CLINICAL VIGNETTE

Opioid Induced Noncardiogenic Pulmonary Edema, A Growing Concern

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Introduction

The use and misuse of opiates has increased precipitously over the past several decades, with the incidence of overdose rising as well. In the United States, the National Institute on Drug Abuse estimated deaths from overdose of all opioids has increased from 8,048 in 1999 to 47,600 in 2017.[1] As heroin becomes cheaper and more readily available, deaths from heroin overdose have also increased from 1,960 to 15,482 deaths during this same period of time.[1,2] Opioids derive their effects from their interaction with mu, kappa, and delta opioid receptors and can have toxic effects on multiple organ systems including the central nervous, cardiovascular, and pulmonary.[3] With regard to the pulmonary system, opioids exert multiple pathologic processes and may affect all aspects of respiration. These includes direct effects such as noncardiogenic pulmonary edema, bullous changes, pulmonary hemorrhage, and granulomatous changes. Indirect effects include reduced respiratory drive and truncal rigidity, infectious processes (pneumonia, tuberculosis and septic emboli), immunologic processes (bronchospasm and eosinophilic pneumonia), and direct airway complications (pneumothorax, nasal perforation, and vocal cord paralysis).[3] We present a case of noncardiogenic pulmonary edema (NCPE) as a result of heroin inhalation.

Case Report

A 27-year-old male with no significant past medical history presented to the emergency room with a one month history of gradually worsening shortness of breath and cough productive of thick yellow sputum. He had recently completed a five day course of azithromycin. He also reported three months of subjective relapsing fevers, night sweats, nausea, diarrhea, and vomiting. He denied abdominal pain, headache, vision changes, myalgias, hemoptysis, or rashes. There was no recent travel or sick contacts.

Social history includes smoking one pack of cigarettes daily for the past fifteen years as well as smoking black tar heroin for the past four months, increasing frequency to daily use with his last use on the day of presentation. He otherwise denies intravenous drug or alcohol use. He works in a dry cleaning facility but denies exposure to or inhalation of toxins.

Upon presentation to the emergency room, the patient had a temperature of 38.0 ^{o}C, blood pressure 107/60mmHg, heart rate 139, respiratory rate 26, and oxygen saturation of 84% on room air. He appeared uncomfortably but without respiratory distress. Exam was remarkable for no lymphadenopathy, and tachycardia without murmurs. Lungs were remarkable for diffuse rhonchi and mild diffuse expiratory wheezing and rales. Initial laboratory tests were remarkable for a leukocytosis of 16.1 10E3/uL with an absolute neutrophil count of 10.5 10E3/uL and absolute eosinophil count of 1.5 10E3/uL. Basic chemistries and liver function test were unremarkable. Arterial blood gas showed a pH of 7.35, pCO2 of 50mmHg, and a pO2 of 35mmHg. Chest x-ray showed patchy consolidations in both perihilar zones and right upper lobe (Figure 1), and chest CT scan showed patchy ground-glass opacities in both lung fields and enlarged hilar lymph nodes (Figure 2).

The patient was admitted for hypoxemia with concern for infection due to leukocytosis and low grade temperature. He was started on ceftriaxone and azithromycin for community acquired pneumonia, as well as oseltamivir for influenza. Given his subacute course, indolent infections such as mycobacterium tuberculosis and pneumocystis jiroveci were considered. Induced sputum for acid fast bacterium and PCP were collected and returned negative. Coccidiomycosis was ruled out with negative compliment fixation. Murine typhus was considered due to vague gastrointestinal symptoms but thought less likely. The hilar lymphadenopathy raised concern for malignancy including lymphoproliferative process, particularly in the setting of B-symptoms, but thought less likely given normal peripheral smear and lactate dehydrogenase. Sarcoidosis was considered but did not fit the clinical picture with normal ACE levels. Transthoracic echocardiogram showed an estimated ejection fraction of 60-65% with no valvular abnormalities, ruling out cardiac causes of pulmonary edema.

After excluding other causes, the patient's symptoms and imaging were thought to be secondary to heroin inhalation. Antibiotics were discontinued and his fever and leukocytosis resolved by the second day of hospitalization with marked improvement of respiratory symptoms consistent with non-infectious etiology. The patient's occasional diaphoresis, diarrhea, and nausea were attributed to heroin withdrawal, and successfully managed with clonidine and low-dose methadone. Subsequent imaging at follow up showed complete resolution of pulmonary infiltrates and lymphadenopathy.

