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Successful Treatment of Pulmonary Lymphangioliomyomatosis With Progestins *

Xavier Denoo, Ginette Hermans, Raoul Degives and Jean-Michel Foidart

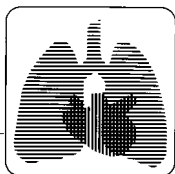
Chest 1999;115:276-279
DOI 10.1378/chest.115.1.276

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A M E R I C A N C O L L E G E O F
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The "Fairy Ring"*

A New Radiographic Finding in Sarcoidosis

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A patient who had the "fairy ring" finding shows another new radiographic presentation of pulmonary sarcoidosis that clinicians can add to the list of signs of the disease.

(*CHEST* 1999; 115:275-276)

Key words: alveolar disease; computed tomography; sarcoidosis

The "fairy ring" radiographic finding is another radiographic presentation of pulmonary sarcoidosis. The patient reported here had this, as well as other symptoms. Such radiographic evidence should prompt the clinician to suspect sarcoidosis and to treat the patient appropriately.

CASE REPORT

A 43-year-old black woman, a lifelong nonsmoker, presented with a cough of 9 months' duration. Initially, her cough was nonproductive. Later, she produced sputum and occasionally had bouts of hemoptysis. Two months prior to presentation, she developed painful, red eyes, which transiently responded to cold compresses. Later, she also noticed a red spot on her lower right shin which was painful, but it resolved spontaneously. One month prior to presentation, she noted dyspnea. She went to the emergency department with the preceding complaints and was referred to a pulmonologist because sarcoidosis was suspected. Spirometry values revealed a FVC of 62% of predicted and a FEV₁ value of 59% of predicted. A chest CT scan (Fig 1) and chest radiograph (Fig 2) were performed. Sputum specimens were negative for tuberculosis. A transbronchial biopsy revealed noncaseating granuloma with stains and cultures negative for fungi and mycobacteria; therefore, the biopsies were consistent with sarcoidosis. Therapy with corticosteroids was started. Her pulmonary symptoms and spirometric abnormalities resolved within 6 months.

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Manuscript received May 19, 1998; accepted May 22, 1998.

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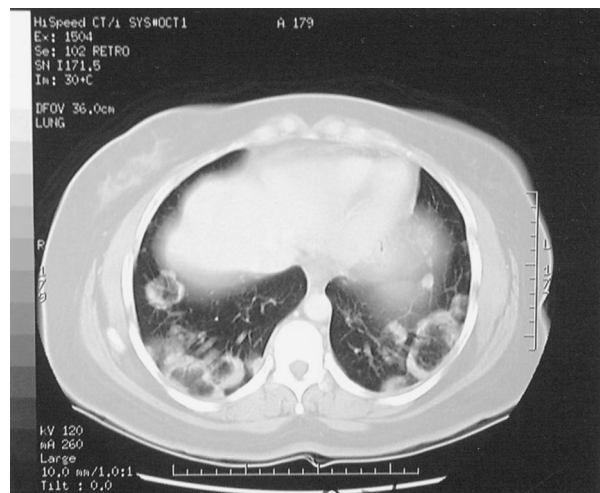


FIGURE 1. CT chest (lung windows). There is bilateral involvement of the posterior lung fields with rings of granulomatous tissue, all of different sizes. The central areas of each lesion are normally aerated. Note the vasculature in the normal central parenchyma. This is the typical appearance of the "fairy ring" finding in sarcoidosis.

DISCUSSION

Sarcoidosis is an idiopathic systemic granulomatous disease which is more common in black women, although men and nonblacks can be affected. Radiographic manifestations have been documented in virtually every organ system. The most common sites of involvement are the lungs, skin, eyes, and lymph nodes.

Radiographic findings in sarcoidosis are diverse. Indeed, many physicians have called sarcoidosis "the great imitator" because it mimics many lung diseases, including tuberculosis, asbestosis, carcinoma, and fungal disease. Lung involvement in sarcoidosis is definitively diagnosed by the presence of noncaseating granulomas in the parenchyma. Depending on their arrangement, they can create lesions which are either nodular, reticular, or alveolar in appearance (Fig 2).

With the exception of adenopathy, nodules are the most frequent finding in pulmonary sarcoidosis.¹ These are caused by the accumulation of many granulomas which are a reaction to the initial lesion of alveolitis.² They may reach 1 cm in size and usually are found around the bronchovascular tree or abutting pleura or septae in the lung. Ground-glass attenuation is less common, tends to follow the bronchovascular tree, and probably also is the result of accumulation of many granulomas.³ Alveolar sarcoid occurs when confluent granulomas involve the alveolar space. This typically results in large opacities with air bronchograms,⁴ but central necrosis often is observed.⁵

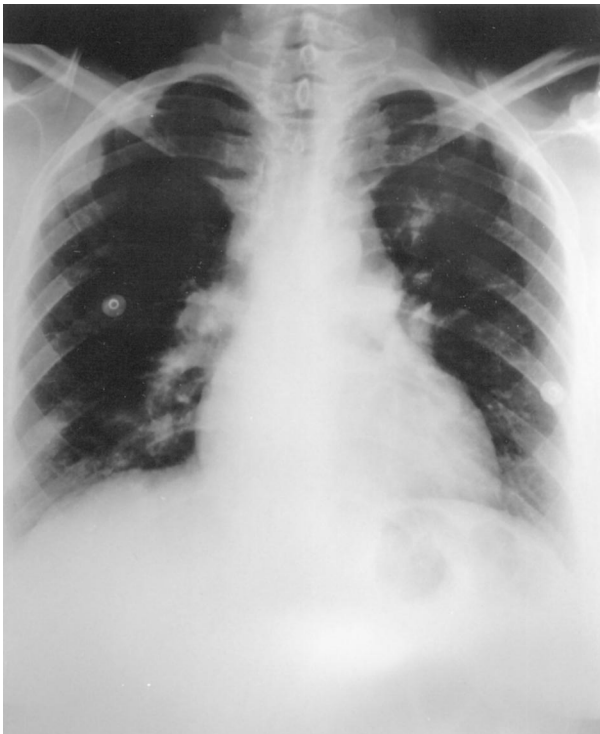


FIGURE 2. Frontal view of the chest. This film, taken prior to the CT scan, shows the classic "pawbroker's sign" of right paratracheal and bilateral hilar adenopathy. No evidence of the "fairy ring" is found on the plain film.

The patient in this report appeared to have alveolar sarcoid with central necrosis on CT mediastinal windows. On lung windows, however, it was noted that the central areas of the lesions were comprised of normal lung tissue. This finding may be a distinct new type of alveolar sarcoidosis with a ring of granulomatous tissue extending concentrically from a given point in the lung. Strangely, the lung tissue inside the ring appears undisturbed and without disease. No air bronchograms are appreciated, and the process appears to behave in an organized, circumferential fashion. Unlike the airspace distortion in some focal sarcoid lesions, this entity shows no evidence of abnormal air distribution. The center of the ring comprises normally aerated lung tissue. We have called these lesions the "fairy ring" sign.

Fairy rings are well described in Celtic mythology. According to legend, fairies would come out at night and dance in small circles in the grass. Their tiny feet would beat a bare circular path at the edge of the ring. When tired, the fairies would sit and rest on the toadstools that defined the circle's periphery. The next day, passing travelers saw only a circle in the grass with a ring of mushrooms. The fairy ring pattern is actually created by the *Marasmius oreades* mushroom, a fungus which may live to be more than 600 years old. Some botanists believed it to be the largest organism on the planet.⁶

The granulomatous inflammation of sarcoidosis can resolve spontaneously without therapy.⁷ Perhaps fairy ring lesions are formed by central granulomatous inflammation

which has spontaneously resolved while new granulomatous inflammation develops at the periphery. The fairy ring sign should be added to the list of radiographic presentations of pulmonary sarcoidosis.

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Successful Treatment of Pulmonary Lymphangioleiomyomatosis With Progestins*

A Case Report

Xavier Denoo; Ginette Hermans, MD; Raoul Degives, MD; and Jean-Michel Foidart, MD, PhD

The diagnostic approach, clinical evolution, and treatment of a patient with primary pulmonary lymphangioleiomyomatosis are reported. This patient presented a restrictive respiratory syndrome resistant to conventional glucocorticoid therapy. The diagnosis, based on clinical and histologic examinations, was confirmed by immunohistochemical localization of one of the desmins, the smooth muscle cell actin, and HMB45 antigen. The patient received treatment with an anti-estrogenic agent (tamoxifen citrate) and high doses of medroxyprogesterone acetate, an antigonadotropic progestin. Respiratory function improved rapidly with clinical relief.

(*CHEST* 1999; 115:276-279)

Key words: anti-estrogen; progestin; pulmonary lymphangioleiomyomatosis

Abbreviation: LLM = lymphangioleiomyomatosis

Lymphangioliomyomatosis (LLM) is a rare pathologic finding, for fewer than 100 cases have been described. It consists of a smooth muscle cell proliferation into the perilymphatic pulmonary interstitium. LLM occurs primarily in women of childbearing age. One third of the cases arise in women less than 20 years of age.¹⁻⁶

LLM also may appear as a forme fruste of tuberous sclerosis (Bourneville's disease)⁵ or may belong to the syndrome described by Carney et al,⁴ which includes the triad of pulmonary chondroma, extra-adrenal paraganglioma, and gastric leiomyosarcoma. The past histories of women with LLM frequently include hysterectomy or myomectomy,³ and a premenopausal state⁵ associated with tobacco use.³ Finally, benign leiomyomas represent fewer than 2% of the benign tumors of the lower respiratory tract.⁶

The onset of the disease is paucisymptomatic. Although the diagnosis is most often evoked by a routine chest x-ray film, a histologic examination of a surgically or transbronchially^{1,3} obtained pulmonary biopsy specimen is essential to confirm it. LLM must be differentiated from other pathologic states, including smooth muscle cell hyperplasia. The main differential diagnosis is benign metastasizing leiomyoma associated with a uterine leiomyoma. This last entity responds favorably to corticosteroids in contrast to LLM which is resistant to glucocorticoids but is favorably influenced by oophorectomy, progestins, anti-estrogenic agents, or luteinizing hormone-releasing hormone agonists.²⁻⁴

The histologic, clinical, and therapeutic characteristics of an LLM case successfully treated with an anti-estrogenic agent and a progestin are described.

CASE REPORT

In May 1987, a 36-year-old patient was admitted to the emergency department with a dry cough, a morning fever, and diffuse sweating. Her general condition was satisfactory. Clinical examination detected a temperature of 36.5°C; heart rate, 80 beats per minute; BP, 135/70 mm Hg. She complained of profound asthenia and considerable anxiety. Digital clubbing was noted as well as rales on the right side of the chest and severe dyspnea (grade III, Sadoul scale⁷ equivalent to grade II MRC⁸). The chest x-ray film revealed pneumonia of the median right lobe (anterior segment), bronchopneumonia in the lower lobes of both right and left lungs (Fig 1). Clinical biology was characterized by an acute inflammatory syndrome. Antibiotics (doxycycline, 200 mg/d) and anxiolytics (alprazolam) were prescribed.

Six weeks later, the patient was readmitted with increased dyspnea. The chest x-ray film was abnormal, suggesting a possible

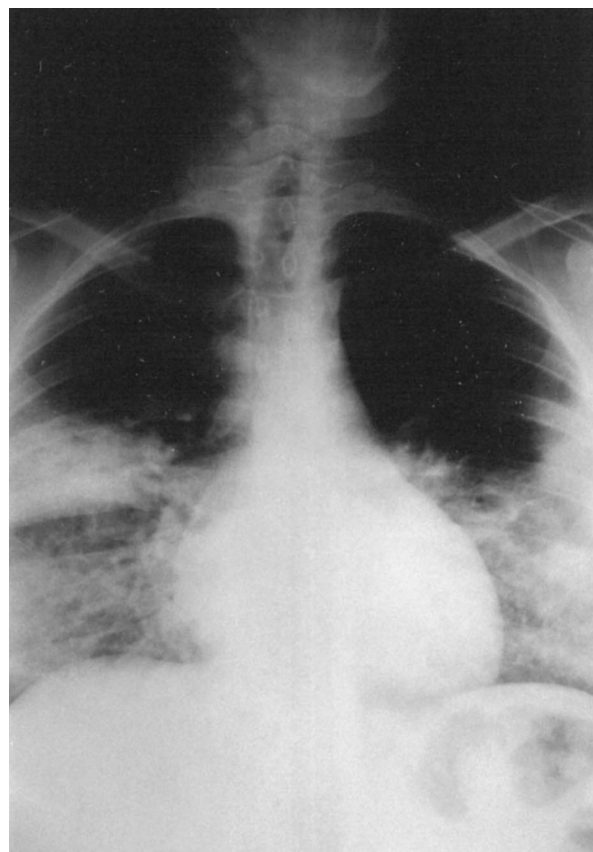


FIGURE 1. Chest x-ray film at onset of symptoms.

interstitial alveolar pneumopathy and fibrous sequelae of the median right lobe pneumonia. Bronchofibroscopy was performed with BAL. A liver biopsy was obtained in order to exclude sarcoidosis. No *Mycoplasma* organisms were detected in the BAL fluid. Pulmonary biopsy specimens suggested the possibility of idiopathic pulmonary fibrosis or LLM or interstitial desquamative pneumopathy (Fig 2). Treatment with glucocorticoids (methylprednisolone, 16 mg/d) was initiated. No attenuation of the

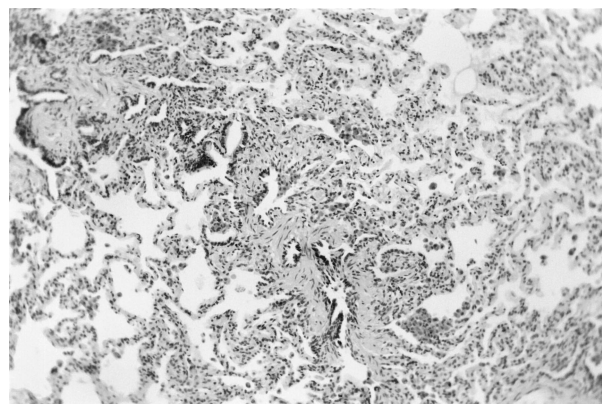


FIGURE 2. Pulmonary biopsy specimen showing LLM (hematoxylin-eosin, original $\times 250$).

