Pulmonary Manifestations of Immune Dysregulation in CTLA-4 Haploinsufficiency and LRBA Deficiency

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Abstract

Objective: The primary immunodeficiency syndromes of cytotoxic T lymphocyte-associated protein 4 (CTLA-4) haploinsufficiency and lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency present with multisystem immune dysregulation. The aim of this study was to characterize and compare the pulmonary manifestations of these two diseases. Methods: We retrospectively analyzed the pulmonary clinical, radiologic, and histopathologic characteristics of 6 patients with CTLA-4 haploinsufficiency and 4 patients with LRBA deficiency with pulmonary involvement followed at a large tertiary care center. Results: Chronic respiratory symptoms were more frequent in patients with LRBA deficiency versus CTLA-4 haploinsufficiency (4/4 versus 1/6). Cough was the most common respiratory symptom. Abnormalities in pulmonary exam and pulmonary function testing were more frequent in LRBA deficiency (4/4, 2/4) compared to CTLA-4 haploinsufficiency (1/6, 2/6). Chest CT findings included mediastinal lymphadenopathy (4/4 in LRBA deficiency versus 1/4 in CTLA-4 haploinsufficiency), pulmonary nodules (4/4, 3/4), ground-glass opacification (4/4, 3/4), and bronchiectasis (3/4, 1/4). Lymphocytic inflammation, concentrated bronchovasculocentrically and paraseptally, was observed in all patients who had lung biopsies (N=3 with LRBA deficiency; N=3 with CTLA-4 haploinsufficiency). Granulomas were seen in all patients with CTLA-4 haploinsufficiency and in no patients with LRBA deficiency. Conclusion: Despite phenotypic overlap amongst these diseases, LRBA deficiency demonstrated greater severity of pulmonary disease, indicated by respiratory symptoms, pulmonary exam, and intrathoracic radiologic findings. Lymphocytic inflammation is a key histologic feature of both of these disorders. Pediatric pulmonologists should suspect these disorders in the appropriate clinical, radiological, and pathological context to better diagnose and treat these patients.

Introduction

Primary immune deficiency syndromes predispose to chronic lung disease as a consequence of immune dysregulation, encompassing immune deficiency and autoimmunity[1]. With our evolving understanding of their genetic underpinnings, new monogenic disorders of immune dysregulation affecting regulatory T cell function are being identified. Previously classified as common variable immunodeficiency (CVID), cytotoxic T lymphocyte-associated protein 4 (CTLA-4) haploinsufficiency and lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency were first described in 2012 and 2014, respectively[2; 3]. The features of immune dysregulation that characterize both disorders are strikingly similar, and include hypogammaglobulinemia, autoimmune cytopenias, recurrent infections, enteropathy, lymphoproliferative infiltration of organs, and lung disease[4-7].

CTLA-4 and LRBA play important roles in regulation of T-cell activation and expansion[8; 9]. CTLA-4 is an inhibitory protein that is constitutively expressed on the cell surface of regulatory T cells. In conventional T cells, CTLA-4 is predominantly located in recycling endosomes, with maintenance of intracellular stores facilitated by LRBA binding to the cytoplasmic tail of CTLA-4[9]. In response to T-cell activation, CTLA-4 is trafficked to the cell surface and functions to inhibit cellular proliferation through blockade of T cell costimulation by antigen presenting cells. As demonstrated in *Ctla4* knockout mice, the loss of this inhibitory checkpoint results in immune dysregulation and lymphocytic infiltration of multiple organs[10; 11]. Both CTLA-4 haploinsufficiency and LRBA deficiency may be effectively managed with abatacept, a CTLA-4-Ig fusion protein[9; 12; 13].

