Angiocentric Systemic Granulomatosis

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Abstract: As part of a review of substance abuse deaths in Dutchess County, New York, the Dutchess County Medical Examiner's Office identified 3 cases of angiocentric systemic foreign-body granulomatosis discovered at autopsy. Our investigation disclosed that in all 3 cases patients surreptitiously injected crushed oral prescription medication. Of the patients, 2 obtained intravenous access through central venous lines, the other patient was found to have injected herself intramuscularly. Autopsy demonstrated lung abnormalities due to diffuse deposits of foreign material within and around vessels, associated with foreign-body granulomatous reaction. We also identified a systemic distribution of this foreign material deposited beyond the lungs in the brain, heart, kidneys, and spleen. We present these cases along with a review of the literature of systemic embolization of foreign material in previously documented cases of deaths due to parenteral abuse of oral medications.

Key Words: pulmonary granulomatosis, drug abuse, excipients

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The Office of Applied Studies' 2007 National Survey on Drug Use and Health estimated 8.0% of the US population aged 12 years or older were current illicit drug users; 2.8% used prescription-type psychotherapeutic drugs nonmedically in the past month.[1] Intravenous injection of crushed and solubilized oral medication results in the deposition of excipients or filler materials in the lungs. This filler material, in turn, may produce foreign body granulomatous inflammation in the pulmonary parenchyma where it embolizes.[2–4] Several names have been used to refer to such lesions descriptive of the identified pathology (self-induced pulmonary granulomatosis, pulmonary angiothrombotic granulomatosis, pulmonary mainline granulomatosis, and pulmonary granulomatous vasculitis)[4–7] or the foreign material identified (eg, talc granulomatosis, cellulose granulomatosis, etc).[2,3,8,9] Pulmonary angiothrombotic granulomatosis, pulmonary granulomatous vasculitis, and talc granulomatosis are the most commonly used terms. In a review of drug-related deaths investigated by the Dutchess County Medical Examiner's Office, we identified 3 cases in which the cause of death was due to the massive deposition of filler material secondary to parenteral ingestion of crushed oral tablets. We characterize the systemic localization and distribution of this material in these cases.

MATERIALS AND METHODS

A retrospective analysis of drug-related deaths, as certified on death certificates issued by the Dutchess County Medical Examiner's Office, was performed. Total number of drug-related deaths, the type of drugs involved (ie, illicit drugs, prescription medications, or mixed illicit and prescription medications) and demographics were categorized. Three cases with drug-related pulmonary granulomatosis were identified. In the 3 cases, complete autopsies with toxicology were performed. Past medical records and radiologic films were reviewed and standard hematoxylin and eosin histologic sections were examined under incandescent and polarized light.

RESULTS

There were 972 autopsies performed by the Dutchess County Medical Examiner's Office during a 5-year period (2003–2007). The cause of death was certified as due to drug overdose in 141 cases (14.5%) (93 males and 48 females, ratio of 1.9:1). Of these 141 deaths, 60 (42.5%) were due to prescribed medications; 60 (42.5%) were due to nonprescribed drugs of abuse, and 21 (15%) were due to a mixture of prescribed and nonprescribed drugs. In the subcategory of prescription medication overdoses, there were 26 males and 34 females (ratio of 0.76:1). In the combined subcategories of drugs of abuse and mixed drug overdoses, there were 67 males and 14 females (ratio of 4.8:1). In 3 cases, angiothrombotic foreign-body granulomatosis was discovered at autopsy. These cases are summarized below.

Case 1

A 33-year-old woman was found unresponsive by her healthcare proxy roommate. Paramedics found her in an idioventricular rhythm and she could not be resuscitated. Her medical history included multiple hospitalizations for respiratory decompensation, asthma and angioedema, requiring endotracheal intubation and eventually tracheostomy. Her symptoms were allegedly due to "allergies" that were never identified or proven. Three months prior to her death she was admitted for bacterial endocarditis with tricuspid valve vegetations and blood cultures positive for *Enterobacteria* sp. and *Streptococcus* sp. A week prior to her death she had incision and drainage of several abscesses on her arms and buttocks. Past psychiatric diagnoses included major depression and a borderline personality disorder with self-destructive and attention-seeking behavior. She was prescribed morphine and diphenhydramine for "chronic pain."

