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Fatal Anaphylaxis After Intravenous Iron Dextran

Iron dextran (Imferon®) is a complex of ferric iron and dextran widely used for the treatment of iron deficiency anemia. It became commercially available in the United States in 1957. Since that time the intramuscular administration of iron dextran has been considered a relatively safe manner of administering iron to patients unable to tolerate oral iron therapy. However, untoward side effects have been reported. The most common of these are discomfort or staining of the skin at the injection site. The more disturbing reactions, however, appear to be allergic in nature and include lymphadenopathy, fever, urticaria, angioneurotic edema, arthralgias, and transient shocklike conditions [*1-5*]. Recently four cases of fatal anaphylaxis following intramuscular injection of iron dextran have been reported [*6, 7*].

In 1971 the drug was approved for intravenous administration. This route of administration eliminates the local discomfort associated with intramuscular injection. The other side effects have been uncommon but do occur. Reported reactions include dyspnea, cyanosis, and transient vasomotor collapse [*5-8*]. This report records the first reported case of fatal anaphylaxis following the intravenous infusion of Imferon®. It also illustrates many of the pathologic changes which may be produced by any anaphylactic reaction.

Case Report

The patient was a 75-year-old woman who had been followed for many years with a myeloproliferative syndrome associated with anemia and thrombocytosis.

She was first noted to be anemic at age 46 by her gynecologist. She was treated with oral iron but the anemia persisted. Eight years later a hematologic evaluation demonstrated hemoglobin of 10 g%, white blood count of 15,300 per mm^3, hematocrit 35%, reticulocyte count of 2%, and a platelet count of 800,000 per mm^3. The differential count of the peripheral blood film showed 4 myeloblasts, 1 promyelocyte, 1 metamyelocyte, 7 stabs, 55 segmented neutrophils, and 32 lymphocytes. There was moderate variation of the size and shape of the red blood cells. A bone marrow aspirate was described as being hypercellular and containing masses of platelets. There was no stainable iron. No therapy was prescribed and for the next 20 years she was followed irregularly by the hematologists with no significant variation in her well-being or hematologic picture.

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At age 74 she was admitted for reevaluation. Her hemoglobin was 9 g%, hematocrit 33%, white blood cells 13,400 cells per mm^3, and platelet count 725,000 per mm^3. Differential count of the peripheral blood film demonstrated 71 segmented neutrophils, 1 stab, 1 metamyelocyte, 2 myeloblasts, 17 lymphocytes, 3 monocytes, 3 eosinophils, and 1 basophil. Little bone marrow could be obtained for evaluation, even after multiple aspirations and biopsies of the sternum and iliac crest. However, a technetium-99 sulfur colloid bone marrow scan demonstrated normal marrow activity. Serum iron, folic acid, and vitamin B_{12} levels were within normal limits. The clinical impression was a variant of a myeloproliferative syndrome.

During the next year she was treated at various times with melphalan (up to 2 mg four times per week), folic acid (5 mg three times daily), and fluoxymesterone (20 mg per day). Her hemoglobin varied from 8.5 to 11 g%.

At the time of her last clinic visit she was noted to be a well-developed, well-nourished white female in no acute distress. Her physical examination was described as within normal limits for an individual her age. She was still taking the androgens. Because her hemoglobin had not increased significantly, she was begun on an intravenous infusion of iron dextran (2 g in 500 cm^3 of 5% dextrose and water). After less than 10 cm^3 of the solution had been administered, she quickly developed a hyperemic rash on the trunk and legs, laryngeal stridor, and respiratory arrest. Attempts at resuscitation were not successful. These resuscitative procedures included external cardiac massage and intravenous epinephrine. Intubation was also attempted but the laryngeal tube could not be inserted beyond a tightly closed glottis.

Autopsy

At autopsy examination the decedent was noted to be a short, mildly obese, white female with moon facies, increased suprascapular fat, and slight hirsutism. The hyperemia of the trunk and legs that was described by the clinicians at the time of resuscitation was apparent. Conjunctival hemorrhages were also noted.

