The use of methamphetamine is emerging as a serious problem in Taiwan. The incidence of smoking crystalline methamphetamine is increasing among young adults [1]. Although the occurrence and symptoms of heroin-induced noncardiogenic lung edema are well established, the adverse pulmonary consequences of methamphetamine smoking have not been well described. Here, we describe a patient who developed symptoms of lung toxicity associated with misuse of both heroin and methamphetamine.

**Case Report**

This 23-year-old unmarried Taiwanese woman with unstable employment status was living alone. She had a 10-year history of smoking methamphetamine but admitted to using heroin only intermittently for 3 to 4 years. Six months before this admission, she was hospitalized in a recovery center because of drug misuse. Her family reported that she had shown symptoms of auditory and visual hallucinations, delusions of persecution, tolerance, and methamphetamine withdrawal syndrome in the past.

In August 1999, she was found unconscious at home one morning after appearing well the previous afternoon. She was brought to a local hospital in a comatose state (Glasgow Coma Scale GCS E1M1V1), with a body temperature of 37.6°C, pinpoint pupils (bilateral 1 mm), tachypnea with a respiratory rate of 21 per minute, tachycardia with a heart rate of 153 per minute, and hypotension with a blood pressure of 79/53 mmHg. Her percutaneous oxygen saturation (SaO2) on pulse oximetry was 28%. Venous blood gases revealed hypoxemia with mixed respiratory and metabolic acidosis (pH 7.13, PCO2 53mmHg, PO2 24mmHg, HCO3– 17 mEq/L, base excess –13 mEq/L). She became irritable after naloxone...
(0.8 mg) injection (GCS E3M4V2, bilateral pupil size 3 mm). She was transferred to National Taiwan University Hospital on the same day with intravenous sodium bicarbonate and normal saline supplementation. Upon admission to the emergency room, blood pressure was 112/56 mmHg, pulse rate 76 beats per minute, body temperature 36.7°C, and SaO₂ 56% in room air. Miosis without light reflex was noted. She had rapid and shallow respiration with coarse breathing sounds.

She was intubated due to hypoxemia (SaO₂ 80%, PaO₂ 52 mmHg with a non-rebreathing mask). Chest roentgenography showed diffuse ill-defined densities over both lower lung fields (Fig. 1). A Swan Ganz catheter was inserted, revealing a pulmonary artery pressure (PAP) of 22/16 mmHg and pulmonary artery wedge pressure (PAWP) of 6 mmHg. The pulmonary vascular resistance index (PVRI) was 338 dynes x seconds/cm²/m². The cardiac index (CI) was 2.84 L per minute/m² with a calculated systemic vascular resistance index (SVRI) of approximately 1,774 dynes x seconds/cm²/m². She became hemodynamically stable after infusion of fluids and inotropic agents. Inotropic agents were tapered off on the first hospital day. However, pulmonary hypertension was observed (PAP 47/29, PAWP 8, CI 4.16, SVRI 1,306, PVRI 557). Fever, leukocytosis, and poor oxygenation persisted even though the patient was stabilizing hemodynamically.

Initially, laboratory tests revealed a C-reactive protein (CRP) of 10.3 mg/dL and a mild left shift of leukocytes (white blood cells 5,260/µL, neutrophils 80.2%). Muscle enzyme creatine phosphokinase (CPK) was elevated (307 U/L) on the second hospital day. Qualitative competitive immunoassay for urine drug screening detected the presence of opiates, benzodiazepine, and methamphetamine [Drug of abuse 5 test card, BIONIKE, South San Francisco, CA, USA]. High-pressure liquid chromotography also showed positive results for methamphetamine and morphine (REMEDi HS drug profiling system, BIO-RAD, Herculus, CA, USA). The urine level of amphetamine/methamphetamine was 3,793 ng/mL (TDX/TDXFLX, Abbott, Chicago, IL, USA), which was much higher than the cut-off value for addiction of 300 ng/mL [2].

The patient continued to receive ventilator therapy with positive end-expiratory pressure support and oxygen therapy in the intensive care unit. She also underwent bronchofiberoscopy, bronchial washing for cultures, and trans-bronchial lung biopsy (TBLB) on the third day of hospitalization. TBLB was complicated by left-sided pneumothorax. The infiltrative lesions found on the chest roentgenogram at admission had resolved on the fourth hospital day (Fig. 2). She was extubated after oxygenation improved on the fifth hospital day and was transferred to a general ward. Psychiatric examination found clear consciousness, euthymic mood, normoactive behavior, and coherent speech. No delusion or hallucination was detected. She denied suicidal ideation. She received supportive psychotherapy but no medication.

No specific conclusions could be drawn from the TBLB because of an inadequate specimen. Gram stain of her sputum indicated no predominant organism. Cultures obtained from bronchial lavage yielded few Pseudomonas aeruginosa and Haemophilus influenzae colonies. Empiric antibiotic treatment with 500 mg amoxicillin and 250 mg clavulanate every 8 hours and 160 mg gentamicin every 24 hours was administered for 2 weeks. As the patient's fever subsided, her hemogram showed that leukocytosis had subsided and CRP returned to the normal...
range on the twelfth day. Though mild exertional dyspnea persisted, the patient was discharged on the fifteenth day. She was referred to the outpatient clinic at Taipei City Psychiatric Center for relapse prevention and group therapy but was lost to follow-up after discharge.

