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FULL PAPER

Increased prevalence of tracheal diverticula in cystic fibrosis patients

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Objective: This investigation sought to evaluate the prevalence and imaging characteristics of tracheal diverticula (TD) among patients with cystic fibrosis (CF).

Methods: A total of 113 patients with CF at our institution, with a median age of 29 years, had chest CT examinations between 2002 and 2014. These imaging studies were retrospectively reviewed to assess for the presence and characteristics of TD, including quantity, size and location. The severity of the CF disease was assessed using the Bhalla CT scoring system and pulmonary function tests.

Results: Of the 113 cases reviewed, 20 (17.7%) patients were found to have 1 or more TD. The presence of TD was associated with more severe disease by imaging criteria, with a Bhalla CT score of 13.9 ± 4.3 in patients with TD

and 11.5 ± 4.3 in patients without TD. For the pulmonary function tests, forced expiratory volume in 1 s (FEV1) and FEV1 percent predicted demonstrated a trend towards worsening function in patients with TD, although the difference was not statistically significant.

Conclusion: The prevalence of TD in our patient population with CF based on chest CT exams was 17.7%. In addition, the presence of TD was associated with more severe CF disease by imaging criteria.

Advances in knowledge: TD appear to have a higher prevalence in patients with CF than in the general population, are associated with more severe CF pulmonary disease by CT criteria and are frequently under-reported by radiologists.

INTRODUCTION

Tracheal diverticula (TD) arise from the posterior tracheal wall where the cartilage rings are incomplete. Their origin can be congenital or acquired, and they usually project to the right side, possibly because of the presence of the oesophagus on the left.^{1–3} Their prevalence was initially estimated to be 1% based on an autopsy series.¹ However, more recent studies evaluating the prevalence of TD on CT have found a higher prevalence of 2–3.7%.^{2–4} TD are commonly asymptomatic; however, rarely, they can cause symptoms such as haemoptysis, dyspnoea and dysphagia.^{3–6} In addition, TD may also serve as a reservoir for secretions that ultimately result in recurrent pulmonary infections.⁵ If symptomatic, TD can be surgically excised or endoscopically cauterized.^{2,7}

Chest CT imaging reveals that TD are visualized as paratracheal air cysts commonly in the right upper posterolateral paratracheal position.⁵ A direct connection may or may not be visible. On virtual bronchoscopy, TD have been characterized with additional detail, with a wider diameter of the connection to the trachea (a wider “mouth”) generally correlated with acquired origin.^{8,9} Subsequent imaging usually reveals stability in

size and appearance, although there may be some subtle increase in size.⁴

While the precise aetiology of TD is unknown, they have been associated with obstructive lung disease, inflammation, tracheal mucus impaction and increased intrathoracic pressures as possible causes.⁴ TD is known to be associated with trachiectasis, congenital human immunodeficiency virus and Duchenne muscular dystrophy.⁴ It might be postulated that conditions associated with chronic cough, such as cystic fibrosis (CF), could predispose to TD. However, to the best of our knowledge, only two case reports describe TD in patients with CF, one with recurrent infections that were attributed to the TD.^{10,11} Recognition of an increased prevalence of TD in patients with CF carries a particular value, as it may increase the risk of additional tracheo-pulmonary infections and hasten the destruction of lung tissue. Our efforts seek to further evaluate the prevalence and imaging characteristics of TD, specifically among patients with CF.

METHODS AND MATERIALS

This study was approved by an Independent Review Board as a retrospective review, and informed consent was waived.

Patient and image selection

Medical records were reviewed for 166 patients with CF who were followed and treated at our academic institution (82 females and 84 males). Of the 166 patients, 113 patients had thin-slice (1.0- or 1.25-mm thickness) chest CT examinations completed during their evaluation and treatment course between the years 2002 and 2014. Medical records and the most recent CT images were included for the evaluation for these 113 patients. Of the 113 patient records and imaging studies, 60 patients were male and 53 were female, with an age range of 16–71 years and median age of 29 years.

Imaging observations

The imaging studies were retrospectively reviewed on a picture archiving and communication system (GE, Little Chalfont, UK) by an experienced chest radiologist (GG) and a radiology resident (JR) in consensus, in order to assess for the presence and characteristics of TD, including the quantity, size, changes with time, location and visible tracheal connection. The most recent chest CT scans of these patients were reviewed and when a diverticulum was seen, prior CT studies were evaluated in order to evaluate the dynamics in size and number of diverticula. Images were reviewed in the lung window and soft-tissue/mediastinal window in axial and coronal planes. The presence of a TD was established when an air-containing round or tubular structure was seen adjacent to the tracheal wall, with or without a definite connecting stalk between the structure and trachea. If there were neither central air bubbles within the paratracheal finding nor a clear stalk connecting the paratracheal finding (TD) to the trachea, the lesion was not determined to represent a TD. The severity of CF disease by imaging criteria was assessed using the Bhalla CT scoring system for CF, which evaluates the peribronchial thickening, bronchiectasis, mucus plugging, presence of sacculations and/or abscesses, presence of bullae, presence of collapse/consolidation and presence of emphysema.¹² This score assigns 0–3 score points to 7 of the parameters and 0–2 points to the remaining 2 parameters, resulting in a maximal score of 25 points. Associated radiology reports were also reviewed, to determine whether the presence of TD had been mentioned in the report. None of the patients had undergone bronchoscopy.

