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*Case Report*

# Malignancy in patients with opioid use disorder: A late diagnosis in patient on maintenance treatment with Buprenorphine, with lethal effect: a case report

**Natasha Simonovska[1*] and Antonio Gligorievski[2]**

[1]University Clinic of Toxicology, Clinical Center "Mother Teresa", Skopje, Republic of Macedonia

[2]University Clinic of Surgery "St Naum Ohridski", Skopje, Republic of Macedonia

***Corresponding Author's E-mail: N.Simonovska@yahoo.com**
**Tel: 0038971277295**

**Abstract**

**Heroin dependents might be at a higher risk of death from cancer than the general population. A 31-year-old male on maintenance treatment with Buprenorphine, came to our Clinic with paralysis of his legs. He also complained on spinal pains. He couldn't walk and he was in forced position. The biochemical analysis showed high values of SE, LDH, globulins, CRP, D-dimer, Tu markers: beta HCG, CYFRA 21-1, presence of paraproteins. The other investigations showed enlarged lymph nodes in the abdomen and small pelvis, thrombosis of v.cava inf and right v. iliaca. The histological finding from the biopsy of the sacrum showed a metastatic process on the skeletal muscles. The patient was treated with buprenorphine, antibiotic therapy, Carbamazepine, anticoagulant therapy and other symtomatic therapy. Despite numerous investigations and treatment, bleeding and abscesses in the cerebrum occurred. The patient immediately underwent surgery and his recovery was well. He was discharged on his request, but his condition was deteriorated sharply at home and he died in a short time. There are few studies on malignant diseases found in heroin dependents. It is a challenge to monitor and also to compare the incidence of malignancy between heroin dependents and healthy population.**

**Keywords:** Buprenorphine, Heroin dependents, Lethal effect, Malignancy Thrombosis

## INTRODUCTION

Some drugs may be linked to cancer as many drugs cause cellular damage in the body. Heroin dependents might be at a higher risk of death from cancer than the general population. Most experts recommend the most effective approach for cancer prevention, and that is a healthy lifestyle without smoking and drug use (Stop Addiction Blog. The link between Drug Use and Cancer, 2013). Effects of heroin on the immune system may be in the form of immunosuppression (frequent infections and neoplasms) and in the form of immunostimulating (hypersensitivity and autoimmune reaction) (Luster and Rosenthal, 1993; Novick et al., 1991).

Dependent opioid users, especially those injecting heroin, have increased somatic and psychological morbidity and reduced health-related quality of life. Opioid dependence is associated with social marginalisation, criminality and socioeconomic deprivation accompanied by malnutrition, chronic diseases and generally impaired health as well as exposure to overdoses and trauma. Mortality among injecting drug users is much greater than in the general population. The main causes of death (in descending order) are overdose, diseases, trauma and suicide. Few studies have investigated opioid maintenance treatment (OMT)-related somatic health effects and morbidity patterns. Drug-related incidents were reduced by about two thirds, but non-drug-related incidents showed a non-significant increase (possibly due to closer contact with health services) and injuries showed no change during treatment. These findings were, however, based upon a

small sample of patients from one municipality. In order to evaluate the effects of maintenance treatment, it is necessary to study morbidity prior to, during and after OMT. Such studies are scarce, and very few include long-term follow-up. Opioid dependents suffer increased health problems and reduced health- related quality of life as well as increased mortality, compared to the general population. In spite of the considerable morbidity, drug users frequently neglect their health problems, and diseases may remain untreated (Skeie et al., 2008).

## Case presentation

We present a case of a 31-year-old male on treatment with Buprenorphine. When he came to our Clinic he told us that the while he was in prison, two months ago he had pain in his spine. Two weeks after he was released from prison he experienced swelling in his legs and genital area. There was no precise medical evidence, but as he told us the doctors from another hospital made investigations and they treated him with anticoagulant therapy, analgesics and antibiotics. His condition was ameliorated, but after one week he had the previous symptoms and pains. When he was admitted to the University Clinic of Toxicology in Skopje he complained on paralysis of his legs and on a large swelling on his right leg and genital area. He also complained on pains in his spine. He has never used heroin intravenously in the past, but he has abused cannabis several times. He began with heroin use when he was 24 years old. Almost 3 years he was on maintenance treatment with Buprenorphine 8mg. The patient was conscious, afebrile, with poor subcutaneous fat, the skin was pale with visible distinct chest veins, palpabile inguinal lymph glands, large swelling on his right leg and on the genital area. He couldn't walk and he was in forced position.

