

Chest Involvement in Inflammatory Bowel Disease

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IN THIS ISSUE OF *Pediatric Allergy, Immunology, and Pulmonology*, Gut and Sivan report on a patient with ulcerative colitis (UC)-related airway involvement,¹ a classic association that may have dire, though often temporary consequences. An adolescent girl with no history of airways disease developed a productive cough within a week after subtotal colectomy for untractable UC. Auscultation of the chest disclosed crackles and wheezes denoting airway involvement. Inhaled corticosteroids (ICSs) and bronchodilators were without any consistent effect. The chest radiograph probably evidenced the “dirty chest” or predominantly basilar tramline appearances. Bronchiectasis was present in the high resolution computed tomography (HRCT) scan. No gross airway inflammation was seen on endoscopy, but an increase in neutrophils was noted in the bronchoalveolar lavage (BAL) fluid. In a few months, this young patient became a respiratory cripple. However, she improved after therapy with a combination of macrolides and a moderate dose of ICS. Of note, ICS dosage may be increased, should flares or deterioration of the UC-related airway condition occur in the future. These investigators should also be commended for their careful review of earlier pediatric cases.

Although potentially devastating, IBD-related chest involvement is not quoted in every review article on IBD. Contrary to adult cases where the majority of inflammatory bowel disease (IBD) cases with respiratory involvement have UC (as in Gut and Sivan’s),^{2–5} more children with the association had Crohn’s disease (CD). This said, children and adults may develop similar patterns of IBD-related chest involvement. The connection of UC (the more common of the two IBD) and severe, at times life-threatening, tracheo-bronchial involvement was first established in 1962, in a seminal paper from Valencia, Spain,⁶ which went totally overlooked. Further cases, case series, and reviews^{2,5,7–9} delineated the distinctive clinical, endoscopic, imaging, BAL, and pathologic characteristics of IBD-associated or -related airway, parenchymal, and serosal involvement with about 400 cases overall at the present time.¹⁰ IBD-related chest involvement has an inflammatory basis, which is readily apparent on endoscopy and bronchial biopsies in those patients with IBD-related large airway involvement. Still, such patients may escape timely recognition and appropriate management, or they undergo superfluous invasive diagnostic procedures, causing unnecessary delay in treatment

with oral and or ICSs, the mainstay of therapy for this group of conditions.

In the vast majority of patients (*ca.* 80%), chest involvement develops in a patient with an established diagnosis of IBD, though generally quiescent at the time of onset of chest symptoms. In about 10% of cases, respiratory manifestations predate the onset of the IBD by months or years, raising complex diagnostic issues. In another 10% of patients bipolar, namely synchronous intestinal and bronchial onset, takes place. Rarely chest and intestinal involvement undergoes flares and remission in parallel.¹¹ Strikingly, IBD-related airway involvement can occur after colectomy^{1,2,8} and in a few cases, symptoms related to the airways developed in a few days after surgery (as in Gut and Sivan’s), as though the colonic inflammation shifted to the bronchial tree after removal of inflamed bowel tissue.¹¹ Of note, both the airways and bowel emanate embryologically from the primitive foregut.⁸ Cases with severe airway disease developing years after colectomy also raise difficult diagnostic issues, as the link between the 2 condition may not be self-evident. At any rate, colectomy is *not* an appropriate therapeutic option to be offered to patients with IBD-related airway involvement, as respiratory deterioration or progression may follow the procedure.²

The dominant form of respiratory involvement in IBD (Table 1) is central or large airway involvement.^{2,4} and is in the form of friable, hemorrhagic circumferential mucosal redness, bulging, a cobblestone appearance, and/or ulceration.¹² Patients may exhibit sectoral inflammation/stenosis dominant in either the glottis, subglottic area, trachea, or it is remote in distal or in the tiny peripheral airways. Some patients exhibit diffuse airway involvement, from the trachea up to the bronchioles. Large airway involvement is heralded by incessant barking cough, at times profuse bronchorrhea, and in some patients, asphyxiating episodes can develop.² The list of differentials is limited: classic bronchiectasis tends to develop earlier in life. Antineutrophil cytoplasmic antigen (ANCA)-related (Wegener’s) central airway involvement is diagnosed using c-ANCA testing, and those IBD patients with ANCA tend to exhibit p- as opposed to c- (anti PR3) ANCA specificity. Distal bronchial involvement may occasion irreversible damage to the airways in the form of bronchiectasis as in Gut and Sivan’s patient, or a pattern of severe obstruction to airflow that can be irreversible. There is a definite plea for early recognition and

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TABLE 1. PULMONARY MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

