Histologic Changes In Recreational Drug Misuse

Christopher M. Milroy, Charis Kepron, Jacqueline L. Parai

ABSTRACT

Use of recreational drugs is associated with a number of histologic changes. These may be related to the method of administration or due to systemic effects of the drugs. This paper reviews the histopathological features seen following recreational drug use. With injection, there may be local effects from abscess formation and systemic effects may result in amyloidosis. Injections have been associated with necrotizing fasciitis, anthrax, and clostridial infections. Systemic effects include infective endocarditis, with the risk of embolization, and abscesses may be seen in organs in the absence of infective endocarditis. Viral complications of injection include hepatitis and human immunodeficiency virus (HIV) infection. Injecting crushed tablets can result in intravascular granulomata in the lungs. Smoking drugs is associated with intraalveolar changes, including black- and brown-pigmented macrophages in crack cocaine and cannabis smoking, respectively. Snorting may result in intraalveolar granulomata forming when crush tablets are used and there may be systemic granulomata. Stimulants are associated with cardiovascular and cerebrovascular pathology, including contraction band necrosis and myocardial fibrosis, as well as coronary artery dissection. Stimulants may cause hyperpyrexia and rhabdomyolysis, which may be associated with changes in multiple organs including myoglobin casts in the kidney. Opioids cause respiratory depression and this can be associated with inhalational pneumonia and hypoxia in other organs if there is resuscitation and a period of survival. Ketamine use has been associated with changes in the urothelium and the liver. This paper reviews histology changes that may be seen in drug-related deaths using illustrative cases. *Acad Forensic Pathol.* 2018 8(3): 653-691

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INTRODUCTION

Recreational drug abuse is extensive in multiple societies (1) and can have both physiological and psychological effects (2, 3). Substances used vary between different countries and over time, but wherever used, there are often pathologic changes seen in tissues following both acute and chronic use. Pathology associated with recreational drug use may be related to the methods used to administer the substances and also the direct pharmacological effects of the drug (2, 3).

This paper provides a brief review of organ histology associated with drugs of abuse other than ethanol, which has its own distinct pathology (4-5). Drugs typically associated with pathologic changes discussed in this article include use of opiates/opioids; stimulant drugs including cocaine, amphetamine, amphetamine derivatives, and synthetic cathinones; as well as the dissociative anesthetic agent ketamine. Cannabis is briefly discussed. Many drugs are not associated with any specific pathology, particularly opioids, though the respiratory depression associated with opioid overdose may cause pneumonia (see below) and hypoxic brain damage in those resuscitated (3). Other systemic complications include hyperpyrexia that may be induced by drugs, as well as by environmental conditions, and the pathology seen in drug use and environmentally induced hyperpyrexia is similar (6-9). This review uses case studies to illustrate the possible patterns of histopathology that can be seen with recreational drug use.

DISCUSSION

Organ Histopathology Associated with Routes of Administration

The main routes of administration of recreational drugs are injection, smoking, insufflation (snorting), and oral ingestion. The latter typically leaves no histopathological features, but the other routes may have local and systemic effects.

Injection

Injection is a common method of administering drugs. The principal complication of injecting drugs is infection, both locally at the site of administration and systemically (10-12). Injection is typically intravenous, but may be subcutaneous ("popping") and intraarterial. The main local complications are infection, which may result in abscess formation, phlebitis with occlusion of veins requiring new sites of injection, and rarely other complications including necrotizing fasciitis, anthrax, botulism, and clostridial infections (13-19). When the groin is injected, sinus tracks may form between the skin and the femoral vein. Local abscess formation may form the nidus for systemic complications including amyloidosis (20, 21).

Systemic effects may occur from the introduction of bacterial infections, the most common being systemic sepsis and infective endocarditis (22-25). This may be complicated by systemic embolization with the development of mycotic aneurysms. Sepsis with septicemia resulting in abscess formation in distant organs may also rarely occur (see illustrative case). Viral infections, including human immunodeficiency virus (HIV), are common and there is a high incidence of hepatitis C infection in intravenous drug users (26-31).

Illustrative Case—Injection with Necrotizing Fasciitis

A 54-year-old man with a history of drug use, hepatitis C, and chronic pain from osteoarthritis presented to the emergency department requesting pain killers. He reported the pain had been so bad he had a friend inject him with a pain killer. He was given opioids, including a fentanyl patch, as well as clindamycin as he had cellulitis at the injection site. He was discharged home but re-presented 17 hours later. He was hypotensive with tachycardia and rapidly went into cardiac arrest. Investigations revealed a white cell count of $3.1 \times 10^9/L$ with a markedly elevated creatine kinase of 11356 U/L. He could not be resuscitated.

