

Complete Remission of Pulmonary Spindle Cell Carcinoma After Treatment With Oral Germanium Sesquioxide*

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Spindle cell carcinoma (SCC) is a rare form of lung cancer representing 0.2 to 0.3% of all primary pulmonary malignancies. Even with combined surgery, chemotherapy, and radiation therapy, these tumors are associated with a poor prognosis and only 10% of patients survive 2 years after diagnosis. We describe a patient with an unresectable SCC who, following no response to conventional treatment with combined modality therapy, chose to medicate herself with daily doses of germanium obtained in a health food store. She noted prompt symptomatic improvement and remains clinically and radiographically free of disease 42 months after starting her alternative therapy. (CHEST 2000; 117:591-593)

Key words: germanium sesquioxide; spindle cell carcinoma

Abbreviation: SCC = spindle cell carcinoma

CASE PRESENTATION

The patient is a 47-year-old woman admitted with shortness of breath and cough. She had been in good health until 5 months earlier, when she noted mild

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dyspnea and a nonproductive cough. These symptoms progressed to include pleuritic chest pain and night sweats. Her medical history included childhood asthma. Physical examination revealed decreased breath sounds

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throughout the left lung field. Thoracic CT showed atelectasis of the left lung and a mass measuring 3.4×4.5 cm extending posterior to the left mainstem bronchus and displacing it anteriorly (Fig 1, top, A). During bronchoscopy, an endobronchial lesion producing 75% occlusion of the left main bronchus was visualized. Biopsy specimens were obtained. At thoracotomy, the lung mass encircled the pulmonary artery and invaded the esophagus, the posterior wall of the pericardium, and the right pulmonary vein, and was deemed unresectable. Additional biopsy specimens were obtained.

Pathologic Findings

Bronchoscopic and open biopsies showed a proliferation of spindle-shaped cells with pleomorphic nuclei, variable amounts of cytoplasm with basophilia, and occasional mitoses (Fig 2, top, A). Small foci of dysplastic squamous epithelium merged with the spindle cells (Fig 2, middle, B). Immunohistochemical stains for cytokeratin (MAK 6 and CAM 5.2) decorated the cytoplasm of occasional neoplastic cells (Fig 2, bottom, C) consistent with spindle cell carcinoma (SCC). Stains for leu M1, carcinoembryonic antigen, and B72.3 were negative. The background was myxoid with small amounts of collagen. The lesion eroded through the bronchial surfaces and was covered by a layer of fibrinous exudate.

Ultrastructural studies revealed abundant rough endoplasmic reticulum in the spindle-shaped tumor cells, and subplasmalemmal thin filaments with dense bodies in some of the neoplastic cells. Tonofilaments were not observed.

Follow-Up

The patient received chemotherapy including one cycle of etoposide/ifosfamide, and one cycle of paclitaxel/cisplatin followed by radiation therapy (4,500 cGy) to the thorax. Despite two additional cycles of mesna, adriamycin, ifosfamide, and dacarbazine, her symptoms worsened and she had radiographic evidence of tumor progression. The patient opted to discontinue all therapy.

While on a cruise 6 weeks later, the patient met a man who claimed that daily self-medication with germanium had cured him of oat cell carcinoma of the lung that was diagnosed 15 years earlier. The patient started daily self-medication with the same regimen (bis-betacarboxyethylgermanium sesquioxide, 7.2 g qd, followed by a taper of the drug). Within a few days of beginning therapy, she felt her lungs "opening up" and required less supplemental oxygen. A chest radiograph 3 months later revealed 60% clearing of the left lung, and thoracic CT scans at 5 and 7 months showed near complete disappearance of the thoracic mass (Fig 1, bottom, B). At the time of this report, > 4 years after initial diagnosis, the patient continues to show no evidence of recurrent disease and has also continued to take low-dose germanium sesquioxide. The patient denies any significant side effects from her treatment.

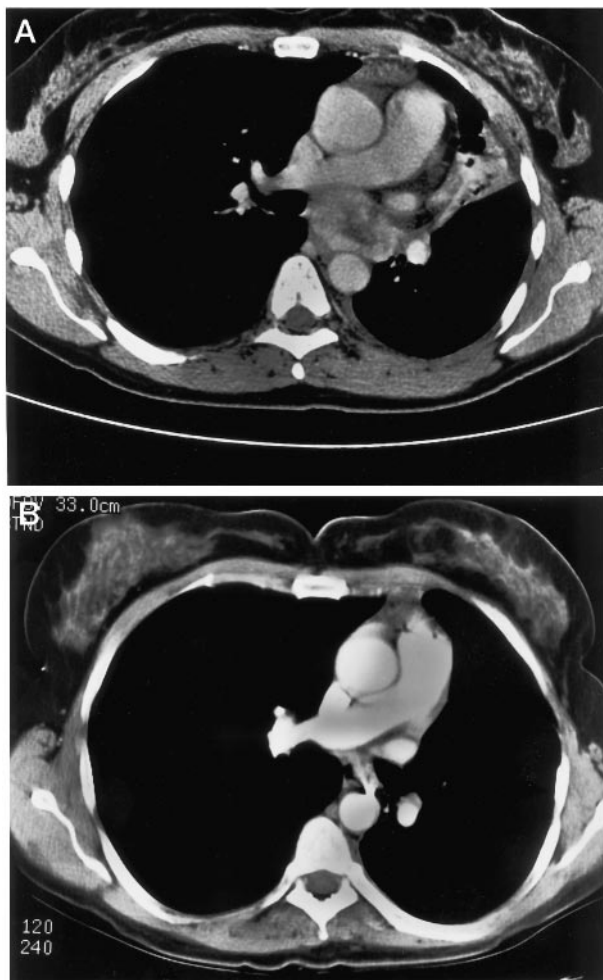


FIGURE 1. *Top, A:* a CT of the thorax at the level of the aortic arch revealing a 3.5 × 4.5 × 6.5-cm left hilar mass. *Bottom, B:* a CT of the thorax after self-medication with germanium sesquioxide for 5 months, showing resolution of the hilar mass and left lung atelectasis.

DISCUSSION

Pulmonary SCC is a rare form of lung cancer that is more common in male than female patients (4 to 5:1), in smokers, and in patients between 50 and 80 years of age.¹ Carcinosarcoma, like SCC, contains malignant epithelial and sarcomatous elements, often forms a polypoid endobronchial mass, and may be part of a spectrum with SCC.² Surgery remains the primary therapeutic modality, with the most important predictor of survival being the completeness of tumor resection.² In our patient, complete excision of the tumor was considered impossible because of the extension of the tumor into vital structures. Chemotherapy and radiation therapy were administered with the object of palliation, recognizing that a significant response was unlikely. Our patient's lack of response to these agents is in accord with previous reports.³ Overall survival is usually poor unless complete resection of the tumor can be accomplished.⁴

Germanium is an elemental metal discovered in 1886

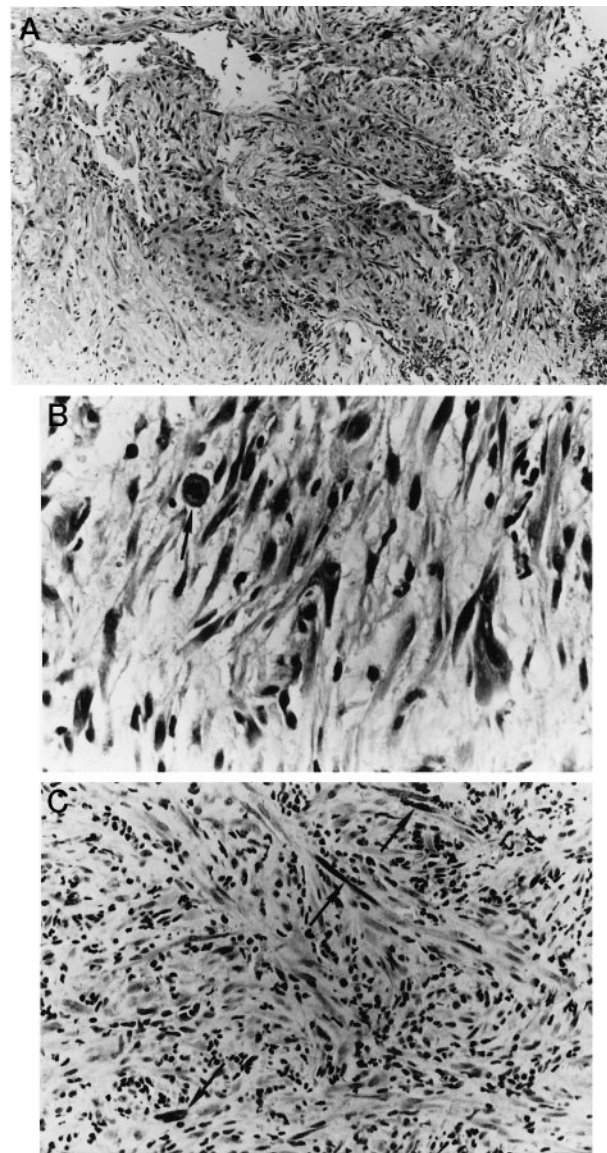


FIGURE 2. *Top, A:* an endobronchial lesion associated with extensive ulceration of the bronchial surface. Small foci of dysplastic squamous epithelium merge with the predominant spindle cells (hematoxylin-eosin, original magnification × 100). *Middle, B:* spindle-shaped tumor cells with pleomorphic nuclei, variable amounts of basophilic cytoplasm, and occasional mitoses (arrow), in a myxoid background with a mixed inflammatory infiltrate consistent with SCC (hematoxylin-eosin, original magnification × 400). *Bottom, C:* occasional neoplastic cells (arrows) show cytoplasmic staining for cytokeratin consistent with SCC (immunoperoxidase stain with MAK 6 antibody, original magnification × 200).

and was used primarily in transistor technology. Preclinical studies during the 1970s showed that two germanium compounds had antineoplastic activity: spirogermanium and germanium sesquioxide. Preclinical studies with germanium compounds revealed antitumor activity in several tissue culture cell lines, including Walker 256 carcinosarcoma,⁵ and promoted several phase I/II clinical studies on advanced malignancies including lung,⁶ breast,⁷ renal,⁸

and prostate cancers.^{9,10} Unfortunately germanium sesquioxide and spirogermanium showed extremely limited activity in these studies and significant dose-related nephrotoxicity and neurotoxicity.¹¹

Clinically and radiographically, our patient experienced complete tumor regression that was temporally related to the initiation of germanium therapy. While the precise mechanism underlying this patient's response to germanium sesquioxide is not known, this compound has been reported to enhance immunity through stimulation of T cells, natural killer cells, lymphokines, and macrophage activity,¹² and may have played a role in promoting tumor cell ablation in this patient. Less likely, although equally interesting, is the possibility that this patient had a "spontaneous remission" of a particularly aggressive malignancy unrelated to chemotherapy, radiation therapy, or germanium use. Although the promoting event that led to the dramatic and durable improvement seen in this patient cannot be absolutely determined, the use of germanium sesquioxide may merit further studies in the treatment of unresectable SCC.

