

## Up-to Date Review And Case Report

# Krokodil (Desomorphine)-induced osteonecrosis of the maxilla: a case report and literature review

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**Abstract – Introduction:** Desomorphine is an opioid formerly used to treat acute pain. It is simple to manufacture, which has recently led to an increase in its clandestine production under the name “Krokodil”. This article presents a case of oral problems related to its use first ever reported in France. **Observation:** A 36-year-old male patient presented with bone exposure in sector 1. He admitted to actively consuming “Krokodil IV” for several years. In the course of the clinical and radiological examinations, the patient was diagnosed with osteochemonecrosis of the maxillary induced by krokodil, considering that severe intrinsic and extrinsic adverse effects have been attributed to the drug. **Discussion:** A systematic literature review was conducted using articles from the Medline and Web of Science databases. To treat such a condition, two authors have described a process consisting of total excision of the necrotic tissue with 0.5 cm margins, combined with discontinuing the intake of the drug. However, these observations should be considered with caution because of the absence of any prospective studies. **Conclusion:** There are a number of etiologies for osteonecrosis in the context of radiotherapy, intake of bisphosphonates, and administration of bone resorption inhibitors. Unfortunately, in the case of krokodil, its high addictive nature makes it difficult for the patient to wean off the drug. Further, the heterogeneity of its manufacturing make it challenging to pharmacokinetically analyze its prolonged use. In view of the current literature, surgical therapy associated with weaning appears to be the most appropriate treatment, without being able to rule out addiction or necrotic relapses.

## Introduction

Desomorphine is a fast-acting opioid that was formerly used to treat severe-intensity acute pain [1]. It was distributed in Russia until the early 1980s before being withdrawn from the market due to its respiratory and emetic depressant effects associated with a higher addictive potential than morphine [2].

It can easily be produced using codeine, iodine, and phosphorus under the name krokodil, which has led to an increase in its clandestine production. There are estimated 100,000 krokodil consumers in Europe in 2013 [2–4].

This clinical case presents an oral manifestation related to krokodil toxicity, which has never before been described in France. The purpose of this article is to introduce a rare form of osteonecrosis and to review the literature for understanding the mechanism and management of the disease.

## Observation

A 36-year-old Georgian patient came into the clinic in January 2019 reporting masticatory discomfort on the right side of the jaw.

The medical history showed active untreated hepatitis C, multiple cases of untreated drug abuse, and depressive episodes. His daily treatment included opioid substitution with buprenorphine (Subutex<sup>®</sup>), tramadol (Contramal<sup>®</sup>), and pregabalin (Lyrica<sup>®</sup>). No addictological or virological family history was found. The patient smoked 20 cigarettes a day.

The patient admitted to taking krokodil intravenously for several years. The history of the disease began in 2014 following dental avulsions in sector 1 without any suggested cause. According to the patient, the operative site never healed.

Clinical examination revealed necrosis in sector 1 with bone exposure extending beyond the first right maxillary premolar (14) to the maxillary tuberosity of the distal right-hand maxilla (Image 1). There was no pus. The ganglionic

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**Image 1.** Intraoral examination of sector 1. The intraoral examination revealed bone exposure of necrotic tissue distal to 14.

areas were unaffected. The gum was inflamed and sensitive to the touch. The oral mucosa was unremarkable. The rest of the dental examination was normal although there were multiple cavities.

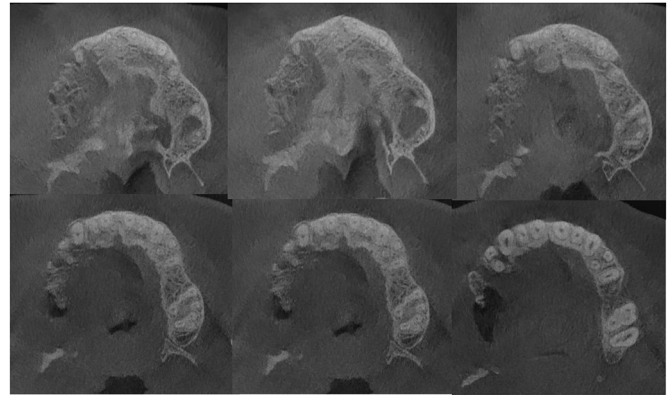
As a first-line test to assess other necrotic areas, large-field cone beam computed tomography was performed. The scan revealed a single heterogeneous hypodense lesion with vague contours suggestive of right hemi-maxillary osteonecrosis with involvement of the mesopalatine suture within nasal fossae and above maxillary sinus (*Image 2*).

