Selected Reports

Spontaneous Dissection of Three Major Coronary Arteries Subsequent to Cystic Medial Necrosis*

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This case report describes the devastating consequences of spontaneous coronary dissection in a 36-year-old female patient. Surgical revascularization was attempted, but diffuse myocardial infarction developed. The patient was bridged to heart transplantation but died secondary to multiple organ failure. To our knowledge, this is the only reported case of spontaneous dissection of the three main coronary arteries due to severe cystic medial necrosis.

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Key words: coronary artery; cystic medial necrosis; dissection; spontaneous

Abbreviations: CK = creatine kinase; LAD = left anterior descending artery; RCA = right coronary artery;

We present a case of a spontaneous dissection of the three main coronary arteries due to severe cystic medial necrosis. To our knowledge, this is the first such case ever reported.

Case Report

A 36-year-old white woman experienced prolonged crushing precordial pain that started during light exercise. On admission to the hospital, acute anterior myocardial infarction was diagnosed and IV alteplase was administered. Cardiac enzymes were moderately increased (creatine kinase [CK]) max of 1,500 U/L, 13% MB fraction), and echocardiography revealed only a limited region of hypokinesia confined to the left ventricular apex. The patient was referred to a tertiary hospital 2 days later so that diagnostic coronary arteriography and subsequent revascularization could be performed, if indicated.

The patient had a fairly unremarkable medical history. She had two healthy children and underwent surgical sterilization 5 years before, at which time oral contraceptives were stopped. There was no history of hypertension, but she was a heavy smoker (1 pack/d) and had moderately elevated cholesterol levels (total cholesterol, 265 mg/dL; low-density lipoprotein cholesterol, 169 mg/dL). Because of regular bouts of migraine (once a month), she intermittently used ergotamine.

Twelve hours after referral, the patient was urgently catheterized because of unstable angina. The coronary angiogram showed dissection of both the right coronary artery (RCA) and the left anterior descending artery (LAD). In the middle portion of the RCA, a well-delineated intimal flap and thrombus were visualized (Fig 1, top). The ostium of the LAD was irregular and concealed the origin of the dissection progressing into the middle part and resulting in Thrombolysis in Myocardial Infarction Trial flow grade 1 (Fig 1, bottom). There was an intermediate lesion in a small intermediary branch. Because the disease was so widespread, no attempt was made to perform balloon dilatation or stent implantation. The patient was treated with heparin, aspirin, metoprolol, and nitrates, and a semiurgent surgical revascularization was scheduled. The following day, recurrent myocardial ischemia prompted emergency coronary artery bypass grafting. The left internal thoracic artery was sequentially grafted on the first diagonal branch and the distal LAD. The right internal thoracic artery was used as a graft on the intermediary branch, and a saphenous vein was grafted on the RCA. Weaning from cardiopulmonary bypass was difficult because of refractory cardiac failure. Inotropic therapy with milrinone and dobutamine was infused, and the patient was eventually able to be weaned off bypass. After < 1 h, however, she became hypotensive and developed therapy-resistant ventricular fibrillation. She was transferred to the operating room while internal cardiac massage was performed, and extracorporeal circulation was reinitiated. Despite intra-aortic balloon counterpulsation and maximal inotropic support, attempts to wean her from bypass were unsuccessful, and a biventricular assist device (Abiomed BVS 5000; Abiomed, Inc; Danvers, MA) was inserted. The ECG showed inferior and anterolateral infarction and CK-MB reached a peak of 420 U/L (CK, 16,164 U/L).

During the following days, based on echocardiographic evaluation, it was decided that recovery of the severely damaged right and left ventricles was virtually impossible. The patient was, therefore, listed for urgent heart transplantation. After 18 days of biventricular assist support, she ultimately received a marginal donor heart (hypotensive and unstable donor, high inotropic support) and developed right heart failure that finally resulted in multiple organ failure and death.

The explanted heart showed widespread infarction of the left and right ventricle. In the middle part of the RCA, the lumen was obliterated by a nearly circumferential dissecting intramural hematoma (Fig 2, top, A). The left coronary artery was dissected starting from its ostium and progressing into the LAD and the circumflex artery over their full length. Both the dissected and nondissected parts of the coronary tree showed extensive cystic medial necrosis with loss of smooth muscle cells, fragmentation of elastic fibers, and accumulation of acid mucopolysaccharides.

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CHEST / 116 / 5 / NOVEMBER, 1999 1473
Although less pronounced, both arterial bypass conduits and the ascending aorta exhibited the same changes.

**DISCUSSION**

Spontaneous dissection of the coronary arteries is a rare entity, mostly recognized postmortem in young victims of sudden death. It is the result of an intramural hematoma in the media of the arterial wall that creates a false lumen. Expansion of this lumen through blood or clot accumulation leads to compression of the real lumen and myocardial ischemia. An intimal tear is only seldom observed. Most reported patients are apparently healthy, young to middle-aged women (78%; mean age, 40 years) without overt risk for coronary artery disease and without severe coronary atheromatosis. A review by Jorgensen et al of the reported cases depicts poor survival (30%) and frequent postmortem diagnosis (69%). In women with spontaneous coronary dissection, there is a predilection for the left coronary system (84%), whereas in men, the right coronary artery is usually affected (67%).

The etiology remains uncertain, although a significant proportion of these women (25%) are in the puerperium. The use of oral contraceptives and the exceptional hormonal balances in the peripartum period are supposed to weaken the arterial wall and to predispose it to rupture or dissection.

Other reported possible causes of spontaneous coronary dissection are cocaine abuse and intense physical exercise.

In the absence of an intimal tear, primary disruption of the vasa vasorum and subsequent hemorrhage into the media of the arterial wall has been proposed as an underlying mechanism.

Several authors noted the presence of periadventitial inflammatory infiltrates, with frequent preponderance of....
Cystic medial necrosis of the coronary arteries is a rare finding, and few case reports have been published illustrating spontaneous coronary dissection due to this arterial wall anomaly. \(^1\) \(^6\) \(^7\) This disease involves focal fragmentation of elastic fibers and loss of smooth muscle cells of the media associated with deposits of varying amounts of acid mucopolysaccharides. These lesions are typically present in the ascending aorta of patients with Marfan's syndrome and predispose them to aortic dissection. Such abnormalities are, to a much lesser extent, seen with advancing age and appear to be the result of chronic injury (eg, arterial hypertension) of great vessels. Our patient showed no stigmata of Marfan's syndrome and had no family history of this inherited disease.

The outlook for patients presenting with spontaneous coronary artery dissection is rather grim, as it usually provokes acute and severe myocardial ischemia that often leads to sudden death. Angiographic demonstration of the dissection in patients who present with ongoing ischemia should prompt urgent revascularization. The available modalities, however, are less than ideal and should depend on the persistence of myocardial ischemia, the area at risk, and the number of vessels involved. \(^8\) In theory, thrombolytic therapy could lyse a compressing intramural clot, but it could also contribute to the expansion of an intramural hematoma. In the case of a well-localized dissected coronary lesion, stenting is considered standard therapy. With a complicated dissection involving thrombus and a nearly occluded lumen, however, this approach could prove difficult. Although surgical revascularization in case of multivessel involvement seems the most controlled strategy, the anastomosis of a graft circuit on a dissected coronary artery is hazardous. In the case of severe heart failure, bridging to heart transplantation is probably the most reasonable choice.

REFERENCES


Pneumoparotid due to Spirometry*

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Pneumoparotid has been described in patients who generate increased intraoral pressures when playing wind instruments, while coughing, and when undergoing dental work. Some patients have intentionally created pneumoparotid to avoid duties at school or in the military, or to gain attention. We describe a patient who developed pneumoparotid during pulmonary function testing. The diagnosis of pneumoparotid depends on a suggestive clinical situation and glandular swelling with or without crepitus. Observation of aerated saliva per Stensen's duct or in the parotid duct and/or gland by any imaging study is diagnostic if infection with a gas-forming organism can be reasonably excluded. No specific treatment is required, other than the avoidance of predisposing activities.

