CASE REPORTS

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# Severe acute caffeine poisoning due to intradermal injections: mesotherapy hazard

## Teško akutno trovanje kofeinom usled intradermalnih injekcija: opasnost od mezoterapije

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**Abstract**

**Introduction.** Caffeine is indicated in the treatment of migraine headaches, as well as neonatal apnea and bradycardia syndrome. In mild poisoning, the most prevalent symptoms are nausea, vomiting, diarrhea, tremor, anxiety and headache. In more severe cases, symptoms consist of heart rythym abnormalities, myocardial infarction and seizures. Due to its common lipolytic effect, caffeine is used in mesotherapy, usually in combination with drugs of similar effect. We presented a patient with acute iatrogenic caffeine poisoning. **Case report.** A 51-year-old woman, with preexisting hypertension and hypertensive cardiomyopathy was subjected to cosmetic treatment in order to remove fat by intradermal caffeine injections. During the treatment the patient felt sickness, an urge to vomit, and a pronounced deterioration of general condition. Upon examination, the patient exhibited somnolence, hypotension and nonsustained ventricular tachycardia, which was sufficient enough evidence for further hospitalization. On admission to the intensive care unit the patient was anxious with increased heart rate, normotensive, with cold, damp skin, and visible traces of injection sites with surrounding hematomas on the anterior abdominal wall. Paroxysmal supraventricular tachycardia (PSVT) on electrocardiographic monitoring was found. The laboratory analysis determined a lowered potassium level of 2.1 mmol/L (normal range 3,5 – 5.2 mmol/L), and a toxicological analysis (liquid chromatography with ultraviolet detection) proved a toxic concentration of caffeine in plasma – 85.03 mg/L (toxic concentration over 25 mg/L). On application of intensive therapy, antiarrhythmics, and substitution of potassium, as well as both symptomatic and supportive therapy, there was a significant recovery. The patient was discharged without any sequele within four days. **Conclusion.** A presented rare iatrogenic acute caffeine poisoning occured due to massive absorption of caffeine from the subcutaneous adipose tissue into the circulation when injected directly into the tiny blood vessels, as evidenced by hematoma formation. Poisoning manifestations were registered in gastrointestinal, CNS (anxiety, somnolence) and cardiovascular (hypotension, ventricular tachycardia and nonsustained PSVT) system. In this era of mesotherapeutic treatment promotion, one should keep in mind toxic prevention, with application being carried out exclusively in a specialized institution

**Key words:**
**caffeine; poisoning; cosmetic techniques; risk assesment.**

**Apstrakt**

**Uvod.** Kofein se primenjuje u lečenju migrenozne glavobolje, a kod dece u lečenju neonatalne apneje i sindroma bradikardije. Kod lakših trovanja kofeinom najčešće se javljaju mučnina, povraćanje, dijareja, tremor, anksioznost i glavobolja, a kod teških trovanja poremećaji srčanog ritma, infarkt miokarda i konvulzije. Zbog poznatog lipolitičkog efekta kofein se koristi i u mezoterapiji, obično u kombinaciji sa supstancama koje slično deluju. **Prikaz bolesnika.** Bolesnica, stara 51 godinu, sa postojećom hipertenzijom i hipertenzivnom kardiomiopatijom, bila je podvrgnuta estetskom tretmanu uklanjanja masnih naslaga putem intradermalnog ubrizgavanja kofeina. Tokom tretmana osetila je mučninu, nagon za povraćanjem i izrazito pogoršanje opšteg stanja. Pri prvom pregledu utvrđeni su somnolencija i hipotenzija, a u EKG ventrikularna tahikardija *nonsustained*, zbog čega je upućena na bolničko lečenje. Pri prijemu u jedinicu intenzivne nege bolesnica je bila anksiozna, tahikardična, normotenzivna, sa hladnom i vlažnom kožom, a na trbuhu su bili vidljivi tragovi uboda sa okolnim hematomima. Elektrokardiografskom kontrolom regi-

