



## Association of pulmonary histopathological findings with toxicological findings in forensic autopsies of illicit drug users

Povezanost patohistološkog nalaza na plućima sa toksikološkim nalazom kod sudskomedicinski obdukovanih narkomana

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### Abstract

**Background/Aim.** Drug abuse remains a significant social problem in many countries. The aim of the study was to estimate association between pulmonary histopathological changes and results of toxicological analyses in forensic autopsies of illicit drug users. **Methods.** This investigation was performed in the Institute of Forensic Medicine, Belgrade, and in the Clinical Center, Department of Forensic Medicine, Kragujevac, from 2000 to 2004, and included 63 medicolegal autopsies of heroin or other drug consumers who suddenly died. Autopsies, postmortem toxicological examination of drugs and serological analyses of anti-HIV/HBV/HCV antibodies were performed. **Results.** The deceased persons were mostly male, 46/63 (73.01%), ranged in age from 19 to 49 years (mean 31 years) and all were whites. Postmortem toxicological examination was performed on all of the deceased persons and drugs in the fatal range were identified in only eight of them (12.7%), in the toxic range in ten (15.87%), and in minimal concentrations in 35 (55.56%) of the deceased persons. Drugs identified in

the fatal, toxic or minimal range included heroin-morphine (38/53), cocaine (4/53), tramadol (3/53), and lorazepam (1/53). In the 7 remaining subjects, ethanol in combination with heroin was found in 4 cases, and diazepam in combination with heroin in 3 cases. Dominant pathomorphological changes were findings in the lung tissue. Most common histological changes observed in drug users were pulmonary edema – 55/63 (87.3%), acute alveolar hemorrhages – 49/63 (77.78%), hemosiderin-laden macrophages (siderophages) – 52/63 (82.54%), and emphysematous changes – 51/63 (80.95%). **Conclusion.** Pulmonary edema is the frequent non-specific autopsy finding which is associated with virtually all routes of drug administration. The histopathological study is necessary to determinate a cause of death when a deceased person has the history of dependence or abuse of psychoactive drugs with negative toxicological results.

### Key words:

autopsy; histological techniques; overdose; pulmonary edema; substance-related disorder; toxicology.

### Apstrakt

**Uvod/Cilj.** Zloupotreba droga i dalje predstavlja značajan društveni problem u mnogim zemljama. Cilj istraživanja bio je da se ispita udruženost, patohistoloških promena i rezultata toksikoloških analiza kod sudskomedicinski obdukovanih narkomana. **Metode.** Istraživanje je obavljeno u Institutu za sudsku medicinu u Beogradu i Službi za sudsku medicinu Kliničkog centra Kragujevac u periodu od 2000. do 2004. godine, i obuhvatilo je 63 sudskomedicinske obdukcije iznenadno umrlih heroinskih zavisnika i korisnika drugih droga. Urađene su obdukcije, postmortalna toksikološka ispitivanja na prisustvo droga i serološke analize na prisustvo antiHIV/HBV/HCV antitela. **Rezultati.** Većina umrlih

osoba bili su muškarci 46/63 (73,01%), najmlađi je imao 19, a najstariji 49 godina (prosečna starost 31 godina) i svi su bili bele rase. Postmortalno toksikološko istraživanje obavljeno je kod svih umrlih osoba i droge u letalnoj koncentraciji pronađene su samo kod njih 8 (12,7%) osoba, u toksičnoj koncentraciji kod 10 (15,87%) i u minimalnoj koncentraciji kod njih 35 (55,56 %). Droge koje su identifikovane u letalnoj, toksičnoj ili minimalnoj koncentraciji bile su: heroin-morfin (38/53), kokain (4/53), tramadol (3/53) i lorazepam (1/53). Od preostalih sedam leševa, kod četiri pronađen je etanol u kombinaciji sa heroinom, a kod tri diazepam u kombinaciji sa heroinom. Najizraženije patomorfološke promene pronađene su u plućnom parenhimu. Najčešće uočene histološke promene kod korisnika droga bili su: plućni

edem, 55/63 (87,3%), akutne alveolarne hemoragije 49/63 (77,78%), hemosiderofagi 52/63 (82,54%) i emfizematozne promene 51/63 (80,95%). **Zaključak.** Plućni edem je najčešći nespecifični obdukcijski nalaz povezan sa svim načinima unošenja droga. Neophodno je uraditi patohistološko ispitivanje preminulih osoba sa negativnim toksikološkim nala-

zom, ali pozitivnom anamnezom o zavisnosti ili predoziranju psihoaktivnih lekova.

