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A Curious Case of Inhalation Fever Caused by Synthetic Cannabinoid

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 29
Final Diagnosis: Inhalation fever induced by synthetic cannabinoid
Symptoms: Agitation • smoked synthetic cannabinoid
Medication: Ringer's lactate solution • Ceftriaxone • Azithromycin• Magnesium sulfate • Potassium Phosphate • Levofloxacin • Risperidone
Clinical Procedure: Chest radiograph • CBC • urine toxicology
Specialty: Pulmonology

Objective: Unusual clinical course

Background: This case report describes inhalation fever as an uncommon pulmonary adverse effect of synthetic cannabinoids.

Case Report: A 29-year-old man was brought in for severe agitation after smoking K2, a synthetic cannabinoid. He required multiple doses of lorazepam and haloperidol for sedation. His vital signs were notable for a mild fever and tachycardia. Otherwise, the rest of his exam was unremarkable. The laboratory test was significant for leucocytosis and diffuse reticular-nodular and interstitial infiltrates on chest radiograph. Urine drug toxicology was negative. Interestingly, his symptoms and pulmonary infiltrates on the chest radiograph resolved spontaneously after 24 hours of observation.

Conclusions: This patient developed transient pulmonary infiltrates and fever following the synthetic cannabinoid inhalation, as seen in self-limiting inhalation fever. Inhalation fever as a consequence of synthetic cannabinoid has not been described previously and there is a need for further research in this field.

MeSH Keywords: Cannabis • Pneumonia • Smoke Inhalation Injury

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/898500

Background

Synthetic cannabinoids (SC) consumption has been increasing steadily [1–4] due to its appeal to users as an alternative to natural marijuana and its wide availability commercially [2,3]. The substance is usually sold as herbal blends, potpourri, and incense [2,3,5]. It is smoked or ingested for simulated effects of the endocannabinoid system [5,6].

An online global survey found a higher relative risk of synthetic cannabinoids compared to cannabis users among 22 289 respondents using emergency medical services [7]. The American Association of Poison Control Centers reported 1900 synthetic cannabinoid exposure calls from January 1 to April 22 2015, four times the rate of calls received in 2014 [6].

Dyspnea is common among SC users [8]. On the other hand, pulmonary sequelae have been reported rarely, as evidenced by a case series of 4 patients with organizing pneumonia, a case report of severe lung injury after chronic SC inhalation, and a case report of diffuse alveolar hemorrhage after SC use [9–11].

We present a case of a young man with fever who developed transient pulmonary infiltrates after inhalation of K2, a synthetic cannabinoid.

Case Report

A 29-year-old man, previously healthy, was brought in to the emergency department (ED) for severe agitation after smoking K2, a synthetic cannabinoid. He was asymptomatic of myalgia, upper respiratory tract symptoms, pleuritic chest pain, and dyspnea. He admitted to smoking K2 and was found by the ED team to be in possession of K2. He had a past history of schizoaffective disorder and was not on any treatment. He denied prior history of illicit drug use. He had no prior hospital admission to our center for substance abuse. There was no other medical history.

He required multiple doses of lorazepam and haloperidol to be sedated. On examination, he was found to be drowsy but arousable. His vital signs were a mild fever of 100.2ºF (37.9ºC), blood pressure 110/50 mmHg, tachycardia of 109/min, respiratory rate of 18/min, and oxygen saturation of 95%. The chest examination showed good air entry on both lung fields, no crackles, no wheeze, and no rhonchi on auscultation. A cardiovascular exam noted that JVP was not elevated, S1 and S2 were heard, no additional heart sounds, no murmurs, no rubs, rate and rhythm were regular. Otherwise, the rest of examination was unremarkable. The laboratory test (Table 1) was significant for leukocytosis (18.5) with predominant neutrophilia (83.4%). Urine drug toxicology (Table 1) was negative for cannabinoids, phencyclidine, cocaine, benzodiazepine, methadone, opiates, and barbiturates. The chest radiograph (Figure 1) on admission noted diffuse reticular-nodular and interstitial infiltrates. Two blood culture samples were taken on admission, returned later as no growth after 5 days of incubation.

The patient was hydrated with Ringer's lactate solution and given stat doses of Ceftriaxone 1 g intravenously, Azithromycin 500 mg intravenously, magnesium sulfate 2 g intravenous for hypomagnesemia, potassium phosphate 22 mEq intravenous for hypophosphatemia, Famotidine 40 mg oral daily for gastrointestinal prophylaxis, and heparin 5000 units subcutaneously twice daily for venous thromboembolism prophylaxis.

At 24 hours after admission, his mentation improved and temperature returned to within normal limits. A repeat chest radiograph 24 hours after admission (Figures 2, 3) noted resolution of the pulmonary infiltrates. However, he refused repeat blood investigations to assess for improvement of abnormal blood values from admission.

The patient was concluded to have a diagnosis of inhalation fever caused by synthetic cannabinoid. He was discharged in stable condition from the hospital with advice to abstain from synthetic cannabinoids and he was given a course of oral levofloxacin 750 mg daily for 7 days for empirical treatment of pneumonia and Risperidone 1 mg oral twice daily for 2 weeks for schizoaffective disorder. Although an outpatient clinic appointment was scheduled for the patient, he was lost to follow-up and the long-term outcome is unknown.

