A menstrual rhythm has been documented for exacerbations of asthma, which may have important clinical relevance to the patient with severe asthma. We report the case of a 26-year-old patient with menstruation-associated asthma who showed a dramatic response to oral contraceptives. It was noted that falls in peak respiratory flow rate coincided with ovulation. We concluded that oral contraceptive therapy is useful in this particular group of asthmatic patients.

**Key words:** asthma; menstruation-associated asthma; oral contraceptive

**Abbreviations:** LH = luteinizing hormone; PEFR = peak expiratory flow rate

We report the case of a 26-year-old patient with menstruation-associated asthma. In addition to receiving oral prednisolone, β2-agonist, inhaled beclomethasone dipropionate and theophylline, the patient was given an increased dose of oral prednisolone at the exacerbation of asthma every month. Falls in peak expiratory flow rate (PEFR) were noted to coincide with ovulation. The

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**Figure 1.** Clinical course showing PEFR before and after treatment with Planovar, which was given once a day (Planovar 1T) for 21 days of the menstrual cycle. Spirometry and blood test results are also listed, including concentrations of methacholine and eosinophil that provoked a 20% fall in FEV1 percentages. Hormone levels were determined during the follicular phase on the seventh day of the menstrual cycle and on the 21st day of the menstrual cycle during the luteal phase in two consecutive menstrual cycles. There were no differences in levels of LH, follicle-stimulating hormone, LH-releasing hormone, and adrenocorticotropic hormone in both phases of the menstrual cycle. Although the levels of chemical mediators including blood histamine, urinary leukotriene E, and urinary 11-dehydroTXB2 were determined, they did not differ during the follicular and luteal phases. * = p < 0.05 vs luteal phase; ** = p < 0.01 vs luteal phase; PSL = prednisolone; BDP = beclomethasone dipropionate; ECP = eosinophilic cationic protein; Eo = eosinophils; PC20 = methacholine concentration that provoked a 20% fall in FEV1.
patient showed a dramatic response to an oral contraceptive, which provided a stable level of progesterone throughout the menstrual cycle.

**CASE REPORT**

We report the case of a 26-year-old woman with severe atopic asthma. Asthma developed at 23 years of age and had since been associated with premenstrual exacerbation. The patient was receiving oral prednisolone (5 mg/d), beclomethasone dipropionate (1.600 µg/d), and theophylline (400 mg/d); to control asthma, the dosage of prednisolone was increased to 30 to 40 mg/d every month before the menstrual period. The menstrual cycle was regular, including abolition of the menstrual cycle (Fig 1). After two menstrual cycles, the body temperature became monophasic, suggesting a state of anovulation. Luteinizing hormone (LH)-releasing hormone, LH, follicle-stimulating hormone, progesterone, and estradiol levels were normal during the follicular and luteal phases. Recording of body temperature showed that ovulation coincided with the falls in PEFR (Fig 1). Thus, suppression of ovulation seemed to be a plausible therapeutic option. An oral contraceptive (Planovar; Wyeth; Tokyo, Japan) consisting of norgestrel (0.5 mg) and ethynyl estradiol (0.05 mg) was given for 21 days of the menstrual cycle (Fig 1). After two menstrual cycles, the body temperature became monophasic, suggesting a state of anovulation. This was associated with improvement in PEFR and amelioration of symptoms. Using the same treatment, her asthma has been under control for almost 3 years.

**DISCUSSION**

Patients with menstrual asthma comprise 30 to 40% of menstruating female asthmatics. Although the relationship between progesterone or estradiol levels and airway hyperresponsiveness has been evaluated, no definite relationship has been described between each set of factors. While aldosterone levels may be related to the exacerbation of asthma, the levels measured in our patient during the follicular and luteal phases were not different, and administration of a diuretic agent (furosemide) was ineffective. Adrenocorticoestroid agents or hormone therapy have been used to treat the exacerbation of menstrual asthma. Oral contraceptives have also been used but were ineffective.

Effective therapy using high-dose progesterone has been reported, and the response is thought to involve smooth-muscle relaxation and control of microvascular leakage. However, the risk of serious side effects potentially limits the use of high doses of progesterone. Because the exacerbation of symptoms coincided with ovulation in our patient, an oral contraceptive was given despite previous negative results. This completely eliminated premenstrual exacerbation of asthma. On the basis of clinical features, blood test results, and response to therapy, we speculate that menstrual asthma was due to rapid fall in the progesterone level during the late luteal phase. Symptomatic exacerbation was observed soon after ovulation and was eliminated by suppression of ovulation. This observation suggests that improvement of asthma was due to the maintenance of stable levels of sex hormones and the disappearance of cyclic changes in these levels by administration of oral contraceptives. We conclude that symptomatic exacerbation of menstruation-associated asthma may be prevented by suppression of ovulation. Oral contraceptives are useful in this particular group of asthmatic patients.

**REFERENCES**


**Wegener’s Granulomatosis and α1-Antitrypsin-Deficiency Emphysema**

**Proteinase-Related Diseases**

V. Theodore Barnett, MD, FCCP; Marin Sekosan, MD; and Abid Khurshid, MD, FCCP

Wegener’s granulomatosis (WG) and α1-antitrypsin (α1-AT)-deficiency emphysema are both uncommon disorders. A relationship may exist between these diseases involving the proteinase and antiproteinase balance in the lung. A case is presented of WG and α1-AT-deficiency emphysema occurring in the same patient. Previous studies concerning the correlation between abnormal α1-AT alleles and WG are discussed. Potential mechanisms for the relationship and recommendations for screening are given.

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**Key words:** α1-antitrypsin deficiency; antibodies, antineutrophil cytoplasmic; emphysema; Wegener’s granulomatosis

**Abbreviations:** α1-AT = α1-antitrypsin; ANCA = antineutrophil cytoplasmic antibody; cANCA = cytoplasmic antibody; cANCA; PR3 = proteinase 3; WG = Wegener’s granulomatosis

Wegener’s granulomatosis (WG) is a disease of unknown origin. α1-Antitrypsin (α1-AT) deficiency is a genetic deficiency of α1-AT with multiple autosomal codominant alleles. It has been reported that patients with

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WG have a higher than expected rate of abnormal alleles for α₁-AT. We report a patient with WG and severe emphysema from α₁-AT deficiency.