The epiglottis and vocal cords (Figs. 1 and 2) were edematous and the latter could not be easily separated by probing with a finger. The right and left lungs weighed 320 and 290 g, respectively. Gross and microscopic examination of the lungs demonstrated pulmonary edema and congestion, intra-alveolar hemorrhage, and alternating areas of obstructive emphysema and atelectasis (Fig. 3). Many of the bronchioles and small bronchi appeared constricted (Fig. 4) when compared to the bronchioles of a normal lung (Fig. 5). Fibrinoid deposits occluded some of the pulmonary vessels (Fig. 6). Petechial hemorrhages were present on the visceral pleura and on the mucosal surfaces of the airway. There was passive congestion of the liver. The bone marrow was hypercellular and contained an increased number of megakaryocytes and myeloid elements.

Discussion

Imferon® is a solution of iron dextran complex with a molecular weight of 180,000 and providing an equivalent of 50 mg of elemental iron in each cm^3. The solution contains 0.9% sodium chloride and has a pH of 5.2 to 6.5.

Iron dextran is prepared by neutralizing ferric chloride in the presence of alkali-modified dextran. The dextran from which the preparation is made is produced by the fermentation of sucrose and has a molecular weight of little more than 5000. Cox et al [9] note that in order to have a molecular weight greatly exceeding 150,000, there must

