Pulmonary Emboli From Therapeutic Sodium Hyaluronate

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A patient presented with shortness of breath and pleuritic pain shortly after bilateral knee synovial injections with sodium hyaluronate (HA). He was discharged after a brief hospitalization without a diagnosis when no Doppler or radiologic evidence of deep vein thrombosis or pulmonary emboli was found. Radiologic studies found patchy ground glass opacities that were predominantly peripheral in disposition, with prominent septal lines in the lungs; a subsequent pulmonary function test showed a reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}). These results prompted a lung biopsy that revealed multiple emboli composed of HA and fibrin in medium size pulmonary arteries, enlarged lymphatic vessels, and a bone marrow embolus. This is the first report of HA emboli following therapeutic HA injections and demonstrates that pulmonary function tests can be used to infer the reduction in pulmonary vascular area consequent to pulmonary emboli, and so can contribute to the detection of pulmonary emboli in unusual presentations. *Key words: adult; pleuritic pain; shortness of breath; pulmonary function tests; diffusing capacity; D_{LCO}; chest radiography; spiral computed tomography; high resolution computed tomography; pulmonary emboli; hyaluronan; hyaluronate; hyaluronic acid; binding protein.* [Respir Care 2012;57(10):1670–1673. © 2012 Daedalus Enterprises]

Introduction

While dermal and intra-articular injections of hyaluronan (HA) have proven to be a safe and effective treatment for cosmesis and for pain relief, a small dermal injection has been reported to cause local thromboembolic disease.[1] With a larger volume infused, a dermal injection and a joint infusion have both been reported to cause dyspnea attributable to pulmonary emboli, but by an unknown mechanism.[2,3] In this report we present a case of pulmonary emboli consequent to a therapeutic injection of HA, whose diagnosis was prompted by an abnormal lung diffusion capacity by single breath technique (D_{LCO})[4] and a lung biopsy that showed emboli composed of HA itself.

Case Report

A 57-year-old white male was admitted to the GV Sonny Montgomery Veterans Affairs Medical Center, after waking up at 3:00 AM with shortness of breath associated with sharp chest pain radiating to the right shoulder and back, which was made worse by deep inspiration and by coughing. He had a 60-pack-year smoking history and was being

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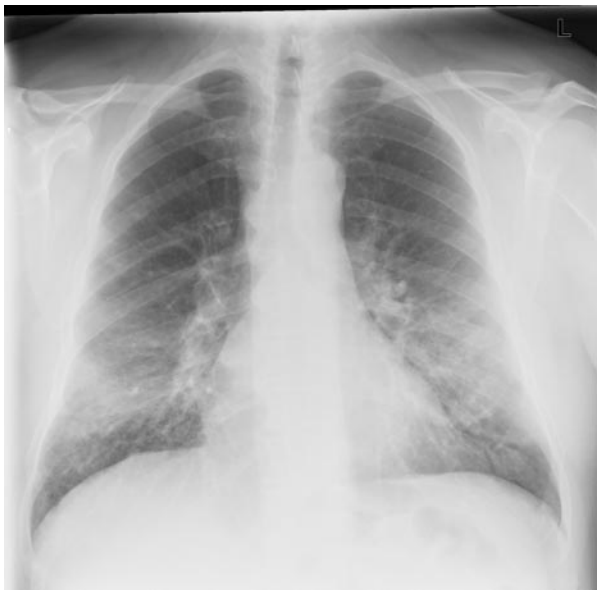

Fig. 1. Chest radiograph. The chest radiograph (posterior-anterior, left) from the day of admission shows bibasilar peripheral hazy opacities in the middle and lower lobes.

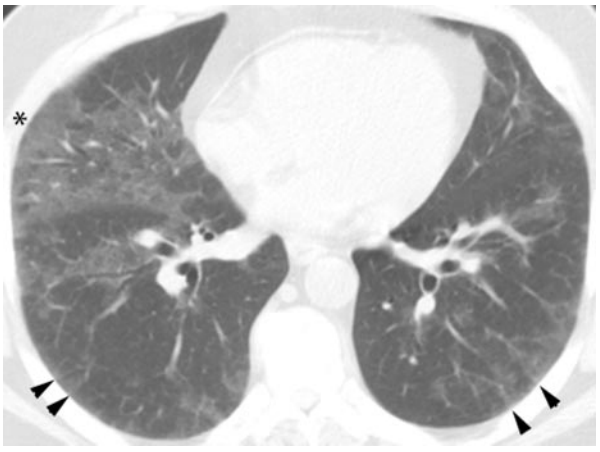

Fig. 2. Chest computed tomogram. An image from the tomography pulmonary angiogram taken just inferior to the carina shows ground glass opacities, as well as prominent septal lines at the dependent pleural edge (arrowheads). The asterisk marks the site where the biopsy would be taken. No abnormalities are visible on the mediastinal window.

