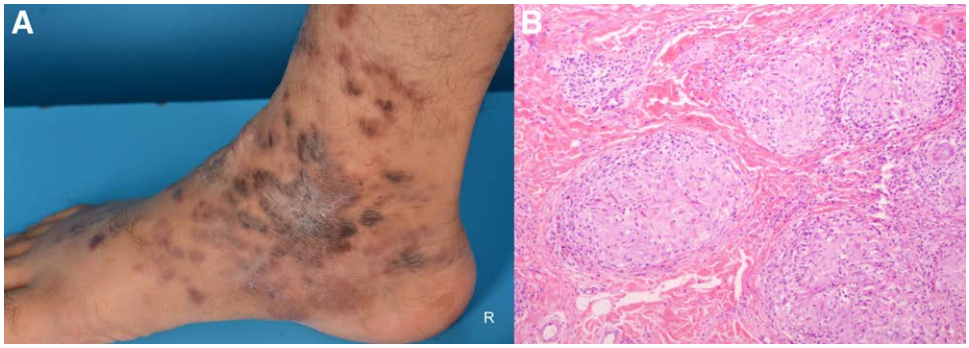

Figure 1. **(A)** Violaceous papules and nodules over right leg of patient 1. **(B)** Skin biopsy showing non-necrotizing granulomas within the dermis in patient 1 (Hematoxylin and eosin stain, magnification ×200).

Expression of CTLA-4

	Mean Fluorescence Intensity (MFI)		CTLA-4 fold increase after stimulation*
	Unstimulated	Stimulated^	
Patient	404	4396	10.9
Control	789	8243	10.4

^Cells stimulated with anti-CD3 & CD28
*Calculation of CTLA-4 fold increase is $MFI_{stimulated}/MFI_{unstimulated}$

Comments : Patient's cells show reduced expression of CTLA-4 on both unstimulated and stimulated Foxp3+ T cells (Treg).

Figure 2. Surface staining of CTLA-4 in unstimulated and stimulated Foxp3+ T cells in patient 1. CTLA-4, Cytotoxic T-lymphocyte antigen 4.

IVIG while continuing to require topical corticosteroid for control of eczema. Two years later, he developed immune-mediated thrombocytopenia. He later developed photosensitive eczematous patches on his face, chest, and legs (Fig. 3). Phototest performed supported a diagnosis of chronic actinic dermatitis. He was eventually found to have a novel deletion on his CTLA-4 gene c.522del (p.Leu174Phefs*13) on the next-generation sequencing PID panel. This deletion is a frameshift variant that disrupts the last 50 amino acids of the CTLA-4 protein and truncates the transmembrane form of the CTLA-4 protein, leading to a complete loss of the cytoplasmic tail, which may disrupt endocytosis, internal cell signaling, and receptor recycling. This variant is not present in population databases. Functional testing showed reduced CTLA-4 expression on resting T regulatory cells by flow cytometry, with levels returning to normal with stimulation. The CTLA-4 transendocytosis assay is not available locally. As LRBA binds to the cytoplasmic tail of CTLA-4, we postulate that this patient resembles more like LRBA deficiency. His family members declined genetic testing. He is treated with regular IVIG, prednisolone, and methotrexate.

3. Discussion

CTLA-4-H is an autosomal dominant immune dysregulation disorder with an estimated penetrance of 60% to 70% [4, 5]. Primary immune regulatory disorders are an increasingly recognized and growing subgroup of PIDs with predominant noninfectious manifestations including autoimmunity, hyperinflammation, early-onset malignancy, and severe atopy [6].

Advances in genetic testing have resulted in an accelerated increase in the rate of discovery of new genetic defects in PID in the last decade. Genetic testing is useful to achieve a molecular diagnosis and may change the diagnosis and management for targeted therapies [7]. In our 2 patients, the added benefits of diagnosing CTLA-4 or LRBA deficiency over their presumed CVID diagnosis include allowing for better prognostication, antenatal counseling, and the potential use of targeted therapies such as abatacept. One of the challenges is the interpretation of variance of uncertain significance (VUS), a common encounter in our experience, likely due to the under-representation of the Asian population in human genomics research. Functional assays for the analysis of VUS are important for pathogenic classification, yet there is often a lack of such testing available, especially in the Asia-Pacific region. Countries with limited diagnostic capabilities or resources can tap on regional collaborative networks to improve the management and care of PID patients [8].