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Asthma and Cushing's Syndrome*

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A female patient was treated with high-dose inhaled fluticasone propionate for her asthma. Over 2 years, she developed features of Cushing's syndrome with proximal myopathy, osteopenia, hypertension, depressive psychosis, and cushingoid appearance. She had biochemical evidence of marked adrenal suppression with a 9:00 AM serum cortisol of 20 nmol/L that returned to normal (315 mol/L) after her therapy was changed to budesonide, 0.8 mg/d. Her appearance, mental state, and myopathy also improved with no loss of asthma control. This case illustrates the potential for developing clinically relevant adverse effects of inhaled corticosteroids when given at licensed doses.

(*CHEST* 2000; 117:593–594)

Key words: adrenal suppression; Cushing's syndrome; fluticasone propionate; osteoporosis

Inhaled glucocorticoids are widely accepted as first-line preventative anti-inflammatory therapy for the treatment of asthma. This is based on the principle of delivering a relatively low nominal dose of topically active glucocorticoid to achieve a high local concentration within the airway, while at the same time minimizing systemic bioactivity. Although it is recognized that inhaled glucocorticoids cause dose-related adrenocortical suppression, it is less well known that they may be a cause of overt cushingoid presentation. The etiology of systemic bioactivity is multifactorial, depending on the glucocorticoid potency, dose, duration of therapy, inhaler delivery device, and individual patient's glucocorticoid-receptor sensitivity. The following case illustrates the severity of systemic glucocorticoid activity in a susceptible patient and how this may pose a potential diagnostic problem.

CASE REPORT

A 59-year-old female patient with chronic severe asthma was first seen in the chest clinic in March 1995 with deterioration in her asthma control, having intermittently taken inhaled beclomethasone. Her FEV₁ at that time was 41% of predicted normal. She was prescribed inhaled fluticasone propionate at a nominal dosage of 1 mg/d (1 mg ex-valve equivalent to 0.88 mg ex-actuator dose) via a Volumatic spacer (Glaxo Wellcome; Middlesex, UK) plus an inhaled long-acting β_2 -agonist (salmet-

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erol) and slow-release oral theophylline bid. The same physician increased the dosage of fluticasone propionate to 2 mg/d (2 mg ex-valve equivalent to 1.76 mg ex-actuator) at a subsequent visit, and she was then discharged from the clinic to be followed up by her general practitioner (FEV₁ of 52% predicted at that time).

She was next seen in hospital > 2 years later (August 1997), when she was referred to the metabolic bone clinic (A.B.) because of back pain thought to be due to osteoporosis. She had received two tapering courses of prednisolone (1-week duration of each) for her asthma and had been taking inhaled fluticasone propionate, 2 mg/d (1.76 mg ex-actuator), over the previous 3 years. At that time, she was noted to have a markedly cushingoid appearance, with a moon-shaped face, hirsutism, kyphosis, and widespread bruising. She was also hypertensive (BP, 180/110 mm Hg) and had proximal muscle weakness and a depressive psychosis. Osteopenia was evident on both thoracic and lumbar radiographs, with a wedge fracture of the fifth thoracic vertebrae. Bone densitometry showed evidence of significant osteopenia (left ultra-distal radius Z score, 2.02; T score, 1.39; 67% of expected for age; and mid-distal radius Z score, 1.39; T score, 3.06; 85% of expected for age), as assessed by dual energy x-ray absorptiometry. She was therefore prescribed oral cyclical etidronate.

As it was considered that her degree of cushingoid appearance could not be explained by her inhaled corticosteroid therapy, she was referred to an endocrinologist (R.T.J.), who arranged further tests to evaluate her adrenocortical function. Her results showed a lack of normal diurnal variation in serum cortisol: 9:00 AM cortisol of 20 nmol/L (lower limit of normal, 190 nmol/L) and a 12:00 midnight cortisol of 13 nmol/L. Her 24-h urinary free cortisol excretion was less than the lower limit of the reference range (< 60 nmol/24 h). A dexamethasone suppression test (dexamethasone, 1 mg, at 11:00 PM) was performed that showed a postsuppression 9:00 AM serum cortisol concentration of < 20 nmol/L.

After consultation with another chest physician (B.J.L.), it was considered that inhaled fluticasone propionate was probably responsible for her condition. Fluticasone propionate was changed to budesonide, 0.8 mg/d, via a dry powder inhaler (Turbuhaler; Astra Pharmaceuticals; Herts, UK) and her salmeterol was changed to an oral leukotriene receptor antagonist (montelukast). Her cushingoid features markedly improved as did her muscle weakness, and her mental state returned to normal. When repeated in May 1998, her 9:00 AM serum cortisol had also returned to normal, with serial values of 315 nmol/L and 308 nmol/L, as did her 24-h urinary free cortisol excretion (100 nmol/24 h). Despite reducing the total daily dose of inhaled corticosteroids, she had improved diurnal asthma control of symptoms, peak flow, and FEV₁ (66% of predicted normal). She remained hypertensive and was treated with an angiotensin-receptor antagonist (losartan).

This case illustrates the potential for inhaled glucocorticoids to cause overt secondary Cushing's syndrome. Indeed, primary Cushing's syndrome was considered to be the most likely diagnosis at first presentation. Hence, a 24-h urinary cortisol collection and a dexamethasone suppression test were initially performed to establish the diagnosis. Dynamic stimulation testing with tetracosactin (adrenocorticotrophic hormone) was not performed, as tetracosactin is contraindicated in the UK for use in asthmatic subjects because of occasional reports of anaphylactic reactions.

There are other reported cases of children and adults with cushingoid features and adrenal suppression due to inhaled fluticasone.^{1,2} However, our case also showed documented evidence of osteoporosis as well as having a depressive psychosis. There has also been a reported case of an acute Addisonian crisis

on withdrawal of budesonide in a 38-year-old man³ and on withdrawal of beclomethasone dipropionate in a 7-year-old girl.⁴

Had our patient received prolonged courses of oral prednisolone, this could have accounted for the systemic effects observed. However, she only received two tapering courses of oral prednisolone for 1 week each. In a study by Webb and Clark,⁵ it was shown that short courses of prednisolone do not cause long-term adverse effects because (after 3 weeks of prednisolone, 40 mg/d) both early-morning cortisol and response to dynamic stimulation with cosyntropin, 250 µg, recovered after 3 days.

Fluticasone propionate is the most potent of the available glucocorticoids for inhalation. A recent meta-analysis of 22 studies⁶ showed fluticasone to exhibit significantly steeper dose-related adrenal suppression compared to beclomethasone (2.1-fold), budesonide (2.5-fold), or triamcinolone acetonide (3.6-fold). These effects are due to the particular pharmacologic and pharmacokinetic properties of fluticasone resulting in more prolonged drug retention at receptors, in blood, and in systemic tissues.

Our case highlights the importance of following asthma management guidelines in terms of stepping down to the lowest effective maintenance dose of inhaled corticosteroid, particularly with higher potency corticosteroids such as fluticasone propionate.

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Acute Massive Pulmonary Embolism in a Jehovah's Witness*

Successful Treatment With Catheter Thrombectomy

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A 71-year-old woman presented with an acute, massive pulmonary embolism. As a Jehovah's Witness, she was not willing to accept thrombolysis because of

the potential risk of bleeding requiring blood transfusion. The patient was successfully treated with catheter thrombectomy, using rheolytic and fragmentation devices.

(CHEST 2000; 117:594–597)

Key words: catheter thrombectomy; Jehovah's Witness; pulmonary embolism; thrombolysis

Abbreviation: PE = pulmonary embolism

Acute massive pulmonary embolism (PE) accounts for approximately 50,000 deaths per year in the United States.¹ The options for treatment of massive PE, in addition to the standard treatment of anticoagulation with heparin, include the following: thrombolytic therapy, open surgical embolectomy, and catheter thrombectomy.² Intracranial hemorrhage after thrombolysis for PE is an infrequent but grave complication.³ In addition to specific contraindications to thrombolytic therapy, a patient may be unwilling to accept the potential risk of bleeding that would require the transfusion of blood products. With recent technologic advances in thrombectomy devices, catheter thrombectomy may be an option. We report a Jehovah's Witness patient with an acute massive PE who was successfully treated with catheter thrombectomy.

CASE REPORT

The patient is a 71-year-old African-American woman with a history of poorly controlled arterial hypertension. She presented with the acute onset of shortness of breath at rest, worsening over 4 days. There was no cough, hemoptysis, fever, or chest pain. She denied any history of smoking, cancer, or immobilization.