Autopsy demonstrated numerous injection sites with scar and abscess formations of the skin, subcutis, and underlying skeletal muscle of her arms, shoulders, and buttocks. Her heart was enlarged, globular and showed a 0.5-cm organized vegetation on the tricuspid valve. Her lungs were focally firm and edematous. Histologic examination of her abscesses revealed acute and chronic foreign body granulomatous inflammation with polarizable material consistent with microcrystalline cellulose in her skeletal muscle and skin. There was diffuse interstitial fibrosis of her lungs and numerous foreign body emboli surrounded by multinucleated giant cells and chronic inflammation in the pulmonary interstitial arteries, arterioles, and capillaries. Similar polarizable material consistent with microcrystalline cellulose was identified in pulmonary vessels. Examination of sections of her kidneys, adrenal glands, and ovaries also demonstrated foci of microcrystalline cellulose with granulomatous inflammation. Her liver demonstrated a few granulomata without demonstrable polarizable material. Postmortem toxicology was positive for morphine and diphenhydramine.

Case 2

A 28-year-old hospitalized man was discovered to be unresponsive and cyanotic in bed with a syringe in his hand. The syringe was noted to contain a light pink suspension, identical to what was

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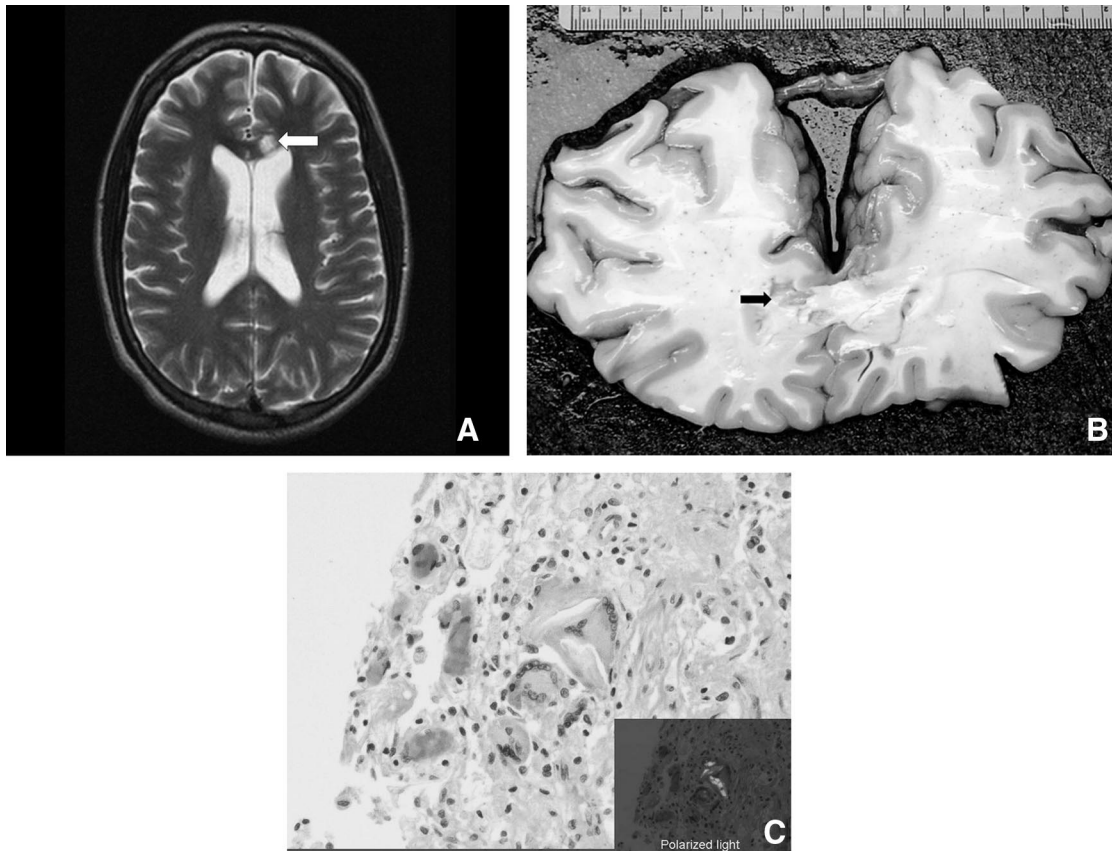

