Bronchiectasis Associated with Electronic Cigarette Use: A Case Series

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Abstract

Bronchiectasis (BE) is defined as a permanent, irreversible dilation of the bronchial tree. In the pediatric population, this disease process is most commonly associated with patients with Cystic Fibrosis (CF). However, bronchiectasis unrelated to cystic fibrosis is increasingly noted as a cause of chronic respiratory related morbidity worldwide. Chronic inflammation and recurrent infection result in cellular cascades that lead to irreversible structural changes of the airways. When these architectural changes occur, they confer extensive risks to morbidity usually due to continued infections. In the adult population, bronchiectasis has been associated with chronic obstructive pulmonary disease, which is mainly caused by cigarette smoking. In this report, the authors reviewed various cases of bronchiectasis in the pediatric population where the only inciting factor was electronic cigarette use.

Bronchiectasis Associated with Electronic Cigarette Use: A Case Series

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Abbreviations:

-Bronchiectasis (BE)

-Bronchoalveolar Lavage (BAL)

-Chest Xray (CXR)

-Complete Blood Count (CBC)

-Computed Tomography (CT)

-Cystic Fibrosis (CF)

-Electronic Cigarettes (E-Cigarettes)

-Electronic Cigarette or Vaping use Associated Lung Injury (EVALI)

-Electronic Medical Record (EMR)

-Eosinophilic Esophagitis (EoE)

-Forced Expiratory Flow at 25-75% (FEF 25-75)

-Forced Expiratory Volume (FEV1)

-Forced Vital Capacity (FVC)

-Immunoglobulin (Ig)

-International Statistical Classification of Disease (ICD)

-Primary Care Physician (PCP)

-Primaryciliary Dyskinesia (PCD)

-Pulmonary Function Testing (PFT)

-Tetrahydrocannabinol (THC)

-Tuberculosis (TB)

Contributors' Statement Page

Dr. Mull, pulmonary fellow, was the primary author of this manuscript. Completed the IRB and chart review prior to composing this manuscript

Dr. Shell, Section Chief of Pulmonary Medicine, was the precepting physician for Dr. Mull. He contributed revisions to the manuscript and approved final version.

Dr. Holtzlander, Assistant Professor of Pediatrics, Pulmonary Medicine, was the precepting physician for Dr. Mull. She contributed revisions to the manuscript and approved final version.

Abstract:

Bronchiectasis (BE) is defined as a permanent, irreversible dilation of the bronchial tree. In the pediatric population, this disease process is most commonly associated with patients with Cystic Fibrosis (CF). However, bronchiectasis unrelated to cystic fibrosis is increasingly noted as a cause of chronic respiratory related morbidity worldwide. Chronic inflammation and recurrent infection result in cellular cascades that lead to irreversible structural changes of the airways. When these architectural changes occur, they confer extensive risks to morbidity usually due to continued infections. In the adult population, bronchiectasis has been associated with chronic obstructive pulmonary disease, which is mainly caused by cigarette smoking. In this report, the authors reviewed various cases of bronchiectasis in the pediatric population where the only inciting factor was electronic cigarette use.

Introduction:

Bronchiectasis in the absence of CF has been increasingly detected in the pediatric population, leading to the belief that it is more prevalent than previously documented. Although few reliable estimates exist for bronchiectasis, the published data suggests its prevalence ranges widely (0.2-735 cases per 100,000 children). [1] This pathologic, irreversible, architectural airway dilatation signals underlying pulmonary disease and is an important cause of morbidity.[6]

There are several highly recognized causes of bronchiectasis in the non-Cystic Fibrosis pediatric patient population [Table 1]. Chronic and recurrent infections are most closely associated with the disease pathology. Many congenital diseases are known to cause bronchiectasis, such as alpha-1 antitrypsin deficiency, pri-

mary ciliary dyskinesia (PCD), and pulmonary sequestration. The most common cause of an obstructing lesion resulting in the formation of bronchiectasis is aspiration of a foreign body with incidence peaking by the second year of life. Bronchiectasis may even be found in the context of severe uncontrolled asthma.[3]

The use of electronic cigarettes is widely popular and continued growth in users since the introduction in the USA market in 2007 has been documented. Their appeal to the adolescent population can be attributed to the variety of the devices and multiple flavor options provided. This inhalation delivery method for Tetrahydrocannabinol (THC) use is popular among adolescents and young adults. For the first time in several decades of a steady decline of cigarette smoking among 15 to 19-year-old individuals, the statistics did not significantly change between 2015-2017. The proportion of adolescents, who used e-cigarettes at least 20 days within a month, increased from 20% in 2017 to 28% in 2018.[4] As of February 18, 2020, approximately 2,800 hospitalizations occurred as a result of e-cigarette or vaping use with associated lung injury (EVALI) and deaths were reported in all 50 states. In addition to THC use, vitamin E acetate was strongly associated with the EVALI outbreak reported in the fall of 2019, but it was only one of several additives in this relatively unregulated product that may have caused chronic airway inflammation.[5] As the devices age, the risk of inhalation due to rust, solder, and benzene is posed to the user.[6]