On admission, her BP was 130/108 mm Hg, pulse rate was 148 beats/min, and respiration rate was 26 breaths/min. The examination was significant for a right ventricular S3 gallop, and left basilar rales. The chest radiograph showed a small left pleural effusion and oligemia of the right upper lung field. An arterial blood gas analysis, drawn while breathing room air, showed pH 7.46, PaCO₂ of 27 mm Hg, and PaO₂ of 50 mm Hg. ECG revealed sinus tachycardia, left ventricular hypertrophy, and lateral ST-segment depression. An emergency transthoracic echocardiogram in the emergency department was technically limited, and showed normal left ventricular function and normal right ventricular size. The patient was started on IV heparin for suspected PE. The oxygen saturation was 95% while breathing 100% oxygen. A ventilation/perfusion scan (Fig 1) showed absent perfusion of the right lung with normal ventilation, consistent with a high probability of PE.

Over the next 3 days, the patient remained tachypneic, with desaturation with movement and persistence of the S3 gallop. The BP remained at 120/80 mm Hg. Thrombolysis was discussed with the patient, and the risk of bleeding and the potential requirement for blood product transfusion was explained. As a practicing Jehovah's Witness, she refused thrombolysis because of this risk of bleeding and transfusion.

Because of the severe compromise from massive PE and the

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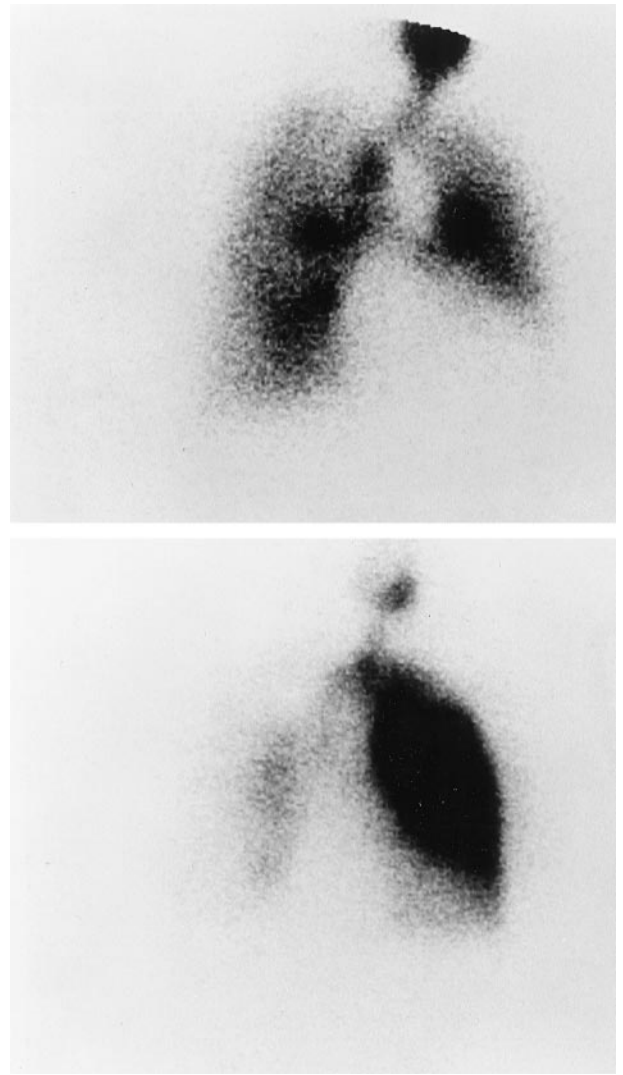


FIGURE 1. Ventilation (technetium Tc 99m-diethylenetriamine pentaacetic acid aerosol)/perfusion (technetium 99m-macro-aggregated albumin) scan on admission. Anterior ventilation scan (*top*) is normal, and perfusion scan (*bottom*) shows almost absent perfusion to the right lung.

perfusion scan suggesting a central right pulmonary artery thrombus, the patient was referred to the interventional radiologist for an attempt at catheter thrombectomy. Pulmonary angiography revealed thrombus completely occluding the right main pulmonary artery and the mean pulmonary artery pressure to be 30 mm Hg. A catheter thrombectomy was performed using rheolytic and fragmentation devices. A 10F Arrow flexible sheath (Arrow International; Reading, PA) was placed in the right pulmonary artery. A 0.018-inch wire was advanced into multiple thrombosed distal basal segments followed by the 5F 105-cm thrombectomy system (Angiojet; Possis; Minneapolis, MN). The system was activated for 2 to 3 min in segments of the lower and middle lobes, and in one upper lobe segment. The Possis system was then replaced with an 8F 120-cm Amplatz thrombectomy device (Microvena; White Bear Lake, MN). The device was activated in the right main pulmonary artery and proximal interlobar and upper lobe arteries for approximately 6 min.

There was definitive angiographic improvement in the perfusion of the right upper lobe and right middle lobe vessels, with



FIGURE 2. Anterior perfusion scan 2 days following catheter thrombectomy shows improved right lung perfusion. Small subsegmental perfusion defects may have resulted from distal embolization of the right main pulmonary artery thrombus.

restoration of approximately 60% of the right pulmonary perfusion. An inferior vena cava filter was placed.

The following morning, the patient appeared less dyspneic and the S3 gallop was no longer auscultated. A lower-extremity duplex Doppler ultrasound examination was negative for thrombus.

A ventilation/perfusion scan 2 days postthrombectomy showed reperfusion of the right upper and middle lobes (Fig 2). Perfusion was further improved on scanning 2 weeks later. The patient was discharged on the 17th hospital day receiving warfarin anticoagulation. The patient is doing well, without dyspnea, 4 months later.

DISCUSSION

Thrombolysis is indicated for circulatory and respiratory failure from massive PE. However, thrombolysis may be complicated by bleeding, with infrequent but often fatal intracranial hemorrhage.³ For patients at risk of bleeding or unwilling to accept the risk of hemorrhage or transfusion, catheter thrombectomy may be an alternative emergency treatment.

There are currently three catheter thrombectomy techniques: aspiration thrombectomy, fragmentation thrombectomy, and rheolytic thrombectomy.^{4,5} The first percutaneous catheter thrombectomy device, an aspiration catheter, was introduced in 1969 by Greenfield et al⁶; in 1993, he reported his long-term experience showing a success rate of 82% for massive PE.² In 1997, a rheolytic thrombectomy, in which high-pressure saline solution jets at the tip of the catheter lyse the thrombi (which are then aspirated), was successfully used in two patients with severe PE.⁵

Uflacker et al⁷ reported the use in five patients of a fragmentation technique, the Amplatz thrombectomy device, in which an impeller creates a vortex that pulverizes the thrombus. There was marked improvement in perfusion in one patient and moderate improvement in three patients. In a series reported by Schmitz-Rode et al,⁸ a pigtail rotation catheter was successful in 7 of 10 patients with acute massive PE.

Reported complications of catheter thrombectomy in-

clude pulmonary infarction, wound hematoma and infection, myocardial infarction, and ventricular perforation.² A reperfusion syndrome with hemorrhage and focal pulmonary edema has been described.⁷

In our case, an acute massive PE in a Jehovah's Witness was successfully treated with catheter thrombectomy. The use of two catheter thrombectomy techniques, rheolytic and fragmentation, during one procedure was unique. The patient's previously untreated arterial hypertension was a risk for an intracranial hemorrhage; however, the BP was in the normal range during the critical care unit course. As a Jehovah's Witness, she was not willing to undergo a transfusion of any blood products in the event of bleeding at any site.

Jehovah's Witnesses hold religious beliefs that preclude accepting blood products, although this issue must be addressed with each individual patient. Major surgery and management of bleeding may be accomplished without transfusion⁹; however, offering thrombolytic therapy raises other issues.

The scope of this problem in patients receiving thrombolytic therapy for acute myocardial infarction has not been formally addressed in the literature. In 1991, Sugarman et al¹⁰ described a patient who was given thrombolysis for myocardial infarction and died of GI hemorrhage; the patient was a Jehovah's Witness and refused blood transfusion, despite the risk of death. The authors raised the question of whether refusal of blood products should be considered in the decision to administer thrombolytic therapy. Sugarman et al¹⁰ specifically did not want to exclude Jehovah's Witnesses from receiving the benefit of thrombolysis, and stressed informed consent about the potential complications and potential transfusion requirement. In addition, the authors suggested that this consideration be applied to patients who refuse blood products for any reason.

In a patient with massive PE in whom thrombolysis is medically indicated and who, after informed consent, refuses thrombolysis and potential transfusion, catheter thrombectomy may be an attractive alternative.

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Carbamazepine-Induced Systemic Lupus Erythematosus Presenting as Cardiac Tamponade*

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Here we report the case of a patient who presented with acute cardiac tamponade due to drug-induced systemic lupus erythematosus (SLE). The patient had been treated for a seizure disorder with carbamazepine, a drug that has previously been demonstrated to cause SLE-like syndromes. Further serologic analysis demonstrated the likelihood of drug-induced SLE in this patient, with the rare presentation of cardiac tamponade.

(*CHEST* 2000; 117:597–598)

Key words: carbamazepine; systemic lupus erythematosus; tamponade

Abbreviations: dsDNA = double-stranded DNA; SLE = systemic lupus erythematosus

Carbamazepine is a medication commonly employed for the treatment of seizure disorders, chronic pain syndromes, trigeminal neuralgia, and psychiatric illness. Although carbamazepine is usually well tolerated by most people, the potential side effects of therapy can vary from mild symptoms to severe systemic reactions. Common side effects include drowsiness, ataxia, diplopia, nausea, and vomiting. More serious adverse reactions include drug-induced systemic lupus erythematosus (SLE), pseudolymphoma syndrome, aplastic anemia, agranulocytosis, and hypersensitivity.¹ Here we describe the case of a patient who developed cardiac tamponade as a severe manifestation due to carbamazepine-induced SLE-like syndrome.

