RESPIRATORY CARE Paper in Press. Published on October 22, 2013 as DOI: 10.4187/respcare.02645

REVISED VERSION (Clean)

Unexplained persistent dyspnea in a young woman with eosinophilic angiocentric fibrosis

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The material has not been published previously. And, all listed authors have no conflicts of

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interest.

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Abstract

Eosinophilic angiocentric fibrosis (EAF) is a rare inflammatory disease that primarily involves the nose and sinuses. Involvement of the orbit and larynx has also been described. However, it is very rare for this disease to involve the lower respiratory tract and cause dyspnea. We describe a rare case of EAF involving the lower respiratory tract with airway narrowing. A 29-year-old female with a 7-year history of nasal obstruction presented with unexplained persistent dyspnea. EAF was diagnosed via endoscopic biopsy of an irregular mucosal lesion in the posterior wall of the right maxillary sinus. Chest computed tomography and bronchoscopy showed a diffuse inflammatory narrowing of the airway in the tracheobronchial trees. EAF can affect lower respiratory tracts with airway narrowing that can be characterized by dyspnea. We must consider narrowing of the lower respiratory tracts in patients with EAF complaining of unexplained persistent dyspnea.

Key words: Dyspnea, eosinophilic angiocentric fibrosis, airway narrowing

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Introduction

Eosinophilic angiocentric fibrosis (EAF) is an unusual fibrotic condition of unknown etiology that most commonly affects the sinonasal cavity. It was first described by Holmes and Panje in 1983, who reported a case with recurring intranasal mass.[1] Other than the nose and sinuses, the other systemic organs such as the orbit, gums, larynx and upper trachea can be involved as well.[2-5] However, lower airway involvement is very rare, and was reported for the first time in 2011 by Deshpande et al.[6]

The precise etiology of EAF still remains unclear. Atopy, immunologic disease, previous surgery, and trauma have been suggested to be predisposing factors, but the evidence for any of each of these origins is weak.[7, 8]

To the best of our knowledge, there are a few case reports that show diffuse inflammatory narrowing of the tracheobronchial tree in EAF. In this report, we describe a rare case of EAF with diffuse narrowing of lower respiratory tract in a patient presenting with dyspnea.

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Case report

A 29-year-old female presented with a 7-year history of nasal stuffiness presented with frequent productive cough and dyspnea. The dyspnea was not paroxysmal. Breathlessness had gradually deteriorated over four years. It was described as persistent for the previous year, but she did not have fever, chills, arthralgia, or hemoptysis. She was a never-smoker. Ostiomeatal unit (OMU) computed tomography (CT) revealed chronic sinusitis involving the right maxillary sinus, and obstruction of the right OMU (Fig. 1-A). Nasopharyngoscopy showed purulent nasal discharge with diffuse mucosal swelling. She underwent endoscopic biopsy of an irregular mucosal lesion in the posterior wall of her right maxillary sinus. This lesion of the sinuses suggested differential diagnoses such as granulomatosis with polyangiitis (Wegener's), Churg-Strauss syndrome, Kimura disease, and granuloma faciale from EAF. To exclude these mimickers, laboratory investigations and histopathological assessment of the biopsy tissue were performed. The biopsy result was characterized by a perivascular eosinophil-rich inflammatory infiltrate and fibrosis leading to a characteristic whirling, onion-skin-type pattern that is pathognomonic for EAF (Fig. 1-B & C). On immunohistochemical staining of the nasal biopsy, a few cells (red arrows, 5~6 cells per high-power field) showed an immunoreactivity toward IgG4 (Fig. 1-D).

