Pulmonary embolism after intra-articular injection of methylprednisolone and hyaluronate

Sirs,

Intra-articular injections are safe with a low risk of sepsis and injury to surrounding structures (1). There are no reports in the literature of pulmonary embolism complicating this procedure. We would like to report such a case here.

A 66-year-old woman with rheumatoid arthritis had shaking chills and fever (41.7°C) 6 hours after the injection of both hips with a methylprednisolone depot preparation (40 mg) and hyaluronate (20 mg). Fever persisted for 3 days with daily peaks to 38°C and shortness of breath.

Seropositive rheumatoid arthritis had been diagnosed in this patient when she was 31 years old. The search for other autoantibodies was repeatedly negative. The patient had been on a stable dosage of hydroxychloroquine sulfate (200 mg twice a day), prednisone (30 mg/day), and diclofenac (75 mg twice a day) over the last 6 months. Three days before her admission prednisone was increased to 60 mg/day because of active disease and an intra-articular injection of both hips with methylprednisolone and hyaluronate was performed for severe pain.

Rheumatoid factor was 420 IU per l, Westergren erythrocyte sedimentation rate 45 mm/hr, and C-reactive protein 2.1 mg/dl.

On admission, the patient had moderate respiratory distress; physical examination disclosed only severe rheumatoid deformities of the hand joints. Fever was absent and the sites of the hip injections were painless with no swelling or redness. Laboratory showed leukocytosis (12,300 white blood cells with 81% neutrophils) with elevated blood levels of D-dimer (14.2 mg/ml; normal < 0.5) and fibrinogen splitting products (40 mg/ml; normal < 5). Arterial blood gases were pH 7.43. An electrocardiogram and a chest X-ray were normal.

A cardiac trans-esophageal ultrasonography showed a slightly dilated right ventricle with moderately increased pulmonary artery pressure (35 mmHg) and no right-sided valvular vegetation. A ventilation-perfusion pulmonary scintigraphy showed several segmental and bilateral mismatched perfusion defects, consistent with a high probability of lung embolism. A venous Doppler-ultrasonography failed to disclose any embolic source and blood cultures grew no pathogens. Anti-cardiolipin and anti-phospholipid antibodies were negative; prothrombin C, protein S, and antithrombin were normal. Antibiotics and unfractonated heparin were given for one week and then coumadin with a full recovery. Repeat pulmonary scintigraphy and laboratory tests were normal two weeks later.

The differential diagnosis included a broad spectrum of diseases in this case. High fever with the clinical features of septic fever suggested septic pulmonary embolism. However, blood cultures were negative and no obvious source of venous embolism was found. Chest X-ray was normal with no round or wedge-shaped infiltrates, a typical finding of septic embolism (2). The hypothesis that the procedure caused thrombosis of the hip veins, which subsequently embolized blood vessels in the lungs appears speculative.

The preparation was not injected intravenously so as to produce emboli of hyaluronic acid or crystalline steroid suspensions. Furthermore, if embolism had been due to steroid crystalline suspensions, hair particles or skin fragments clinical symptoms would have developed immediately rather than several hours after the procedure was done.

The clinical findings are consistent with an incomplete form of the fat embolism syndrome, a multi-system disorder characterized by pulmonary and neurological dysfunction, fever, and a petechial rash (3, 4).

Embolism of fat across a patent foramen ovale accounts for the systemic features of the syndrome (5). Incomplete forms have been described with sub-clinical, mild and, fulminating presentations (3, 4).

The syndrome is an early complication, occurring within 24 to 48 hours of skeletal trauma with fractures of the long bones (3, 4). No case has been described in association with intra-articular injections. It may be rarely seen in non-traumatic conditions (3, 4); iatrogenic causes include the use of oil as the contrast medium for lymphangiography, parenteral infusion of lipids, and subcutaneous silicone injection (6).

Long-term treatment with corticosteroids is a predisposing factor (6).

The definitive diagnosis is established by means of histologic examination; the clinical diagnosis should be regarded as presumptive. There are no standard recommendations for treatment. The common strategy is supportive; heparin, intravenous ethanol, low-molecular-weight dextran, and corticosteroids have been administered with variable success (3, 4).

The exact mechanism of fat embolism in our case is unclear. Relatively minor manipulations of the marrow space can inadvertently occur during the intra-articular injection of drugs, causing fat necrosis and embolism despite no obvious trauma to the bone or other fatty tissues. This probability was augmented as the procedure was performed at both hips using 2 different drugs.

The rationale for intra-articular hyaluronate in rheumatoid arthritis is still under debate. Symptom improvement and pain reduction has been demonstrated in osteoarthritis (7), due to the down-modulation of pro-inflammatory cytokines and prostaglandins (8).

Hyaluronate might improve the course of rheumatoid arthritis by altering the properties of synovial fluid and articular synovium (9, 10). We underline the risk of pulmonary embolism with this procedure, particularly if performed on major joints.

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