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strovana je paroksizmalna supraventrikularna tahikardije (PSVT). Laboratorijskim analizama utvrđen je snižen nivo kalijuma – 2,1 mmol/L (3,5–5,2 mmol/L), a toksikološkim analizama (tečna hromatografija sa ultravioletnim detektorom) dokazan je kofein u toksičnoj koncentraciji – 85,03 mg/L (toksična koncentracija preko 20 mg/L). Na primenjenu intenzivnu terapiju, antiaritmike i supstituciju kalijuma, simptomatsku i suportivnu terapiju, došlo je do oporavka, te je četvrtog dana bolesnica otpuštena bez posledica. **Zaključak.** Opisano retko jatrogeno akutno trovanje kofeinom nastalo je atipično – zbog masivne resorpcije kofeina iz potkožnog adipoznog tkiva u cirkulaciju. Ubrizgavanje direktno u sitne krvne sudove potvrđeno je prisustvom hematoma. Manifestacije trovanja bile su prisutne u gastrointestinalnom, centralnom nervnom (anksioznost, somnolencija) i kardiovaskularnom (hipotenzija, ventrikularna tahikardija *nonsustained* i PSVT) sistemu. U eri promocije mezoterapijskih estetskih tretmana treba imati na umu takvu opasnost i estetske intervencije sprovoditi isključivo u visokospecijalizovanim ustanovama.

**Ključne reči:**
**kofein; trovanje; kozmetičke tehnike; rizik, procena.**

## Introduction

The biochemical structure of caffeine is 1,3,7-trimethylxanthine. This compound belongs to a class of theophyllines with the chemical structure of 1,3-dimethylxanthine and theobromine, 3,7-dimethylxantine. Being an ingredient that is found in coffee, tea, cocoa and various drinks, caffeine is used routinely. The therapeutic use of caffeine in adults is an adjuvant therapy in combined analgesics for the treatment of migraine headaches, in children for the treatment of neonatal apnea, and in bradycardia syndrome. Caffeine, theophylline and theobromine belong to the group of methylxanthines, which cause the release of endogenous catecholamines, leading to the stimulation of adrenergic receptors. They are structural analogues of adenosine and pharmacologically function as adenosine antagonists. In higher doses, methylxanthines inhibit phosphodiesterase, the enzyme responsible for degradation of intracellular cyclic adenosine monophosphate (cAMP). The increase in cAMP leads to the clinical effects of adrenergic stimulation, muscle relaxation, stimulation of the myocardium, peripheral vasodilatation, stimulation of the respiratory center and the excitation of the central nervous system (CNS). Caffeine is bioavailable after oral, intravenous, subcutaneous, intramuscular and rectal application [1, 2]. Caffeine metabolism occurs *via* hepatic cytochrome P450 oxidase, the main processes including demethlylation and hydroxylation, with metabolic by-products (3,7-dimethylxanthine) teobromin, and (1,3-dimethyxsanthine) theophylline. For this reason, in patients with caffeine poisoning, serum concentrations of theophylline must be determined [1, 3]. Methylxanthines have a positive chronotropic and inotropic effect on the myocardium, leading to supraventricular tachycardia, atrial fibrillation, atrial flutter, multifocal atrial tachycardia, ventricular tachycardia and ventricular fibrillation. Electrolyte imbalances may be a factor in enhancing the development of arrhythmias. Caffeine and theophylline stimulate the respiratory center and increase respiratory rate (frequency of breathing), and therefore are used to treat sleep neonatal apnea syndromes. Effects on the CNS are manifested as headache, anxiety, agitation, insomnia, tremor, irritability, hallucinations and seizures. The effects exhibited on the musculoskeletal system result in an increase of intracellular calcium, muscle excitation, tremors, fasciculations and rhabdomyolysis [1]. The most common and mild clinical effects of caffeine toxicity are sinus tachycardia, hypertension, nausea, vomiting, anxiety, CNS agitation and palpitations. Severe clinical effects, fortunately less common, are seizure, dysrhythmias, myocardial infarction, hypertensive crisis, hyperthermia and delirium [3].

Treatment of patients with severe caffeine intoxication includes admission to the intensive care unit, electrocardiographic (ECG) monitoring, intensive therapy with isotonic solutions, as well as other forms of symptomatic and supportive therapy. In methylxantine severe poisoning, charcoal and hemodialysis are used in order to counteract caffeine's resistance. Indications for hemoperfusion through activated charcoal and hemodialysis are: serum levels of caffeine which are greater than 90 mg/L, severe poisoning with convulsions, hypotension resistant to parenteral infusion therapy, and heart rhythm disorders [1, 4].