Clinical data

Medical records were reviewed by a researcher (ER) blinded to the CT findings. Forced expiratory volume in 1 s (FEV1) values were obtained for each patient as a clinical marker of disease severity. Absolute FEV1 litres (l) and FEV1 percent predicted (%) values using the National Health and Nutrition Examination Survey III (NHANES-III) reference predicted normal values were collected within 1 year of the associated and reviewed chest CT, resulting in 94 total data points.

Statistical analysis

One-tailed *t*-tests were performed to evaluate the association of the presence/absence of TD with the Bhalla CT score of disease severity. The Bhalla CT score was compared with patient age using the Pearson's correlation test to evaluate the relationship between disease severity score and patient age. The size of TD was also compared with patient age using the Pearson's correlation test to evaluate for the relationship between TD size and patient age. One-tailed *t*-tests were performed to evaluate the

association of the presence/absence of TD with clinical FEV1 values as the percentage of expected normal.

RESULTS

Patient population and imaging characteristics of tracheal diverticula

Of the 113 patient records and imaging studies reviewed, 20 (14 males, 6 females) patients were found to have one or more TD present (17.7%). The 14 male patients reflect a prevalence of 23.3% within our male study group and the 6 females reflect a prevalence of 11.3% within our female patient population. All of these TD were located in the same right posterolateral paratracheal location along the upper trachea at the level of T2–T4. Of the 20 patients, 9 patients had a single TD and 11 patients had multiple TD, up to 4 in total. TD size ranged from 2 to 18 mm (mean 8.2 ± 5.6 mm). A fine, thin wall around the TD was seen in the smaller TD (Figure 1). Larger TD were filled with dense soft-tissue contents (presumably mucus material), with little or no air present, making them appear as round soft-tissue nodules (Figures 2, 3). A clear tract or stalk connecting the TD to the trachea was present in 8 (40%) of the 20 patients (Figures 1, 3), and some TD had several connecting stalks. Prior CT studies were available for 10 of the 20 patients, but change in size was demonstrated in only 1 patient, with a slight increase of the TD diameter. Radiology reports available in the medical record mentioned the TD finding in only 4 (20%) of the 20 patients.

Correlation between tracheal diverticula and overall disease severity, by imaging

Bhalla CT score was 13.9 ± 4.3 in patients with TD, significantly higher than the 11.5 ± 4.3 score in patients without TD ($p = 0.01$ for the standard *t*-test), with higher score indicating greater severity of disease. Of note, Bhalla CT score and age were not statistically significantly correlated, with $p = 0.327$ ($p > 0.05$) for $r = -0.09$. The size of TD was inversely correlated with patient age, with $p = 0.008$ ($p < 0.05$) for $r = -0.57$.

Correlation between tracheal diverticula and overall disease severity, by FEV1 data

One-time measurements of FEV1 percent predicted within 6 months' time of CT imaging were $57 \pm 22\%$ in patients with TD and $61 \pm 24\%$ in patients without TD ($p = 0.28$ for the standard *t*-test), not a statistically significant difference. The absolute FEV1 values for the same time points were 2.37 ± 1.01 l in patients with TD and 2.42 ± 1.12 l in patients without TD ($p = 0.43$ for the standard *t*-test), also not a statistically significant difference.

DISCUSSION

The prevalence of TD in our population with CF based on chest CT imaging was approximately 18%, which is much higher than the estimated 1–4% prevalence in the general population.^{1–3} Despite the significant prevalence, TD are commonly unreported by radiologists. In our study, 80% of TD went unreported in the initial radiology interpretation. This may be due to the lack of recognition, but also owing to the lack of clearly demonstrated clinical significance, even in a population with CF.^{12–14} In addition, TD containing mucus secretions may be

Figure 1. Multiple tracheal diverticula (TD) in a 21-year-old male with cystic fibrosis. (a-c) Several sequential axial images show multiple TD (arrows) measuring up to 1.1 cm in size, with thin walls and no visible contents.

difficult to differentiate from upper mediastinal lymph nodes, as both appear as paratracheal soft-tissue nodules. Lack of visibility of a clear connection between the paratracheal air cyst and the trachea may also lead to underreporting. In our series, a clear connection between the TD and trachea was visible in only 8 (40%) of the 20 patients with TD, although some TD had several stalks or communications with the trachea, consistent with prior descriptions in an autopsy series.¹ These stalks are in fact frequently invisible on CT, given their very small diameter, and the connections may sometimes be too small even for visualization with bronchoscopy.

