Hypersensitivity Pneumonitis Following Anthrax Vaccination *

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insecticides, because people, especially children, can be endangered by the misuse of contaminated equipment as well. The easy availability of these materials in developing countries leads to accidental and suicidal poisoning.[1] While the ingestion of an OP is the most common route in cases of suicide attempts, nevertheless, inhalation and dermal contact have also been observed in patients who do not remember having had contact with an insecticide compound.[1]

Health-care workers may be affected via contaminated equipment, clothes, or even by the patients themselves. Emergency staff should pay extra attention to hazardous chemicals, volatile compounds, or particulate matter.[6]

Geller and coworkers[7] reported that three health-care workers were affected in an ED after they had cared for an intoxicated patient who was known to have been exposed to OP over a period of 1 h. In that case, the investigators applied gastric lavage, intubation, and decontamination of the skin, provided respiratory support, and transferred the patient later to the ICU. All three health-care workers were affected, but one was so seriously affected that she had to be kept in the hospital for 9 days. The first day she received breathing support with a ventilator, and for the other 8 days of her hospital stay she was treated with atropine. The National Institute for Occupational Safety and Health identified 46 health-care workers between 1987 and 1998 who had experienced acute pesticide-related illnesses after providing care to pesticide-contaminated patients.[6]

Depending on the extent of the contamination, health-care workers caring for chemically contaminated patients should use full face masks to prevent dermal and inhalational exposure.[7,8] ED and ICU sections of hospitals should review their precautions for health-care workers because of the cases described here.

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Hypersensitivity Pneumonitis Following Anthrax Vaccination*

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A case of hypersensitivity pneumonitis (HP) following anthrax vaccination is described. The patient is a 39-year-old, previously healthy man on active duty in the US Marine Corps, in whom a urticaral skin rash and progressive dyspnea on exertion developed following subcutaneous anthrax vaccination. A diagnosis of bronchiolitis obliterans with organizing pneumonia was made from transbronchial lung biopsy samples after evaluation excluded multiple infectious and collagen vascular etiologies. This appears to be the first recorded case of HP following an anthrax vaccination; however, a case report of pulmonary and cutaneous vasculitis following hepatitis B vaccination has been reported in the literature and is reviewed. ***(CHEST 2002; 122:741–745)***

Key words: anthrax vaccine; complication; hypersensitivity pneumonitis

Abbreviations: BOOP = bronchiolitis obliterans with organizing pneumonia; DLCO = diffusion capacity of the lung for carbon monoxide; ED = emergency department; HP = hypersensitivity pneumonitis; TLC = total lung capacity

Large-scale vaccination strategies have been instrumental in preventing the spread of many epidemic diseases. Unfortunately, the introduction of protein-based vaccine compounds has been accompanied by several complications. Anthrax vaccine has been used for nearly 30 years by workers in veterinary medicine and the animal fiber industry as an effective means of preventing transmission of the disease from spore-containing animal products. The recent threat of anthrax as a biological weapon has prompted the US military to initiate an immunization program. This case represents the first reported pulmonary complication from this anthrax vaccination program.

Case Report

On February 2, 1999, a 39-year-old previously healthy, nonsmoking man on active duty in the US Marine Corps received the

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first of six anticipated injections in the standard anthrax vaccine series (0.5 mL; Bioport Corporation, Lansing, MI). On the same day, an erythematous, tender, indurated area at the injection site developed on his right arm. The next morning, the patient noted a raised pruritic urticaral rash that involved his entire right upper extremity. Over the next week, the rash spread to involve the left upper extremity, axillae, waist, and the flexor surfaces of both legs. He also reported dyspnea on exertion that began the day after the injection and progressed over the subsequent week. On February 10, 1999, he was referred to the emergency department (ED) for evaluation. Although his peripheral oxygen saturation on room air was 93%, a review of ED records showed the patient had normal pulmonary examination and chest radiographic findings. The patient received a diagnosis of generalized allergic reaction and was administered the following: parenteral diphenhydramine, 50 mg; ranitadine, 50 mg; and methylprednisolone, 125 mg. He was released with prescriptions for oral ranitidine, diphenhydramine, and prednisone at a dosage of 40 mg/d for 4 days, and was referred to the allergy clinic. The rash resolved on the day following the ED visit.