(CHEST 1999; 116:1475–1478)

Key words: pneumoparotid; pneumoparotitis; pulmonary function testing; spirometry

The major salivary glands are the parotids, the submandibulars, and the sublinguals. \(^1\) The parotid gland, named for its proximity to the ear (para-otid), produces about 25% of the saliva used for food digestion and lubrication and is a source of secretory IgA. Unlike the submandibular salivary glands, normal parotids are not usually palpable \(^2\) and parotid enlargement is suggestive of disease. The differential diagnosis of parotid gland enlargement includes both acute and chronic disorders. Etiologies can be divided among infections (viral, bacterial, fungal, and mycobacterial); autoimmune disorders (eg, Sjogren's syndrome and Wegener's vasculitis); malnutrition; endocrine disorders (eg, diabetes, Cushing's disease, and hypothyroidism); noninfectious granulomatous diseases (eg, sarcoid); liver failure; drugs; allergy; duct obstruction; pregnancy; and a host of benign and malig-
nent neoplasms. Although parotid gland enlargement due to air insufflation has been described in the past (vide infra), it is not mentioned in most comprehensive reviews and has not previously been reported in patients performing pulmonary function tests.

CASE REPORT

A 41-year-old male smoker was referred to the pulmonary diagnostics laboratory because of persistent wheezing and dry cough for 4 months after a viral upper respiratory tract infection. He had been treated with albuterol by metered-dose inhaler on an as needed basis and with fluticasone, two puffs bid, by metered-dose inhaler. The patient had pulmonary function testing consisting of spirometry and measures of gas-diffusion lung volumes and single-breath carbon monoxide diffusing capacity. The patient used a nose clip and scuba-type mouthpiece while performing pulmonary function tests. He had no coughing during test maneuvers, and β-agonist aerosols were not used. Immediately after the full battery of tests, the patient noticed left facial swelling and a sense of fullness without pain. The patient had noncrepitant, nontender left facial swelling anterior and inferior to the left ear. An intraoral examination of Stensen’s duct was normal, but the parotid gland was not massaged or compressed. Examination of the chest showed normal breath sounds without wheezing. The results of pulmonary function testing, including spirometry, were completely normal. A noncontrast CT scan of the head was done within 1 h of testing at a time when the facial swelling had begun to resolve. Air was demonstrated within the left parotid gland and in Stensen’s duct (Fig 1). The patient was then questioned closely about similar episodes, and he recalled that he had bilateral facial swelling that quickly resolved after an airplane flight, and that he could sometimes produce facial swelling at will by coughing or blowing forcefully against his closed mouth. The patient was advised to return to the clinic if the glandular swelling failed to completely resolve or if facial tenderness or fever developed.

DISCUSSION

The presence of air within the parotid gland has variously been called pneumoparotitis, pneumosalivadenitis, and pneumatocele glandulae parotis. Parotid swelling after general anesthesia or surgery has been called anesthetic or surgical mumps, and there are case reports of acute parotid swelling after endoscopy, but there is little evidence to confirm that these cases are due to pneumoparotid. In the absence of demonstrable inflammation or infection, the term pneumoparotid seems most appropriate for demonstrable air within the parotid gland. The parotid gland is a subcutaneous structure located in the area between the mandibular ramus and the external auditory canal anterior and inferior to the ear, and it drains into the oral cavity by way of Stensen’s duct (also known as the parotid duct). Stensen’s duct leaves the lateral surface of the gland and runs over the lateral surface of the masseter muscle before diving into the buccinator muscle and emerging into the oral cavity just lateral to the second upper molar. In the absence of a gas-producing bacterial parotitis, gas in the parotid duct and/or gland is assumed to be due to the reflux of pressurized air from the mouth into Stensen’s duct. The anatomic features of Stensen’s duct that are thought to prevent reflux of air, saliva, and bacteria from the mouth into Stensen’s duct are as follows: (1) the orifice of the duct has a smaller diameter than the duct itself; (2) the duct opening forms a slit that is embedded in redundant mucosal folds, and (3) when the cheeks are flattened and buccal musculature is contracted, the duct is compressed in its lateral course along the masseter muscle and in its passage through the buccinator muscle. Some authors suggest that contraction of the buccal musculature with the cheeks flattened instead of distended may help prevent insufflation of the parotid during forced exhalation by obstructing Stensen’s duct. It is thought that a normal parotid duct may become dilated due to transient obstruction with mucus, which then leads to initial ductal incompetence and reflux of air into the parotid. This may set in motion a cycle of duct dilation, sialectasis, further ductal incompetence, and insufflation. It is unclear why pneumatic inflation of the submandibular salivary glands is rare, since their ducts (Wharton’s ducts) are shorter and straighter in their path from the glands to either side of the sublingual frenulum.

Pneumoparotid usually presents as a unilateral or bilateral facial swelling over the parotid region. The swelling may be painless or tender, and it may be associated with warmth and erythema. There is crepitus on palpation of the gland in 50% of patients and frothy saliva or air bubbles may be observed emanating from Stensen’s duct during massage of the gland. Swelling may resolve over minutes to hours or it may take days. Extension of air beyond the parotid may produce subcutaneous emphysema of the face, neck, and mediastinum and subsequent pneumomediastinum. Plain radiographs films may show air in the soft tissues and may even outline the course of the parotid duct. Sialography may demonstrate air bubbles in the duct and may show sialectasis if repeated episodes of pneumoparotid have resulted in infection and destruction of the duct. Ultrasound has been used to demonstrate air within the parotid gland and duct. CT elegantly shows air in both the duct and gland. A suspension of dilute contrast placed in the

![Figure 1. Computerized axial tomogram of the head at the level of the parotid glands. The upper arrow indicates air in the left Stensen’s duct. The lower arrow indicates the left parotid, which contains pockets of air scattered throughout the gland.](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21933/ on 03/31/2017)
mouth may be shown to reflux into the parotid duct and gland by fluoroscopy23 or by CT scan.24 Although visualization of air in the parotid gland or duct is impressive, a diagnosis of pneumoparotid may be made clinically when there is a predisposing factor and when the gland is enlarged and crepitant, and when air bubbles are observed emanating from the duct orifice.17 Treatment of this condition is rather simple. Avoidance of further increases in intraoral pressures is essential,15 and the glandular enlargement usually resolves spontaneously. Some clinicians use prophylactic antibiotics directed toward the pneumococcus, Haemophilus influenzae and Staphylococcus aureus,1,2 because of the fear that refluxed oral bacteria may cause an acute suppurative parotitis leading to a true pneumoparotitis.5,11,21

The first description of pneumoparotid is credited to Hyrtl in 1865, as noted by Markowitz-Spence et al,1,3 and there have been many subsequent reports (Table 1). Forceful exhalation with a closed mouth can generate intraoral pressures of 150 cm H2O20 which does not seem to insufflate the parotid gland in most people. Pneumoparotid has been described in patients who generate increased intraoral pressures due to facial tics or habits.4,5,10,12,20,23,24 These maneuvers may consist simply of forcefully exhaling against a closed mouth5,10,12,17,23 or against an obstruction at the mouth, such as a hand.5,22 Some patients are unaware of these maneuvers until the parotid enlarges, and other patients seem to intentionally create this problem for secondary gain. Patients who intentionally insufflate their parotids may have psychologic problems7,10,23 or may have an adjustment reaction to school13,25 or parental discipline.22 In general, if the patient can be convinced to cease the maneuvers that increase intraoral pressures, subsequent episodes of pneumoparotid do not occur.4

Our patient had left pneumoparotid confirmed by a CT scan that showed air in Stensen’s duct and in the parotid gland. He probably insufflated air into the gland as a result of the increased intraoral pressures generated during spirometry. Unfortunately, we did not massage the gland to look for air in the duct, which would have obviated the necessity of performing CT scanning. This entity should be considered in patients who develop acute or recurrent facial swellings in association with such maneuvers as coughing, sneezing, nose blowing, or performance of pulmonary function testing. Once the diagnosis has been confidently made, treatment usually consists of cessation of the precipitating activity, reassurance, and possibly the use of prophylactic penicillinase-resistant antibiotics. Extension of air into the tissues surrounding the parotid and dissection into the mediastinum and pleural space is a very rare occurrence. In view of the recommendations made by Ferlito et al10 and Greisen,17 spirometry with cheeks flattened and buccal musculature contracted may prevent parotid insufflation during forceful exhalation.