CASE REPORT

A 38-year-old woman presented, at age 27, in April 1985, with arthralgias, sinusitis, and episcleritis. She subsequently experienced digital ischemia. She had no renal disease. She had smoked one pack of cigarettes per day since age 17. Prednisone was begun for possible polyarteritis nodosa, and she experienced improvement. Within several months, while on prednisone, she had dyspnea and wheezing. A chest radiograph showed an irregular 4-cm thick-walled cavity in the left lower lobe. The erythrocyte sedimentation rate was 38 mm/h. Spirometry revealed an FVC of 3.97 L (106% of predicted) and an FEV₁ of 1.84 L (58% of predicted). The diagnosis of WG was confirmed by open lung biopsy, which showed necrotizing granulomatous inflammation (Fig 1), vasculitis (Fig 2), and focal alveolar hemorrhage. There was no evidence of emphysema. She was continued on prednisone and begun on cyclophosphamide with resolution of systemic symptoms. Her dyspnea worsened over the next several years. In 1987, a chest radiograph showed emphysema that was most marked at the lung bases. By 1992, she was significantly limited by dyspnea. Her α₁-AT level was 32 mg/dL (normal, 150 to 300 mg/dL), and her α₁-AT phenotype was PiZZ. She had no recurrence of WG.

She quit smoking in 1994 and was referred to this institution for lung transplantation. At that time her FEV₁ was 0.40 L (13% of predicted). The test for antineutrophil cytoplasmic antibody (ANCA) was negative.

She underwent bilateral lung transplantation in July 1995. The explanted lungs showed severe panlobular emphysema (Fig 3) but no evidence of WG. She experienced post-transplantation lymphoproliferative disorder 14 months after her operation. She died of sepsis and respiratory failure 17 months after transplantation. An autopsy showed no evidence of emphysema or WG.

DISCUSSION

Studies evaluating α₁-AT alleles in cohorts of patients with WG have found the frequency of abnormal phenotypes to be increased. Savige et al¹ evaluated 31 patients with anti-proteinase 3 (PR3) antibodies and found 4 patients with abnormal α₁-AT phenotypes (2 MZ, 1 S, 1 Z). However, none of these patients had low serum levels of α₁-AT. Esnault et al² reported 14 patients with ANCA-positive systemic vasculitis; 6 patients had abnormal α₁-AT phenotypes (3 PiZZ, 3 PiMZ). Lhotta et al³ found 4 abnormal α₁-AT phenotypes (2 PiZZ, 2 PiMZ) among 29 patients with WG. Elzouki et al⁴ identified 15 heterozygotes (PiMZ, PiSZ, or Pi-null Z) and no homozygotes among 66 PR3-ANCA-positive patients with WG. The frequency of abnormal α₁-AT alleles in each of these studies far exceeds that expected.

The patient reported here had pulmonary and multiorgan involvement from WG, and severe emphysema from α₁-AT deficiency. No test for the autoantibody directed against neutrophil PR3 and elastase (cANCA) was performed in this patient at the time of diagnosis of WG because the test was not widely available at that time. The occurrence of pathologically confirmed pulmonary involvement from WG and α₁-AT-deficiency emphysema have not been described in the same
patient. Two previous reports discuss patients who may have had both WG and α1-AT-deficiency emphysema but without definite confirmation. The diagnosis of WG relies on granulomatous inflammation on biopsy and clinical criteria of abnormal urinary sediment, abnormal findings on chest radiograph, oral ulcers, or nasal discharge. A patient whose case was reported by Esnault et al. had a PiZZ phenotype and had both panlobular emphysema and severe pulmonary vasculitis; it is not clear whether criteria for the diagnosis of WG were present. Mazodier et al. reported a case of WG that did not involve the lung in association with clinically diagnosed emphysema. Further information was not given.

cANCA, which is present in approximately 95% of patients with active WG, is generally undetectable in patients in remission. The primary inhibitor of PR3 in human lungs is α1-AT. The association of WG and abnormal α1-AT alleles points to a relationship between the diseases, and the current case further strengthens this association. Although it is possible that both diseases stem from a common underlying defect, it seems more probable that there is a causal relationship between α1-AT-deficiency alleles and WG, particularly as α1-AT is an important regulatory protein in the suppression of immune and inflammatory responses.

It has been proposed that there is an increased propensity of unbound and uninhibited PR3 to stimulate autoantibody production. Increased PR3 can occur in inflammatory conditions of the lung or with relative deficiency of α1-AT activity. In susceptible individuals, this increase in PR3 activity may lead to the production of cANCA autoantibodies. It is unclear whether cANCA is directly involved in the pathogenesis of WG, or if it is one of the products of a larger response responsible for producing WG.

The present case demonstrates that significant pulmonary disease from both WG and α1-AT deficiency can occur in the same patient. The diagnosis of WG may precede that of α1-AT-deficiency-induced emphysema. We believe that all patients diagnosed with WG should have an analysis of their 1-AT. The association of WG and α1-AT may be beneficial.

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References


Management of Aortobronchial Fistula With an Aortic Stent-Graft*

Riyad Karmy-Jones, MD; Christine A. Lee, MD; Stephen C. Nicholls, MD; and Eric Hoffer, MD

Aortobronchial fistula presenting as massive hemoptysis is a rapidly fatal process that is extremely difficult to manage. We report a case in which endovascular occlusion of a fistula between a thoracic aortic pseudoaneurysm and lung was successfully managed by placement of an aortic endovascular stent-graft. Stent-grafting is a promising technique in managing complications of thoracic aneurysms and grafts.

Key words: aortic aneurysm; endovascular stent; hemoptysis

Abbreviations: ABF = aortobronchial fistula; PSA = pseudoaneurysm

Massive hemoptysis caused by aortobronchial fistula (ABF) may be a complication of both thoracic aneurysms and pseudoaneurysms (PSAs) after thoracic graft replacement. Management usually entails resection and graft interposition, but there are significant risks for death and paralysis, particularly in the setting of PSAs. Aortic stent-grafts have been used to manage thoracic aneurysms in high-risk patients, including those with ABF. We present a case of ABF complicating a PSA successfully managed with a stent-graft.

Case Report

An 83-year-old woman presented with shock (systolic BP, 80 mm Hg) and massive hemoptysis. Her history was significant for mild Parkinson’s disease, aortic valve replacement 17 years previously.