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CASE REPORT

A 45-year-old white man with a medical history of a generalized seizure disorder whose anticonvulsant therapy had been changed from phenytoin to carbamazepine 8 months prior to this admission presented to the emergency department with the chief complaint of chest discomfort and dyspnea. Although his symptoms had been present for several days, a sudden worsening of his pain and new onset shortness of breath prompted his seeking medical attention. His initial vital signs were BP of 90/60 mm Hg; heart rate, 114 beats/min; respiratory rate, 26 to 30 breaths/min; and temperature, 36.5°C. In addition, the patient had a pulsus paradoxus of 20 mm Hg. On physical examination, the patient's chest was clear to auscultation bilaterally, and cardiac auscultation revealed distant heart sounds, with S1, S2, and S3 gallop present. Pertinent laboratory data included a carbamazepine level of 7.8 µg/mL (therapeutic range, 4 to 10 µg/mL); BUN, 18 mg/dL; creatinine, 0.7 mg/dL; total bilirubin, 0.9 mg/dL; aspartate aminotransaminase (serum glutamic oxalacetic transaminase), 13 IU/L; alanine aminotransaminase (serum glutamic pyruvate transaminase), 9 IU/L; albumin, 2.8 g/dL; creatinine phosphokinase, 53 IU/L; WBC count, 10.5 × 10³/µL with a normal differential; hemoglobin 12.1 g/dL; and hematocrit, 35.5%. A chest radiograph revealed a "waterbottle" cardiac silhouette (Fig 1), a right-sided pleural effusion without evidence of pulmonary infiltrate. The ECG demonstrated sinus tachycardia and low voltages without electrical alternans. An emergent echocardiogram showed a large circumferential pericardial effusion, persistent inversion of the right atrium, and right ventricular diastolic collapse, all consistent with tamponade physiology.

An urgent therapeutic pericardiocentesis was performed with approximately 850 mL of fluid removed. The patient immediately began to feel relief of pain in addition to improved breathing. A follow-up echocardiogram demonstrated substantial reduction in the pericardial effusion with the elimination of tamponade physiology. The patient was subsequently transferred from the emergency department to the coronary care unit for further observation. Routine pericardial fluid studies showed a pH of 7.28; RBC count, 6,215 cells/µL; WBC count, 3,030 cells/µL (neutrophils 25%, lymphocytes 72%, monocytes 3%); protein, 5,013 mg/dL; glucose, 72 mg/dL; and lactate dehydrogenase, 238 IU/L. Further laboratory studies including bacterial, mycobacterial, viral, fungal, and cytologic studies indicated no evidence of infection or malignancy. Blood serologic studies showed antinuclear antibodies positive (1:320 dilutions), anti-double-stranded-DNA (dsDNA) negative, antihistone antibodies positive, and Smith autoantibody negative, all highly suggestive of a drug-induced SLE syndrome. Serum studies for echovirus, Coxsackievirus, Lyme disease, and HIV were all negative. Complement levels of C3, C4, and CH50 were all within normal limits. The patient was subsequently switched to phenobarbital for antiseizure therapy and was discharged with an uneventful hospital stay.

DISCUSSION

Several major criteria have been used to make the diagnosis of drug-induced SLE. These criteria include the following: (1) the development of SLE-like symptoms during drug therapy; (2) the cessation of the SLE-like symptoms within weeks of discontinuing the drug therapy; (3) no clinical or laboratory evidence of SLE prior to beginning the drug therapy; and (4) the presence of antihistone antibodies with the absence of high titers of anti-dsDNA antibodies.^{2,3} The presence of these criteria is highly suggestive of drug-induced SLE, and serologic studies are often the most helpful clinically. Antihistone



FIGURE 1. Portable anteroposterior chest radiograph showing a classic waterbottle cardiac silhouette and a right pleural effusion.

antibodies are present in only 50% of patients with idiopathic SLE, but are present in 95% of patients with drug-induced SLE; while anti-dsDNA antibodies are usually absent in drug-induced SLE and present in 85% of patients with idiopathic SLE.^{4,5} Antinuclear antibodies are not helpful in making this distinction, since they are present in >85% of patients afflicted with either idiopathic or drug-induced SLE.^{4,5}

In addition to laboratory criteria, drug-induced SLE has characteristic clinical manifestations that distinguish populations of patients with drug-induced SLE from those with idiopathic SLE. Utilizing the 80 cases of drug induced SLE-like syndrome reported to Ciba-Geigy from 1963 to 1990 in countries from all over the world, several clinical findings can be noted.⁶ Cutaneous manifestations, as with idiopathic SLE, represented the most frequent finding, accounting for 34% of reported cases. Unfortunately, cutaneous manifestations are also present in > 80% of patients with idiopathic SLE. Renal and CNS manifestations were extremely rare in drug induced-SLE while being common in idiopathic SLE. Pericarditis and pericardial effusions accounted for 5% of cases.

Subsequent follow up after 1 year demonstrated the return of this patient's serology to negative antinuclear antibodies, anti-dsDNA, and antihistone antibodies, without recurrence of pericardial effusion. The development of drug-induced SLE is a well-described adverse reaction to carbamazepine therapy. Both the clinical and laboratory findings supporting the diagnosis of drug-induced SLE are present in this patient. Although the development of cardiac tamponade is a rare complication of drug-induced SLE, it has been noted with other medications.⁷ In patients receiving carbamazepine who develop chest pain and dyspnea, it is imperative to consider the possibility of drug induced cardiac tamponade/pericarditis, since its prompt recognition and treatment can be lifesaving.

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Pedal ^{99m}Tc-Sulfur Colloid Lymphoscintigraphy in Primary Isolated Chylopericardium*

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Primary isolated chylopericardium is a rare disorder in which chylous fluid accumulates in the pericardial space. In this case report of a 61-year-old man with chylopericardium, pedal ^{99m}Tc-sulfur colloid (SC) lymphoscintigraphy was performed after emergent pericardiocentesis, and when there was a recurrent massive pericardial effusion. The results showed that ^{99m}Tc-SC lymphoscintigraphy can clearly reveal the lymphodynamics in patients with primary isolated chylopericardium. This noninvasive investigation is valuable and can be easily performed either before or after pericardiocentesis.

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Key words: chylopericardium; lymphoscintigraphy; pericardiocentesis

Abbreviations: RN = radionuclide; SC = sulfur colloid

Primarily isolated chylopericardium is an unusual entity in which chylous fluid accumulates in the pericardial space with no history of trauma or intrathoracic surgery, or any evidence of mediastinal tumor. In evaluating abnormalities of the thoracic duct pathway and the chyloperi-

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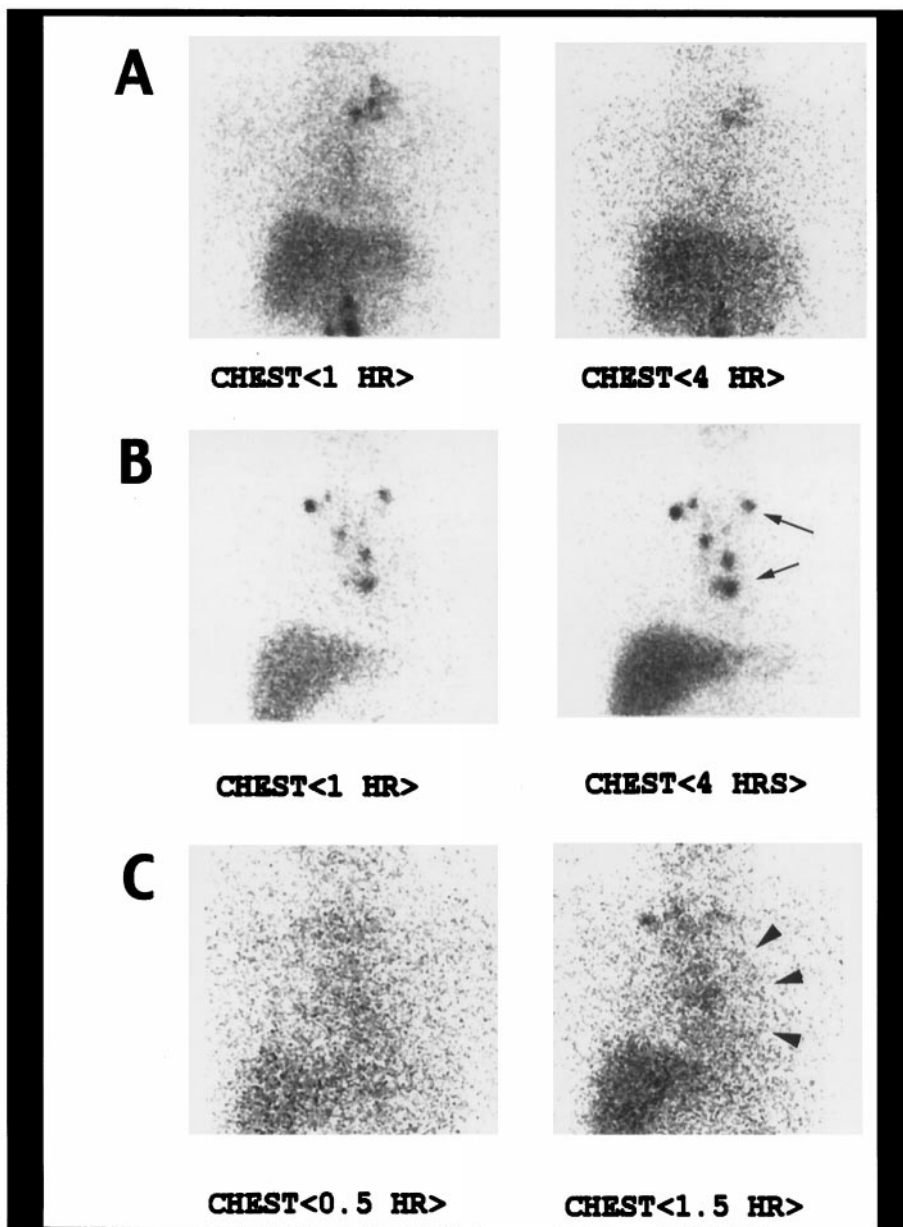