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Laboratory investigations for antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), cytoplasmic ANCA, perinuclear ANCA, urinalysis (including proteinuria and hematuria) and C-reactive protein (CRP) were all negative. The only abnormal finding was a mildly elevated erythrocyte sedimentation rate (32 mm/h). Immunoglobulin levels (IgG, 1280mg/dL; IgE, 29.6 IU/mL) and eosinophil count (1.7%) were within the normal range. A pulmonary function test showed a primarily moderate obstructive pattern with a mild restrictive pattern [forced expiratory volume in 1 s (FEV_1), 1.62 (58%); forced vital capacity (FVC), 2.7L (78%); FEV_1/FVC, 60%; residual volume, 0.82L (62%); total lung capacity, 3.52L (78%)], suggesting chronic respiratory diseases such as COPD, bronchiectasis, or others. The diffusing capacity of the lung for carbon monoxide (DLCO) was within the normal range (18.4 $mL \cdot mmHg^{-1} \cdot min^{-1}$, 87%). There was no significant reversibility of the airway obstructive pattern and she had no history of allergies. To palliate her symptoms, she was prescribed bronchodilators. However, she still presented with persistent dyspnea with wheezing on mild exertion. Chest CT was performed to further evaluate her symptoms. CT revealed diffuse, smooth, concentric tracheal wall thickening as well as thickening of the bilateral main, lobar, segmental, and some subsegmental bronchi, with luminal narrowing of the tracheobronchial trees (Fig. 2-A & B). Bronchoscopy revealed overall erythematous mucosal thickening and narrowing of entire tracheobronchial trees that were thought to be

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related to a chronic inflammatory condition. A single bronchoscopic biopsy was done at the carina because of severe dyspnea and desaturation during bronchoscopy. It showed squamous metaplasia with neutrophils, consistent with chronic inflammation (Fig. 3). Bronchial washing was negative for bacteria, fungus, and tuberculosis. Surgical biopsy for lesions of the lower respiratory tract was recommended to confirm the tracheobronchial involvement of the EAF. However, the patient refused surgical biopsy of the lower respiratory airways. The patient was subsequently treated with systemic steroid (prednisone) and bronchodilators (fluticasone/salmeterol inhaler and doxofylline) for 3 months. Mucolytics, including erdosteine, were also prescribed. Nasal and respiratory symptoms have somewhat waxed and waned over time. Systemic steroid treatment with dose escalation was effective when nasal and respiratory symptoms waxed. A follow-up chest CT showed more improvement of tracheobronchial narrowing (Fig. 2-C & D). We measured the dimensions of the airways at the same anatomic locations before and after treatment. The improvement of airway involvement was evaluated as an increase in inner luminal diameter and a decrease in airway wall thickness. The patient's tracheal dimensions were measured at the level of the aortic arch. The tracheal inner diameter increased from 13.9 mm to 15.1 mm, and the tracheal wall thickness decreased from 2.0 mm to 1.8 mm after treatment. The inner diameters of the segmental bronchi also appeared to increase. Airway measurements are

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detailed in our previous publication[9]. These measurements suggest that some of the improvement in dyspnea may be linked to improved airway dimensions. However, bronchodilator treatment has been maintained to palliate her symptoms because of continued exertional dyspnea.

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Discussion

EAF is a rare inflammatory disease, primarily involving the orbit and upper respiratory tract, particularly the sinonasal cavity.[4] It was first described by Holmes and Panje in 1983[1]. EAF has distinct histological features characterized by a perivascular eosinophil-rich inflammatory infiltrate and fibrosis with a whirling, onion-skin-type pattern.[1] It presents as a slowly progressive upper airway obstruction in association with a submucosal inflammatory fibrosing lesion.[4]

There are few case reports that show EAF involvement of the trachea and lower respiratory tract. Deshpande et al.[10] reported a 63-year old man with EAF who had mediastinal, hilar and axillary lymphadenopathies with extensive ground-glass pulmonary opacities and bronchial wall thickening. Seven years later, they detected a worsening in his pulmonary lesions, an increase in the size of the lymph nodes, and a polypoid lesion from the bronchial wall. In this case, the patient presented with chronic dyspnea and diffuse airway wall thickening that was comparable to the previous report. However, we did not see any mediastinal/hilar lymphadenopathies or parenchymal lesions in our case. This suggests that the airway thickening of the lower respiratory tract can develop as a result of EAF involvement. However, patterns of respiratory system involvement could be variable and could change over time. Chest CT or bronchoscopy can be helpful for evaluating the

involvement of the tracheobronchial trees in a patient with EAF who complained of unexplained persistent dyspnea or respiratory symptoms. Long-term follow-up is necessary because of the possibility of progression.