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atrial fibrillation (for which she was receiving warfarin sodium), and a descending thoracic aortic graft placement for aneurysm shortly after her aortic valve procedure. One year previously, she had been treated for hemoptysis, which was thought to be caused by pneumonia. At that time, chest CT revealed PSAs at both the proximal and distal anastomoses of the thoracic tube graft. On this hospital admission, her laboratory findings included an initial hematocrit of 21 and an international normalized ratio of 5.2. A CT scan of the chest demonstrated a thrombosed distal PSA and contrast within the proximal anastomotic PSA. The adjacent lung was consolidated, which suggested communication of the PSA with the lung parenchyma or the tracheobronchial tree (Fig 1). Because of the presence of shock and the patient's age and general condition, it was deemed that direct surgical repair posed a prohibitive risk. The patient was intubated, placed in the left lateral decubitus position, and aggressively resuscitated with blood products (10 U packed cells and 10 U fresh-frozen plasma). Within 12 h, her coagulopathy had been corrected and vital signs stabilized. An aortogram was obtained to determine whether an endovascular stent-graft placement would be feasible. This study demonstrated an occlusion of the left subclavian artery (Fig 2). Before stent placement, bronchoscopy demonstrated that the left mainstem bronchus was patent, and that the mass was smaller and nonpulsatile. No obvious tracheobronchial defect could be identified. A CT scan on the second postoperative day demonstrated

Bronchoscopy demonstrated that the previously occluded left mainstem bronchus was now patent, and that the mass was smaller and nonpulsatile. No obvious tracheobronchial defect could be identified. A CT scan on the second postoperative day demonstrated

Figure 1. Chest CT demonstrating contrast in the lumen of the aorta and PSA (arrow), which is in proximity to the left tracheobronchial tree.

Figure 2. Thoracic angiogram delineating the PSA (arrow). Measurements suggested a diameter of $27 \times 31$ mm. Other views demonstrated that the occluded left subclavian filled by retrograde flow from the left vertebral artery.

Figure 3. Postoperative CT scan demonstrating the stent-graft in place and the occlusion of the PSA. a = ascending aorta; s = stent in descending aorta.
occlusion of the PSA (Fig 3). A repeat angiogram was performed on the fourth postoperative day. This was prompted by the presence of persistent blood-streaked sputum, the need for anticoagulation, and concerns that there might still be some leak around the graft into the PSA. This study revealed that there was no leak and that there was an absence of filling of the PSA, consistent with occlusion. The patient was extubated on the seventh postoperative day. She did well for 3 weeks but then developed vancomycin-resistant staphylococcal pneumonia (by sputum cultures). Repeat CT did not demonstrate a patent PSA but did demonstrate bilateral infiltrates (left greater than right) consistent with pneumonia. She refused intubation and eventually died of respiratory failure.

**Discussion**

Operative repair of PSAs of the thoracic aorta is associated with a mortality as high as 41%, markedly greater than the operative mortality of primary thoracic aneurysms, even those complicated by aortobronchial or aortoesophageal fistula (30-day mortality, 18%).1 Morbidity included intraoperative hemorrhage, paralysis, and multiple organ failure.1 Endovascular stent-grafts have been described in the management of both noninfected and infected thoracic aneurysms and PSAs.2–7 They offer an alternative method of management in patients who are at prohibitive risk for direct surgical repair, but the long-term outcome has yet to be determined for this technique. Semba et al.2 in a series of 100 patients, demonstrated a perioperative mortality of 6.8% and 35-month actuarial survival of 52%. There have been two other reports of stent occlusion of ABF, one arising from a pseudoaneurysm repair with endovascular stent-grafts. J Vasc Interv Radiol 1998; 9:33–40. The delayed traumatic hemothorax in this case occurred on treatment with ticlopidine and did not recur with continuation of aspirin alone.

(CHEST 1999; 116:257–260)

**Key words:** aspirin; coronary stent; hemothorax; percutaneous transluminal coronary angioplasty; pleural effusion; rib fracture; ticlopidine

**Ticlopidine** is a potent inhibitor of platelet aggregation and acts via the adenosine diphosphate pathway. At present, ticlopidine has therapeutic indications in two common illnesses: coronary artery disease and cerebrovascular disease. Ticlopidine therapy may cause a wide range of side effects and toxicities affecting multiple organ systems, but it most commonly causes hematologic abnormalities.1

Rib fractures are often associated with pneumothorax or hemothorax, especially in multiple traumatic injuries such as motor vehicle accidents.2–3 Hemothorax when associated with rib fractures usually follows within hours after the trauma. A MEDLINE search of the literature from 1966 to 1998 revealed only two references citing delayed traumatic hemothorax occurring > 24 h after rib fracture.4,5

We describe a case of delayed traumatic hemothorax presenting 28 days after rib fractures and 7 days after the addition of ticlopidine to aspirin therapy after coronary stent placement. The hemothorax had not developed while the patient was being treated for coronary ischemia.

**References**


**Delayed Traumatic Hemothorax on Ticlopidine and Aspirin for Coronary Stent**

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A 64-year-old man presented with worsening dyspnea on exertion and hemothorax of the left chest 7 days after discharge from the hospital on ticlopidine and aspirin after coronary stent placement to his left circumflex artery. He had suffered traumatic rib fractures to the seventh, eighth, and ninth left ribs 28 days before this presentation and 21 days before starting the ticlopidine. Results of chest radiography at discharge 7 days earlier while on aspirin and after brief IV heparin had been negative except for minimal atelectasis and rib fractures barely visible on posteroanterior view. The delayed hemothorax had lowered the peripheral blood hematocrit to 23% and required tube thoracostomy drainage and blood transfusion. The delayed traumatic hemothorax in this case occurred on treatment with ticlopidine and did not recur with continuation of aspirin alone.

(CHEST 1999; 116:257–260)
with aspirin or heparin. This unusual complication of ticlopidine had not previously been reported. Common traumatic injuries such as rib fractures may occur in patients receiving ticlopidine. This report serves to raise the index of suspicion for delayed hemorrhage complicating such injuries.