Pulmonary manifestations of CTLA-4 haploinsufficiency and LRBA deficiency are becoming increasingly well characterized. Respiratory tract infections are frequently reported among LRBA-deficient patients (61-80%)[4; 14; 15]. Bronchiectasis has been reported in up to one-third of patients with LRBA deficiency[4; 16]. Radiographic findings of ground glass opacities (GGOs) and pulmonary nodules and the pathologic diagnosis of granulomatous-lymphocytic interstitial lung disease (GLILD) are reported in the literature as noninfectious pulmonary manifestations of LRBA deficiency[4; 14-16]. Recently, Schwab et al described pulmonary disease in 133 subjects with CTLA-4 haploinsufficiency including pneumonia (39%), GLILD (36%), bronchiectasis (25%) and asthma (2%)[7].

CTLA-4 haploinsufficiency and LRBA deficiency are likely under-recognized causes of pulmonary morbidity in the pediatric population. In order to provide appropriate diagnosis and management, it is imperative that the clinical, radiologic, and histologic spectrum of lung disease be recognized by the subspecialists likely to encounter these patients. Here, we provide a comprehensive multidisciplinary retrospective review of the pulmonary manifestations of patients with CTLA-4 haploinsufficiency and LRBA deficiency evaluated in the pulmonary clinic at a single tertiary care center in order to alert pediatric pulmonologists to suspect these monogenic disorders of immune dysregulation in the appropriate clinical context.

Materials and Methods

Patients

The retrospective study was conducted at Boston Children's Hospital, Boston, MA, USA, with institutional review board approval. All patients diagnosed with CTLA-4 haploinsufficiency or LRBA deficiency by confirmed pathogenic mutation in the *CTLA4* or *LRBA* genes, and followed in pulmonary clinic between April 2002 and March 2020, were included in the study. Gene mutations were identified using targeted sequencing by comparative genomic hybridization. Patients 1-3 and 7-9 have been previously reported[7; 17; 18].

Study design

Medical records of six patients with CTLA-4 haploinsufficiency and four patients with LRBA deficiency were retrospectively reviewed. Data extracted from the electronic medical record included clinical course, evaluation, management, and outcome. Review included detailed re-evaluation of pulmonary function tests (PFTs), chest x-rays (CXR), chest computed tomography (CT) studies, and lung biopsy specimens by our multidisciplinary team of pulmonologists, immunologists, radiologists, and pathologists.

Results

Patient demographics and clinical characteristics

We identified six patients with CTLA-4 haploinsufficiency and four patients with LRBA deficiency followed in pulmonary clinic at Boston Children's Hospital. Individual patient characteristics are summarized in Table 1 and Table 2, for CTLA-4 haploinsufficiency and LRBA deficiency, respectively. One patient with CTLA-4 haploinsufficiency and three patients with LRBA deficiency had a history of parental consanguinity. Median age at genetic diagnosis was 17 years (range 14-23 years) in the CTLA-4 cohort compared to 7 years (range 3-11 years, 2 unknown) in the LRBA cohort. For CTLA-4 patients, clinical symptom onset was at <1 year of age for 3/6 patients and 6-10 years of age for 3/6 patients. The clinical phenotype included enteropathy

(6/6), autoimmune cytopenias (5/6), and lymphoproliferative disease (5/6). Lymphoproliferative disease was defined clinically by lymphadenopathy, hepatomegaly, or splenomegaly. For LRBA patients, clinical symptom onset was at <1 year of age for 1/4 patients and 1-5 years of age in 3/4 patients. The clinical phenotype included enteropathy (2/4), autoimmune cytopenias (3/4), and lymphoproliferative disease (4/4). Age at onset of pulmonary disease manifestations could not be determined from chart review.

Pulmonary manifestations in CTLA-4 haploinsufficiency

Median age at initial evaluation in pulmonary clinic was 14.6 years (range 9-18 years of age). At the time of initial evaluation in pulmonary clinic, only one patient reported chronic respiratory symptoms whereas the majority (5/6) were asymptomatic from a respiratory standpoint. Asthma had previously been diagnosed in two patients. History of cough was the most frequently reported respiratory symptom (4/6). Recurrent respiratory infections were reported by three patients. One patient had a history of prior ICU admission for respiratory illness. None of the patients had baseline hypoxemia. The pulmonary exam was normal in most patients (5/6); crackles were observed in one patient. PFTs at the time of initial evaluation by a pulmonologist were abnormal in 2/6 patients. Abnormal PFTs demonstrated a restrictive pattern (2/6) and reduced diffusion capacity (1/6).