FIGURE 1. Pedal ^{99m}Tc -SC lymphoscintigraphy was performed after total drainage of the chylopericardium. As compared with the normal control (*top, A*), this patient showed an abnormal pooling of tracer in the mediastinal and hilar lymph nodes at 1 h (HR) and 4 h (HRS) after injection (*middle, B*, arrow). Four weeks later, lymphoscintigraphy was repeated once the massive pericardial effusion had reaccumulated. This picture shows not only an abnormal lymphatic flow in the mediastinal and hilar area, but also a donut-like abnormal accumulation of radiotracer in the pericardial region, at 1.5 h after injection (*bottom, C*, arrowheads).

cardium, radionuclide (RN) imaging techniques have been considered as a noninvasive method.^{1,2} Although pericardial imaging performed after oral administration of ^{131}I -triolein has been used for the diagnosis of idiopathic chylopericardium,^{1,2} there has been little experience using the pedal ^{99m}Tc -sulfur colloid (SC) lymphoscintigraphy.³

CASE REPORT

Primary isolated chylopericardium associated with recurrent syncope and dyspnea on exertion was diagnosed in a 61-year-old

man. On his first admission, chest radiography showed cardiomegaly, and an immediate two-dimensional echocardiographic study demonstrated a massive pericardial effusion. There was no history of major systemic disease, trauma, body weight loss, mediastinal irradiation, or exposure to patients with tuberculosis. Pericardiocentesis was performed via a subxyphoid approach, draining 760 mL of white-yellow chylous fluids. Triglyceride and cholesterol levels were 152 mg/dL and 183 mg/dL, respectively, in the serum, and were 506 mg/dL and 165 mg/dL, respectively, in the pericardial effusion. Microscopic studies revealed numerous foamy cells with fat glob-

ules, as shown by Sudan III staining. Three days later, the pigtail drainage tube was removed because the drained effusion amount was < 10 mL/d. Pedal ^{99m}Tc -SC lymphoscintigraphy was then performed. Compared with a normal control subject (Fig 1, *top*, A), the patient showed an abnormal pooling of tracer in the mediastinal and right hilar lymph nodes at 1 h and 4 h after injection (Fig 1, *middle*, B). He was managed by using medium-chain triglycerides as a substitution for dietary fat, and was then discharged. Unfortunately, the pericardial effusion gradually reaccumulated, becoming massive after 4 weeks. Pedal ^{99m}Tc -SC lymphoscintigraphy was repeated immediately after his second admission. This RN lymphoscintigraphy showed not only an abnormal lymphatic flow in the mediastinal and hilar area but also a donut-like abnormal accumulation of radiotracer in the pericardial sac at 1.5 h after injection (Fig 1, *bottom*, C). Radiographic lymphangiography combined with CT scanning was performed, revealing a continuous and pulsatile spread of contrast medium from the thoracic duct to the pericardial sac at the level just below the bifurcation of the tracheal carina (Fig 2, *top*, A, and *bottom*, B). There was no mediastinal tumor mass. Ligation and resection of the thoracic duct were performed, and a pericardial window was also made in order to drain the intrapericardial fluid. The patient responded well and was later discharged with diet control. Follow-up for 4 months with two-dimensional echocardiography showed no further accumulation of pericardial effusion and no evidence of pericardial constriction.

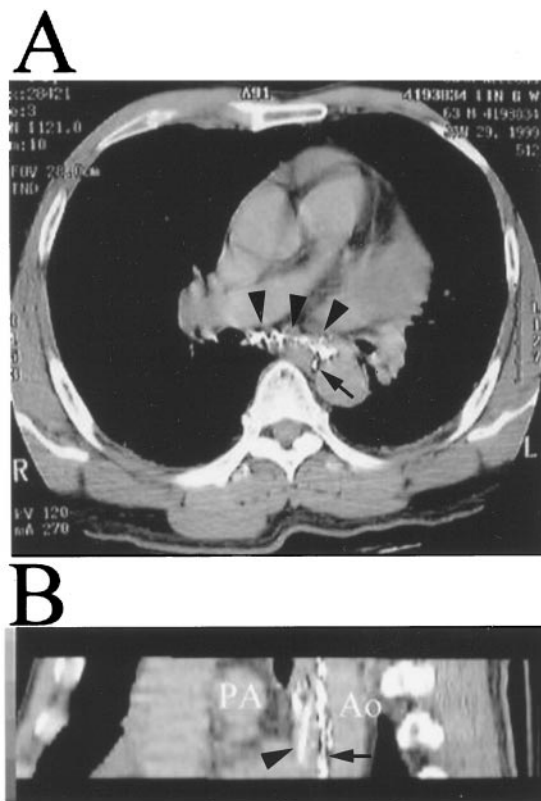


FIGURE 2. A CT scan (*top*, A) performed at the mean time of lymphangiography showed spreading of the contrast medium (arrowheads) into the pericardial cavity from the thoracic duct (arrow). Sagittal reformation of the CT scan more clearly demonstrates this abnormality (*bottom*, B, arrowheads); PA = pulmonary artery; Ao = descending aorta.

DISCUSSION

Since the first report by Groves and Effler in 1954,⁴ further reports of primary chylopericardium have increased in number. Most of these reports combined lymphangiography and CT for preoperative evaluation of abnormalities of the thoracic duct, providing a full picture of the thoracic duct pathway and its relation to the surrounding organs, and in some cases demonstrating the lymphatic leak and its interconnections with the pericardial sac, which are usually difficult to identify. To the best of our knowledge, there has been only one interesting image using ^{99m}Tc labeled human serum albumin (^{99m}Tc -HSA) to demonstrate chylopericardium.³ An interpretation of lymphodynamics using pedal ^{99m}Tc -SC in patients with primary chylopericardium has never been reported.

What is the optimal time to perform pedal ^{99m}Tc -SC lymphoscintigraphy for an idiopathic chylopericardium patient? In this case report, the first RN lymphoscintigraphic study was performed after complete drainage of the pericardial effusion. Sequential RN lymphoscintigraphic images were collected each hour. ^{99m}Tc -SC appeared in the mediastinal and bilateral hilar lymph nodes after 1 h. The intensity of radiotracer became more obvious at 4 h, compared with the results at 1 h. However, neither the pericardial space nor the subclavian vein were seen throughout the whole course of this study. This picture is completely different from that of normal people, with whom the density of ^{99m}Tc -SC reached the mediastinal and left subclavian areas within 1 h, and almost completely disappeared after 4 h. These findings suggest that the retention of ^{99m}Tc -SC in the mediastinal and bilateral hilar lymph nodes may be due to an obstruction of the lymphatic drainage system, probably at the upper mediastinum.

Repeated pedal ^{99m}Tc -SC lymphoscintigraphy performed when there was recurrent massive pericardial effusion showed not only an accumulation of radiotracer in the mediastinal and hilar area but also in the pericardial sac. A slowly accumulating pericardial chylous effusion, due to inadequate lymphatic collateral circulation, may explain the differences between panels *middle*, B and *bottom*, C in Figure 1. These findings suggest that pedal ^{99m}Tc -SC lymphoscintigraphic studies performed at different intervals are all valuable in the evaluation of the chylopericardium.

As demonstrated in the literature,⁵ lymphangiography combined with CT is the standard procedure for detecting the obstruction site of the thoracic duct or a tumor mass in the mediastinal area. With this patient, the images of the communication between the pericardium and the thoracic duct could be more clearly identified, due to improvements in computerizing techniques. Preoperatively, these images can clearly reveal the thoracic duct pathway for surgeons. However, the procedure required for lymphangiography is more time-consuming and brings more suffering to patients.

In summary, pedal ^{99m}Tc -SC lymphoscintigraphy can clearly reveal the lymphodynamics in patients with

primary isolated chylopericardium. This investigation can be performed either before or after pericardiocentesis.

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A Large False Aneurysm of the Right Ventricle Within a Giant Epicardial Lipoma*

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Lipomas, which account for approximately 10% of all neoplasms of the heart, may be detected in asymptomatic patients by chance during echocardiography, CT scan, or MRI scan. Occasionally, lipomas are complicated by arrhythmias. We describe a patient who presented with severe cardiomegaly and paroxysmal supraventricular tachycardia. An MRI scan showed a large intrapericardial lipoma with two large cavities inside communicating with each other and with the right ventricular chamber through a defect of the right ventricular wall. The mass was partially removed, and the right ventricle was patched. Surgery combined with antiarrhythmic therapy resulted in a good short-term result.

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Key words: heart neoplasms; lipoma; MRI

Primarily tumors of the heart are rare. Lipomas account for approximately 10% of all neoplasms of the heart and represent 14% of benign cardiac tumors.¹ Symptoms may be produced by large lipomas, but more often the

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patients are asymptomatic and the diagnosis is made by chance. Recently, the ready availability of high-definition noninvasive imaging, such as echocardiography, CT, and MRI, have allowed easier diagnosis. Therefore, more cases have been reported. To date, > 70 cases of lipoma have been described.¹⁻³ We describe a case of false aneurysm of the right ventricle resulting from an epicardial giant lipoma infiltrating the right ventricular wall.

CASE REPORT

A 56-year-old woman was admitted because of palpitations. Twenty years before this admission, a chest radiograph had revealed severe cardiomegaly, which was not investigated further. Nine years later, she was admitted to the hospital because of palpitations. An echocardiogram showed that the cardiomegaly was due to a large anterior mass containing echo-free spaces. On admission to the emergency department, the patient had moderate dyspnea, arterial pressure of 110/80 mm Hg, and a heart rate of 270 beats per minute. The physical examination, aside from tachycardia, was unremarkable.