Laboratory tests showed normal findings except for high sedimentation values: 108.. 120 (ref.val.: 4-10 mm/1h)), lactate dehydrogenase: 2141.. 2827.. 3144.. 4721.. 5678.. 6059 (ref.val.:up to 248 U/L), total proteins, particularly globulins: 55 (ref.val:27-35g/l), C-reactive protein: 114,7 (ref.val: up to 6mg/l). Electrophoresis detected paraprotein, especially increased gamma globulin fraction. Bence-Jones proteinuria was negative. He was serologically negative on hepatitis B, C and HIV. Toxicological tests were negative for methadone, opiates, benzodiazepines, and positive for buprenorphine. Peripheral smear test showed neutrophils with toxic granules. Fibrin degradation products showed secondary activated fibrinolysis and high level of D-dimer: 2629.. 4500 ng /ml. Microbiological finding of urine was sterile. Tumor markers showed high values of beta HCG:161112,68 (ref.val up to 3,0U/L), CYFRA 21-1: 24,98 (ref. Val: up to 3,3µg/l) and the other Tu markers (CEA, AFP, CA19-9, CA72-4, PSA, PAP) were with normal finding. Electrocardiogram was also normal. On the first ultrasonographic examination of the abdomen the liver was diffusely enlarged and the other organs were with normal ultrasonography findings. There were also several enlarged lymph glands around the blood vessels in the small pelvis, epigastric region and retroperitoneal enlarged lymph glands. Ultrasonographic examination of the testicles: right testicle slightly smaller 27 / 16 mm, homogeneous parenchyma without Tu formations. The left testis with dimension of 37 / 18 mm, had free liquid, thickened epididymis 11.2 mm. This finding was with differential diagnosis of epididymitis or orchitis. On Abdominal Color Doppler ultrasonography, v. cava inferior in subhepatic segment was with normal signal while in distal segment there was no signal. The left v. iliaca was with normal Color Doppler signal, but on the right v. iliaca there was thrombus. Collor Dopler imaging of the lower extremities showed phlebothrombosis of the right v. ileofemoralis. Echocardiography showed mild regurgitation of the mitral and tricuspid valve, without vegetation and any signs of pulmonary thromboembolism. Chest X-ray was with normal finding.

During hospitalization the pain in his spine has become stronger. The pain was evaluated according to Pain Assessment Scale (Pain Assessment Scales. National Initiative of Pain Control, 2003). X-ray of the thoracic and lumbal spine showed dextroconvex deviation and reduced lumbar lordosis. On the bone scan (skeletal scintigraphy with technetium 99MDP) performed in forced positions, there was no detection of pathological accumulations on skeleton. Multidetector computed tomography (MDCT) of the abdomen and pelvis in a series with intravenous contrast showed that liver, spleen, gall bladder, biliary tract, kidneys, adrenal glands and pancreas were without pathological lesions. Below the renal arteries there were visible enlarged lymph nodes, especially in the area of aortic bifurcation. Enlarged lymph glands were seen in the small pelvis. Other investigations with MNR of the distal part of the abdomen and small pelvis were (Figures 1-6). Magnetic resonance of the pelvis was made in forced position of the patient, only in one sequence. It detected thrombosis of the vena cava (the intraluminal clot reached the height of the distal renal veins and got into both iliac veins to the inguinal region). Osteolysis at the sacrum level S1 was also detected; the body of the sacrum was with lytic lesions predominantly on the right side and the process extended to the sacroiliac joint. There was substrate in the spinal canal. The magnetic resonance also showed increased retroperitoneal and paraaortal lymph glands. This investigation led to differential diagnosis between systemic disease and primary lesion of the sacrum, osteosarcoma. CT arteriography (phlebography) of the abdomen and the lower limbs showed that there was no compromising of the arterial circulation in aorta, iliac arteries, femoral arteries and a. poplitea. Clot filling was predominant in v. cava inferior, which started at 5cm below renal veins and continued to the bifurcation and in


**Figure 1.** CT of the abdomen, postcontrast series, arterial phase, section at kidneys height. Paraaortal on the left side, package of enlarged lymph nodes (arrow) with a diameter of 23 mm