At autopsy, he was noted to have a red, swollen right arm and a culture from the arm grew Group A streptococcus organisms. Histology of the arm revealed necrotizing fasciitis with Gram-positive cocci (**Images 1 and 2**). Toxicology revealed hydromorphone, oxycodone, cocaine, and quetiapine.

Illustrative Case—Infective Endocarditis

A 52-year-old woman with a history of intravenous drug use was said to have been feeling generally ill, weak, and eating little. She became drowsy and emergency services were called, but she went into cardiac arrest and could not be resuscitated.

At autopsy, there were multiple injection sites on the forearms with bruising present. Vegetations were on the mitral valve that grew *Staphylococcus aureus* and *Streptococcus viridians* (**Images 3 and 4**). Septic emboli were in the kidneys (**Image 5**) and clumps of bacteria in the liver and spleen. In addition to systemic emboli, septic emboli were in the pulmonary circulation, in association with pulmonary infarcts (**Images 6 and 7**).

Illustrative Case—Systemic Infection with Cardiac Abscesses

A 44-year-old woman was found with a decreased level of consciousness. She was brought to hospital

Image 1: Necrotizing fasciitis (H&E, x200).

and diagnosed with fever, tachycardia, and tachypnea. A troponin was elevated at 25.12 $\mu\text{g/L}$ and her white blood cell count was elevated at $16.7 \times 10^9/\text{L}$ with a neutrophil count of $13.86 \times 10^9/\text{L}$. She was a known drug user with track marks on her legs. A recent echocardiogram did not show any evidence of infective endocarditis and none was seen at autopsy. Histology of an injection site revealed abscess formation and foreign body material (**Images 8 and 9**). Multiple abscesses were in the myocardium, kidney, and liver (**Images 10 to 12**).

Noninfectious Complications

A noninfectious complication of injection is the development of intravascular granulomata in the lungs

(32-36). This most commonly occurs when tablets are crushed and injected. A particular problem may be encountered when patients have indwelling intravenous catheters, which facilitate the injecting habit. These catheters may be placed because of the need for repeated administration of drugs, such as treating infectious endocarditis with intravenous antibiotics. Tablets are made with bulking agents, also known as excipients. These substances include starch, talc, microcrystalline cellulose, and croscopovidone. All but the latter can be seen by polarizing light and a number of stains can be helpful including Movat pentachrome (all but starch), periodic acid-Schiff (PAS) (microcrystalline cellulose and croscopovidone), and Congo red (microcrystalline cellulose) (37). When injected in arteries rather than veins, ischemic limbs may result (38-39).

Image 2: Necrotizing fasciitis. Gram-positive cocci (Gram, x400).

Illustrative Case—Intravascular Granulomata

A 44-year-old woman had been treated in hospital for polymicrobial sepsis. She was discharged with a peripherally inserted central catheter (PICC) line in place for antibiotic therapy. She had admitted to crushing tablets and injecting them and was later found collapsed at home and could not be resuscitated.

At autopsy, a PICC line was present. Examination of the cut surface of the lungs revealed multiple white nodules 1-2 mm in diameter. Microscopic examination of the lungs revealed multiple foreign body intravenous granulomata (**Images 13 and 14**).

Insufflation

Insufflation, also known as snorting, is another common method of self-administration of drugs. Snorting of some drugs may lead to local effects, such as nasal perforation in cocaine use (2, 3). These are often photographed at autopsy but not usually subject to histology. If tablets are crushed and snorted, then a reaction to the tablet material may be seen in the lungs on routine autopsy histology.

Illustrative Case—Insufflation (Snorting)

A 42-year-old man had a history of a psychotic mood disorder and was prescribed olanzapine, citalopram,

Image 3: Endocarditis vegetation (H&E, x50).

and clonazepam, but was thought to have run out four days before his death. He was found in the afternoon lying on the floor talking incoherently. He was brought to the ambulance walking with assistance, but suffered cardiac arrest in the ambulance. He was recorded in the ambulance as having a core temperature of 41°C (105.8°F). Microscopic examination of the lungs revealed intraalveolar and perivascular macrophages with foreign birefringent material, best demonstrated on a Movat stain (**Images 15 to 17**). In the liver, there were increased neutrophils in the sinusoids with focal hepatocyte necrosis and a predominantly microvesicular fatty change, findings reported in hyperpyrexia (**Images 18 and 19**). There were also foreign body granulomata in portal tracts and sinusoids

similar to those seen in the lung (**Images 20 and 21**). Toxicological analysis revealed methylenedioxypyrovalerone (MDPV) at a concentration of 5.8 mg/L.