The ECG showed supraventricular paroxysmal tachycardia with a ventricular rate of 270 beats per minute. The chest radiograph showed a balloon-like enlargement of the heart similar to the previous one made 20 years earlier (Fig 1).

On the basis of the echocardiographic findings, we hypothesized the existence of a communication between the right ventricular chamber and the cavity within the mass. We next obtained an MRI examination to confirm and amplify the echocardiographic findings.

A T1-weighted, ECG-synchronized MRI scan of the transaxial plane and the oblique sagittal plane demonstrated that the density of the large intrapericardial mass was consistent with fat. Two cavities, one large and the other smaller, communicating with each other, were identified inside the mass. The larger cavity communicated with the right ventricle through a large defect of the basal free wall. Gradient-echo cine sequences showed blood flow between the right ventricle and the two cavities, but neither cavity expanded during systole. The larger cavity had a inferior-superior diameter of approximately 10 cm and a lateral diameter of 8.5 cm. The heart was displaced posteriorly; the right atrial cavity was compressed, and the inferior vena cava and the hepatic veins were dilated (Fig 2).

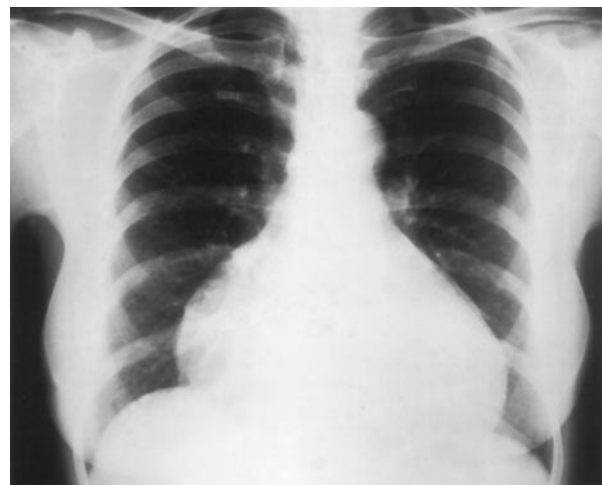


FIGURE 1. Posteroanterior chest radiograph shows an enlarged cardiac silhouette.

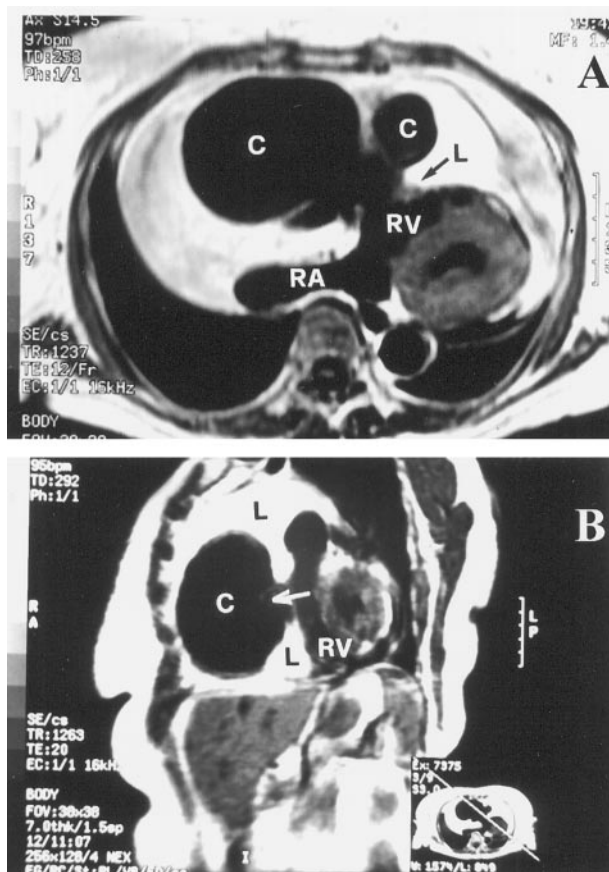


FIGURE 2. Axial (top, A) and oblique sagittal (bottom, B; compare with reference image at bottom right) nuclear magnetic resonance images of the chest display the lipoma (L), the cavity (C), and the communication (arrows) with the right ventricle residual volume (RV). The heart is displaced to the left and posteriorly. The right atrium (RA) appear compressed against the vertebral bodies.

Coronary arteriography showed healthy coronary arteries. The lipomatous mass was perfused by a large vessel originating from the right coronary artery and by small vessels originating from the circumflex and left anterior descending arteries.

On the basis of these findings, the patient underwent surgical therapy. During the operation, a large anterior intrapericardial mass was found that was not adherent to the parietal pericardium and that was attached by a stalk to the lateral wall of the right ventricle. A large cavity in the mass communicated with the right ventricular cavity through an orifice that had a diameter of 3 cm. The right ventricle was patched, but the lipoma could be only partially removed, because the right coronary artery was encased within it.

Pathologic examination demonstrated that the mass was composed of fatty cells, aggregated in a lobular pattern with a network of small vessels. The inner surface of the cavity was lined by flattened cells. The endothelial nature of these cells was demonstrated by the expression of factor VIII antigen and CD34 antigen, which were detected by immunohistochemical reaction. The orifice connecting the right ventricle to the cavity was composed of dystrophic muscular fibers mixed with fatty cells. The orifice also was delimited by the endothelium. The patient's recovery was fairly good with only one occurrence of atrial fibrillation. She was discharged from the hospital with sotalol, 80

mg bid, prescribed. After 12 months, she was asymptomatic. The patient will be observed with a yearly MRI scan.

DISCUSSION

Cardiac lipomas are very rare. They can arise subendocardially, subepicardially, or from the myocardium.¹⁻⁴ In the case we report, the lipoma arose from the epicardium and invaded the right ventricular myocardium. Fatty infiltration of the right ventricular wall and the associated myocardial atrophy, which were demonstrated by histologic findings, led to an area of reduced resistance, which facilitated the formation of the right ventricular false aneurysm. We presume that the communication was already present at the time of the first chest radiograph, considering that the enlargement of the cardiac shadow had not increased. The slow process leading to the defect of the right ventricular wall and, consequently, to the formation of the aneurysm allowed the formation of endothelial cells in the cavity. As far as we know, while a case of right atrial lipoma with cystic regions communicating with the atrial cavity has been published,⁴ the literature does not show any case of communication between the right ventricular chamber and a cavity inside a large intrapericardial lipoma. Cases of both atrial and ventricular arrhythmias as complications of cardiac lipomas have been reported. Cooper et al⁵ described a case of atrial flutter in a child with an intrapericardial lipoma compressing the left atrium, which was treated by the excision of the mass.

In the present era, echocardiography, CT scans, and MRI scans allow the diagnosis of cardiac masses. Echocardiography is the first examination to be performed in a case of cardiomegaly in an otherwise healthy subject. In the case reported in this paper, echocardiography revealed not only the diagnosis of the mass, but also the detection of the defect of the right ventricular wall. Tissue characterization of a mass remains difficult to obtain by echocardiography. MRI, however, can demonstrate the lipomatous nature of a mass and can delineate more precisely its spatial extension.⁶ Coronary arteriography may define coronary anatomy, may demonstrate a vascular pedicle arising from a coronary artery, and thus, as in this case, may guide the surgical approach. In our patient, the surgeon judged that the lipoma was only partially resectable. No recurrences are described after complete surgical removal.² Due to incomplete resection of the lipoma, the long-term prognosis for our patient is unpredictable.

In conclusion, we report a unique case of a large epicardial lipoma involving the right ventricular wall, with consequent disruption of myocardial fibers and the formation of a false aneurysm in the right ventricle. Compression of the right atrium probably induced atrial flutter with 1:1 atrioventricular conduction. Partial surgical removal of the mass, combined with antiarrhythmic therapy, resulted in a good short-term result.

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Paraneoplastic Pemphigus Associated With Bronchiolitis Obliterans*

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Paraneoplastic pemphigus (PNP) is an autoantibody-mediated mucocutaneous blistering disease associated with underlying neoplasms. Autoantibodies of PNP bind to the plakin family of cytoplasmic proteins and desmogleins of cell-surface target antigens. We describe a 36-year-old female patient with PNP who had non-Hodgkin's lymphoma, and who developed bronchiolitis obliterans and died of respiratory failure. Autopsy findings confirmed luminal narrowing of bronchioles by scarring, which is a histopathologic feature of bronchiolitis obliterans. After the onset of respiratory failure, the reaction of autoantibodies against the plakins detected by immunoprecipitation at the onset of PNP disappeared with negative immunofluorescence within the bronchial epithelium. It is thought that autoantibodies against some of these antigens play a role in causing acute inflammation of the respiratory epithelium. In treating PNP, the possibility of the patient developing the lethal complication bronchiolitis obliterans should be kept in mind. Furthermore, prevention of the initial autoantibody-mediated injury to the respiratory epithelium should be an important treatment goal.

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Key words: autoantibody; bronchiolitis obliterans; paraneoplastic pemphigus; plakins; respiratory failure

Abbreviations: DP = desmoplakin; ENV = envoplakin; PER = periplakin; PNP = paraneoplastic pemphigus;

Paraneoplastic pemphigus (PNP), a rare autoimmune bullous disease related to underlying neoplasia, is characterized by distinctive clinical symptoms such as severe, painful mucosal erosions and polymorphous skin lesions.¹ Histopathologic hallmarks include acantholysis and interface dermatitis or keratinocyte necrosis.² PNP patients develop characteristic autoantibodies directed against multiple antigens, mostly identified as members of the plakin family of intermediate filament-associated proteins and the desmogleins of the cadherin family in desmosomes.^{3–6} Since the first report of PNP by Anhalt et al,¹ several cases of PNP with respiratory failure caused by airway obliteration have been reported,^{7–9} but these reports did not describe the histopathologic features of the lung lesions in detail.