The etiology and pathogenesis of EAF are unknown, but some suggest that it may be part of the spectrum of IgG4-related systemic diseases (IgG4-RSDs).[10] Deshpande et al. reported that EAF lesions were associated with a large numbers of IgG4-positive plasma cells. However, there is no consensus regarding the minimal numbers of IgG4-positive cells required for IgG4-RSD diagnosis.[10] In our case, a few cells showed immunoreactivity for IgG4 upon nasal biopsy staining.

EAF has usually been distinguished from some of its mimickers, including granulomatosis with polyangiitis (Wegener's), Churg-Strauss syndrome (CSS), Kimura disease, granuloma faciale, and angiolymphoid hyperplasia with eosinophilia.[10, 11] These mimickers have been excluded on the basis of laboratory investigations and histopathological assessment of biopsy tissue. The histology of EAF is pathognomonic and is characterized by perivascular inflammatory cell infiltration with fibrosis around small vessels, leading to a characteristic onion-skin-type pattern.[4] Absence of geographic necrosis, necrotizing vasculitis, and granulomatous inflammation excludes granulomatosis with polyangiitis and CSS.[2, 12] Positive blood tests for cytoplasmic and perinuclear ANCA support the diagnoses of granulomatosis

with polyangiitis and CSS, respectively. The absence of dense lymphoid aggregates with prominent germinal centers excludes Kimura's disease.[2] Some authors have suggested an association between EAF and granuloma faciale, a benign cutaneous disease characterized by circumscribed plaques and skin nodules with a predilection for the facial region.[13, 14] Granuloma faciale lacks the onion-skin-type pattern of collagen whirling around a central vessel that is characteristic of EAF. There is another opinion that EAF is not a distinct entity other than granulomatosis with polyangiitis (Wegener's) and atopy.[15] EAF is believed to have an allergic etiology. On the contrary, some cases clearly had no allergic etiology,[12] and the patient in our case also had no allergic history. However, we did not perform specific allergic examinations, such as allergic skin tests. This is a limitation of our study. Further studies are necessary to define the etiology and pathogenesis of EAF.

Treatment guidelines for EAF also remain unclear; there are no definitive treatment modalities. Surgical resection has been performed for progressive or persistent disease,[16] and local and systemic corticosteroid therapies have been pursued with minimal clinical resolution of disease.[4, 14, 17, 18] In our case, the sinonasal lesion was well controlled by surgical resection and systemic steroids. However, steroid treatment with dose escalation was needed when nasal and respiratory symptoms waxed.

Rituximab has been proposed as a reasonable approach to therapy in patients with EAF refractory to glucocorticoids. This suggestion is based on an idea that EAF is part of the spectrum of IgG4-related systemic disease.[10] Additional studies are needed to clarify its treatment.

Pulmonary function test showed a mixed pattern; primarily obstructive disorder with mild restrictive pattern. We formed the hypothesis that airflow obstruction resulted from airway narrowing, as seen in chronic obstructive pulmonary disease, and that the mild restrictive disease may be nonspecific or may be caused by mild parenchymal damage that can be caused by recurrent respiratory infection. She had a history of chronic cough with frequent exacerbations, suggesting recurrent respiratory infections.

Another major limitation of this case is the lack of tissue confirmation from the lower respiratory tract. However, in our opinion, the tracheobronchial involvement in this case was caused by EAF for the following reasons. 1) The pattern of airway involvement was comparable to the previous report. 2) There was no evidence of the other diseases that cause diffuse airway narrowing, such as granulomatosis with polyangiitis (Wegener's). 3) EAF usually has pathologic changes below the mucosal level (at the submucosal level). The lesions lead to thickening of the submucosal connective tissues. However, in this case, tracheobronchial tissue was only obtained from mucosal level because the patient

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experienced severe hypoxia during the bronchoscopy. This could be the reason that the pathologic confirmation was not done from the mucosal biopsy of the lower respiratory tract.