Table 1—Situations or Maneuvers Reported To Produce Pneumoparotid

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Aortic dissection is a catastrophic event that is commonly associated with severe pain, massive hemorrhage, and high mortality. In this report, we present the case of a 31-year-old man who presented with painless, hemorrhagic left pleural effusion. Further investigation revealed a 9-cm dissecting ascending aortic aneurysm that was thought to be due to a congenitally bicuspid aortic valve. We suggest that ascending aortic aneurysm be included in the differential diagnosis of hemorrhagic pleural effusion, even in the absence of the classic features of aortic dissection, such as chest pain, advanced age, or history of hypertension.

(CHEST 1999; 116:1478–1480)

Key words: aortic aneurysm; aortic dissection; bicuspid aortic valve; hemorrhagic effusion; pleural effusion

A hemorrhagic pleural effusion is an important but uncommon clinical problem that is often due to a serious underlying illness. The differential diagnosis includes traumatic injury to the heart, great vessels, or chest wall; pleuropulmonary malignancy; tuberculosis; pulmonary thromboembolic disease; subphrenic disease, such as splenic injury; a hemorrhagic diathesis; and a dissecting aneurysm of the descending aorta. Aortic dissection is an uncommon, catastrophic event that is characterized by dissection of blood along the laminar planes of the aortic media, with the formation of a blood-filled channel within the aortic wall. Rupture of this channel typically causes massive hemorrhage and has been associated with a mortality rate > 50%. A complete breach of the arterial wall may lead to formation of a contained, perivascular hematoma, termed a pseudoaneurysm.

Case Report

A 31-year-old white man was referred to the Division of Respiratory admitting service with a presumptive diagnosis of aspiration pneumonia and a parapneumonic effusion. He had been well until 5 weeks previously, when he experienced a single, witnessed, generalized seizure. Over the past 3 weeks, he had developed fatigue, intermittent chills, and new onset dyspnea on moderate exertion. The patient denied any cough, sputum, IV drug use, high-risk sexual activity, travel, trauma, or risk factors for pulmonary thromboembolism. He had a 15-pack-year smoking history and consumed 1 to 2 oz of alcohol per week.

On physical examination, the patient appeared pale. Vital signs were as follows: BP, 120/80 mm Hg in both arms, with no postural change; heart rate, 90 beats/min and regular; respiratory rate, 18 breaths/min; and temperature, 36.5°C. In the chest, there was dullness to percussion and diminished breath sounds at the left base. The patient had a normal apex beat and heart sounds, with no murmurs or pericardial rub detected. Jugular venous pressure was 4 cm above the sternal angle, and no peripheral edema was noted. Peripheral pulses were symmetric. Abdominal, musculoskeletal, and neurologic examination findings were unremarkable.

Initial laboratory investigations revealed a normochromic and normocytic anemia with a hemoglobin content of 10.8 g/100 mL; WBC count, 7,700/μL (7.7 × 10⁹/L); platelets, 566,000/μL (566 × 10⁹/L); international normalized ratio, 1.3; and partial thromboplastin time, 33 s (control, 30 s). Electrolytes and renal function were normal. An arterialized capillary blood gas sample while breathing ambient air revealed pH of 7.47; PaO₂, 67 mm Hg; PaCO₂, 33 mm Hg; and HCO₃⁻, 24 mEq/L. An ECG was normal. Chest radiograph revealed a moderate-sized left pleural effusion and a prominent convexity along the right mediastinal border (Fig 1). A left thoracentesis revealed thin, grossly hemorrhagic, reddish-brown pleural fluid that did not clot, did not clear on sequential samples, and had no obvious odor. Fluid chemistry findings included the following: lactate dehydrogenase, 187 U/L (serum lactate dehydrogenase, 130 U/L); protein, 4.5 g/100 mL (serum protein, 7.1 g/100 mL); and pH, 7.44. A manual cell count revealed the following: nucleated cells, 2,700/μL; and RBC count, “too many to count” (> 5.0 × 10⁹/mL). No organisms were identified on Gram’s stain or culture, nor were malignant cells identified by cytology.

The patient was admitted for monitoring and further imaging of the prominent right mediastinal border using CT while IV antibiotics were continued. The next day, the patient’s symptoms were unchanged; however, hemoglobin content had decreased to 8.5 g/100 mL. On physical examination, a new, grade 4/6 diastolic decrescendo murmur was noted at the left sternal border. An urgent thoracic aortogram revealed a 9-cm-diameter ascending aortic aneurysm that communicated freely with the aortic lumen, consistent with a pseudoaneurysm. Transesophageal echocardiography demonstrated dissection of the ascending aorta with a tented intimal flap, confirmed the aortic regurgitation, and also demonstrated a moderate-sized pericardial collection and a congenitally bicuspid aortic valve.

The patient underwent an urgent modified Bentall procedure
involving prosthetic replacement of both the bicuspid aortic valve and the ascending aorta. The patient’s postoperative course was unremarkable, and he remains well 18 months later. Histopathologic examination of the ascending aortic aneurysm showed degenerative changes, complicated atherosclerosis, and superimposed blood clot. There was no evidence of mural inflammation, granulomas, or cystic medial necrosis. The venereal disease research laboratory serology finding was subsequently negative.

**DISCUSSION**

In patients who survive the initial tear, the typical presentation of aortic dissection is that of severe, “tearing”-type pain, either in the anterior chest, which is suggestive of an ascending aortic dissection, or in the posterior chest or back, which is suggestive of a descending aortic dissection. The pain may radiate anywhere in the thorax or abdomen, and the initial differential diagnosis is often extensive. In one large series of 236 cases of aortic dissection, the most common symptom for all types of dissection was pain, most often severe. Of the 33 patients (15%) who presented with painless aortic dissection, congestive heart failure, stroke, and syncope were the next most common presentations.

Aortic dissection commonly occurs in two groups of patients. The first group consists principally of older hypertensive men, in whom painful dissection of the descending aorta is by far the most common presentation. The second major subgroup consists of patients with a systemic or localized abnormality of aortic connective tissue. In these typically younger patients, predisposing factors include aortic coarctation, a bicuspid aortic valve, and disorders of collagen, including Marfan’s syndrome, Ehlers-Danlos syndrome, and degeneration of the aortic media. In the aforementioned case series, bicuspid aortic valve was uncommon, being diagnosed in 7% by echocardiography, intraoperatively or by postmortem examination, but was the second most common predisposing factor after hypertension (78%).

A hemorrhagic left pleural effusion as the presenting feature of aortic dissection has been reported, but only in the context of descending aortic dissection. A review of the English language literature using MEDLINE and manual journal searches did not uncover any similar reports of an association of a left hemorrhagic pleural effusion with painless ascending aortic dissecting aneurysm. The presence of a left hemorrhagic effusion in the present report is most likely related to the localized para-aortic, anterior mediastinal pseudoaneurysmal collection and resulting leak into the adjacent left pleural space. Although this type of presentation of ascending aortic dissection is decidedly rare, the risk factor of a bicuspid aortic valve is not rare. Bicuspid aortic valve is the most frequent congenital cardiac malformation and is present in approximately 1 to 2% of the North-American population.