Mesotherapy was discovered in Europe as a medical and cosmetic method for intradermal injection of a mixture of specific substances. Although traditionally used in the treatment of pain, it has recently been used for cosmetic purposes, especially in the treatment of cellulitis, as well as in the local reduction of fatty deposits [5]. In these procedures, the process of inhibition of phosphodiesterase contributes to its overall lipolytic effect.

## Case report

A 51-year old woman, underwent aesthetic treatment of excess adipose tissue through lipolysis. The treatment took about sixty minutes and was performed in a beauty salon, under the control of a plastic surgeon specialist. It consisted of 20 intradermal injections of caffeine solution. The patient felt discomfort after the first two applications, and soon felt ill with anxiety, nausea and the urge to vomit. Because of a sudden disturbance of general condition, the patient was further examined in the Emergency Center, Clinical Center of Serbia, ascertaining suffering from somnolence and hypotension. Electrocardiographic (ECG) examination registered sinus rhythm and occasional nonsustained ventricular tachycardia. Due to suspicion of underlying systemic toxic effects during the treatment the patient was admitted to the Poison Control Center, Military Medical Academy.

On admission the patient complained of nausea, vomiting, and chest palpitations. The patient was anxious, afeb-

rile, hyperventilating, with cold/moist skin, and mydriatic pupils. The auscultatory findings in the lungs were normal. The patient's heart rate was 150 beats per min, tones cleares without additional sounds. Blood pressure on admission was 130/80 mmHg. Injection marks on anterior abdominal wall were present with surrounding hematomas (Figure 1). The personal history of the patient indicated treatment of previous hypertension with nifedipine. ECG recorded paroxysmal supraventricular tachycardia (PSVT) with the frequency of 146/min, changes in repolarization, ST segment depression of 6 mm in left-sided leads (V4–V6) D1 and AVL (Figure 2).

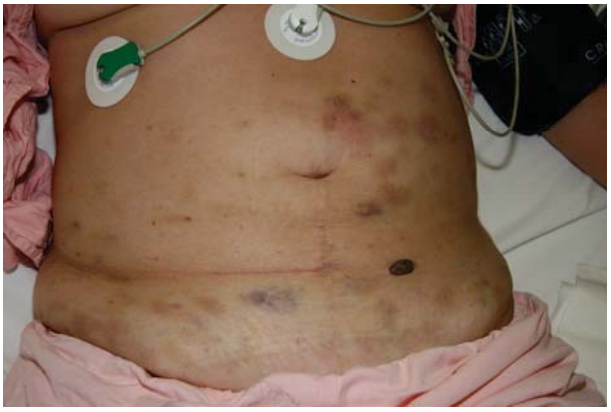

**Fig.1 – Injection marks on the anterior abdominal wall with surrounding hematomas.**

mal range 4.00 to 10.8 × $10^9$)], with normal values of red blood cells, hemoglobin and platelets. Arterial blood gases indicated acute respiratory alkalosis with a hypocapneic level of carbon dioxide partial pressure (pCO2) 30.4 mmHg (normal range 32–48 mmHg), total pH 7.486 (normal range 7.35 to 7.45) and no underlying metabolic disorders.

Toxicology screening of the blood in the patient upon admission confirmed the presence of caffeine in the concentration of 85.03 mg/L (therapeutic cocentration of 1 to 10 mg/L (toxic being more than 25 mg/L) [using high performance liquid chromatography with ultraviolet scanning detection (HPLC-PDA)] and theophylline, 7.43 mg/L [therapeutic concentration of 8 to 20 mg/L immuno-fluorescence polarization method (AXYM)].

The patient was admitted to the intensive care unit with continuous ECG monitoring and parenteral therapy. The first 6 h of parenteral therapy included 5 mg of verapamil, diazepam 20 mg, 10 mg metoclopramide, infusion therapy with 3,000 mL of isotonic solution, and substitution with 100 mEq potassium chloride. Diuresis following this therapy was an amount of 1,800 mL. In addition to the therapy, symptoms included heart rate slowing to 90/min, confirmed by ECG finding (Figure 3), with repeated attack of PSVT at the frequency of 170/min, which is the reason for inclusion of beta blockers in the standard therapy.

On the second day of hospitalization the patient complained of nausea, warranting removal of metocloperamide.