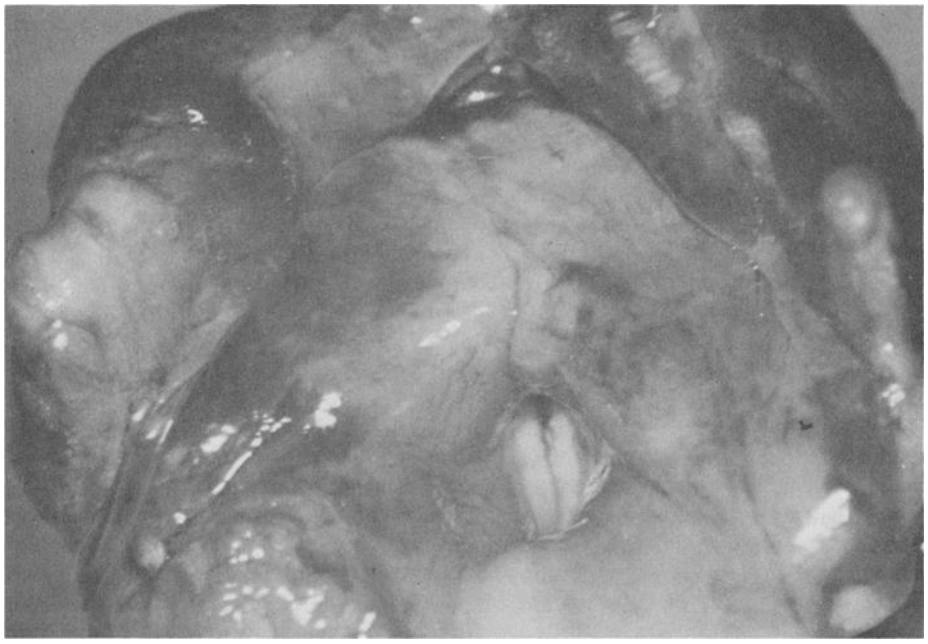

FIG. 1—*Edema of patient's larynx with tightly opposed vocal cords.*

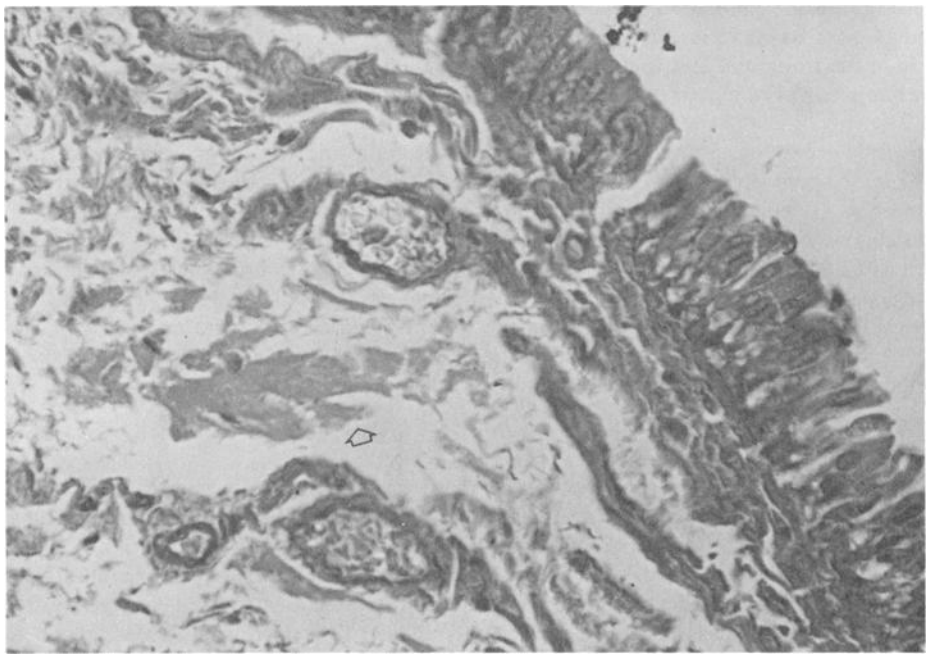

FIG. 2—*Histologic section of larynx with vascular congestion and submucosal edema* (arrow). *Hematoxylin and eosin; original magnification ×250.*

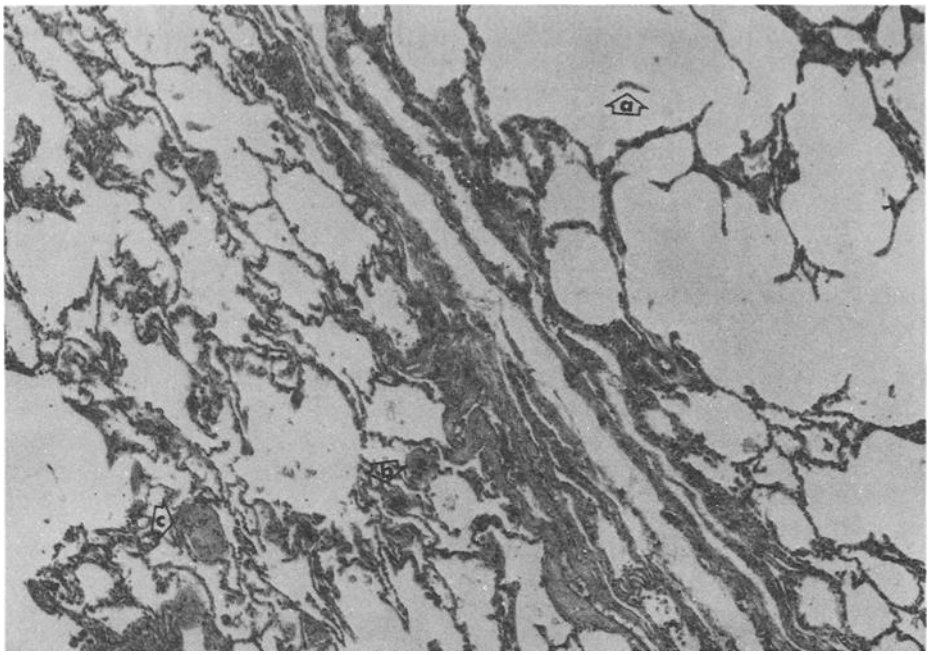

FIG. 3—*Histologic section of lung with isolated alveolar fragments* (Arrow A) *and alveolar distention characteristic of obstructive emphysema* (upper right). *Adjacent area of atelectasis* (lower left), *with vascular congestion* (Arrow B) *and vascular occlusion* (Arrow C). *Hematoxylin and eosin; original magnification* ×25.

be considerable cross-linking or association of molecules to form the complex. Bailey et al [*10*] report that a large proportion of uncombined low molecular weight dextran as well as small amounts of very high molecular weight dextran are present in the preparations.