Although it is not possible to definitively link the history of the recent seizure to the evolving aortic
dissection, the association is highly probable, given previous reports of syncope and stroke with aortic dissection. Furthermore, the advanced degree of aortic atherosclerosis and mural thrombosis noted on histologic examination suggests that the seizure was likely due to a cerebral embolic event.

In summary, this case highlights the notoriously variable clinical presentation of a potentially disastrous condition, dissecting aortic aneurysm. We suggest that aortic dissection be included in the differential diagnosis of painless, hemorrhagic pleural effusion, even in the absence of hypertension and advanced age.

**REFERENCES**


**Eosinophilia in Wegener’s Granulomatosis**

Mark B. Potter, MD; Roger K. Fincher, MD; and David R. Finger, MD

Significant eosinophilia is a prominent feature in Churg-Strauss syndrome but has only rarely been described in Wegener’s granulomatosis (WG). We describe two Wegener’s granulomatosis patients with > 30% eosinophilia in their initial presentations. Other etiologies that could account for their eosinophilia were excluded. Both patients had pulmonary alveolar hemorrhage, sinusitis, arthritis, high-titer cytoplasmic antineutrophil cytoplasmic antibodies (cANCA), and proteinase-3 antibodies, but no evidence of renal disease. Herein we discuss eosinophilia, the differential diagnosis of pulmonary infiltrates and eosinophilia, the role of cANCA in vasculitis and autoimmune disease, compare Wegener’s granulomatosis and Churg-Strauss syndrome, and review possible pathogenic mechanisms.

**Key words:** eosinophilia; vasculitis; Wegener’s granulomatosis

**Abbreviations:** cANCA = cytoplasmic antineutrophil cytoplasmic antibody; CEP = chronic eosinophilic pneumonia; CSS = Churg-Strauss syndrome; pANCA = perinuclear antineutrophil cytoplasmic antibody; WG = Wegener’s granulomatosis

**SIGNIFICANT EOSINOPHILIA**

Significant eosinophilia is a prominent feature of conditions such as Churg-Strauss syndrome (CSS), atopic disorders, helminthic infections, Loeffler’s syndrome, and allergic bronchopulmonary aspergillosis. Mild eosinophilia has also been reported previously in Wegener’s granulomatosis (WG) in the peripheral blood,1–3 on lung biopsy,4,5 and in both.6 We describe two patients with WG who had > 30% peripheral blood eosinophilia along with pulmonary tissue eosinophilia. Other common etiologies for their eosinophilia were excluded. Both presented with pulmonary alveolar hemorrhage, sinusitis, arthritis, and high-titer cytoplasmic antineutrophil cytoplasmic antibody (cANCA) and proteinase-3 antibodies. Renal disease was absent in both patients, and their illnesses were quite responsive to therapy.

**REPORT OF CASES**

**Case 1**

A 29-year-old previously healthy white man presented with a 1-month history of migratory polyarthralgias, sinus congestion, cough, and epistaxis. He also noted fatigue, night sweats, fevers, and occasional hemoptyosis. He lacked a history of atopic disease or asthma, had no risk factors for communicable diseases such as HIV infection, and had an unremarkable travel or family history. Examination revealed the following: normal vital signs; synovitis of his right elbow, both wrists, right knee, and left ankle; mid-lung field crackles bilaterally; nontender sinuses; and no nasal ulcerations. Laboratory studies revealed normal urinalysis and creatinine, an elevated level of C-reactive protein at 6.38 mg/dL (normal < 0.8 mg/dL), an erythrocyte sedimentation rate of 60 mm/h (normal 0–15 mm/h), normal WBC count of 8,500 mg/dL with 33% eosinophils (total eosinophil count 2,805 cells/μL), hematocrit 30%.1–4 with a baseline level of 45% in 1994, negative rheumatoid factor and antinuclear antibodies, negative stool hemocult as well as ova and parasite testing on three occasions, high-titer canCA (> 1:640) and proteinase-3 antibodies, and negative perinuclear antineutrophil cytoplasmic antibody (pANCA). Chest radiography revealed patchy bilateral alveolar infiltrates (Fig 1, top), and sinus films showed bilateral maxillary mucosal thickening. Measures of spirometry, lung volumes, diffusion of carbon monoxide, and methacholine challenge were normal.

Results of initial blood, sputum, and stool cultures were negative. Rhinoscopy revealed nasal ulcerations, but the biopsy was nondiagnostic. BAL with transbronchial biopsy revealed...
negative cultures, alveolar hemorrhage, and nondiagnostic tissue histopathology. Open lung biopsy revealed alveolar hemorrhage, eosinophilic pneumonitis, and eosinophilic vasculitis, although no granulomas were noted. No fungal or atypical bacterial elements were found with special stains. Therapy was initiated with prednisone, 60 mg/d; methotrexate, 25 mg/wk, subcutaneously; and trimethoprim/sulfamethoxazole bid. The patient’s symptoms resolved 1 month into therapy, as did his anemia and eosinophilia, and repeat chest radiography showed complete resolution of alveolar infiltrates (Fig 1, bottom). He was maintained on a therapy of alternate-day prednisone for 6 months and methotrexate for a total of 1 year and was in remission 5 months after discontinuing all immunosuppressive therapy.

Case 2

A previously healthy 39-year-old woman presented with the subacute onset of cough, dyspnea, polyarthralgias, sinus congestion, and hemoptysis. She had no significant travel or family history, and she denied an earlier history of asthma or atopic disease. Initially, she received a diagnosis of community-acquired pneumonia and was treated with antibiotics without improvement. Physical examination revealed normal vital signs, joint tenderness with mild synovitis, no cutaneous or nasal lesions, but bibasilar lung crackles were present. Laboratory testing revealed the following: WBC count of 11,800 cells/μL with 38% eosinophils (total eosinophil count of 4,484 cells/μL), elevated levels of C-reactive protein of 3.36 mg/dL (normal < 0.8 mg/dL), normal hematocrit, negative rheumatoid factor and antinuclear antibodies, normal creatinine and urinalysis, negative hepatitis B and C antibodies, stool negative for ova and parasites, highly positive cANCA (1:640) and proteinase-3 antibodies, negative pANCA, and negative glomerular basement membrane antibody. Of note, the eosinophilia was observed before the initiation of antibiotic therapy. Chest radiography and CT revealed bibasilar and right middle lobe focal alveolar consolidation without adenopathy or pleural effusions (Fig 2), while sinus films were normal.

Bronchoscopy with transbronchial biopsy revealed alveolar hemorrhage, no evidence of infection, and nondiagnostic inflammatory tissue histopathology. A thoracoscopic lung biopsy was notable for alveolar hemorrhage with chronic eosinophilic inflammatory tissue changes, although granulomas and definitive necrotizing vasculitic changes were not identified. Special tissue stains for fungus, bacteria, parasites, and acid-fast bacilli were negative. The patient was started on prednisone 60, 60 mg/d; methotrexate, 15 mg/wk; and trimethoprim/sulfamethoxazole. Her pulmonary symptoms diminished rapidly, with resolution of her eosinophilia and improvement in her chest radiograph. Methotrexate was ultimately discontinued because of persistently elevated transaminase levels, but oral cyclophosphamide and alternate-day prednisone therapy has kept her disease in remission thus far for 1 year.

Discussion

Eosinophils usually comprise only 1 to 3% of peripheral WBCs, but when excessive, eosinophilia is arbitrarily defined as mild (351 to 1,500 cells/μL), moderate (1,500 to 5,000 cells/μL), and severe (> 5,000 cells/μL). Eosin-
Eosinophilic pulmonary disorders can be categorized into parenchymal, airway-based, or a mixture of both. The differential diagnosis of parenchymal eosinophilic lung diseases include simple pulmonary eosinophilia, chronic eosinophilic pneumonia (CEP), acute eosinophilic pneumonia, CSS, idiopathic hypersinusoidal syndrome, allergic bronchopulmonary aspergillosis, bronchocentric granulomatosis, certain parasitic infections, and drug-induced disorders. Infectious etiologies were thoroughly excluded in our patients with negative findings on blood, sputum, and BAL cultures, as well as negative findings on tissue stains for fungal and acid-fast organisms.