Krokodil has a strong chronological and semiological imputability. Considering this, the patient was diagnosed with krokodil-induced stage 3 maxillary osteochemonecrosis (according to the American Association of Oral and Maxillofacial Surgeons) in the absence of a conclusive differential diagnosis. Patient's medical history did not show any antecedent of cervicofacial radiotherapy, intake of bone resorption inhibitors (bisphosphonates or anti-RANKL), or administration of any oncological antecedents (anti-angiogenics).

An Ear-nose-throat specialist (ENT) consultation was undertaken to review the sinuses before considering any treatment. After consultation, no surgical indication was retained during the first consultation in view of active krokodil intoxication, vague boundaries, and the diffuse aspect of the lesion. In addition, the patient would have to stop smoking and his hepatitis would need to be monitored.

## Discussion

A systematic review was undertaken of the articles from the Medline and Web of Science databases to identify the available literature on this topic. The search strategy was based on the



**Image 2.** CBCT, axial views of the maxilla. Single, heterogenous, low-density lesion with vague contours reminiscent of an osteonecrosis of the right hemi-maxilla reaching the mesio-palatal suture, the nasal cavities and the maxillary sinus.

association of following keywords: (krokodil OR desomorphine) AND (necrosis OR osteonecrosis) AND (maxilla OR mandible OR jaws).

The selection of the articles was carried out independently by two examiners with the following inclusion criteria (*Fig. 1*):

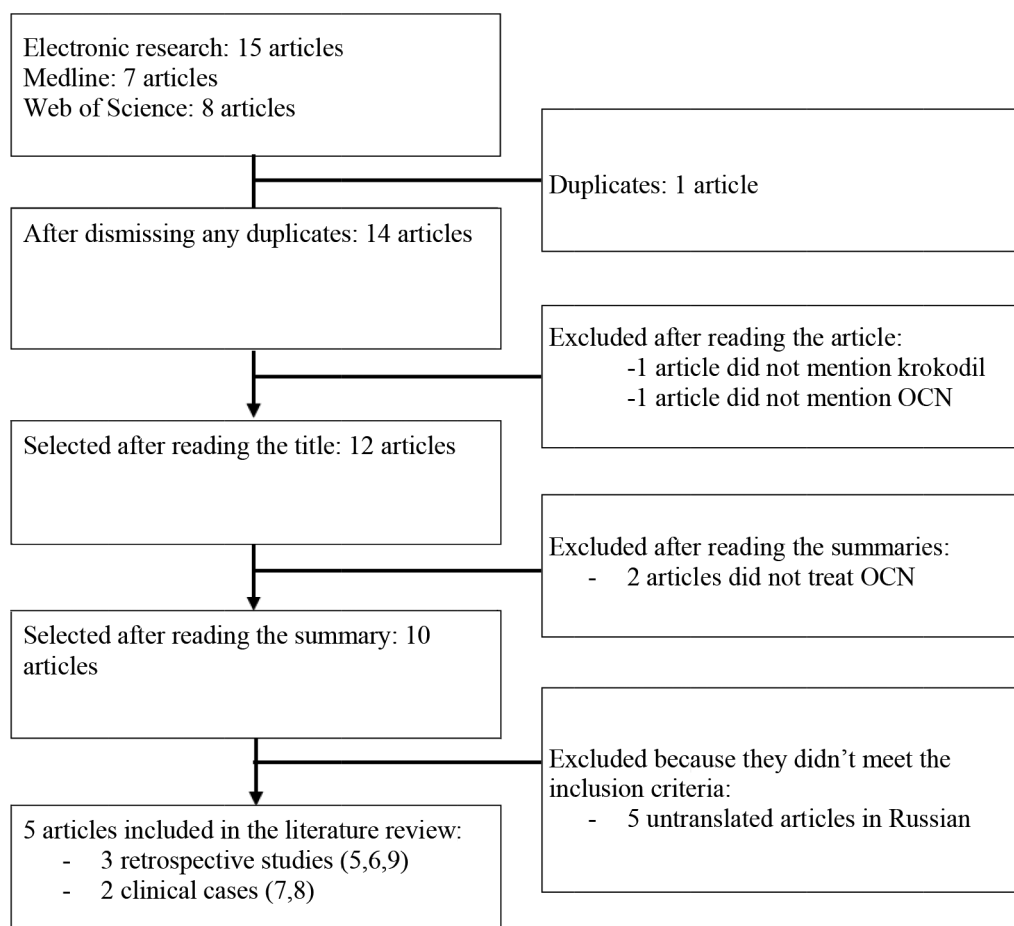
- Study or clinical case in humans is presented
- Treatment of osteonecrosis induced by the intake of desomorphine or krokodil is described
- Language of the article is English or French

The research found five articles that met the inclusion criteria [5–9] (*Tab. I*).