In the allergy clinic on February 16, 1999, his only complaint was "chest tightness." Pulmonary function testing revealed a FVC of 3.97 L (77% predicted), FEV_1/FVC ratio of 96% of predicted, and a FEV_1 of 3.1 L (73% of predicted) without a bronchodilator response. Serum studies revealed normal complement levels and an erythrocyte sedimentation rate of 19 mm/h. Skin testing was performed and demonstrated no immediate reaction to either anthrax vaccine (skin-prick test with full strength vaccine) or glycerine. The patient received a diagnosis of urticaral vasculitis and was prescribed inhaled corticosteroids, bronchodilators, and a methylprednisolone dose pack. His dyspnea initially improved, but over the subsequent 2 weeks he was unable to carry his youngest child or walk uphill without breathlessness.

On referral to the pulmonary service on March 18, 1999, he denied cough, wheezing, arthralgias, chest pain, weight loss, fever, joint pain, or swelling. His medical history was only remarkable for seasonal rhinitis and an allergic reaction to diazepam that consisted of severe dyspnea. He specifically denied any food allergies, toxic inhalations, or occupational exposures. He did admit that his wife had a pet bird. The cockatiel was kept indoors and had been in the home for the past 4 years. The patient denied any dyspnea prior to this episode. The physical examination was unremarkable. Findings of repeat chest radiography were normal. Resting, room-air arterial blood gas analysis revealed a pH of 7.40, P_{CO_2} of 35 mm Hg, P_{O_2} of 75 mm Hg, and an oxygen saturation of 93%. An exercise desaturation study on room air demonstrated significant desaturation to 81% with a 5-min walk at 2.0 miles per hour, 0% grade. Results of the laboratory examination, including CBC count, liver function panel, coagulation studies, urinalysis, and electrolytes, were normal. Repeat pulmonary function testing again revealed mild restrictive changes with a decreased total lung capacity (TLC) of 4.62 L (69% predicted) and a moderately reduced diffusion capacity of the lung for carbon monoxide (DLCO) of 15.14 mL/min/mm Hg (46% predicted). A high-resolution CT scan of the chest demonstrated a "mosaic" pattern with nodular-appearing ground-glass opacities that were accentuated in the upper lobes and spared the bases (Fig 1). A ventilation/perfusion scan demonstrated homogenous uptake without perfusion mismatches. Fiberoptic bronchoscopy revealed normal airways, and the ensuing culture findings were negative for bacterial or fungal growth. Transbronchial lung biopsies revealed uniform interstitial fibrosis with occasional plugs of immature fibroblastic tissue and a poorly formed granuloma in an alveolar space on a background of chronic peribronchial inflammation (Fig 2). A minimal number of desquamated alveolar cells were noted. No multinuclear giant cells were found. Special stains of the biopsy

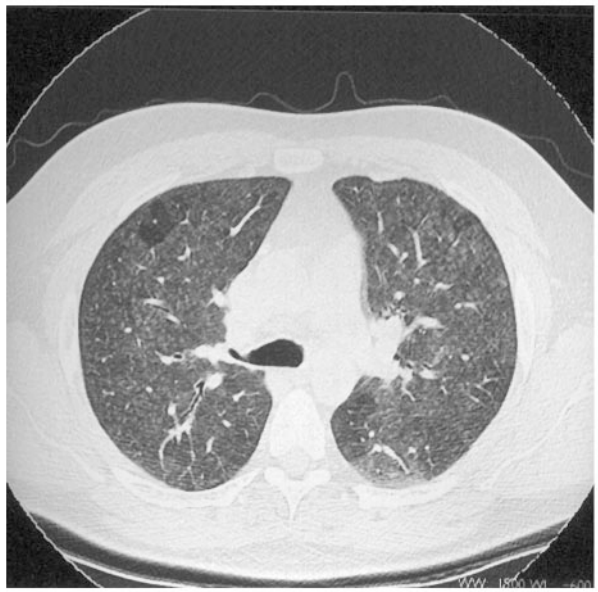

FIGURE 1. CT scan of the chest in a patient with BOOP following anthrax vaccination demonstrated a mosaic pattern with nodular-appearing ground-glass opacities that were accentuated in the upper lobes.

specimens, including periodic acid-Schiff, Gomori methenamine-silver, and Fite stain (modified acid-fast bacilli), were negative. The biopsy findings were consistent with bronchiolitis obliterans with organizing pneumonia (BOOP).