The increase in use by the general population has been attributed to the perceived view that e-cigarette use is a safer alternative to traditional cigarettes to inhale. Presently, there is no evidence to support that belief and negative health effects cannot be ruled out.[7] Bronchiectasis was previously linked to cigarette use due to tobaccos effect on proteolysis. Proteolysis is a form of post-translational modification that can modify protein function leading to changes that alter airway hydration, mucus clearance, and inflammation, which contribute to the pathogenesis of bronchiectasis. Unlike chronic tobacco from cigarette use, bronchiectasis caused by e-cigarettes has not been established.

Methods:

The data presented here represents a retrospective case series of patients presenting to a single, academic, medical center, Nationwide Children's Hospital (NCH), in Columbus, Ohio. The patients studied were from an encompassing chart review with inclusion and exclusion criteria based on the International Statistical Classification of Disease (ICD) and Related Health Problems composed by the World Health Organization (WHO) and was related to ICD-10 codes. (Table 2) Patients with ages ranging from 13 to 21 years with the ICD-10 codes of interest established after 2018 were targeted and reviewed. This data request analysis yielded an initial total of 116 potential cases. After a detailed review of each of the patient's medical records and establishing a history of vaping with the absence of other potential etiologies of bronchiectasis, three patients met the criteria to be discussed in this manuscript. Patients with other potential etiologies for the occurrence of bronchiectasis were excluded, such as those comprising neuromuscular diseases leading to aspirations, immunodeficiencies, Cystic Fibrosis, chromosomal anomalies, history of organ transplantation, and previous need for chemotherapy.

Results:

From January 1, 2018 through March 31, 2020, a total of 3 patients presented to the Pulmonary Division at NCH with unexplained findings of bronchiectasis. The patients in the respective cases will be denoted as Patient 1 (P1), Patient 2 (P2), and Patient 3 (P3). According to their social histories, each patient's illness appeared to be contributed to use of e-cigarettes. The median age of these patients was 17 years old with two (66.7%) of the patients being male and one (33.3%) being female. All 3 of the patients were reportedly healthy other than all three (100%) reporting symptoms of anxiety and depression. In each of the three cases, tetrahydrocannabinol (THC) was used in conjunction with nicotine products.

The patients reported use of e-cigarettes between 1-2.5 years with a median usage of 1.83 years. Based on their social histories documented in the electronic medical record (EMR), the exact frequency of daily use was difficult to discern. Reported use revealed: P1 at 2-3 times a day, P3 at 3-4 times a week, and P2 had no information documented other than the length of time used. Of the three patients, P3 was diagnosed secondary to a hospitalization for respiratory distress resulting in a computed tomography (CT)

of the chest where bronchiectasis was visualized. The other two individuals, P1 and P2, were diagnosed following their referral to Pulmonary Outpatient Clinic for a history of a chronic cough and a workup that included performing a Chest CT. All of the cases demonstrated diffuse bilateral bronchiectasis with bronchial wall thickening.[Figure 1]. Two individuals, P2 and P3, were observed to have nodules of ground glass density appearance, also known as acinar nodules, while the third individual, P1, had a single 8 mm x 8 mm x 8 mm nodule of the anterior right upper lobe, suggestive of an inflammatory vs. infectious process [Figure 2]. Prior to the Chest CT being obtained, all three individuals received a standard of care Chest Xray (CXR). The individual, P3, whose course resulted in hospitalization had a normal appearing CXR. Regarding the two patients that were evaluated on an outpatient basis, P2 had findings consistent with peribronchial thickening, but normal with no evidence of air trapping. Patient 1, who was evaluated in clinic, had reported abnormal CXR prior to the evaluation, but the radiologic report from the outside institution was not available on the EMR at NCH. Pulmonary function testing (PFT) was obtained on P1 and P2. Although performing PFT was determined to be included in the standard of care, it was delayed in P3 due to COVID-19 restrictions at our institution.