Discussion

There are more than 50 specific types of SC reported in the United States [12–14]. SC markedly differs from natural marijuana in terms of metabolism, receptor affinity, and clinical effects [13–15]. Frequently encountered SC molecular structures include JWH-018, AM-2201, AB-001, AM-1220, and JWH-015 [13].

Both synthetic cannabinoids and delta-9 tetrahydrocannabinol act on the endocannabinoid receptors, the cannabinoid (CB) receptor-1 that is found in the central nervous system and CB-2 receptors in the immune system [13,14]. A study by Bronova et al. showed CB-1 receptor-mediated signalling of pulmonary fibrogenesis in radiation-exposed mice [16]. Transient receptor potential vanilloid 4 (TRPV-4) that can be activated by endogenous N-acylamine cannabinoids and fatty acid-derived products related to anandamide during lung injury (chlorine gas or intratracheal hydrochloric acid). TRPV-4 activation can increase lung capillary permeability and trigger alveolar edema and has inflammatory effects. TRPV-4 inhibitors were shown to have anti-inflammatory effect [17,18].

Table 1. Summary of blood and urine investigations results on admission with the reference ranges.

	Result	Reference range
CBC		
White cell count	18.5 K/uL	4.5–11.5 K/uL
Hemoglobin	13.5 g/dL	14–18 g/dL
Hematocrit	39.4%	40–54%
Platelet	239 K/uL	150–450 K/uL
Neutrophil	15.4 K/uL (83.4%)	1.9–7.7 K/uL
Lymphocyte	1.3 K/uL (7.1%)	0.7–5.0 K/uL
Eosinophil	0.1 K/uL (0.5%)	0.0–0.8 K/uL
Chemistry		
Serum sodium	142 mmol/L	136–145 mmol/L
Serum potassium	3.77 mmol/L	3.5–5.1mmol/L
Serum chloride	105 mmol/L	98–107mmol/L
Serum bicarbonate	27 mmol/L	21–32 mmol/L
Blood urea nitrogen	13 mg/dL	7–18 mg/dL
Serum creatinine	1.2 mg/dL	0.61–1.24 mg/dL
Serum magnesium	1.7 mg/dL	1.8–2.4 mg/dL
Serum phosphorus	1.9 mg/dL	2.5–4.9 mg/dL
Hepatic profile		
Aspartate aminotransferase	52 U/L	15–37 U/L
Alanine aminotransferase	32 U/L	12–78 U/L
Alkaline phosphatase	93 U/L	50–136 U/L
Total bilirubin	0.7 mg/dL	0.2–1.0 mg/dL
Total protein	6.2 g/dL	6.4–8.2 g/dL
Albumin	3.3 g/dL	3.4–5.0 g/dL
Other tests		
Urine cannabinoid	Negative	<50 ng/mL
Urine opiate	Negative	<300 ng/mL
Urine barbiturate	Negative	<200 ng/mL
Urine cocaine	Negative	<300 ng/mL
Urine benzodiazepine	Negative	<200 ng/mL
Urine methadone	Negative	<300 ng/mL
Urine phencyclidine	Negative	Not available
Blood alcohol level	<3.0 mg/dL	<5 mg/dL
Serum creatinine kinase	606 U/L	39–308 U/L
HIV-1/HIV-2 Ab	Negative for both	Negative for both
Blood culture (first sample)	No growth after 5 days	Not applicable
Blood culture (second sample)	No growth after 5 days	Not applicable

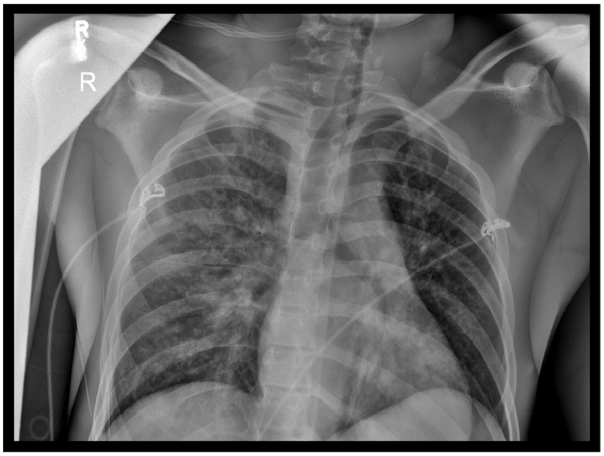

Figure 1. Chest radiograph on admission that demonstrates diffuse reticulo-nodular and interstitial infiltrates.