Pulmonary manifestations in LRBA deficiency

Median age at initial evaluation in pulmonary clinic was 17.9 years (range 10-20 years of age, 1 unknown). At the time of initial evaluation in pulmonary clinic, most patients (3/4) reported chronic respiratory symptoms. Asthma had previously been diagnosed in one patient. History of cough was the most frequently reported respiratory symptom (4/4). Recurrent respiratory infections were reported in all patients (4/4). All four patients had a history of prior ICU admission for respiratory illness. Mild baseline hypoxemia was observed in 2/4 patients. The pulmonary exam was abnormal in all patients (4/4); crackles and clubbing were the most common findings (2/4). PFTs at the time of initial evaluation by a pulmonologist were abnormal in 2/4 of patients, demonstrating mixed obstructive/restrictive (1/4) and restrictive (1/4) defects.

Comparison of pulmonary manifestations between CTLA-4 haploinsufficiency

and LRBA deficiency

When the clinical pulmonary manifestations of CTLA-4 haploinsufficiency and LRBA deficiency were directly compared, a higher frequency of recurrent respiratory infections in patients with LRBA deficiency compared with CTLA-4 haploinsufficiency (4/4 versus 3/6) and baseline hypoxemia (2/4 versus 0/6) were reported. ICU admission for respiratory illness occurred more commonly in patients with LRBA deficiency (4/4 versus 1/6). Abnormalities on pulmonary exam (4/4 versus 1/6) and pulmonary function testing (2/4 versus 2/6) were more prevalent in LRBA-deficient patients.

Chest radiographic findings in CTLA-4 haploinsufficiency

Four of six patients had available chest radiographs. Two patients had a standard chest one view, and two patients had a standard chest two views. Bilateral, symmetric, and multifocal ground-glass opacities were seen in 2/4 patients (Figure 1A). The geographic extent of lung abnormality was between 50-75% in one patient, between 25-50% in one patient, and less than 25% in two patients. No patients had mediastinal lymphadenopathy.

Chest radiographic findings in LRBA deficiency

All four patients had available chest radiographs. Two patients had a standard chest one view, and the remaining two patients had a standard chest two views. Bilateral, symmetric, and multifocal ground-glass opacities were seen in 4/4 patients. Bilateral and symmetric interstitial thickening was seen in one patient (Figure 2A). Pulmonary nodules were seen in 2/4 patients (Figure 3A). Consolidation was seen in 1/4 patients. Mediastinal lymphadenopathy was seen in 3/4 patients (Figure 3A). The geographic extent of lung abnormality was greater than 75% for all four patients.

Chest CT findings in CTLA-4 haploinsufficiency

Four of six patients had chest CT studies available for review. Two patients had chest CT studies performed with intravenous contrast and two patients had chest CT studies without intravenous contrast. The initial chest CT was abnormal in all four patients (range 6-18 years of age). On chest CT studies, subcentimeter pulmonary nodules (mean diameter = 7 mm) were seen in 3/4 patients (Figure 1B). Additional pulmonary parenchymal findings included ground-glass opacification in 3/4, interstitial thickening in 1/4, and bronchiectasis in 1/4 patients. The geographic extent of lung abnormality was between 50-75% in one patient, between 25-50% in one patient, and less than 25% in two patients. Mediastinal lymphadenopathy was seen in one of the four patients and small in size and extent.

Chest CT findings in LRBA deficiency

All four patients had chest CT studies with intravenous contrast available for review. The initial chest CT was abnormal in all four patients (range 3-19 years of age). On chest CT studies, pulmonary nodules (mean diameter = 20 mm) were seen in all four patients. Other findings include ground-glass opacification in 4/4, bronchiectasis in 3/4, consolidation in 2/4, and interstitial thickening in 1/4 patients (Figures 2B and 3B). The geographic extent of lung abnormality was greater than 75% in all four patients. Mediastinal lymphadenopathy was seen in all four patients and large in size and extent (Figure 3C).