**Ključne reči:**  
**autopsija; histološke tehnike; predoziranost; pluća, edem; poremećaji izazvani supstancama; toksikologija.**

## Introduction

Drug abuse remains a significant social problem in many countries. Drugs and poisons are divided into four groups: group I – drugs listed in the Single Convention on Narcotic Drugs 1961, schedule I (cocaine, dextromoramide, heroin/morphine, ketobemidone, methadone, oxycodone, etc.), and schedule II (codeine, ethylmorphine, pholcodine, propoxyphene, etc.); group II – drugs listed in the International Convention on Psychotropic Substances 1971, schedules I and II (amphetamines, MDMA of ecstasy, tetrahydrocannabinol, etc.); group III – drugs listed in the International Convention on Psychotropic Substances 1971, schedules III and IV (most barbiturates, benzodiazepines, buprenorphine, meprobamate, ethaqualone, etc.); group IV – all other drugs and poisons, including ethanol and carbon monoxide. Drug addict is defined as “a person who according to information from the police and/or autopsy report is known to have abused drugs intravenously and/or abused drugs listed in the Single Convention on Narcotic Drugs 1961, shedule I and/or the International Convention on Psychotropic Substances 1971, shedules I and II”<sup>1</sup>.

According to postmortem toxicological examination, concentration of illicit drugs is not always in fatal or toxic range. Therefore, histopathological study is necessary for determination of a cause of death when a deceased person has the history of dependence or abuse of psychoactive drugs with negative toxicological results.

The respiratory system is unvariably exposed to these drugs and is affected by them, either directly or secondarily, on the temporary or permanent basis. Illicit drugs and psychoactive substances affect all anatomical lung compartments producing diverse morphological changes. The major classes of drugs which cause respiratory manifestations are opiates, stimulants and cannabinoids<sup>2</sup>. Intrapulmonary site of injury and histological pattern of response depend not only on the pharmacological agents, but also on the dose, duration of abuse, route of delivery, and the presence of additives and adulterants<sup>3</sup>. Pulmonary pathohistological findings most commonly include edema, pulmonary hemorrhage and the presence of siderophages, pulmonary artery medial hypertrophy, panacinar emphysema, bronchiolitis obliterans, interstitial pneumonia or fibrosis<sup>4</sup>. The aim of the study was to examine association of pulmonary histopathological changes with results of toxicological analyses in forensic autopsies of illicit drug users.

