An unusual mimicker of asthma in an active duty army physician: Common variable immunodeficiency presenting as granulomatous lymphocytic interstitial lung disease

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A B S T R A C T

Active duty service members are frequently diagnosed with asthma after referral to pulmonary for undifferentiated cough and dyspnea. Occasionally, patients have symptoms despite optimal therapy necessitating evaluation for asthma mimickers. We present a 48 year-old active duty physician who initially presented in 2007 with dyspnea and cough. Despite the absence of variable obstruction on spirometry, a clinical diagnosis of asthma was made. The patient’s symptoms were temporized with inhaled corticosteroids and bronchodilators, titrated to his symptoms, until eventual therapeutic failure resulted in re-referral to pulmonary. Chest computed tomography (CT) showed ground-glass nodules and patchy airspace opacities with evidence of thoracic lymphadenopathy. A positron emission tomography CT (PET CT) showed diffuse adenopathy throughout his thorax and abdomen with high avidity for fluorodeoxyglucose (FDG)-18. This prompted a comprehensive pathologic and serologic evaluation that unveiled a diagnosis of granulomatous-lymphocytic interstitial lung disease (GLILD) secondary to common variable immunodeficiency (CVID). Once the diagnosis was made, the patient was treated with intravenous immunoglobulin resulting in clinical improvement. Given the dynamic airway collapse, vocal cord dysfunction, respiratory bronchiolitis, eosinophilic bronchitis, interstitial lung disease, eosinophilic granulomatosis with polyangiitis, bronchiectasis, and chronic obstructive pulmonary disease masquerading as asthma that should be considered in refractory cough and dyspnea with radiographic abnormalities.

1. Background

Respiratory complaints among active duty service members are common. Earnest and thorough evaluations of pulmonary symptoms are particularly important in service members given the impact these symptoms can have on operational readiness [1]. These evaluations often result in a diagnosis of asthma which is as common amongst military members as in the general population [2]. However, there are numerous ways asthma may present and many asthma mimickers can result in misclassification or misdiagnosis [3]. Patients diagnosed with asthma and unsuccessfully treated with appropriately dosed inhaled corticosteroids, bronchodilators and other asthma therapies may actually suffer from one such mimicker [4]. Asthma mimickers often include dynamic airway collapse, vocal cord dysfunction, respiratory bronchiolitis, eosinophilic bronchitis, interstitial lung disease, eosinophilic granulomatosis with polyangiitis, bronchiectasis, and chronic obstructive pulmonary disease [1,5–7]. Here we describe the case of an active duty service member treated for asthma with minimal success over the course of several years. A more in depth evaluation uncovered a rare disease masquerading as asthma that should be considered in cases of refractory asthma.

2. Case report findings

A 48 year-old active duty service member presented to his primary care provider in 2007 for dyspnea on exertion without exercise limitations. He denied any history of recurrent sino-pulmonary infections but cited significant seasonal allergies during childhood requiring immunotherapy. Physical exam did not reveal any acute findings. Laboratory analysis was notable for a negative throat culture, mild microcytic anemia with normal iron studies as well as mild hypoproteinemia. Chest plain film was unremarkable. Spirometry revealed normal flow-volume loops (pre and post bronchodilation) with forced vital capacity (FVC) of 100% of predicted, forced vital capacity at 1 sec (FEV1) of 92% of predicted, forced vital capacity at 1 sec (FEV1/FVC) of 92% of predicted and an FEV1/FVC of 80% of predicted. Bronchoprovocation testing with methacholine was negative. Despite these findings, the patient was ultimately given a diagnosis of “asthma”. He tried numerous medications for symptomatic management with multiple courses of azithromycin for upper respiratory infections and oral corticosteroids for exacerbations of his symptoms. The patient’s symptoms were
controlled well enough for him to deploy to the Middle East. While in theater, he was treated with several more courses of oral corticosteroids and short-acting beta-agonists for exacerbations. In the setting of persistent symptoms, the patient was referred for allergen testing and repeat spirometry which were unrevealing. Treatment for gastroesophageal reflux disease was attempted, however, did not provide symptom relief. A high-resolution computed tomography (CT) scan did not show any obvious pulmonary parenchymal abnormalities at that time.