CASE REPORT

A 64-year-old white man presented with a complaint of worsening dyspnea on exertion and new left pleural effusion 28 days after suffering traumatic fracture of three left ribs (Fig 1). He had previously been admitted to the hospital 10 days earlier for unstable angina and treated initially with aspirin and \( \beta \)-adrenergic blockade. Coronary angiography had revealed significant one-vessel disease in the circumflex artery. He received treatment with coronary angio-plasty and coronary stent placement. During the catheterization, he received unfractionated heparin as an IV bolus of 8,000 U followed by an IV infusion of 1,000 U/h for 2 h. A chest radiograph obtained 1 day after the stent procedure on the day of discharge revealed mild left lung atelectasis caused by fractures of the seventh to ninth ribs (Fig 2). The rib fractures had occurred 28 days before the admission with hemothorax as a result of an accidental fall onto the wooden arm of a couch. Rib pain, which worsened on deep inspiration, had slowly improved. His discharge medications after stenting included ticlopidine, 250 mg bid, and aspirin, 325 mg/d. Dyspnea on exertion now was occurring at < 50 feet of level walking compared with a baseline of 2 blocks. Cough and sputum production had also slightly increased. He denied recurrent anginal chest pain or any other chest pain or pressure. Additional medical history included left ventricular systolic dysfunction with an ejection fraction of 35%, a remote myocardial infarction, moderate COPD, hypertension, and remote tobacco use. Review of systems was otherwise noncontributory to include a negative history for alcohol use, tuberculosis, or positive purified protein derivative test. There was no history of additional traumatic injury.

Physical examination revealed a man who appeared ill and older than stated age with the following vital signs: temperature, 36.6°C; respiratory frequency, 24 breaths/min; pulse oximetry, 92%; pulse, 68 beats/min; and BP, 119/55 mm Hg. Chest examination revealed crackles at the right base and decreased breath sounds over the lower half of the left lung field, with corresponding dullness to percussion and decreased tactile fremitus. Cardiac examination revealed regular rate and rhythm without murmur, rub, or gallop. There was no jugular venous distention or hepatojugular reflux. Abdominal examination was unremarkable. Rectal examination was negative for occult blood. Extremity examination revealed stable 2+ pitting edema to the knees bilaterally with skin changes consistent with chronic stasis with normal sensation.

Laboratory evaluation of the peripheral blood revealed the following: WBC count, 18,600/\( \mu \)L with a normal differential; RBC count, 2,500,000/\( \mu \)L; hematocrit, 24% (baseline, 41% 1 week earlier); and platelet count, 481 \( \times \) 10\(^3\)/\( \mu \)L. Coagulation studies revealed a prothrombin time of 11.3 s and a partial thromboplastin time of 28 s. The results of electrolyte and glucose tests were normal, and renal function tests revealed the BUN level at 39 mg/dL and creatinine level at 1.7 mg/dL compared with baseline values of 20 mg/dL and 1.1 mg/dL, respectively. The results of liver function tests were normal except for an alkaline phosphatase of 126 U/L (normal, 36 to 124 U/L). The results of antinuclear antibodies were found to be normal. ECG revealed normal sinus rhythm with nonspecific ST-wave and T-wave changes.

The decline in hematocrit, a new left pleural effusion, and absence of signs or symptoms consistent with GI bleeding suggested the diagnosis of hemothorax, and pleural fluid analysis confirmed it.Thoracentesis with analysis of the pleural fluid revealed an RBC count of 1,230,000/\( \mu \)L, and a WBC count of 18,000/\( \mu \)L, with a differential count of 45% neutrophils, 46% lymphocytes, 1% eosinophils, and 8% macrophages. The results of a culture and a Gram’s stain of the fluid were negative for bacteria. Chest CT scan excluded retroperitoneal hemorrhage.

Ticlopidine therapy was discontinued, but the aspirin therapy was continued to prevent stent occlusion. The patient received a transfusion with 3 U of packed RBCs. His hematocrit rose to 31% and remained stable (at 30.5%) until discharge. Initial chest tube placement yielded a return of 1.6 L of bloody fluid in the first 15 min and an additional 0.7 L during the first 24 h after chest tube placement. Output amounted to 0.3 L during the second day. At that time, instillation of urokinase increased output to approximately 0.75 L per day. The chest tube was removed after 4 days with substantial improvement. A follow-up chest radiograph several months later revealed no effusion.
Discussion

We have reported a case of delayed traumatic hemothorax presenting 28 days after rib fractures and 7 days after the addition of ticlopidine to aspirin therapy after stent placement. This unusual complication of ticlopidine had not previously been reported. Common traumatic injuries such as rib fractures may occur in other patients receiving ticlopidine. This report serves to raise the index of suspicion for delayed hemorrhage complicating such injuries in patients receiving combined antiplatelet therapy.

Rib fractures occur in 7 to 10% of multiple trauma admissions.3,4 Motor vehicle accidents represent the most common cause of rib fractures.2,6,7 Rib fractures are often associated with other injuries such as pneumothorax or hemothorax in one third of cases and extremity fractures, splenic injury, hepatic injury, CNS injury, and thoracic aorta injury in others.2,3,8,9 As the number of rib fractures increases, so does the mortality, such that with seven or more rib fractures the mortality approaches 30%.2,8 Approximately 50% of rib fractures will not be detected by plain posteroanterior chest films; however, most will be detected on physical examination of the conscious patient.10

Hemothorax associated with rib fractures usually follows within hours after the trauma. A MEDLINE search of the literature from 1966 to 1998 revealed only one reference4 in the English-language literature citing delayed hemothorax occurring > 24 h after rib fracture. Ross and Cordoba4 described two cases of delayed hemothoraces 3 and 4 days after rib fractures. A report in the Chinese-language literature (abstracted in English) also cited multiple rib fractures, vascular injuries, and foreign body retention among the causes of delayed hemothorax.5 Penetrating traumatic injury to the internal mammary artery has also caused delayed hemothorax in which the hemothorax presented within 4 h of injury in most cases, but took as long as 6 days to present in one case.11 An unusual and fatal case of delayed hemothorax in a 12-year-old girl resulted from an atypical dissection of a traumatic carotid aneurysm a week after a sledding accident.12 Iatrogenically induced delayed hemothoraces caused by procedures such as subclavian access for hemodialysis, as well as vascular surgery with prosthetic graft placement, have been reported.13,14