Poghosyan and co-workers have published the most on the issue and have the largest body of work. They studied 40 addicts who consumed krokodil and presented with osteonecrosis. They found maxillary involvement in 27.5% of cases, mandibular involvement in 52.5% of cases, and maxillomandibular involvement in 20% of cases [5].

Their proposed management consists of total excision of the necrotic tissue with margins of 0.5 cm combined with the patient discontinuing his drug use (minimum one month of weaning). Surgery was required in some cases with the segmental resection of the mandible. A recurrence of necrosis in the mandible was observed in 23% of cases, but no maxillary recurrence was described in the literature [5]. In these patients, the management of oral-sinus communication following maxillary necrosectomies with adipose tissue flaps seemed to have good results, but a case of spontaneous closure was also described [6,7]. Hakobyan *et al.* described spontaneous bone neoformation following a segmental mandibulectomy without bone reconstruction in a former drug addict [8].

From a biological point of view, the C-terminal telopeptide (CTX) assay would be a predictive factor for the visual identification of a sequestrum during surgery: a high rate would be correlated with the formation of a sequestrum, a reflection of an increased bone turnover. On the contrary, significantly lower



**Fig. 1.** Flow chart of research.

levels are found in patients with non-sequestered ONJ (Osteonecrosis of the jaw). These variations are evidence of the anti-resorption effect of krokodil as well as phosphoric necrosis [9].

The proposed treatment is the result of the authors' personal reflection following retrospective work. In this context, these results should be considered with caution, in the absence of recommendations from studies with better methodologies.

Krokodil is the street name given to the clandestinely synthesized desomorphine, as its users develop a scaly skin appearance, similar to that of crocodiles [4]. The skin disorders are manifested by ulcers at injection sites, sometimes accompanied by phlebitis with an indurated and desquamative appearance of the epidermis. Spontaneous necrosis at injection sites has been reported. Further, muscle and cartilage involvement leading in some cases to the amputation of affected limbs has been described [10]. These results are due to the different ingredients used in producing the drug (sulfur, hydrochloric acid, solvents, etc.) and are not related to the opioid effect of desomorphine [11].

The clinical manifestations of krokodil are often systemic because of its intravenous administration. Grund *et al.* described several cases of organ failure including myocardial infarction, septicemia, pneumopathy, and

infectious meningitis [4]. Co-infections with human immunodeficiency virus (HIV) and hepatitis A, B, and C virus are common, linked to the use of contaminated injection devices [12]. There is a higher prevalence of HCV than HIV among consumers [13], probably related to higher transmissibility.

The maxillomandibular lesions are mainly described Poghosyan and co-workers [5–9] and are marked by the occurrence of aseptic osteonecrosis. According to Ruggiero *et al.*, osteonecrosis is linked to high exposure to red phosphorus [14], a ubiquitous component of clandestinely synthesized desomorphine. More often than not, when the patient reveals drug intake during medical history interview, etiological diagnosis becomes possible.

Bisphosphonates, in which phosphate groups bonded to a carbon atom constitute the basic structure of the drug, can cause OCN in their own capacity. Similarly, phosphorus present in krokodil leads to an alteration of bone metabolism at the cellular level through apoptosis induced by osteoclasts [15]. This hypothesis seems consistent with the pathology of osteonecrosis by exposure to phosphorus found in workers who came into contact with this substance (match industry in the nineteenth and twentieth century) [16].