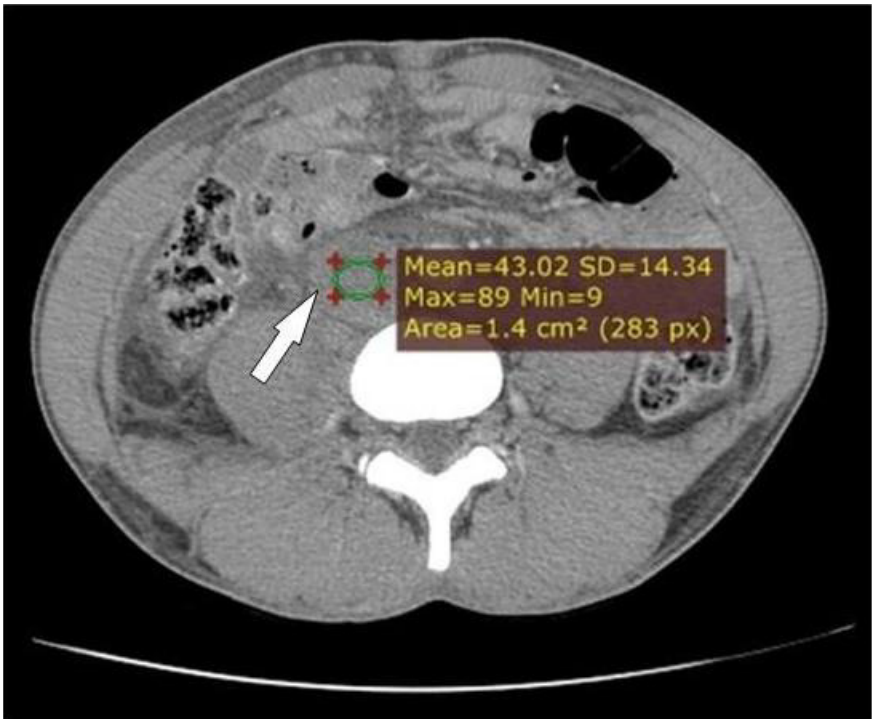


**Figure 2.** CT of the abdomen, postcontrast series, venous phase, section at height below the renal lodges. Vena cava inferior (VCI) is with expanded lumen and visible intraluminal thrombotic masses (arrow), with an average density of 43 HU.

**Figure 3.** CT of the abdomen, postcontrast series, venous phase, section at height of the entrance to the small pelvis. Clear display of the iliac veins (arrow), the right vein is with wider lumen and with visible intraluminal thrombotic masses. Right lateral mass of sacrum is structurally modified with osteolytic changes and soft tissue substrate (black arrow). Soft tissue substrate is in the spinal canal.

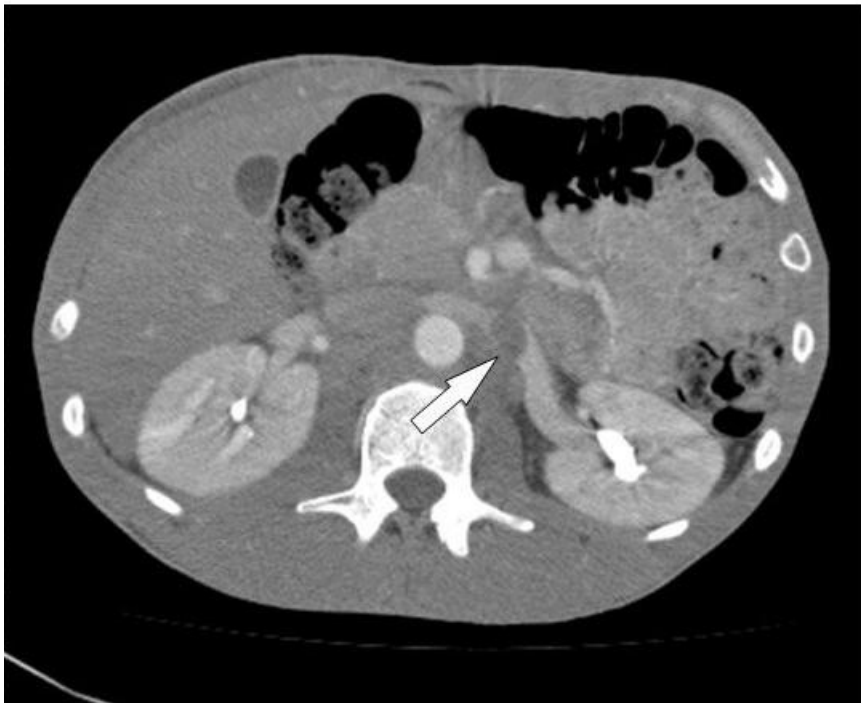

**Figure 4.** CT of the abdomen, postcontrast series, late phase, section at the kidneys height. Clear display of the left renal vein. In the lumen of the vein there is a filling oval defect - intraluminal clot (arrow).

**Figure 5.** CT of the abdomen, postcontrast series, late phase, section at the height of the small pelvis. Clear display of the right external iliac vein which is with expanded lumen and visible thrombotic masses in the lumen (arrow). Enlarged lymph nodes in the small pelvis (black arrows).