We have recently encountered an additional Japanese female patient with PNP associated with non-Hodgkin's lymphoma who developed severe airflow obstruction and died of respiratory failure. An autopsy examination revealed scarring, which narrowed the lumens of terminal bronchioles, which is the typical histopathologic feature of bronchiolitis obliterans.¹⁰ Another unique finding is that after the onset of respiratory failure, the reaction of autoantibodies against the plakins detected by immunoprecipitation at the onset of PNP disappeared with negative immunofluorescence within the bronchial epithelium. In this report, we describe precisely the histopathologic features of this lung disease and consider the prevention of autoantibody-mediated inflammation of the respiratory epithelium that results in scarring.

CASE REPORT

In September 1996, a 36-year-old woman developed infiltrating erythema on her hands and feet, which was accompanied by pseudomembranous conjunctivitis (Fig 1, *top left, A*) and painful erosions and blisters on the lips and oral mucosa (Fig 1, *top right, B*) after radiotherapy following intensive chemotherapy for non-Hodgkin's lymphoma (stage Csb, follicular, medium-sized, B-cell), which had ended in March 1996. The chemotherapy agents used were combinations of methotrexate, mitoxantrone hydrochloride, cyclophosphamide, vincristine, etoposide and prednisolone, ranimustine and enocitabine, and carboplatin. In addition, vulvar and cervical erosions were seen. Productive cough and shortness of breath also were present. Based on an initial diagnosis of herpes simplex infection, an IV infusion of acyclovir was administered, but the patient's condition worsened. Histopathologic examination of a skin biopsy specimen showed mild suprabasilar acantholysis, individual keratinocyte necrosis, and vacuolar interface dermatitis, features that are suggestive of PNP. The diagnosis of PNP was confirmed by three findings. First, direct immunofluorescence showed pronounced IgG and C₃ deposits in the cell surfaces of the epidermis and along the dermoepidermal junction (Fig 1, *bottom left, C*). Second, indirect immunofluorescence demonstrated the presence of antibodies that reacted against the epithelial cell surface in the rat urinary bladder (Fig 1, *bottom right, D*). Third, an immunoprecipitation showed a strong reactivity against the 250-, 230-, 210-, 190-, and

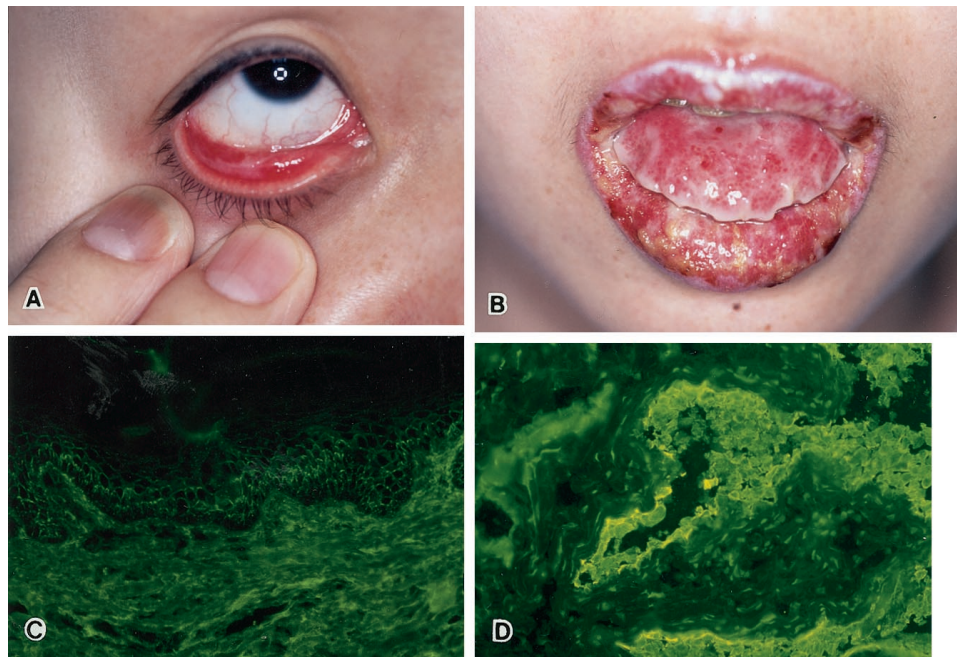


FIGURE 1. Mucosal lesions of PNP. *Top left, A:* pseudomembranous conjunctivitis. *Top right, B:* erosive lesions on the lips and tongue. Immunofluorescence studies at the onset of PNP. *Bottom left, C:* direct immunofluorescence shows IgG deposits on the cell surfaces and basement membrane zone in a skin biopsy specimen. *Bottom right, D:* indirect immunofluorescence of rat bladder section detected IgG autoantibodies reactive with transitional epithelia in the patient's serum (original magnification $\times 200$).

170-kd PNP antigens, as well as the 130-kd protein (Fig 2, lane 1). The patient was treated orally with 50 mg of prednisolone daily for a month and 40 mg daily for another month, and her skin and lip lesions improved quickly. While she became free from severe mucosal pain, oral and conjunctival mucosal lesions persisted with minimal improvement. All the respiratory symptoms also seemed to improve. The dose of prednisolone was slowly tapered during the next 2 months to 10 mg.

Six months after the onset of PNP, the patient developed severe dyspnea with wheezing. On pulmonary function testing, her FEV₁ decreased to 1,120 mL (41% of the predicted value), maximal flow at 50% of FVC decreased to 730 mL (16.3% of the predicted value), maximal flow at 25% of FVC decreased to 310 mL (12.9% of the predicted value), and PaO₂ decreased to 66 mm Hg. A chest radiograph and CT scan of the lungs showed no specific findings. No clinical or laboratory evidence of infection was present. A diagnosis of bronchiolitis obliterans was considered. Immunoprecipitation detected antibodies only against 170- and 130-kd proteins in the serum at this time (Fig 2, lane 2). Standard treatments for asthmatic bronchiolitis were not effective, but 30 mg prednisolone combined with 175 mg cyclosporine with the inhalant beclomethasone dipropionate showed some effect for a limited period. Bronchoscopy performed 3 months after the onset of dyspnea showed only moderate bronchial mucosal edema. Bronchial biopsy specimens showed no obvious cantholysis or blister formation by respiratory epithelial cells. Direct immunofluorescence of the biopsy specimen did not show any deposition of Igs or complement components. Despite treatment for respiratory failure with noninvasive positive-pressure ventilation combined with an inhalant steroid, dyspnea gradually worsened and pulmonary function continued to deteriorate. Within the last month of the patient's life, respiratory tract infections

occurred repeatedly, and the patient died of respiratory failure 10 months after the onset of dyspnea.

A postmortem examination of the lung revealed extensive cavitation caused by fungal infection and hemorrhagic necrosis. The bronchial epithelium showed squamous metaplasia and chronic inflammatory infiltrates with associated fibrin deposition. Alveolar ducts were dilated significantly with abundant mucin inside. No nuclear inclusion bodies were found in alveolar epithelial cells. In addition, where healthy lung structures were relatively preserved, luminal narrowing was prominent in terminal bronchioles (Fig 3). In these areas, suprabasilar acantholysis was not observed; ciliated bronchiolar epithelial cells were partially exfoliated with the formation of granulation tissue and were infiltrated by a small number of lymphocytes and foamy macrophages (Fig 3, *top right, B*). Elastica van Gieson staining showed a remarkable mural thickening of bronchioles as a result of submucosal collagenosis (Fig 3). Direct immunofluorescence of autopsy specimens did not show any deposition of Igs or complement components within the bronchial epithelium.

DISCUSSION

Our patient died of progressive airflow obstruction resulting in respiratory failure. Autopsy clearly demonstrated luminal narrowing that resulted from submucosal collagenosis, which is consistent with the effects of bronchiolitis obliterans.¹⁰ Because no other known causes of this condition, such as smoking, infections, collagen diseases, mineral dust or toxic/fume exposure, or transplantation,¹⁰ were found, its occurrence was ascribed to PNP.

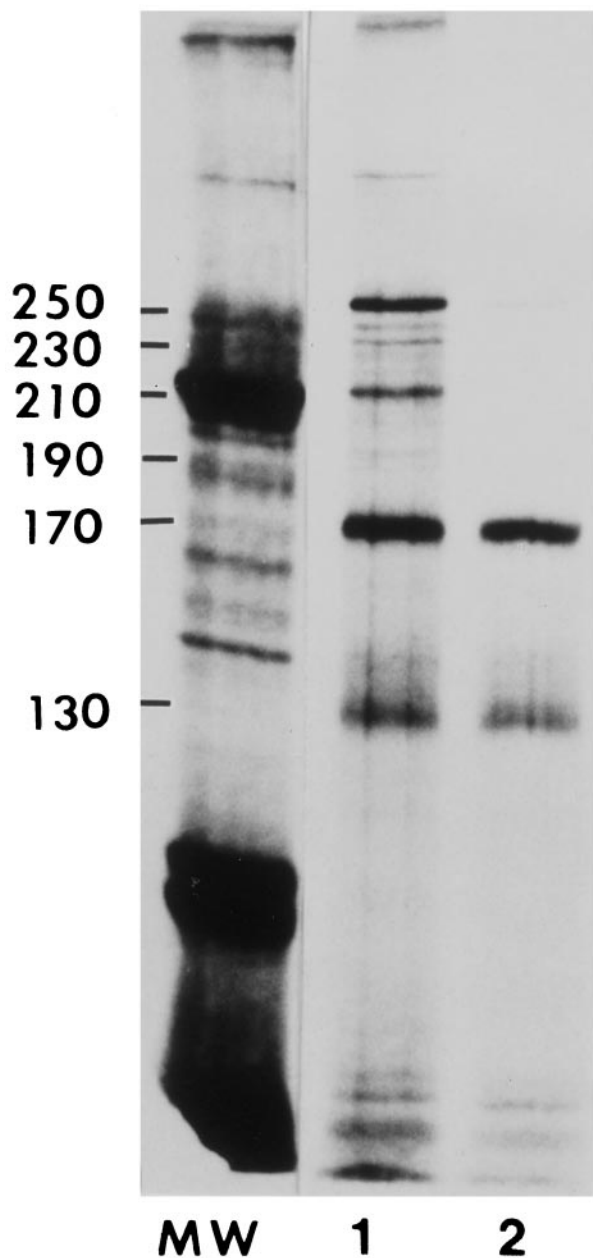


FIGURE 2. Immunoprecipitation showed two sera taken from our patient. The lane labeled MW is for molecular markers. Lane 1 shows the reaction for the serum of our patient obtained at the onset of PNP. Lane 2 shows the reaction for the serum of our patient obtained after the onset of respiratory failure.