It is unusual for low molecular weight dextran to cause anaphylaxis according to Gonzalez et al [*11*]. However, high molecular weight dextran is recognized as an allergenic product and the reactions to it may be due to a natural hypersensitivity [*12*]. Dextran is a common contaminant of commercial sugar. Also, sensitization to dextran may be a result of previous contact or infection with polysaccharide-producing microorganisms [*13, 14*].

MacKenzie and Lawson [*5*] describe two cases of severe, nonfatal anaphylaxis with intravenous Imferon®. They regard the reactions as anaphylactic and not toxic on the following grounds: (1) the nature of the reaction (that is, vasomotor collapse, dyspnea, cyanosis, and sweating), (2) the time relationship (reactions occurred within minutes after the injection), (3) the reactions occurred irrespective of dose (after only a small amount of the drug had been infused), (4) the serum was not saturated with iron, (5) previous injection with iron dextran had produced no reactions in the same patients, and (6) the reactions appeared after well-tolerated injections.

Becker et al [*6*] described a fulminant fatal reaction in one patient after intramuscular injection. The reaction appeared clinically and pathologically to have been anaphylactic. The reaction was not thought to be toxicologic because other patients had received comparable injections from the same lot of iron dextran.

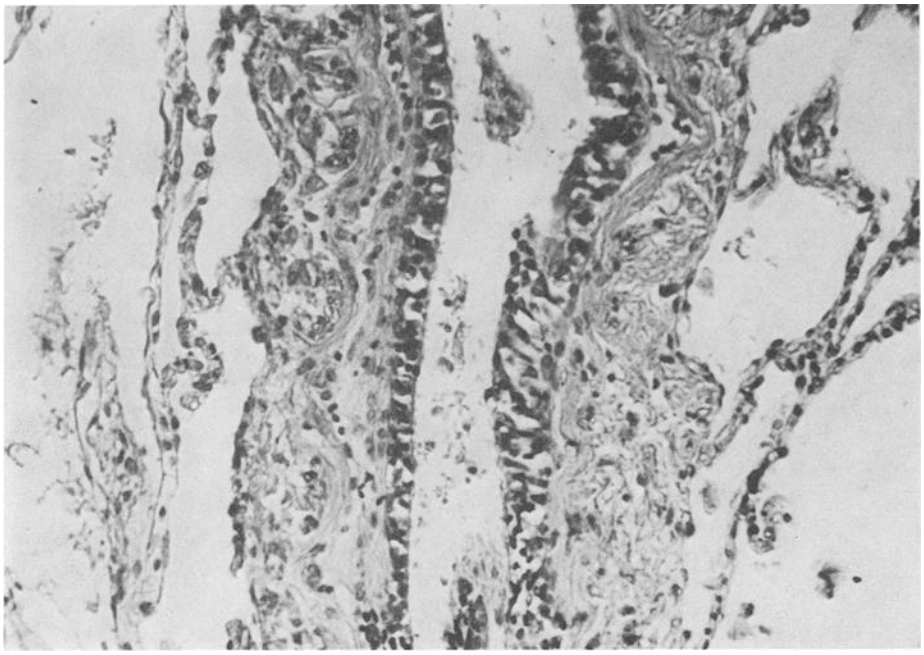

FIG. 4—*Constricted bronchiole from patient's lung. Hematoxylin and eosin; original magnification ×125.*