The patient was started on prednisone, 60 mg/d. Serologic findings for rubella, adenovirus, coccidiomycosis, and mycoplasma were negative. Rheumatoid factor, antinuclear factor, and antineutrophil cytoplasmic antibody levels obtained while the patient was receiving prednisone were undetectable. The patient's symptoms of dyspnea rapidly improved with steroid therapy. Pulmonary function after 3 months of high-dose steroid therapy demonstrated an increase in FVC to 4.45 L (92% of predicted), FEV_1 to 3.26 L (81% of predicted), DLCO to 20.81 (63% of predicted), and TLC to 5.82 L (87% of predicted). A CT scan of the chest after 3 months of steroid therapy showed almost complete resolution of the ground-glass opacities (Fig 3). However, the patient's symptoms of dyspnea returned 6 weeks after stopping the steroids. Pulmonary function testing revealed a decrease in FVC to 3.28 L (68% of predicted), FEV_1 to 2.51 L (63% of predicted), DLCO to 14.56 (45% predicted), and TLC to 4.80 L (72% predicted). A CT scan demonstrated a return of the ground-glass opacities and mosiacism. Open-lung biopsies of the left upper and lower lobes were consistent and contained an inflammatory infiltrate of lymphocytes and histocytes with poorly formed granulomas. These findings are consistent with a diagnosis of hypersensitivity pneumonitis (HP). The patient was started on prednisone therapy at a dose of 1 mg/kg/d and instructed to give away the cockatiel. Serum precipitin findings to cockatiel droppings and feathers were positive; this signifies the patient's exposure to the bird but does not establish it as the etiology of the HP. The patient improved over the subsequent months and was successfully tapered off steroids. Repeat pulmonary function testing showed an increase in FVC to 3.74 L (78% predicted), FEV_1 to 2.79 L (70% of predicted), DLCO 16.42 (50% of predicted), and TLC to 5.83 L (87% predicted). During a follow-up visit, the patient admitted that he never removed the cockatiel from the house.

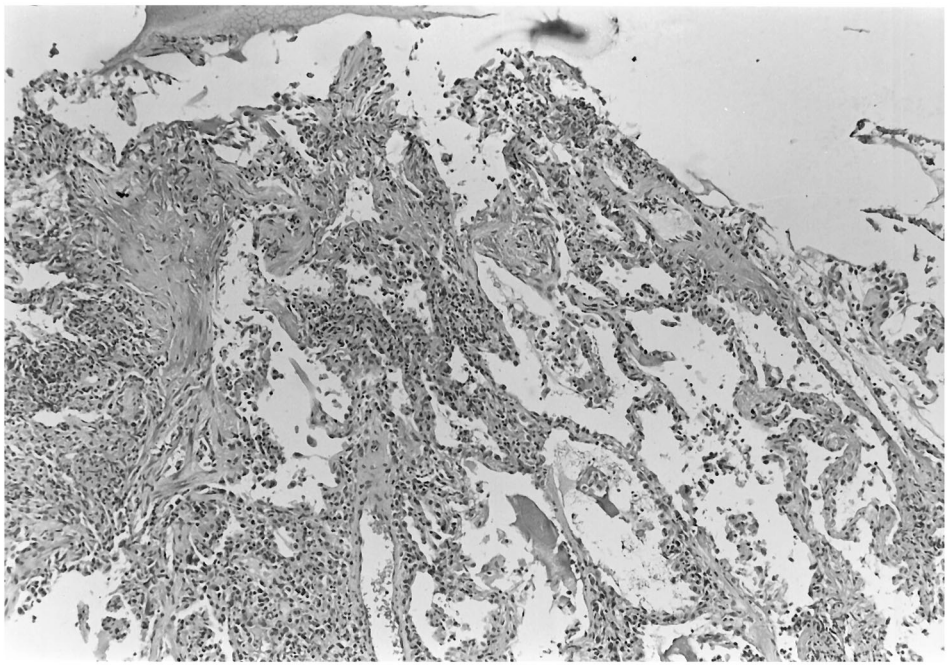

FIGURE 2. Transbronchial lung biopsy of the same patient stained with hematoxylin-eosin (original × 100) revealed uniform interstitial fibrosis with occasional plugs of immature fibroblastic tissue and poorly formed granulomata in alveolar spaces.