**Table I.** Studies included in the literature review.

Authors	Title	Article type	Objective	Materials and methods	Results	Conclusion
Poghosyan <i>et al.</i> [5]	Surgical treatment of jaw osteonecrosis in "Krokodil" drug addicted patients	Retrospective study	To propose a therapeutic management of maxillo-mandibular osteonecrosis induced by krokodil	n = 40 patients (M = 39, F = 1) age = 41 ± 1 year 11 maxillary necroses, 21 mandibular necroses, 8 maxillomandibular necroses Protocol put in place: 1 – Addiction weaning 2 – Necrosectomies with 0.5 cm margins associated with local flap closure	- 100% (n = 11) of success of maxillary necrosectomies - 23% (n = 8) of recurrence in mandibular necrosectomies - 38% (n = 8) of oral-sinus communications after maxillary surgery	According to this study, surgery combined with drug withdrawal is the treatment of choice for krokodil-induced necrosis.
Hakobyan <i>et al.</i> [6]	The use of oral adipose tissue in "Krokodil" drug-related osteonecrosis of the maxilla	Retrospective study	Describe the value of reconstructing substance losses associated with krokodil-induced MON surgeries	n = 6 patients (M = 6, F = 0) age = 42.7 +/- 2.4 years Stage 3 Maxillary Necrosis (AAOMS) After 1 month of weaning, excision of the necrotic tissue and closure of the sinus fundus using flaps made from adipose tissue from the cheek and mucoperiosteal local flaps.	- 100% (n = 6) of first-line closure without postoperative complication	Radical debridement of necrotic bone associated with partial sinusotomy and transposition of an adipose fat flap of the cheek can be used as an effective and predictable means of treating posterior maxillary osteonecrosis induced by krokodil
Hakobyan and Poghosyan[8]	Spontaneous bone formation after mandible segmental resection in "Krokodil" drug-related jaw osteonecrosis patient: case report	Case report.	Presentation of a necrosectomy case study	48-year-old patient with maxillo-mandibular osteonecrosis induced by taking krokodil for 1.5 years, weaned for 8 months. Performing a maxillary sequestrectomy and a partial resection of the mandible without reconstruction.	Postoperative follow-up over three years shows bone neo-formation in place of mandibular resection.	Spontaneous bone formation is possible after segmental mandibular resection in a patient with weaned osteonecrosis.

**Table I.** (continued).

Authors	Title	Article type	Objective	Materials and methods	Results	Conclusion
Hakobyan <i>et al.</i> [9]	C-Terminal Telopeptide Level in "Krokodil" Drug-Related Jaw Osteonecrosis Patients.	Retrospective study	To determine whether there is a relationship between serum CTX and sequestration in patients with krokodil-induced MONs	n = 17 patients (M = 17, F = 0) age 40.65 ± 2.1 years Patients weaned for 5.1 ± 1 month (1 to 15 months) Divided into two groups: - Group 1: n = 9 patients without evidence of sequestration -Group 2: n = 8 patients with osteonecrosis with sequestration	Group 1 showed low CTX levels illustrating the inhibition of turnover induced by the krokodil anti-resorption effect. Group 2 showed significantly higher CTX levels with a positive correlation between CTX level and the presence of a sequestrum.	According to this study, a high level of CTX would indicate increased bone turnover. This would allow the creation of a demarcation zone and the formation of a sequestrum.
Hakobyan and Poghosyan [7]	Spontaneous Closure of Bilateral Oro-Antral Communication Formed After Maxillary Partial Resection in "Krokodil" Drug-related Jaw Osteonecrosis Patient: Case Report.	Case report.	Presentation of a necrosectomy case study	40-year-old patient with maxillary osteonecrosis induced by krokodil for 1.5 years, weaned for 5 months. Performing resection of the necrotic bone with margins at 0.5 cm affecting all the alveolar processes, the hard palate, the sinus and the floor of the nasal fossae. Oral-nasal and oral-sinus communication could not be closed without tension.	Postoperative control at 2 months shows bilateral spontaneous closure of naso and bucco-sinus communication.	Spontaneous cicatrization of postoperative oral-antral communication is possible despite the absence of first-line closure in a weaned patient.

The risk factors for triggering these necroses would then be the same as those for OCN. Local factors play a major role: dental extraction, the presence of dental or periodontal infectious foci, and poorly adapted prostheses. [17]. In consumers of krokodil, as in the case of our patient, osteonecrosis of the maxilla arises in 92.3% of the cases of avulsion of one or more teeth [5].

There are also general factors to be taken into account: smoking cessation and the management of comorbidities (in this case hepatitis C) are necessary [17].

In Georgia, the country of origin of our patient, krokodil is the most widely spread opioid [18]. Krokodil consumers from these countries emigrating to other European countries including France would be the patients of krokodil-induced toxicity being reported in these countries [19]. The average survival rate of an active consumer is 1–2 years. Therefore, the stage 0 and 1 of OCN probably remains under-diagnosed. Further, disease monitoring remains random in these populations and low life expectancy does not allow for the observation of more advanced stages [20].

## Conclusion

There are a number of etiologies for osteonecrosis outside the context of radiotherapy, intake of bisphosphonates, and administration of bone resorption inhibitors. Unfortunately, in the case of krokodil, the heterogeneity of its manufacturing methods and its high addictive nature make it difficult to wean and to analyze the pharmacokinetics of continued use, which are essential elements in the management of patients with krokodil-induced osteonecrosis.

In view of the current literature, surgical therapy associated with weaning appears to be the most appropriate treatment, without being able to rule out addiction or necrotic relapses. In the absence of recommendations, prospective studies are needed.

## Conflict of interest

The authors declare that they have no conflicts of interest in relation to this article.

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