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Negative Pressure Pulmonary Hemorrhage*

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Negative pressure pulmonary edema, a well-recognized phenomenon, is the formation of pulmonary edema following an acute upper airway obstruction (UAO). To our knowledge, diffuse alveolar hemorrhage has not been reported previously as a complication of an UAO. We describe a case of negative pressure pulmonary hemorrhage, and we propose that its etiology is stress failure, the mechanical disruption of the alveolar-capillary membrane.

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Key words: negative pressure pulmonary edema; pulmonary hemorrhage; stress failure

Abbreviations: ITP = intrathoracic pressure; NPPE = negative pressure pulmonary edema; NPPH = negative pressure pulmonary hemorrhage; OSA = obstructive sleep apnea; Pms = mean systemic pressure; Ppc = pulmonary capillary hydrostatic pressure; Ppi = pulmonary interstitial hydrostatic pressure; Ptm = pulmonary capillary transmural pressure; UAO = upper airway obstruction

Formation of noncardiogenic pulmonary edema has been anecdotally observed following various forms of upper airway obstruction (UAO), with one series in adults describing an incidence as high as 11%.[1] The principal physiologic mechanism underlying the formation of edema in this setting involves the generation of markedly negative intrathoracic pressure leading to a net increase in the pulmonary vascular volume and the pulmonary capillary transmural pressure (Ptm). We report a case of an adult man who suffered diffuse alveolar hemorrhage following an acute UAO. We postulate that the mechanism underlying negative pressure pulmonary hemorrhage (NPPH) is stress failure of the alveolar-capillary membrane caused by the marked elevation of pulmonary capillary wall tension. Decreases in pericapillary interstitial pressure might contribute significantly to the development of stress failure in NPPH.

Case Report

A 46-year-old muscular African-American man with a medical history significant for high myopia, glaucoma, mild mental retardation, and cocaine abuse underwent elective vitreous debridement and cataract removal for scarring due to bleb-associated endophthalmitis of his right eye. Preoperative testing was not performed. General anesthesia was induced with propofol and fentanyl and was maintained with isoflurane and nitrous oxide. The patient was given succinylcholine prior to an atraumatic endotracheal intubation, and mivacurium was used for the intraoperative paralysis. Clear bilateral breath sounds were noted, and the capnography trace was normal. The surgery proceeded uneventfully with normal intraoperative hemodynamic and respiratory indexes. The patient received 2 L of lactated Ringer's solution, and his urinary output totaled 480 mL over 4 h.

At the end of the procedure, peripheral twitch monitoring showed 4/4 twitches with a train-of-four, and the patient met the standard criteria for extubation without the need for neuromus-

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cular relaxant agent reversal. Following extubation, he became agitated and began to make vigorous inspiratory efforts without significant air movement. He became tachycardic to 120 beats/min, hypertensive to 170/100 mm Hg, and hypoxemic with a pulse oximeter saturation of 88% on a 100% nonrebreather mask. Despite artificial oral and nasal airways and intermittent positive pressure applied with a bag-valve mask, he continued to make inspiratory "crowing" sounds. He became increasingly hypoxemic and was atraumatically reintubated 5 min after extubation. A direct laryngoscopy excluded the presence of supraglottic edema, upper airway bleeding, or laryngospasm. Coarse inspiratory rhonchi were heard bilaterally on auscultation, and copious, pink, frothy sputum was obtained with suctioning. The patient was stabilized and transferred to the postanesthesia care unit.

A chest radiograph revealed asymmetric, right greater than left, fluffy perihilar infiltrates, and a small left pleural effusion. An initial arterial blood gas measurement revealed a pH of 7.35, a P_{CO_2} of 52.9 mm Hg, a Pa_{O_2} of 35 mm Hg, and an arterial oxygen saturation of 68% on a fraction of inspired oxygen of 1.0. The patient's endotracheal secretions became progressively bloody, consistent with frank hemorrhage. The clinical impression of the anesthesiologists was that the patient had experienced negative pressure pulmonary edema (NPPE) secondary to UAO; the etiology of the hemoptysis was unknown. Supportive treatment included IV furosemide, supplemental oxygen, and 10 cm H_2O positive end-expiratory pressure. Before the patient was transfered to the medical ICU, his oxygenation had improved; the pulse oximeter saturation was 94% on a fraction of inspired oxygen of 0.5, and a repeat arterial blood gas measurement revealed a pH of 7.42, a P_{CO_2} of 40.3 mm Hg, and a Pa_{O_2} of 158 mm Hg. The patient received a total of 4,300 mL of crystalloid, and his total urinary output was 2,845 mL.

Following his stabilization, the patient denied having a history of previous cough, hemoptysis, hematuria, or epistaxis, but he did acknowledge a history of loud snoring. He denied any recent use of cocaine or IV drugs, and he had a negative tuberculin skin test within the past year. His only medication was timolol eyedrops, and he had no drug allergies. The family history was noncontributory.

The initial examination revealed an African-American man with blood in his endotracheal tube. His temperature was 39.1°C (102.4°F) with rapid spontaneous defervescence. He had no petechiae, telangiectasias, or oral or mucosal bleeding. There was no jugular venous distention. He had diffuse inspiratory rales, normal heart sounds, and no peripheral edema. The laboratory investigation was notable for a hematocrit of 58%, with a repeat value 7 h later of 46.9%. The WBC count and coagulation profile were normal. The urinalysis revealed 3 to 5 nondysmorphic RBCs/high-power field and 0 to 2 WBCs/high-power field, without casts or proteinuria. A urine toxicology screen was negative for cocaine metabolites.

The bronchoscopy in the medical ICU revealed a small amount of fresh blood in the proximal airways. The endobronchial mucosa was normal and was without masses or an identifiable bleeding source. A BAL was performed to help clarify the origin and chronicity of the bleeding. A lavage of the lingula and the right middle lobe with 6 aliquots of 20 mL normal saline each revealed a progressively bloody return consistent with alveolar hemorrhage. The BAL fluid contained 5.6×10^3 WBC/mL with 99% polymorphonuclear leukocytes and no organisms. The cytology was negative for hemosiderin-laden macrophages, and all cultures were negative. An ECG revealed a sinus tachycardia, and the echocardiography showed normal valves and normal right and left ventricular function. Test results were negative for anti-glomerular basement membrane antibody, antineutrophil cytoplasmic antibody, and HIV. There was no evidence of cryoprotein.

The patient's oxygen requirement decreased progressively over the ensuing 24 h. By hospital day 2, his hematocrit had decreased to 40%, and he was extubated. He remained stable thereafter. Sequential anteroposterior portable chest radiographs revealed the persistence of bilateral acinar disease until an improvement became apparent on hospital day 3. Prior to the patient's discharge on hospital day 4, a chest radiograph showed a slight interval clearing. An ear, nose, and throat evaluation was notable for a mild redundancy of oropharyngeal tissue and normal vocal cords. A sleep study revealed a respiratory disturbance index of 20 events/h that was consistent with obstructive sleep apnea (OSA). The patient was discharged in stable condition, but he did not return for his scheduled follow-up.

Discussion

We have presented a case of a 46-year-old man who underwent routine surgery with general anesthesia and suffered from hypoxemic respiratory failure following extubation. He likely experienced acute UAO secondary to redundant pharyngeal soft tissue and loss of muscle tone related to the postanesthetic state. Vigorous inspiratory efforts against an obstructed upper airway (the modified Mueller maneuver) led to the development of acute NPPE. Our patient, however, developed frank alveolar hemorrhage, a condition that, to our knowledge, has not been reported previously in this setting.

NPPE has been well-described in cases of acute UAO.[2–5] In children, it has been observed after intubation secondary to croup and epiglottitis.[2] In both children and adults, it has been reported as a complication of postanesthetic laryngospasm,[2,3,5] strangulation, hanging,[6] foreign body airway obstruction, upper airway tumors,[3] and OSA.[7]

NPPE is characterized by a rapid onset (within minutes) and resolution, with a significant clinical and radiographic improvement in 12 to 24 h.[5] Most patients require temporary intubation and positive end-expiratory pressure.[3] Diuresis and/or fluid restriction are often utilized. Hemodynamic measurements, including pulmonary capillary wedge pressure, pulmonary arterial pressure, and central venous pressure taken following the development of edema, are normal.[5]

Markedly negative intrathoracic pressure (ITP) augments normal inspiratory hemodynamic physiology (Fig 1). Venous return is increased through the combination of reduced right atrial pressure secondary to the transmission of negative ITP and the elevation of the mean systemic pressure (Pms) related to catecholamine-induced venoconstriction from anxiety, hypoxia, and hypercarbia. As the right ventricular volume increases, the interventricular septum may shift leftward, indicative of reduced left ventricular diastolic compliance.[8] Negative ITP transmission to the cardiac fossa and a catecholamine-induced elevation of the systemic vascular tone cause an increase in the left ventricular transmural pressure, thus raising ventricular wall tension.[9] This increase in afterload depresses left ventricular ejection. The effect of these changes is a net translocation of blood from the systemic to the pulmonary circulation. The formation of edema in this setting requires an increased Ptm: pulmonary capillary hydrostatic pressure (Ppc) minus the pulmonary interstitial hydrostatic pressure (Ppi). The Ppc rises secondary to