Comparison of chest CT imaging findings between CTLA-4 haploinsufficiency and LRBA deficiency

When chest CT imaging findings of CTLA-4 haploinsufficiency and LRBA deficiency were directly compared, a higher frequency of mediastinal lymphadenopathy (4/4 versus 1/4), pulmonary nodules (4/4 versus 3/4), ground-glass opacification (4/4 versus 3/4), bronchiectasis (3/4 versus 1/4), and consolidation (2/4 versus 0/4) were detected in patients with LRBA deficiency in comparison to CTLA-4 haploinsufficiency. In addition, the size of pulmonary nodules was larger (mean 20 mm in LRBA deficiency versus mean 7 mm in CTLA-4 haploinsufficiency) in patients with LRBA deficiency. Furthermore, the presence (4/4 versus 1/4) and extent (large versus small) of mediastinal lymphadenopathy as well as the extent of parenchymal abnormalities (including ground-glass opacification, bronchiectasis, and consolidation) were higher in pediatric patients with LRBA deficiency.

Lung pathology in CTLA-4 haploinsufficiency (Figures 4A and 4B)

Lung tissue biopsy specimens were obtained in three of the six patients at ages 13 (P1), 14 (P3) and 18 (P6); all were obtained prior to initiation of abatacept or HSCT. Two lung biopsies (P1 and P6) showed patchy interstitial lymphoid hyperplasia and sparse scattered well-formed (P1) and poorly formed (P6) granulomas; one lung biopsy (a small sample; P3) showed dense and confluent granulomatous and lymphoplasmacytic inflammation. In the two larger biopsies (P1 and P6), there was paraseptal and perivascular prominence of lymphoid infiltrates. Chronic small airway remodeling, with increased mural smooth muscle, was present in all cases. Interlobular septal thickening was present in all cases. Organizing fibrinous pleuritis was observed in one case (P1). Alveolar septal fibrosis was not identified.

Lung pathology in LRBA deficiency (Figures 4C and 4D)

Lung tissue biopsy specimens were obtained in three of the four patients at ages 4 (P10), 9 (P7) and 20 (P9) prior to abatacept initiation or HSCT. All biopsies showed patchy interstitial lymphoid hyperplasia with areas of paraseptal and perivascular accentuation. Chronic small airway remodeling, with increased mural smooth muscle, was present in all cases. Interlobular septal thickening was present in all cases. One patient (P9) had sparse patchy peripheral endogenous lipoid pneumonia. Alveolar septal fibrosis was identified in only one patient (P10), characterized by a loose fibroblastic expansion without substantial collagen deposition. Pleural fibrosis was seen in all 3 cases, accompanied by patchy pleural lymphocytic inflammation in one (P9). Granulomatous inflammation was not observed.

Comparison of pathology findings between CTLA-4 haploinsufficiency and LRBA deficiency

When pathology findings of CTLA-4 haploinsufficiency and LRBA deficiency were directly compared, all patients with lung biopsies demonstrated interstitial lung disease with lymphocytic inflammation. None of the LRBA-deficient patients had granulomas whereas all CTLA-4-deficient patients with lung biopsies showed granulomatous disease. Alveolar septal fibrosis was a rare finding, observed in a single patient with LRBA-deficiency.

Treatment and outcome in CTLA-4 haploinsufficiency

Median length of pulmonary follow-up was 35.5 months (range 0-209 months). Treatment strategies included systemic steroids (4/6), IVIG (4/6), hydroxychloroquine (3/6), rapamycin (3/6), mycophenolate mofetil (2/6), and other immunomodulatory therapies (Table 1). All patients were managed with abatacept (6/6). Available data indicated improvement in symptoms (3/6), pulmonary function testing (3/6) and chest CT imaging (3/6) after initiation of abatacept. Three patients were referred to our pulmonary clinic for evaluation after initiation of abatacept for enteropathy (P3-P5) and two were on abatacept at the time of initial outpatient pulmonary evaluation (P4,5). Three patients underwent hematopoietic stem cell transplant (HSCT). Two patients died secondary to HSCT complications.