Discussion

Noncardiogenic pulmonary edema (NCPE) as a complication of opioid overdose was first described in 1880 by Osler.[4] While NCPE is most commonly seen in heroin and methadone use, it has also been described with propoxyphene, codeine, buprenorphine, and nalbuphine. It occurs with either injection or inhalation of opioids.[3,5,6] Initial retrospective studies estimated the incidence of NCPE in heroin overdose requiring hospitalization at 48-80%, however the true incidence is likely much lower.[2] One retrospective chart review reported that of the 125 charts of heroin overdose reviewed between 1996 and 1999, 13 (10.4%) developed pulmonary edema.[5] Larger, more recent retrospective studies estimate incidence of 0.8-2.4% (2,6). This lower incidence is likely due to early estimates not including the full denominator of overdose cases, especially those not requiring hospitalization.[6]

The pathophysiology of opioid induced NCPE is incompletely understood, but several mechanisms have been proposed. Patients with opioid induced NCPE have normal capillary wedge pressure and evaluation of alveolar fluid shows a protein level very similar to plasma levels, suggesting increased capillary permeability as a primary etiology.[3] Increased capillary-alveolar leakage may be due to direct drug toxicity, right to left shunting causing a respiratory acidosis, and hypoventilation.[3] Heroin has been specifically shown to increase pulmonary histamine release which may also contribute to increased pulmonary vasculature permeability.[6] NCPE has also been attributed to a catecholamine surge with the use of high dose, low dose, and extended release formulations of naloxone.[3,7] One hypothesis is that long term opioid use causes changes in the sympathoadrenal system which may lead to a large catecholamine response from naloxone.[3] However, one retrospective evaluation of fatalities from opioid overdose found that 50-90% of patients had evidence of NCPE despite never receiving naloxone.[7]

One observational review cited several risk factors increasing risk for opioid induced NCPE.[5] The majority of patients were males in their thirties. Eighty- five percent of patients had a Glasgow Coma Scale score of <8 in the field. All patients had radiographic evidence of pulmonary edema on initial chest X-ray. Duration of heroin use was also associated, with an average duration of use in patients developing NCPE of 2.9 +/- 5.1 years versus duration of 14.3 +/- 11 years in patients without pulmonary edema. Finally, nearly half of patients with NCPE had co-intoxication with ethanol or cocaine.

The diagnosis of opioid induced NCPE begins with recognition of opioid intoxication syndrome, described as the triad of an altered level of consciousness, a respiratory rate of less than 12 breaths per minute, and miotic pupils.[2] Symptoms typically develop within two hours of opioid ingestion and usually are present on presentation.[2] NCPE should be suspected if hypoxia persists after the resolution of respiratory depression.[6] Patients typically will develop frothy, pink-tinged pulmonary secretions. Typical radiographic findings include diffuse, fluffy CXR pulmonary infiltrates and diffuse scattered ground glass opacities on CT scan.

Treatment of opioid induced NCPE is largely supportive with supplemental oxygen administered via nasal cannula or facemask.[6] Mechanical ventilation may be necessary in severe cases, with 27-39% of cases requiring intubation.[3,8] Symptoms typically resolve in 24-48 hours,[6] and while DLCO may remain depressed for several weeks, there appears to be no long term sequelae to opioid induced NCPE.[3,5] Because the majority of symptoms are present on admission or develop within two hours of arrival to the ER, one to two hours of observation for NCPE in heroin overdose is typically adequate, with a longer period of observation likely needed for methadone or other oral opiate overdoses.[2,6]

Conclusion

Opioid induced noncardiogenic pulmonary edema is a rare but potentially life-threatening complication of opioid use and may be seen with multiple drugs and routes of ingestion. This should be considered in those with opioid intoxication and continued hypoxia despite resolution of respiratory depression. Risk factors include a relatively short duration of opioid use and co-ingestion of ethanol or cocaine. Although treatment is largely supportive, roughly one third of patients will require mechanical ventilation highlighting the importance diagnosis recognition.