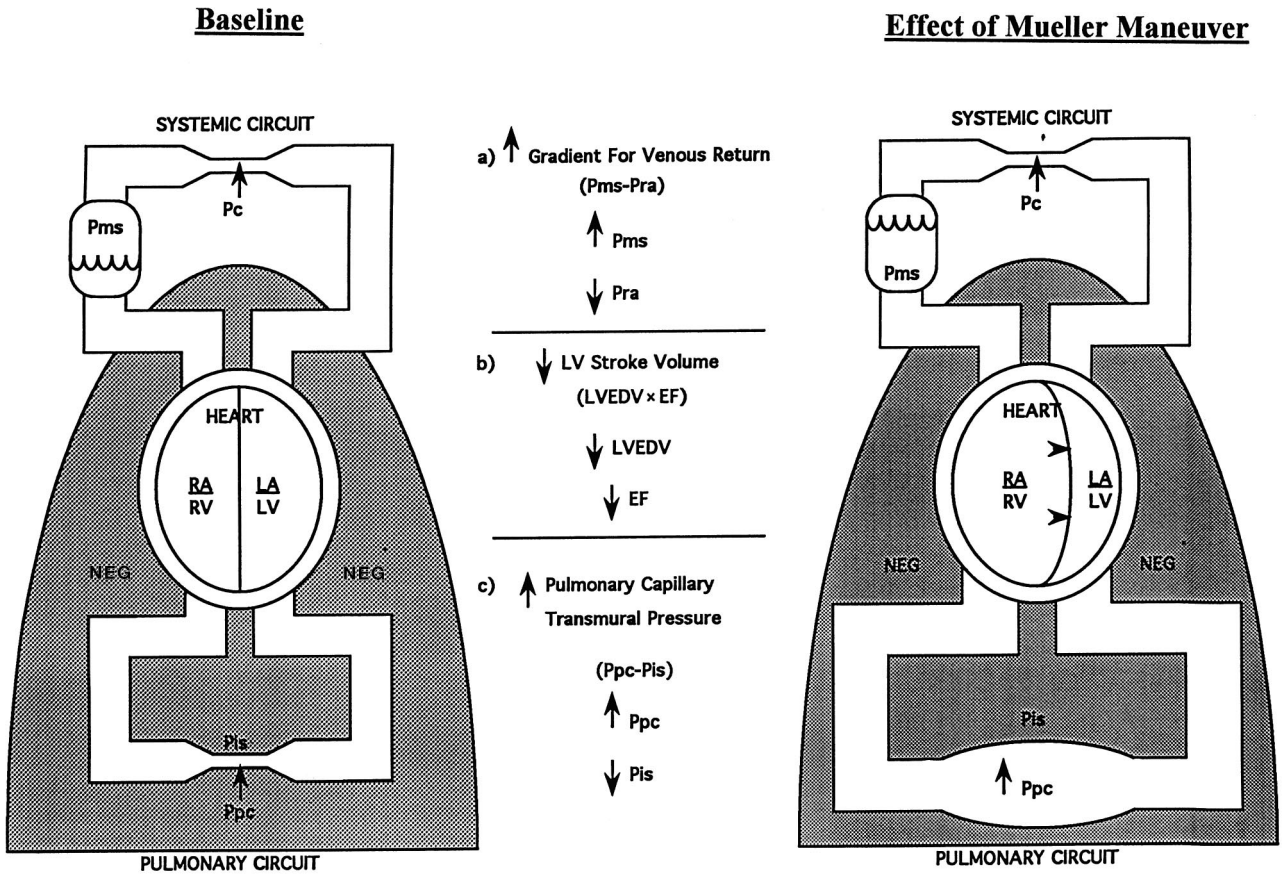

FIGURE 1. A diagrammatic representation of changes in thoracic and vascular pressure during a forced inspiration against a closed glottis (a Mueller maneuver). Circulation is depicted as an intrathoracic pulmonary circuit in series with a systemic circuit lying partly outside of the thorax. The pressure within the thorax (the shaded area marked NEG) is considered the surrounding pressure for all of the intrathoracic vessels and cardiac chambers. The secondary changes relate to catecholamines, hypoxia, and hypercarbia from prolonged obstruction (see text for details). With increased negative ITP comes: (a) an increased systemic capillary pressure (Pc) inflow from the increased upstream pressure (Pms depicted as an elevated venous reservoir) and the decreased downstream pressure (the right atrial pressure [Pra]); (b) a decreased systemic circuit outflow from the increased left ventricular (LV) afterload and the decreased LV preload (the arrowheads depict a septal shift from ventricular interdependence); and (c) an increased Ptm from the increased pulmonary circuit blood volume and tone (the increased Ppc) and the decreased extramural pressure (the pulmonary vascular interstitial pressure [Pis]). EF = ejection fraction; LVEDV = left ventricular end-diastolic volume; RA = right atrial; RV = right ventricular; LA = left atrial; ↑ = increased; ↓ = decreased.

the increased blood volume and the increased pulmonary vascular tone (due to hypoxia and acidosis). During a Mueller maneuver, the Ppi, approximating the change in the alveolar and pleural pressures, becomes quite negative (around −100 cm H_2O),[10] contributing to high capillary transmural pressure. These changes predict the formation of a transudative edema free of RBCs. The development of exudative, high-protein edema, however, has been reported following the relief of acute UAO.[11] In published reports of NPPE,[2,4,5] numerous examples are given of RBC leakage into the edema, including the early description of postobstructive pulmonary edema by Oswalt et al[4] describing "pink, frothy fluid" in all three cases.

Although our patient may have developed NPPE, his presentation and course were consistent with diffuse alveolar hemorrhage. He had blood in his endotracheal tube, a drop in the hematocrit, and a BAL strongly suggestive of alveolar bleeding. The time course of improvement was consistent with alveolar hemorrhage,[12] and the absence of hemosiderin-laden macrophages supported its acuity.[13] Perhaps NPPH is a suitable term for the development of diffuse alveolar hemorrhage following exposure to negative ITP. Although the precise etiology of the bleeding in NPPH is uncertain, the disruption of pulmonary capillaries could play a role.

Increased pulmonary capillary wall stress (defined as Ptm × radius of curvature/wall thickness) can cause the mechanical disruption of the alveolar-capillary membrane with the subsequent impairment of barrier function, a process termed "stress failure."[14] When the alveolar-capillary membrane is viewed under the scanning electron microscope, stress failure is characterized by breaks in the

capillary endothelial and alveolar epithelial barriers and, occasionally, in the basement membrane.[15] In animal models, stress failure occurs at a Ptm of 40 mm Hg (rabbit), 70 mm Hg (dog), and 100 mm Hg (horse).[14,16,17] Ultrastructural evidence of damage to the capillaries exists in both animal models and human cases of high-altitude pulmonary edema[18] and neurogenic pulmonary edema[19], and in exercise-induced pulmonary hemorrhage in thoroughbred racehorses.[17] Additionally, stress failure may contribute to edema and/or hemorrhage in cases of mitral stenosis and pulmonary veno-occlusive disease,[20] and following periods of intense exercise in elite athletes.[21]

In each of the aforementioned cases, a high Ptm is due to an elevated Ppc. However, the stress failure model predicts that the loss of membrane integrity would also occur when decreased Ppi contributes to a high Ptm, as seen in NPPE. The model allows for the development of a spectrum of abnormalities ranging from transudative edema to pulmonary hemorrhage.[22] Although small increases in Ptm result in low-protein edema through alterations in the Starling forces, higher pressures causing ultrastructural changes in the capillary endothelial barrier can lead to exudative edema.[14] Extreme elevations in the Ptm break the alveolar-capillary membrane, allowing RBC leakage into the alveoli and, possibly, frank hemorrhage. Rapid changes in the Ptm, independent of the peak pressure, could favor the development of bleeding, as in exercise-induced pulmonary hemorrhage and postexercise hemoptysis.[20]

Given the relatively high estimated incidence of NPPE following acute airway obstruction, we are surprised that NPPH has not been reported previously. Without further data, we can only surmise the cause of our patient's extreme presentation. In patients with OSA, we speculate that nighttime "inspiratory muscle training" could enable the production of exaggerated negative intrathoracic pressures sufficient to cause hemorrhage. In a study of 10 patients with sleep apnea/obesity-hypoventilation syndrome, intra-alveolar hemorrhage and extensive hemosiderosis were noted that were "disproportionately severe for the morphologic abnormalities present in the left ventricle".[23] Alternatively, the intrinsic weakness of the alveolar-capillary membrane could increase the severity of stress failure for a given rise in the Ptm. The use of crack cocaine induces increased alveolar permeability, and pulmonary hemorrhage and edema have been noted in a histopathologic series of cocaine users.[24] Bleeding following acute UAO has been observed previously, but it was attributed to the rupture of the bronchial vasculature.[11,25] In our patient, the bleeding appeared to originate in the alveoli, indicating that the pulmonary capillaries were the likely source. The dual mechanism for the increased capillary Ptm found in acute UAO would provide ideal conditions for the development of stress failure.

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Propofol-Induced Pancreatitis*

Recurrence of Pancreatitis After Rechallenge

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We report a case of pancreatitis, which occurred while the patient was on a propofol drip and then recurred after resolution following an inadvertent rechallenge with propofol. The initial episode was associated with hypertriglyceridemia, whereas the latter was not. The association between propofol and pancreatitis is definite and may occur independently of significant hypertriglyceridemia.

(CHEST 1999; 115:1198–1199)

Key words: drug-induced pancreatitis; hypertriglyceridemia; propofol

Case Report

A 51-year-old woman with a past medical history of seizure disorder, schizophrenia, and bronchial asthma was admitted to the hospital because of worsening dyspnea from a community-acquired pneumonia. The patient was transferred to the medical ICU, intubated, and mechanically ventilated for acute respiratory failure. A propofol (Diprivan; Zeneca; London, UK) infusion was started, and the dose was titrated to achieve adequate sedation. The patient was on a propofol infusion continuously for 7 days (maximum dose of 200 μg/kg/min), receiving a total dose of 26.5 g over the same period.

On the fourth day of the propofol infusion, serum triglycerides were noted to be elevated at 938 mg/dL. By day 7, the serum triglyceride level peaked at 1,498 mg/dL, accompanied by elevated serum amylase and increasing serum lipase levels (Fig 1). This was associated with a mild elevation in liver transaminases and alkaline phosphatase levels (hepatocellular pattern; Fig 2). The patient also developed epigastric tenderness and abdominal distension; therefore, propofol infusion was stopped (day 7).

That same day, the tracheostomy tube was dislodged due to patient agitation. This culminated in a brief episode of cardiac arrest requiring cardiopulmonary resuscitation. After resuscitation, the patient developed ischemic acute tubular necrosis requiring a brief course of dialytic therapy.

The lipase levels peaked 4 days after the discontinuation of the propofol infusion (622 mg/dL). The workup for pancreatitis included an ultrasound, which demonstrated

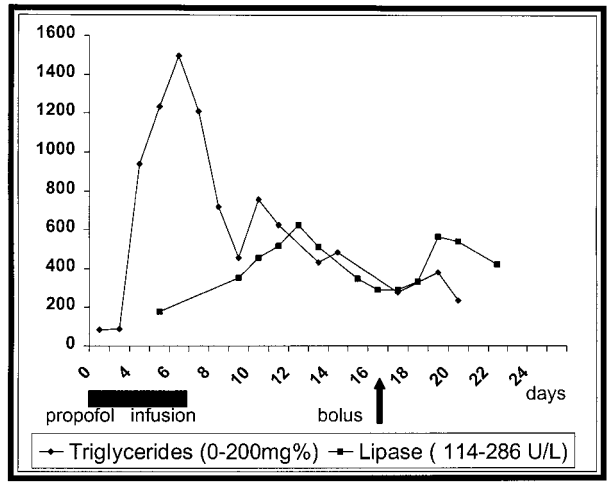

FIGURE 1. Trend of triglyceride and lipase levels in relation to propofol infusion and bolus.

that the patient had a normal liver, small gallstones in a normal gallbladder with no evidence of common bile duct enlargement, and a mildly hyperechoic pancreas. Serum triglycerides gradually subsided over the next 7 days, and pancreatitis responded to supportive therapy. The patient's past medical history was unremarkable for previous cholelithiasis, cholecystitis, pancreatitis, hypertriglyceridemia, and significant alcohol ingestion.

The patient underwent tracheostomy revision on hospital day 17. Postoperatively, the patient developed abdominal pain and elevated lipase levels (peaking at 564 mg/dL), and there was a mild elevation in triglyceride levels (380 mg/dL). On review of the anesthetic record, it was noted that the patient had received a dose of 200 mg of propofol for the procedure. The patient improved

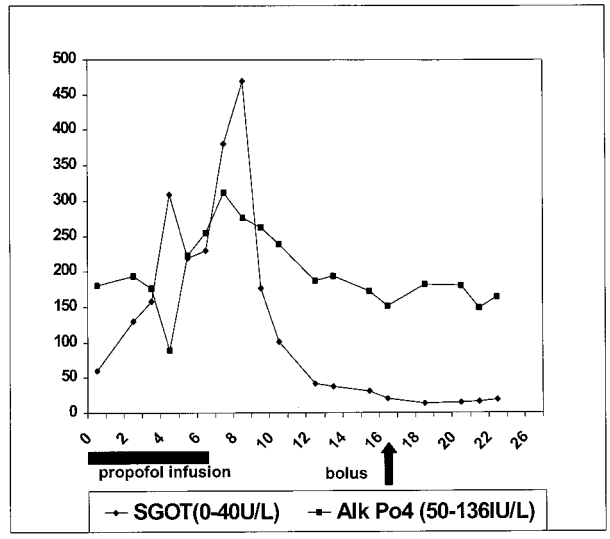

FIGURE 2. Trend of liver enzymes (serum glutamic-oxaloacetic transaminase, $ALKPO_4$) in relation to propofol infusion and bolus.

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clinically, and the biochemical markers of pancreatitis resolved over the next several days. The patient was then transferred to a chronic care facility for weaning from the ventilator. A lipoprotein electrophoresis done prior to the patient's transfer revealed no hyperchylomicronemia.

Discussion

To date there are 25 reported cases of pancreatitis associated with propofol in the federal drug administration registry. The only details available are those about three medical and eight surgical patients described in the literature.[1] Whereas six of these patients had confounding illnesses, the remaining five, all of whom were surgical patients (two with a fatal outcome), previously had been healthy individuals who developed pancreatitis after induction of anesthesia with propofol. The association between propofol and pancreatitis is regarded as probable, but causality remains to be proven.