We believe that the ticlopidine is responsible for the development of the delayed hemothorax in our patient. Ticlopidine, a thienopyridine derivative, is structurally and functionally unrelated to other platelet aggregation inhibitors such as aspirin, sulfipyrazone, and dipyridamole. Aspirin, which is commonly used in coronary artery disease and cerebral vascular disease, inhibits platelet aggregation through the arachidonic acid pathway. Ticlopidine appears to act through the adenosine diphosphate pathway by inhibiting the platelet 2-methylthio-adenosine diphosphate-binding receptor subtype and the adenosine diphosphate-induced exposure of the fibrinogen binding site of the platelet glycoprotein IIb/IIIa receptor.15,16

Ticlopidine has different effects from aspirin in comparison studies of induction of platelet aggregation. Ticlopidine administered at 200 mg qd significantly reduced the amount of platelet aggregation caused by adenosine diphosphate (59% decrease) and platelet activating factor (48% decrease), but did not significantly affect the aggregation induced by arachidonic acid (17% decrease). Aspirin administered at 300 mg qd significantly reduced arachidonic acid- and adenosine diphosphate-induced aggregation by 83% and 37% decrease, respectively, but did not significantly reduce the platelet activating factor-induced aggregation (28% decrease).17 Additional studies showed that ticlopidine potentiates the inhibitory effects of aspirin and other nonsteroidal anti-inflammatory drugs on the collagen-induced platelet aggregation. Aspirin had no effect on the inhibition of the adenosine diphosphate-induced platelet aggregation by ticlopidine.18

Multiple-dose ticlopidine causes inhibition of the adenosine diphosphate-induced platelet aggregation within 24 to 48 h after initiating therapy. A two- to threefold increase in bleeding times has been reported with ticlopidine. Maximal effects are achieved within 3 to 7 days after initiating therapy. These effects persist after withdrawal of ticlopidine for the lifetime of the platelet.1,19

We hypothesize that ongoing microvascular trauma from recurring displacement of unstable rib fractures caused small recurrent hemorrhages, which in the presence of ticlopidine antiplatelet therapy resulted in the hemothorax. We infer that platelet plug stability while on aspirin alone had been sufficient to maintain hemostasis. The additional effects of ticlopidine may have caused platelet plug instability, which, in the setting of ongoing microvascular trauma, resulted in hemorrhage and development of the hemothorax.

Ticlopidine therapy is associated with a wide range of side effects and toxicities, including gingival hemorrhage, hemorrhrosis, hematuria, bleeding from the arterial junction of an arteriovenous shunt, and postoperative bleeding, as well as neutropenia, thrombocytopenia, and anemia and thrombotic thrombocytopenic purpura. GI side effects include dyspepsia, gastritis with bleeding, abdominal pain, nausea, and diarrhea. Hepatic effects include elevated liver function test results and cholestasis jaundice. Dermatologic effects most commonly consist of maculopapular or urticarial rashes and promptly resolve with discontinuation of ticlopidine.2,20 There have been no reports to date that ticlopidine impairs wound healing. Also we are unaware of any thrombolytic or fibrinolytic effects of ticlopidine.

For the present time, it appears reasonable to carefully monitor patients who have had similar blunt trauma injuries after starting ticlopidine. Delay of elective interventions requiring ticlopidine or selection of other alternatives appears appropriate in patients after blunt trauma, fractures, and possibly invasive procedures. The “safe” interval to begin ticlopidine after injury remains to be determined, but appears to be not < 4 weeks. Future studies may be helpful in defining the risk and refining the recommendations for combined antiplatelet therapies.

In conclusion, we report a case of transfusion-requiring delayed hemothorax presenting 4 weeks after traumatic rib fractures. Hemothorax developed while the patient was receiving combination antiplatelet aggregation therapy
with aspirin and ticlopidine to prevent coronary stent thrombosis. No hemothorax had developed earlier when the patient was receiving aspirin and brief IV heparin for coronary ischemia. Hemorrhage resolved after discontinuing ticlopidine.

References

Noninvasive Positive-Pressure Ventilation Facilitates Tracheal Extubation After Laryngotracheal Reconstruction in Children*

James H. Hertzog, MD; Linda B. Siegel, MD; Gabriel J. Hauser, MD, FCCP; and Heidi J. Dalton, MD

Tracheal extubation after laryngotracheal reconstruction in children may be complicated by postoperative tracheal edema and pulmonary dysfunction. The replacement of a tracheal tube in this situation may exacerbate the existing injury to the tracheal mucosa, complicating subsequent attempts at tracheal extubation. We present two cases where noninvasive positive-pressure ventilation was employed to treat partial airway obstruction and respiratory failure in two children following laryngotracheal reconstruction. Noninvasive positive-pressure ventilation served as a bridge between mechanical ventilation via a tracheal tube and spontaneous breathing, providing airway stenting and ventilatory support while tracheal edema and pulmonary dysfunction were resolved. Under appropriate conditions, noninvasive positive-pressure ventilation may be useful in the management of these patients.

Key words: laryngotracheal reconstruction; noninvasive positive-pressure ventilation; pediatric intensive care

Abbreviations: ABG = arterial blood gas; EPAP = expiratory positive airway pressure; FIO2 = fraction of inspired oxygen; ID = internal diameter; IPAP = inspiratory positive airway pressure; LTR = laryngotracheal reconstruction; NPPV = noninvasive positive-pressure ventilation; PICU = pediatric ICU

Children with subglottic stenosis who undergo laryngotracheal reconstruction (LTR) may benefit postoperatively from several days of deep sedation and immobility in order to optimize the surgical-site healing and to avoid further tracheal damage.1,2 To achieve this, tracheal intubation and mechanical ventilatory support during the period of sedation and neuromuscular blockade are required. While tracheal intubation is necessary, it can directly result in tracheal trauma and mucosal edema, complicating subsequent attempts at tracheal extubation.

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Furthermore, prolonged tracheal intubation and mechanical ventilation may predispose the patient to several other complications, including tracheitis, pneumonia, and atelectasis. As a result of these complications, children may fail their initial trial of tracheal extubation after LTR and require tracheal reintubation, further increasing the risk of tracheal injury.