Treatment and outcome in LRBA deficiency

Median length of pulmonary follow-up was 23 months (range 15-28 months). Management included systemic steroids (4/4), IVIG (4/4), azithromycin (3/4), inhaled corticosteroids (3/4), and other immunomodulatory therapies (Table 1). All patients were managed with abatacept (4/4). Available data indicated improvement in symptoms (3/4), pulmonary function testing (2/4) and chest CT imaging (3/4) after initiation of abatacept. One patient (P10) did not have follow up after initiation of abatacept. One patient underwent HSCT; all four patients were alive at last pulmonary follow-up.

Discussion

This retrospective study provides a comprehensive review of the pulmonary manifestations of CTLA-4 haploinsufficiency and LRBA deficiency. Consistent with prior studies, there was phenotypic overlap amongst CTLA-4- and LRBA-deficient patients, which is consistent with the shared underlying pathogenesis of disease as LRBA is a key player in the recycling of CTLA-4 to the surface of regulatory T cells[9]. To our knowledge, this report represents the first comparison of pulmonary findings in CTLA-4-and LRBA-deficient patients. Despite the similarities in immunologic features, LRBA deficiency appears to confer greater severity of pulmonary disease as indicated by respiratory symptoms, pulmonary exam findings and intrathoracic radiologic findings in pediatric patients.

With regard to clinical characteristics, patients with LRBA deficiency had more chronic and severe respiratory symptoms and clinical exam abnormalities than patients with CTLA-4 haploinsufficiency. While clinical symptom onset was earlier for patients with LRBA deficiency, the timing of onset of pulmonary disease manifestations could not be determined retrospectively in this small cohort. Of interest, pulmonary function testing was normal in some patients in both groups at initial pulmonary evaluation, but a majority of patients had radiographic and pathologic abnormalities.

The imaging findings in our study are comparable to the findings seen in previously published studies in both diseases, including pulmonary nodules, ground-glass opacification, interstitial thickening, and bronchiectasis[4; 7; 14-16]. However, our study showed a substantial difference in the frequency and extent of thoracic abnormalities when imaging findings of CTLA-4 haploinsufficiency and LRBA deficiency were directly compared. In our study, the size of pulmonary nodules was larger, and the geographic extent of lung abnormalities was higher in pediatric patients with LRBA deficiency in comparison to those seen in pediatric patients with CTLA-4 haploinsufficiency. In addition, the results of our study demonstrate a higher frequency and extent of mediastinal lymphadenopathy seen in pediatric patients with LRBA deficiency. Although the patient population is small in our study, the findings suggest that LRBA deficiency may lead to more severe thoracic abnormalities than CTLA-4 haploinsufficiency in the pediatric population.

The pathology findings in our study expand upon prior studies describing lung involvement in patients

with LRBA deficiency and CTLA-4 haploinsufficiency. Presently, the term GLILD has been used to denote inflammatory lung disease occurring in the setting of CVID, broadly encompassing findings such as lymphocytic interstitial pneumonia, lymphocytic bronchiolitis, and/or granulomatous inflammation, amongst others[19]. GLILD has also been used to describe lung pathology in patients with LRBA deficiency and CTLA-4 haploinsufficiency[7; 15]. In this cohort of patients, we focused on detailed characterization of the specific histologic patterns of disease with the goal of elucidating additional diagnostic and mechanistic information.

In this cohort of patients, the lymphocytic inflammation was compartmentalized, and accentuated around blood vessels, airways, and interlobular septa. Since it was not confined to airways, as would be expected in a reaction to a descending infection or other airway irritant, this architectural pattern of inflammation, which has not yet been described in LRBA or CTLA-4 deficiency, may support primary immune dysregulation as an etiology. The lack of granulomas in LRBA deficiency is intriguing because it suggests a pathobiologic difference between CTLA-4 and LRBA lung disease. It would be interesting to determine whether confinement of granulomatous disease to patients with CTLA-4 haploinsufficiency observed in this small cohort is also present in prior studies in which lung disease was reported broadly as GLILD.