There are more than 85 drugs reported to cause acute pancreatitis.[2] These drugs could be further classified as those with a definite association (azathioprine, mercaptopurine, estrogen, etc), those with a probable association (L-asparaginase and steroids, among others), and those with a proposed association but with inadequate evidence (amphetamines, opiates, rifampin, etc).[3] In the absence of other risk factors, the occurrence of pancreatitis during treatment with a drug, its resolution on drug withdrawal, and its recurrence on rechallenge with the same drug is sufficient evidence to place a drug under the definite association category.[3] Propofol meets these criteria in our patient in that the temporal profile of events, borderline elevations of alkaline phosphatase, and negative biliary ultrasonsography rule out gallstone pancreatitis despite the cholelithiasis.

The mechanism of drug-induced pancreatitis includes hypersensitivity (to azathioprine or mercaptopurine, among others) or direct toxic injury (from pentamidine or valproate, among others).[2] Estrogen, vitamin A, and fat emulsions in total parenteral nutrition cause pancreatitis indirectly by inducing hypertriglyceridemia.[4] Propofol has been speculated to cause pancreatitis by this mechanism.

Propofol is administered as a fat emulsion, and it has a fat content very similar to 10% fat emulsion in total parenteral nutrition solution (100 mg/mL soybean oil, 22.5 mg/mL glycerol, and 12 mg/mL egg lecithin). It has been shown to increase triglyceride levels when given as a prolonged infusion, usually after 72 h.[5] Serum triglyceride levels of $>$ 1,000 mg/dL are associated with pancreatitis, although there are case reports of pancreatitis at much lower levels of triglycerides. Hypertriglyceridemia leads to an increase in pancreatic lipase in pancreatic capillaries, which leads to lipolysis, ischemia, capillary damage, and microthrombi. The further release of lipase continues the inflammatory cycle.[6] Patients with moderate obesity, diabetes mellitus, alcohol ingestion, Fredrickson's type 4 and 5 lipoproteinemia, and a family history of diabetes or lipoproteinemia are reported to be more susceptible to hypertriglyceride-mediated pancreatitis.[4]

Not all propofol-associated pancreatitis can be explained by hypertriglycerides, especially the cases occurring after a single bolus is used for the induction of anesthesia. The initial bout of pancreatitis in our patient was associated with significant hypertriglyceridemia, but the pancreatitis on rechallenge with propofol was not. It has been shown by Cameron et al [4,6] that patients recovering from pancreatitis have a persistent defect in lipid metabolism for up to 6 months, and recurrence of pancreatitis can occur if patients are given a small fat load during recovery. This mechanism does not explain the recurrence of pancreatitis in our patient because there was only a small increase in serum triglyceride levels (380 mg/dL) on rechallenge with propofol. We postulate that there may be more than one mechanism for propofol-induced pancreatitis. This implies that monitoring triglyceride levels with propofol use is not a guarantee against the occurrence of pancreatitis in these patients. This is congruent with the observation that pancreatitis may occur without associated hypertriglyceridemia after a single bolus dose of propofol is used in healthy surgical patients.

Based on this experience and prior literature, we suggest that propofol should be included in the list of drugs with definite causal association with pancreatitis. We also propose that it could cause pancreatitis by a mechanism other than hypertriglyceridemia.

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Recurrent Pulmonary Embolism Associated With Klippel-Trenaunay-Weber Syndrome*

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Klippel-Trenaunay-Weber syndrome (KTWS) is a rare, congenital disorder characterized by the triad of varicose veins, cutaneous hemangiomas, and hypertrophy of soft tissue and bone. We present the case of a woman with KTWS, cor pulmonale, and death due to recurrent pulmonary embolism (PE).

The risk of deep venous thrombosis and PE in patients with KTWS is evaluated, and treatment recommendations are made with emphasis on the role of early, aggressive management in the subset of patients with KTWS known to have thromboembolic disease. ***(CHEST 1999; 115:1199–1201)***

Key words: Klippel-Trenaunay-Weber syndrome; pulmonary embolism; deep venous thrombosis

Abbreviations: DVT = deep venous thrombosis; INR = international normalized ratio; KTWS = Klippel-Trenaunay-Weber syndrome; PE = pulmonary embolism

Klippel and Trenaunay first described the syndrome of varicose veins, cutaneous hemangiomas, and hypertrophy of soft tissue and bones in 1900.[1] To date, there are less than 1,000 reported cases of Klippel-Trenaunay-Weber syndrome (KTWS). We report our experience with a woman with KTWS who had recurrent pulmonary embolism (PE) leading to her death. This case report will help increase recognition of the clinical manifestations of KTWS and suggests a more aggressive approach to associated thromboembolic disease.

Case Report

A 48-year-old woman with KTWS was referred to a university hospital with a history of increasing shortness of breath over 2 months, jugular venous distention, and lower extremity edema. On examination, she had a BP of 110/80 mm Hg, a pulse of 108 beats/min, and a respiratory rate of 20 breaths/min. Her lungs were clear to auscultation. Cardiac examination revealed widely split second heart sounds and a prominent pulmonic valve closure. The lower extremities were both edematous, the right more affected than the left, with palpable cords and varicosities covering the entire extremity. Multiple areas of grouped hemangiomas were seen on the posterior hand, dorsal right foot, upper mid back, and the right labia majora. The remainder of the examination was normal. Initial evaluation included a chest CT scan revealing pulmonary artery enlargement (Fig 1), a ventilation-perfusion scan that revealed multiple unmatched perfusion defects, and an echocardiogram. The echocardiogram was significant for right atrial enlargement (58 mm), a fractional shortening of 37%, 3+ tricuspid valve regurgitation, 2+ pulmonic valve regurgitation, and a dilated inferior vena cava without collapse. Right ventricular peak pressure was estimated by echocardiogram to be 64 mm Hg. A Doppler ultrasound of the lower extremities was normal except for multiple varicosities in the distal right lower extremity. The patient refused further evaluation. A presumptive diagnosis of recurrent PE with secondary pulmonary hypertension prompted initiation of heparin. She was started on warfarin and a diuretic and discharged from the hospital. After an initial adjustment period, her international normalized ratio (INR) remained between 2.2 and 3.9 on periodic outpatient visits.

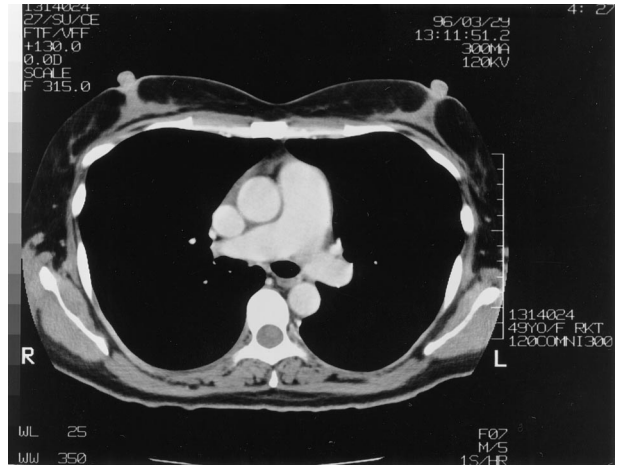

FIGURE 1. CT scan of the chest showing pulmonary artery enlargement.

Ten months after her initial hospitalization, she was readmitted for decompensated right heart failure. Her INR at admission was 2.31. A repeat ventilation-perfusion scan showed new perfusion defects in the anterior and posterior segments of the right upper lobe. Heparin was administered and warfarin was continued. A pulmonary angiogram demonstrated distal pruning of the pulmonary arterioles bilaterally and a pulmonary artery pressure of 94/42 mm Hg. Because the patient had new PEs adequate anticoagulation, an inferior vena cava filter was placed. She was maintained on warfarin and her INR ranged between 2.3 and 4.1.

On the eighth hospital day the patient became acutely dyspneic. She was cyanotic and hypotensive with a systolic BP of 78 mm Hg. A blood gas revealed a pH of 7.09, a $Paco_2$ of 51 mm Hg, and a Pao_2 of 24 mm Hg. The patient was transferred emergently to the ICU where she remained hypoxemic and hypotensive despite ventilatory support, pressor agents, and thrombolytics, and she subsequently died.

Results of Autopsy

The pathologic cause of death was cor pulmonale secondary to PE. Internal examination revealed right ventricular hypertrophy of the heart and congested lungs. Microscopically, a thickened pulmonary interstitium was noted, with areas of alveolar hemorrhage, edema, and hemosiderin-laden macrophages. The pulmonary arterioles showed hypertrophied muscular layers with numerous thrombi of different ages, ranging from recent to remote with complete organization of some vessels. Trichrome stains of the lung confirmed the presence of recanalization and the absence of plexiform lesions (Fig 2).

Discussion

The etiology of KTWS is unknown. Manifestations of the syndrome begin at birth or shortly after, with most patients displaying cutaneous hemangiomas of the port-wine type. As children begin to walk, varicosities become more obvious. The varicosities tend to be located along the lateral aspect of a lower limb and medially at the groin.[1] Chronic venous insufficiency develops in the second and third decades with associated venous stasis ulcers, recur-

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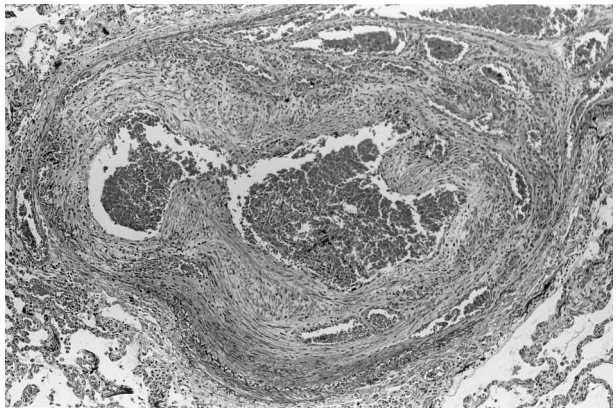

FIGURE 2. Transverse section of a muscular pulmonary artery. There is a thick muscular wall, organized thrombotic material, intimal fibrosis, and recanalization of the artery. There was no evidence of plexiform lesions. All vessels showed evidence of thromboembolic vasculopathy (elastic trichrome, original magnification ×250).

rent thrombophlebitis, and cellulitis. Limb and soft tissue hypertrophy usually manifests several years later and involves a single lower extremity. Rarely, one entire side of the body is involved producing hemihypertrophy.

The pulmonary abnormalities associated with this syndrome include pulmonary vein varicosities,[2] pulmonary lymphatic obstruction,[3] cavernous hemangiomas of the pleura leading to hemothorax,[1] and thromboembolic phenomena.[4–6] Pulmonary varicose veins are apparently rare as judged by the small number of reported cases.[3] Smooth muscle hyperplasia leads to plexiform lymphatic lesions and ultimately obstruction.

Thromboembolic events are relatively common among patients with KTWS. Baskerville et al[7] reported a 17% incidence of radiographically demonstrated deep venous thrombosis (DVT) in a series of 49 patients with KTWS seen at one institution. In comparison, the incidence of autopsy-proven DVT in nonhospitalized patients is estimated to be 5%.[8] In the same study by Baskerville et al, there was a 10-fold increase in the incidence of postoperative thromboembolism in patients with KTWS compared with other surgical patients.

The most acceptable explanation for a higher incidence of DVT in this patient population has been the abnormalities in the venous system. However, Baskerville and colleagues, using plethysmography, could not differentiate the venous anatomic abnormalities of patients with KTWS with DVT or PE from those patients without DVT or PE.[6] The same study did demonstrate that fibrinopeptide A was markedly elevated and thrombin activity was abnormal in KTWS patients with thromboembolic disease, suggesting a procoagulant state as an etiology for the high incidence of DVT. This study, however, was uncontrolled and retrospective.