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This work was supported by a grant from the Fonds de la Recherche Scientifique Médicale in Belgium (No. 3.4573.95). Manuscript received December 10, 1997; revision accepted May 19, 1998.

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Table 1—Evolution of Pulmonary Function in an LLM Patient*

Pulmonary Function Tests	Normal Calculated Values†	Before Corticoid Therapy	After 2 mo of Corticoid Therapy	Under Hormonal Treatment for 2 mo	Under Hormonal Treatment for 6 mo	Under Hormonal Treatment for 30 mo	Under Hormonal Treatment for 7 yr
FVC, L	2.96	1.90	1.99	2.74	2.93	2.69	2.82
FEV ₁ , L	2.55	1.65	1.65	2.24	2.36	2.22	2.26
FEV ₁ /FVC, %	80–100	80	83	82	81	79	80
DLCO, % of predicted value	8 mmol/kPa × min	26	26	55	59	68	58
VC, % of predicted value	3.03 L	80	80	85	89	94	85
TLC, % of predicted value	4.61 L	75	77	82	84	94	87
FRC, % of predicted value	2.58 L	60	60	53	65	75	78

*DLCO = diffusing capacity of the lung for carbon monoxide; VC = vital capacity; TLC = total lung capacity; FRC = functional residual capacity.

†For a normal subject with the same physical characteristics as the patient in this report.

symptoms was obtained after 4 weeks, at which time the dosage was adjusted to 8 mg/d; again, there was no clinical improvement.

In the meantime, electron microscopical examination of the lung biopsy specimen indicated the presence of ectopic smooth muscle cells infiltrating the alveolar septae. These cells were immunohistochemically labeled by anti-smooth muscle cell actin and anti-vimentin antibodies; they did not contain factor VIII, HMB45, protein S-100, or the estradiol receptor, but some did express the progesterone receptor. A diagnosis of incipient LLM or benign metastasizing leiomyoma was then advanced. The clinical gynecologic examinations and pelvic echography excluded the presence of uterine fibromas.

Oral contraception (30 µg of ethinyl estradiol and 150 µg of desogestrel) was stopped due to the possible effect of sex steroids on the proliferation of smooth muscle cells. Glucocorticosteroid therapy also was discontinued. A regimen specifically designed to suppress the proliferation of the smooth muscle cells was then established: daily administration of an anti-estrogenic agent (tamoxifen citrate, 20 mg/d) in combination with high doses of an antigonadotropic progestin (medroxyprogesterone acetate), 300 mg intramuscularly every 15 days for 2 months and then 500 mg/mo intramuscularly.

The objective parameters of the pulmonary function improved rapidly (Table 1) as well as her general health status. The classic side effects of this type of treatment were noted: artificial menopause and a weight gain of 15 kg over a period of 8 months. Presently, the patient remains asymptomatic with stable cardio-respiratory functions. After 2 years of receiving the initial regimen, medroxyprogesterone acetate was replaced with norethindrone acetate (10 mg/d) and tamoxifen therapy was maintained at the same dose. The gynecological and breast status have remained normal.

DISCUSSION

The diagnosis of LLM in this patient was suggested by the clinical symptoms and by the histologic examination (conventional histologic findings and immunohistochemical search for cytoskeletal proteins). The most specific criterion was the identification of ectopic smooth muscle cells by electron microscopy.^{1,6} The tissue required for all pathologic examinations was obtained by surgical biopsy, although the amount required for all examinations could have been provided by transbronchial biopsy.

In this case, the study showed all smooth muscle cells consistently reacted with anti-smooth muscle actin, anti-vimentin, and desmin antibodies but were not recognized by anti-HMB45 or anti-protein S-100 antibodies.¹

Bonetti et al¹ detected HMB45 in 2 of their 3 cases, thereby confirming the cellular heterogeneity of LLM proliferations. This heterogeneity also has been noted by immunohistochemistry and classic light and electron microscopic observations. It may reflect different degrees of differentiation of the same cell types or the coexistence of several cell types.

The presence of cytoplasmic progesterone receptors (but not estradiol receptors) in 10% of the cells suggested a possible benefit of high doses of the progestin medroxyprogesterone acetate. Uchida et al⁹ described the existence of estradiol and progesterone receptors in smooth muscle cells in one case of benign metastasizing leiomyoma. They think that, even if normal lung tissue possesses hormone receptor, it is rational to consider that multiple leiomyomatous lesions in the lung should be diagnosed as benign metastasizing leiomyoma when they possess positive estrogen and progesterone receptors. The presence of such functional receptors might explain the efficacy of this type of treatment in the administration of a luteinizing hormone-releasing hormone agonist.^{3,4}

Progestin therapy for LLM has been reported in at least 11 patients.^{2,5} It seems that most women have either improved or remained stable while taking medroxyprogesterone acetate whereas the condition of a few worsened despite the use of this drug or an luteinizing hormone-releasing hormone agonist. Tamoxifen therapy and oophorectomy were also recommended.^{2,5}

The rationale for combining medroxyprogesterone acetate and tamoxifen, despite the absence of a demonstrable estradiol receptor, was that no correlation between the status of progesterone and estrogen receptors and the response to hormonal therapy has been observed.⁵ It is also known that estrogen aggravated this condition.²

Ten years after the initial event, this woman remains asymptomatic, thus further confirming the hypothesis that progestins are highly effective and should be prescribed as the first-line treatment. According to the meta-analysis conducted by Eliasson et al,² oophorectomy represents a valuable alternative.

Because LLM is a very rare disease, it is likely that the best way to resolve questions of optimal treatment and prognosis will be through multicenter trials. Adequate

documentation of diagnosis, treatment, and pulmonary function is, however, essential for meta-analysis evaluation of treatment.

CONCLUSION

In one case of LLM, diagnosed on the basis of light and electron microscopic histologic and immunohistochemical findings that confirmed the presence of actin, desmin, and vimentin in the smooth muscle cell proliferation and detected progesterone receptors in some of the cells, dramatic clinical improvements of the subjective and objective respiratory function parameters were obtained by prescribing a regimen combining an anti-estrogenic agent (tamoxifen) and a progestin (medroxyprogesterone acetate).

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Hemoptysis Due to MDI Therapy in a Patient With Permanent Tracheostomy*

Treatment With Mask AeroChamber

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Persistent minor hemoptysis resulted from extensive granulation tissue on the main carina and adjacent bronchi due to frequent spraying of metered-dose inhaler (MDI)-generated aerosol medications directly into a permanent tracheostomy. Salbutamol, containing oleic acid, was considered the most likely cause. After an AeroChamber equipped with an

infant mask was interposed between the MDI and the tracheal stoma, hemoptysis and the pathologic changes gradually resolved.

(CHEST 1999; 115:279-282)

Key words: AeroChamber with mask; hemoptysis; granulation tissue; MDI; oleic acid; tracheostomy;

Abbreviations: MDI = metered-dose inhaler; URT = upper respiratory tract

CASE REPORT

Hemoptysis in a 65-year-old laryngectomized man was found to be due to extensive granulation tissue on the tracheal carina and adjacent mucosa. This was thought to have resulted from frequent administration, directly into the stoma, of large doses of bronchodilator and steroid aerosols from oleic acid excipient-containing metered-dose inhalers (MDIs) of albuterol (Ventolin; Glaxo Wellcome; Research Triangle Park, NC) and beclomethasone (Beclforte; Glaxo Wellcome). The use of an AeroChamber (Monaghan Medical, Inc; Plattsburg, NY) equipped with an infant (6.5-cm) mask applied to the stoma for aerosol administration resulted in rapid resolution of the hemoptysis and marked but incomplete improvement, after 6 weeks, of the gross changes observed initially at bronchoscopy. Nine months later, the carina and adjacent tracheal and bronchial mucosa appeared normal.

This 65-year-old man, a 60-pack-year ex-smoker and long-retired steel company crane operator with severe chronic airflow limitation, was seen in January 1995 for recurring minor episodes of hemoptysis that had been occurring for about 6 weeks. The episodes occurred several times a week, with each incidence of hemoptysis expelling not > 5 mL of blood, which was often mixed with very small amounts of a mucoid or slightly purulent secretion. The patient had undergone a permanent tracheostomy following a laryngectomy for carcinoma of the larynx in 1983 and had stopped smoking at that time after having smoked for about 30 to 40 pack-years. During a physical examination, the patient appeared well, and the stoma was unremarkable, with no crusting or other evidence of abnormality. The tracheal mucosa visible through the stoma showed edema and hyperemia. Examination of his chest revealed hyperinflation, decreased breath sounds, and rhonchi present only on forced expiration. A few bibasal crackles were heard.

The chest radiograph showed evidence of marked hyperinflation compatible with long-standing and severe COPD. His current and best postbronchodilator FEV₁ and FVC (obtained by means of a stomal adapter to facilitate connection to the spirometer) during the previous 3 years were 0.6 and 1.6 L, respectively (predicted, 3.2 and 4.1 L, respectively).

For the previous 10 years, the patient's regular aerosol

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medications included ipratropium bromide 80 μg (4 puffs) qid, albuterol 200 to 400 μg (2 to 4 puffs) every 4 h as required, and beclomethasone (250 μg /actuation) 500 μg bid. He was instructed to administer the aerosol medication through the stoma by means of a valved holding chamber equipped with an infant mask (the AeroChamber) and not to spray the medication directly into the trachea.

A tentative diagnosis of bronchogenic carcinoma was made.

Fiberoptic bronchoscopy via the stoma showed considerable hyperemia and edema of the tracheal mucosa at and distal to the stoma. An extensive, irregular, firm, raised pale ridge of tissue about 2 cm long and 4 mm wide was seen straddling the carina in an anteroposterior direction. It extended onto the adjacent tracheal wall. An oozing hemorrhage was seen intermittently at its junction with the hyperemic tracheal mucosa, especially along its right margin. The gross appearance suggested an inflammatory or malignant change. No other abnormalities were noted during the bronchoscopy. Biopsies were performed at several locations along the carinal tissue ridge, and all of these showed classical granulation tissue (Fig 1) with some metaplastic changes but with no evidence of malignancy.

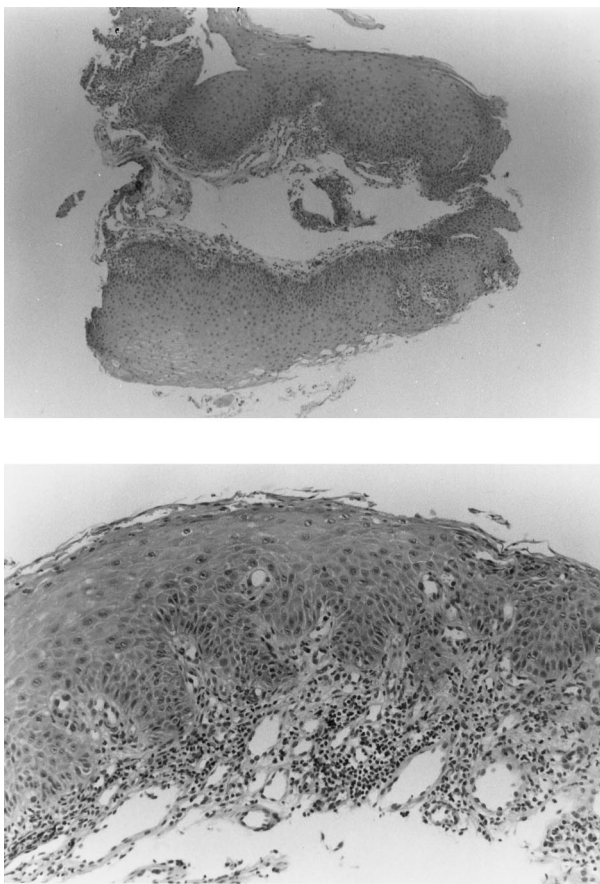


FIGURE 1. *Top*: low-power photomicrograph of carinal biopsy (original $\times 110$). *Bottom*: high-power photomicrograph of a carinal biopsy showing features of granulation tissue (hematoxylin-eosin, original $\times 55$) (see text).

Cytologic examination of a lower tracheal saline lavage was negative for malignancy and infection.

The cause of the abnormality was not immediately apparent. However, on further questioning the patient admitted to having sprayed his MDIs directly into the stoma for more than 6 months, without using the AeroChamber with mask, because carrying the MDI alone was more convenient. Thus, the majority of the aerosolized drugs and excipients, particularly oleic acid (the surfactant contained in the Ventolin and Becloforte MDIs) would probably impact in the trachea just distal to the stoma. It could be anticipated that turbulence at the tracheal carina would likely encourage the greatest deposition of the larger aerosol droplets there.

The patient resumed the regular use of the AeroChamber with mask for aerosol inhalation, and over the ensuing 3 to 4 weeks the hemoptysis gradually ceased. Figure 2 shows the patient administering the aerosol therapy to himself directly into the stoma from an MDI (*top*) and by means of the AeroChamber equipped with an infant mask (*bottom*).

A repeat bronchoscopy 6 weeks after the patient was first evaluated showed marked improvement in the appearance of the carina, with only moderate residual thickening of the mucosa and no bleeding. The rest of the tracheal mucosa appeared normal. Bronchoscopy about 9 months later revealed a completely normal carina and adjacent mucosa.

DISCUSSION

This case illustrates an as yet unreported cause of hemoptysis, probably due to chronic tracheal mucosal injury by MDI-generated, inhaled aerosols that were sprayed directly onto the tracheal mucosa through the stoma.