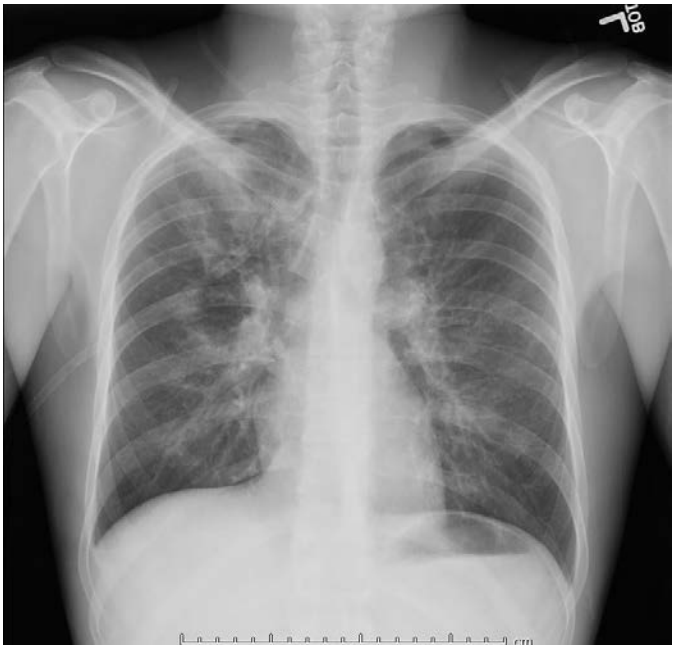

Figure 1: Chest X-ray demonstrating patchy airspace infiltrates in bilateral perihilar areas and right upper lobe.

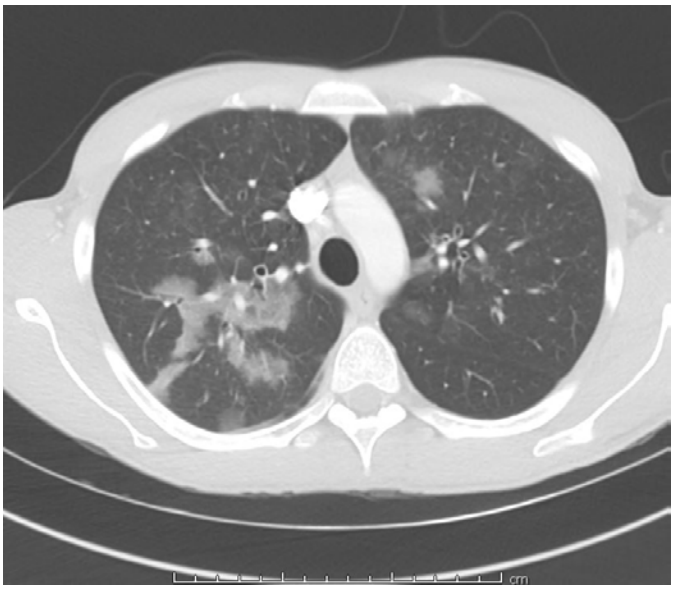

Figure2: Chest computed tomography (CT) demonstrating bilateral ground-glass opacities.

REFERENCES

1. Drugabuse.gov. (2020). *Overdose Death Rates*. [online] Available at: https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates [Accessed 5 Feb. 2020].
2. **Sporer KA**. Acute heroin overdose. *Ann Intern Med*. 1999 Apr 6;130(7):584-90. Review. PubMed PMID: 10189329.
3. **Radke JB, Owen KP, Sutter ME, Ford JB, Albertson TE**. The effects of opioids on the lung. *Clin Rev Allergy Immunol*. 2014 Feb;46(1):54-64. doi: 10.1007/s12016-013-8373-z. Review. PubMed PMID: 23636734.
4. **Osler W**. Oedema of the left lung – morphia poisoning. *Montreal General Hospital Reports Clinical and Pathological*, Vol 1. Dawson Bros Publishing, Montreal 1880. p. 291.
5. **Sterrett C, Brownfield J, Korn CS, Hollinger M, Henderson SO**. Patterns of presentation in heroin overdose resulting in pulmonary edema. *Am J Emerg Med*. 2003 Jan;21(1):32-4. PubMed PMID: 12563576.
6. **Sporer KA, Dorn E**. Heroin-related noncardiogenic pulmonary edema: a case series. *Chest*. 2001 Nov;120(5): 1628-32. PubMed PMID: 11713145.
7. **Mell HK, Sztajnkrycer MD**. Clinical images in medical toxicology: heroin overdose with non-cardiogenic pulmonary edema. *Clin Toxicol (Phila)*. 2006;44(4):399. PubMed PMID: 16809144.
8. **Ng B, Godwin J, Purssell R**. Noncardiogenic pulmonary edema associated with ultrapotent opioid overdoses. *BCMJ*. 2019;61:256-9.