PULMONARY GRANULOMATOSIS ASSOCIATED WITH INSOLUBLE FILLERS IN A HEROIN ADDICT

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Abstract: We report a case of acute respiratory distress syndrome (ARDS) and pulmonary granulomatosis after intravenous injection of heroin. This 46-year-old male had a 2-year history of heroin addiction. The recent admission was due to loss of consciousness after intravenous injection of diluted heroin with unknown filler. Initial chest X-ray revealed a picture of ARDS. Blood routine and biochemistry were normal except for leukocytosis. Urine morphine test was positive. The blood and sputum culture yielded no pathogens. After supportive treatment, his condition improved, and the follow-up chest X-ray showed diffuse micronodules in both lung fields. Subsequently, open-lung biopsy of the right upper and lower lobes on the 26th hospital day showed large amounts of foreign-body granulomas distributed over perivascular areas, bronchiolar areas and interstitium. Staining for bacteria, fungi, and mycobacteria was all negative. The pathological diagnosis of pulmonary granulomatosis was made based on the finding of filler foreign bodies. The nature of these foreign bodies remained undetermined. The case suggests that pulmonary granulomatosis with the radiographic appearance of chronic interstitial pneumonia can occur in patients with a history of heroin use.

Key words: Granuloma, respiratory tract; Granuloma, foreign-body; Heroin dependence; Substance abuse, intravenous

Pulmonary granulomatosis has been reported in drug abuse cases including cocaine or heroin by nasal insufflation or intravenous injection.1,2 Heroin is usually acetylated from the parent compound morphine in a pure form as a white colored powder. Street heroin in Taiwan has a purity which is labeled as numbers 1 through 4, reflecting decreased content of filler substances; the color varies from brown, brownish-white, to white. Using impure heroin mixed with unknown substances, especially insoluble substances, or intravenously injecting filler-containing heroin intended for oral use can cause physical damage to the body.2–5 Common fillers in oral medications include microcrystalline cellulose, talc, and cornstarch.4 Acute pulmonary edema, embolic phenomena, and infections are well-documented complications of the lungs in heroin intoxication.2,5–9 Progressive pulmonary fibrosis and bronchiectasis have also been found in long-term heroin abuse cases.2,3,6–9 We report a case of pulmonary granulomatosis that developed in a patient with long-term heroin addiction.

Case Report

This 46-year-old male was found unconscious after intravenously injecting ‘number 3’ heroin. He had a past history of buccal carcinoma and heroin addiction for 2 years. On arrival at the emergency room, he had a consciousness level of E1M2V1 on the Glasgow coma scale, with sluggish, isocoric pupils measuring 2.0 mm. Vital signs included unmeasurable blood pressure, pulse rate of 60 beats per minute, and a body temperature of 36°C. Physical examination revealed diffuse crackles or rhonchi over bilateral lung fields. The remainder of the examination revealed no particular finding. The patient was immediately intubated and ventilated on 100% oxygen and then transferred to the intensive care unit. Arterial blood gas examined prior to intubation showed: pH, 6.99; PCO2, 92 mm Hg; PO2, 35.4 mm Hg; HCO3-, 22.3 mmol/L; base excess, –12.3 mmol/L; and oxygen saturation, 41.2%. The chest X-ray (Fig. 1) demonstrated a picture of
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Acute respiratory distress syndrome. White blood cell count was 17,200/mm³. Urine morphine test was positive. The other laboratory tests were within normal limits or unremarkable, including anti-HIV test and the serum level of phenobarbital and ethanol. Spiking fever developed on the second hospital day, and was treated with piperacillin-tazobactam (tazocin) and gentamicin. Sputum culture yielded Enterobacter aerogenes and Candida species. Three sets of serial blood cultures did not yield any growth. Follow-up chest X-ray (Fig. 2) and chest computed tomography (Fig. 3) taken on the 19th hospital day showed a diffuse micronodular pattern over bilateral lung fields. Either interstitial lung disease or metastatic carcinoma was suspected. Therefore, open-lung biopsy of right upper and lower lobes was performed on the 26th hospital day. The pathological examination showed massive amounts of foreign-body granulomas distributed over the perivascular areas, bronchiolar areas and interstitium (Fig. 4A). Emphysema was also noted. Periodic acid-Schiff (PAS), acid-fast and methenamine silver stains showed no micro-organism. Two types of foreign-bodies with different morphology could be seen on PAS stain. One appeared to be a round aggregation of cellulose-like fine crystals (Fig. 4B), and the other demonstrated talc-like yellow or unstained irregular crystals (Fig. 5). The pathological diagnosis was pulmonary granulomatosis arising from unknown filler substances.

The patient’s condition improved after supportive treatment. He regained full consciousness. Symptoms of respiratory distress resolved and fever subsided. He showed no clinical disease throughout a follow-up period of 1 year.