FIGURE 1. A, Case 2: axial T2-weighted Magnetic Resonance Image (MRI) of head with hyperintense lesion in left side of genu of corpus callosum (arrow). B, Case 2: gross image of coronal section through genu of corpus callosum demonstrating plaque-like area mimicking multiple sclerosis (arrow). C, Case 2: photomicrograph of necrotic white matter lesion with foreign-body granulomatous inflammation surrounding polarizable microcrystalline cellulose (insert). H and E ×200.

identified in the transparent plastic tubing of his triple lumen subclavian intravenous catheter. The patient had been admitted through the emergency room 2 days prior when he alleged that he had been involved in a roll-over motor vehicle accident. The patient came to the hospital to be evaluated for chest and low back pain. His medical history was significant for intravenous drug abuse, gastrointestinal hemorrhage, multiple sclerosis, and back surgery. A recent work-up for multiple sclerosis included magnetic resonance imaging of his brain that demonstrated a T2-weighted hyperintense lesion in the genu of his corpus callosum (Fig. 1A), in his occipital white matter, and in his pons. His psychiatric problems included depression and abuse as a child, self-abusive behavior, and Munchausen syndrome. During this hospitalization cardiology, orthopedics, and psychiatry evaluations were unremarkable, and the patient had been scheduled to be discharged on the day of his death. Postmortem examination demonstrated no evidence of recent traumatic injury. Examination of the hospital therapy that had been left in place until autopsy confirmed the presence of a slightly pink-white fluid within his triple lumen catheter and 7 mL of similar liquid within the recovered 10 mL syringe. Several scars and tattoos were noted on the upper extremities without gross abscess formations. Both lungs revealed multiple firm 0.1 to 0.2 cm light tan to white nodules, miliary in appearance, throughout all lobes (Fig. 2A); combined weights were 910 g. The brain grossly showed a focus of tan-gray softening, consistent with a plaque, within the left side of the genu of his corpus callosum (Fig. 1B). Microscopic examination of his lungs revealed multiple foci of foreign body granulomata centered in and about vessels but focally extending into adjacent septae, which markedly distorted normal alveolar architecture. These were associated with 2 types of foreign materials: a light amphophilic colored, polarizable substance consistent with microcrystalline cellulose and an annular, deeply basophilic substance that resembled calcification consistent with crospovidone (poly[N-vinyl-2-pyrrolidone]) (Fig. 2B). Sections of the corpus callosum demonstrated a focus of necrosis within the white matter associated with granulation tissue formation, astrogliosis, and rare granuloma with polarizable material consistent with microcrystalline cellulose (Fig. 1C). Sections of cerebellar white matter and basal ganglia also were positive. Similar granulomata with polarizable material were noted within heart, kidneys, and spleen (Fig. 2C, D). Postmortem toxicology tested positive for codeine, diphenhydramine, promethazine, and mirtazapine in the blood; the syringe fluid tested positive for codeine, diphenhydramine, and mirtazapine.

Case 3

This 35-year-old woman had a experienced seizure at her home before going into cardiorespiratory arrest; she was taken to an emergency room by paramedics but could not be resuscitated. The patient had her first seizure 6 months prior but never had a neurologic work-up and did not have a prescription for anticonvulsants at the time of her death. Past medical history was also significant for the recent removal of a benign rectal tumor complicated by a methicillin-resistant *Staphylococcus aureus* infection, ovarian cysts,