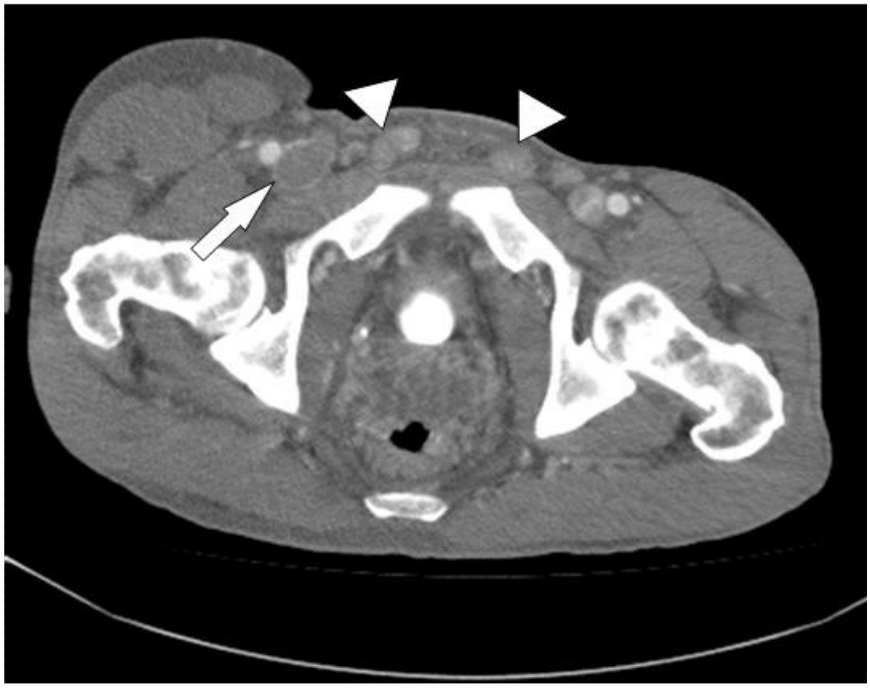

**Figure 6.** CT of the abdomen, postcontrast series, late phase, section at the height of the hips. Clear display on the right common femoral vein, which is with expanded lumen with intraluminal thrombotic masses (arrow). Increased number of lymph nodes perirectal and in the small pelvis. Also, on both sides of the inguinal region there are enlarged lymph nodes (triangles).

the right iliac vein, right femoral vein and v. saphena several cm below the inguinal region. In the distal segments there was no thrombosis of the venous circulation. The clot in the left iliac vein was about 4 to 5

cm long without compromising the distal segments of the femoral vein. There was a small recanalization clot in the middle of the left renal vein and the kidney was with normal findings. The investigation also showed enlarged inguinal, retroperitoneal, paraaortal, paracaval lymph nodes of 1-3 cm dimension. One of the lymph node was with central necrosis. There was osteolysis and destruction with osteosclerosis on the sacrum S1 and S2 segment at the right side. According to the size of the lymph nodes one of the differential diagnoses could be lymphoma. The magnetic resonance of the lumbosacral spine involving the thoracic part Th11 and Th12 to the level of the sacral part showed advanced bone destruction of sacrum from S1 to S4. The substrate filled the spinal canal from vertebrae L4 to L5 and compromised the nerve roots from L3 and L4 on the right side and the nerve root of L5 bilaterally. The finding showed differential diagnosis of neoinfiltrative process or lymphoma or secondary deposits.

During hospitalization inguinal lymph gland was extirpated by a plastic surgeon. Histological findings were dermatopathic lymphadenitis. Immunohistochemical analysis of the lymph gland indicated that it could be dermatopathic lymphadenitis or a part of tumor vascular proliferation that need further clinical investigations. During hospitalization the following specialists were consulted: hematologist, anesthesiologist (Center for Pain), psychiatrist for the dependence problem, oncologist, pulmonologist, rheumatologist, digestive surgeon, gastroenterologist, urologist, plastic surgeon, specialist in transfusion medicine, cardiologist, orthopedic surgeon.