EAF is a rare, progressive, fibroinflammatory disease primarily involving the sinonasal tract. However, it can affect lower respiratory tracts with airway narrowing that can be characterized by dyspnea. Unexplained persistent dyspnea in a patient with EAF should prompt the clinician to consider diffuse airway narrowing involving the lower respiratory tract.

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Acknowledgments

The authors would like to thank Enago (www.enago.kr.com) for the English language review.

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Figure legend

Figure 1. Ostiomeatal unit (OMU) computed tomography (CT) and biopsy of a mucosal lesion in the right maxillary sinus

: A CT image (A) showed chronic sinusitis involving the right maxillary sinus (black arrow), obstruction of the right OMU, and a deviation of the nasal septum to the left side (black arrowhead). The biopsy from the mucosal lesion in the right maxillary sinus was compatible with EAF; a distinctive perivascular fibrosis with an 'onion-skin-type' appearance (H&E, X20) (B) and cellular inflammatory cells composed of eosinophils, lymphocytes, plasma cells, neutrophils, and histiocytes. (H&E, X200) (C). On IgG4 immunohistochemical staining of the nasal biopsy, a few cells (red arrows, 5-6 per high-power field) showed immunoreactivity toward IgG4. (X200) (D).

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Figure 2. Chest computed tomographic images at baseline and at 3 months after treatment initiation

: (A, B) Initial images showed a diffuse wall thickening with luminal narrowing of the trachea (arrowhead) and bronchial trees (arrows). (C, D) Three months after treatment, the tracheal (red arrowhead) and bronchial (red arrows) wall thicknesses had decreased and the luminal diameters had increased.

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Figure 3. Bronchoscopic mucosal biopsy from the carina revealed squamous metaplasia with neutrophil infiltration (H&E, X200).

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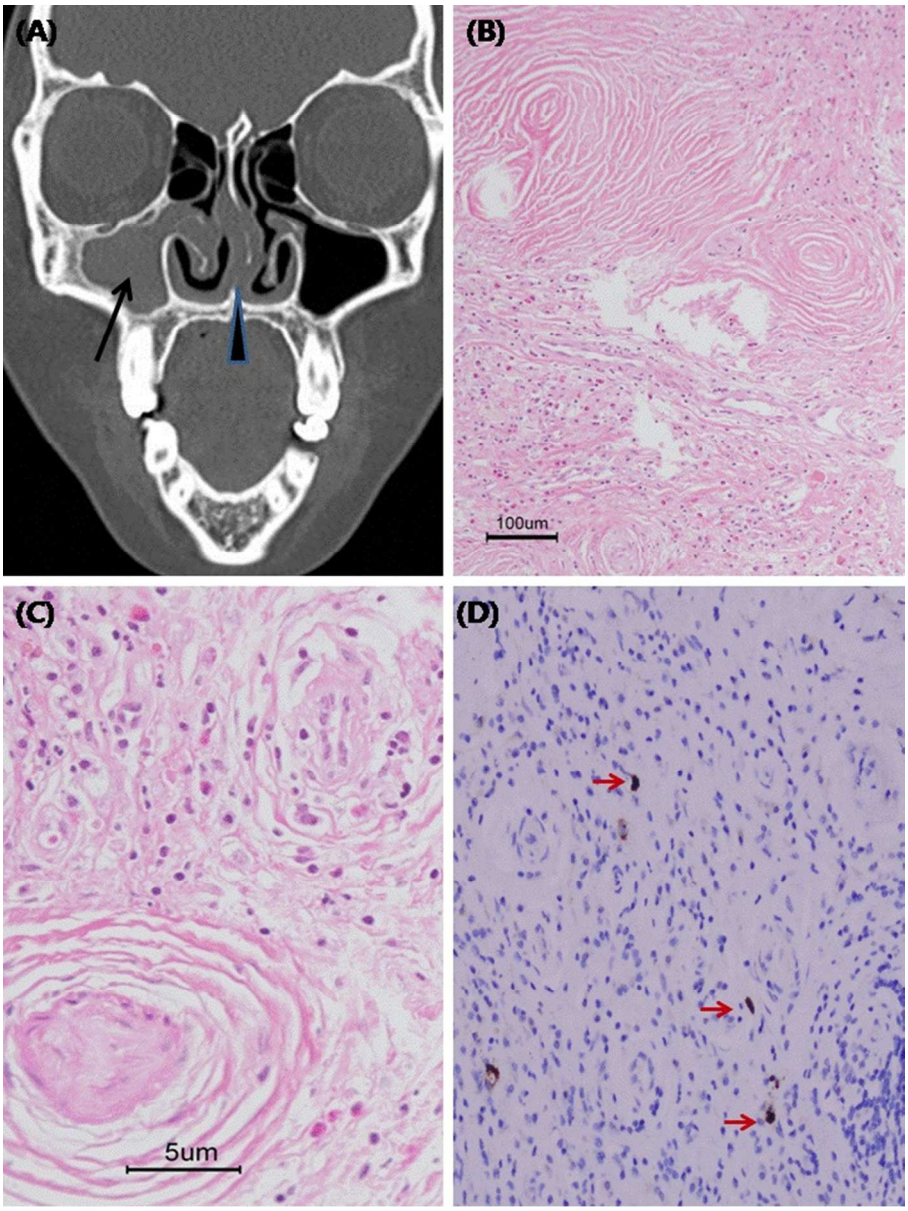