Spraying the MDI directly into the stoma, thus bypassing the aerodynamic filtration of large particles normally accomplished by the upper respiratory tract (URT), results in an approximately 10-fold increase in the deposition of aerosol medication and excipients onto the mucosa of the lower respiratory tract. The large particles, comprising about 60 to 70% of the aerosol discharged from the MDI mouthpiece, would normally be deposited in the URT if the aerosol is inhaled po directly or would be retained in the valved holding chamber of the AeroChamber, if it is being used to facilitate aerosol therapy.¹

Two of the three inhaled medications (Ventolin and Becloforte) used by the patient regularly contain 7 μg /puff of the excipient oleic acid for a total dose to the tracheobronchial tree of approximately 250 μg in 24 h. During inhalation, most of the aerosol mass discharged at a velocity of about 100 km/h would impact in the trachea and the first few bronchial divisions, particularly around the main carina, due to the high flow rate and turbulence.² Oleic acid has been shown experimentally to cause mucosal ulceration in the tracheobronchial tree of rabbits following the spraying of as few as 5 puffs of Ventolin (500 μg of albuterol), containing 35 μg of oleic acid, onto the tracheal mucosa directly. In this study, the URT was bypassed by means of a 0.8 \times 15-cm plastic catheter

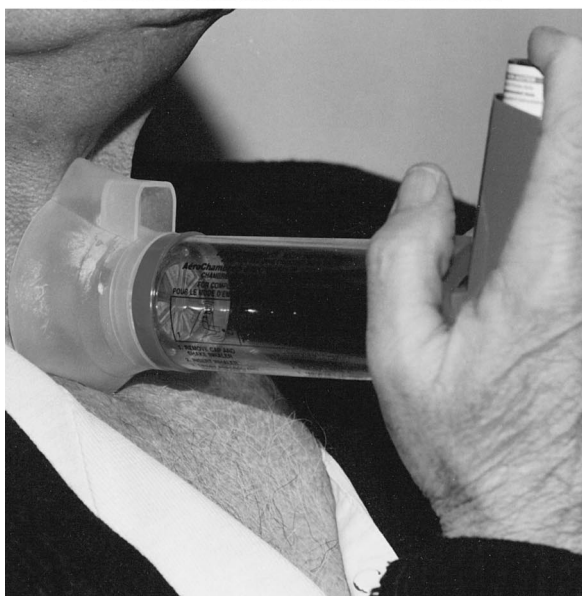


FIGURE 2. *Top*: MDI being sprayed directly into the stoma. *Bottom*: inhalation of MDI aerosol via the tracheal stoma by means of an AeroChamber with the 6.5-cm mask originally designed for aerosol therapy in infants up to 6 months of age.

extension attached to the MDI canister, which was passed into the distal one third of the trachea through an endotracheal tube. This study supports the pivotal role of oleic acid in the production of the mucosal injury in the rabbit model, since similar changes were caused by a Ventolin placebo (which contained oleic acid but not albuterol) but not by an albuterol solution or a fenoterol MDI, which contains lecithin instead of oleic acid as a surfactant.³ Thus, it is not surprising that spraying large doses of oleic acid into the tracheostomy stoma might cause serious mucosal injury over time that gradually resolved after the patient stopped spraying MDIs directly into the tracheal stoma.

The AeroChamber with infant mask adapts readily to the stoma and functions almost like the normal URT to retain about 70% of the aerosol droplets from the MDI, containing large drug particles and excipients.⁴

The efficiency of the AeroChamber in reducing URT aerosol deposition has been demonstrated clinically, since in patients who previously had a systemic steroid dependence, and who were treated with beclomethasone (Beclonvent; Glaxo Wellcome) 800 µg/d by inhalation, the approximately 12-fold reduction in the oropharyngeal dose, due to the addition of an AeroChamber to the MDI, resulted in the elimination of oral candidiasis. This is in contrast to the 25% prevalence of thrush in patients using the MDI inserted into the mouth.⁵ Furthermore, a recent study of a radiolabeled drug aerosol from our laboratory showed a 12-fold decrease in the oropharyngeal dose of albuterol when an AeroChamber was added to the MDI compared to when an MDI was sprayed directly into the mouth.⁶

Resolution of the hemoptysis after 3 to 4 weeks and regression to a normal mucosa following several months of the same doses of identical aerosols administered via the AeroChamber with infant mask applied to the stoma provides further confirmation that the excipients in Ventolin and Becloforte were the likely cause of the mucosal injury.³ It is probable that the more than 10-fold decrease in the deposition of oleic acid excipient onto the tracheal mucosa resulting from the use of the AeroChamber¹ allowed gradual healing of the tracheal mucosa.

This cause of hemoptysis should be considered in patients with permanent tracheostomies who are taking aerosol medications dispensed from MDIs if the medications are sprayed directly into the tracheal stoma. In these patients, the delivery of the aerosol medication to the pulmonary airways and the avoidance of tracheal mucosal injury can be accomplished by delivering MDI-generated aerosols into the tracheal stoma via the AeroChamber with a 6.5-cm mask that was designed for use in infants up to 6 months of age. Physicians and tracheostomized patients needing aerosol therapy with MDIs should be made aware of this potential problem, and physicians should encourage the use of the infant holding chambers with mask for aerosol administration. The use of MDI formulations with minimal or no oleic acid also would be advisable, where possible.

ACKNOWLEDGMENTS: My thanks to Dr. Michael Kay of the St. Joseph's Hospital/McMaster University Pathology Department for providing the photomicrographs, to Dr. Chris Allen for reviewing the manuscript and providing many helpful suggestions, and to Janice Rutgers for preparing the manuscript for publication.

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Two Cases of Repeatedly Recurrent Atypical Thymoma*

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Two cases of repeatedly recurrent thymoma with myasthenia gravis are detailed here. A 41-year-old woman had 5 recurrent thymomas, including local recurrences and lumbar and lung metastases; she was alive at the time of this writing, which was 22 years after her first surgery. A 36-year-old man had 3 recurrent thymomas, including local recurrence, dissemination, and lung metastasis; he was alive at the time of this writing, which was 16 years after his first surgery. Both recurrent lesions were diagnosed as "atypical thymoma" with moderate nuclear atypia. The patients with atypical thymoma must be followed up carefully due to a possible recurrence. Surgical treatment with chemoradiotherapy can lengthen their survival.

(*CHEST* 1999; 115:282-285)

Key words: atypical thymoma; recurrence; thymic carcinoma; thymoma

Levine and Rosai¹ classified thymic epithelial tumors into three categories: benign (encapsulated thymoma), malignant thymoma type 1 (invasive or metastatic thymoma without overt cytologic atypia), and malignant thymoma type 2 (thymic carcinoma with overt cytologic atypia). Recently, Suster and Moran² reported 22 cases of

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Manuscript received January 21, 1998; revision accepted May 20, 1998.

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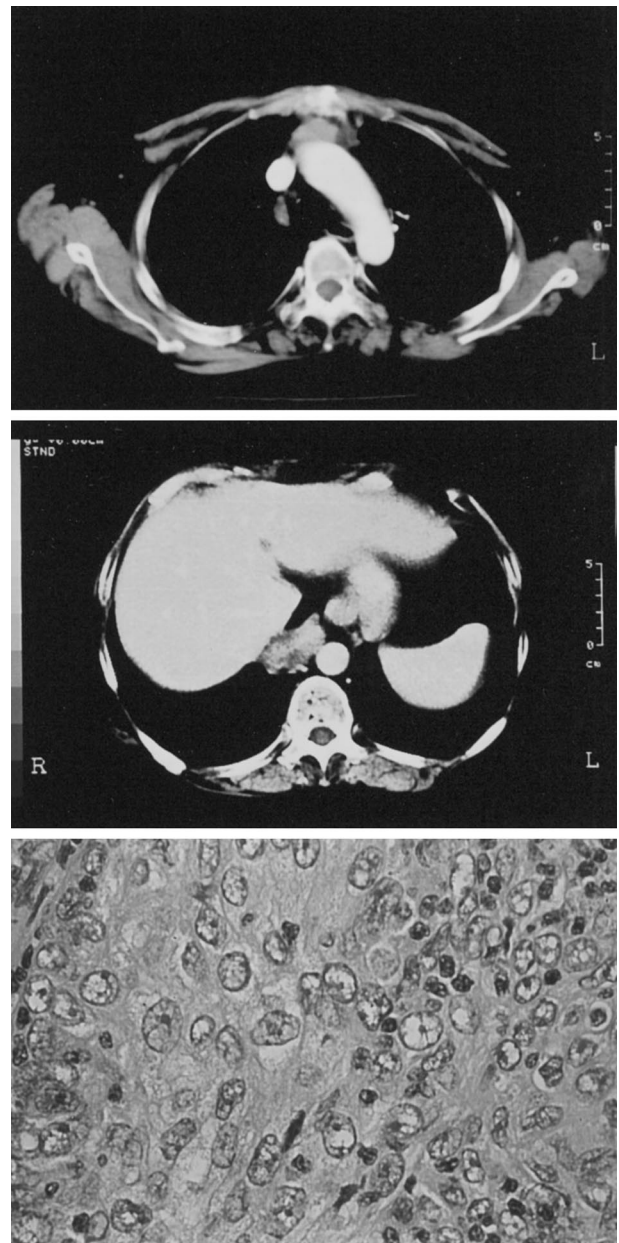


FIGURE 1. *Top:* thoracic CT scan demonstrating a homogeneous mass (1.5 × 3.0 cm) in the anterior mediastinum. *Center:* thoracic CT demonstrating a heterogeneous mass (3.0 × 5.0 cm) in the right S-10 region of the lung field. *Bottom:* high-power view demonstrating polygonal cells with moderate nuclear atypia, occasional nucleolar prominence, and more abundant eosinophilic cytoplasm showing squamoid arrangement (atypical thymoma) (hematoxylin-eosin, original ×400).

primary thymic epithelial neoplasms showing combined features of thymoma and thymic carcinoma. The borderline between thymoma and thymic carcinoma is unclear. Two cases of thymic epithelial tumors with repeated recurrences are delineated, and the medical literature is reviewed.

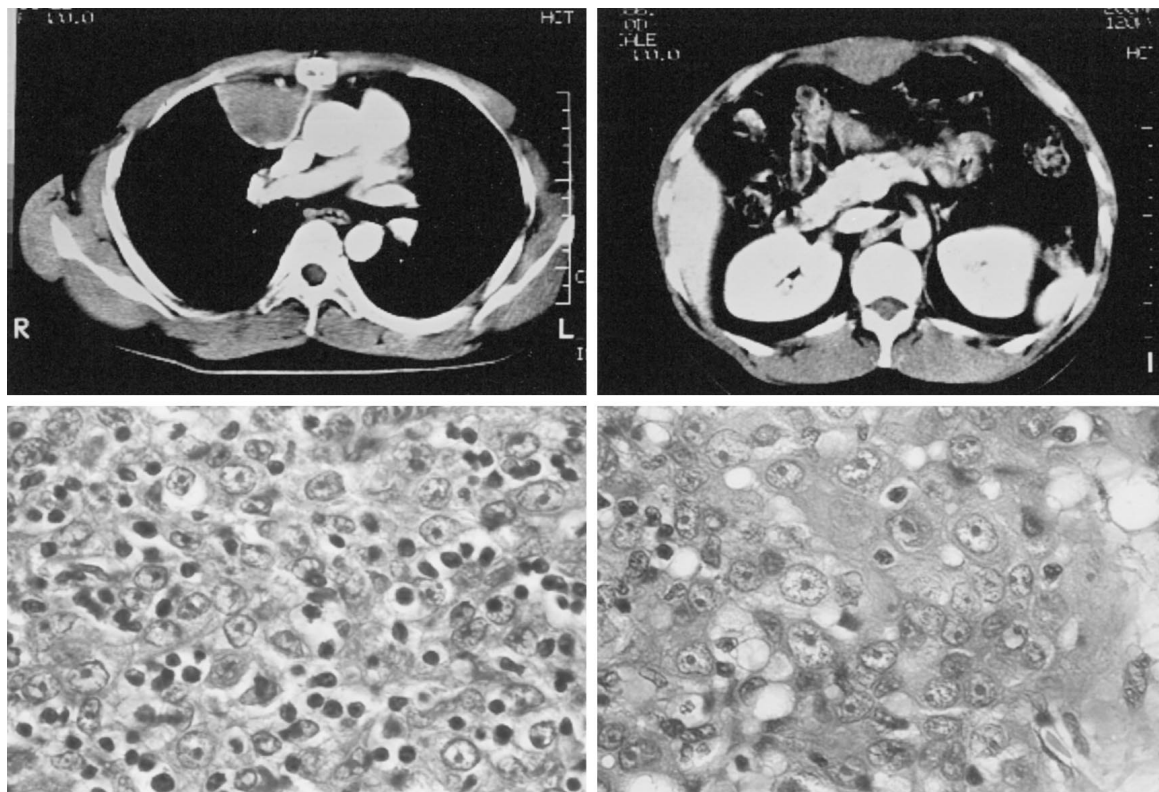


FIGURE 2. *Top left:* thoracic CT demonstrating a homogeneous mass (5.0×9.0 cm) protruding into the right thoracic cavity from right anterior mediastinum. *Top right:* abdominal CT demonstrating a homogeneous mass (5.0×6.0 cm) in the upper abdominal wall. *Bottom left:* High-power view demonstrating an admixture of polygonal cells with moderate nuclear atypia and nucleolar prominence and a moderate amount of lymphocytes (mixed lymphocytic and epithelial thymoma with atypia; hematoxylin-eosin, original $\times 400$). *Bottom right:* high-power view demonstrating more atypical tumor cells with enlargement of nuclei and nucleolar prominence and abundant eosinophilic cytoplasm without an admixture of the lymphocytes (squamous cell carcinoma; hematoxylin-eosin, original $\times 400$).

CASE REPORTS

CASE 1

A 41-year-old woman was admitted to the hospital on September 4, 1996. A diagnosis of myasthenia gravis with thymoma was made when she was 20 years old. Thymothymectomy was performed. The anterior mediastinal tumor was identified as mixed or epithelial-rich thymoma. When the patient was 28 years old, a mediastinal mass (local recurrence) was detected by chest radiograph. Complete resection of the tumor was performed. A mediastinal tumor (local recurrence) was again detected by chest CT when she was 34 years old. Radiation therapy and surgery were performed. At the age of 35, she developed lumbago. Lumbar MRI demonstrated metastases to lumbar vertebrae L2 and L3. Surgery and postoperative radiation were performed. At the age of 39, a tumor in the left lung (lung metastasis) was detected by chest radiograph. Left upper lobectomy and postoperative chemotherapy were performed. For 21 years thereafter, symptoms of myasthenia gravis fluctuated despite the recurrent tumors. At admission, myasthenic symptoms (ptosis, double vision, fatigue of the extremities) were present, and values for anti-acetylcholine receptor antibody (47 nmol/L) and SCC tumor marker (4.84 ng/mL) were elevated. A chest x-ray film revealed a coin-sized lesion in the lower area of the right lung. A thoracic CT scan demonstrated a homogeneous mass ($1.5 \times$

3.0 cm) in the anterior mediastinum (Fig 1, *top*) and a heterogeneous mass (3.0×5.0 cm) in the right S-10 region of the lung (Fig 1, *center*). Thoracotomy was performed on September 11, 1996. A tumor located in the right S-10 region was completely resected. An anterior mediastinal tumor had invaded the left brachiocephalic vein. The excision of the tumor and a partial resection of the left brachiocephalic vein were performed. The tumor was grayish white and elastic hard, but both necrosis and hemorrhage were absent. Microscopically, the tumor showed polygonal cells with moderate nuclear atypia and occasional nucleolar prominence and had more abundant eosinophilic cytoplasm. A diagnosis of "atypical thymoma" was made (Fig 1, *bottom*). The patient was discharged and received therapy with steroids and anticholinesterase on November 9.