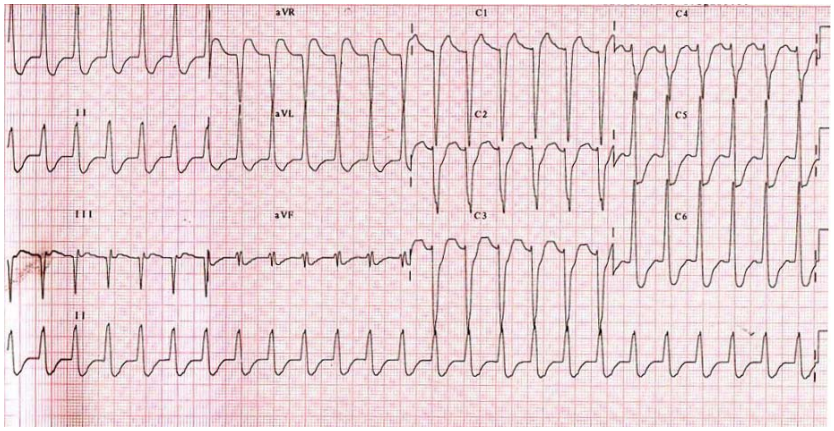


**Fig. 2 – The ECG on admission showed sinus rhythm, frequency of 146/min, changes in repolarization, ST segment depression of 6 mm in left-sided leads (V4–V6, the D1 and AVL).**

Biochemical analysis of the blood sodium level determined values of 147 mmol/L (normal range 135–147 mmol/L), potassium 2.1 mmol/L (normal range 3.5 to 5.2 mmol/L), chloride 99 mmol/L (normal range 98–111 mmol/L), glucose 17 mmol/L (normal range 3.5 to 6.4 mmol/L), urea 5.6 mmol/L (normal range 1.7 to 8.3 mmol/L), creatinine 69 mmol/L (normal range 50–124 mmol/L), aspartate aminotransferase (AST) 33 U/L (normal range 10–37 U/L), alanine aminotransferase (ALT) 49 U/L (normal range 20–65 U/L), creatinine kinase (CK) 79 U/L (normal range 21–232 U/L). The complete blood count showed elevated white blood cells [(the first day of 22 × $10^9$, a second day of 15.7 × $10^9$ (normal range 4.00 to 10.8 × $10^9$)], with normal values of red blood cells, hemoglobin and platelets. Arterial blood gases indicated acute respiratory alkalosis with a hypocapneic level of carbon dioxide partial pressure (pCO2) 30.4 mmHg (normal range 32–48 mmHg), total pH 7.486 (normal range 7.35 to 7.45) and no underlying metabolic disorders.

From that day until hospital discharge, the patients ECG rhythm was at a normal frequency. Serum potassium level was 2.3 mmol/L. Detection of blood caffeine levels of 57.73 mg/L and theophylline at a concentration 6.59 mg/L were obtained.

On the third day, the patient complained of a headache, as well as pains in the neck area. Hypertension was established at 170/90 mmHg. Laboratory analysis determined hypokalemia (serum potassium level 2.8 mmol/L). The concentration of caffeine in blood was 27.43 mg/L, which was between the range of concentrations considered to be toxic. The concentration of theophylline was 7.43 mg/L. The

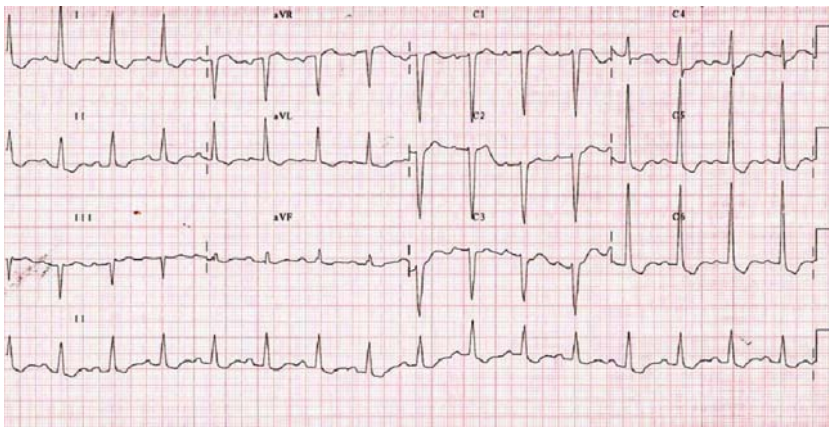

**Fig. 3 – The ECG after beginning the treatment showed heart rate slowing to 90/min with changes in repolarization (the first day)**

treatment started with an angiotensin converting enzyme (ACE) inhibitor, administered both parentally and orally, resulting in correction of hypertension, as well as hypokalemia.