In this report, we described the case of a patient with PNP with clear histopathologic confirmation of bronchiolitis obliterans.

In previous reports, airflow obstruction was not evident at the onset of PNP and developed at least a few months later.⁷⁻⁹ Bronchiolitis obliterans is caused by severe inflammation and destruction involving the bronchiolar epithelium that induces fibrosis and remodeling of bronchiolar walls. Our patient showed some respiratory symptoms

at the onset of PNP, suggesting the presence of acute bronchiolitis. Because of the patient's good response to prednisolone, this symptom was not thought to be infection but, rather, an autoimmune reaction. Neither biopsy nor autopsy specimens near the areas showing bronchiolitis obliterans-like changes disclosed findings of an acute-phase inflammation. This absence is probably because the specimens were obtained during the late stage of the disease. A biopsy was deferred until > 9 months after the onset of PNP, since respiratory symptoms present at the onset of PNP largely abated with initial therapy. Later severe respiratory failure further delayed performance of a bronchoscopic biopsy. Although high-dose prednisolone therapy appeared to suppress acute bronchiolar inflammation that was present at the onset of PNP, mucosal lesions persisted until the patient's death. Our therapy proved insufficient to quickly and completely suppress the inflammation, and postinflammatory fibrosis of the bronchioles supervened.

In PNP patients with respiratory complications, the deposition of IgG has been demonstrated on bronchial epithelial cell surfaces and/or basement membranes.⁷⁻⁹ Nousari et al⁹ also proved that acantholysis-like lesions developed in the bronchial pseudostratified columnar epithelium. PNP patients develop characteristic autoantibodies against multiple antigens, including a diagnostic antigen complex of proteins with relative molecular weights of 250, 230, 210, 190, and 170 kD. The 250- and 210-kD proteins were identified as desmoplakin (DP) I and DP II, which are the major cytoplasmic plaque proteins of desmosomes. The 230-kD protein was bullous pemphigoid antigen 230, the major plaque protein of the epidermal hemidesmosomes.^{1,4,5} The 210-kD protein was subsequently recognized to be a doublet of DP II and envoplakin (ENV).³⁻⁵ The 190-kD protein corresponds to periplakin (PER), and the 170-kD is a transmembrane cell-surface protein that has not been identified.^{4,5} DP I, bullous pemphigoid antigen 230, DP II, ENV, and PER belong to the plakin family of proteins, which are involved in the organization of intermediate filaments and cytoskeletal architecture that plays an important role in the anchorage of the cytoskeleton to filament attachment sites on plasma membranes.^{4,5} The 130-kD protein corresponds to desmoglein 3 (pemphigus vulgaris antigen), a member of the cadherin family of cell-to-cell adhesion molecules in desmosomes.^{5,6} The healthy human bronchial epithelium expresses DP I, bullous pemphigoid antigen 230, DP II, ENV, PER, and plectin but neither the 170-kD PNP antigen nor desmoglein 3.⁹ Therefore, tissue-bound autoantibodies have been considered important to epithelial cell detachment and inflammation in the bronchial epithelium. In the present case, however, no deposition of IgG or C₃ was demonstrable in respiratory mucosa, another negative finding that is explained by the late timing of the histologic examination. After the onset of respiratory failure, reaction against the plakins, DP I, bullous pemphigoid antigen 230, DP II/ENV, and PER, which were detected by immunoprecipitation and were present at the onset of PNP, disappeared. This reactivity might already have been decreased by ther-

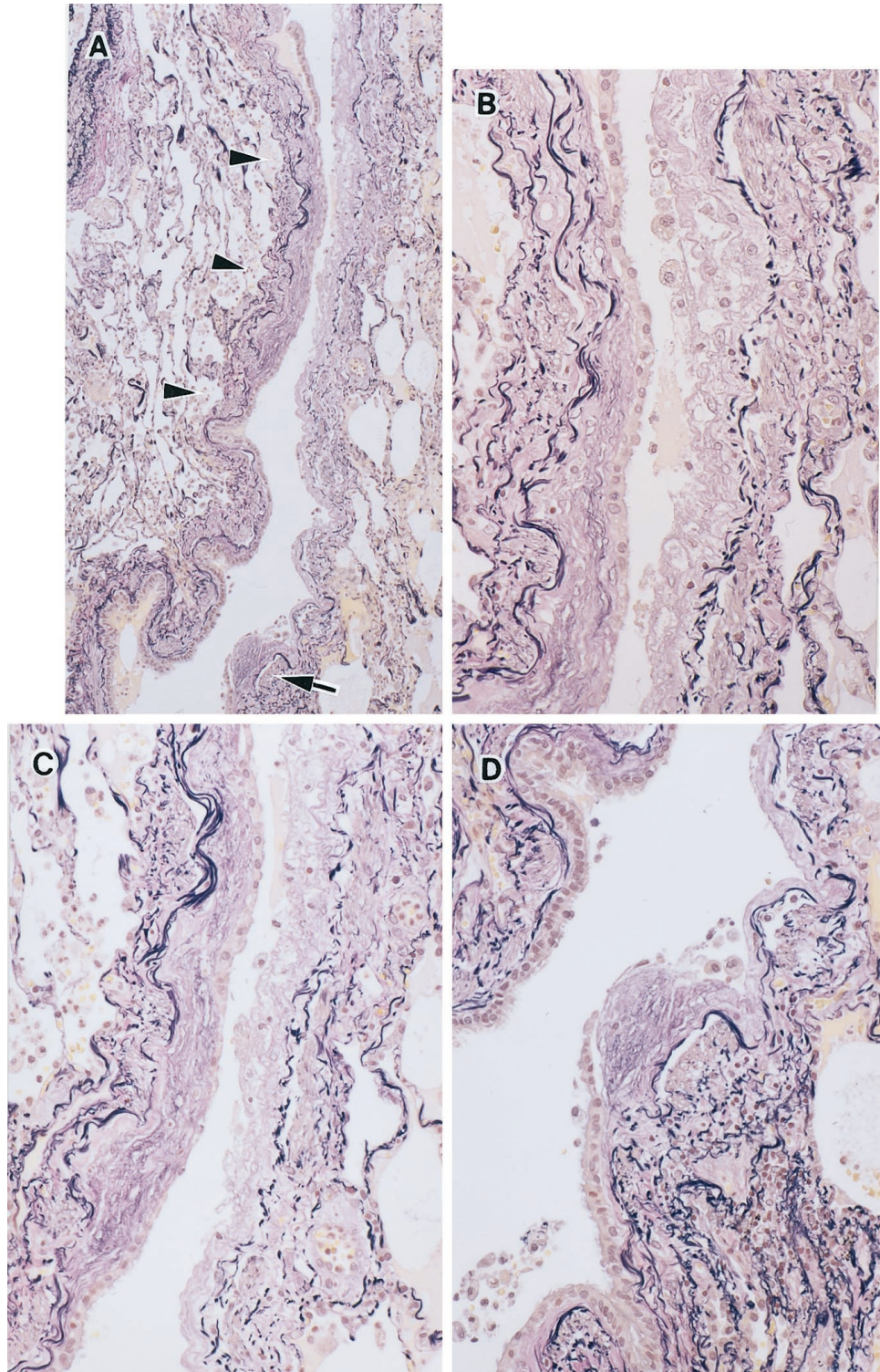


FIGURE 3. Longitudinal sections of affected bronchioles. Note the luminal stenosis caused by submucosal fibrosis (*top left, A*; original magnification $\times 25$). The sites indicated by arrowheads and arrow in *top left, A*, are depicted at higher magnifications in *bottom left, C* ($\times 66$), and *bottom right, D* ($\times 66$), respectively. Bronchiolar epithelial cells are partially exfoliated and replaced by granulation tissue, in which the infiltration of lymphocytes and foamy macrophages is seen (*top right, B*; original magnification $\times 66$). *Top right, B*, and *bottom left, C*, represent serial sections. Elastica van Gieson staining was used in all parts of the figure.

apy, which may explain the negative immunofluorescence finding for tissue-bound IgG and complement in the respiratory mucosa. These findings suggest that some of the autoantibodies against these proteins were deposited in the respiratory mucosa at the early stage and played a role in causing the acute inflammation, although another initiative factor may be needed for these autoantibodies directed against intracellular antigens to bind to their target antigens within respiratory epithelium.

The association of bronchiolitis obliterans must be kept in mind when we treat patients with PNP. In particular, symptoms of respiratory epithelial inflammation at the onset of PNP should demand intervention. Once severe inflammation occurs in bronchioles, an irreversible fibrotic reaction leading to bronchiolitis obliterans appears to follow. Therefore, quick and complete suppression of acute-phase inflammation is essential. Although typical immunosuppressive therapy may have suppressed the acute phase of inflammation and abolished tissue-bound IgG, this treatment did not prevent bronchiolar fibrosis. Therefore, additional therapy must be needed. Recently, Schoen et al¹¹ have reported that immunoapheresis was effective against the oral mucosal lesions of PNP, which are well known to be refractory to standard immunosuppressive therapy. Therefore, immunoapheresis may be able to prevent the development of bronchiolitis obliterans, especially when used in combination with intensive immunosuppressive drug treatment in the early stage of PNP.

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