The patient was referred back to pulmonary in 2011 for progression of his symptoms with exertional dyspnea that precluded him from passing his military physical fitness tests. Once again, his worsening symptoms were attributed to recurrent asthma exacerbations and episodes of bronchitis for which he was treated with antibiotics and systemic steroids with minimal improvement. Due to continued progression of his disease, the patient was referred to our pulmonary clinic in the spring of 2016. A thorough chart review uncovered a CT abdomen/pelvis performed for a bout of appendicitis that demonstrated numerous ground glass nodular densities without further testing. A dedicated CT chest was obtained revealing innumerable ground glass and consolidative nodules concerning for multifocal pneumonia, mycobacterial or fungal infection, cryptogenic organizing pneumonia, chronic eosinophilic pneumonia, systemic rheumatologic disease or malignancy (Figs. 1 and 2). Additionally, significant mediastinal, supraclavicular and axillary lymphadenopathy were identified. A PET CT was ordered to further characterize these findings which re-demonstrated numerous ground glass nodular densities without further testing. A dedicated CT chest was obtained revealing innumerable ground glass and consolidative nodules concerning for multifocal pneumonia, mycobacterial or fungal infection, cryptogenic organizing pneumonia, chronic eosinophilic pneumonia, systemic rheumatologic disease or malignancy (Figs. 1 and 2). Additionally, significant mediastinal, supraclavicular and axillary lymphadenopathy were identified. A PET CT was ordered to further characterize these findings which re-demonstrated numerous ground glass nodular densities without further testing. 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These results were confirmed by the Joint Pathology Center in Maryland. In addition to pathologic evaluation, an expanded laboratory evaluation (Table 1) was performed which was notable for hypogammaglobulinemia [IgG 143 mg/dL (reference range: 400–1600 mg/dL), IgA 9 mg/dL (reference range: 70–400 mg/dL), IgM 23 mg/dL (reference range: 40–230 mg/dL)]. Allergy/immunology evaluated the patient and reviewed these results which led them to a diagnosis of CVID. The constellation of axillary lymph node granulomas, focal nodular lymphoid infiltration on TBBx, CVID and the patient’s pulmonary symptoms led to the patient’s pulmonologist diagnosing GLILD secondary to CVID. The patient was started on 600mg/kg of intravenous immunoglobulin therapy (IVIG) with marked clinical improvement and activity tolerance; however, he continues to have persistent nodular consolidations on surveillance CT scan which may necessitate systemic corticosteroids in the future.

3. Discussion

CVID refers to a cluster of genetic diseases characterized by hypogammaglobulinemia without an alternative explanation [8]. It is a diverse group of diseases in which immunoglobulin production can be impaired through a variety of mechanisms. Diagnostic criteria for CVID have evolved over the years, however, the most cited definition is that of the European Society for Immunodeficiency (ESID). They define CVID based upon clinical parameters, antibody titers and absence of co-existing T-cell pathology or hypoproliferation of T-cells [9]. Clinically, CVID results in defective B-cell unable to appropriately produce immunoglobulins despite appropriate stimulation. CVID also contributes to humoral immune system dysfunction most commonly manifesting as diseases and/or infections of the gastrointestinal tract, liver and lungs. Both the relapsing and remitting nature of CVID and myriad ways in

Fig. 1. Coronal non-contrast CT chest - image demonstrating numerous, diffuse, ground glass nodular opacities.
which it can present make it difficult to determine prevalence with certainty, however, estimates suggest 1 in 25,000 to 1 in 50,000 individuals worldwide have CVID [10].

With respect to pulmonary manifestations of CVID, one of the most challenging to manage is interstitial lung disease (ILD). A small study by Maarschalk-Ellerboek et al., demonstrated interstitial lung disease (ILD) in 34% of adult patients with CVID [11]. Specifically, this included granulomatous lung disease, lymphoid interstitial pneumonia, organizing pneumonia and lymphoproliferative disorders. GLILD represents a particularly challenging type of ILD that is rarely seen in patients with CVID, notable for both discrete granulomas and diffuse interstitial lung disease [12]. Although rare, it is one of the most concerning non-infectious complications of CVID as it carries a significant risk of mortality owing to disease progression and association with other CVID-related illnesses [13].