CASE 2

A 36-year-old man was referred to the hospital on June 23, 1994. At the age of 23 years, he had received a diagnosis of myasthenia gravis with thymoma. Thymothymectomy had been performed. On the basis of findings from the anterior mediastinal tumor, a diagnosis of lymphocyte-rich thymoma was made. At the age of 28, he received therapy with steroids and anticholinesterase again, as symptoms of myasthenia gravis had deteriorated. At the age of 30, tumor recurrence in

the anterior mediastinum was detected by chest CT scan. The recurrent tumor was resected, and he received postoperative irradiation therapy (50 Gy). At admission, myasthenia gravis was controlled by steroids and immunosuppressive drugs. Values for anti-acetylcholine receptor antibody (110 nmol/L) and SCC tumor marker (5.0 ng/mL) were elevated. A chest x-ray film revealed a shadow suggestive of a mass in the right hilar region. A thoracic CT scan demonstrated a homogeneous mass (5.0 × 9.0 cm) protruding into the right thoracic cavity from the right anterior mediastinum (Fig. 2, *top left*) and a homogeneous mass (5.0 × 6.0 cm) in the upper abdominal wall (Fig 2, *top right*). Thoracotomy was performed on September 18. As the right anterior tumor invaded the right upper lobe of the lung, a partial resection of the right lung was performed. The abdominal tumor was completely resected. The tumor was grayish white, elastic hard, and partially necrotic. Microscopically, most of the tumor consisted of a biphasic cell population containing polygonal cells with moderate nuclear atypia and nucleolar prominence and lymphocytes. The tumor was identified as "atypical thymoma" (Fig 2, *bottom left*). The tumor cells around the necrotic lesion had severe nuclear atypia, nucleolar prominence, and more abundant eosinophilic cytoplasm. Lymphocytes were almost absent in these tumor nests. This lesion was diagnosed as poorly differentiated squamous cell carcinoma. (Fig 2, *bottom right*). Postoperatively, the patient received chemotherapy (CDDP, ADM, VDR, CPA). Values for the SCC tumor marker normalized (1.02 ng/mL). Two years later, he was found to have a nodule of 10 mm in diameter in the right lung; this nodule was resected on October 7, 1996. Histologically, it was similar to the previous atypical thymoma portion of the previous tumor.

DISCUSSION

Recently, several pathologists who have experienced a considerable number of thymic tumors have recognized relatively aggressive tumors possessing vesicular nuclei with moderately prominent nuclei, occasional mitotic figures, perivascular spaces with epithelial palisades, and a mixture of immature thymocytes (CD1a+).^{1,3,4} These tumors were named "well differentiated thymic carcinoma" or "atypical thymoma."^{4,5} The boundary between thymoma and thymic carcinoma has become increasingly blurred.

The atypical thymoma cases presented herein showed an aggressive or malignant course. The patient in case 1 had 5 recurrent thymomas, including local recurrences and hematogenous metastases, although she was alive at the time of this writing, which was 22 years after her first surgery. The patient in case 2 also had 3 recurrent thymomas, including local recurrence, dissemination, and hematogenous metastasis, although he was alive at the time of this writing, which was 16 years after his first surgery. Kirchner et al⁵ reported that well-differentiated thymic carcinoma (or atypical thymoma by others) was more aggressive than thymomas of other subtypes. Further, Quintanilla-Martinez et al⁶ demonstrated that well-differentiated thymic carcinoma was always invasive and had a significantly increased risk of relapse and death. When the pathologic diagnosis at the time of initial surgery is atypical thymoma, even if the tumor is noninvasive or completely resected, patients must be followed up carefully to detect a possible recurrence

after resection. And if they have a recurrence, they may survive longer with surgical treatments plus a combination of radiotherapy and chemotherapy.

The symptoms of myasthenia gravis in these two cases fluctuated repeatedly, but aggravation of myasthenia gravis was not parallel to thymoma relapse. Relapses of thymoma without symptoms were discovered by chest radiograph or chest CT except for the vertebral body metastasis associated with lumbago in case 1, which was discovered by lumbar MRI. Because relapse in the anterior mediastinum, where the thymoma frequently recurred, is hard to detect by chest radiograph until it becomes bulky, periodic chest CT examination during follow-up of atypical thymoma is necessary.

Interestingly, the tumor in case 2 partly transformed to thymic carcinoma (squamous cell carcinoma). Atypical thymoma portions consisted of cortical type epithelial cells and immature lymphocytes, which were immunostained by anti-CD1a antibody (data not shown). On the other hand, thymic carcinoma portions consisted of epithelial cells, which showed eosinophilic cytoplasm with a tendency toward keratinization and no lymphocytes. It is suggested that some regions in this tumor progressed from thymoma to thymic carcinoma, and the function of the thymus disappeared at the same time. This speculation is supported by a recent report. Suster and Moran² reported that a biopsy of 2 anterior mediastinal masses with myasthenia gravis showed features of lymphocyte-rich thymoma. Thoracotomy with excision was carried out 10 and 14 years later because of an increase in the size of the lesions. Histologic examination of the resected specimens, in both cases, showed thymic carcinoma arising from a thymoma.² These cases and the two reported here support the thymoma-thymic carcinoma sequence theory, *ie*, that thymoma shifts to thymic carcinoma although most of the thymic carcinoma may arise *de novo*. It is important to treat thymic epithelial tumors as potentially malignant tumors and to examine histologically the resected tumor in detail.

In both of the reported cases, values for the tumor marker SCC for squamous cell carcinoma were elevated and later became normalized after resection of the recurrent tumor. The tumor in case 2 showed some of the components of squamous cell carcinoma. In case 1, since the tumor cells in the right S-10 region of the lung have an epidermoid arrangement, which is one of the features of atypical thymoma,⁴ this thymoma may have shown a tendency towards squamous differentiation. The tumor marker SCC may be an indicator of the transformation of thymoma to carcinoma during therapy for the recurrent thymoma.

ACKNOWLEDGMENTS: We thank Dr. Yukio Shimosato, Department of Pathology, Keio University School of Medicine, National Cancer Center Hospital, for his pathologic analysis and helpful discussion.

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A Transitional Variant of Castleman's Disease Presenting as a Chylous Pleural Effusion*

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Castleman's disease is an uncommon clinicopathologic entity that results in unregulated growth of lymphoid tissue. It may present as benign involvement of one lymph node group or as multicentric disease with serious systemic symptoms. Pleural effusions are an uncommon manifestation of Castleman's disease. We present a patient with Castleman's disease who initially presented with a chylous pleural effusion. (CHEST 1999; 115:285–288)

Key words: Castleman's disease; chylothorax; giant lymph node hyperplasia; pleural effusion; sickle cell anemia

Castleman's disease, also known as angiofollicular or giant lymph node hyperplasia, is a rare disorder that results in the unregulated growth of lymphoid tissue. Initially, Castleman's disease was reported as an indolent disorder which was usually confined to a single lymph node group.¹ However, recent case reports have described a multicentric form of Castleman's that often manifests a more malignant clinical course. Patients with Castleman's disease may present with a variety of signs and symptoms, but pleural effusions are an uncommon manifestation of this disease.²

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Manuscript received December 18, 1997; revision accepted April 1, 1998.

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We present a case of the transitional or mixed variant of Castleman's disease in a young male with a history of sickle cell anemia, who initially presented with large bilateral chylous pleural effusions. To our knowledge, this is the first case report of Castleman's disease in association with a chylous pleural effusion.

CASE REPORT

A 24-year-old man with a history of sickle cell anemia presented to our emergency department with a 10-day history of dyspnea, both with exertion and at rest. He also reported subjective fevers, occasional night sweats, and a mild cough productive of yellow sputum. During the week prior to admission, his shortness of breath progressively worsened until he could no longer sleep in a recumbent position. During the final 2 days prior to admission, he developed his typical sickle cell crisis pain in his chest, back, and legs.

This patient had been hospitalized on many previous occasions for sickle cell crises. He had a remote history of bilateral subclavian vein thrombosis secondary to multiple central line insertions. He did not drink alcohol, smoke, or use illicit drugs. His only medication at the time of admission was folic acid.

On admission, his temperature was 37.7°C, pulse was 72 beats/min, BP was 148/76 mm Hg, and respiratory rate was 34 breaths/min. He was an ill-appearing, thin young man. There was no palpable lymphadenopathy. The jugular veins were distended to 5 cm at 30 degrees of elevation. His heart rate and rhythm were regular. He had a 2/6 systolic murmur along the left sternal border. Chest examination revealed decreased expansion, decreased breath sounds, and dullness to percussion on the right side. The left side was clear to auscultation and without dullness. The abdominal, neurologic, and skin examinations were unremarkable. The admission chest radiograph is shown in Figure 1.

Laboratory examination revealed a hemoglobin of 9.9 g/dL, hematocrit of 28.6%, WBC count of $14.6 \times 10^9/L$, and platelet count of $433 \times 10^9/L$. His blood chemistries were within normal limits, with a lactate dehydrogenase level of 198 U/L and a total protein level of 6.3 g/dL. The erythrocyte sedimentation rate was 147 mm/h and the reticulocyte count was 7%. An arterial blood gas on 32% supplemental oxygen revealed a pH of 7.45, a PCO_2 of 32 mm Hg, and a PO_2 of 69 mm Hg. The patient underwent a diagnostic thoracentesis, which revealed turbid fluid, 5,944 nucleated cells (1% segmented neutrophils, 96% lymphocytes, and 3% histiocytes), protein 4.3 g/dL, glucose 85 mg/dL, amylase 66 U/L, lactate dehydrogenase 182 U/L, and triglycerides 1,050 mg/dL. Cytologic examination of the pleural fluid revealed no malignant cells. Serum assay revealed an IgG level of 2,730 mg/dL (normal range, 694 to 1,618 mg/dL) and an IgA level of 453 mg/dL (normal range, 63 to 378 mg/dL). The IgM level was normal at 89 mg/dL, and no paraprotein was found. Blood, sputum, and urine cultures revealed no microbial growth. The patient was seronegative for HIV-1 and HIV-2. CT scan of the thorax revealed bilateral pleural effusions, compressive atelectasis of the lower lobes bilaterally, and mediastinal adenopathy.

The patient was initially treated with bilateral chest tube thoracostomies and central hyperalimentation. When a significant decrease in the chylous drainage failed to occur after 14 days of conservative therapy, a surgical approach was deemed necessary. The patient underwent a right thoracotomy with ligation of the thoracic duct above the diaphragm, which was successful in diminishing the amount of chylous drainage. Because of adhesions, the mediastinum could not be reached to biopsy the mediastinal lymph nodes. In an attempt to determine the etiology of the mediastinal adenopathy, a CT-guided needle biopsy was subsequently performed; however, the tissue was nondiagnostic.

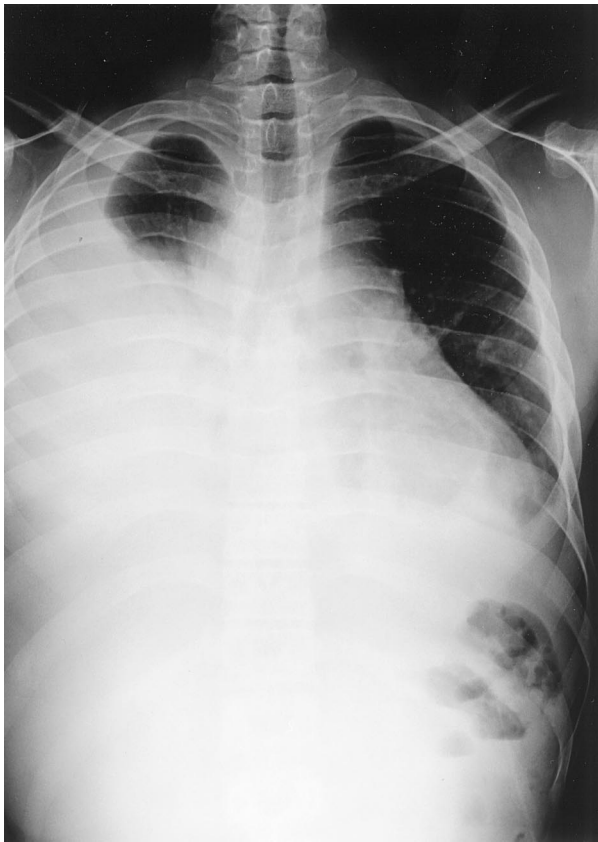


FIGURE 1. Admission chest radiograph demonstrating bilateral pleural effusions.

The patient underwent a Chamberlain procedure to gain access to the mediastinum. The surgeon reported areas of lobulated fat dispersed within a large mass of nodal tissue lying along the thymic region. A biopsy specimen from this nodal tissue revealed rare, small, involuted germinal centers that lacked follicular center cells (Fig 2, 3). The mantle zone of the germinal center was inconspicuous and some of the involuted follicles had a radially oriented, thin-walled blood vessel that originated in the perifollicular tissue and penetrated the germinal center. The remainder of the lymph node revealed sheets of mature plasma cells and increased vascularity of the interfollicular region (Fig 4). The immunohistochemical stain demonstrated positive staining of the interfollicular plasma cells for both kappa and lambda light chains. These morphologic features are consistent with the diagnosis of the transitional or mixed type of Castleman's disease.

The patient was started on high-dose corticosteroid therapy, with an initial dose of 1,000 mg of solumedrol followed by three 125-mg doses of solumedrol. The patient then received 100 mg/d of prednisone. After 2 months of therapy, no response was noted clinically or radiographically on subsequent CT scans of the chest. A total of 2,000 rads of radiation therapy was then delivered to the mediastinum over a 10-day period, followed by chemotherapy with cytoxan 800 mg/m² and vincristine 2 mg. In spite of this aggressive therapy, the patient continued to require increasing amounts of oxygen. A repeat CT scan of the chest demonstrated no change in the size of the mediastinal adenopathy. The patient expired on hospital day 125 after a prolonged and difficult hospital course.