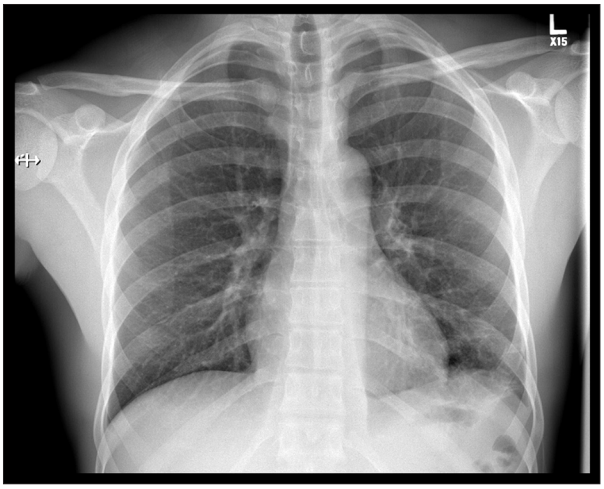

Figure 2. Chest radiograph 24 hours after admission. PA view shows interval resolution of the reticulo-nodular infiltrates and interstitial infiltrates.

Our patient developed inhalation fever caused by K2, given the transient pulmonary infiltrates and fever following SC inhalation [19–22]. Inhalation fever is defined by as a non-allergic, noninfectious, flu-like syndrome, commonly occurring after acute inhalation of organic dusts, metal and plastic fumes [20–22]. However, this patient did not experience symptoms of malaise, nausea, myalgia, headache, cough, or dyspnea, which are symptoms associated with inhalation fever [21,22]. Leucocytosis is a feature seen in inhalation fever [21,22]. Inhalation fever is associated with a transient, self -limiting course and it is treated with supportive care and avoidance of the causative factor [22].

Acute hypersensitivity pneumonitis can present in a similar manner, as they occur rapidly within several hours of exposure to an antigen that triggers an immune response [23,24]. It can be associated with mild or absent symptoms and can resolve after hours or days [23]. Chest radiographic findings have been reported to be normal or numerous poorly defined small (less than 5-mm) opacities throughout both lungs, occasionally with sparing of the apices and bases [24]. Acute hypersensitivity pneumonitis can be non-progressive and intermittent, with spontaneous improvement after antigen avoidance [23].

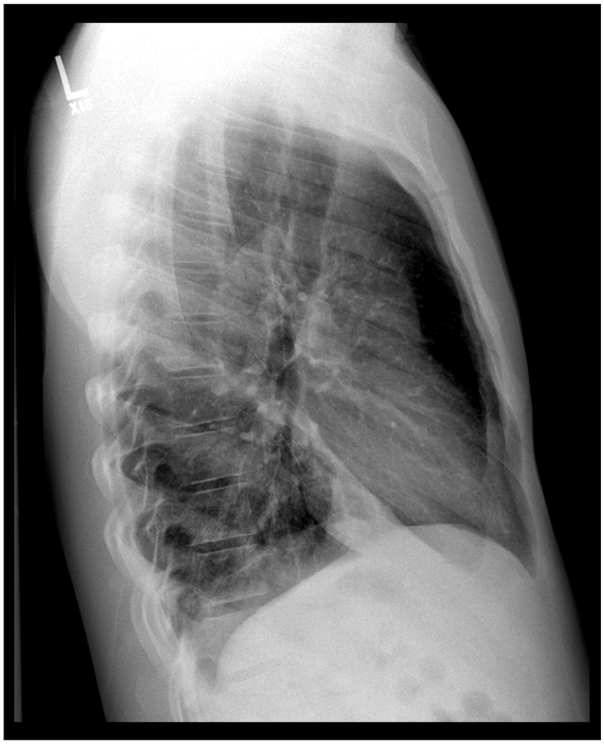

Figure 3. Chest Radiograph lateral view at 24hours after admission shows interval resolution of the reticulo-nodular infiltrates and interstitial infiltrates.

Inhalation of particles can deposit along the respiratory tract from the upper airways to the tracheobronchial tree and alveolus depending on the particulate size and solubility in water [25]. Acute chemical pneumonitis may thus present as an inflammatory reaction to the particulate in the form of bronchitis, bronchiolitis, pulmonary edema, diffuse alveolar hemorrhage, and acute respiratory distress syndrome [25]. Chemical pneumonitis can be an effect of the inhaled drug itself or contaminants present in the inhaled substance [26]. Resolution of the symptoms can occur with withdrawal of the offending substance [26].

Lastly, we had considered a diagnosis of bacterial pneumonia in this patient, as he had presented with low-grade fever, tachycardia, leukocytosis, and chest radiographic evidence of pulmonary infiltrates on admission. He was given a course of oral levofloxacin as empiric treatment. However, infection is less likely, as evidenced by the repeat chest radiograph at 24 hours after admission demonstrating resolution of the infiltrates and negative growth on 2 blood culture samples after

5 days of incubation. Bacterial pneumonia has been shown to have radiographic clearing after 5 weeks in some patients and in most cases within 2–3 months [27].

Conclusions

SC inhalation can present as inhalation fever. This case report adds to the growing body of literature on pulmonary sequelae of SC. As the Emergency Department visits by SC abusers are increasing, the importance of physicians being aware of these adverse effects cannot be overstated. Inhalation fever is self-limiting. Treatment is focused on supportive care and causative factor avoidance. Further scientific research is needed to assess the role of endocannabinoid receptors and synthetic cannabinoids in inhalation fever.

Conflict of interest

There are no conflicts of interest to be declared by the authors.

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