We do not feel that our patients had CEP. Although the presence of pulmonary infiltrates and eosinophilia was seen in patients with both WG and CEP, a review of the medical literature revealed that the presence of a high-titer, proteinase-3-directed cANCA has not been described in CEP. Furthermore, our patients did not have a history of asthma, which is noted in half of patients with CEP, and they had alveolar hemorrhage, which is uncommon seen in patients with CEP. Mild eosinophilia has also been noted to occur commonly in various autoimmune rheumatic diseases such as scleroderma, rheumatoid arthritis, polyarteritis, and Sjogren’s syndrome, but peripheral blood eosinophilia > 5% is seen in > 90% of patients with CSS.

Peripheral blood and tissue eosinophilia have been previously described in WG, but are uncommon. Mild eosinophilia has been reported in ≤ 12% (6/50) of WG patients, but tissue eosinophilia in WG has also been described. Fahey and Chrug described 1 of 7 WG patients with tissue eosinophilia on lung biopsy, and Fienberg reported this in 2 of 12 patients. Yousem and Lombard reported four WG patients with lung biopsies notable for prominent eosinophilic infiltration in the absence of peripheral blood eosinophilia. Many of these cases were reported before the onset of ANCA testing, and the cases may have represented CSS.

The emergence of ANCA testing has helped the classification of systemic vasculitides, with two indirect immunofluorescence patterns being cytoplasmic (cANCA), directed against proteinase-3, and perinuclear (pANCA), directed primarily against myeloperoxidase. It has been reported that 51% of CANCA-positive WG sera contain antibodies against proteinase-3, compared with 8% of CSS patients. In a recent large meta-analysis, Rao and coworkers reported the specificity of cANCA to be 88 to 100%, with pooled specificity of active and inactive patients of 98%, and an overall specificity of 95%.

We feel the diagnosis in our patients was most likely WG with eosinophilia rather than CSS or another eosinophilic pulmonary disorder. Both patients lacked a history of asthma or atopic disease, including a negative methacholine challenge in one. Infection was excluded in both patients by BAL, and fungal and acid-fast organisms were excluded by tissue staining. High-titer cANCA and proteinase-3 antibodies, uncommon in CSS and other disorders, were present in both patients. Neither patient had allergic rhinitis or nasal polyposis commonly seen in CSS, while patient 1 had epistaxis and nasal ulcers typical of WG. Although lung biopsies failed to reveal classic granuloma formation, patient 1 had eosinophilic vasculitis, patient 2 had perivascular eosinophilic inflammatory infiltrates, and both had alveolar hemorrhage, a finding more commonly seen in WG than CSS. These cases may represent an overlap between CSS and WG, which has been previously described.

Classic necrotizing granulomatous vasculitis on tissue biopsy is not an absolute requirement for the diagnosis of WG, nor is it required to initiate therapy. Hoffman and Specks point out that, with infectious etiologies excluded and in the setting of characteristic clinical findings such as sinusitis, pulmonary infiltrates, and/or glomerulonephritis, the presence of a high-titer cANCA directed against proteinase-3 is highly specific for WG. They further point out that the need for definitive tissue confirmation is not required in this setting before initiating therapy.

WG associated with eosinophilia may portend a more favorable prognosis, given the rapid response to therapy and lack of renal involvement in our patients. However, one third of all previously reported cases had significant renal disease and did not seem to have more favorable outcomes. While the clinical significance of eosinophilia in WG is uncertain, it has been suggested that this may represent a reaction toward an extrinsic allergen or a host response to material released by the injured lung from the vasculitic process.

In summary, we describe two patients with responsive WG involving the lungs and sinuses associated with significant peripheral blood and tissue eosinophilia. Clinicians should recognize the differential diagnosis for eosinophilia and should, in the appropriate clinical setting, consider ANCA-positive vasculitis such as CSS and WG.

References
Pulmonary Hypertension Caused by Graves’ Thyrotoxicosis* 

Normal Pulmonary Hemodynamics Restored by $^{131}$I Treatment 

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We describe a case of pulmonary hypertension, initially thought to be idiopathic, which resolved after treatment of Graves’ hyperthyroidism. Results of pulmonary artery catheterization before and after treatment are reported, and the effects of thyrotoxicosis on hemodynamics and pulmonary function are briefly reviewed. Possible mechanisms for development of pulmonary hypertension caused by hyperthyroidism include pulmonary vascular endothelial dysfunction or damage because of autoimmunity or the high cardiac output state, or increased metabolism of intrinsic pulmonary vasodilators.

(CHEST 1999; 116:1483–1485)

**Key words:** hyperthyroidism; pulmonary hypertension; thyroid disease

The cardiovascular manifestations of thyrotoxicosis are profound and characteristic. These include sinus tachycardia, atrial dysrhythmias, increased cardiac output, widened pulse pressure, and occasionally cardiac failure.1 Recently, the presence of elevated pulmonary artery pressures by noninvasive testing methods in hyperthyroid patients has been observed.2 We present a patient initially diagnosed with primary pulmonary hypertension, who was later found to be hyperthyroid. Her pulmonary hemodynamics normalized on correction of her hyperthyroidism. Invasive hemodynamic testing, both during thyrotoxicosis and after normalization of thyroid function, are reviewed. 

**Case Report**

A 46-year-old woman with a past history of hypertension and smoking presented with dyspnea on exertion, peripheral edema, and tachycardia. A chest radiograph demonstrated cardiomegaly and a prominent pulmonary artery (Fig 1). Pulmonary function tests showed a moderate restrictive defect with an FVC of 1.33 L (43% of predicted), FEV1 of 1.10 L, FEV1/FVC of 83%, and a carbon monoxide diffusing capacity of 14.87 mL·min$^{-1}$·mm Hg$^{-1}$ (76% of predicted). The restrictive defect presumably was at least partly caused by her morbid obesity (weight, 136 kg; height, 157 cm), her small thorax, and the presence of cardiomegaly. An echocardiogram demonstrated right atrial and ventricular dilation with an estimated pulmonary artery systolic pressure of 71 mm Hg (normal, 15 to 30 mm Hg). A thoracic CT failed to reveal definitive parenchymal pulmonary disease. A ventilation/perfusion scan was interpreted as indicating a low probability for pulmonary embolism. Antinuclear antibodies showed a mixed pattern, with a titer of 1:40 uniform pattern and 1:160 nucleolar pattern. The absence of symptoms of autoimmune diseases such as Raynaud’s phenomenon suggested that a diagnosis of collagen vascular disease was unlikely. A diagnosis of primary pulmonary hypertension was made, and the patient was transferred to our institution for pulmonary catheterization and assessment of response to vasodilators. Her baseline hemodynamic testing results are shown in Table 1.

The presence of an elevated cardiac index and development of atrial fibrillation led to the testing of thyroid function. The results were consistent with pronounced thyrotoxicosis, with a total thyroxine concentration of 20.8 μg/dL (normal, 5.0 to 10.6 μg/dL), free thyroxine index of 6.0 ng/dL (normal, 1.0 to 2.2 ng/dL), and thyroid-stimulating hormone < 0.04 μIU/mL (normal, 0.10 to 6.3 μIU/mL). On examination, the thyroid gland was small without any irregularities. She did not have any stare, lid lag, or proptosis. Auscultation of the lungs revealed clear lung fields, and her cardiac sounds were notable for splitting of both S1 and S2. In addition, she had extensive pitting edema in both extremities. A mild fine tremor was observed in both hands, as was mild hyperreflexia. Titer of antithyroglobulin (positive at a titer of 1:2,560; normal, < 1:10), antiperoxidase (556 IU/mL; nonreactive, < 1:5), and thyroid-stimulating hormone (163%; nonreactive).