We have noticed that, despite a higher incidence of DVT in patients with KTWS, PE appears to be a seldom-recognized complication of this syndrome. In an extensively studied small group of patients with KTWS, Baskerville and associates[7] estimated the incidence of PE in patients with KTWS to be 14% to 22%. Although approximately 1,000 cases of KTWS have been reported to date, only 10 cases of PE in patients with KTWS have been published.[4–7,9] Of the 10 reported cases, PE was recurrent in three patients, leading to pulmonary hypertension and subsequent death.[4,5] One of the patients was similar to our own, experiencing recurrent DVT and PE despite adequate anticoagulation.[5]

For lack of large experience there are no established treatment regimens for thromboembolic phenomena in patients with KTWS. It appears reasonable, based on the significant incidence of venous thromboembolism in this patient population, to recommend avoidance of estrogen use and provision of aggressive DVT prophylaxis in patients undergoing surgical procedures. Based on the poor outcome of our patient and four others described in the literature,[4,5,9] we suggest aggressive treatment of thromboembolic disease, including anticoagulation with warfarin to a goal INR between 3 and 4, and early placement of an inferior vena caval filter. We recommend venographic evaluation of the pelvic and abdominal venous anatomy in order to assess for significant collateral venous circulation, which may warrant suprarenal filter placement. For this reason, currently accepted noninvasive studies used in the evaluation of patients with suspected DVT are probably inadequate in this patient group.

In summary, KTWS is a rare cause of DVT and PE and should be considered when the characteristic historical and physical findings are present. Awareness of this syndrome and knowledge of its clinical implications are important for appropriate management.

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Heart Transplantation After Successful Donor Postpartum Pulmonary Embolectomy*

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A fulminant pulmonary embolism can be treated surgically if thrombolytic therapy is contraindicated. A 31-year-old woman developed a fulminant pulmonary embolism after right-sided deep venous thrombosis 1 day after undergoing a cesarean section. A pulmonary embolectomy with cardiopulmonary bypass was performed, but the patient was brain-dead. After 2 days of echocardiographic observation, her heart was explanted for a 61-year-old man with ischemic cardiomyopathy. His right heart data were unremarkable, and he remains well 16 months after transplantation. Despite the sudden strain on the right ventricle that occurs with a pulmonary embolism, such a heart may be transplanted successfully after a pulmonary embolectomy. ***(CHEST 1999; 115:1202–1203)***

Key words: donor pool; heart transplantation; organ donor; pulmonary embolectomy; pulmonary embolism

Abbreviations: PVR = pulmonary vascular resistance

With increasing numbers of patients awaiting heart transplantation, donor selection criteria have become more and more liberalized in an attempt to prevent a further widening of the gap between donors and transplant candidates. The accepted "marginal donor" criteria include an age > 40 years, high-dose inotropes, undersizing by > 20% of body weight, significantly impaired wall motion by echocardiography, and longer ischemic times.[1]

Although brain death following prolonged cardiopulmonary resuscitation and a pulmonary embolectomy is a cause of death in 4%[2] to 33%[3] of the cases studied, the hearts from these patients have not been used for cardiac transplantation. Certain contraindications to thrombolysis, such as pregnancy, early perioperative phase, and cardiopulmonary resuscitation, leave a pulmonary embolectomy with cardiopulmonary bypass as the last resort to save the patient.[4] Blondel et al[5] estimated that a pulmonary embolism causes complications for 0.5 of 1,000 pregnancies before delivery, and he described a postpartum pulmonary embolectomy using cardiopulmonary bypass.

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Case Report

A 31-year-old woman developed a massive pulmonary embolism after right-sided deep venous thrombosis 1 day after undergoing a cesarean section and was resuscitated immediately. She was taken to the operating room under continuous cardiopulmonary resuscitation, and a pulmonary embolectomy on cardiopulmonary bypass was performed. Her postoperative blood gases included a Pa_{O_2} of 154 mm Hg, a Pa_{CO_2} of 34 mm Hg, and an oxygen saturation of 98% on 50% oxygen with 10 synchronized intermittent mandatory ventilations/min. A right heart catheterization revealed a right atrial pressure of 12 mm Hg and a mean pulmonary arterial pressure of 33 mm Hg. Over the next 12 h, the appropriate diagnostic tests revealed that the patient was brain-dead. After informed consent was obtained, her heart, liver, and kidneys were explanted. At the time of explantation, the patient had been hemodynamically stable for 2 days with 3 μg/kg/min dopamine and 0.5 μg/min norepinephrine. Her postoperative cardiac function had been assessed by daily echocardiography that showed a continuous reduction of right ventricular dilation and hypokinesis. The heart recipient, a bedridden 61-year-old man with ischemic cardiomyopathy, had coronary artery bypass graft surgery 13 years previously and had been on inotropes for 3 weeks before transplantation. His preoperative pulmonary vascular resistance (PVR) was 2.2 Wood units. The heart was transplanted with bicaval anastomoses, and the patient was weaned from cardiopulmonary bypass with 2 μg/min epinephrine, 3 μg/kg/min dopamine, 3 μg/kg/min dobutamine, and 2 mg/h nitroglycerine. A Swan-Ganz catheter was inserted, and pressure recordings showed an arterial pressure of 147/69 mm Hg (mean, 88 mm Hg), a pulmonary pressure of 40/23 mm Hg (mean, 31 mm Hg; wedge, 18 mm Hg), and a cardiac index of 2.8 L/min/m^2. The PVR was 2.5 Wood units. Pulmonary pressures were monitored for 7 days (Table 1). Post-transplant echocardiographic studies on postoperative day 2 showed good right ventricular contractility and second-degree tricuspid insufficiency that gradually improved over the following days. The patient required prolonged respiratory support for 10 days because of muscular weakness, and venovenous hemofiltration was used for 2 weeks. He was discharged 6 weeks after transplantation. Sixteen months after transplantation, he continues to be well and has no sign of right heart insufficiency.

Discussion

A fulminant pulmonary embolism resulting in acute right ventricular failure is associated with extremely high rates of mortality. The overall surgical mortality rates range between 6%[6] and 30%[7], and increase to 60% in cases of preoperative cardiopulmonary resuscitation. Preoperative cardiac arrest is an independent risk factor of operative death.[4] In the reported case, three contraindications to thrombolytic therapy were present: the patient had just finished her pregnancy, she had undergone a cesarean section the day before, and she had been resuscitated. Therefore, a pulmonary embolectomy with cardiopulmonary bypass became the last remedy. We learned, quite expectedly, that most of the patients who succumbed to brain death despite a successful embolectomy either had been resuscitated preoperatively or had been operated on under continuous cardiac massage. The use of a heart from a brain-dead patient after a successful pulmonary embolectomy needs careful consideration. The reduction of the pulmonary vascular bed by a massive pulmonary embolism increases right ventricular afterload, leading to consecutive right ventricular dilation and hypokinesis. Right ventricular and pulmonary artery pressures rise. The acute increase in right ventricular pressure shifts the interventric-

Table 1—*Right Heart Pressure Recordings and Drug Therapy

Pulmonary Pressure and Therapy	POD						
	1	2	3	4	5	6	7
Pressures							
RAP, mm Hg	13	13	10	13	12	7	10
PAS, mm Hg	31	37	34	39	33	28	45
PAM, mm Hg	22	24	22	27	23	17	26
PAD, mm Hg	15	16	17	21	17	11	16
PCWP, mm Hg	11	15	15	13	15	12	20
CO, L/min	6	5.3	4.9	5.5	5.5	5.3	7
PVR, WU	1.8	1.7	1.4	2.6	1.5	0.94	0.86
Drugs							
Epinephrine, μg/min	3	3	5	12	–	2	2
Dobutamine, μg/kg/min	5	5	5	–	–	–	–
Dopamine, μg/kg/min	3	3	4	3	3	3	3
Nitroglycerine, mg/h	2	2	–	2	2	2	2
PGE1, ng/kg/min	–	–	–	30	–	–	–

*POD = postoperative day; RAP = right atrial pressure; PAS = pulmonary arterial systolic; PAM = pulmonary arterial mean; PAD = pulmonary arterial diastolic; PCWP = pulmonary capillary wedge pressure; CO = cardiac output; PVR = pulmonary vascular resistance; PGE1 = prostaglandin E1; WU = Wood units.

ular septum toward the left, decreasing left ventricular diastolic filling.[8] Right heart failure is the most frequent cause of death, and this needs to be considered when evaluating such hearts for transplantation. However, a pulmonary embolectomy leads to an early reduction in the size of the pulmonary artery, the right ventricle, and the atrium, with consecutive normalization of the interventricular septal position. This implies that some changes in cardiac geometry may be reversible soon after a marked afterload reduction. Despite somewhat elevated pulmonary pressures, this donor remained absolutely stable after a pulmonary embolectomy with low-dose inotropic support. Daily postoperative echocardiographic exams had shown continuously decreasing right ventricular hypokinesis and dilation. After 2 days of hemodynamic stability, we assumed that the right ventricle would adapt to the remaining afterload increase, as evidenced by the elevated pulmonary arterial pressures. The outcome of the recipient proved our assumption to be correct.

Faced with an increasing demand for donor organs from a growing number of transplantation candidates, cardiac surgeons have extended their acceptance criteria for marginal donors by accepting longer ischemic times, older donors, and hearts after cardiopulmonary resuscitation.[1] To date, hearts from brain-dead patients after a successful pulmonary embolectomy with cardiopulmonary bypass have not been transplanted. We believe that these hearts should be considered for cardiac transplantation after several days of observation. The observation period allows for an assessment of the donor's hemodynamics and an evaluation of right ventricular function with echocardiographic exams before the organ is procured. However, the recipient should not have an extremely elevated PVR because the transplanted heart has sustained an injury to the right ventricle. Such hearts should be evaluated carefully because they may help to alleviate the chronic organ shortage.

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Severe Intrapulmonary Shunting Associated With Metastatic Carcinoid*

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A 37-year-old woman with a 10-year history of metastatic carcinoid presented to her oncologist with increased dyspnea. Further evaluation revealed hy-

poxemia and intrapulmonary vasodilatation. We describe a case of hepatopulmonary-like physiology associated with metastatic carcinoid in a patient with intact liver function. To our knowledge, this is the first documented case of intrapulmonary shunting and hepatopulmonary-like physiology associated with metastatic carcinoid.

(CHEST 1999; 115:1203–1207)

Key words: carcinoid syndrome; hepatopulmonary syndrome; hypoxemia

Abbreviations: DLCO = diffusing capacity of the lung for carbon monoxide; HPS = hepatopulmonary syndrome

The carcinoid syndrome is most often seen in patients with GI carcinoid tumors metastatic to the liver, and these tumors produce a variety of vasoactive substances. The release of these substances often results in flushing and diarrhea, characteristic of the carcinoid syndrome. High concentrations of mediators from the hepatic carcinoid traverse the tricuspid and pulmonic valves commonly causing right-sided valvular lesions. Subsequent metabolism of these mediators in the lung tends to protect the left-sided heart valves from carcinoid-related disease.

The hepatopulmonary syndrome (HPS) is defined as liver dysfunction, hypoxemia, and intrapulmonary vascular dilatations. The mechanism is believed to be an imbalance of vasodilators and vasoconstrictors resulting from metabolic liver insufficiency. Reduced diffusing capacity of the lung for carbon monoxide (DLCO) and orthodeoxia are also typical features of HPS.

We describe a case of severe intrapulmonary shunting with hepatopulmonary-like physiology associated with metastatic carcinoid. Despite the hepatic tumor involvement, this patient had otherwise normal liver function.

Case Report

A 37-year-old woman with known metastatic carcinoid tumor (Fig 1) was admitted to the hospital with a complaint of increasing dyspnea. Her carcinoid was diagnosed 10 years earlier. At that time, she had known liver metastasis and symptoms of the carcinoid syndrome manifested by profound flushing, diarrhea, and bronchospasm. The primary site of her tumor has never been identified, but was presumed to have originated in the GI tract. Her carcinoid was treated with somatostatin for 4 years prior to hospital admission with good control of her symptoms. Three years prior to hospital admission, she was diagnosed as having carcinoid heart disease manifested by tricuspid stenosis and tricuspid insufficiency.