Discussion

In Asia, drug misuse remains a serious social problem, with the most commonly affected group being men between the ages of 20 and 39 years. The most commonly misused substances include methamphetamine, heroin, and cannabis. In Taiwan, the use of heroin and smokable methamphetamine has become more prevalent in recent years, with more than 70% of drug misuse cases involving methamphetamine, and the remaining 30% involving heroin [1].

Reported side effects of oral and intravenous amphetamine misuse include drug-induced psychosis, rhabdomyolysis, hyperpyrexia, disseminated intravascular coagulation, vascular spasm, cardiomyopathy, and acute myocardial infarction [3]. Chronic use of amphetamine can cause pulmonary hypertension. In cases of severe exposure, unusual complications such as pulmonary edema and acute respiratory distress syndrome (ARDS) can also occur [4]. Despite the widespread misuse of methamphetamine, the toxic effects associated with this substance are not well documented.

Methamphetamine can be synthesized into a crystalline form. Crystalline methamphetamine is smoked and produces an almost instantaneous euphoria similar to intravenous methamphetamine. Methamphetamine is heated in tinfoil or in a glass bottle and then inhaled directly through the nose or mouth. After being absorbed through the nasal mucosa, methamphetamine is metabolized to amphetamine and its effects last from 8 to 24 hours. Toxict clinical effects are more common with the smoking of crystalline methamphetamine than with the oral or intravenous forms. The average amount of crystalline methamphetamine smoked by a high-dose user ranges from 2.5 to 15 g per day [5]. This quantity is 150 to 1,000 times the recommended daily dosage for therapeutic use (for example, 5–60 mg/day for narcolepsy) and at least three times the average quantity used by high-dose intravenous amphetamine users.

Nestor et al reported a case of crystal methamphetamine-induced noncardiogenic pulmonary edema in a 28-year-old female drug abuser which developed 24 to 36 hours after inhaling crystal methamphetamine [6]. Clinical and radiographic improvement was extremely rapid. Kendrick et al also reported a case of noncardiogenic pulmonary edema caused by amphetamine misuse [7]. A 23-year-old known phenterazine user was found unresponsive. After resuscitation and intensive care, his neurologic status improved within 1 hour, and he clinically stabilized and was extubated within 3 days. Pulmonary edema with dilated cardiomyopathy associated with the smoking of crystal methamphetamine has also been reported [3].

Our patient developed ARDS and pulmonary hypertension as possible complications of smoking crystal methamphetamine. Fever and leukocytosis persisted through the intensive care course. The observations of refractory hypoxemia, bilateral lower lung infiltration on chest roentgenogram, normal cardiac index, and low PAWP are compatible with noncardiogenic lung edema. These findings suggest that use of methamphetamine is associated with pulmonary hypertension and can also result in ARDS.

Because of her initial presentation with pinpoint pupils and dramatic consciousness response to naloxone, opiate abuse was highly suspected. Although the etiology of ARDS remains uncertain, the possibility of a hypersensitivity reaction to heroin use seems a reasonable explanation for the development of ARDS in our patient [8]. There was no evidence of aspiration or gastric contents in the trachea when she was intubated. Aspiration pneumonia was not supported by clinical findings at presentation. A series of examinations revealed only low colony counts for *H. influenzae* and *P. aeruginosa* in the cultures of the bronchial lavage fluids on the third day of hospitalization. Gram stain of sputum indicated no predominant organism. Community-acquired pneumonia-related ARDS was also not supported by the clinical course. The patient’s history of chronic drug abuse, very high urine level of amphetamine, and clinical presentation of severe amphetamine intoxication (coma, tachycardia, hypotension, fever, elevated CPK), as reported by Kendrick et al [7], suggest that methamphetamine use was the most likely etiology of ARDS.

Methamphetamine is lipophilic and can be easily absorbed through the nasal mucosa and metabolized to amphetamine, which explains the high urine concentration. Amphetamine has been shown to concentrate in the lungs of several animal species through an active carrier-mediated transport process [9]. Hemorrhagic pulmonary edema was reported in three patients with acute amphetamine intoxication [10], all of whom had been exposed to high environmental temperature at the time of death. Both cardiogenic [3] and noncardiogenic [4] pulmonary edema have been described with methamphetamine use. A 53-year-old patient died of ARDS, disseminated intravascular coagulopathy, and acute renal failure after suicide by overdose of 3,4-methylenedioxymethamphetamine (MDMA, “Ecstasy”) [11]. Clinical and roentgenographic improvement in our patient was extremely rapid, suggesting that the primary effect of methamphetamine smoking was on pulmonary...
capillary permeability. Nevertheless, we were unable to exclude the possibility of heroin-induced noncardiogenic lung edema.

The use of heroin and methamphetamine is a serious social problem among young adults in Taiwan. Antidotes such as naloxone allow differentiation of narcotic intoxication from amphetamine misuse. For amphetamine intoxication, immediate treatment for hyperthermia and hypertension is required in some patients. It is important to correct acidosis and hypotension in severe cases. Patients with ARDS due to possible capillary leakage should undergo intensive care with mechanical ventilation and adequate oxygen supplementation. Empiric treatment with antibiotics should be discontinued once negative culture results become available. Patients with drug abuse are being seen with increasing frequency in Taiwan [11]. In addition to the immediate needs for symptomatic management and intensive care for acute toxic effects, long-term follow-up for chronic complications and participation in rehabilitation programs should be emphasized for patients admitted for drug abuse.

References