DISCUSSION

Bacillus anthracis is an anaerobic, spore-forming, Gram-positive, rod-shaped bacterium that is a common soil contaminant. Anthrax infection occurs by inoculation or inhalation and causes three forms of disease: cutaneous, inhalational, and GI. Inhalational forms of anthrax infection cause initial nonspecific symptoms including malaise, fatigue, myalgias, low-grade fever, and nonproductive cough, but swiftly progress to severe respiratory distress, fever, shock, and ultimately death.[1] Due to its ability to form spores that can be easily stored prior to dispersion, anthrax has been developed as a biological weapon.

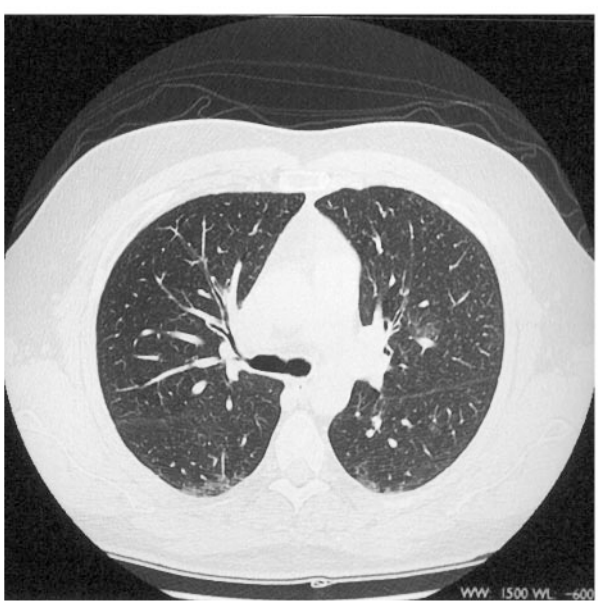

FIGURE 3. CT scan of the chest after steroid therapy showed almost complete resolution of the ground-glass opacities.

From a historical perspective, Roger Koch was the first person to culture the bacillus on artificial media in the 1870s. In 1881, Pasteur developed the first anthrax vaccine for veterinary use. The toxin of anthrax was discovered in 1954 by Smith and Keppie.[2] The current US vaccine contains protein supernatant purified from *B anthracis* cultures. There are three major components to the culture filtrate: protective antigen, edema factor, and lethal factor. The protective antigen is most important for the immune response of the vaccine. The contributions of the edema and lethal factors to immunity remain undefined.[3,4] The US vaccine that has been approved by the US Food and Drug Administration since 1970 is administered in six injections. The recommended schedule is 0.5 mL administered subcutaneously at 0, 2, and 4 weeks, followed by boosters at 6, 12, and 18 months. An annual booster is also required to sustain immunity. The vaccine is predominantly composed of protective antigen adsorbed to aluminum hydroxide. The final product contains not more than 2.4 mg of aluminum hydroxide per 0.5-mL dose (0.02%), a small amount of formaldehyde (≤ 0.02%), and benzethonium chloride (≤ 0.0025%) as preservatives. The US vaccine has been administered to military personnel since May 1998. By the end of July 1999, > 1,000,000 doses had

been administered to 340,000 service members. In total, 274 vaccine adverse event reports have been submitted, with 104 adverse event reports from the Department of Defense. One hundred fifty-one of the most significant reports have been reviewed by a national anthrax vaccine expert committee, with this case representing the only complication of HP.[5]

The reaction found on our patient's biopsy specimens was consistent with a clinical diagnosis of either BOOP or HP. The histopathologic pattern of BOOP is not diagnostic for a single entity but can be seen following a variety of different pulmonary insults. The differential diagnosis of BOOP includes infection, ARDS, posttransplantation reactions, collagen vascular disease, HP, toxic inhalation, aspiration pneumonitis, as well as an idiopathic variety. The finding of preserved end-expiratory aeration of the secondary pulmonary lobules or mosiacism on CT of the chest is commonly seen in HP. The exposure to cockatiels is a common precipitant of HP. Since both BOOP and HP are treated with high-dose corticosteroids and the patient improved on this therapy, an open-lung biopsy was not initially pursued. However, when the patient's symptoms recurred, video-assisted thoracoscopic open-lung biopsy was performed and demonstrated HP. The fact that the patient improved despite keeping the cockatiel in the house suggests that his HP may be due to the anthrax vaccine. It is possible that his symptoms resolved with the steroids, but one would have expected them to return when the steroids were discontinued. The patient remains without dyspnea 6 months later.