Despite a number of investigations there was no precise diagnosis, and it was unclear whether it was lymphoma, osteosarcoma, systemic disease or some specific process was ongoing. So we planned to do a biopsy of the sacrum. But 20 days after hospitalization, the condition of the patient deteriorated and he began to lose consciousness. A neurosurgeon was immediately consulted and computer tomography of the brain was made. The computer tomography of the brain showed subcortical in parietal-occipital region clearly limited hyperdense lesion, intracerebral hemorrhage and compressive effect on the central brain structures. There was no indication of traumatic injury. The patient immediately underwent surgery and histological diagnosis confirmed abscess and bleeding in the cerebrum. Postoperative recovery went well. After 10 days biopsy of the sacrum was done. Two days after biopsy the patient asked to be discharged from the hospital by signing his history. However, after 5 days his condition rapidly deteriorated at home, he lost consciousness and died in a short time (His mother gave us these data). The histological finding from the biopsy of the sacrum showed metastatic process on the skeletal muscles. Unfortunately, despite a number of investigations we found no primary lesion.

During hospitalization the patient was treated with buprenorphine which dose was constantly increased to 32 mg. Buprenorphine was first reduced and stopped when the patient showed consciousness disturbance. Antibiotic therapy (ceftriaxone 2g) was also given, along with vitamins B and C, magnesium, Carbamazepine 2x400mg, analgesic agent (NSAIL), anticoagulant therapy (first he was treated with Clexane subcutaneously twice a day 2x40mg and after that he was given oral anticoagulant therapy - Sintrom which was controlled by INR, pentoxifylline 2x400mg and other symtomatic therapy.

## DISCUSSION

The management of dependence in patients with advanced cancer can be time-consuming, labor-intensive, and difficult. Some clinicians believe that it is not worth the effort, due in part to a failure to appreciate the deleterious impact of dependence on palliative care efforts and a view of dependence as intractable in any case. Indeed, it is possible that some clinicians perceive dependence not only fatalistically but, because of common misconceptions, believe that managing or attempting to decrease the patient's use of alcohol or illicit substances would be tantamount to depriving a dying patient of a source of pleasure. Managing dependence is an essential aspect of palliative care for chemically-dependent and patients with alcochol use disorder. The goal of such efforts is not complete abstinence, but exerting enough control over illicit drug and alcohol use to allow palliative care interventions to decrease suffering (Passik and Theobald, 2000).

Randal and colleagues examined cancer mortality in a population-based cohort of opioid-dependent persons. They observed New South Wales opioid substitution therapy (OST) program registrants from 1985 to 2005 (n=43,789) who were probabilistically linked to the National Death Index. Crude and standardised mortality rates and standardised mortality ratios (SMRs) were calculated. The crude cancer mortality rate increased from 4 to 65 deaths per 100,000 person-years (p trend <0.001). Overall, OST registrants were 1.7 times more likely to die of cancer than the general population. Site-specific SMRs were significantly elevated for lung cancer (3.6, 95% CI 2.8–4.6), liver cancer (6.9, 95% CI 4.3–10.5), and anogenital cancers (2.8, 95% CI 1.3–5.3), and significantly reduced for breast cancer (0.4, 95% CI 0.1–0.9). They concluded that cancer is an increasingly important cause of death among OST registrants as they live longer with their dependency. The site-specific excess deaths suggest the role of tobacco, alcohol, and infection with hepatitis C and human papillomavirus (Randall et al., 2011).

The most important use of heroin and other opioid is the treatment of severe pain. For a long time heroin was

a standard component of the famous Brompton Cocktail. Initially this cocktail contained heroin or morphine, cocaine and sometimes small amounts of alcohol. A review was published in 1974 including 500 patients with advanced malignancy treated with oral heroin/cocaine mixture or with heroin injection if they were unable to take medicine by mouth (Carnwath and Smith, 2002).

Degenhardt and colleagues examined changes in causes of death in a cohort treated for opioid dependence. There were 43 789 people in the cohort, with 412 216 person-years of follow-up. The proportion of the cohort aged 40+ years increased from 1% in 1985 to 39% in 2005. Accidental opioid overdoses, suicides, transport accidents and violent deaths declined with age; deaths from cardiovascular disease, liver disease and cancer increased (Degenhardt et al., 2014).

Many studies on mortality in heroin users report traditional mortality data, which does not account for age at death. To examine causes of premature death and years of potential life lost (YPLL) among heroin users, researchers assessed 581 ethnically diverse men who had been admitted to a compulsory drug treatment program in California for heroin-dependent criminal offenders. Subjects were evaluated every 10 years over 33 years. The leading causes of death were heroin overdose (17% of deaths), chronic liver disease (15%), cardiovascular disease (12%), cancer (11%), accidents (8%), and homicide (7%) (Smyth et al., 2007).

## CONCLUSION

Very often somatic comorbidities can occur in patients with opioid use disorder. None somatic problem should be neglected and should be followed in detail. There are few studies on malignancy in heroin users. It is a challenge to monitor and also to compare the incidence of malignancy between heroin users and healthy population.

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