Her symptom of dyspnea gradually increased over the past 5 years. At the time of hospital admission, she experienced dyspnea on exertion and intermittently at rest. She experienced increased dyspnea with rapid changes in position, both assuming a supine and upright posture. She quit smoking cigarettes 5 years prior to hospital admission but had a 20-pack-year history.

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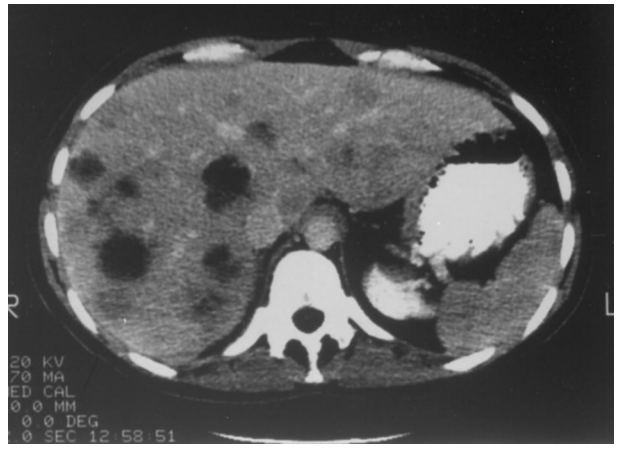

FIGURE 1. Metastatic carcinoid tumor in a 37-year-old woman.

Initial physical examination showed a BP of 123/73 mm Hg, pulse rate of 98 beats/min, respirations of 19 breaths/min, temperature of 36.8°C, and pulse oximetry on room air of 80%. Her physical examination was notable for large facial and upper chest telangiectasias with violacious nonblanching discoloration. A 2/6 systolic and 1/6 diastolic cardiac murmur was auscultated. She had no evidence of right heart failure or ascites. Results of hepatitis A, B, and C serologic tests were all normal. Initial liver-associated enzymes revealed an alkaline phosphatase level of 75 U/L, aspartate transaminase of 12 U/L, alanine transaminase of 9 U/L, lactate dehydrogenase of 141 U/L, and γ-glutamyl transferase of 17 U/L—all within normal limits. Hepatic functional capacity was normal, as manifested by an albumin of 3.5 g/dL, a total bilirubin of 0.3 mg/dL, a prothrombin time of 13.1 s, and a partial thromboplastin time of 25.2 s. Arterial blood gas on room air revealed a pH of 7.44, P_{CO_2} of 30 mm Hg, and P_{O_2} of 46 mm Hg. Arterial blood gas on 100% fraction of inspired oxygen showed a pH of 7.57, P_{CO_2} of 19 mm Hg, and P_{O_2} of 71 mm Hg with an estimated shunt fraction of 31%. Pulmonary function testing showed FVC of 3.11 L (92% predicted), FEV_1 of 1.99 L (75% predicted), FEV_1/FVC of 64%, and DLCO of 62% predicted. Echocardiogram revealed tricuspid stenosis with severe tricuspid regurgitation and mild aortic insufficiency. Bubble contrast echocardiogram showed delayed microbubble opacification of the left atrium consistent with intrapulmonary vasodilatation (Fig 2). Pulmonary angiogram revealed dilated pulmonary capillary beds (Fig 3).

Discussion

This patient, with long-standing carcinoid syndrome, presented with profound hypoxemia, positional dyspnea, and severe intrapulmonary shunting. Her evaluation revealed pulmonary vascular abnormalities remarkably similar to that of the hepatopulmonary syndrome. Despite the similarity with HPS, she had no evidence of synthetic or metabolic liver dysfunction and no ascites or evidence of portal hypertension. We believe the metastatic carcinoid caused her gas exchange abnormality by releasing a variety of humoral mediators into her central venous system. These mediators clearly exerted a vasodilatary effect as manifested by her symptom of profound flushing.

The HPS is defined as liver dysfunction, hypoxemia,

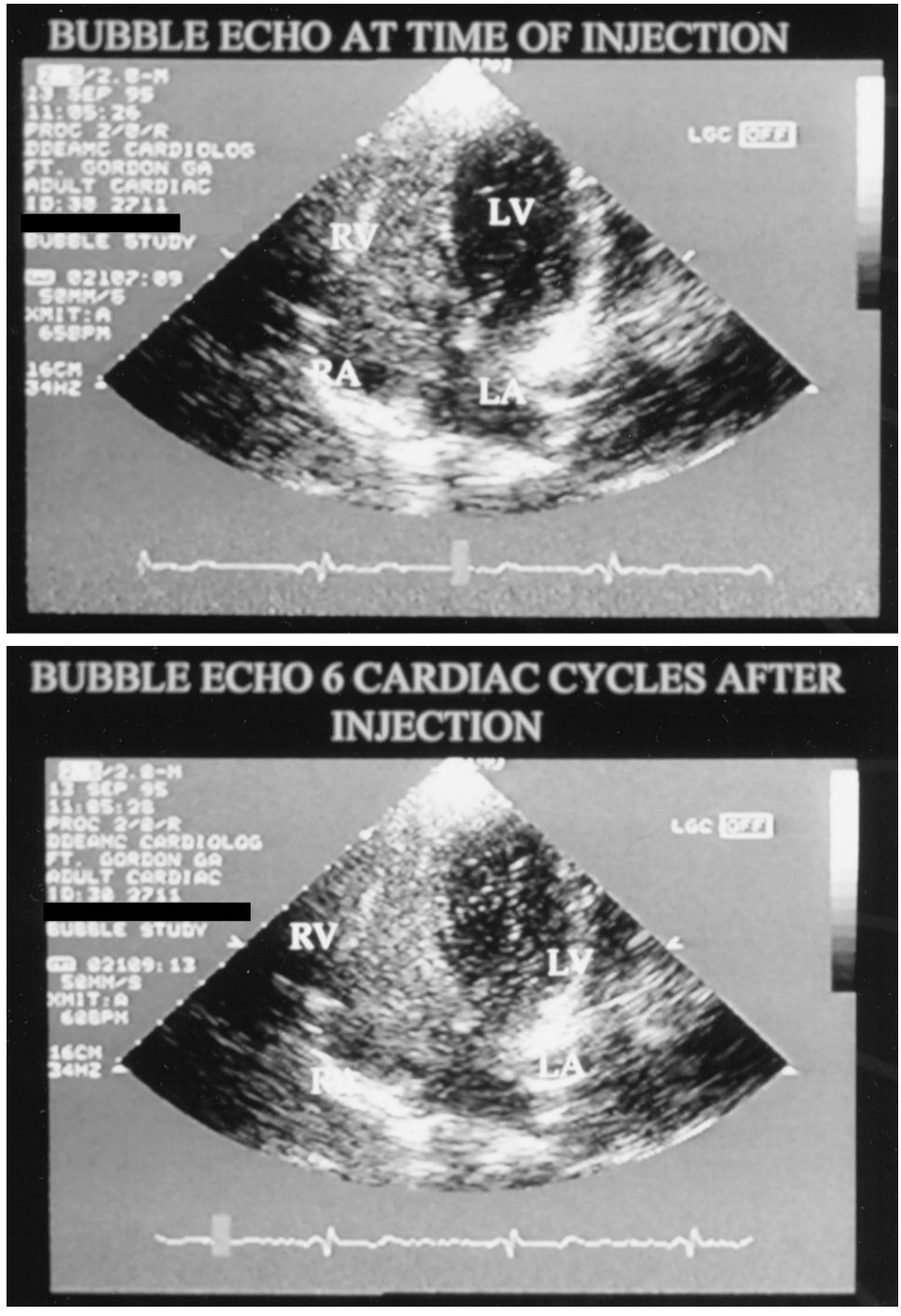

FIGURE 2. Bubble contrast echocardiogram showed delayed microbubble opacification of the left ventricle consistent with intrapulmonary vasodilatation.

and intrapulmonary vascular dilatations. Reduced DLCO and orthodeoxia are also common findings in HPS.[1] All reported cases of HPS are associated with gross evidence of hepatic dysfunction.[1–4] The pathophysiology of HPS is believed to result from metabolic liver insufficiency causing an imbalance of vasodilators and vasoconstrictors. This imbalance is thought to cause dilation of the pulmonary vasculature, resulting in ventilation/perfusion mismatch and shunting.[5] The pulmonary vascular abnormalities can be imaged by contrast-enhanced two-dimensional transthoracic echocardiography[4,6] or by pulmonary angiograms that show diffuse, small "spider-like" branches.[5] This patient's contrast-enhanced echocardiogram, pulmonary angiogram, and pulmonary hemodynamic profile are all consistent with those seen in the HPS.

Carcinoid is found anywhere in the body, but > 95% of

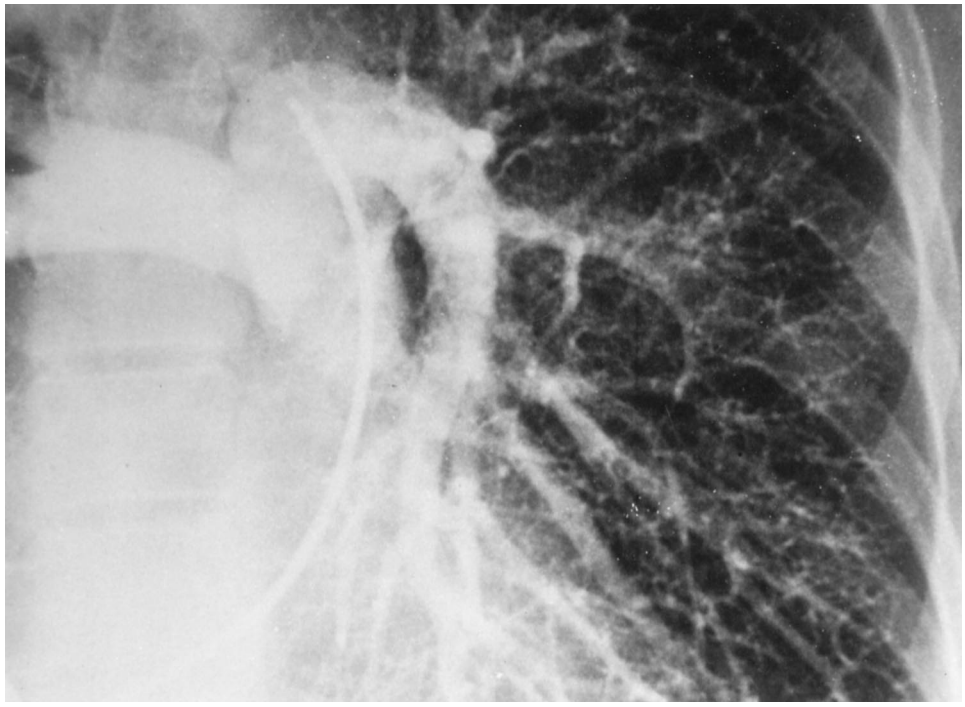

FIGURE 3. Pulmonary angiogram revealed dilated pulmonary capillary beds.

these tumors arise in the appendix, rectum, or small bowel. The carcinoid syndrome is a common manifestation of GI carcinoid that has metastasized to the liver and is less frequently seen when the carcinoid tumor arises from other organs.[7] The carcinoid syndrome includes flushing, diarrhea, valvular heart disease, bronchospasm, telangiectasias, and paroxysmal hypotension.[1] The median survival with malignant carcinoid syndrome is 38 months from the time of the first flush. This decreases to 14 months if the 5-hydroxyindoleacetic acid is >150 mg/24 h, and to only 11 months with clinical evidence of carcinoid heart disease.[7] This woman has survived 10 years with known carcinoid syndrome and 3 years with known carcinoid heart disease. The fact that she outlived the typical life expectancy given the extent and duration of her disease may contribute to her unusual pulmonary pathophysiology.