Noninvasive positive-pressure ventilation (NPPV) by nasal mask is a method of providing mechanical ventilatory support in the absence of tracheal intubation, and it has been employed in adults with both acute and chronic respiratory failure, effectively improving oxygenation and ventilation. More recently, the use of NPPV has been reported in pediatric patients. In addition, NPPV avoids the trauma to the trachea associated with the insertion and maintenance of a tracheal tube. NPPV may therefore serve as a bridge between mechanical ventilation (via a tracheal tube) and spontaneous breathing in patients after LTR, providing airway stenting and ventilatory support while tracheal edema and pulmonary dysfunction dissipate.

In this report, we present the cases of two children with subglottic stenosis treated with LTR who developed respiratory failure following tracheal extubation. Subsequent management included NPPV. In both cases, NPPV facilitated the transition to spontaneous breathing while avoiding tracheal intubation during a period of respiratory insufficiency.

Case Reports

Case 1

A 25-month-old male patient was admitted to the pediatric ICU (PICU) after elective laryngoscopy, tracheoscopy, and LTR. The child was born at 33 weeks' gestation and required tracheal intubation and mechanical ventilation for 1 week secondary to hyaline membrane disease. At 4 months of age, the child again required tracheal intubation and mechanical ventilation due to laryngotracheobronchitis. A tracheostomy was subsequently placed due to subglottic stenosis, and the child was removed from mechanical ventilatory support and did well.

Laryngotracheal reconstruction was performed with anterior and posterior cricoid splits and autogenous rib-cartilage graft placement. The patient was admitted to the PICU postoperatively with a 4.0-mm internal diameter (ID) nasotracheal tube sutured in place. Sedation, analgesia, and neuromuscular blockade were commenced with a 4.0-mm ID nasotracheal tube. The patient was transferred to a hospital closer to his home to complete his recovery.

On postoperative day 22, the child’s trachea was again extubated. He received supplemental oxygen via a face mask and nebulized racemic epinephrine. Initially, the child appeared comfortable, but he developed stridor and respiratory distress within an hour, along with increasing hypercarbia. Interventions, including an increase in supplemental oxygen, administration of IV and aerosolized steroids, aerosolized racemic epinephrine, aerosolized bronchodilators, and inhaled heliox, did not improve the child’s status. The results of arterial blood gas (ABG) measurements deteriorated to a pH of 7.11, PaO2 of 76 mm Hg, and PaCO2 of 171 mm Hg.

In an attempt to avoid further airway trauma from tracheal intubation, NPPV via a nasal mask was instituted in the timed spontaneous mode, using a ventilatory support system (BiPAP: Respironics; Murrysville, PA). Initially, the inspiratory positive airway pressure (IPAP) was set at 10 cm H2O, and the expiratory positive airway pressure (EPAP) was set at 5 cm H2O with a mechanical respiratory rate of 15 breaths/min, while the child adjusted to the device. A 3-L/min flow of oxygen with a fraction of inspired oxygen (FIO2) of 1.0 was introduced at the mask. Subsequent changes in the level of ventilatory support were made based on the patient’s lung auscultation findings, level of comfort, and ABG results. A nasogastric tube was electively placed to minimize gastric distention. Over the course of an hour, the IPAP was increased to 15 cm H2O, and the EPAP was increased to 8 cm H2O. The mechanical respiratory rate was increased over the following 9 h to 25 breaths/min, and the FIO2 was decreased to 0.7, while the gas flow was maintained at 3 L/min. Following the institution of NPPV, ABG results improved, demonstrating a pH of 7.31, PaCO2 of 46 mm Hg, and PaO2 of 84 mm Hg, 3 h after therapy was started. The child required infusions of medications for sedation and to maintain placement of the nasal mask. By the second day of NPPV, the child was generally more comfortable and required less sedative medications.

NPPV was used for 41 h with no change in the preset ventilator settings, except for a decrease in the FIO2. Over this period of time, the patient’s respiratory status and ABG results continued to improve, with a resolution of the stridor and an ABG just prior to discontinuation of NPPV showing a pH of 7.45, PaCO2 of 44 mm Hg, and PaO2 of 85 mm Hg. NPPV was discontinued on postoperative day 24 with no recurrence of airway obstruction or respiratory insufficiency. On postoperative day 28, the patient was transferred to a hospital closer to his home to complete his recovery.

Case 2

A 22-month-old female patient was admitted to the PICU after elective laryngoscopy, tracheoscopy, and LTR. The patient was born after a full-term gestation with an interrupted aortic arch, an atrial septal defect, and a ventricular septal defect. She underwent repair of these congenital heart defects during infancy and subsequently required a tracheostomy for severe subglottic stenosis.

Laryngotracheal reconstruction was performed with an anterior cricoid split and an autogenous thyroid cartilage graft placement. She was admitted postoperatively to the PICU with a chest tube placed to drain a right-sided pneumothorax. Bronchoscopy on postoperative day 14 revealed wound dehiscence at the inferior aspect of the laryngotracheoplasty graft. A 4.0-mm ID cuffed endotracheal tube was placed for conservative management of the wound dehiscence and associated air leak. IV steroids were discontinued. Supportive therapies were continued through postoperative day 21, when the patient again underwent bronchoscopy, demonstrating no wound dehiscence or granulation tissue.

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4.0-mm ID nasotracheal tube sutured in place. Sedation and analgesia were maintained with continuous medication infusions, and neuromuscular blockade was achieved with intermittent doses of medication. Episodes of atelectasis were responsive to chest physiotherapy and suctioning. The patient developed an air leak around her nasotracheal tube on postoperative day 5, and her trachea was extubated after receiving IV steroids. The child was awake and agitated prior to tracheal extubation, but she subsequently became more somnolent and developed signs of upper airway obstruction. She received aerosolized epinephrine twice without relief and had a worsening of her respiratory status. An ABG revealed a pH of 7.29, Pa$_{CO_2}$ twice without relief and had a worsening of her respiratory status.

NPPV in the spontaneous mode via a nasal mask (Nellcor Puritan Bennett; Pleasanton, CA) was initiated in an attempt to avoid tracheal intubation and further airway trauma, as well as to decrease the need for ongoing sedation. Initial ventilatory settings consisted of an IPAP of 10 cm H$_2$O and an EPAP of 5 cm H$_2$O, with a 2.5 L/min flow of oxygen (FiO$_2$ being 1.0) introduced at the mask. The flow of oxygen was gradually decreased based on pulse oximetry measurements, and after 3 h, her ABG results improved to a pH of 7.36, Pa$_{CO_2}$ of 53 mm Hg, and Pa$_{O_2}$ of 94 mm Hg. No additional sedation was required during this time.