## Methods

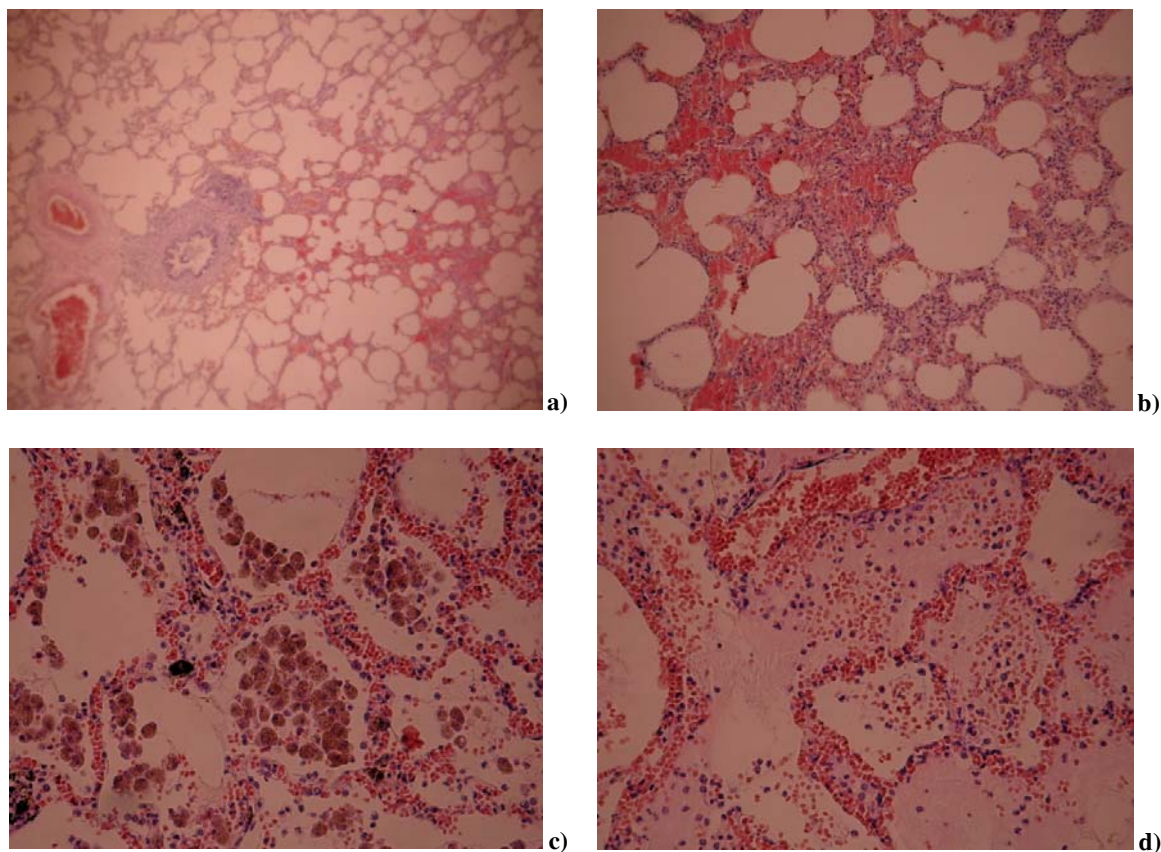
This investigation was performed in the Institute of Forensic Medicine in Belgrade and in the Clinical Center,

Department of Forensic Medicine in Kragujevac, and included 63 medicolegal autopsies of heroin or other drug consumers, who suddenly died during the period 2000 – 2004. The sample consisted of illicit drugs related deaths where a psychoactive substance directly caused the fatal outcome, or where the person had a history of dependence or abuse of psychoactive drugs with negative toxicological results.

Autopsies, postmortem toxicological analyses of drugs and serological research of anti-HIV/HBV/HCV antibodies were carried out. Multiple lung sections from each case were taken, microscopic slides were prepared, routinely stained with hematoxylin and eosin staining, and (H&E) under a light microscope (Carl Zeiss, Axioskop 40) and CCD camera (Canon PC 1089). During autopsy blood from the femoral vein, urine, samples of renal and liver tissue and vitreous samples were collected and submitted to the Department of Toxicology, the Institute of Forensic Medicine, Belgrade, where all the samples were routinely screened for illicit substances, pharmaceutical drugs and ethanol by conventional methods.

## Results

The experimental group consisted of 63 individuals ranging in age from 19 to 49 years. Individuals were mostly male, 46/63 (73.01%), and all were whites. Twenty-nine deceased persons had serological evidence of hepatitis C virus infection, 12 of them had hepatitis B virus surface antigen, and 4 were HIV positive. In the majority of cases the manner of death was “natural”, with the pulmonary edema as the most frequent mode of death. The drugs in the fatal range were identified in only 8 (12.7%) of them, in the toxic range in ten (15.87%), and in minimal concentrations in 35 (55.56%) of the deceased persons. The most common histological features observed in drug users were pulmonary edema – 55/63 (87.3%), acute alveolar hemorrhages – 49/63 (77.78%), siderophages – 52/63 (82.54%), and emphysematous changes – 51/63 (80.95%). The above mentioned microscopic changes are presented in Figure 1, a–d. In 10 cases with the history of dependence or abuse of psychoactive drugs, the postmortem toxicological results were negative. Drugs identified in fatal, toxic or minimal ranges included: only heroin-morphine (38/53), only cocaine (4/53), only tramadol (3/53), and only lorazepam (1/53). In the 7 remaining subjects, ethanol in combination with heroin was found in 4 cases, and diazepam in combination with heroin in 3 cases.



**Fig. 1 – The most common pulmonary histopathological findings in forensic autopsies of illicit drug users**

- a) pulmonary edema with erythrocytes and neutrophils in alveoli (H&E staining,  $\times 40$ );
- b) acute emphysematous changes and arterial medial hypertrophy (H&E staining,  $\times 20$ );
- c) siderophages in alveoli (H&E staining,  $\times 40$ );
- d) alveolar hemorrhages (H&E staining,  $\times 20$ ).