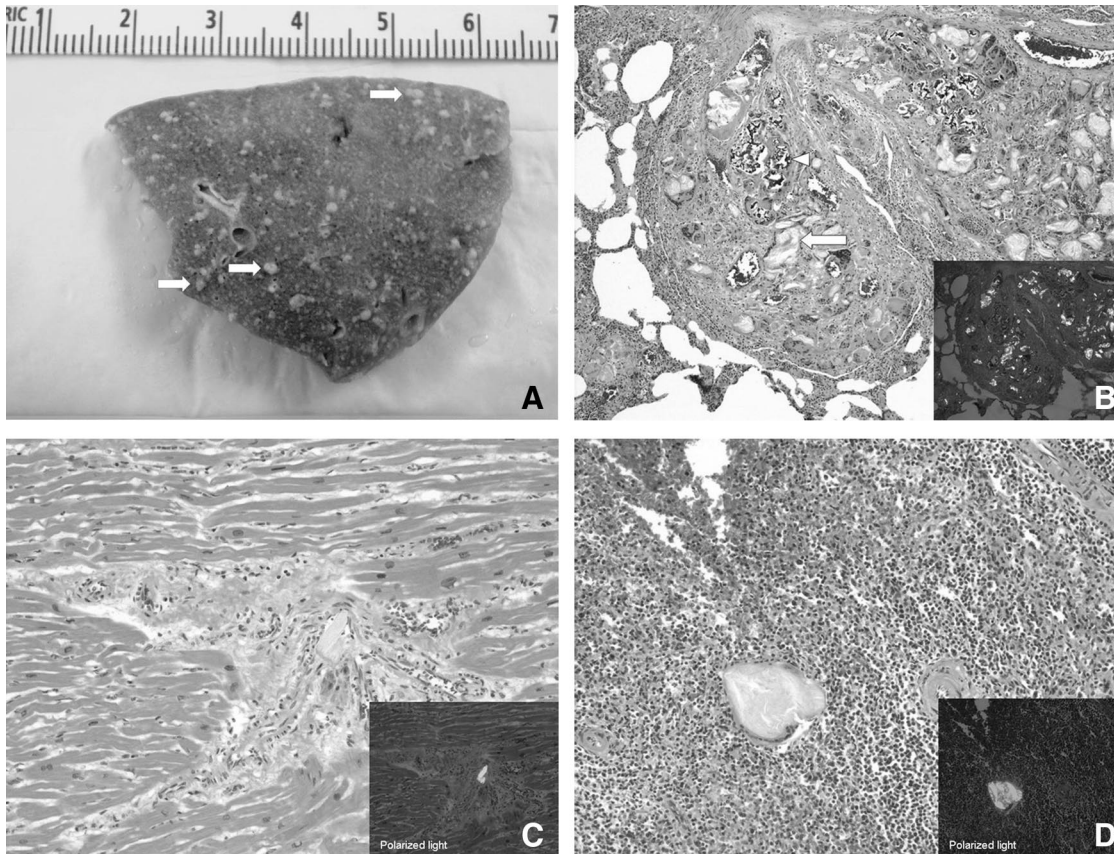

FIGURE 2. A, Case 2: gross image of cross section of lung with numerous white, solid, firm nodules throughout pulmonary parenchyma. B, Case 2: pulmonary vessels occluded by foreign polarizable material consistent with microcrystalline cellulose (arrow) and basophilic annular material consistent with crospovidone (arrow head). H and E × 40. C, Case 2: myocardium with granulomatous inflammation surrounding polarizable material. H and E ×100. D, Case 2: spleen with polarizable material. H and E ×100.

hypothyroidism, endometriosis, and chronic anemia. As a result of her *Staphylococcal* infection the patient had a subclavian subcutaneous port inserted for administration of intravenous antibiotics and total parenteral nutrition. In addition to intravenous antibiotics, the patient was prescribed an oral analgesic, oxycodone, for painful ovarian cysts, and epoetin alpha (Procrit, Ortho Biotech Products, LP., Bridgewater, NJ) for anemia. Further investigation revealed that the patient had visited emergency departments at local hospitals 19 times in the last year. There was no known history of drug or alcohol abuse or psychiatric problems. Postmortem examination revealed heavy, congested, and edematous lungs (combined weight 1850 g) that also showed several paler nodular and granular, firm to rubbery foci that measured up to 0.3 cm in diameter (Fig. 3A). The spleen was enlarged, 460 g, and congested; the left ovary showed a few benign cysts; other organs were grossly normal. Microscopic examination of the lungs demonstrated multiple emboli of polarizable material consistent with microcrystalline cellulose and crospovidone associated with foreign body granulomatous reaction and fibrosis (Fig. 3B). Left and right ventricular myocardium, kidneys, ovaries, spleen, and cerebellar white matter were also positive for emboli of microcrystalline cellulose with varying degrees of chronic inflammation and multinucleated giant cells. Postmortem toxicology results were positive for oxycodone, acetaminophen, sertraline, and dicyclomine.