PID is commonly perceived to be a pediatric disease; however, the reality is that more than 50% of incident PID cases worldwide are diagnosed over the age of 25 years [9]. There is a lack of awareness among the adult medicine community. Cases frequently go undiagnosed for many years, resulting in high cumulative medical expenses, lost productivity from medical absenteeism, and early death [10]. The adult-onset presentation and presentation with autoimmunity rather than recurrent or serious infections in the first patient led to a diagnosis made 9 years after his presentation. It is thus important to recognize the other manifestations of immunodeficiencies beyond infections as these may present with mimics

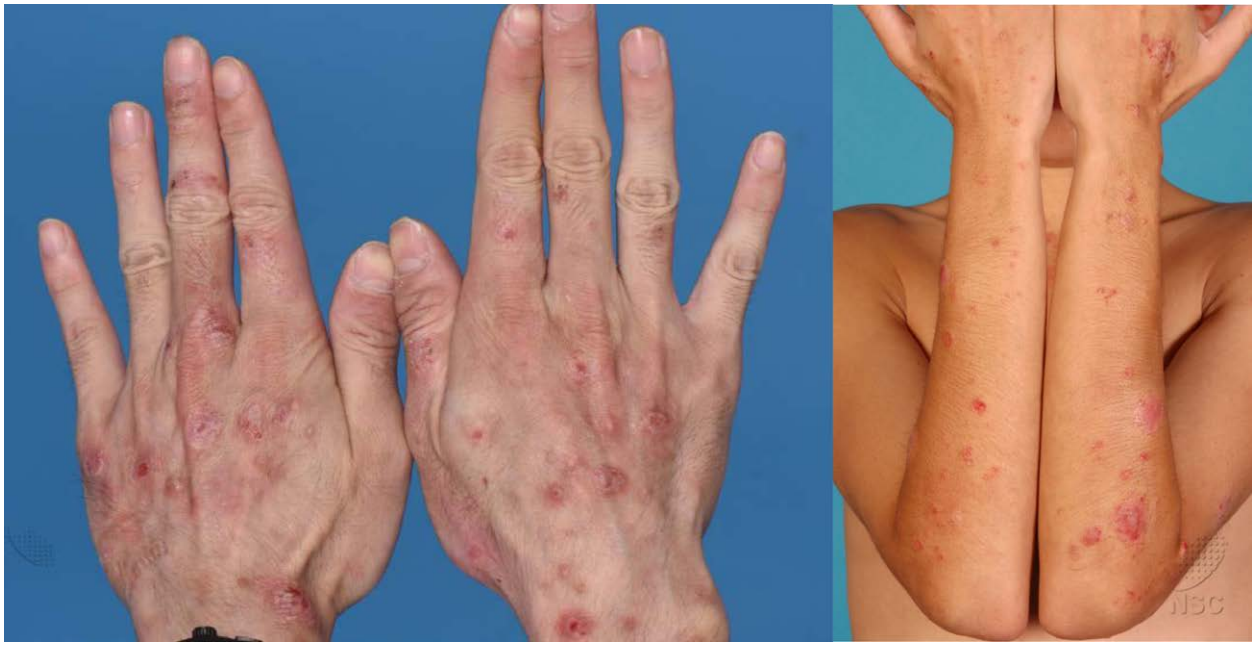

Figure 3. Eczematous discoid plaques over the hands and forearms in patient 2.

to rheumatologists, allergists, gastroenterologists, hematologists, and various internal medicine specialties [11]. Finally, it is important to develop adult clinical immunology services specializing in adult PID, as early diagnosis, evaluation, and management are key to avoiding the development of the 4 major comorbidities in life: recurrent infections, autoimmunity/lymphoproliferative disorders, malignancies, and end-organ impairments.

4. Conclusion

Diagnosis of adult-onset PID can be a challenge when these present with autoimmune phenomena rather than recurrent infections. Genetic testing in this era of rapidly expanding knowledge of inborn errors of immunity and the detection of VUS may have potential clinical and therapeutic implications.

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None.

Conflicts of interest

The authors have no financial conflicts of interest.
Both patients provided their consent for publication.

Author contributions

X.R.L., Y.Y.L., W.J.T.: conception and design, acquisition of data, drafting of the article. C.C.G., Y.L.L., S.S.J.L., C.W.L., Y.B.T.: provision of resources and acquisition of data. All authors have read and agreed to the published version of the manuscript.

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