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normal, < 130% of basal activity) antibodies were elevated. As a result of these findings, a diagnosis of Graves’ disease was made.

The patient was treated with furosemide, warfarin, metoprolol, and propylthiouracil. Her thyroid function tests improved, and the patient experienced a significant reduction in her dyspnea and edema. After 3 months, however, agranulocytosis developed. In preparation for radioactive ablation, 123I uptake was 87% at 24 h and a technetium thyroid scan showed homogeneous uptake throughout the gland, confirming the diagnosis of Graves’ disease. She was subsequently treated with 15 mCi of 131I. Seven months after initiation of antithyroid therapy, her thyroid function tests were normal with a free thyroxine index of 1.7 (normal, 1.4 to 3.0). A repeat pulmonary artery catheterization showed reversal of her original abnormalities (Table 1). One year after therapy, she remains off medications, is euthyroid, and has no symptoms of pulmonary hypertension or cardiac failure.

**DISCUSSION**

Pulmonary hypertension (mean pulmonary artery pressure > 25 mm Hg at rest or > 30 mm Hg during exercise) may be caused by left ventricular dysfunction, myocardial or valvular disease, congenital heart disease, left atrial myxoma, severe obstructive or restrictive lung disease, sleep-disordered breathing, pulmonary embolism, connective tissue diseases, or anorectic sympathomimetic amines (ie, fenfluramine, etc.). Primary pulmonary hypertension has a prevalence of 0.13% and is found at autopsy in approximately 1% of patients with cor pulmonale. Typical symptoms include exertional dyspnea, fatigue, substernal chest pain, and exertional or postexertional syncope. Many of these features were exhibited by our patient. Her pulmonary hypertension was believed to be idiopathic until marked abnormality in thyroid function was discovered, which, in retrospect, was the cause of her high-output cardiac failure. The normalization of her intrapulmonary hemodynamics with correction of her thyrotoxicosis strongly suggests a cause and effect relationship between her thyrotoxicosis and her pulmonary hypertension.

Thyrotoxicosis results in major disturbances in both the respiratory and cardiovascular system. Systemic vascular resistance decreases by 50 to 70%, because thyroid hormone itself acts as a vasodilator. As vascular resistance declines, so does diastolic BP, which results in an increase in heart rate, increased incidence of atrial dysrhythmias, and increased myocardial contractility. Finally, the cardiac index increases by 200 to 300% in thyrotoxicosis because of vasodilation, reflex tachycardia, and increased contractility. The changes in cardiac physiology may lead to substantial changes in renal physiology, with increased glomerular filtration rate and increased net tubular reabsorption of sodium, the latter of which results in an increase in blood volume of 25%. This may result in exacerbation of underlying congestive heart failure.

It is well known that, clinically, hyperthyroidism is associated with dyspnea on exertion. Proposed mechanisms include increased oxygen consumption and carbon dioxide production (from increased metabolic rate). Although there is no change in airway resistance in hyperthyroid patients, both lung compliance and respiratory muscle strength may be decreased, and both improve with restoration of the euthyroid state.

Several associations between the thyroid and pulmonary hypertension have been reported. In their group of 40 patients with primary pulmonary hypertension, Yanai-Landau and colleagues found that 30% had antithyroglobulin antibodies. This represents an approximate 8-fold increase over the published incidence in the general population. The explanation for this association is not clear, but antithyroid antibodies may be a marker for generalized immune activation, and may provide a clue to the pathogenesis of some cases of

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**Figure 1.** Chest radiograph demonstrates cardiomegaly and prominent proximal pulmonary arteries.

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**Table 1—Hemodynamic Monitoring Before and After Treatment of Hyperthyroidism**

<table>
<thead>
<tr>
<th>Thyroid Status</th>
<th>RV (15–20/0–6 mm Hg)</th>
<th>PA (25/6–12 mm Hg)</th>
<th>MPAP (10–18 mm Hg)</th>
<th>PCWP (6–12 mm Hg)</th>
<th>CI (2.5–4.5 L·min⁻¹·m²⁻)</th>
<th>PVR (20–120 dyne·sec·cm⁻⁵)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroid</td>
<td>80/18</td>
<td>78/40</td>
<td>53</td>
<td>20</td>
<td>4.6</td>
<td>256</td>
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<tr>
<td>Euthyroid</td>
<td>38/4</td>
<td>32/7</td>
<td>15</td>
<td>7</td>
<td>3.3</td>
<td>80</td>
</tr>
</tbody>
</table>

*Normal values are given as a range in parentheses. RV = right ventricle; PA = pulmonary artery; MPAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; CI = cardiac index; PVR = pulmonary vascular resistance.*
primary pulmonary hypertension. An association between thyrotoxicosis and increased pulmonary artery pressures has been described by Martos Velasco,¹⁴ Okura and Takatsu,¹⁵ Alcázar et al.,¹⁶ and Agaon et al.,¹⁷ who each reported a single patient with elevated mean pulmonary artery pressures (as estimated by Doppler echocardiography) during hyperthyroidism, resolving after antithyroid therapy. Subsequently, Thurnheer et al² studied four patients with thyrotoxicosis by Doppler echocardiography during hyperthyroidism, resolving pulmonary artery pressures (as estimated by Doppler echocardiography) and found an elevated mean pulmonary artery pressure of 40 ± 11 mm Hg, which decreased to 25 ± 6 mm Hg after achievement of an euthyroid state. Ours is the first reported case of hyperthyroidism and pulmonary hypertension in which invasive hemodynamic testing was performed before and after resolution of the patient’s thyrotoxicosis. It is conceivable that her elevated pulmonary artery pressures were a direct result of high-output cardiac failure. Possible pathogenetic mechanisms for the association between pulmonary hypertension and Graves’ disease include (1) autoimmune phenomenon associated with endothelial damage or dysfunction, (2) increased cardiac output resulting in endothelial injury, and finally (3) increased metabolism of intrinsic pulmonary vaso-dilating substances.

In summary, several associations between the thyroid and pulmonary hypertension exist, and hyperthyroidism can result in important changes in pulmonary and cardiac functions. Specifically, thyrotoxicosis appears to result in increased pulmonary artery pressures, presumably because of the increase in cardiac output. In our patient, the clinical presentation was initially thought to represent primary pulmonary hypertension. Her hyperthyroidism was only suspected after the results of hemodynamic testing and the new onset of atrial fibrillation. After Graves’ hyperthyroidism was diagnosed and treated, her symptoms resolved and repeat measurement of pulmonary hemodynamics reverted to normal. Hyperthyroidism should be included in the differential diagnosis of pulmonary hypertension. In addition, further investigation into the exact nature of the association between thyroid disease and pulmonary hypertension appears warranted.

REFERENCES

Diffuse Alveolar Hemorrhage and Pulmonary Capillaritis Due to Propylthiouracil*

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Propylthiouracil (PTU) has recently been observed to be associated with antineutrophil cytoplasmic antibody (ANCA)-positive small vessel vasculitis, resulting in crescentic glomerulonephritis and, infrequently, diffuse alveolar hemorrhage (DAH). We describe a case of a 23-year-old pregnant woman who developed a perinuclear ANCA and antmyeloperoxidase-positive small vessel vasculitis manifesting as DAH and crescentic glomerulonephritis after she began taking PTU. An open lung biopsy was consistent with pulmonary capillaritis. She responded to corticosteroid therapy and discontinuation of PTU. DAH can be caused by pulmonary capillaritis, bland hemorrhage, or diffuse alveolar damage. To our knowledge, this represents the first documentation of an underlying pulmonary capillaritis in a case of PTU-induced DAH.