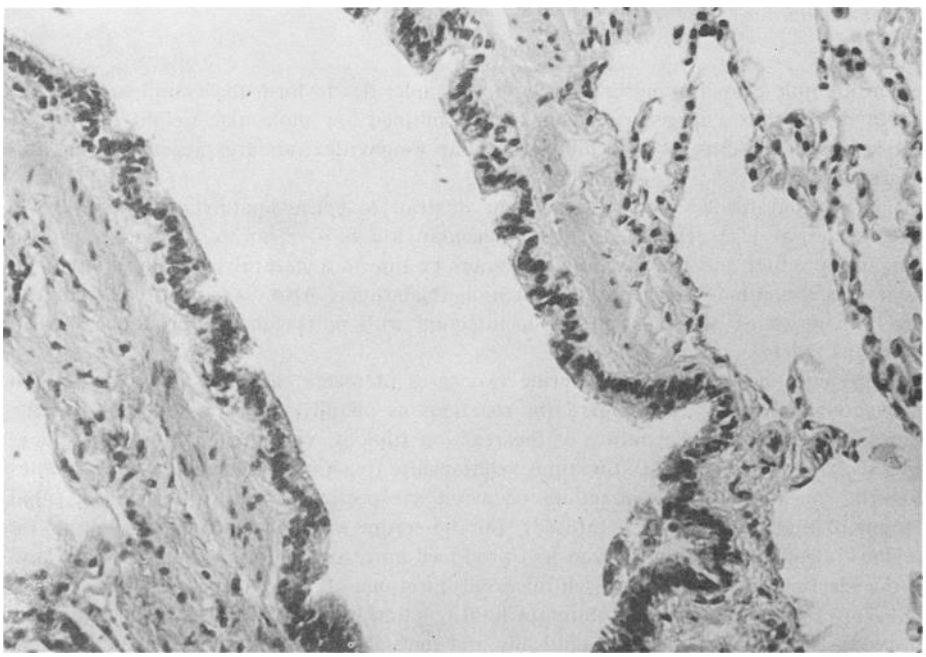

FIG. 5—*Normal bronchiole from unaffected lung. Hematoxylin and eosin; original magnification ×125.*

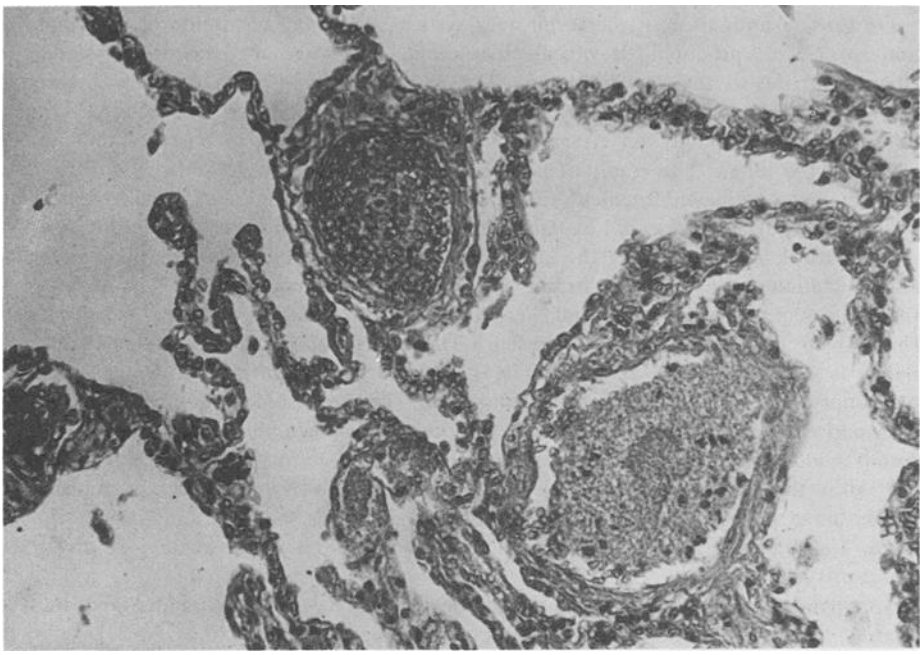

FIG. 6—*Vessels distend due to vascular congestion and thrombus. Hematoxylin and eosin; original magnification ×125.*

Callender and Smith [*3*] report four patients who developed severe allergic reactions after intramuscular injections of iron dextran. Injections of iron and dextran separately produced no ill effect. However, later injections of a different batch of iron dextran complex gave further urticarial reactions in these patients. This experience suggests that the combination of iron and dextran may result in a sensitizing compound with the appropriate molecular weight and configuration to produce an allergic reaction.

Anaphylaxis is an immediate type of hypersensitivity reaction resulting from the interaction of antigen with antibody "fixed" on tissue cells. The reintroduction of antigen locally or systemically results in an acute release of short-lived pharmacalogically active factors such as histamine, 5-hydroxytryptamine, kinins, and "slow reacting substance A," with both local and systemic effects [*15,16*].