Two case reports of carcinoid syndrome with hypoxemia were described in the literature.[8,9] One had indications of liver dysfunction, and no angiographic proof of intrapulmonary dilation. The other patient showed liver dysfunction and pulmonary hypertension. In both of these patients, documented liver dysfunction potentially produced mediators contributing to their hypoxemia. Our case describes a patient without any evidence to impugn metabolic liver dysfunction in the etiology of her hypoxemia. In addition, all other causes of hypoxemia were excluded. The only remaining possibility is that the carcinoid-related mediators resulted in pulmonary vascular dilation. This certainly seems plausible given the marked systemic vascular dilation caused by these vasoactive mediators.

In summary, we postulate that the excess vasoactive mediators produced by the carcinoid tumor resulted in pulmonary vascular dilation. Once the pulmonary vasculature is dilated, the subsequent hypoxemia, reduced DLCO, and orthodeoxia occur by pathophysiology similar to HPS. Unlike the proposed mechanism of HPS, our patient did not demonstrate clinical or biochemical liver insufficiency. The similarity of this patient's physiology to HPS lends credence to the hypothesis of an imbalance of vasoactive substances in the pathogenesis of HPS. To our knowledge, this is the first case that clearly documents HPS pathophysiology in a patient with metastatic carcinoid.

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Pulmonary Intravascular Lymphomatosis*

Presentation with Dyspnea and Air Trapping

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Intravascular lymphomatosis (IVL) is a rare lymphoid neoplasm that is typically of B-cell lineage and characterized by proliferation of malignant cells within small arterioles, capillaries, and venules. We report a patient with pulmonary IVL who presented clinically with progressive dyspnea, fever, and a dry cough. Pulmonary function tests revealed a marked decrease in diffusion capacity with airflow obstruction and severe air trapping. High-resolution CT (HRCT) of the chest with inspiratory and expiratory images revealed mosaic attenuation consistent with air trapping. Transbronchial biopsies revealed the diagnosis of IVL with capillary expansion in the alveolar and peribronchiolar interstitial tissue. IVL should be considered in the differential diagnosis of a patient with an interstitial lung disease, air trapping on pulmonary function tests, and mosaic attenuation on HRCT. Transbronchial biopsies may be the initial diagnostic procedure of choice. ***(CHEST 1999; 115:1207–1210)***

Key words: air trapping; high-resolution CT; intravascular lymphomatosis; mosaic perfusion

Abbreviations: HRCT = high-resolution CT; HU = Hounsfield units; IVL = intravascular lymphomatosis; LDH = lactate dehydrogenase

Intravascular lymphomatosis (IVL) is a rare lymphoma that usually originates from B-cells and has a predilection for the lumen of small blood vessels. Clinical symptoms occur when the malignant cells proliferate within the vasculature and eventually compromise blood flow. Typical sites of involvement with lymphoma such as the lymph nodes, bone marrow, and solid organs are usually spared in IVL. The syndrome was first described in 1959,[1] and dermatologic and neurologic symptoms dominate the clinical presentations of the case reports and series that have been reported to date.[2–5] There have, however, been case reports that describe a predominant involvement of the lungs.[5–10] In these cases, the diagnosis is frequently difficult to make antemortem because the clinical and radiographic findings are often nonspecific. This report describes the first case, to our knowledge, of IVL that presented with evidence of air trapping on pulmonary function tests and a mosaic attenuation pattern on high-resolution CT (HRCT) of the chest.

Case Report

A 63-year-old man who had quit smoking 30 years previously, presented with a 3-month history of progressive dyspnea on exertion, 1-month history of a dry nonproductive cough, intermittent-fevers as high as 40°C, night sweats, and an 8.6-kg (19-lb) weight loss from his baseline of 80 kg. Dyspnea progressed to the point of breathlessness after 100 yards of ambulation. Two courses of oral antibiotics for presumed bronchitis did not improve his symptoms. There was no prior history of lung disease or occupational dust exposure. Physical examination revealed faint bibasilar crackles but no adenopathy, skin changes, peripheral edema, dementia, or focal neurologic deficit.

Laboratory findings included normal electrolytes and renal function with a creatinine of 1.0 mg/dL, BUN of 15 mg/dL, and an unremarkable urinalysis. The CBC revealed a hemoglobin of 12.0 g/dL, hematocrit of 34.8%, and a WBC count of 5,100. The erythrocyte sedimentation rate was 102 mm/h. The serum lactate dehydrogenase (LDH) was 1,825 U/L (normal, 105 to 233 U/L) associated with an elevated aspartate transaminase of 124 U/L (normal, 0 to 37 U/L). The total bilirubin, alanine transaminase, and haptoglobin were normal. The evaluation for rheumatic disease was unremarkable, including negative results for rheumatoid factor, antinuclear antibodies, and C- and P-antineutrophil cytoplasmic antibodies. The purified protein derivative with the anergy panel revealed the patient to be anergic. A bone marrow biopsy and aspiration did not reveal any malignancy or diagnostic abnormality. Pulmonary function tests were performed, revealing an FVC of 2.96 L (75% predicted), an FEV_1 of 1.81 L (60% predicted), and an FEV_1/FVC ratio of 61%, which are consistent with moderately severe airflow obstruction. Total lung capacity was 9.22 L (148% predicted) with a residual volume of 6.42 L (280% predicted). The diffusion capacity was 5.35 mL/min/mm Hg (20% predicted).

The initial chest radiograph revealed mild hyperinflation with linear opacities in the medial lung bases bilaterally. On the lateral view, the left hemidiaphragm was silhouetted in the posterior sulcus with a patchy opacity. A chest CT was ordered to further characterize the infiltrate, and it showed the left lower lobe area to contain a linear

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stranding density. A patchy bilateral mosaic pattern was observed, and the hila and mediastinum contained no significant adenopathy. An abdominal and pelvic CT revealed only splenomegaly with a craniocaudal dimension of 15 cm and several subcentimeter hypodensities within the spleen. All other organs appeared normal, and no retroperitoneal, pelvic, or inguinal adenopathy was noted.

An HRCT was obtained to evaluate the mosaic attenuation seen on conventional CT. The initial inspiratory HRCT revealed heterogeneous lung opacity in a patchy or mosaic distribution (Fig 1, *top*, *A*). This mosaic attenuation or "mosaic perfusion"[11] pattern was thought to be secondary to air trapping. This was confirmed by the expiratory HRCT (Fig 1, *bottom*, *B*). The lobular area of air trapping (black arrow) in the left lower lobe underwent a postexpiratory increase in lung attenuation of 40 Hounsfield units (HU). In contrast, the normal appearing lung immediately adjacent to the area of air trapping increased in attenuation by 155 HU. The CT scan also revealed several small pulmonary nodules.

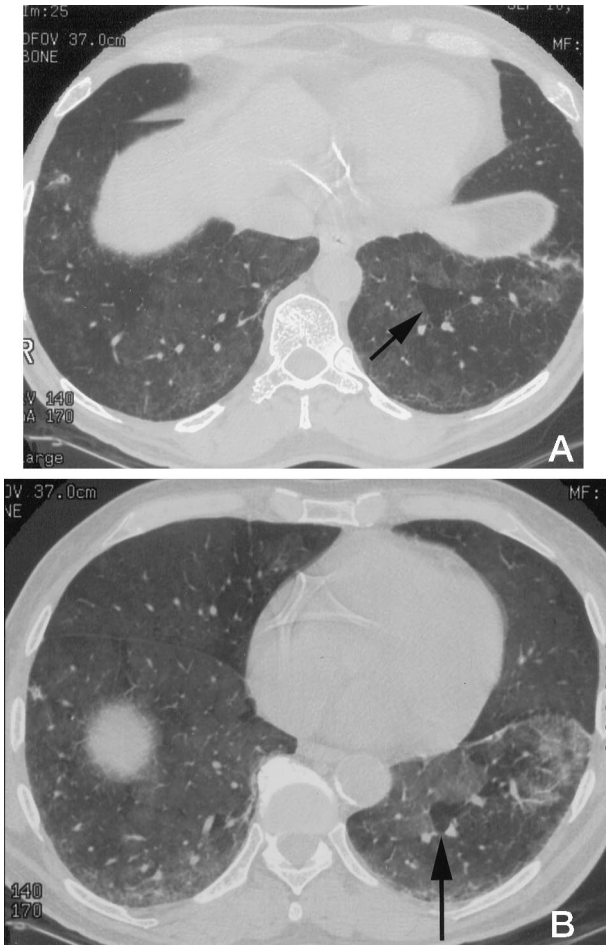

FIGURE 1. *Top*, *A*: Inspiratory HRCT reveals mosaic attenuation at the lung bases. A lobular area of decreased attenuation in the left lower lobe is demarcated (black arrow). *Bottom*, *B*: Expiratory HRCT performed at approximately the same level as the above image. The lobular area of decreased attenuation in the left lower lobe remains lucent on expiration (black arrow). This confirms air trapping. Multiple other areas of air trapping are also present.

When the patient presented for diagnostic bronchoscopy, his symptoms had progressed with worsening shortness of breath, chills, and cyanosis. The pulse oximetry revealed the saturation to be consistently below 88%. Transbronchial biopsies were performed of the right lower lobe after endobronchial exploration revealed no abnormalities. BAL was performed and was negative for atypical cells or infection. He was admitted to the hospital for further evaluation and treatment.

Histologic examination of biopsy sections revealed prominent capillary expansion within the alveolar and peribronchial interstitial tissue by a cellular infiltrate. The alveolar walls appeared rigid, and the alveolar spaces were not involved by the process (Fig 2). The infiltrate was composed of large cells with little cytoplasm, high nucleus to cytoplasm ratios, and irregular nuclear contours. Many cells had vesicular nuclei with peripheral chromatin condensation and one to three nucleoli. Immunohistochemistry studies revealed positive staining in tumor cells with leukocyte common antigen (Dako; Gloftrup, Denmark) and L-26 (Dako), which identified the tumor as a lymphoma of B-cell lineage (Fig 3). The stains further demonstrated that the tumor cells were confined to the expanded capillary lumena in both the alveolar septa and in the tissue adjacent to the bronchioles. The tumor cells were negative for the T-cell marker UCHL-1 (Dako) and cytokeratin (Kermix; Dako; Indianapolis, IN).

The patient received 6 cycles of systemic combination chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone without complications and obtained a complete remission. After treatment, repeat pulmonary function testing revealed marked improvement with an FVC of 4.71 L (120% predicted), FEV_1 of 2.94 L (98% predicted), and FEV_1/FVC ratio of 65%. The diffusion capacity increased to 13.82 mL/min/mm Hg (53% predicted). Total lung capacity remained approximately the same at 9.32 L (150% predicted), but the residual

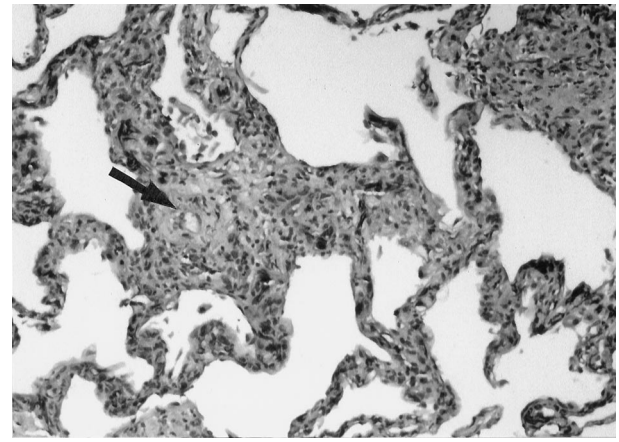

FIGURE 2. Histologic section demonstrating expansion in alveolar and peribronchial interstitial tissue by lymphoma. The alveolar spaces are free of involvement by the process. An arteriole with a patent lumen is present (black arrow) with no identifiable adjacent bronchiole (hematoxylin-eosin, original magnification ×200).