(CHEST 1999; 116:1485–1488)

Key words: antineutrophil cytoplasmic antibody vasculitis; diffuse alveolar hemorrhage; propylthiouracil; pulmonary capillaritis

CHEST / 116/5 / NOVEMBER, 1999 1485
The syndrome of diffuse alveolar hemorrhage (DAH) is caused by the disruption of alveolar-capillary basement membrane as a consequence of the injury to the arterioles, venules, and alveolar septal capillaries. The three histologic patterns accounting for the majority of DAH are pulmonary capillaritis, bland pulmonary hemorrhage, and diffuse alveolar damage. Davies et al1 were the first to describe an antineutrophil cytoplasmic antibody (ANCA)-positive small vessel vasculitis, and Dolman et al2 described the relationship between propylthiouracil (PTU) and small vessel vasculitis for the first time in six patients. We describe a case of PTU-induced ANCA-positive vasculitis in a woman who was in the first month of her pregnancy, resulting in DAH and crescentic glomerulonephritis. To our knowledge, four similar cases3–6 have been described; however, this is the first one in which an underlying pulmonary capillaritis was documented.

**CASE REPORT**

A 23-year-old woman in her first trimester of pregnancy presented with a 4-day history of flu-like symptoms and mild hemoptysis. She had been taking azithromycin as an outpatient. Physical examination findings were normal except for mild thymomgaly and bibasilar inspiratory rales. The chest radiograph revealed bibasilar alveolar and interstitial infiltrates. She had received a diagnosis of hyperthyroidism at age 13 and was taking PTU and methimazole intermittently. She had been untreated for the past 3 years after developing a skin rash attributed to PTU and methimazole intermitently. She had been untreated for the past 3 years after developing a skin rash attributed to methimazole. However, 2 weeks prior to presentation, PTU therapy was restarted.

On the second day of hospitalization, she deteriorated rapidly after a bout of massive hemoptysis. She was transferred to the ICU, and mechanical ventilatory support was initiated for hypoxic respiratory failure. Bronchoscopy performed revealed hemorrhagic return from the distal alveoli consistent with DAH. At that point, her hemoglobin dropped to 8.1 g/dL, from the baseline level of 10.5 g/dL. Other laboratory values showed a WBC count of 6,300 cells/μL; platelets, 146,000/μL; BUN, 25 mg/dL; creatinine, 0.7 mg/dL; erythrocyte sedimentation rate, 30 mm/h; β-human chorionic gonadotropin, 1,445 IU/L (reference range for nonpregnant women, < 3 IU/L); thyroid stimulating hormone, < 0.1 mU/L (reference range, 0.4 to 4.6 mU/L); T3U, 34.4% (reference range, 27.8 to 40.7%); free T3, 0.28 nmol/L (reference range, 0.35 to 0.65 nmol/L); T4, 138 nmol/L (reference range, 58 to 154 nmol/L); and a normal coagulation profile.

A chest radiograph showed extensive diffuse bilateral alveolar infiltrates. Urinalysis revealed > 20 RBCs/high power field and 1+ protein. Serum studies for antiglomerular basement membrane antibodies, antinuclear antibodies, hepatitis serology, HIV, and bacterial and viral titers were negative. The two-dimensional echocardiogram was normal. Indirect immunofluorescence revealed serum perinuclear antineutrophil cytoplasmic antibody (p-ANCA) positivity with a titer of 1:80 (reference laboratory range: positive if > 1:40).

The patient continued to deteriorate and had significant pulmonary hemorrhage requiring 10 U of packed RBCs. She was treated with IV corticosteroids (methylprednisolone 250 mg every 6 h) and plasmapheresis. The latter was discontinued when the antigelominale basement membrane antibody test was negative. An open lung biopsy showed alveolar wall disruption with acute intra-alveolar hemorrhage, intra-alveolar fibrin tufts, hemosiderin-laden macrophages, type II pneumocyte hyperplasia, and foci of interstitial polymorphonuclear infiltrates with fragmentation and nuclear dust, especially around the small blood vessels (Fig 1). Immunofluorescent microscopy showed no evidence of Ig deposition, and serum viral studies were negative. After initiation of corticosteroid therapy, the patient’s alveolar hemorrhage stabilized, and she rapidly improved and was extubated. PTU therapy was also discontinued at the same time, and the patient continued to improve despite weaning of corticosteroids. She was discharged after several days. An outpatient renal biopsy revealed focal crescentic glomerulonephritis (Fig 2). The corticosteroid dosage was tapered down over a period of 5 months. The patient remains in clinical remission 18 months later. A repeat p-ANCA test at 11 months was negative, and a test for anticytochrome oxidase (anti-MPO) was positive with a titer of 10 U/mL (reference laboratory range: positive if > 7 U/mL).

**DISCUSSION**

This patient developed a PTU-induced p-ANCA-positive vasculitic syndrome resulting in DAH and crescentic glomerulonephritis. DAH can result from pulmonary capillaritis, bland hemorrhage, or diffuse alveolar damage. In this case, DAH was associated with pulmonary capillaritis.

**FIGURE 1.** Lung biopsy specimen showing intra-alveolar hemorrhage, hemosiderin-containing macrophages, prominent type II pneumocytes, and scattered neutrophils in the interstitium (hematoxylin-eosin, original ×400).

**Abbreviations:** ANCA = antineutrophil cytoplasmic antibody; anti-MPO = antimalperoxidase antibody; DAH = diffuse alveolar hemorrhage; MPO = myeloperoxidase; p-ANCA = perinuclear antineutrophil cytoplasmic antibody; PTU = propylthiouracil

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PTU is responsible for ANCA-positive syndrome, and several reports documenting crescentic glomerulonephritis have been described.5–11 Choi et al12 described a patient in whom Wegener’s granulomatosis was initially diagnosed. This was associated with cytoplasmic ANCA and antiproteinase 3 antibodies. The patient developed hyperthyroidism and PTU therapy was started, followed by the return of vasculitic symptoms and the antibody type changed to p-ANCA and anti-MPO. His ANCA type reverted back to antiproteinase 3 with a cytoplasmic ANCA immunofluorescence pattern after stopping PTU. There are four case reports of PTU-associated ANCA-positive syndrome with DAH in the English literature. D’Cruz et al3 described a 62-year-old man who developed DAH after taking PTU for 11 months. The p-ANCA and anti-MPO antibodies were positive. Romas et al4, Ohtsuka et al5 and Harper et al6 each reported a case of DAH in young women, who took PTU for periods ranging from 7 to 36 months. In each case, serum ANCA was detected. All of these patients had a preceding influenza-like prodrome, and all improved with discontinuation of PTU. Two of them required immunosuppressive therapy with corticosteroids and cyclophosphamide. Transbronchial biopsies were performed in three patients and indicated hemo siderin-laden macrophages, but no evidence of vasculitis was reported. Two patients had renal biopsies revealing focal crescentic glomerulonephritis.

The present patient is the youngest of the reported cases of DAH associated with PTU. She developed symptoms 2 weeks after the initiation of PTU, whereas the other patients had taken PTU for 7 to 36 months. However, she had used PTU on and off for the last 13 years and could have developed some sensitization to it. Hers is the only case of PTU-induced DAH in which the DAH caused life-threatening hypoxemia requiring mechanical ventilatory support, but the patient still responded to discontinuation of PTU and initiation of corticosteroid therapy. In this report, we describe for the first time the documentation of underlying pulmonary capillaritis in PTU-induced DAH.

Pulmonary capillaritis is characterized by neutrophilic infiltration of the alveolar interstitium with fibrinoid necrosis and capillary thrombosis. There is a loss of integrity in the alveolar capillary basement membrane with leakage of RBCs into the alveolar space resulting in DAH. Pulmonary capillaritis has also been described in the setting of microscopic polyangiitis, Wegener’s granulomatosis, systemic lupus erythematosus, Goodpasture’s syndrome, progressive systemic sclerosis, rheumatoid arthritis, mixed connective tissue disease, and other disorders.13,14

Elevated ANCA levels have been reported to be induced by other drugs such as hydralazine, antithyroid medications (propylthiouracil, methimazole, carbimazole), penicillamine, minocycline, and clozapine.3,15–25 A similar picture to that described in our patient (ie, DAH or glomerulonephritis) has been seen in cases of ANCA-positive vasculitis induced by penicillamine, hydralazine, and carbimazole.