Ostiomeatal unit (OMU) computed tomography (CT) and biopsy of mucosal lesion in the right maxillary sinus
60x81mm (300 x 300 DPI)

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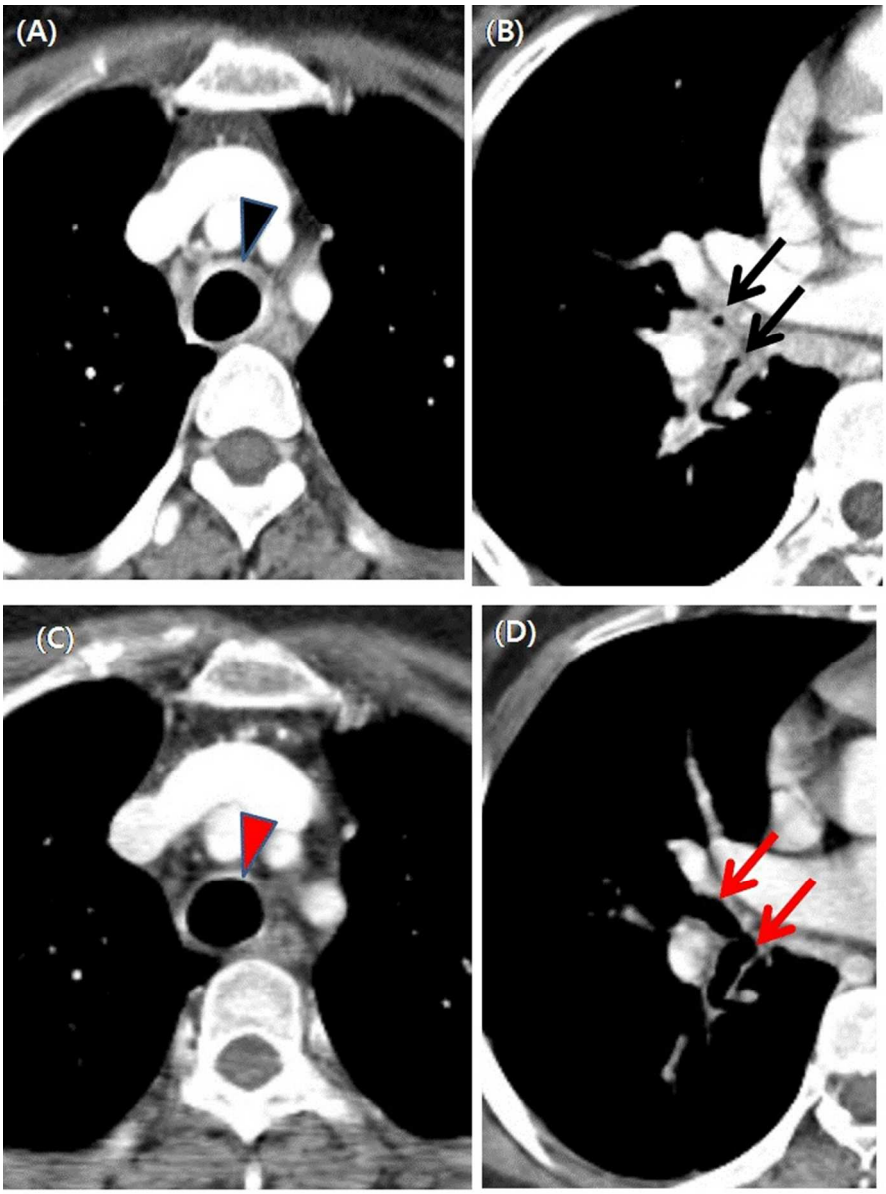