On the fourth day of hospitalization the patient was in good condition and discharged. The ECG at discharge was found to be a sinus rhythm, at the frequency of 67/min (Figure 4), with the signs of hypertrophy and left ventricular overload. Normal values for biochemical parameters were recorded. The concentration of caffeine in blood was 8.39 mg/L and 1.86 mg of theophylline/L, which was at the therapeutic level. On echocardiographic examination, there was an enlarged left atrium of 4.3 cm, normal left ventricular dimensions, with concentric hypertrophy and a wall thickness of 13 mm. There was no failure of segmental contractility; ejection fraction was 65%. Diastolic function was altered by delayed relaxation.

acidosis with confirmation of toxic concentrations of caffeine. The symptoms gradually retreated after 7 days, and the concentration of caffeine was then between 60–70 mg/L [6, 7]. Ingestion of large amounts of caffeine can cause significant agitation, severe hypotension, tachycardia, ventricular arrhythmia, cardiac arrest, myocardial infarction, hypokalemia, rhabdomyolysis, seizures and acute renal impairment [8, 9]. Waring et al. [10] showed clinical data of 38 patients with caffeine ingested at an average dose of 1,040 mg (600 to 1,500 mg), which is equivalent to the amount found in about 10 cups of coffee. Out of them, 28 (73.7%) patients attempted suicide by deliberate self-poisoning, 8 (21.1%) patients ingested caffeine in order to enjoy (energy drinks), and 2 (5.3%) patients did it for weight loss.

We reported acute poisoning caused by intradermal caffeine intake by intentional injections for aesthetic purpose.

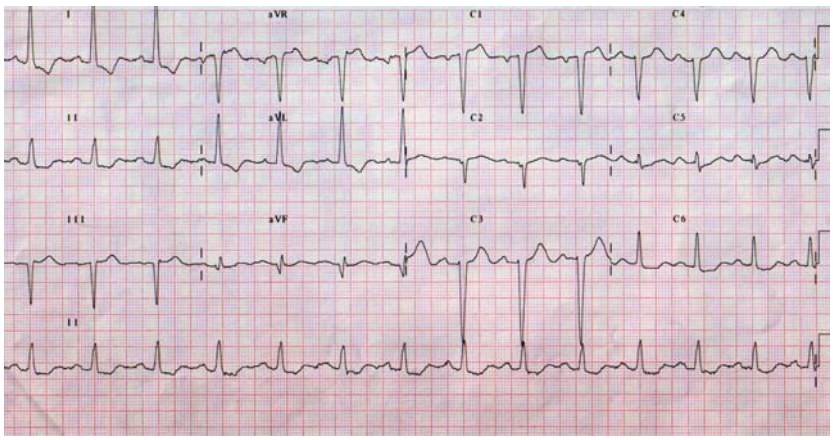

**Fig. 4 – The ECG at discharge showed sinus rhythm, frequency of 80/min with signs of hypertrophy and left ventricular overload**

## Discussion

Caffeine side effects and systemic toxicity in adults is usually documented after oral administration, and during intravenous use in pediatric patients or neonates [1].

Intravenous caffeine in neonates has been presented with a number of severe toxic effects such as hypertension, tachycardia, tachypnea, tremor, opisthotonus, tonic-clonic convulsions, cardiac failure, pulmonary edema and metabolic

So, that differs from accidental poisoning with caffeine, usual entry of the toxin.

So far, it has not been proven that consuming caffeine from coffee increases the risk of cardiovascular disease. Also, there is no clear evidence that drinking moderate amounts of coffee, 3 to 4 cups per day (about 300 to 400 mg per day), poses a risk to health. However, certain groups of people, including people with hypertension, children and adolescents may be more sensitive to caffeine in terms of

side effects [11]. Before the treatment, the presented patient had already had hypertension, but this higher risk to adverse effects of caffeine was not taken into account.