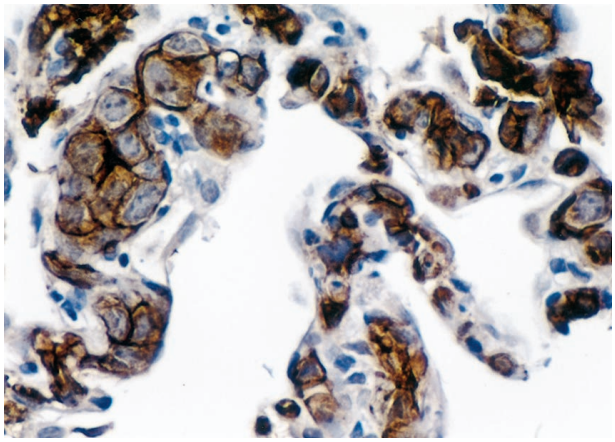

FIGURE 3. Immunohistochemistry staining of tumor cells within alveolar capillaries with L-26, demonstrating a strong staining reaction and highlighting some of the cytologic characteristics of the tumor (original magnification ×400).

volume decreased to 4.75 L (207% predicted). Repeat HRCT performed after treatment revealed interval resolution of the pulmonary nodules and mosaic perfusion pattern. Since then, the LDH has decreased to 169 U/L, and the patient has resumed working, no longer requires supplemental oxygen, and is disease-free at 14 months follow-up.

DISCUSSION

IVL is a rare neoplasm that remains confined primarily to the lumena of small capillaries, venules, and arterioles. This malignancy was originally believed to be of endothelial origin; however, further studies revealed the lymphoid, typically B-cell, origin of the disease.[2,3] The reason why these cells stay within the vasculature and do not involve lymph nodes and organ parenchyma remains unknown. In the majority of cases, clinical manifestations of IVL have included cutaneous nodules or plaques, fever, neurologic abnormalities, including dementia or focal defects, anasarca, and renal failure.[3] Pulmonary vascular involvement with IVL but without other organ involvement has rarely been reported and is a difficult antemortem diagnosis.[5–10] The clinical presentations are nonspecific and include dyspnea, fever, cough, night sweats, and the syndrome of inappropriate secretion of antidiuretic hormone.[9] In addition, the serum LDH is commonly elevated. Pulmonary IVL shares many clinical features with pulmonary tumor embolism, a syndrome in which malignant cells from a distant tumor such as breast, lung, and prostate carcinoma embolize to the pulmonary vasculature. In both diseases, patients frequently experience dyspnea, tachypnea, and hypoxemia. The malignant cells in pulmonary tumor embolism, however, induce intravascular thrombosis and intimal proliferation, which may lead to complete and irreversible obstruction with resulting pulmonary hypertension and cor pulmonale.[12] In contrast, thrombosis and intimal proliferation have been rarely reported in pulmonary IVL, and there has been only one report of pulmonary hypertension and cor pulmonale.[7] In pulmonary IVL, there is no lymphadenopathy or localizing mass, and the radiographic evaluation can be unremarkable[5] or show interstitial infiltrates[6] and ground-glass opacities.[10] Pulmonary function testing is typically remarkable for a decrease in diffusion capacity with normal,[7,10] restrictive,[6] or obstructive[5] patterns reported on spirometry. Our case represents the first case where marked air trapping has been observed on both plethysmography and high-resolution CT, and the third reported case where the diagnosis was made by transbronchial biopsy.[5,10]

Mosaic perfusion on HRCT may have several etiologies. It is commonly seen in patients with small airway diseases, which result in focal air trapping or decreased ventilation of lung parenchyma. Reflex vasoconstriction results in a poorly ventilated lung becoming poorly perfused. This is a frequent finding in patients with bronchiolitis obliterans but can be seen in any disease associated with small airways obstruction such as cystic fibrosis or bronchiectasis of any cause. Air trapping is best seen on expiratory HRCT when the abnormality is patchy in distribution, because normal lung can then be contrasted with abnormal, lucent lung on the expiratory images. Measuring lung attenuation increase with expiration may help confirm that the abnormal lucency represents air trapping.[13] Normal lung usually increases in attenuation by 150 HU or more on expiration; areas of lung that trap air often show an increase in attenuation of less than 50 HU, as noted in our patient.

Mosaic perfusion is also associated with pulmonary vascular obstruction, usually from pulmonary embolism.[14] Also, patchy areas of ground-glass opacity can simulate a mosaic perfusion pattern. In these cases, postexpiratory HRCT can be very helpful in differentiating mosaic perfusion related to airways obstruction from other causes. Expiratory HRCT will accentuate differences in lung attenuation resulting from airways obstruction; this is not the case with ground-glass opacity or pulmonary vascular obstruction. The mosaic perfusion in our patient, therefore, is most consistent with air trapping, which was confirmed by plethysmography. The vascular obstruction that IVL causes, however, may have contributed to the dramatic mosaic perfusion that was observed in our patient.

The etiology of the air trapping in our patient remains unclear. Histopathology revealed expansion of the peribronchiolar interstitial tissue, which may compromise small airways by extrinsic compression. In addition, decreased blood flow to alveoli has been shown to result in reflex bronchoconstriction, an effect thought to be due to alveolar hypocapnia.[15] The intravascular malignant cells in our patient could have compromised blood flow enough to cause air trapping by this mechanism. Local mediators may have also contributed to local edema or bronchoconstriction.

IVL is potentially curable. Reports of long-term disease-free survival and presumed cure have been achieved with the use of combination chemotherapy for intermediate and high-grade lymphomas. Unfortunately, assessment of therapeutic interventions are difficult to analyze because of the relatively small number of cases managed antemortem as well as the lack of randomized studies and adequate long term follow up. DiGiuseppe et al [4] identified 35 cases

treated with different combination chemotherapy regimens and noted a 54% complete response rate. Five patients had no evidence of disease at a median of 48 months and were considered to be cured. Demirer et al [5] reviewed 23 patients who received therapy for IVL, and 6 of 11 patients (55%) receiving cyclophosphamide, doxorubicin, vincristine, and prednisone obtained a complete response.

In summary, our case demonstrates that IVL should be considered in the differential diagnosis when mosaic perfusion seen on HRCT is associated with air trapping on plethysmography. Other common clinical features include fever, weight loss, night sweats, and high elevations in serum LDH. This case also demonstrates the potential diagnostic utility of transbronchial biopsy in making the diagnosis early and relatively noninvasively. As has been reported, a standard lymphoma treatment regimen may result in a dramatic clinical response as demonstrated with our patient.

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Extraction of a Rubber Bullet From a Bronchus After 1 Year*

Complete Resolution of Chronic Pulmonary Damage

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Inhalation of a foreign body (FB) into the bronchial tree rarely occurs asymptomatically and, if leading to recurrent pneumonia, can be very difficult to diagnose. The present report deals with the case of a 10-year-old boy who had three episodes of pneumonia in the left lower lobe caused by the asymptomatic inhalation of a FB 12 months before. Standard thoracic CT, done during the third episode, revealed a slight reduction in the volume of the left lung with air bronchograms, multiple areas of bronchiectasis, and parenchymal consolidation of a segment of the lower lobe. Flexible fiberoptic bronchoscopy revealed a FB at the distal end of the left lower lobar bronchus, surrounded by granulation tissue and fully obstructing the anterior basal segmental bronchus. High-resolution CT (HRCT) images showed an inverted C-shaped image obstructing a bronchus. Removal of the FB was successful only with rigid bronchoscopy under total anesthesia. The FB was an air-pistol rubber bullet that the boy remembered playing with 12 months before. Two months after removal of the FB (*ie*, 14 months from its asymptomatic inhalation) and treatment with oral steroids, antibiotics, and respiratory physiotherapy, the patient recovered completely, and HRCT showed complete normalization of the lung. We conclude that, when the radiographic density of the FB is greater than the surrounding pulmonary parenchyma, HRCT can reveal the FB, and diagnostic flexible fiberoptic bronchoscopy can be avoided.

(CHEST 1999; 115:1210–1213)

Key words: bronchiectasis; foreign body inhalation–complication; pulmonary consolidation; recurrent pneumonia; thoracic high-resolution CT

Abbreviations: CXR = chest radiograph; FB = foreign body; HRCT = high-resolution CT

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Bronchial aspiration of a foreign body (FB) is a frequent accident during childhood and can cause serious lung damage. Clinical history and findings are typically characterized by violent cough, wheezing, vomiting, cyanosis, and sometimes apnea; in such cases, diagnosis is quite obvious. Asymptomatic inhalation of an FB, however, is a rare event (3.5% of cases, according to Aytac et al[1]) and becomes apparent only if, after a certain period of time, it causes chronic respiratory signs such as hemoptysis, cough, and pneumonia recurring in the same pulmonary district.[1,2] In these cases, the FB remains in the bronchial tree for rather long periods of time, either because of the absence of respiratory symptoms or because it is undetected by bronchoscopy.[3–6] The sequelae of asymptomatic inhalation have been widely described in the literature; they include bronchiectasis (1.6% of cases, according to Kürklü et al[7]), necrotizing pneumonia, organizing pneumonia, and pleural effusion.[3–9] It has also been suggested that these patients should be carefully analyzed by radiologic and instrumental procedures to differentiate FB inhalation from other pulmonary diseases, especially during childhood. However, in many instances, owing to the failure of bronchoscopy to remove or identify the FB, the histopathologic damage, particularly bronchiectasis and organizing pneumonia, has been regarded as irreversible, and the treatment of choice has been the surgical removal of the affected pulmonary segment or lobe.[3–6]

In the present report, we describe the case of a 10-year-old boy who had three episodes of pneumonia of the left lower lobe (without any previous clinical history of respiratory disease) caused by the asymptomatic inhalation of an FB 12 months before. When the patient was referred to our department, the FB had already led to the development of multiple areas of bronchiectasis and pulmonary consolidation. The case herein described shows that thoracic high-resolution CT (HRCT) can reveal an FB, thus proving a useful and noninvasive way of diagnosing the presence of an FB in the bronchi and possibly foregoing the need for diagnostic flexible bronchoscopy.

Case Report

A 10-year-old boy was referred to our department because of high fever and productive persistent cough; over the previous few months, he had lost weight (about 2 kg) and was complaining of asthenia.

In the previous 6 months, he had experienced two episodes (4 months apart) of persistent cough and fever, due to pneumonia of the left lower lobe, as shown by chest radiograph (CXR); the first pneumonia was complicated by ipsilateral pleural effusion, and both were associated with middle ear otitis. Both pneumonias responded to antibiotic treatment, and normalization of the CXR ensued. During the 2 months before the first pneumonia, the boy had experienced several undefined respiratory tract infections with productive cough and fever, which had been cured by a few days of antibiotic treatment.