Chest computed tomographic images at baseline and at 3 months after treatment initiation
60x81mm (300 x 300 DPI)

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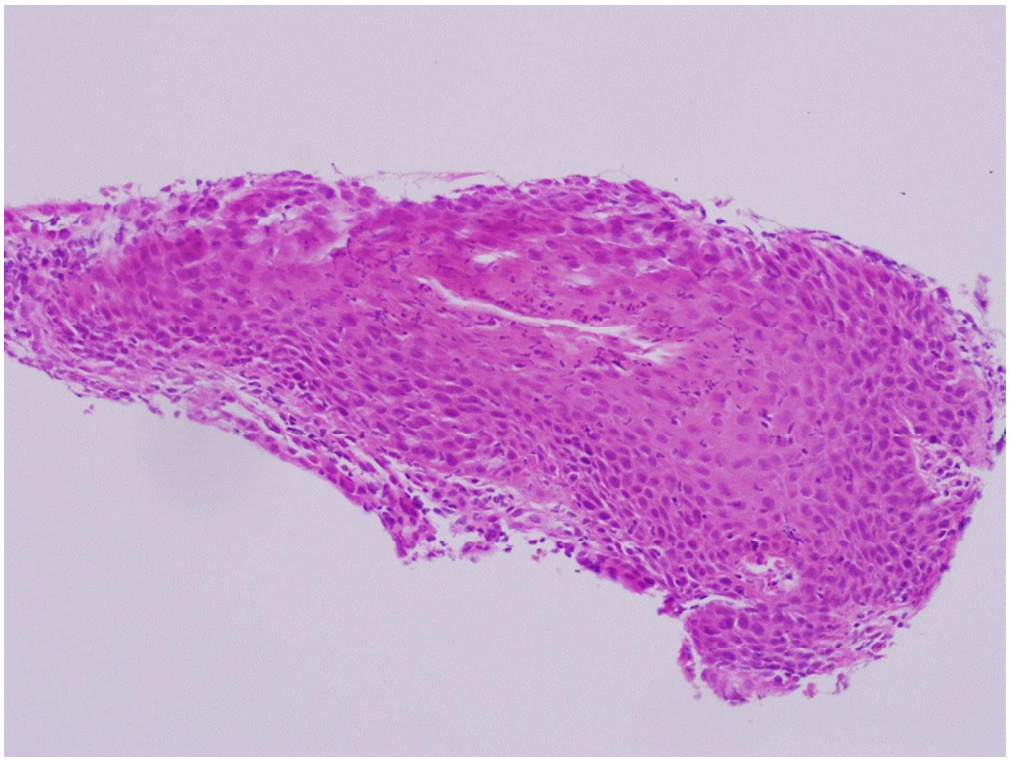

Bronchoscopic mucosal biopsy from the carina
81x60mm (300 x 300 DPI)