DISCUSSION

The foreign materials we observed inside and obstructing pulmonary vessels are derived from crushed suspensions of oral medications and consist of excipients. These are filler substances such as talc, corn starch, microcrystalline cellulose, or crospovidone that compose part of oral medications.[10] Pathologic findings in pulmonary vessels of intravenous drug abusers were described by Tomashefski and Hirsch.[11] The forensic pathologist should become familiar with such changes to distinguish them from the patterns of distribution of foreign material in cases of pneumoconiosis. Inhalational dusts accumulate in different compartments: intra-alveolar, interstitial, subpleural, and around bronchovascular bundles with the centroacinar region being the primary site of deposition.[12] Dust particles may also affect the upper airway and result in sinusitis, asthma, and tracheobronchitis.[13] Common forms of pneumoconiosis include the silicotic nodule (crystalline silicon dioxide), the carbon-pigmented macule (washed coal dust), diffuse interstitial fibrosis (asbestosis), chronic granulomatous disease (talcosis, berylliosis), subacute fibrosing alveolitis with giant cell interstitial pneumonitis (cobalt/hard-metal pneumoconiosis), chemical pneumonitis (cadmium), airway irritation (mercury), sinusitis and asthma (nickel), and metal fume fever (zinc oxide). Some dusts produce more than one pathology, eg, aluminum can result in chronic bronchitis, pulmonary fibrosis, granulomatous disease, and tracheobronchitis;

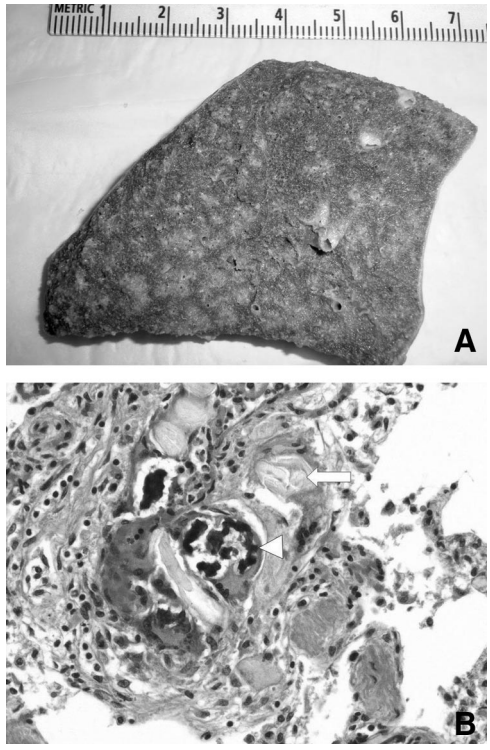

FIGURE 3. A, Case 3: gross image of cross section of lung with paler nodular and granular areas. B, Case 3: foreign body granulomatous inflammation surrounding microcrystalline cellulose (arrow) and crospovidone (arrow head) filler materials deposited in lungs. H and E ×200.

some dusts result in surprisingly little pathology, eg, siderosis/arc welder pneumoconiosis and copper. In cases of pneumoconiosis, foreign materials will not be found predominantly within the lumina and walls of pulmonary vessels, ie, with an angiocentric distribution. This distinction is relevant for pathologists asked to help establish the accuracy of claims of the adverse effects from dust inhalation. For example, following the September 11, 2001 World Trade Center collapse have come reports of some rescue workers and survivors who developed a granulomatous pneumonitis that resembles sarcoidosis.[14–17]