The contraindications to mesotherapy are [12, 13]: pregnant and lactating females, insulin dependent diabetes mellitus, history of bleeding disorders, history of strokes, history of thromboembolic phenomena, patients on medication for cardiac arrythmias, aspirin, warfarin, heparin, history of recent cancer, severe heart disease, renal disease, any severe chronic systemic disease.

The main clinical effects at both, caffeine therapeutic doses as well as in case of poisonings with proven toxic concentrations, are from adenosine antagonism, beta adrenergic receptor stimulation and phosphodiesterase inhibition. On admission to the hospital, the presented patient's ECG showed repeated attacks of PSVT, with evidence of hypertensive cardiomyopathy and hypoklemia.

Severe caffeine poisoning is relatively rare and accompanied by unwanted hemodynamic complications, including a high mortality rate. Among complications are the most severe forms of cardiac abnormalities: sinus tachycardia, ventricular tachycardia and ventricular fibrillation, generalized convulsions, multiple organ failure (MOF) and cardiac arrest [1, 8, 9, 14]. The presented patient was initially observed to have hypotension, nonsustained ventricular tachycardia, and PSVT, fortunately with a favorable outcome. Sinus tachycardia is a common sign of poisoning, and is most likely benign in people with no previous cardiac disease. However, sinus tachycardia in methylxanthine poisoning, can progress to severe arrhythmias. Atrial fibrillation, atrial flutter, multifocal atrial tachycardia, ventricular tachycardia and ventricular fibrillation may result from methylxanthine poisoning [1]. Caffeine stimulates the respiratory center in the CNS, increasing the frequency of breathing, causing hyperventilation, respiratory alkalosis, respiratory failure, respiratory arrest and acute lung injury (ALI). On admission to the intensive care unit, arterial blood gas values described in the presented patient indicated respiratory alkalosis and hypocapnea, which was correlated with increased respiration and tachypnea.

In the article of Scottish authors [10], 24 (63.2%) patients showed only gastrointestinal symptoms, nausea and vomiting. In the first 6 hours of the treatment, the presented patient showed gastrointestinal symptoms, nausea and vomiting, which responded favorably to the use of metoclopramide.

It is known that caffeine causes psychiatric disorders under certain circumstances. Caffeine, which is widely used especially in younger population, is also found in many energy drinks, and can cause marked anxiety in otherwise healthy individuals. This is particularly true in sensitive persons with existing anxiety disorders. Caffeine may be associated with symptoms of depression, sleep disorders, and worsening of psychotic disorders in people with schizophrenia [15]. The presented patient was anxious upon admission, and later complained of a headache. According to the Scottish Poison Centre (for the period 2000 – 2008) dizziness, headache, tremor and agitation were much less common symptoms of caffeine poisoning in comparison to those with gastrointestinal symptoms [10].

Hypokalemia is a common manifestation of acute poisoning with methylxanthines resulting in beta adrenergic agonism and stimulation of $Na^+/K^+$ ATP-ase, which leads to a shift of potassium from the extracellular to intracellular space. This can be accelerated by vomiting and loss of potassium through the kidneys. In patients with theophylline intoxication, hyperkalemia occurs early and is independent of the initial laboratory analysis with vomiting [16]. The presented patient had a potassium concentration of 2.1 mmol/L, which was interpreted as a loss of potassium due to vomiting. After the first analysis of toxic concentrations of caffeine, hyperkalemia was interpreted as caffeine toxic effect. We performed a parenteral and oral potassium replacement, which exhibited parallel falls in toxic concentrations of caffeine, but not to completely normal levels. The concentration of caffeine in blood of the patient before mezotherapy remains unknown, but there are recommendations that coffee or caffeine-containing beverages must not be used for at least 12 h before the treatment [17]. In the presented patient, the concentration of caffeine was 85 mg/L immediately after mezotherapy, and 57.73 mg/L on the second day.

The immediate cause of death in severe caffeine poisoning is ventricular fibrillation, as has been shown by an experimental work [18]. Generally speaking, a concentration of caffeine in the blood of more than 100 mg/L is considered lethal [19, 20].