In general, the diagnosis of GLILD is quite uncommon. A careful history is critical, as well as serologic testing for bacteria, viruses and fungi [17]. History should focus on potential exposures to toxins or infectious agents, as well as identifying constitutional symptoms which may suggest malignancy. Pulmonary function testing should be performed, specifically looking for reduced DLCO which may indicate ILD. However, pulmonary function testing may be normal in ILD, especially in more regional disease, and does not rule out conditions such as GLILD.
Chest CT is a valuable tool for examining the lung parenchyma for evidence of ILD. CT findings such as widespread pulmonary nodules predominately in the lung bases, interlobular septal thickening, multifocal consolidations, lymphadenopathy and splenomegaly should raise suspicion for GLILD [14]. Such findings should prompt serologic testing for rheumatologic disease as well as immunoglobulin levels. The importance of these tests cannot be overstated as identifying GLILD may be the means by which underlying CVID is diagnosed, prompting a specific therapeutic approach. Additionally, bronchoscopy with BAL and TBBx can be helpful to rule-out infection and obtain tissue for pathologic evaluation, such as in this case.

Hematoyxlin and eosin staining of peribronchial lymph node samples may show non-necrotizing, well-defined granulomas with lymphoid hyperplasia [15]. This may also be seen in other extra-thoracic lymph nodes, such as the axillary lymph node samples in our patient. If extra-thoracic lymph nodes appear abnormal, pathologic testing can be helpful to rule out malignancy or other disease processes. Following the conclusion of our patient’s work up, we had uncovered non-granulomatous peribronchial inflammation and granulomatous inflammation in the axillary lymph node sample analyzed. Additionally, the transbronchial biopsies demonstrating focal nodular lymphoid infiltration and T-cell predominance within germinal centers solidified the pathologic diagnosis of GLILD.

Historically, the approach to therapy once a diagnosis of GLILD is made has been variable. A 2010 review by Park and Levinson describes several instances where corticosteroids were used to induce symptomatic and pathologic improvement [16]. In 2017, the British Lung Foundation/United Kingdom Primary Immunodeficiency Network published a consensus statement on GLILD in CVID where they recommend a multidisciplinary team including immunologists and pulmonologists. They further discuss the importance of IVIG therapy as a lead-in to corticosteroid therapy in order to attempt to normalize immunoglobulin levels prior to systemic steroid initiation as well as the use of other immunomodulatory agents as adjunctive therapy in certain circumstances. Notably, in this case our patient had a robust response to the IVIG allowing for a steroid-sparing treatment strategy.

As alluded to, CVID with GLILD is an exceedingly rare finding in the general population. To provide perspective, a 2004 review of CVID cases authored by Bates et al. of National Jewish Medical and Research Center (an international referral center for lung disease) identified only 18 cases of CVID featuring GLILD between 1985 and 2001 [13]. Of these 18 cases, only 5 of them were characterized by granulomatous inflammation which was identified in our patient following TBBx. Regarding more recent cases, Table 2 provides a summary of the cases of CVID manifesting as GLILD in the adult, identified in a PubMed search. This shows 5 cases since 2013, not including the case presenting here. Regarding our patient, there were additional findings that make this case unique amongst others described in the literature. Our patient, a middle-aged male in the United States, was symptomatic for over ten years without a diagnosis. We suspect his respiratory symptoms were due to smoke exposure.