Systemic or arterial distribution of crystalline material indicates that foreign material is able to enter the left-sided venous circulation, and bypass the pulmonary capillary filter. Similar to our cases Paré et al observed talc granulomas in lungs, liver, kidneys, and lymph nodes in a postmortem examination of a drug abuser.[6] In a postmortem study of intravenous drug abusers (n = 33) Kringsholm and Christoffersen searched for deposits of talc, potato and corn starch, microcrystalline cellulose, magnesium stearate and siliciumoxid in different organs.[18] Of these materials, only talc deposits were found outside of the lungs, namely in the spleen, liver, portal lymph nodes, and bone marrow. Further evidence that systemic embolism takes place in intravenous drug abusers is the observation of talc deposits in the retina,[19–22] brain, and spinal cord.[20,23] It should be noted that it is not only in intravenous drug abusers that this phenomenon has been recorded. Lunetta et al demonstrated that barium sulfate particles passed through the lungs to be deposited in the kidney and brain after this contrast medium was iatrogenically introduced into the right-sided (venous) circulation.[24]

In such cases, emboli may pass through a patent ductus arteriosus; although, in each of our cases the ductus was closed. Or, perhaps, tiny microemboli pass through pulmonary capillaries or larger "recruitable pulmonary vessels" as some have proposed to explain the occasional appearance of systemic fat globules following orthopedic procedures or liposuction.[25,26] The presence of recruitable arteriovenous shunts has been shown in animal fetal circulation,[27] in postmortem studies of human lungs,[28] transiently in massive pulmonary embolism in humans,[29] and in end-stage pulmonary disease in humans.[30] In a postmortem study by Lovering et al, microspheres up to 50 μm in diameter were demonstrated to pass through functional arteriovenous shunts under physiologic condition.[31] It may be that a certain minimum burden of pulmonary pathology must develop before such channels become functional and/or perhaps certain physiologic activities must take place, such as has been demonstrated to occur during strenuous exercise.[32–34] The extensive distortion of normal pulmonary architecture identified in our cases may also have predisposed to opening up such recruitable arteriovenous shunts. The clinical correlate is this: that a patient who injects foreign material into the venous circulation and passes an arterial embolism may present with symptoms and signs that mimic another disease.

This occurred in Case 2, in a patient with a diagnosis of multiple sclerosis supported by a demonstrable T2-weighted hyperintense lesion on MRI. Multiple sclerosis is an autoimmune disease characterized by the development over time of more than one demyelinating plaque in the central nervous system.[35] The differential diagnosis is large, thus, multiple sclerosis is a diagnosis of exclusion.[36] Magnetic resonance imaging complements the clinical evaluation of these patients and aids in the diagnosis and assessment of their response to treatment. In general, water containing tissue or fluid is hyperintense or bright and fat is hypointense or dark on a T2-weighted MRI. Cerebrospinal fluid and edema will appear hyperintense on a T2-weighted MRI. Active demyelinating plaques show gadolinium enhancement on T1-weighted MRI which reflects a local disruption in the blood brain barrier; these lesions are also hyperintense (bright) on T2-weighted MRI lesions which reflects focal edema.[37] Unfortunately, MRI is not pathologically specific[38] as demonstrated in our case of the intravenous drug abuser who infarcted his corpus callosum due to an excipient embolism.

To summarize, we present the pathologic findings of 3 parenteral abusers of oral prescription medications. The forensic pathologist should be aware that prescription type medications are the second leading category of abused drugs in the United States. Of further concern is the reported trend (years 2002–2007) of an increase in the number of youths, ages 18–25 who abuse prescription medications in the United States.[1] We note that in our jurisdiction a relatively larger percentage of women abuse prescription medications than in the population that abuses illicit "street" narcotics. In our 3 cases we identified both a pulmonary deposition and systemic distribution of crystalline filler material. Most previous reports emphasize pulmonary pathology without calling attention to the systemic burden of deposited excipients. Hence, the condition has been designated: self-induced pulmonary granulomatosis, pulmonary angiothrombotic granulomatosis, pulmonary mainline granulomatosis or pulmonary granulomatous vasculitis. Although we concur with the vascular nature of this process, we propose that a more accurate description for this entity is systemic angiocentric (or angiothrombotic) granulomatosis.

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