treated for obesity, hypertension, diabetes, and sleep apnea. The patient also had a history of bilateral knee pain, with a right medial meniscectomy having been performed 7 years previously, during which severe chondromalacia was noted. There had been one course of 5 weekly injections of 1% sodium HA (2.5 mL of Supartz) in the right knee a year prior to admission, and a second course of bilateral injections concluding a month before admission, interrupted after 4 of the 5 planned injections. There was a distant history of asbestos exposure, but no history of home or occupational exposure to known allergens, and no history of farm work.

His physical exam was unremarkable other than shallow rapid breaths and a pulse of 99 beats/min. Arterial oxygen saturation was $>$ 95% on 2 L/min of oxygen by nasal cannula; the blood gas on admission showed a P_{aO_2} of 73 mm Hg, P_{aCO_2} of 41 mm Hg, and a pH of 7.42 on room air. His initial D-dimer was 2.6 μg/mL fibrinogen equivalent units (normal is 0.0–0.5 μg/mL fibrinogen equivalent units). The chest radiograph showed bibasilar peripheral hazy opacities (Fig. 1). A Doppler study of the lower extremities was negative for venous thrombosis. The computed tomography (CT) pulmonary angiogram of his chest did not show any evidence for pulmonary emboli or emphysema, but did reveal extensive patchy bilateral ground glass opacities that were predominantly in the periphery of the right middle lobe but also present in the right and left lower lobes and the left lingula (Fig. 2). Prominent septal lines were also visible on the lung windows of the CT (ie, the Kerley B lines of chest radiographs, see Fig. 2, arrowheads along the dependent edge). The symptoms resolved spontaneously within 48 hours, and the patient was discharged home with analgesics for knee pain; no supplementary oxygen was required.

Pulmonary function tests (PFTs) performed 3 weeks after this hospitalization showed normal spirometry, and no further pulmonary testing was performed, according to the institution's therapist-directed PFT algorithm. While a chest CT continued to show areas of ground glass opacity, the patient refused the recommended bronchoscopy since he was asymptomatic.

During a follow-up clinic visit 3 months later, the pulmonary consultant ordered a full set of PFTs. Again, the air flows were normal, as were the lung volumes, but the D_{LCO} was abnormal (19.1 mL/min/mm Hg, 63% of predicted).

Since the ground glass opacities continued to persist, the patient consented to fiberoptic bronchoscopy and an open lung biopsy. The bronchoalveolar lavage fluid showed macrophages with a few neutrophils and eosinophils; benign bronchial epithelial cells were also present. A 2-dimensional echocardiogram showed normal left ventricular function, with no important valvular abnormalities. The biopsy was performed on the right middle lobe (marked by an asterisk on Fig. 2), which showed respiratory bronchiolitis with an amorphous substance present in many medium and small pulmonary arteries (Fig. 3). Lymphatic vessels were dilated, and numerous alveolar pigmented macrophages were present (Fig. 4). A diagnosis of respiratory bronchiolitis and emphysema associated with mild bronchiolar fibrosis and focal peribronchial metaplasia was confirmed in a review of the case by the Armed Forces Institute of Pathology. A bone marrow embolus was also noted. Subsequently, special stains indicated that the amorphous material contained HA co-localized with fibrin (Fig. 5).

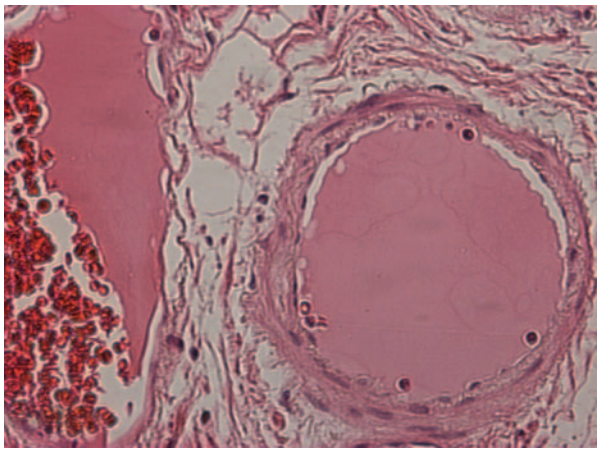

Fig. 3. Tissue biopsy with hematoxylin and eosin stain. Hyaline material is present in multiple small pulmonary arteries in the tissue biopsy obtained 4 months after the initial hospitalization (hematoxylin and eosin staining, high power).