At this level of support, NPPV was continued for 24 h. Prior to the discontinuation of NPPV, the ABG results had improved to a pH of 7.40, Pa$_{CO_2}$ of 48 mm Hg, and Pa$_{O_2}$ of 92 mm Hg. The child’s respiratory status continued to improve, with no further evidence of upper airway obstruction, and she was discharged to her home on postoperative day 10.

**DISCUSSION**

The medical management of children after LTR includes a period of tracheal intubation and mechanical ventilation while the airway heals. However, prolonged tracheal intubation can lead to further tracheal injury. Irritation and edema from surgery and tracheal intubation may complicate tracheal extubation in this patient population, with patients often failing their initial trial of tracheal extubation. Subsequent tracheal reintubation may increase the risk of further tracheal injury and edema, as well as other complications.

We have reported the cases of two children who had undergone LTR and subsequently developed upper airway obstruction and respiratory failure following tracheal extubation. Tracheal reintubation was avoided in both cases by the use of NPPV. NPPV facilitated the reversal of respiratory failure without the trauma of tracheal intubation and allowed time for the resolution of tracheal edema following tracheal extubation. One patient required sedation while receiving NPPV, but at lower doses than when tracheally intubated, whereas the second patient required no sedation. Neither patient experienced any complications related to the use of NPPV, which was required for only a short period of time, and both patients subsequently did well.

NPPV has been employed extensively in adults with both acute and chronic respiratory failure. More recently, there have been reports in the literature about the use of NPPV in pediatric patients with acute respiratory failure. These reports suggest that NPPV may prevent tracheal intubation in many patients with minimal complications. By avoiding tracheal intubation, NPPV may allow time for airway healing and resolution of edema while providing ventilatory support and airway stenting. The mode of NPPV employed for any given patient (spontaneous, timed/spontaneous, or timed) will depend on the needs of the patient, but in general we prefer to utilize a spontaneous mode with NPPV to allow mechanical support and synchrony with the patient’s respiratory effort. Likewise, the initial levels of IPAP and EPAP will depend on the patient’s needs. We generally start with relatively low levels of pressure, such as an IPAP of 6 to 10 cm H$_2$O and an EPAP of 3 to 5 cm H$_2$O, allowing the child to accommodate to the mask pressure. Subsequently, IPAP and EPAP may be increased as needed, based on the patient’s physical examination, pulse oximetry measurements, and ABG results. NPPV cannot be performed when the size of the nasal mask is too large for the child, but NPPV has been successfully performed in infants as young as 4 months. Furthermore, tracheal intubation is appropriate in those cases where hemodynamic instability or a loss of protective airway reflexes has occurred.

The potential complications of NPPV include nasal skin breakdown, gastric distention, and aspiration of gastric contents. The breakdown of skin over the nasal bridge can be minimized by the use of protective padding but must be monitored carefully. Gastric distention has been uncommon in pediatric studies and can be minimized with the use of a nasogastric tube to decompress the stomach if needed. The aspiration of gastric contents has not been reported thus far in the pediatric population. In children, sedation may be necessary to facilitate tolerance of the mask but should not be more than that needed while the patient is tracheally intubated. Increasing acceptance of the mask may develop over time and allow sedation use to be decreased or discontinued. The risk of gastric reflux and aspiration may increase, however, with the use of sedation. Tracheal intubation may provide relative protection against gastric aspiration, so that this benefit may need to be weighed against the risks associated with tracheal intubation in those patients whose airway protective reflexes have been blunted by sedation. A theoretical danger of NPPV in children who have received LTR is that the pressure delivered by the mask could cause airway distention and injury at the surgical site. Although no evidence of this problem was apparent in our patients, further research into this possibility is warranted. Furthermore, the minimal levels of IPAP and EPAP needed to maintain the desired clinical effects should be employed.

Our cases are unique in that they describe for the first time the use of NPPV in children who have respiratory failure secondary to upper airway obstruction that developed after LTR. NPPV served as a bridge between mechanical ventilation (via a tracheal tube) and spontaneous breathing, allowing time for a critical decrease in airway edema while avoiding further airway trauma. It is possible that NPPV will also be useful in the treatment of children with respiratory failure secondary to airway obstruction of different etiologies. Before its role can be completely delineated, further evaluation of NPPV is needed in the management of respiratory failure associated with upper airway obstruction after LTR.

In conclusion, we have described the cases of two
Pulmonary Cysts as the Sole Metastatic Manifestation of Soft Tissue Sarcoma*

Case Report and Consideration of the Pathogenesis

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A 29-year-old woman with an unusual form of pulmonary metastasis from epithelioid sarcoma of the right forearm is presented. Since she manifested left pneumothorax due to metastatic pulmonary cyst 7 years ago, the only metastatic manifestation has been the presence of bilateral multiple thin-walled pulmonary cysts; no other types of pulmonary lesions, such as nodules, cavitary lesions with thick or irregular walls, or extrapulmonary metastases, have been found. Pathologic studies revealed metastatic proliferation of sarcoma cells in the wall of the pulmonary cysts and infiltration of malignant cells inside the microscopic cavitory metastases surrounded by normal lung parenchyma.

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Key words: cystic metastasis; pneumothorax; pulmonary cyst; pulmonary metastasis; sarcoma

Cystic pulmonary lesions caused by metastasis of soft tissue sarcoma are rare. When accompanied by multiple pulmonary nodules, such lesions can be easily identified as possible metastases from an unidentified primary tumor. However, when a pulmonary cyst is not accompanied by pulmonary nodules or a noticeable primary lesion, it may not be readily identified as a pulmonary metastasis.

We describe a 7-year follow-up of a patient in whom spontaneous pneumothorax and multiple pulmonary cysts were the initial clinical manifestations of epithelioid sarcoma of the forearm. Detailed serial histologic studies revealed the possible mechanism by which the malignant cysts developed.