The mechanism of PTU-induced ANCA-positive vasculitis is unknown. Jiang et al26 proposed that activated neutrophils in the presence of hydrogen peroxide release myeloperoxidase (MPO) from its granules, which converts PTU into cytotoxic products. Von Schmiedeberg et al27 speculated that, in the presence of MPO, PTU gets converted to PTU sulfonate, which is immunogenic for T cells, and these T cells in turn activate B cells, which mediate the vascular injury. Lee et al28 suggested that PTU interacts with MPO to change the heme structure of the enzyme, which may then act as a hapten. Patients who have been taking PTU for years can develop the vasculitis at any time, and most have a preceding flu-like illness. It is possible that the etiology of PTU-induced ANCA-positive vasculitis may be multifactorial and a viral infection triggers the cascade of events that ultimately result in vascular injury.

This patient developed vasculitis and DAH after several courses of PTU treatment. From the information provided by the patient and her pharmacy, all the PTU was from the same drug company. The dramatic improvement of the clinical status of patients after stopping PTU definitely points toward PTU as the etiologic factor. PTU is also known to cause immunologic reactions such as drug-induced lupus. As pointed out by Jiang et al,28 neutrophils have to be primed in order to convert PTU into cytotoxic products. It is possible that an individual who receives multiple courses of PTU may develop vasculitis only when the neutrophils are appropriately primed by a viral infection. In several case reports, a flu-like illness precedes PTU-induced vasculitis.2–9

It is possible that pregnancy might have a contributory role in this case. The immunologic alterations in pregnancy are complex and not completely understood. It remains unknown how the maternal immune system adjusts to the presence of an antigenically foreign fetus. There are increases in maternal suppressor T cells and a decrease in helper T cells, accompanied by an increase in serum IgG.29 Remissions of rheumatoid ar-
antineutrophil cytoplasmic antibody: drug-induced vasculitic syndrome. DAH and crescentic glomerulonephritis due to an ANCA-positive vasculitis associated with PTU is an unusual but important syndrome to recognize because the discontinuation of PTU combined with the initiation of corticosteroids and sometimes cyclophosphamide results in recovery.

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Pulmonary Tumor Embolism From Primary Cardiac B-Cell Lymphoma*

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We report the case of a 54-year-old man with pulmonary embolism during convalescence from “idiopathic” pericarditis. A transthoracic echocardiographic examination indicated a large mass within the right atrium. Subsequently, he died from refractory hypotension. On autopsy, two large whitish nodules were found in the right atrium; there was also nodular epicardial infiltration. Both lungs showed multiple, grossly visible tumor emboli with pulmonary infarction and no evidence of conventional thromboembolism. This is the first report of pulmonary tumor embolism due to large cell B-cell primary cardiac lymphoma. Refractory unexplained pericardial effusion, pulmonary embolism without risk factors for venous thrombosis, and/or the existence of a mass in the right heart should arouse clinical suspicion for this rare malignancy. (CHEST 1999; 116:1489–1490)

Key words: B-cell; heart neoplasms; lymphoma; pulmonary embolism

Case Report

A 54-year-old man was transferred to our institution from a regional hospital because of a sudden deterioration in his clinical condition. He had been treated there because of fever, weakness, dyspnea on exertion, and a large pericardial effusion without evidence of tamponade. On the basis of extensive laboratory investigation (including negative findings on an HIV test) that suggested acute idiopathic pericarditis, methylprednisolone, 48 mg/d, was given.

On the ninth day of hospitalization, although the pericardial effusion had disappeared and his overall condition had improved, the patient experienced a sudden worsening of his condition with a reappearance of dyspnea, even at rest. On admission to our department, a physical examination showed pallor, tachypnea, a heart rate of 115 beats/min, and an arterial pressure of 105/80 mm Hg. The resting ECG showed sinus rhythm, P pulmonale, and incomplete right bundle branch block. There was no evidence of venous thrombosis. A ventilation/perfusion lung scan was interpreted as high probability (using criteria from the Prospective Investigation of Pulmonary Embolism Diagnosis study) for pulmonary embolism of the right inferior lung lobe, and treatment with heparin was started.

A transthoracic echocardiogram indicated a slightly echo-dense mass in the right atrium, filling four fifths of the right atrial cavity and protruding through the tricuspid valve into the right ventricle. Further evidence for the existence of this mass was the presence of a filling defect on the color Doppler echocardiogram, showing the location of the mass with surrounding color flow. The mass showed a small degree of motion, but no free-floating movement suggestive of a mobile thrombus. A transesophageal echocardiogram was planned for the next morning, but the patient’s condition deteriorated further, with refractory hypotension, despite thrombolysis, and a fatal outcome ensued soon after due to electromechanical dissociation.

An autopsy revealed a thickened pericardium with adhesions to myocardial tissue. The epicardium showed whitish nodular infiltration. In the right atrium, near the atrioventricular groove, there were two whitish nodules, 1.2 cm and 2 cm in diameter (Fig 1). The latter extended

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Figure 1. Histologic section from a medium-sized branch of the pulmonary artery exhibiting an occluding neoplastic embolus (hematoxylin-eosin, original × 25). The left upper insert shows the neoplasm within the opened right heart chambers, while the right lower insert illustrates representative lymphoma cells (hematoxylin-eosin, original × 200).
into the right atrial cavity and had an irregular and friable surface. Both lungs showed multiple, grossly visible tumor emboli with pulmonary infarction and no evidence of conventional thromboembolism. The bone marrow and other organs showed no evidence of lymphoma.

Histologic examination of the right atrial mass, epicardial nodes, and the pulmonary emboli revealed diffuse proliferation of large lymphoid cells with high mitotic index. Most of the neoplastic cells were positive to CD45, leukocyte common antigen (DAKO; Carpinteria, CA) and CD20, L-26 (DAKO), an antibody identifying B lymphocytes, while a minority of neoplastic cells were positive to CD-45RO, UCHL1 (DAKO), an antibody identifying T-lymphocytes.

Thus, primary cardiac B-cell lymphoma with fatal pulmonary tumor embolism was the postmortem diagnosis.

**DISCUSSION**

Pulmonary embolism in the majority of cases implies an embolus from thrombotic material, whether it is from a vein, the right heart chambers, the tip of an in-dwelling venous catheter, and so on. Nevertheless, right-sided cardiac malignancies may be the source of emboli from thrombotic or neoplastic material, and this, despite its rarity, is a well-known complication of atrial myxomas. The absence of risk factors or evidence for thrombosis may arouse suspicion of nonthrombotic pulmonary embolism, and in such cases further echocardiographic evaluation of the right heart chambers may be crucial. Among 50 cases of primary cardiac lymphoma that have been reported in the literature, there is only one report of pulmonary tumor embolism, and that was from small cell lymphoma. As far as we know, this is the first case of pulmonary embolism due to large cell B-cell primary cardiac lymphoma.

Primary cardiac lymphoma is an extremely rare and rapidly evolving malignancy, arising from the right heart in the majority of cases. Its incidence is higher in immunocompromised patients. Pathognomonic clinical presentation has not been described, but unresponsive heart failure, precordial pain, rhythm abnormalities, and pericardial effusion-tamponade are the most common features. Its inconsistent presentation, along with its rarity, make diagnosis of the condition difficult. Since early therapy seems to offer the only chance for cure, in the presence of clinical or imaging evidence of cardiac mass or unexplained refractory pericardial effusion, aggressive diagnostic procedures may be indicated in order to obtain specimens for cytologic or histologic examination. This applies particularly to immunocompromised patients. Transesophageal echocardiography, ECG-gated MRI, and gallium-67 uptake can often be helpful in clarifying the diagnosis.

**REFERENCES**