Cardiovascular and Cerebrovascular Complications of Stimulants

Cocaine, methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA) are frequently encountered stimulant drugs that are associated with cardiovascular complications, including coronary artery atherosclerosis at a younger age, myocardial fibrosis, cardiomegaly, and myocardial infarction (40-49). Other complications include coronary artery dissection (50-51) (**Image 22**), aortic dissection (52,

Image 4: Endocarditis vegetation (Gram, x50).

53), and thrombosis of other vessels, including effects on the gastrointestinal tract (54). Acute stimulant use may result in myocardial contraction band necrosis (see illustrative case). In the absence of resuscitation, this can be a useful finding to show that a stimulant drug has exerted cardiovascular effects. Cerebrovascular effects include cerebral infarction, cerebral hemorrhage, and rupture of berry aneurysms (55-65).

Illustrative Case—Cardiomegaly and Cocaine

A 28-year-old woman with a history of intravenous drug abuse and previous endocarditis was found dead in her bed. At autopsy, old injection sites (“track marks”) were in the forearms and calves. The heart

was enlarged, weighing 426 g (expected upper limit 387 g) and there was a 0.5 cm calcified nodule on the tricuspid valve. The lungs were congested and edematous, the right weighing 634 g and the left 498 g. On microscopic examination, the myocardium showed perivascular fibrosis (**Image 23**) and the lungs showed prominent carbon pigmented macrophages, typical of smoking “crack cocaine” (**Image 24**).

Toxicological analysis revealed a benzoylecgonine concentration of 0.14 mg/L; cocaethylene was also present.

The black carbon pigmented intraalveolar macrophages seen in crack cocaine smoking need to be

Image 5: Kidney with embolic abscess (H&E, x50).

contrasted with the brown pigmented intraalveolar macrophages that can be seen following tobacco and cannabis smoking (**Image 25**).

Illustrative Case—Contraction Band Necrosis in Cocaine Use

A 32-year-old man with a history of drug and alcohol use was found dead on the floor of his bedroom. At autopsy, there were no injection marks. Macroscopically, the heart appeared normal, weighing 390 g. There was no significant coronary artery atherosclerosis. The lungs were heavy and edematous, the right weighing 802 g and the left 758 g. Toxicological analysis revealed the presence of carfentanil at a concentration

of 46 ng/mL, alprazolam, cocaine and benzoylecgonine, ethanol at a concentration of 217 mg/100 mL, and cocaethylene. Microscopically, the heart showed myocyte necrosis with prominent contraction bands and a neutrophilic infiltrate (**Images 26 to 28**). These microscopic changes were due to cocaine toxicity.

Inhalational (Aspiration) Pneumonia/Pneumonitis

When there is a prolonged period of unconsciousness, typically seen with opiate/opioid overdose, there is often inhalation (aspiration) of gastric contents because of the ability to maintain the integrity of the airway (3). This can result in inflammation as a response to the acid in the gastric contents as well as infection

Image 6: Lung with septic emboli (Movat, x100).

from inhaled bacteria. The finding may be helpful when drugs may have been metabolized and postmortem concentrations are lower than typically seen in fatal toxicity (66).

Illustrative Case—Inhalation with Pneumonia

A 24-year-old man was found dead in bed. He had a history of drug use and drug paraphernalia was found at the scene. At autopsy, there were no stigmata of intravenous injection. His lungs were heavy, with a combined weight of 1526 g.

Toxicology revealed a fentanyl concentration of 5.6 ng/mL, cocaine of 0.008 mg/mL, and benzoylec-

gonine of 0.31 mg/L. Microscopic examination of the lungs revealed evidence of an inhalational pneumonia (**Images 29 and 30**).

Other Systemic Effects

Recreational drugs may have effects upon other organ systems. Heroin smoking has been associated with spongiform leukoencephalopathy, a rare brain disorder that has been reported from several countries (67-70). It has also been reported with methadone use (71). Cocaine has been associated with movement disorders including parkinsonism (72-77), which has also been seen in patients taking 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which was

Image 7: Lung with septic emboli (Gram, x100).