Case Report

A 29-year-old Japanese woman was admitted to Nagahama City Hospital in June 1996 because of recurrent left pneumothorax. She had several episodes of pneumothorax in both lungs. She had undergone left thoracotomy in November 1991 and right thoracotomy in December 1993, and the histologic diagnosis of the resected lung tissue was pulmonary bulla with metastasis of the lining cells in all instances.

Chest CT on admission revealed bilateral pulmonary thin-walled cysts measuring up to 2.0 cm in diameter. Results of physical and laboratory examinations were unremarkable, except for a tumor on the right forearm. The patient underwent partial resection of the left S10 segment, which contained several subpleural bullae. No other intrapulmonary or pleural lesions were found during surgery. Although pulmonary bulla with inflammatory reaction was the histologic diagnosis, pathologists could not rule out mesothelioma or other malignant diseases of the lung, because the lining cells of the cyst wall showed atypia.

After completion of the treatment for left pneumothorax, a detailed examination of the tumor on the right forearm was performed. The patient had noticed (1) slight but progressive disturbance in extension of the right middle and ring fingers

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References


since 1986 and (2) a small nodule on her right palm since 1991. Radiologic studies revealed a longitudinal mass located on the ulnar side of her distal forearm measuring 2 to 4 cm in diameter and 15 cm in length, and a small nodule on the medial-distal side of the right upper arm measuring 1 cm in diameter. A biopsy led to a pathologic diagnosis of epithelioid sarcoma of the right forearm and metastasis to the regional lymph nodes.

A detailed histologic reassessment of lung specimens obtained in 1991, 1993, and 1996 was made. Pulmonary tissue was compared with the tissue removed from the forearm, and they were similar. Thus the cystic lesions in these specimens were diagnosed as metastases of epithelioid sarcoma. Systemic screening with CT and MRI was performed, but no other metastatic lesions were found. No abnormal uptake was observed by whole-body scintigraphy with 99mTc-methylene diphosphonate and gallium citrate Ga 67, and slight uptake was observed only in the right forearm tumor with thallous chloride Tl 201.

The patient is currently well, her only symptom being motor disturbance in the right upper extremity. Her laboratory results show no abnormalities and there is no evidence of distant metastasis except to the lungs.

Radiologic Study

Multiple pulmonary cysts with thin and smooth walls in both lungs were observed by chest CT in June 1996 (Fig 1, top, A). Most of these lesions were intraparenchymal and a few were subpleural. Serial CT studies revealed that these cystic lesions appeared where only normal lung parenchyma had been seen in previous CT scans, and that they grew slowly (Fig 1, bottom, B). No nodules, cavitary lesions with thick or irregular walls, necrotic tissue in the cysts, pleural lesions, or enlarged lymph nodes were found throughout the follow-up period.

Pathologic Study

The macroscopic features of the cysts in the resected lung were consistent with those of pulmonary bullae. Light-microscopic studies were performed on formalin-fixed, paraffin-embedded, and hematoxylin-eosin-stained samples. The walls of the cysts lacked lining epithelium and consisted of a dense proliferation of large spindle cells with eosinophilic cytoplasm (Fig 2). Nuclear atypism of the tumor cells was prominent, but no mitoses were observed. Both fresh and old hemorrhages, hemosiderin deposits, and necrotic tissue were present. This histologic appearance suggested a metastatic epithelioid sarcoma.

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and partial calcification were seen in the cyst walls. There were several microscopic cavitary lesions surrounded by normal lung parenchyma, and the walls of the cavities were lined with sarcoma cells (Fig 3).

**DISCUSSION**

Pulmonary metastases of soft tissue sarcomas commonly take the form of solid nodules. However, only 14 cases, including the present case, of cystic pulmonary metastases from soft tissue sarcomas have been reported. In four of these cases, thin-walled cysts were the only manifestation of pulmonary metastases. The cases involved the following patients: a 20-year-old woman with leiomyosarcoma of the uterus, a 19-year-old woman with leiomyosarcoma of the ankle, an 86-year-old man with angiosarcoma of the scalp, and the 29-year-old woman of the present study1–10 (Table 1).

<table>
<thead>
<tr>
<th>Age, yr/Sex</th>
<th>Neoplasm</th>
<th>Location of Primary Tumor</th>
<th>Outcome</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/F</td>
<td>Leiomyosarcoma</td>
<td>Uterus</td>
<td>Died of pneumothorax</td>
<td>6</td>
</tr>
<tr>
<td>19/F</td>
<td>Leiomyosarcoma</td>
<td>Ankle</td>
<td>Alive and well</td>
<td>9</td>
</tr>
<tr>
<td>86/M</td>
<td>Angiosarcoma</td>
<td>Scalp</td>
<td>Died 1 mo after diagnosis</td>
<td>10</td>
</tr>
<tr>
<td>29/F</td>
<td>Epithelioid sarcoma</td>
<td>Forearm</td>
<td>Alive and well</td>
<td>Present case</td>
</tr>
</tbody>
</table>

*None of the patients had received previous chemotherapy or radiation therapy. F = female; M = male.

There is confusion or overlapping concepts about excavating, cavitary, and cystic pulmonary metastatic tumors. Excavating pulmonary metastasis may be defined by the mechanism of its formation; it is initially a solid mass and its air-filled cavity is formed after discharge of the necrotic material inside. Therefore, such lesions usually have a thick and irregular wall and are seen with other lesions at various stages of excavation. A cystic pulmonary metastasis is a thin-walled, bulla-like lesion with or without accompanying nodular lesions.

Three possible mechanisms for the development of malignant cysts have been described9,11,12: (1) excavation of a nodular tumor through discharge of the necrotic material inside, (2) infiltration of malignant cells into the walls of a preexisting benign pulmonary bulla, and (3) infiltration of malignant cells into the walls of air sacs formed by cystic distension of small airways through the ball-valve effect of the tumor. Involvement of the first mechanism in the present case was ruled out because no nodules or thick-walled cavity lesions appeared during the 7-year follow-up period. The second mechanism was also unlikely, because the consistent increase in the number of pulmonary cysts could hardly be explained by a progressive emphysematous change in the lungs of this young, nonsmoking woman. The likelihood of the third mechanism is strengthened by the presence of microscopic cavitary metastases; these lesions are considered to be an early stage in the development of macroscopic thin-walled cysts. Thus we conclude that the pathogenesis of the metastatic cysts in the present case may have involved the third mechanism.

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