Patient 1 was a 17 year old male of Southeast Asian descent with a history significant for severe allergies and asthma that required a year of immunotherapy injections for control. He was referred to NCH pulmonary clinic for concerns of chronic cough, nasal congestion, and an abnormal CXR that prompted a chest CT resulting in a mild diffuse bronchiectasis and a nodule in the right upper lobe measuring 8 mm by 8 mm by 8 mm. The imaging was obtained prior to the clinic visit. Family and social history were significant for maternal grandmother having CF and his maternal grandfather and aunt having primary tuberculosis (TB). His mother was exposed to the two family members with active TB, but P1 had no contact with them. Social history was significant for the use of e-cigarettes for both nicotine and THC containing products for the past 2.5 years. This was confirmed by the screening of urine samples by the family. For his asthma and allergy management, he utilized fluticasone propionate (Flovent^{TM}) 44 mcg 2 puffs twice a day, montelukast 10 mg daily, fexofenadine (Allegra^{TM}) as needed, and albuterol as needed. Complement levels, rheumatoid factor, anti-smooth muscle, and antinuclear antibody testing all resulted within the normal reference ranges. Serology for endemic fungi of Blastomyces, Aspergillus, Coccidioides, and Histoplasma resulted as negative. To evaluate TB given the family history and CT chest findings of a nodule, Quantiferon and TB antigen were obtained and unremarkable for active infection or previous exposure.

During clinical visit for P1, PFTs showed no abnormalities with a forced expiratory volume (FEV1) of 99% as predicted. His FEV1 to forced vital capacity (FVC) ratio was 85% of predicted and his forced expiratory flow at 25-75% (FEF 25-75) was 92 % of predicted. The patient underwent a post bronchodilator challenge with no significant changes in his measure values that would suggest a bronchospastic component of his complaints. Given his radiologic findings and concerning history, a comprehensive workup was completed. To evaluate for CF, the chloride sweat test was performed on two separate sites and resulted in 16 and 18 mmol/L with < 30 mmol/L in the normal range. Immunoglobulin (Ig) panel was within normal limits, other than IgA being low at 38 mg/dl (reference range 60-327 mg/dl) and IgE being elevated at 878 mg/dl (reference range 0-257 mg/dl). Myeloperoxidase autoantibodies were obtained to evaluate for vascular inflammation process that can possibly result in the formation of bronchiectasis and were negative. Following this broad evaluation with unremarkable findings, it was believed that his symptoms and radiologic findings were secondary to EVALI.

Patient 2, who was a 16-year-old, Caucasian male, was referred to pulmonary by his primary care physician (PCP) for concerns of chronic cough, CXR findings of "mild pneumonia," utilization of multiple antibiotic courses, and history of e-cigarette use. Prior to his visit, he obtained a CXR where peribronchial thickening was noted with no air trapping. History was only significant for e-cigarette use with THC since October 2018 and documented ulcerative colitis. Chest CT was obtained showing multifocal bronchiectasis with associated bronchial wall thickening, mucoid plugging and acinar nodule of in the right lower lobe. Spirometry was performed and showed a mild obstructive pattern with small airway involvement with an FEV1 80% of predicted, FEV1/FVC ratio of 79% of predicted, and FEF 27-75 of 72% of predicted. Following a bronchodilator challenge, there was a significant improvement in his FEV1 with an increase of 14%. Sweat

chloride testing was obtained via two skin testing sites that resulted as 24 and 30 mmol/L (reference range <30 mmol/L) and was interpreted as normal results. The immunoglobulin panel was within normal limits

Bronchoscopy was performed electively one month following his chest CT. During that procedure, P2 was noted to have a mild tracheomalacia, as well as a follicular or cobblestone pattern in the distal airways (3^{rd} generation). [Figure 3] After obtaining a specimen for cytologic review via bronchoalveolar lavage, bleeding of the mucosa was noted with gentle suctioning. No structural abnormalities or significant mucus plugging were reported. Cultures obtained from bronchoalveolar lavage (BAL) showed normal respiratory flora with no acid-fast bacterium or fungal pathogens reported. Although there are case reports of inflammatory bowel disease causing bronchiectasis, it is relatively uncommon. Patient 2 was well-controlled on only mesalamine, a topical aminosalicylate. He never required biologic therapy for management. His gastroenterologist did not suspect his ulcerative colitis to be the etiology of his bronchiectasis, resulting in a strong clinical suspicion that his symptoms and findings may be attributed to EVALI.