Most patients in our cohort underwent biopsy during childhood and therefore our pediatric series may help establish the pathology of "early" LRBA and CTLA-4 lung disease. We propose that florid lymphocytic inflammation characterizes the early phase of disease, possibly progressing to fibrosis later in the disease course. The presence of alveolar septal fibrosis was a finding in the oldest patient in the cohort with LRBA deficiency (P9; age 20 at biopsy).

Taken together, the findings in this small cohort of patients suggest that LRBA deficiency and CTLA-4 haploinsufficiency are not uniform in severity of pulmonary disease. This difference has been hypothesized to be the result of LRBA control of CTLA-4 post-translational expression with defective LRBA resulting in CTLA-4 degradation and lower levels of surface CTLA-4 overall in LRBA deficiency as compared to CTLA-4 haploinsufficiency[9; 18; 20]{Alroqi, 2018 #732}. Additional studies are required to understand the exact role of LRBA and CTLA-4 in the pathogenesis of lung disease as well as genetic and epigenetic factors that may be contributory to the observed clinical heterogeneity in these disorders. A limitation of this study is the small sample size, which may bias the results.

In summary, CTLA-4 haploinsufficiency and LRBA deficiency present with clinical, radiological, and histopathological characteristics of interstitial lung disease, distinct from structural lung damage due to recurrent infections. At our center, chest CT and serial pulmonary function testing were used to monitor for development and progression of pulmonary disease. However, no guidelines currently exist with regard to the approach to and frequency of evaluating pulmonary disease in this population[21]. As suggested by our data, reliance on report of symptoms and pulmonary function testing may be insufficient for early detection of lung disease. In a recent study of patients with CVID, pulmonary function testing did not correlate with the presence of pulmonary abnormalities on CT study[22]. Thus, if chest CT is performed only on a clinical basis, preclinical disease in asymptomatic patients may be missed.

With regard to outcomes, the limited longitudinal data presented here demonstrates that a precision medicine approach, management with the CTLA-4-Ig fusion protein abatacept, may lead to radiographic and functional improvement as well as normalization of the soluble form of the IL-2 receptor alpha chain (sCD25/IL2R), which is a marker of T cell activation (data not shown). Studies are needed to further define the role of sCD25/IL2R as a potential biomarker of regulatory T cell activity in monitoring treatment and disease progression, and to identify new biomarkers to advance a precision medicine approach. While management with abatacept is promising for preventing uncontrolled lymphoproliferation and immune dysregulation, larger prospective studies of the long-term safety and efficacy of abatacept for the treatment of these conditions is needed[12]. Of the four patients who underwent HSCT, two are alive with a mean follow-up of 28.5 months (range 10-47 months) in the surviving patients.

This retrospective investigation highlights the importance of considering monogenic disorders of immune

dysregulation in pediatric patients presenting with lung disease in the context of other clinical features of immune deficiency and autoimmunity. Pulmonologists should consider screening for mutations in *CTLA4* and *LRBA,*amongst other genes implicated in immune dysregulation syndromes, in patients presenting with a CVID-like phenotype and pulmonary complications (Figure 5). CTLA-4 haploinsufficiency and LRBA deficiency likely represent underrecognized causes of chronic respiratory disease as demonstrated by the number of patients referred with a diagnosis of asthma and the number of patients with chronic respiratory symptoms at the time of referral for pulmonary evaluation. It is important to note that some of the patients in these genetically defined cohorts had normal physical exam findings and pulmonary function testing at initial evaluation, but subsequently were found to have strikingly abnormal imaging and pathologic findings. Therefore, when referred patients who are known to have these genetic diagnoses, comprehensive pulmonary evaluation including baseline chest CT and close long-term pulmonary follow up is crucial to monitor for the presence of active pulmonary disease. Given the potential for immunomodulatory agents, particularly targeted therapy with abatacept, to dramatically alter disease trajectory by preventing infectious and autoimmune sequelae as well as malignancy, it is crucial that pulmonologists focus on increased awareness and early recognition of these conditions.

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