DISCUSSION

Castleman's disease is an unusual disorder of immune regulation that results in abnormal proliferation of B lymphocytes and plasma cells in lymphoid organs. Histologically, it is usually differentiated into three types: a hyaline vascular variant, a plasma cell variant, and a transitional (mixed cell) type.³ Pathologically, the hyaline vascular type features abnormal follicles with a striking interfollicular vascularity, expanded mantle zones composed of small lymphocytes, and one or more small blood vessels. These vessels may have thickened walls that form hyalinized germinal centers. In contrast, the plasma cell variant displays lymph nodes with an intact mantle zone surrounded by sheets of mature plasma cells and no vascular proliferation.³ The transitional or mixed cell variant is the least common type of Castleman's disease and, as in our case, it is characterized by histologic features predominantly of the hyaline-vascular type with foci of numerous plasma cells and some large normal-appearing germinal centers.⁴

Clinically, patients with Castleman's disease may present with an asymptomatic abnormality on chest radiograph, localized symptoms caused by compression of the tracheobronchial tree, or systemic symptoms such as fever or weight loss. The latter, known as multicentric disease, is most often associated with the plasma cell variant.³ Typically, the multicentric variant occurs in individuals in their fourth or fifth decade as an aggressive malignant-like syndrome with associated features of elevated sedimentation rate, hepatosplenomegaly, hypergammaglobulinemia, granulocytosis, and plasmacytosis of the bone marrow. The multicentric variety has been reported to have mortality rates as high as 50%.³

The presence of pleural effusions is an uncommon occurrence in patients with Castleman's disease. Presently, only seven cases of Castleman's disease presenting as a pleural effusion have been reported in the literature. Several of these were described as large effusions, but none were chylous in nature.² Chylous pleural effusions result from disruption of the thoracic duct with subsequent leakage of lymphatic fluid or chyle into the chest cavity. It occurs most commonly with malignancy (usually lymphoma) and trauma, but several other causes have been described, including sarcoidosis, tuberculosis, yellow nail syndrome, Turner's syndrome, Noonan's syndrome, and lymphangiomyomatosis. There have been several reported cases of chylous pleural effusions associated with subclavian vein thrombosis. All of the reported cases have occurred in newborn infants.⁵ Although our patient had a remote history of a subclavian vein thrombosis, the CT scan shortly after his admission revealed patent subclavian veins bilaterally.

The diagnosis of a chylous pleural effusion is usually suspected when cloudy or milky fluid is obtained on thoracentesis. However, 50% of chylous effusions may not have the classic milky appearance and the diagnosis should be suspected if a cloudy, serosanguineous or bloody effusion does not clear with centrifugation.⁶ A pleural effusion is diagnosed as a chylous effusion if the pleural fluid triglyceride level is greater than 110 mg/dL.⁷ The

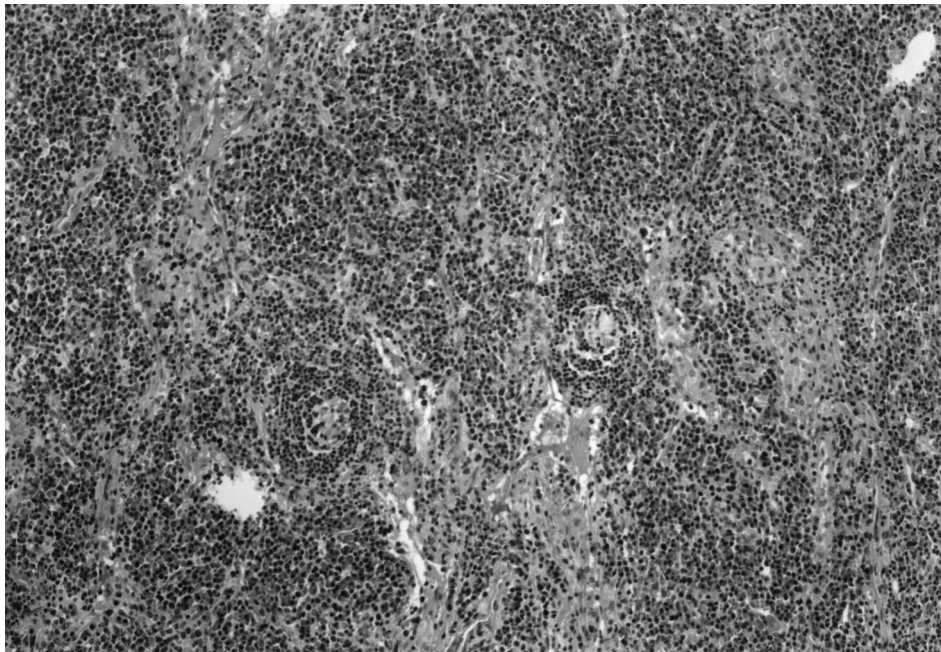


FIGURE 2. Compact germinal centers are associated with sheets of lymphoid cells in the interfollicular regions (hematoxylin-eosin stain, original $\times 100$).

location of the pleural effusion is related to the level of obstruction of the thoracic duct. Normally, the thoracic duct crosses to the left side of the thoracic cavity between the fourth and sixth vertebrae.⁸ Therefore, the critical obstruction in this patient with a right pleural effusion was below the level of the fourth thoracic vertebra.

Once the diagnosis of a chylothorax is established, a course of therapy should be chosen to avoid the known sequelae of malnutrition, metabolic abnormalities, and an immunocompromised state.⁹ By administering total parenteral nutrition with a low-fat, high-calorie, and high-protein formula, chyle formation will be decreased while

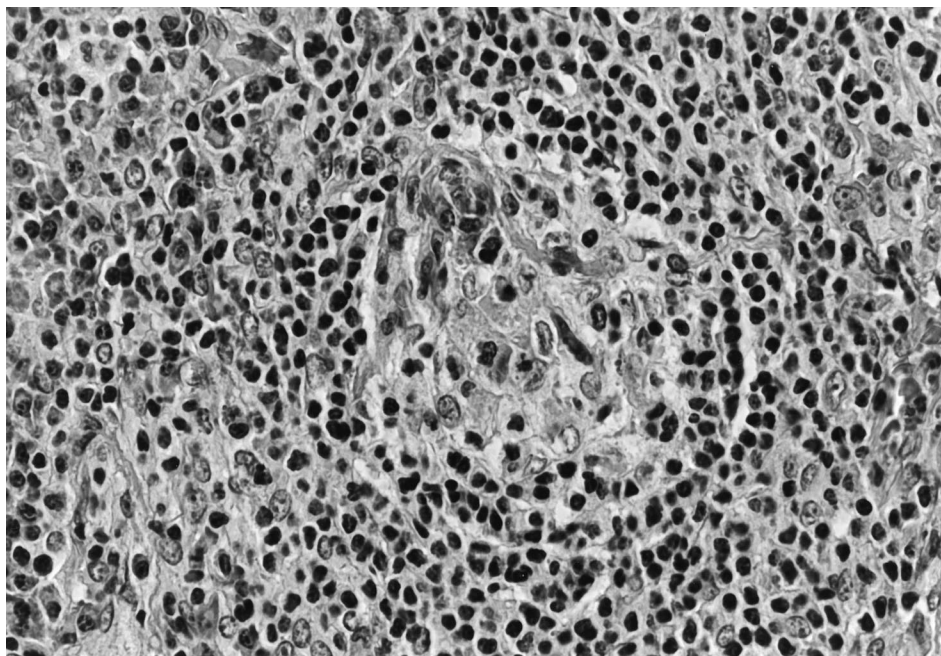


FIGURE 3. The involuted germinal center is devoid of follicle center cells. A radially oriented artery that originated in the interfollicular region of the lymph node penetrates the small germinal center (hematoxylin-eosin stain, original $\times 400$).

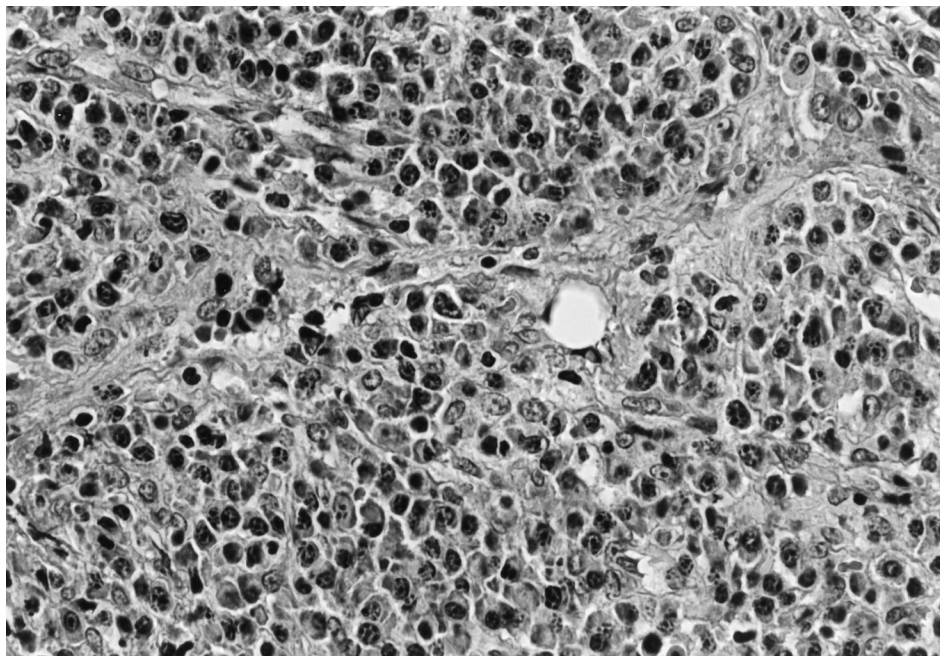


FIGURE 4. There is a dense plasmacytosis of the interfollicular region of the lymph node. Interfollicular vessels are increased (hematoxylin-eosin stain, original $\times 400$).

an adequate nutritional status is maintained. The chylothorax should also aspirated either by repeated thoracentesis or by tube thoracostomy.¹⁰ When appropriate, therapy should also be directed at the specific etiology of the chylothorax, such as radiation or chemotherapy therapy for lymphoma involving mediastinal structures. If there is a loss of chyle of more than 500 mL/d in an adult or more than 100 mL/d in a child for more than 14 days, conservative therapy should be abandoned and surgical intervention with either thoracic duct ligation or pleuroperitoneal shunt insertion should be considered.¹¹

To our knowledge, this is the first case report of any variant of Castleman's disease presenting as a chylous pleural effusion, and we suggest that Castleman's disease be added to the differential diagnosis of a chylous effusion.

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Tension Fecopneumothorax Due to Colonic Perforation in a Diaphragmatic Hernia

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A traumatic diaphragmatic hernia is a well-known complication following blunt abdominal or penetrating thoracic trauma. Although the majority of cases are diagnosed immediately, some patients may present later with a diaphragmatic hernia. A tension fecopneumothorax, however, is a rarity. We report on a patient who, 2 years after being treated for a stab wound to the chest, presented with an acute tension fecopneumothorax caused by the incarceration of the large bowel in the thoracic cavity after an intrathoracic perforation. The etiology and management of this condition are discussed.

(*CHEST* 1999; 115:288-291)

Key words: diaphragmatic hernia; pneumothorax; stab wound; surgical treatment

A traumatic diaphragmatic hernia is a well-known complication following blunt or penetrating injuries to the diaphragm. However, the diagnosis may be delayed because of a lack of symptoms. Clinical signs occur when diaphragmatic hernias are associated with a small or large bowel obstruction resulting from incarceration. A pneumothorax resulting from the intrathoracic perforation of the bowel has only rarely been noticed.

We report on a 20-year-old man with a tension pneumothorax resulting from an intrathoracic perforation of the colon into the chest after a penetrating stab wound and a traumatic diaphragmatic hernia.

CASE REPORT

A 20-year-old man was admitted to the hospital with a 2-day history of diarrhea and the acute onset of severe left thoracic pain in combination with vomiting and dyspnea. His medical history was significant for a pneumothorax following a stab wound to his left chest 2 years earlier, which was treated using a chest tube.

Twelve days before the present admission, the patient was admitted to the hospital because of cramping epigastric pain. He was afebrile, and his physical examination was unremarkable. The WBC count was $15.7 \times 10^9/L$. An abdominal ultrasound revealed no pathology, and an upright abdominal radiograph was normal. The patient was put on IV fluids and observed. The pain disappeared over the next few days. An esophagogastroduodenoscopy demonstrated an axial hiatal hernia and grade 1 reflux esophagitis. Omeprazole was prescribed, and the patient was dismissed without complaints. Four days later he was readmitted as an emergency patient.

The patient was in acute distress with dyspnea and jugular venous distention, and he required oxygen. His respiratory rate was 30 beats/min, and his oxygen saturation as determined by pulse oxymetry was 90%. The BP was 100/70, and the pulse rate was 100 beats/min. A physical examination revealed no breath sounds in the left chest. An abdominal examination showed mild diffuse tenderness but no signs of peritonitis. Because a tension pneumothorax was suspected, a large-bore needle was inserted in the second left costal interspace. This maneuver stabilized the patient. Subsequently, a 20 Charriere chest tube (Mallinckrodt Medical; Athlone, Ireland) was inserted in the second left intercostal space, and 700 cm³ of feculent fluid was drained. A CT scan of the thorax demonstrated a portion of the large bowel in the left chest cavity (Fig 1). An esophagram could not confirm any leakage. A colonic enema with gastrografin revealed a colopleural fistula from the splenic flexure into the left thorax (Fig 2).