A review of the literature found no other reports of HP following anthrax vaccine administration. Allen et al[6] reported a case of pulmonary and cutaneous vasculitis following hepatitis B vaccination; rash, distal finger necrosis, and arthralgias developed 2 days after the patient received hepatitis B vaccine. Biopsy of the rash showed a perivascular lymphocytic infiltrate of the dermis consistent with a diagnosis of vasculitis. The patient also had marked dyspnea, basilar crackles on examination, and bilateral interstitial basilar opacities on the chest radiograph, as well as a restrictive lung disease pattern on pulmonary function testing. Tissue diagnosis of the pulmonary process was not documented. The proposed mechanism of disease in the case was a hypersensitivity illness with immune complex deposition. The laboratory examination in their case and ours did not reveal microscopic hematuria, peripheral eosinophilia, or low complement levels. All viral and fungal culture findings were negative in both patients. Additionally, an extensive serologic battery finding for collagen vascular disease was negative. In our patient, the mechanism for the pulmonary reaction is unlikely to be IgE mediated as a positive immediate skin test reaction to the vaccine was not demonstrated. Greidanus[7] reported a case of a delayed-type hypersensitivity reaction to the anthrax vaccine that manifested as a systemic rash. Previous reports of other nonpulmonary vaccine-related reactions have been linked to the preservatives, specifically thimerasol.[8] The anthrax vaccine contains an aluminum hydroxide preservative that has also been suspected in some vaccine reactions.[9] A hypersensitivity reaction to this preservative is possible in our case.

Conclusion

Studies suggest that the incidence of local reactions to anthrax vaccine increase up to the fifth injection and then decline.[9] Mild local reactions occur in approximately 30% of recipients and consist of a small ring of erythema, 1 to 2 cm in diameter, plus slight local tenderness.[10] This reaction usually occurs within 24 h and begins to subside by 48 h. Occasionally, erythema increases to 3 to 5 cm in diameter. These reactions may last up to 2 to 3 days after the injection and have been observed most often in patients with a history of cutaneous anthrax. Moderate local reactions are defined as an area of inflammation > 5 cm in diameter and occur in 4% of vaccine recipients of a second injection. However, a diffuse systemic urticaral rash and dyspnea developed in our patient within 24 h of receiving the vaccine. Most studies of anthrax vaccine in humans demonstrate a very low incidence of systemic reactions (0.7%). Our patient did receive two unknown vaccinations during the 1990–1991 Persian Gulf War while in the military theater of operation. Clearly, our patient's reaction was systemic, and patients with similar reactions should not receive further injections of anthrax vaccine.

Currently, the anthrax vaccine has been administered safely to $>$ 340,000 military personnel. It is clear that our case represents an important but exceedingly rare complication of anthrax vaccination. Both civilian and military health-care providers must be aware of potential vaccine-related complications and should thoroughly evaluate all patients with similar symptoms. Reports of severe local and systemic reactions have been minimal to date. As the threat of bioterrorism remains an unfortunate reality in the United States and the world, the very low incidence of systemic complications should not justify withholding the anthrax vaccine from those at risk of inhalational anthrax.

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Pulmonary Artery Sarcoma*

A Case Report of Surgical Cure and 5-Year Follow-up

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Pulmonary artery sarcoma is a rare tumor that is frequently misdiagnosed as chronic pulmonary embolism. With heightened clinical awareness and advancement in technology, the diagnosis is now increasingly being made preoperatively. Previous literature has described the disease to be uniformly fatal, with surgical resection as the single most effective modality for short-term palliation. We present the case of a patient in whom pulmonary artery sarcoma was diagnosed preoperatively and who underwent surgical resection with no evidence of recurrence during long-term follow-up, suggesting that early identification and aggressive surgical intervention has the potential to be curative.