The reason for the higher rate of TD in patients with CF is not known. It has been theorized that TD may develop owing to increased intraluminal pressure in the trachea or because of cystic distension of the mucous gland ducts lining the trachea.^{11,15,16} Both mechanisms could theoretically account for the high prevalence of TD in patients with CF. Of particular importance is the fact that TD may serve as a nidi for continued infection risk. In the original autopsy series characterizing TD, MacKinnon described pus or infected material being leaked from TD into the trachea in some cases, giving greater evidence for this concern.¹ Patients with CF are already at great risk for recurrent endobronchial infection, and great measures are sought in order to alleviate any known infectious risk factors.^{12-14,17} TD may reflect yet another treatable risk factor. In terms of long-term treatment and follow-up in patients with CF proceeding to lung

transplant, today, these TD remain untreated, and infection remains the most frequent complication in post-transplant patients with CF.

As a poignant example, during our investigation, a patient presented with fever after bilateral lung transplant. A CT scan showed a retrosternal fluid collection and he was referred for a tagged white-blood-cell scan to evaluate the nature of the collection. While the retrosternal fluid collection had no significant radio-tracer uptake, there was intense uptake within a TD, raising concern for infection of the diverticulum (Figure 4). Further investigation is required to determine whether pre-existing TD are associated with an increased risk of post-transplant infections, as may have been true in this case, and whether TD treatment options would confer improved outcomes.

The presence of TD was associated in our series with more severe pulmonary disease findings related to CF on chest CT. Patients with TD trended towards a lower FEV1% predicted, reflecting more severe lung disease, although this difference was not statistically significant. This may have been owing to underpowering of the data, as a trend towards the expected correlation was present.

This investigation was limited by the sample size and restriction to a single institution's population of patients with CF. Within this population, 113 of the 166 patients with CF had CT, which perhaps could indicate the overall greater severity of the disease in those with CT imaging completed at some time. In addition,

Figure 2. A tracheal diverticulum (TD) mimicking an enlarged right paratracheal lymph node in a 29-year-old male with cystic fibrosis. (a) Axial section at the level of T3 in the soft-tissue window shows a 1.6 cm round soft-tissue density (arrow), mimicking a right paratracheal lymph node. (b) Axial section 2.5 mm caudal to image (a) shows a tiny air bubble (arrowhead) within the soft-tissue density, implying that it is a TD and not a lymph node.

Figure 3. Multiple tracheal diverticula (TD) in a 26-year-old female with cystic fibrosis (CF). (a–c) Axial images at the level of T4–T5, pre-lung transplant, show the diverticula which appear as multiple round soft-tissue nodules (arrows), likely owing to their dense contents. Clear air tracts are seen connecting the diverticula to the trachea (arrowheads). Extensive lung changes typical of CF are seen in the right upper lobe. (d–e) 4 months after lung transplant, the patient presented with fungal infection per bronchoalveolar lavage. The TD are not significantly changed in size and appear again as soft-tissue masses (arrows); however, no air bubbles are seen within the diverticula to attest to their nature.

while TD have a characteristic appearance on CT described in the literature, no anatomic proof with endoscopy was obtained to confirm our CT findings. However, the openings of such diverticula are very small and are often not recognized on endoscopy.^{9,15} Prior studies have found that the orifice is usually

difficult to visualize on bronchoscopy, and even in surgically proven TD, no mucosal orifices were detected on pre-operative bronchoscopy. Therefore, it has been suggested that CT of the trachea be considered the modality for establishing the diagnosis.¹⁵ We chose not to include a control group, since the

Figure 4. A 26-year-old female with cystic fibrosis presented with fever a few months after lung transplant and was found to have a retrosternal fluid collection on a chest CT. A tagged white-blood-cell scan was performed to evaluate the nature of the post-surgical collection. (a, b) Axial image (a, lung window; b, soft tissue window) at the level of T4 prior to lung transplant shows a right paratracheal soft-tissue nodule with a central lucency (arrows), a tracheal diverticulum (TD). (c) A tagged white-blood-cell scan after lung transplant shows intense uptake in the TD (arrowhead) concerning infection. There was no radiotracer uptake within the retrosternal collection.

prevalence of TD as detected on CT has been established to range from 2% in a large series of 3645 patients to 3.7% in a study of 702 patients.^{3,4}

Despite these limitations, a strong association of the presence of TD in patients with CF was demonstrated and characterized. We suggest that greater attention to and reporting of TD should be considered in order to alert treating clinicians who can then assess for the possible clinical impact of these TD. In particular, special attention should be given to detecting and documenting TD in patients at risk for recurrent pulmonary infections, as in patients with CF.¹⁸ Symptomatic TD have proven to be amenable for successful treatment *via*

thoracotomy and/or endoscopic cauterization for the treatment of TD.^{2,7,19} Given the effective available treatment options, improved recognition of TD could potentially lead to improved patient outcomes with adequate treatment. In particular, further investigation is warranted in a population with CF to determine whether targeted management of TD could improve clinical outcomes.

CONCLUSION

TD appear to have a higher prevalence in patients with CF than in the general population, are associated with more severe CF pulmonary disease by CT criteria and are frequently under-reported by radiologists.

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