This patient presented the clinical manifestations of anaphylactic shock. These manifestations include a history of injection of an antigen (insect sting, serum, or drug therapy) in a highly sensitized person which is rapidly followed by acute respiratory distress and asphyxia, severe hypotension, and death.

The determination of the cause of death should not be limited to just the clinical features of fatal anaphylaxis. Specific features can be found at autopsy which will corroborate the diagnosis of anaphylaxis. Many of the following features were seen in the autopsy of this case [*15,16*].

There may be edema of the face, conjunctiva, and lips. However, this could not be evaluated in this patient due to the Cushingoid changes subsequent to her steroid therapy. Generalized petechial hemorrhages of the skin, mucosa, and serosal surfaces are present due to the vasodilatory and increased permeability effects of histamine. The subconjunctival hemorrhages may be the result of asphyxia.

On gross examination of the respiratory system there may be edema of the epiglottis and vocal cords producing laryngeal obstruction. The lungs are heavy, congested, and edematous due to the vasodilatation. The bronchiolar spasm may produce areas of obstructive emphysema which may alternate with areas of collapse. Precipitated antigen-antibody complexes may act either mechanically or chemically to obstruct small blood vessels of the lungs. The resultant acute cor pulmonale and right ventricular dilatation may produce cardiac enlargement and pooling of blood in the venous caval system. This acute right heart failure would explain the acute congestion of the abdominal organs.

Microscopic examination of the larynx confirms the submucosal edema and a moderate infiltration and exudate of chronic inflammatory cells may be noted. The histology of the lungs confirms the pulmonary emphysema with associated areas of atelectasis. Bronchiolar constriction may be present. The interlobular and subpleural connective tissue is edematous and edema fluid is present in the intra-alveolar spaces. The pulmonary vessels may show marked dilatation. The interstitial tissue may contain mast cells and eosinophils. Acute congestion of the liver, spleen, bowel, and porta hepatic lymph nodes may be confirmed. It was not possible to detect either tissue iron or dextran in this patient but if the injection site and a blood sample can be demonstrated to contain a high titer of antigen, a definitive diagnosis of fatal anaphylaxis can be made. Death results from a combination of profound hypotension, acute cor pulmonale, and asphyxia.

Anaphylactic reactions after the use of dextran as a plasma expander and for the treatment of thrombophlebitis are unusual but have been reported [*10,11,17-21*]. Many of the reported patients including the patient in this report developed anaphylactic reactions after less than 25 cm^3 of the polysaccharide had been infused.

A number of investigators, however, have not been able to demonstrate a definite antigen-antibody reaction. Martin found no evidence of antibody production in rabbits by precipitin and complement fixation tests, nor was it possible to produce anaphylactic shock in guinea pigs with the preparation [*22*]. Skin and complement fixation tests have been negative in patients exhibiting anaphylaxis and precipitin reactions have been inconclusive [*2,23*]. Agar jell diffusion tests against iron dextran, performed by Mehta et al [*24*], failed to detect antibodies in patients who developed systemic reactions. These studies do not rule out hypersensitivity as the cause of these reactions, and so far no other hypothesis has been proposed which more adequately explains the pathogenesis of dextran hypotension.

Summary

This report records the first reported case of a fatal anaphylactic reaction to an intravenous infusion of iron dextran. An elderly woman was given an infusion of iron dextran in 5% dextrose. Shortly after the infusion started, she developed laryngeal stridor, shock, respiratory arrest, and died despite attempts at resuscitation. Necropsy findings are described and are consistent with death due to anaphylaxis.

With the increased parenteral use of dextran and iron dextran complexes it is important for the clinician to be aware of the hazards of anaphylactic reactions. Since the reactions generally occur shortly after the administration has begun, a physician should be in attendance during the infusion of the first 25 cm^3 (5 to 10 min). He should be able to promptly recognize and treat the asphyxia and hypotension should it occur.

It is also important for the pathologist to be aware of the occurrence of anaphylaxis after the use of these drugs. However, the cause of death should not be based solely on the presence of classic clinical features of fatal anaphylaxis. Specific features of

anaphylaxis should be searched for at autopsy and other causes of sudden death must be ruled out.

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