During an explorative laparotomy, the splenic flexure of the large bowel was found to be incarcerated and densely adherent in a traumatic diaphragmatic hernia with multiple perforations. A left hemicolectomy with a primary anastomosis was performed. The left pleura was lavaged transdiaphragmatically, the dia-

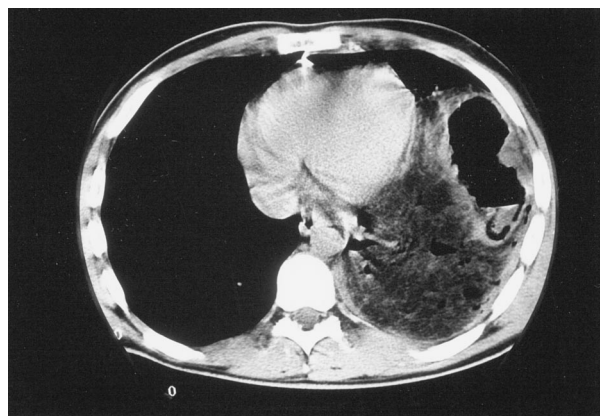


FIGURE 1. A CT scan of the chest demonstrating the bowel in the left thorax.

phragm was closed in two layers, and two 36 Charriere chest tubes were inserted. The postoperative course was complicated by a pyopneumothorax, requiring a thoracotomy with decortication of the left lung 24 days after the initial operation. The diaphragmatic part of the lung could not be decorticated because of multiple adhesions. The patient recovered well from his surgery. At follow-up 6 months after surgery, the patient was well and active.



FIGURE 2. A colonic enema with gastrografin shows contrast extravasation into the left pleural cavity.

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DISCUSSION

The presentation of an incarcerated traumatic diaphragmatic hernia as a tension pneumothorax is rarely reported. In a search of the literature, only nine cases of tension pneumothorax resulting from traumatic diaphragmatic hernia and perforation of the colon into the chest could be found.¹⁻⁹ An acute tension diaphragmatic herniation leading to mediastinal shift and cardiac arrest has also been reported.¹⁰

Blunt abdominal trauma and penetrating injuries through the abdomen or the chest involving the diaphragm are the main etiologic factors for traumatic diaphragmatic hernias. All cases of fecal pneumothorax resulting from diaphragmatic herniation and perforation of the colon share a uniform history of a stab wound to the chest. There is only one report of a tension pneumothorax because of a perforation of the small bowel after a blunt chest trauma and fracture of three ribs.¹¹ Another common finding was delayed clinical presentation.

As long as no bowel is injured, a traumatic diaphragmatic hernia may easily be missed after a stab wound to the chest because of the lack of symptoms. The findings of a chest roentgenogram are often normal. However, the mechanism of the trauma, the level and angle of penetration, the physical findings, and the abnormal findings on the initial chest radiograph such as hydropneumothorax or an "elevated" diaphragm, as well as certain ultrasound findings (interruption of the diaphragm), may raise suspicion of a diaphragmatic hernia. Laparoscopy has recently been used to detect intra-abdominal injuries following penetrating thoracoabdominal traumatic injuries, and it has been proven to be an excellent tool for the detection of diaphragmatic injuries.^{12,13} Laparoscopic exploration at the time of the patient's initial chest trauma may have prevented the subsequent incarceration. The importance of an early diagnosis of diaphragmatic herniation has recently been emphasized by Degiannis et al.¹⁴ In a retrospective study of 45 patients with diaphragmatic herniation after penetrating trauma, the diagnosis was established at the first admission in 29 patients; whereas, in 16 patients the diagnosis was delayed (with a median of 27 months). The mortality rate in the group with early presentation was 3% compared to 25% in the group with delayed presentation. The presence of a gangrenous or perforated stomach, or large bowel in the chest was the most common and aggravating factor.

The diagnosis of tension pneumothorax is usually based on clinical findings. The patient is in acute respiratory distress and is tachypneic, tachycardic, and possibly hypotensive. The jugular venous pressure is elevated when an upper-inflow obstruction caused by mediastinal deviation occurs. Breath sounds at the site of the injury are absent. In this urgent clinical setting, immediate relief is achieved by the insertion of a large-bore needle or by the insertion of a chest tube.

Feculent drainage from the chest tube is highly suspicious for the presence of a colopleural fistula. Prior to surgery, confirmation of the diagnosis should be achieved. A standard frontal chest radiograph should be obtained because it remains the most sensitive method for diagnos-

ing a traumatic diaphragmatic injury.¹⁵ An upper-GI study with water-soluble contrast material may be necessary to exclude the possibility of an esophageal or gastric perforation. A CT scan or MRI may confirm the diagnosis or give additional information about the extent of the lesion.¹⁵ This is particularly helpful to exclude further fluid collections or abscesses. The simplest and most practical way to establish the diagnosis is by using a gastrografin enema. In our case, the connection between the splenic flexure and the pleural cavity was clearly visualized.

Immediate surgical repair is important. A laparotomy with resection of the incarcerated bowel, a transdiaphragmatic lavage, and the closure of the hernia may be one option. Alternatively, an initial thoracotomy may be performed, with the advantage of better exposure of the chest to achieve complete lavage. In six of nine cases reported in the literature, an immediate laparotomy was performed; whereas, in one report the type of treatment was not described. In only two cases, the initial procedure was a thoracotomy followed by a laparotomy to create a colostomy.^{2,4} Postoperative pleural empyema occurred in one patient treated with an initial thoracotomy and in two patients who underwent a laparotomy.^{1,2,5} One patient died secondary to sepsis.⁹ A colectomy followed either by primary anastomosis or creation of a temporary colostomy should be performed. If only a laparotomy is performed, the pleural cavity should be lavaged with large amounts of fluid and the diaphragm closed by standard surgical techniques. However, pleural empyema may be an additional complication despite broad-spectrum antibiotic therapy that requires further surgical intervention.

Fecal pneumothorax is a potential complication following a posttraumatic diaphragmatic hernia resulting from a stab wound to the chest. This clinical finding should be included in the differential diagnosis of an atypical spontaneous pneumothorax, it should be confirmed by contrast studies, and it should be repaired without delay.

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Kirschner Wire Embolization to the Heart*

An Unusual Cause of Pericardial Tamponade

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A 50-year-old man presented with an abrupt onset of sharp, pleuritic, right-sided chest pain. A chest radiograph revealed a metallic foreign body over the cardiac silhouette; a chest CT scan localized the object to within the wall of the right ventricle. The patient subsequently developed pericardial tamponade necessitating pericardiocentesis. A 25-mm-long Kirschner wire protruding through the wall of the right ventricle was removed via thoracotomy. Forty-two months previously, the patient had undergone open reduction and fixation of a left radius fracture with two Kirschner wires. Clinicians caring for patients with orthopedic wires in place should be aware of wire migration with cardiac embolization as a potential complication.

(*CHEST* 1999; 115:291-293)

Key words: complication; embolism; Kirschner wire; pericardial tamponade; pericarditis

Abbreviations: \dot{V}/\dot{Q} = ventilation perfusion

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Orthopedic fixation wires are regularly utilized in the management of fractures and dislocations. Wire migration is believed to be a rare but potentially devastating complication with a variety of possible clinical manifestations. This report describes a patient with orthopedic wire migration and cardiac embolization with subsequent pericardial tamponade.

CASE REPORT

A 50-year-old man presented to an outside hospital with a 12-h history of right-sided, sharp chest discomfort that was sudden in onset and worsened with deep inspiration. He denied any recent cough, sputum production, fevers, or chills. The initial workup included a chest radiograph, an ECG, electrolyte and creatinine levels, a CBC count, and cardiac enzymes, which were all interpreted as normal. A ventilation perfusion (\dot{V}/\dot{Q}) scan was subsequently performed, and the results indicated an intermediate probability for pulmonary embolus. Heparin infusion was initiated, and the patient was transferred to the Milwaukee Veterans Administration Medical Center for continued care.

Shortly after transfer, the patient experienced worsening chest discomfort. A physical examination revealed distended neck veins, clear lung sounds, and normal first and second heart tones without extra heart sounds. An upright anterior-posterior chest radiograph (Fig 1) revealed a metallic foreign body over the cardiac silhouette; a 12-lead ECG revealed 3-mm concave upward ST segment elevations localized to the inferior and lateral precordial leads. Echocardiography was performed and interpreted as showing a dilated, diffusely hypokinetic right ventricle with grossly normal left ventricular function and no pericardial effusion; no foreign body was visualized. Laboratory evaluation now showed metabolic acidosis and acute renal failure, as well as a marked elevation of the international normalized ratio and hepatic transaminases (bicarbonate of 11 mEq/L, BUN of 68 mg/dL, creatinine of 4.8 mg/dL, international normalized ratio of 13.45, aspartate aminotransferase of 11,155 U/L, and alanine aminotransferase of 4,049 U/L). Heparin therapy was discontinued, and repeat \dot{V}/\dot{Q} scanning was interpreted as low probability for pulmonary embolus; lower extremity duplex ultrasound study showed no evidence of deep venous thrombosis. The patient experienced progressively worsening pleuritic chest discomfort and dyspnea. Echocardiography was repeated approximately 12 h after the initial study and revealed a large pericardial effusion and evidence of pericardial tamponade with right-ventricular diastolic compromise. The patient underwent pericardiocentesis after which he developed acute alcohol withdrawal necessitating intubation for adequate sedation. Over the subsequent 10 days, the patient had resolution of his hepatic and renal failure (presumed to be secondary to hypoperfusion) and acute alcohol withdrawal. A CT scan of the chest localized the foreign body to within the posterior wall of the right ventricle.

After the patient was extubated, he informed us that 4 years prior at an outside hospital he had undergone an orthopedic procedure for a wrist fracture that involved the placement of wires. A review of records revealed that in September of 1994 an open reduction and fixation of a comminuted distal left radius fracture was performed using two Kirschner wires. Several months after the procedure, the patient noticed the subcutaneous presence of a wire which over time migrated up his forearm and was then no longer palpable. A comparison of the postoperative (Fig 2, *Top*) and current (Fig 2, *Bottom*) radiographs of the left wrist revealed that the most distal Kirschner wire was now absent. A thoracotomy was performed 18 days after admission revealing a thickened pericardium with granulation tissue consistent with previous pericarditis. A 2.5-cm Kirschner wire was

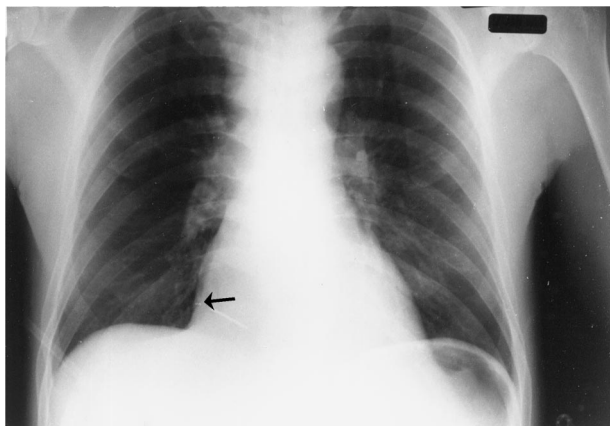


FIGURE 1. A chest radiograph demonstrating the foreign body (arrow) located over the cardiac silhouette.

found protruding from the posterior wall of the right ventricle. A cardiopulmonary bypass was instituted, the wire was removed, and the defect was oversewn. Postoperatively, the patient recovered well and walked out of the hospital in stable condition.

DISCUSSION

Since the 1930s, metallic fixation pins and wires have been regularly used in the management of fractures and dislocations.¹ The actual incidence of pin and wire migration is unknown, although in case reports it is a well-documented complication with potentially devastating consequences. In an extensive review of case reports of wire migration from the shoulder region, Lyons and Rockwood² referenced 49 cases of migration in which 17 pins migrated to a major vascular structure (4 to the heart, 2 to the subclavian artery, 6 to the ascending aorta, and 5 to the pulmonary artery). Lyons and Rockwood also referenced eight deaths attributable to migration, six of which were associated with pericardial tamponade. In our patient, we believe the wire entered the venous circulation in the arm, but the time of embolization to the heart is uncertain. To our knowledge, there is only one other report in the literature of Kirschner wire migration to the heart from a region as distal as the hand or wrist.³

This case also underscores the need to manage patients presenting with chest pain in the context of a broad differential diagnosis. Our patient's initial signs and symptoms were highly suggestive of pulmonary embolism. Not until later in the clinical course did typical ECG findings of pericarditis (wide spread concave upward ST segment elevations) and ensuing tamponade occur. Furthermore, initial echocardiographic findings were consistent with acute pulmonary embolism despite ECG and radiographic findings suggesting pericarditis. On the basis of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, a high clinical index of suspicion for pulmonary embolism in the context of an intermediate probability scan is consistent with a 66% probability of pulmonary embolism⁴ as was the case with our patient. In clinical application, pulmonary embolism assessment using \dot{V}/\dot{Q} scanning is believed to be most effective when the



FIGURE 2. *Top*: Post-operative radiographs demonstrate the two Kirschner wires in the left distal radius. *Bottom*: Recent left wrist radiographs demonstrate the absence of the most distal Kirschner wire.

results indicate a normal or high probability. \dot{V}/\dot{Q} scan results indicating a low or intermediate probability for pulmonary embolism require further investigations with Doppler ultrasound or impedance plethysmography of the lower extremities for deep venous thrombosis.⁵ Our patient presented with indeterminate scan results and normal lower extremity Doppler studies in a clinical situation limiting the use of IV contrast (acute renal failure) and, therefore, helical chest CT or angiography. The available literature provides little guidance for such clinical situations. The physical exam findings, electrocardiography, and the presence of a foreign body appearing on a chest radiograph reaffirmed suspicion for pericardial disease which was obvious on repeat echocardiography. Clinicians caring for patients with orthopedic wires in place should be aware of wire migration with cardiac embolization as a potential complication.

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Airway Obstruction Arising From Blood Clot*

Three Reports and a Review of the Literature

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Airway obstruction due to presence of blood clot occurs in a variety of clinical settings; however, it is not always preceded by hemoptysis. The impact on respiratory function may be minimal or result in life-threatening ventilatory impairment. Three illustrative cases and a comprehensive literature review are presented.

The presence of endobronchial blood clot is suggested by the clinical and radiographic findings of focal airway obstruction. The diagnosis is established by direct endoscopic evaluation. Initial efforts at removal of the airway clot, if warranted, involve lavage, suctioning, and forceps extraction through a flexible bronchoscope. If unsuccessful, further management options include rigid bronchoscopy, Fogarty catheter dislodgment of the clot, and topical thrombolytic agents.

(*CHEST* 1999; 115:293–300)

Key words: bronchoscopy; endobronchial blood clot; hemoptysis; respiratory failure

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Manuscript received December 15, 1997; revision accepted July 7, 1998.