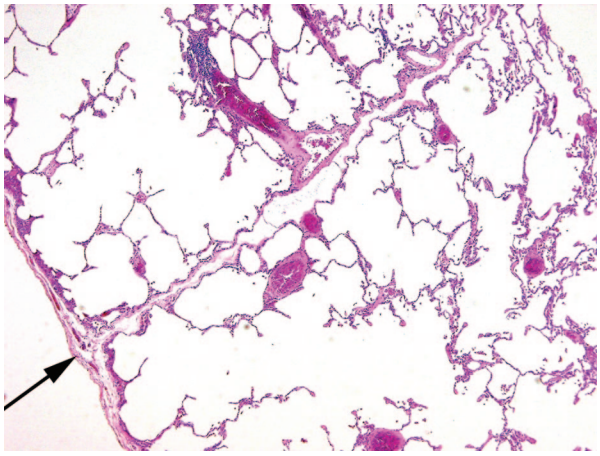

Fig. 4. Dilated lymphatic vessels at the lung periphery. The lymphatic vessels (arrow) draining to the pleural surface are dilated (hematoxylin and eosin stain, low power).

A second episode of shortness of breath and chest pain was experienced the day after the biopsy, and again Doppler studies and a CT pulmonary angiogram of the chest were negative for emboli, but a perfusion scan showed multiple small subsegmental filling defects. The symptoms again resolved and the patient was discharged 5 days later.

Subsequently (but before the results of Fig. 5 were obtained), a course of 4 intra-articular injections of HA was without incident, but also without therapeutic benefit; ultimately, a left medial meniscal tear was confirmed by arthroscopic examination and a meniscectomy was performed, with symptomatic relief.

A follow-up chest CT a year later showed mild residual bibasilar scarring, but a resolution of the ground glass opacities. However, the reduction in the D_{LCO} was unchanged on repeated PFTs (18.1 mL/min/mm Hg, 60% of predicted). A chest radiograph at 31 months was normal.

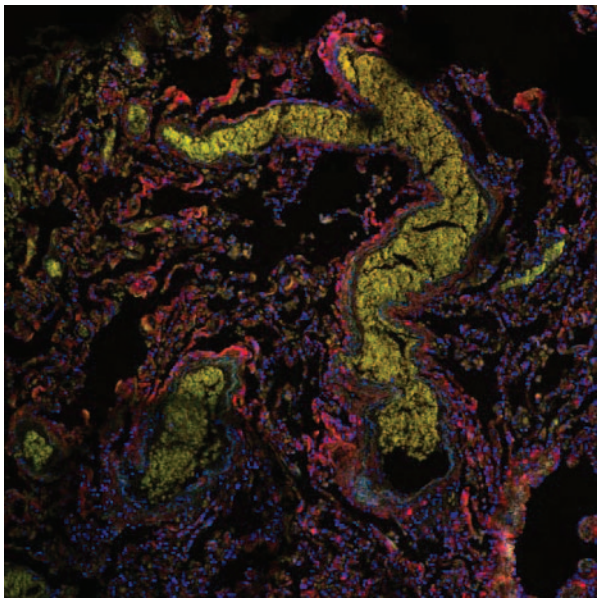

Fig. 5. Lung biopsy stained for fibrin and hyaluronic acid (HA). Fibrin colocalized with HA in multiple small pulmonary arteries appears yellow; HA is identified by hyaluronan binding protein.[5]