## Discussion

The experimental group consisted of 63 individuals ranging in age from 19 to 49 years. Their median age was 31 years, while previous studies showed the median age of illicit drugs users of 25 and 26 years<sup>5,6</sup>. Individuals were mostly male (73.01%), and all were whites. Twenty-nine deceased persons had serological evidence of hepatitis C virus infection, 12 of them had hepatitis B virus surface antigen, and 4 were HIV positive. In the majority of cases the manner of death was “natural”, with pulmonary edema as the most frequent mode of death. The next most frequent manner of death was accident, predominantly heroine overdose. In other cases suicides (1/3 by gunshot, and 2/3 by hanging), and homicide by gunshot were registered.

A postmortem toxicological examination was performed in all cases, and drugs in the fatal range were identified in only 8 of them (12.7%), in the toxic range in ten (15.87%), and in minimal concentrations in 35 (55.56%) of the deceased persons. In 10 cases with the history of dependence or abuse of psychoactive drugs, the postmortem toxicological results were negative. The drugs identified in the fatal, toxic or minimal range included: only heroin-morphine (38/53), only cocaine (4/53), only tramadol (3/53), and only lorazepam (1/53). In the 7 remaining subjects, ethanol in

combination with heroin was found in 4 cases, and diazepam in combination with heroin in 3 cases. In deceased drug addicts heroin is frequently detected. Cocaine was detected only in 4 fatalities, and is seemingly still not commonly used in Serbia. This pattern was confirmed in other countries<sup>7</sup>.

The most common histological features observed in drug users were pulmonary edema (87.3%), acute alveolar hemorrhages (77.78%), siderophages (82.54%), and emphysematous changes (80.95%). Besides them, interstitial fibrosis, bronchiolitis obliterans, arterial medial hypertrophy, and inhaled particles were found in some cases. Pathologically, the lungs of individuals who die acutely are bilaterally heavy, voluminous, and congested<sup>8</sup>. In our research, widened, edematous interlobular septa and perivascular spaces were seen histologically in association with deeply eosinophilic alveolar edema. Pulmonary edema is a frequent non-specific autopsy finding which is associated with virtually all routes of administration of drugs<sup>8,9</sup>. The prototype of drug-induced, non-cardiogenic pulmonary edema is that associated with heroin toxicity<sup>9</sup>. Proposed mechanisms of heroin-induced pulmonary edema include anoxic injury, direct toxicity or a hypersensitivity reaction involving the alveolocapillary membrane, neurogenic causes, or aspiration<sup>9</sup>. According to our study results margination and early exudation of neutrophils is often associated with proteinaceous alveolar edema. Trapped air bubbles cause focal airspace

ectasia and alveolar spaces expanded by trapped air bubbles (acute emphysematous change). The major parenchymal abnormality identified was the presence of numerous hemosiderin-laden macrophages (siderophages), and medial hypertrophy of medium-sized pulmonary artery. The usual findings are acute hemorrhages manifested as intact erythrocytes within the alveolar spaces. Previous investigators have suggested two mechanisms for alveolar hemorrhage: vasoconstriction of the pulmonary vascular bed after inhalation, resulting in ischemic damage of capillary endothelium, and a direct toxic effect of drugs on the capillary endothelium<sup>10</sup>. Our findings do not favor neither of these hypotheses. Although the heart was not specifically examined in our study, the frequent findings of capillary congestion and pulmonary edema in these individuals could indicate that alveolar hemorrhage is the result of passive congestion due to drug-related cardiac compromise<sup>11</sup>.

## Conclusion

Our study reports pulmonary vascular and parenchymal histopathologic changes associated with illicit drug use. Since a postmortem toxicological examination revealed the concentration of illicit drugs not always in the fatal or toxic range, the histopathological study is necessary to determine a cause of death when a deceased person has the history of dependence or abuse of psychoactive drugs with the negative toxicological results. Pulmonary disease is a common cause of death in drug users. Pulmonary edema is a frequent autopsy finding which is associated with virtually all routes of narcotics administration. In addition, hemosiderin-laden macrophages were seen in 82.54% of cases, implying that alveolar hemorrhage may be a frequent complication of illicit drug abuse.

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