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Endobronchial blood clot is an unusual, albeit not rare, cause of airway obstruction. In the setting of substantial hemoptysis, this entity should readily be considered in the differential diagnosis. However, approximately 30% of endobronchial blood clots occur without evidence of hemoptysis. Therefore, it is important to consider the possibility of this condition in the appropriate clinical setting, in order to avoid unnecessary diagnostic tests and to institute proper therapy. We present three representative cases of airway obstruction from endobronchial clot, with a discussion of its clinical aspects and therapy. This review was conducted using a MedLine search of the pertinent English literature published from 1966 to May 1998 with cross-reference analysis.

CASE 1

A 53-year-old man underwent re-induction chemotherapy 1 month previously for acute myelogenous leukemia. His hospital course was complicated by pancytopenia and subsequent right middle and lower lobe pneumonia. The patient remained febrile and ventilator-dependent 1 week after intubation for hypoxemic respiratory failure.

At this point, several acute respiratory events arose, each lasting approximately 1 to 2 min. These events were characterized by peak inspiratory pressures to 90 cm H₂O, difficulty in ventilation, and temporary resolution after endotracheal suctioning. However, minimal secretions were obtained by suctioning, and chest radiographic examination showed no evidence of barotrauma.

Flexible bronchoscopy revealed a large blood clot at the carina, extending into and partially obstructing both mainstem bronchi (Fig 1). Regions of mucosal damage from endotracheal suctioning were seen, but there was no evidence of active bleeding. The clot was removed using endobronchial forceps in piecemeal fashion, and no further obstructive events occurred.

CASE 2

A 54-year-old woman presented to a regional hospital with fever, cough, and right pleuritic chest pain. The chest radiograph confirmed a right lower lobe infiltrate and associated pleural effusion, consistent with community-acquired pneumonia. A thoracentesis was attempted but was unsuccessful. Further attempts resulted in massive hemoptysis (approximately 600 to 700 mL) and respiratory distress requiring endotracheal intubation.

On transfer to our hospital, a chest radiograph was notable for showing complete opacification of the right hemithorax, ipsilateral mediastinal shift, and a cut-off sign of the right mainstem bronchus. Placement of a 32F chest tube was necessary for drainage of the parapneumonic hemothorax. Flexible bronchoscopic airway examination revealed a reddish, smooth lesion obstructing the distal right mainstem bronchus (Fig 2). Examination of the pathology confirmed the mass as a blood clot. Endobronchial lavage and forceps extraction were unsuccessful in removal of the entire obstructing lesion. Although her PAO₂ to Pao₂ gradient was substantially increased due to pneumonia, she remained hemodynamically stable with adequate oxygenation. Her peak inspiratory pressures ranged from 35 to 38 cm H₂O. Therefore no further attempts were made to remove the obstructing clot. A repeat bronchoscopic evaluation 3 days later showed no evidence of the clot, and all airways were patent.

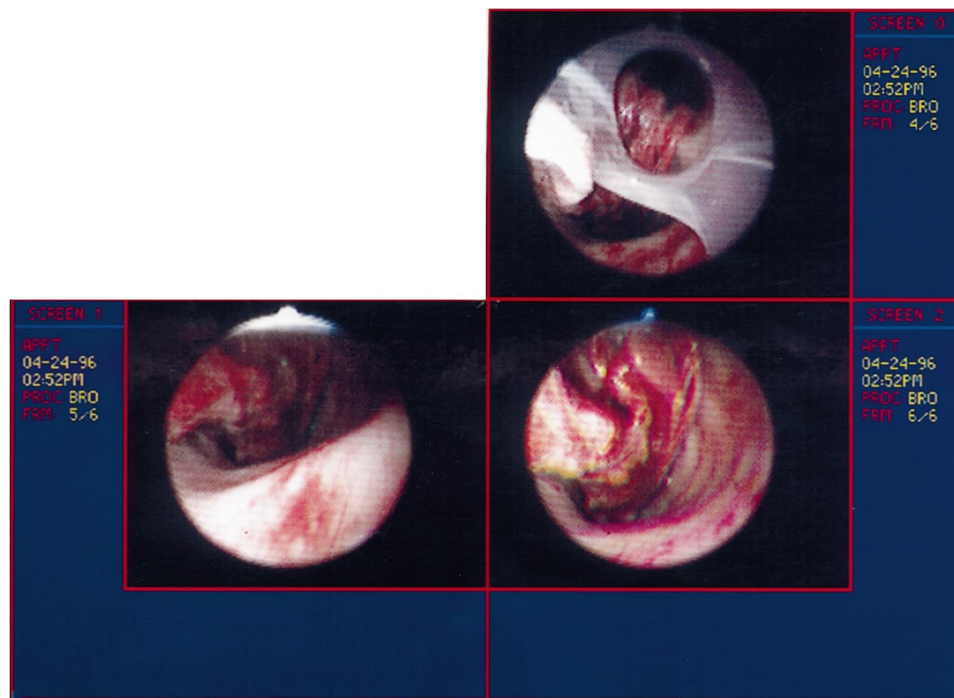


FIGURE 1. A large blood clot is seen straddling the carina and extending into and partially obstructing both mainstem bronchi.

CASE 3

A 33-year-old man was admitted to the ICU with impending respiratory failure. Over the previous 3 days, he had developed a nonproductive cough and fever. A chest radiograph showed diffuse interstitial infiltrates. He was intubated and placed on mechanical ventilation due to hypoxic respiratory failure.

Using transbronchial biopsies, a bronchoscopy of the right lower lobe was performed. After the third biopsy was completed, copious bleeding was noted from the right lower lobe bronchus. The rate of bleeding exceeded the suction capacity of the flexible bronchoscope, with blood appearing in the endotracheal tube and ventilator tubing. However, the patient remained hemodynamically stable, with oximetry saturations between 90 and 97%. An arterial blood gas on 100% oxygen revealed pH 7.11, PCO_2 101 mm Hg, and PO_2 97 mm Hg.

The bleeding subsided after 5 min, with minimal pink frothy secretions emanating from the endotracheal tube. Diffuse wheezing was heard on auscultation. A bronchoscope was inserted down the endotracheal tube, with visualization of a clot virtually obscuring the distal orifice of the endotracheal tube. After unsuccessful attempts to remove the clot with bronchial biopsy forceps, a decision was made to remove the endotracheal tube and re-intubate the patient. On removal of the endotracheal tube, it was discovered that the clot covering the distal portion of the tube had actually extended down both mainstem bronchi and the entire right endobronchial tree (Fig 3). The patient's wheezing resolved immediately on concomitant removal of the tube and blood clot cast, and the arterial blood gases quickly normalized. The patient was extubated within 24 h without difficulty. Pathologic examination of the biopsies showed diffuse alveolar damage, consistent with an acute viral pneumonia.

DISCUSSION

Acute endobronchial obstruction can develop from a variety of conditions, including bronchospasm, mucosal

edema, mucous impaction, and aspirated foreign bodies. In mechanically ventilated patients, kinked or malpositioned endotracheal tubes and overinflated cuffs can also produce obstruction.^{1,2}

Several reports in the early medical literature described atelectasis following episodes of hemoptysis.³ The first confirmed case of endobronchial obstruction from blood clot was reported by Wilson in 1929.⁴ The case involved a 23-year-old woman with tuberculosis and atelectasis. She developed acute respiratory distress 3 days after onset of recurrent hemoptysis. Physical examination and chest radiograph findings were consistent with right middle and lower lobe collapse. She expectorated 6 days later three extensive bronchial casts composed of clot, with rapid improvement of pulmonary symptoms.

Airway obstruction caused by the presence of blood clot has been noted as a complication of bronchiectasis,⁵ tuberculosis,^{3,4,6} mitral stenosis,⁷⁻⁹ pulmonary infarction,^{10,11} pulmonary arteriovenous malformation,^{1,5} sarcoidosis,¹² bronchial carcinoma,¹³ and intrathoracic trauma^{2,14} (Table 1). Mucosal damage from suction catheter manipulation,¹⁸ bronchoalveolar lavage,¹² transbronchial biopsy,^{19,20} and tracheostomy placement²¹⁻²³ have also led to airway blood clots. Although a recent history of endobronchial bleeding can alert the clinician to the possibility of such an event, approximately 30% of the cases reported in the literature had no evidence of preceding hemoptysis. This occult presentation occurs predominantly in the setting of either prolonged mechanical ventilation^{13,14,24-26} or tracheostomy placement.^{21,23} Tracheobronchial mucosal damage from infection, tumor, tracheostomy, or endotracheal suctioning may result in subclinical endobronchial bleeding with subsequent clot formation. Therefore, a

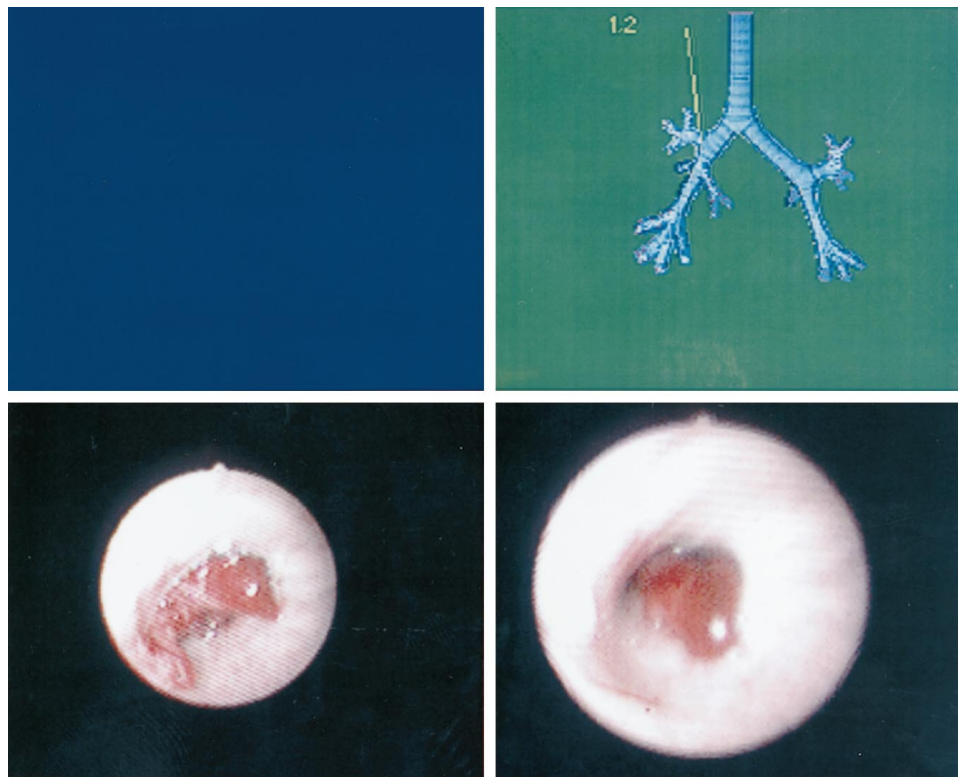


FIGURE 2. Blood clot obstructing the distal right mainstem bronchus. Note the smooth reddish-brown appearance of the clot.

consideration of endobronchial clot is warranted when acute airway obstruction arises under these circumstances, despite the absence of hemoptysis.

Physical examination is notable for decreased or absent breath sounds and an occasional inspiratory or expiratory wheeze over the affected lobe or lung.



FIGURE 3. Extensive blood clot virtually occludes the tip of the endotracheal tubes, extending down into the right mainstem bronchus.

Table 1—Airway Obstruction Arising From a Blood Clot*

Author/Year	Cause of Bleeding	Site of Clot	Presentation	Treatment	Outcome
Wilson ⁴ /1929	Tuberculosis	Right airways (chest film and exam)	Hemoptysis, fever, and dyspnea Right mid and lower lobe collapse	Supportive	Expectoration of clot. Resolution of atelectasis and respiratory distress.
Hennell ⁶ /1929	Tuberculosis	Left airways (physical exam)	Hemoptysis, fever, and dyspnea Lingular and left lower lobe collapse	Supportive	Expectoration of clot. Resolution of atelectasis and respiratory distress.
Mindline ³ /1935	Tuberculosis	Left main bronchus (chest film and exam)	Hemoptysis, fever, dyspnea, and chest pain Left lung collapse	Supportive	Expectoration of clot. Resolution of atelectasis and respiratory distress.
Isaacs et al ⁸ /1953	Mitral stenosis	Right and left bronchial trees (postmortem exam)	Hemoptysis and fever	Supportive	Respiratory arrest and death.
Schwartz et al ⁹ /1966	Mitral stenosis	Left bronchial tree Trachea, right and left bronchial trees	Hemoptysis, fever, and dyspnea Lingula and left lower lobe collapse	Bronchoscopy; forceps extraction	Removal of clot. Improvement in respiratory function.
Brennan and Parker ⁷ /1970	Mitral stenosis	Left bronchial tree (ball valve) (chest film and exam)	Hemoptysis, fever, and dyspnea	Supportive	Expectoration of clot. Resolution of respiratory distress.
Skatrud et al ¹⁰ /1976	Pulmonary emboli (heparinization) and tracheotomy	Bronchus intermedius	Hemoptysis, respiratory failure Right mid and lower lobe collapse	Supportive	Expectoration of clot. Resolution of atelectasis.
Fairshter et al ²⁰ /1979	Pneumonia	Right upper lobe bronchus	Hemoptysis, fever, and dyspnea	Supportive, chest physiotherapy	Expectoration of clot. Radiographic clearing of RUL consolidation.
Fairshter et al ²⁰ /1979	Lobar infiltrate, transbronchial biopsy	Right and left main bronchi, extending to ET tube	Endobronchial bleeding, postbiopsy	Removal of ET tube (concomitant removal of attached blood clot cast)	Removal of clot. Uneventful recovery.
Kruczek et al ¹ /1982	AV malformation and remote tuberculosis	Bronchus intermedius (ball valve)	Hemoptysis, respiratory failure, postobstructive hyperexpansion	Rigid bronchoscopy; lavage and snare forceps extraction	Removal of clot. Resolution of hyperexpansion. Improvement in respiratory function.
Popovich and Babcock ¹⁴ /1982	Right chest gunshot wound, right upper lobe resection, postoperative pneumonia	Right upper lobe bronchus, bronchus intermedius, and left upper lobe bronchus (ball valve)	Hemothorax, infiltrates, and respiratory failure Recurrent bilateral pneumothoraces and mediastinum	Flexible bronchoscopy; lavage and snare forceps extraction	Removal of clot. Resolution of hyperexpansion and pneumothoraces. Death due to sepsis.
Cole and Grossman ²⁷ /1983	Unknown	Right mainstem bronchus, extending across carina to left mainstem	Hemoptysis, fever, and dyspnea Right mid and lower lobe collapse	Flexible bronchoscopy; endobronchial streptokinase, and suctioning	Removal of clot. Resolution of atelectasis. Improvement in respiratory function.
Thomson ¹⁸ /1986	Cavitary histoplasmosis, endotracheal suctioning	Right mainstem bronchus	Hemoptysis, respiratory failure Right lung collapse	Flexible bronchoscopy; endobronchial streptokinase	Partial removal of clot. Improvement in atelectasis and respiratory function.
Underwood and Summerfield ²³ /1986	Legionella pneumonia, motor neuropathy, tracheostomy	Trachea	Acute ventilatory impairment	Flexible bronchoscopy (method of clot extraction not specified)	Removal of clot. Improvement in ventilation.
Underwood and Summerfield ²³ /1986	Motor vehicle accident, closed head injury, tracheostomy	Trachea	Acute ventilatory impairment	Flexible bronchoscopy (method of clot extraction not specified)	Removal of clot. Improvement in ventilation.