Patient 3 (P3) is an 18-year-old Caucasian female with a medical history of Eosinophilic Esophagitis (EoE) diagnosed secondary to hospitalization. She was initially presented to a local urgent care facility where she was noted to have hypoxia and wheezing with lung auscultation. Patient 3 (P3) was transferred to NCH on 4 litres of low flow nasal cannula and admitted to the pediatric intensive care unit (PICU) for bilevel positive airway pressure due to her respiratory distress. She required 3 days of care in the PICU before being transferred to the general pediatric hospitalist service. Her symptoms were reported by the family and prompted an urgent evaluation that included: sudden onset of shortness of breath for the 2 day duration with associated facial color changes, persistent nighttime cough for a month, and audible wheezing for 24 hours prior to evaluation. She was started on the asthma care pathway at NCH with the use of scheduled albuterol and system glucocorticoids for the duration of her 5 day hospital course. Workup was completed during admission, and the diagnosis of bronchiectasis was established. This prompted further evaluation of other etiologies that are commonly associated with architectural changes of the airway. She had previously obtained a complete blood count (CBC) 2 months prior to her admission, which indicated a peripheral eosinophilia of 12.3 % (Reference range 1-4%) that resolved at time of admission. Total IgE was elevated at 289 (Reference range 0-257 mg/dl), as expected with a history of EoE on oral Flovent 44 mcg 2 puffs twice a day. Stool elastase was obtained to evaluate pancreatic function to determine if an additional workup was needed for Cystic Fibrosis. The results were 472 ug/g, where greater than 200 ug/g is considered normal, effectively ruling out CF. No pulmonary function testing (PFT) was obtained as an inpatient, but plans to perform the testing as a follow-up procedure were recommended. However, due COVID-19 and the transition of hospital follow-up clinical visits to telehealth, performing the PFT was delayed.

Discussion:

The pathophysiology of bronchiectasis is well-defined. However, because it can be the result of several different diseases, the etiological investigation is a challenging process. Despite the fact that 50-80% of the cases may be considered idiopathic in genesis, establishing an accurate diagnosis of its etiology can be an extensive process requiring clinical, laboratory, and pathologic testing.[8] Although it is difficult to discern the exact causes in

non-cystic fibrosis patients, attempting to determine the precise diagnosis is imperative to dictate meaningful therapeutic approaches. Chest physiotherapy and antibiotics remain a cornerstone for exacerbations because determining the etiology is vital to preventing the progression of airway architectural changes.[3]

In a 2016 study by Amorim et al., 202 cases of bronchiectasis were reviewed, with the most common cause being post infectious in roughly 30.3% of the population, with an additional 12. 3% of the individuals demonstrating other identifiable causes. The remaining 57.4% of cases exhibited no definitive etiology.[9] In another review of 1577 patients, it was suggested that an investigation of the etiologies of bronchiectasis might change the patient's management and should be incorporated into the routine clinical practice.[10] Therefore, a detailed and comprehensive medical history, in conjunction with a focused laboratory investigation, must be initiated in cases of non-CF bronchiectasis to detect the exact etiology and provide appropriate

interventions to prevent disease progression.

In adults, bronchiectasis has been associated with chronic obstructive pulmonary disease, which is mainly caused by cigarette smoking. With e-cigarette use being a relatively new delivery system for inhaled substances, the long-term effects are yet to be scientifically established. Recent reports from within the United States have relayed clinical symptoms of EVALI being associated with respiratory distress or failure with gastrointestinal symptoms of nausea, vomiting, and diarrhea, while combined with evidence of systemic inflammation. Associated radiologic findings were heterogeneous among EVALI patients and bilateral ground glass opacities were a common finding.[6] A recent report from Ghosh et al. in 2019 stated that e-cigarettes exerted a proinflammatory effect on human alveolar macrophages and could lead to airway remodeling that may risk the individual's health through the development of emphysema and/or bronchiectasis later in life.[7] However, there is currently limited research showing a connection in the formation of bronchiectasis with e-cigarette use.

In this case series of 3 patients that presented with similar complaints of coughing, shortness of breath, and concerns for intermittent respiratory distress, each individual was diagnosed with bronchiectasis. After obtaining a detailed medical history and completing an encompassing workup to exclude other conditions associated with dilatation of the airways, it was strongly believed that the genesis of these patients' bronchiectasis was associated with EVALI.

This case series contained certain limitations. First, this series was limited to a small sample size from a single large academic medical center. This may have been secondary to how relatively recent the diagnosis of EVALI or vaping associated injuries has been established and the appropriate use of ICD-10 coding by physicians in the community. In addition, the limitation of sample size may be attributed to the lack of detailed documentation of the social history, preventing additional potential cases of exhibiting the appropriate inclusion criteria from being included in the case series. Moreover, because symptoms of EVALI can present similar to other respiratory conditions, an evaluation leading to the diagnosis of bronchiectasis may not have occurred in other affected individuals.

In summary, bronchiectasis is a permanent, architectural change of the airways that is associated with a myriad of etiologies. However, a majority of cases remain idiopathic in non-cystic fibrosis patients. The morbidity with this condition is significant and must warrant a thorough investigation of the causes for each diagnosed patient.[2] Through exclusion of other potential causes, this case series intended to highlight the potential association of the genesis of bronchiectasis directly related to the use of e-cigarettes that has not been previously well-documented as an etiology.

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`Table 1 and 2.docx` available at https://authorea.com/users/326440/articles/454266-bronchiectasis-associated-with-electronic-cigarette-use-a-case-series