Table 1

| Laboratory Test (units) | Result | Reference Range |
|-------------------------|--------|-----------------|
| Complete Blood Count and Differential: |
| Hemoglobin (g/dL)        | 12.7   | 14-30.0         |
| Hematocrit (%)           | 37.6   | 38-48.0         |
| White Blood Cell Count (x 10³) | 4.5   | 4.0-11.0       |
| Platelets (x 10³)        | 147    | 140-440.0       |
| Red Blood Cell Count (x 10³) | 4.61  | 4.5-5.9         |
| Mean Corpuscular Volume (FL) | 81.6  | 80-84.0        |
| Neutrophils (%)          | 58.8   | 45-75.0         |
| Lymphocytes (%)          | 27.5   | 20-40.0         |
| Monocytes (%)            | 9.5    | 0-10.0          |
| Eosinophils (%)          | 3.4    | 0-6.0           |
| Basophils (%)            | 0.8    | 0-2.0           |
| Renal Function Panel:    |
| Albumin (g/dL)           | 4.6    | 3.5-5.2         |
| Sodium (mmol/L)          | 140    | 133-145         |
| Potassium (mmol/L)       | 3.9    | 3.5-5.2         |
| Chloride (mmol/L)        | 101    | 96-108          |
| Bicarbonate (mmol/L)     | 25.0   | 22-32.0         |
| Blood Urea Nitrogen (mg/dL) | 24.6 | 8-23            |
| Creatinine (mg/dL)       | 0.96   | 0.67-1.17       |
| Calcium (mg/dL)          | 9.1    | 8.0-10.4        |
| Anion Gap (mmol/L)       | 14     | 5-14            |
| Creatinine Clearance (mL/min) | 144  | >90             |
| Thyroid Function Testing: |
| Thyroid Stimulating Hormone (mIU/mL) | 2.07 | 0.27-5.00     |
| Autoimmune/Inflammatory Markers: |
| Erythrocyte Sedimentation Rate (mm/ hr) | 7   | 0-20            |
| C-Reactive Protein (mg/dL) | <0.03 | 0.00-0.49     |
| Rheumatoid Factor         | Neg    | Neg             |
| Anti-neutrophil Cytoplasmic Antibody | Neg | Neg             |
| Rhonucleoprotein Extractable Nuclear Antibody | Neg | Neg          |
| Smith Extractable Nuclear Antibody | Neg | Neg           |
| Anti-SSA Antibody         | Neg    | Neg             |
| Anti-SSB Antibody         | Neg    | Neg             |
| Immunologic Assessment:  |
| IgG (mg/dL)              | 143.0  | 700-1600        |
| IgA (mg/dL)              | 9.0    | 70-400          |
| IgM (mg/dL)              | 23.0   | 40-230          |
| Microbiologic/Culture Assessment: |
| HIV 1/2 Antibody         | Neg    | Neg             |
| Ultrasensitive HIV-1 Viral Load (copies/mL) | 0  | 0               |
| Blastomyces Antibody     | Neg    | Neg             |
| Histoplasma capsulatum    | Neg    | Neg             |
| Coccidioides immitis      | Neg    | Neg             |
| Rapid Plasma Reagin Panel | Non-reactive | Non-reactive |
| Epstein-Barr Virus Antibody Panel | Neg for acute infection | Neg for acute infection |
| Human Herpesvirus 6 DNA (copies/ mL) | Neg | Neg           |
| Quantiferon Gold          | Neg    | Neg             |
| Respiratory Culture (from BAL) | Neg | Neg          |
| Acid Fast Culture (from BAL) | Neg | Neg           |
| Fungal Culture (From BAL) | Neg    | Neg             |

Fig. 5. Transbronchial Biopsy - peribronchial, chronic inflammation without aberrant antigen expression [H&E, 10x].

Table 2

| Case | Location | Diagnosis | Treatment | Outcome |
|------|----------|-----------|-----------|---------|
| 1    | Canada   | CVID with GLILD | IVIG, steroids | Recovered |
| 2    | United States | CVID with GLILD | IVIG, steroids | Recovered |
| 3    | United Kingdom | CVID with GLILD | IVIG, steroids | Recovered |
| 4    | Australia | CVID with GLILD | IVIG, steroids | Recovered |
| 5    | Spain    | CVID with GLILD | IVIG, steroids | Recovered |
Table 2
Summary of adult case reports of CVID and GLILD diagnosed concurrently (via PubMed Search).

| Article Title & (PMID) | Author | Year of Pub | Patient Age & Sex | Notes: |
|-----------------------|--------|-------------|------------------|-------|
| Granulomatous-lymphocytic interstitial lung disease in a patient with common variable immunodeficiency. (28583609) | Shah J. et al. | 2018 | 25 F | Case from United States. Diagnosed with transbronchial biopsy. Treated with IVIG, azathioprine and rituximab. |
| Granulomatous lymphocytic interstitial lung disease in a patient with common variable immunodeficiency. (28924106) | Hasegawa M. et al. | 2017 | 42 F | Case from Japan. Diagnosis based on surgical lung biopsy. Improved with IVIG and monoclonal antibody. |
| Management of granulomatous lymphocytic interstitial lung disease in a patient with common variable immunodeficiency. (27353655) | Pathira M. et al. | 2016 | 61 F | Case from United States. Diagnosed via transbronchial biopsy. Treated with IVIG, corticosteroids, azathioprine and rituximab. |
| Granulomatous lymphocytic interstitial lung disease as the first manifestation of common variable immunodeficiency (27242323) | Tashtoush et al. | 2016 | 55 F | Case from United States. Treated with IVIG and steroids, followed by Mycophenolate mofetil. |
| Granulomatous lymphocytic interstitial lung disease in a patient with common variable immunodeficiency (24292765) | Sugino et al. | 2013 | 44M | Case from Japan. Diagnosis via transbronchial biopsy. Treated with IVIG and erythromycin. |

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Declaration of competing interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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