<i>Location</i>	<i>Pattern</i>	<i>UC/CD</i>	<i>Main S&S</i>	<i>Postcolectomy</i>	<i>Drug-relatedness</i>	<i>Chest X-ray</i>	<i>HRCT</i>	<i>FOB</i>	<i>BAL</i>	<i>Pathology</i>	<i>Outcome</i>
Sinuses	Sinusitis	1/1	Sinusitis	Y	No	DNA	Mucosal thickening	DNA	ND	ND	?
Glottis/Larynx	Vocal cord inflammation	1/1	Hoarseness	Y	No	Aw narrowing	Aw narrowing	Inflammation	ND	Inflammation, ulceration	Good
Subglottic area	Inflammation/stenosis	2/1	Dyspnea	Y	No	Aw narrowing	Aw narrowing	Inflammation	ND	Inflammation, ulceration	Good
Trachea	Tracheal inflammation	3/2	Dyspnea/cough	Y	Very unlikely	Aw narrowing	Irregularity, narrowing	Cobblestoning	PMN?	Deep-seated inflammation	Variable
Major bronchi	Chronic bronchitis	4/2	Cough, sputum	Y	Very unlikely	"Dirty chest"	Thickened aw walls	Can be normal	PMN	Mural inflammation	Good
.	Bronchial suppuration	2/1	Bronchorrhea			Tramlines	Thickened aw walls	Abundant sputum	PMN	Mural inflammation	Fair
.	Bronchiectasis	4/2	Cough, sputum			SiO, cysts	Bronchiectasis, impaction	Sputum, inflamm.	PMN	Inflammation, dilatation	Fair
Distal airways	Acute/chronic bronchiolitis	3/2	Cough, wheeze	Y	Unlikely	? hyperinflation	Tree in bud, mosaic	NCD	NCD	Acute/chronic inflamm	Fair
.	Suppurative bronchiolitis	2/1	Cough, wheeze			SiO	Tree-in-bud, mosaic	NCD	NCD	Purulent bronchiolitis	Fair
.	Granulomatous inflamm.	0/2	Cough, wheeze			NCD	Tree-in-bud, mosaic	NCD	NCD	Granulomatous inflamm	Fair
.	Constrictive bronchiolitis	1/0	Dyspnea, cough			Can be normal	Mosaic	NCD	NCD	Obliterative bronchiolitis	Poor

(continued)

TABLE 1. (CONTINUED)

Location	Pattern	UC/CD	Main S&S	Postcolectomy relatedness	Chest X-ray	HRCT	FOB	BAL	Pathology	Outcome
.	Diffuse panbronchiolitis	1/0	Dyspnea		NCD	NCD	NCD	NCD	Aw inflam., foam cells	NCD
Lung parenchyma				Rare						
.	Organizing pneumonia	3/2	Dyspnea, fever	Possible	Areas of consol.	Areas of consol.	NCD	Mixed	Organizing pneumonia	Good
.	ILD	2/2	Dyspnea		Ground-glass	Ground-glass	NCD	Lymph	ILD with an NSIP pattern	Good
.	Eosinophilic pneumonia	2/2	Dyspnea		Areas of consol.	Areas of consol.	NCD	Eos	Eosinophilic pneumonia	Good
.	ILD with granulomas	0/3	Dyspnea		Ground-glass	Ground-glass	NCD	Lymphs	Granulomatous inflam.	Good
.	Necrobiotic nodules	2/1	Fever, chest pain		Nodules	Nodules, cavitation	NCD	PMN	Sterile necrotic nodules	Good
Pleuropericardial membrane				Y						
Pleuritis/effusion	Fever, dyspnea, chest pain	2/2	Pleural effusion	Possible						
Pericarditis/effusion	Fever, dyspnea, chest pain		Pericardial thickening/eff							
Pulmonary circulation		1/1		N						
.	Pulmonary vasculitis	Fever, pulmonary opacities		Possible		Consolidation	Consolidation	ND	NCD	Vasculitis
.	Venous thromboembolism	Chest pain, dyspnea		No			Pulmonary embolism	ND	ND	DNA

BAL, bronchoalveolar lavage; 0, undescribed; 1, very rare; 2, uncommon; 3, typical, distinctive; 4, common; Aw, airway; CD, Crohn disease; DNA, does not apply; Eos, eosinophils; FOB, fiberoptic bronchoscopy; HRCT, high resolution computed tomography; ILD, interstitial lung disease; lymphs, lymphocytes; ND, no data; NCD, no current data; NSIP, nonspecific interstitial pneumonia; PMN, neutrophils; S&S, signs and symptoms; SIO, small irregular opacities; UC, ulcerative colitis; Y/N, yes/no; ?, unknown.