Table 1—Continued

Author/Year	Cause of Bleeding	Site of Clot	Presentation	Treatment	Outcome
Allen and Siefkin ⁵ / 1987	AV malformation	Distal trachea, extending to right and left mainstem bronchi	Hemoptysis, respiratory failure	Flexible bronchoscopy; Fogarty balloon catheter dislodgment and suctioning	Removal of clot. Improvement in respiratory function.
Allen and Siefkin ⁵ / 1987	Bronchiectasis, remote tuberculosis	Left mainstem bronchus	Hemoptysis, respiratory failure	Flexible bronchoscopy; Fogarty balloon catheter dislodgement and suctioning	Improvement in respiratory function. Left lower lobe resection for recurrent bleed.
Allen and Siefkin ⁵ / 1987	Sepsis, multiorgan failure, and pulmonary hemorrhage	Left mainstem bronchus, extending across carina to right mainstem	Respiratory failure	Flexible bronchoscopy; Fogarty balloon catheter dislodgment and suctioning	Removal of clot. Improvement in respiratory function. Recurrent pulmonary hemorrhage.
Noble and Sheikh ²⁴ / 1987	Pneumonia, high-frequency jet ventilation, and endotracheal suctioning	Distal trachea	Ventilatory impairment	Rigid bronchoscopy (method of clot extraction not specified)	Removal of clot. Improvement in respiratory function.
Lin et al ² /1989	Motor vehicle accident, hemothorax	Endotracheal tube	Hemoptysis, acute ventilatory impairment	Removal of occluded ET tube, and re-intubation	Resolution of ventilatory impairment.
Campbell and O'Leary ²² /1991	Respiratory failure (due to Guillain-Barré), minitracheotomy	Trachea	Ventilatory impairment	Rigid bronchoscopy; tracheostomy (method of clot extraction not specified)	Removal of clot. Improvement in ventilation.
Campbell and O'Leary ²² /1991	Esophageal cancer, postoperative pneumonia, minitracheotomy	Larynx, extending into trachea	Ventilatory impairment	Laryngoscopy, Magill's forceps extraction, tracheostomy	Removal of clot. Improvement in ventilation.
Ewart and Weston ¹⁷ / 1991	Leukemia, thrombocytopenia	Posterior oropharynx (pedunculated mass)	Intermittent dyspnea while lying supine	Method of clot extraction not specified	Removal of clot. Improvement in ventilation.
Maxwell and Stauffer ¹² /1992	Sarcoidosis	Distal ET tube and right mainstem bronchus	Massive hemoptysis, respiratory failure	Flexible bronchoscopy; endobronchial streptokinase	Removal of clot. Improvement in respiratory function.
Maxwell and Stauffer ¹² /1992	Multiple myeloma and pulmonary infiltrates, bronchoalveolar lavage	Distal ET tube, trachea, and right mainstem bronchus	Endobronchial bleeding, respiratory failure	Flexible bronchoscopy; endobronchial streptokinase	Removal of clot; improved respiratory function
Bailey and Liban ²¹ / 1993	Percutaneous tracheostomy	Distal trachea	Ventilatory impairment	Rigid bronchoscopy (method of clot extraction not specified)	Removal of clot; improvement in respiratory function
Davis ¹⁵ /1993	Epistaxis, Brighton balloon manipulation	Larynx, extending into trachea and mainstem bronchi (postmortem)	Dyspnea, upper airway obstruction	Removal of Brighton balloon device, endotracheal intubation	Cardiopulmonary arrest and death
Sprung et al ²⁵ /1994	Lymphoma, pulmonary embolism, and ARDS	Trachea	Ventilatory impairment, subcutaneous emphysema, and pneumomediastinum	Rigid bronchoscopy; forceps extraction and lavage	Removal of clot; improvement in ventilation

Table 1—Continued

Author/Year	Cause of Bleeding	Site of Clot	Presentation	Treatment	Outcome
Botnick and Brown ^{19/} 1994	Lung cancer and radiation pneumonitis, transbronchial biopsy	Distal ET tube, right and left mainstem bronchi	Endobronchial bleeding, respiratory failure	Removal of occluded ET tube and reintubation; flexible bronchoscopy; endobronchial urokinase; forceps manipulation and lavage; rigid bronchoscopy and clot extraction	Removal of clot; improvement in respiratory function
Duff and Gruber ^{16/} 1996	Sepsis, pulmonary edema, extracorporeal membrane oxygenation (systemic heparinization)	Mid trachea, extending into segmental bronchi	Endobronchial hemorrhage, ventilatory impairment	Rigid bronchoscopy (method of clot extraction not specified)	Removal of clot; improvement in ventilation Recurrent endobronchial hemorrhage and clot formation
Stanislas et al ^{26/} 1996	Motor vehicle accident, postoperative ARDS	Alternating mainstem bronchi with intermittent obstruction (ball valve)	Ventilatory impairment	Flexible bronchoscopy (method of clot extraction not specified)	Removal of clot; improvement in ventilation
Vajo and Parish ^{11/} 1996	Endocarditis and central venous catheter-related pulmonary embolus	Distal trachea and right mainstem bronchus	Hemoptysis, respiratory failure Right mid and lower lobe collapse	Flexible bronchoscopy; endobronchial streptokinase, suctioning, and forceps extraction	Removal of clot; resolution of atelectasis Improvement in respiratory function
Foucher et al ^{13/} 1996	Lung cancer with airway compression and mucosal infiltration	Distal trachea, right and left mainstem bronchi (ball valve)	Respiratory failure, right lung hyperexpansion Cardiopulmonary arrest	Postmortem rigid bronchoscopy; forceps extraction	Death
Arney and Sahn/1997†	AML, nosocomial pneumonia, endotracheal suctioning	Carina, extending to right and left mainstem bronchi	Ventilatory impairment	Flexible bronchoscopy; forceps extraction	Removal of clot; improvement in ventilation
Arney and Sahn/1997	Pneumonia, complication of thoracentesis	Distal right mainstem bronchus	Right hemothorax, respiratory failure Right lung collapse	Flexible bronchoscopy; forceps extraction	Partial removal of clot; spontaneous resolution of remaining clot
Judson/1997	Pneumonia, transbronchial biopsy	Distal ET tube, extending to right and left mainstem bronchi	Endobronchial bleeding, postbiopsy	Flexible bronchoscopy; removal of occluded ET tube and re-intubation	Removal of clot; improvement in respiratory function

*ET = endotracheal; AV = arteriovenous; RUL = right upper lobe.

†The last three author lines refer to the three cases in this article.

Clinical evidence of atelectasis, with diminished chest wall motion, reduction of vocal fremitus, flattening of the percussion note, and ipsilateral tracheal deviation can occur. The most notable finding among ventilated patients is an acute rise in peak inspiratory pressure (typically greater than 60 cm H₂O) and a concomitant decrease in tidal volume. With major atelectasis, the plateau pressure is also elevated. However, if partial obstruction of the endotracheal tube or proximal airways occurs without atelectasis, the plateau pressure

may be normal. The extent of hypoxemia and hypercapnia depends on the site and degree of obstruction, associated pulmonary hemorrhage, and underlying condition of the lungs.

Despite elevated airway pressures, the patient's hemodynamic status may remain essentially unaffected.²⁵ With patent airways and normal lung compliance, such elevated airway pressures are transmitted to the extraparenchymal intrathoracic regions, resulting in decreased venous return and cardiac output. However, in the setting of proximal

airway obstruction, the distal pressures are normal, with a distinct absence of hemodynamic alterations.

Chest radiographs may not reveal acute abnormalities, despite severe airway compromise. This is particularly true with endotracheal tube or proximal airway involvement. Typical findings, when present, are either lobar or segmental atelectasis, or cut-off of the air column of the trachea and mainstem bronchi.

A notable exception to the typical presenting features occurs with ball-valve obstruction. In this situation, the blood clot acts as a one-way valve in the endotracheal tube or airway, allowing air entry into the lower respiratory tract, but blocking expiratory flow. The consequence is ipsilateral hyperexpansion, with resultant risk of tension pneumothorax and hemodynamic compromise. On removal of the obstructing clot, the hyperinflation rapidly resolves. With one exception, the reported events occurred in patients undergoing positive pressure ventilation.^{1,7,13,14} Popovich and Babcock¹⁴ described such a case resulting in bilateral recurrent pneumothoraces and recommended consideration of bronchoscopy in any mechanically ventilated patient with recurrent pneumothorax to assess for ball-valve obstruction.

Definitive management begins with the determination of the site of obstruction, whether it is present in the endotracheal tube or the airways. This differentiation can be made in mechanically ventilated patients by passing a suction catheter into the endotracheal tube, to assess its patency. If a stylet is used, special precautions should be taken to prevent the tip from traversing the length of the tube lumen and causing mucosal damage to the carina or main stem bronchi. Another maneuver used is the "cuff deflation test," as described by Sprung and coworkers.²⁵ The endotracheal tube cuff is deflated, and the degree of air leak around the cuff is assessed during the ventilatory cycle. A dramatic decrease in the inspiratory pressure and a marked increase in the air leak suggests a patent endotracheal tube with distal airway obstruction. An exception is a partially adherent clot at the tip of the tube causing ball-valve obstruction.

Clinical data regarding the natural history of endobronchial clot is limited. The obstructing clot in our second case spontaneously resolved over the 3 days between bronchoscopic evaluations. Expectoration or endotracheal suctioning of the lesion did not occur, and no evidence of the clot was seen on follow-up bronchoscopy. Other reports in the literature, however, have noted persistence of the clot over a period of 36 to 48 h.^{5,10} In one instance, progression of the clot from the lobar bronchi to both mainstem occurred over 3 days, with clinical deterioration.²⁷ It must be kept in mind that any intervention to attempt removal of the clot may induce further bleeding or result in more proximal obstruction. Therefore, in a patient who is hemodynamically stable with adequate gas exchange, the appropriate management may be observation, as illustrated in the second clinical case.

If necessary, the initial effort at removal of the endobronchial clot should involve flexible bronchoscopic evaluation with saline lavage and suctioning. If unsuccessful, the usual next step is forceps extraction through the working channel, either en bloc or in piecemeal fashion.

At times it may be necessary to remove the forceps and bronchoscope together, due to the excessive size of the clot.^{1,25} Should all of the previously mentioned methods fail, subsequent management should be tailored to the individual patient.

Rigid bronchoscopy allows the clinician greater access for suctioning and forceps extraction. If brisk endobronchial bleeding should occur following clot removal, the rigid bronchoscope offers superior airway management. This technique, however, is not always available. Even when accessible, special circumstances need to be considered. If the clot or source of bleeding arises from the upper lobes, airway isolation and tamponade can be suboptimal. Another drawback stems from the underlying impairment in ventilation due to obstruction by clot and resulting atelectasis. Flexible bronchoscopy can be performed through the endotracheal tube, allowing adequate mechanical ventilation. Patients undergoing rigid bronchoscopy are extubated prior to the procedure. Though mechanical ventilation can be performed through a side-port channel, the previously compromised ventilatory status may be further impaired. Rigid bronchoscopy has been performed with an endotracheal tube in place, as described by Sprung and associates.²⁵ However, to pass the bronchoscope through the trachea, the cuff must be deflated, resulting in a significant air leak.

In instances of firmly adherent clot, manipulation with a Fogarty arterial embolectomy catheter has been used successfully. Allen and Siefkin⁵ described three cases in which a number 6 Fogarty catheter was passed down the working channel of a flexible bronchoscope, along the margins of the obstructed airway, and beyond the level of clot. The balloon was then inflated with 1.5 mL of air and partially withdrawn to dislodge the clot, which was subsequently suctioned and removed. The patients met with no immediate complications, but the authors caution that there is risk of re-initiating hemorrhage. They do not recommend this technique unless severe respiratory compromise is present and other alternatives, such as rigid bronchoscopy, have been considered. If brisk bleeding occurs, the Fogarty catheter can be used to tamponade the affected airway.

Recently, topical thrombolysis has been used with success. Under visualization via flexible bronchoscopy, thrombolytics are applied directly onto the surface of the clot, with partial dissolution and forceps removal in piecemeal fashion. Streptokinase has been used most often, in doses of 30,000 to 120,000 U^{11,12,18,27}; 30,000 to 60,000 U of streptokinase are mixed in 30 to 60 mL of normal saline, respectively, for a concentration of 1,000 U/mL. Aliquots of 10 to 15 mL are applied, allowing 5 to 10 min between dosing to take effect.^{11,12,18} Urokinase, the premixed formulation for central catheter clearance, has also been used with success in aliquots of 2,500 U in 5 mL of diluent.¹⁹ Thomson¹⁸ has recommended the use of a plastic catheter to more easily and accurately direct the lytic agent onto the surface of the clot. Although recurrence of bleeding has not been reported with thrombolytics, it should be regarded as a potential consequence, and anticipated management needs should be considered in advance.

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Successful Treatment of Pulmonary Lymphangiomyomatosis With Progestins

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Chest 1999;115: 276-279

DOI 10.1378/chest.115.1.276

This information is current as of June 26, 2009

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