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Key words: arteriopathy; pulmonary angioscopy; pulmonary artery sarcoma; pulmonary embolism; surgical resection

Pulmonary artery sarcoma is a rare tumor of the cardiovascular system with only a few hundred cases reported in literature. The disease was first described at autopsy by Mandelstamm[1] in 1923. Most of the subsequently reported cases have been diagnosed at autopsy. In the last decade, heightened clinical suspicion and improved diagnostic modalities have allowed the diagnosis to be made prior to surgery. The prognosis of pulmonary artery sarcoma is poor, with reported survival times of a few months to a few years regardless of therapy. We present the case of a patient with pulmonary artery sarcoma who, after preoperative confirmation of the diagnosis with pulmonary angioscopy, underwent successful surgical resection of the tumor followed by pneumonectomy. The patient has been observed for 5 years with no apparent recurrence of disease.

Case Report

A 32-year-old woman with no significant medical history was evaluated in early 1996 for chronic cough, low-grade fever with sweats, and a 4.5-kg weight loss over a 6-month period. She also complained of intermittent chest tightness and shortness of breath. There was no history of exposure to tuberculosis. However, she worked as a teacher in a local school, where she was in contact with a large population of immigrant children. On examination, she appeared healthy. There was no palpable lymphadenopathy. Cardiovascular examination revealed a prominent pulmonary component of the second heart sound. Examination of the chest showed slight dullness to percussion at the left base. Digital clubbing was present in both hands.

Among the results of relevant laboratory studies, hemoglobin level was 10.2 g/dL and the erythrocyte sedimentation rate was 72 mm/h. A chest radiograph showed a left lower lobe cavitary lesion. Initially, the patient was empirically treated with antituberculous treatment that was discontinued after a negative result of a purified protein derivative test and the absence of acid-fast bacilli in sputum and bronchoscopic specimens. A week later, she presented with acute shortness of breath. A spiral CT scan with IV administration of contrast material showed a large filling defect in the left main pulmonary artery (Fig 1). An ill-defined cavity also was noted in the left lower lobe. Venous duplex examination of the lower extremities was negative for deep vein thrombosis. A presumptive diagnosis of pulmonary embolism was made, and the patient was treated with 100 mg tissue plasminogen activator followed by unfractionated heparin. A follow-up scan of the chest 24 h later failed to show any dissolution of the clot. The possibility of pulmonary artery sarcoma was entertained, and the patient was referred to the University of California at San Diego for further evaluation.

Evaluation at the University of California at San Diego included a ventilation scan, which demonstrated reduced ventilation to the left lung, and a perfusion scan, which showed an absence of perfusion to the same area. Both ventilation and perfusion of the right lung were normal. Transthoracic echocardiography demonstrated normal left and right ventricle chamber size and function with mild tricuspid regurgitation. Pulmonary angiography showed an intraluminal rounded filling defect causing near-total occlusion of the left main pulmonary artery. Pulmonary angioscopy confirmed the presence of a grayish intraluminal mass. In November 1996, the patient underwent pulmonary artery exploration and resection of the lobulated mass (Fig 2) from the left pulmonary artery with reconstruction of the artery using a bovine pericardial patch. The distal pulmonary artery seemed to be free of tumor. Histopathologic examination of the specimen was consistent with low-grade sarcoma (Fig 3).

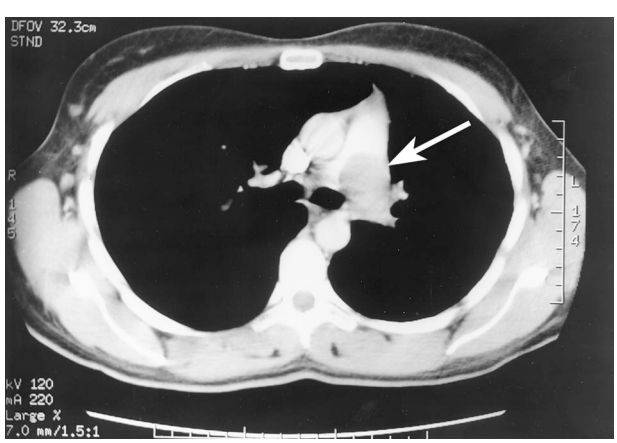

Figure 1. Chest CT scan with IV contrast showing a filling defect (arrow) in the left main pulmonary artery.

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