Discussion

Various pulmonary complications of heroin addiction have been well documented, including aspiration pneumonia, pulmonary edema and subsequent development of bronchiectasis, pulmonary embolism, pulmonary tuberculosis and other infections, emphysema, pulmonary artery medial hypertrophy, mycotic aneurysm of pulmonary arteries, foreign body granuloma, and even progressive massive fibrosis.2,3,6–9 This patient initially presented with acute manifestations of intoxication from heroin. Quadri and Russi reported that non-cardiogenic pulmonary edema is one of the most frequent causes of death in
heroin addicts, especially when it is complicated with conditions such as aspiration pneumonia. Various hypotheses for its mechanism have been suggested, including: 1) anaphylactic reaction caused by culturally unsterile street heroin containing fungal or plant-derived antigen; 2) pulmonary vascular constriction due to acute hypoxemia; 3) capillary injury caused by fillers; and 4) histamine-releasing effect of heroin. Immediate supportive therapy was given to this patient, including ventilation and intubation.

Pulmonary epithelioid granuloma has been reported to be caused by infectious organisms, products of plants and animals and metallic compounds. Muns et al. broadly classified pulmonary granulomatous disease into hypersensitivity type and foreign-body type. Pulmonary embolism and subsequent development of granulomatosis can be caused by intravenous injection of drugs intended for oral use and was first reported in 1950. Intravenous injection of heroin alone does not result in pulmonary foreign-body granuloma since it is frequently diluted with soluble substances such as maltose, lactose and quinine. A small percentage of heroin addicts also frequently inject tablets — including methylphenidate hydrochloride (Ritalin®), methadone hydrochloride, tripelellamine hydrochloride (pyribenzamine) and pentazocine (Talwin®), which contain insoluble fillers such as talc, cornstarch, and microcrystalline cellulose. Microcrystalline cellulose shows positive PAS and methenamine silver staining histologically and bright-yellow green birefringence in polarization of the Congo-red stained crystal. Talc, on the other hand is a needle-shaped crystal which is smaller, and stained neither by PAS nor methenamine silver. Cornstarch granules are circular and have maltese-cross birefringence.
In the pulmonary sections of this case, 2 types of foreign bodies with different morphology were seen under the light microscope, including PAS-positive fine crystals and yellow or unstained irregular crystals. The former was likely to be microcrystalline cellulose, while the latter resembled talc. In a consecutive autopsy study of 33 drug addicts, birefringent materials and granuloma were observed in the wall of pulmonary arteries and/or interstitial tissue.11 The distribution of the granulomas and foreign-bodies are thought to be dependent on the duration of abuse.11 Vallyathan and Craighead studied 7 workers exposed to non-asbestiform talc and reported that the extent of the pulmonary lesions corresponds to the concentration of talc in the tissue.12 In addition to exposure duration and usage amount, an individual’s response to talc is also a factor affecting the outcome of talc-induced pulmonary granulomatosis. Arnett et al described 2 cases in which pulmonary granulomas developed after injection of talc-containing drug intended for oral use.2 One of the 2 cases presented had clinical and histologtical features similar to the case described in this report. Pulmonary arterial hypertension caused by intraluminal talc granulomas of pulmonary arteries are not evident because the talc granulomas distribute mainly in the interstitium and perivascular area. The outcome could be much worse in patients who mainly have intraluminal granulomas which might obstruct the pulmonary arteries, eventually resulting in pulmonary hypertension. Fatal cases showing such features were reported by Arnett et al.2 In some patients, talc granulomas were noted with progressive, massive interstitial fibrosis of lungs, which could also be a fatal condition.13 Crouch and Churg suggested that endothelial injury could be caused by intravenous particulates, and further leads to thrombosis, focal acute inflammation, and destruction of the arterial wall with organization and revascularization.5 This results in transvascular migration of the particles with the formation of perivascular granulomas.5,14

After regression of the diffuse pulmonary infiltrate, diffusely distributed micronodules were demonstrated by chest X-ray and computed tomography in our patient. As in our patient, the radiological findings of talc granuloma are not specific. The differential diagnosis includes miliary tuberculosis, sarcoidosis, fungal disease, and miliary metastases. The distribution of the micronodules in chest radiography is helpful in the differential diagnosis. In our patient, the micronodules were not clearly outlined on the chest X-ray until the pulmonary edema resolved. High-resolution computed tomography is superior to conventional radiography, and shows nodules and their distribution better.14

Our patient first manifested with respiratory insufficiency, similar to the 2 cases of heroin intoxication reported by Wang et al.9 However, there is no direct association between heroin intoxication and pulmonary granuloma. Cases with pulmonary granulomas were caused by filler substances in drugs intended for oral use and were not a direct effect of the drug use.

In conclusion, while foreign body granulomatosis caused by filler substances has been well described in reports from western countries, it is under-recognized in Taiwan. This condition should nevertheless be differentiated from other diffuse micronodular diseases due to different management needs.

References