treatment of IBD-related airways disease. In all cases so tested, bronchial biopsies disclose marked, deep-seated inflammation with lymphocytes and plasma cells infiltrating the submucosa.^{2,9} These changes are reminiscent or pathologically resemble those in the bowel mucosa in UC.¹³ At variance with bronchiectasis from other causes or contexts, signs and symptoms of IBD-related airway involvement rather consistently improve with inhaled and oral corticosteroid therapy, while antibiotics and immunosuppressive agents are generally devoid of any effect except anti-tumor necrosis factor (TNF) agents in a few CD cases.^{14,15} While rare patients need emergent securing of the central airway using repeat topical corticosteroids under endoscopy, debridement, airway dilation, stenting, or tracheostomy, most will respond favorably to a combination of oral and long-term ICSs. Improvement in cough and sputum takes place in a few days, and this is followed by improvement in lung physiology, disappearance of mucoid impaction,² and reduction of airway wall thickness in serial HRCT scans¹⁶ (though exposure to radiation should be taken into account during follow-up, especially in the young). Vigorous initial corticosteroid therapy is needed and is targeted at obtaining or approaching the asymptomatic state, avoiding any relapse even of limited magnitude. A slow taper and prolonged maintenance treatment with ICS is indicated. A few patients refractory to conventional forms of corticosteroid therapy may need regular instillations of corticosteroids directly onto the airway mucosa under fiberoptic bronchoscopy guidance to more fully control the disease. Very few patients deteriorate relentlessly despite therapy with corticosteroids and develop debilitating airway inflammation and scarring.² Although there is no firm evidence for efficacy, azithromycin, other macrolides, and/or anti-TNF agents (provided latent tuberculous infection is ruled out) have met with some success. The former drug may have played a beneficial role in Gut and Sivan patient's recovery while on a low dose of ICS.

Most IBD cases with small airway involvement are to be found in the pathology literature,^{2,14,17} hence the prevalence of pathologic, as opposed to clinical or imaging description in cases with IBD-related large airway involvement. Necrotizing granulomatous bronchiolitis is a notable feature of CD,¹⁴ and interestingly, such cases have responded to therapy with infliximab.¹⁴ In any case with granulomatous inflammation in the airways or lung, involvement from the underlying CD, tissue reaction to the anti-TNF agent or infection with *Mycobacterium tuberculosis* ought to be carefully discussed.

Infiltrative lung disease (ILD) (Table 1) is in the form of diffuse or multifocal pulmonary infiltrates or consolidation at times causing life-threatening acute respiratory failure.² Bronchiolitis obliterans pneumonia (formerly known as "BOOP") and eosinophilic pneumonia classically exhibit distinctive features on imaging and pathology.¹³ The issue of ILD in IBD is complex, as most patients are still on bowel-disease-modifying drugs, including corticosteroids, sulfasalazine, mesalazine, methotrexate, azathioprine, 6-mercaptopurine, and infliximab, and several of these can occasion diffuse pulmonary infiltrates and/or promote infection with *Pneumocystis jiroveci* or other opportunistic microorganisms.¹⁸ Careful exclusion of and appropriate treatment for an infection are required, as opportunistic infections may be fatal in this context. Sorting out the respec-

tive responsibility of drugs as opposed to the IBD rests on careful molecular-targeted examination of the BAL for an infection and on selective drug withdrawal. Drug withdrawal is also indicated in serositis cases, as both the underlying IBD and drugs may cause this complication. Antinuclear antibody testing is necessary in serositis cases, as the *lupus* syndrome appears to be a not uncommon complication of treatments with anti-TNF agents.^{18,19}

While progress has been made in the recognition of IBD-related chest involvement since 1962, several issues remain unresolved:

1. Due to the rarity of IBD-related airway involvement, which accounts for 1–3% of all bronchiectasis cases, a trial evaluating azithromycin, anti-TNF agents in either CD or UC has yet to be conducted. An empiric trial with these medications is left at the discretion of the treating physician in each individual patient.
2. While studies have quite consistently evidenced a sub-clinical reduction in lung volumes or flows, enhanced bronchial responsiveness, minimal changes on HRCT, an increase in lymphocyte percentage in the BAL or of eosinophils in the sputum, increased fractional nitric oxide content in exhaled air, especially concomitant with flares of the IBD, no study has shown that these predict the development of overt airway or lung involvement in IBD. Accordingly, large-scale testing of IBD patients using the techniques just mentioned or empiric corticosteroid therapy in asymptomatic cases is not justified at this time.
3. What is the significance of lone, not otherwise explained chronic cough in IBD?²⁰ An empiric trial of ICS may lead to durable resolution of the cough, suggesting low-grade airway inflammation.
4. Although BAL neutrophils diminish and bronchial wall inflammation decreases after institution of therapy with corticosteroids,² the merit of serially monitoring these semi-invasive tests is not currently established.

To conclude, although much has been published on IBD-related chest involvement, further reports such as by Gut and Sivan are needed especially in children. The full spectrum of IBD-related pleuropulmonary and airway involvement has to be mastered by clinicians in pediatrics, gastroenterology, pulmonary, internal medicine, and intensive care, in such a way that no patient escapes timely recognition, prompt institution of corticosteroids, and appropriate maintenance therapy to reduce the risk of developing acute life-threatening or chronic irreversible airway injury.

Acknowledgment

The author expresses his deep gratitude and appreciation to Dr. Thomas V. Colby of the Mayo Clinic, Scottsdale, Arizona, whose bright impetus has made some of the studies quoted here possible.

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