Physical examination revealed left basal dullness to percussion and bronchial breath sounds without rales. The CXR showed irregular consolidation and reduction of part of the left lower lobe. Laboratory findings were as follows: normal erythrocyte sedimentation rate, normal total and differential leukocyte cell counts, and lymphocyte typing; normal serum IgG, IgM, IgA; C-reactive protein of 3.54 mg/dL; negative purified protein derivative Mantoux test; standard titration of cold agglutinin for *Mycoplasma pneumoniae* of 1:160, stable at two subsequent tests, and negative IgG and IgM against *M pneumoniae*; normal antistreptolysin O titer; negative immunofluorescent staining for

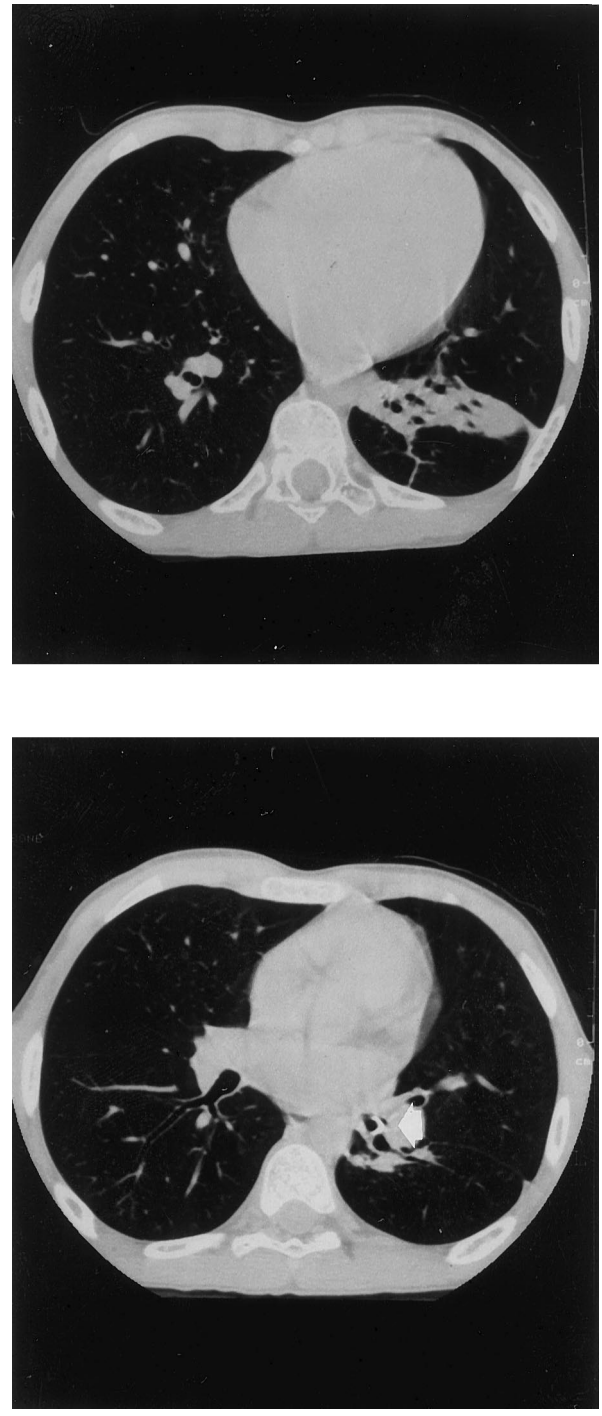

Figure 1. *Top:* thoracic HRCT showing consolidation with air bronchograms and bronchiectasis in the left inferior lobe, with apparent reduction in volume. Note the ipsilateral mediastinal shift. *Bottom:* thoracic HRCT showing an inverted C-shaped structure (about 1 cm in diameter) whose density is higher than the surrounding tissue. The inferior lobar bronchus appears almost completely obstructed.

Chlamydia pneumoniae, C psittaci, and for *Legionella pneumophila;* negative blood and sputum cultures; presence of *Candida albicans* at the microscopic examination of sputum; and normal sweat chloride concentration. Pulmonary function test revealed a slight restriction but no obstructive airway disease; gas diffusion test result was normal.

Since the patient did not respond to amoxicillin-clavulanate plus erythromycin treatment either clinically or radiologically, we performed the following tests: rheumatoid factor (negative); bone marrow analysis (normal). Standard CT scan of the chest revealed a parenchymal consolidation of the anterior basal segment of the left lower lobe, with air bronchograms, bronchiectasis, and slight reduction in the volume of the left lung with ipsilateral mediastinal shift (Fig 1, *top*). In the meantime, the patient's clinical condition improved with ceftriaxone and naproxen, and a flexible fiberoptic bronchoscopy was carried out to establish the etiology of the brochiectasis. Endoscopy revealed an FB at the distal end of the left lower lobar bronchus, surrounded by granulation tissue and fully obstructing the anterior basal segmental bronchus (Fig 2). Several unsuccessful attempts were made to remove the FB with a flexible bronchoscope. We therefore performed rigid bronchoscopy under general anesthesia, alerting the thoracic surgeon because of the risk of bronchial rupture and massive hemorrhage. The FB was then removed with mild bleeding and was found to be an air-pistol rubber bullet that the boy remembered playing with 12 months before. High-resolution reexamination of the CT images, which had been performed prior to bronchoscopy at standard resolution, indeed revealed an inverted C-shaped image obstructing a bronchus that had previously passed unnoticed (Fig 1, *bottom*). Forty-eight hours after removal of the FB, the CXR showed an almost complete reexpansion of the left lower lobe, though the bronchial wall still appeared thickened. Because of the severity of the lung damage, the boy underwent oral steroid treatment with prednisone for 1 month, rather than the few days usually recommended after bronchoscopy.[10] At the same time, he underwent respiratory physiotherapy. One month after FB removal, the boy appeared in good health, and his clinical picture was normal. Two months after FB removal (*ie,* 14 months from its asymptomatic inhalation), HRCT showed complete disappearance of bronchiectasis and normalization of the left lower lobe (Fig 3).

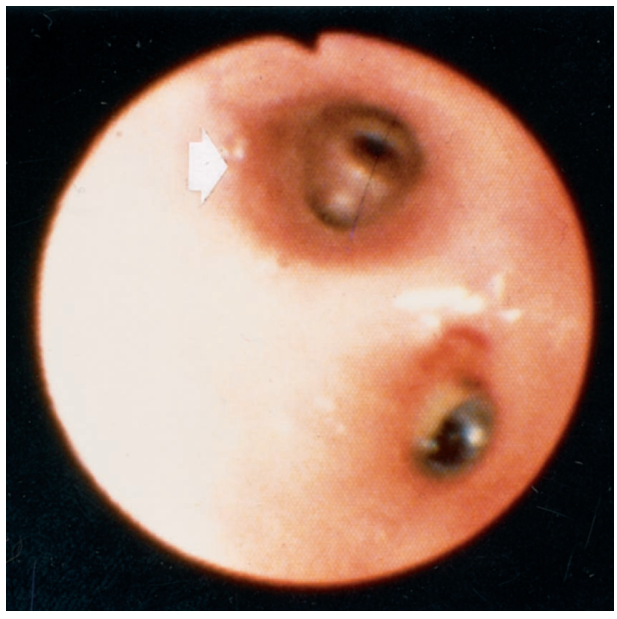

FIGURE 2. Endoscopic view of the FB at the distal end of the left inferior lobar bronchus.

DISCUSSION

The case described herein rarely occurs in pediatric practice; it therefore affords us the opportunity to comment on certain relevant clinical and radiologic aspects. It proves once more that there may be no clinical evidence of the inhalation of an FB and that some months may pass before a FB gives clear signs of its presence; in fact, at the beginning, our patient displayed only nonspecific symptoms of respiratory tract infection (bronchitis, pneumonia). Only the recurrence of pneumonia in the same pulmonary area, in an otherwise normal child, aroused suspicions of an underlying disorder; the obstruction of a bronchus can initially be incomplete, only later becoming progressively more extensive, in part owing to the granulation tissue that encloses the FB. The severity of lung damage appears to be correlated with the duration and degree of bronchial obstruction, as well as with the nature of the FB.[3,6] In our case, standard CXRs never showed the typical signs of acute FB inhalation (hyperinflation, parenchymal collapse, pneumomediastinum, pneumothorax) but only recurrent pulmonary densities in the same pulmonary district.

It is worth noting that other diseases cause recurrent or persistent lung infiltration; thus, it is necessary to implement a series of diagnostic procedures to differentiate them and asymptomatic FB inhalation and to exclude its

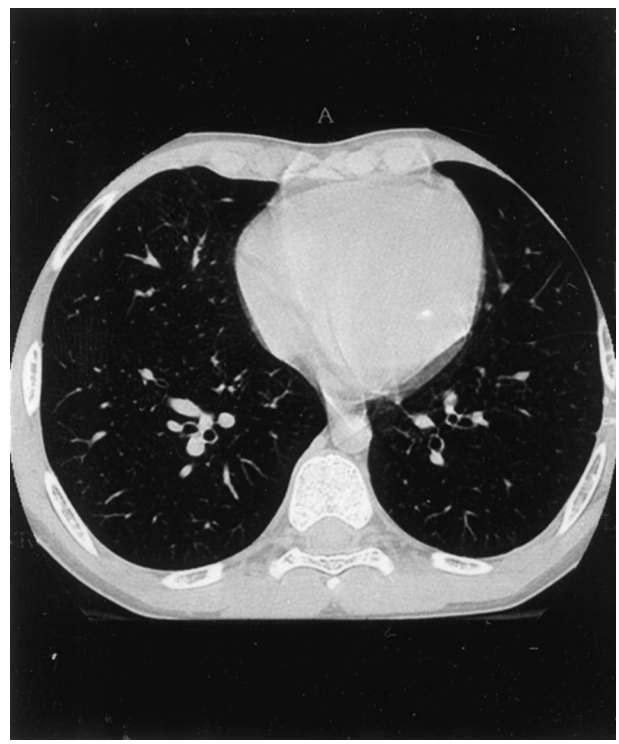

FIGURE 3. Thoracic HRCT performed 2 months after the removal of the FB. Note the complete reventilation of the inferior left lobe and the normal thickness of bronchial walls.

existence, despite normal history and aspecific CXR. Such diseases include asthma, congenital and acquired immunodeficiencies, massive or recurrent inhalation of gastric content, cystic fibrosis, and α_1-antiproteinase deficiency.

If the clinical history excludes FB aspiration, standard CT is of the greatest help in showing lung damage in detail (*ie,* bronchiectasis), but sometimes it gives nonspecific and not easily interpretable images. In fact, in our present experience, only HRCT seemed able to detect FB. The technique makes use of 1-mm collimation to optimize the spatial resolution while preserving clear imaging of the subsegmental bronchi and secondary pulmonary lobule.[11] It serves not only to indicate the existence and location of bronchial FB, but also to assess the extent of the parenchymal damage and to monitor progress after FB removal. A limitation of this technique is the respiratory motion due to rapid breathing in children. Shorter scanning times can now be achieved with spiral CT.[12] In any event, the identification of an FB by HRCT is possible only when its density is greater than the surrounding parenchyma.

Obviously, when the FB is detected by HRCT, flexible bronchoscopy can be avoided since it does not usually allow the removal of the FB. For such an operation, one can proceed directly to rigid bronchoscopy, which is considered the "gold standard" for removing tracheobronchial foreign bodies in the case of infants and children.[13,14] When the FB has been present for a long period of time in the bronchus, rigid bronchoscopy must be performed under total anesthesia, and if the FB is embedded in granulation tissue, a thoracic surgeon should be present in case of massive hemorrhage and bronchial rupture.

In our patient, we suspected the existence of an organizing pneumonia because of the reduced volume of consolidated parenchyma and multiple areas of bronchiectasis (Fig 1, *top*), as well as the repeated pulmonary infections in the same area during the previous few months. Similar severe pulmonary parenchymal damage caused by recurrent pneumonia due to FB bronchial obstruction has been regarded by some authors as irreversible and resolvable only by surgical removal of the affected pulmonary zone.[6]

We undertook steroid therapy in this case owing to the presence of chronic atelectasis,[15] but also, on an empiric basis, to reduce the bronchial inflammation brought on by the FB and by endoscopy. After 1 month of steroid therapy, no clinically significant side effects were apparent; but in any event, given the severity of the pulmonary involvement, any attempt to avert parenchymal fibrosis and lobectomy could only be deemed worthwhile. We cannot claim that steroids contributed to our patient's full recovery; to the best of our knowledge, no controlled trial of the effectiveness of steroids in such cases has ever been carried out, nor, given the highly unusual nature of the attendant circumstances, is it likely that such a trial will be conducted in the foreseeable future.

We therefore suggest that medical therapy in children with severe lung damage due to FB inhalation should always be attempted before surgery.

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