Image 8: Skin with abscess at injection site (H&E, x25).

produced by clandestine laboratories trying to produce a meperidine derivative (78, 79). Patients with cocaine-induced excited delirium have altered dopamine and heat shock protein status (80).

Ketamine is a drug used medically as well as illicitly. It has been associated with disorders of the bladder in abusers of the drug (81). It has also been associated with liver disorders including biliary tract disease and sclerosing cholangitis (82). Heroin has been associated with development of focal segmental glomerulosclerosis (83-87). Rhabdomyolysis has been reported in heroin and stimulant drug users and can be identified at autopsy in the kidney, where myoglobin casts are seen in the renal tubules (**Images 31 and 32**) (88-92).

Hyperpyrexia has been associated with stimulant drug use, particularly with cocaine, amphetamine derivatives such as MDMA (ecstasy), and synthetic cathinones. The pathology of hyperpyrexia was initially reported in environmental conditions but has been shown to have the same pathology in drug-related cases. While the pathology is nonspecific, there may be changes in several organs. Steatosis with individual hepatocyte necrosis and dilatation of the sinusoids may occur, along with contraction and necrosis in the myocardium and ring hemorrhages in the brain. Rhabdomyolysis may occur and myoglobin casts can then be seen in the kidney (6).

Image 9: Skin with abscess at injection site with birefringent material (H&E, x200).

Illustrative Case—Ketamine Organ Toxicity

A 38-year-old man was prescribed ketamine and high dose opioids for chronic pain. His ketamine use was complicated by chronic liver injury, renal injury, and chronic cystitis. He had been starving himself and had previous admissions for starvation ketosis, urinary tract infections, and withdrawal symptoms but would discharge himself from hospital. He was found collapsed at home and died soon after admission to hospital. It was assumed he had had a hyperkalemic cardiac arrest but this could not be substantiated. At autopsy, there was evidence of coronary artery atherosclerosis. The kidneys appeared macroscopically normal but on histology there was a mixed inflammatory cell infiltrate in the renal pelvis (**Image 33**). There was erythema of the bladder mucosa and the liver revealed

areas of hepatic necrosis, primarily in zone 3 with a mixed chronic inflammatory cell infiltrate in the portal tracts with acute injury in bile ducts (**Image 34**).

CONCLUSION

Recreational drug use is associated with pathology in multiple organs relating to both the route of administration and systemic effects. The histological changes can typically be identified by simple histological techniques. Histology can provide confirmation of the route of administration and systemic effects, such as contraction band necrosis following use of cocaine. Use of histology also provides information that is reviewable and can be important when a drug-related death is challenged.

Image 10: Cardiac abscesses (H&E, x50).

Image 11: Cardiac abscess (H&E, x200).

Image 12: Cardiac abscess with Gram-positive cocci (Gram, x100).

Image 13: Intravascular foreign body granulomata (Movat, x50).

Image 14: Lung with intravascular foreign body granulomata with polarization (Movat, x100).

Image 15: Lung with intraalveolar foreign body granulomata (Movat, x200).

Image 16: Lung with perivascular foreign body granulomata (H&E, x200).

Image 17: Lung with perivascular foreign body granulomata (Movat, x200).

Image 18: Liver with predominantly microvesicular steatosis (H&E, x400).

Image 19: Liver with hepatocyte necrosis and neutrophil reaction (H&E, x400).

Image 20: Liver with foreign body granulomata in portal tract (Movat, x200).

Image 21: Liver with macrophages in sinusoids containing foreign material (Movat, x400).

Image 22: Coronary artery dissection (Masson trichrome, x12.5).

Image 23: Myocardium with perivascular fibrosis (H&E, x200).

Image 24: Lung with prominent carbon pigmented macrophages (H&E, x200).

Image 25: Lung with brown pigmented intraalveolar macrophages (H&E, x400).

Image 26: Myocardium with acute ischemia (paler areas) (PTAH, x50).

Image 27: Myocardium at high power showing ischemic areas with contraction band necrosis (PTAH, x400).

Image 28: Myocardium with contraction band necrosis (H&E, 400).

Image 29: Lung with hemorrhage and inflammation from inhalation (H&E, x50).

Image 30: Lung with inflammation from inhalation (H&E, x100).

Image 31: Myoglobin casts in renal tubules (myoglobin, x100).

Image 32: Renal casts in myoglobinuria (H&E, x200).

Image 33: Inflammation in renal pelvis due to ketamine toxicity (H&E, x50).

Image 34: Portal tract inflammation with bile duct damage in ketamine toxicity (H&E, x100).

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