A case of sudden death has been documented involving a 25-year-old woman previously diagnosed with mitral valve prolapse. Cardiac arrest occurred immediately after drinking energy beverage. At autopsy screening, the presence of 19 mg/L caffeine was indicated in the aortic blood. The caffeine concentration was 10 g/L [21] upon further analysis. Swedish forensic experts during a year period witnessed four fatalities, demonstrating caffeine concentration of 80 to 100 mg/L [22] in post-mortem toxicological analysis.

Fatal caffeine overdose in adults is rare and involves more than 5 g of a drug containing caffeine to cause death. American toxicologists [23] from New Mexico, during a one year follow-up documented accidental caffeine poisoning as a cause of death in two patients: in a 39-year-old woman with the history of intravenous drug abuse with the caffeine concentration 192 mg/L in femoral blood and in a 29-year-old man with the disease history of obesity and diabetes mellitus, with caffeine concentration of 567 mg/L in femoral blood.

In both patients, the cause of death was accidental caffeine poisoning. At the begining of the 80's, articles were published about the cosmetic application of phosphodiesterase inhibitors and cAMP in the treatment of lipodystrophy [5]. In animal models, after subcutaneous application, the efficacy of methylxanthines themselves was tested, usually incorporating caffeine and theophylline, methylxanthines, or in combination with other substances that have a lipolytic effect. Their effect on the rate of absorption was monitored in accordance with artificially induced granulomas in adipose tissue. A better effect was achieved by combining preparations [5, 24].

Adverse effects of cosmetic treatments for cellulitis occur with intradermal injection of lipolytic substances, and can be presented as pain and erythema at the puncture site, vagal reactions, injury to nerves and blood vessels, skin necrosis and hematoma formation. Hematomas, which should not follow this type of treatment, are usually the most common side effect, and are a consequence of the effects of the applied substances interfering with the process of coagulation. According to the previously published data there are numerous local side effects associated with therapy [5]. Abdominal wall hematomas in the presented patient are shown as local side effects caused by substances in deeply applied injection (Figure 3). After application there was a massive absorption into the circulation as proved by the elevated concentration of caffeine 85.03 mg/L in the blood.

The most common local complications of mesotherapy are as follows: bruising and edema due to the chemicals used in mesotherapy [13, 24], skin necrosis [25–27], atypical mycobacterial infections [28], allergic reactions due to various chemicals [26, 29], atrophy and lipodystrophy [25], postinflammatory hyperpigmentation nodularity [25], after irregular lipolysis [29] etc.

Few papers describe systemic toxicity of substances applied during and after mesotherapy. Brazilian authors [30] describe the first case of systemic toxicity in a young woman presenting with thyrotoxicosis caused by mesotherapy with triiodthyroacetate acid. Alster and Tanzi [31] reported that in 2003, mesotherapy was banned by the Brazilian National Agency of Health due to its unwanted side effects. There are also systemic complications. "Systemic complications are allergic reactions, vagal syndromes, lipothymia, infections (HIV, hepatitis, etc) and liver toxicity with demyelination of nerves due to large doses of phosphatidylcholine" [24, 25].

In addition to supportive and symptomatic treatment for severe poisoning and systemic toxic effects, hemoperfusion and hemodialysis are strongly recommended [14, 32]. Fortunately, the presented female patient responded favorably to the treatment and did not require the action of extracorporeal detoxification. Cardiopulmonary resuscitation was needed in the worst case scenario. There were documented cases of survival in patients with cardiotoxicity induced by caffeine in which cardiopulmonary support was applied percutaneously [9].

## Conclusion

The severe systemic toxic effects of caffeine applied intradermally in mesotherapy were seen in the presented patient. The cause of massive caffeine absorption from the subcutaneous tissue into the systemic circulation of the patient was partly due to the tiny blood vessels in the skin, as indicated by hematomas in the abdominal wall. The clinical picture showed mild gastrointestinal symptoms (nausea, vomiting), CNS disorders (somnolence, anxiety), and cardiovascular disturbances (hypotension, ventricular tachycardia and nonsustained PSVT). In this era of increasing popularity of mesotherapeutic aesthetic treatment, one should keep in mind the possibility of a significant absorption of the applied substances into circulation and their potential systemic side effects. Proper methods of intervention need to be applied in specialized institutions for cosmetic surgery that are staffed and equipped to respond in case of complications, as well as in poisonings.

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