Discussion

Diagnosis of These Unusual Pulmonary Emboli

Our patient appeared to have a pulmonary embolus, being short of breath and having pleuritic chest pains, with an elevated D-dimer that was consistent with his symptoms. Yet it was difficult to reach a proper diagnosis because usual findings were absent: no demonstrable vascular source for the thrombus (by ultrasonography); no pulmonary vascular filling defects on lung CT; no tachycardia (as the heart rate failed to reach the threshold specified by the Wells rule); and the HA injection was not a surgical procedure requiring general anesthesia.[6] Instead, multiple patchy ground glass opacities were present bilaterally in the middle and lower lobes of the lung, and these findings are generally consistent with airway and interstitial diseases such as hypersensitivity pneumonitis and cryptogenic organizing pneumonia. Of these entities, hypersensitivity pneumonitis was unlikely, because there were no airway symptoms (ie, no rales and no obvious farm or bird source of environmental exposures). The subsequent biopsy confirmed this conclusion, since bronchiolocentric cellular interstitial pneumonia, organizing pneumonia, and multiple poorly formed granuloma were not present. Similarly, cryptogenic organizing pneumonia was unlikely, since there was no consolidation apparent on the chest radiographs and the distribution of the ground glass opacities was diffuse and not peripheral, peribronchial, and perilobar. Finally, late stage interstitial pulmonary fibrosis was unlikely, because there were no signs of fibrosis on

CT. Fortunately, the symptoms resolved quickly, but the patient was discharged without a diagnosis.

The first clinic visit did not lead to a diagnosis either. The scheduled fiberoptic bronchoscopy was refused, as the patient was symptom-free, and the spirometry done at that clinic visit was normal. It was at the second clinic visit that a full set of PFTs were performed and the D_{LCO} was found to be abnormally reduced, indicating a decrease in the global efficiency of the pulmonary gas exchanges, with one reason being a loss of pulmonary vascular surface area. With 2 abnormalities—the abnormal CT and the reduced D_{LCO}—the patient was persuaded to undergo diagnostic fiberoptic bronchoscopy and ultimately an open lung biopsy, which revealed the tissue defect, namely a bone embolus and the amorphous, hyaline material in multiple small pulmonary arteries that later stained positively for fibrin and HA.

Pathogenesis of the HA Emboli

HA is a linear polysaccharide that has many diverse functions: encapsulation, nutrition, embryological development, extravascular turgor, viscosity, and lubrication.[7] It is for the purpose of lubrication that HA is ordinarily present in the synovial fluid, and the rationale for injection of Supartz into joints suffering from osteo- and rheumatoid arthritis. In our case, the presence of a bone marrow embolus and deposits of HA in multiple small arteries of the lung indicate that the bony surface of the joint was damaged and synovial contents were released into the joint vasculature and trapped in the lung. HA binds to endothelial cells throughout the body, but particularly well in the pulmonary vasculature[8]; thus, HA emboli would enter the lung and be bound to endothelial receptors, accumulating as thrombi in the small arteries.[9] The HA emboli were most likely cleared via the lymphatics, since these vessels were dilated in lung biopsy.

On a smaller scale, arterial embolization with local necrosis and ulceration has been observed after Restylane (a cosmetic formulation of cross-linked HA) was injected dermally for glabellar augmentation.[1] In a second case, intradermal injection of 5 mL of HA into the highly vascular tissue of the anterior vagina promptly resulted in signs and symptoms of pulmonary emboli, with bilateral diffuse ground glass opacities in the lung CT, which were predominantly peripheral, with central sparing. A biopsy 4 days after the HA injection showed a granulomatous foreign body reaction with amorphous basophilic inclusions, consistent with polyanionic molecules such as the nucleic acids and HA.[2] Together with the biopsy in our case, which was obtained at 4 months after the presenting symptoms, we can conclude that the HA emboli evolve with the accumulation of fibrin to become eosinophilic, and that the emboli persist longer than the surrounding granulomatous reaction.

Even larger volumes of HA are infused into joints, and a case has been reported of dyspnea with signs of pulmonary emboli starting 6 hours after bilateral hip injections of HA for the therapeutic relief of pain, confirmed by the appearance of bilateral mismatched perfusion defects on a ventilation-perfusion pulmonary scintillogram; fat emboli were tentatively proposed as the mechanism, as no lung biopsy was available from that case.[3] While no more than a single bone marrow embolus was present in our case biopsy, what we did find were multiple instances of amorphous eosinophilic material in the small lung vasculature that stained positive for HA and fibrin, indicating that the great majority of the emboli were of HA and not bone marrow fragments.

The degenerate synovium of an arthritic knee joint can break down, releasing bone marrow fragments and synovial contents into the bloodstream, which then lodge in the pulmonary vasculature. When therapeutic injections of HA restore the volume of the synovial fluid to normal levels, subsequent injury can release HA emboli in sufficient quantities to cause pulmonary symptoms, radiologic signs, and a reduced D_{LCO}.

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