Case Report

Nicolau syndrome: An avoidable iatrogenic complication leading to disabilities

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Nicolau syndrome is a rare complication following intramuscular injection of various medications. The pathophysiology of the condition remains complex. However, corticosteroids are responsible for vasospasm and ischemic necrosis. The objective of this report was to demonstrate the often-preventable nature of this debilitating drug-induced iatrogenesis. Two cases of preventable Nicolau syndrome in children aged 2 and 6 years following an intramuscular injection of dexamethasone causing leg amputation in a context of misuse were notified by the pediatric surgery department of the University Hospital of Bouaké, Côte d'Ivoire. Although very rare, Nicolau syndrome, sometimes preventable, is responsible for numerous serious complications resulting in after-effects.

Key words: Nicolau syndrome, dexamethasone, preventability, disability, iatrogenicity

INTRODUCTION

Nicolau syndrome (SN) or livedoid dermatitis or drug skin embolism is a rare and poorly understood iatrogenic condition of tissue necrosis post-drug injection (Bouvy and Fossoul, 2019). Classically associated with intramuscular injections, it can develop after subcutaneous or other parenteral administration of drugs, especially glucocorticoids (Bouvy and Fossoul, 2019).

The pathophysiology of NS remains complex. However, corticosteroids cause a blockage of prostaglandin synthesis responsible for vasospasm and ischemic necrosis. In general, this condition quickly progresses to necrosis with possible ulceration (Bouvy and Fossoul, 2019). Early diagnosis determines the treatment and prognosis of the patient (Yapo et al., 2021). Venous insufficiency and repeated injections in the same location constitute important risk factors (Bouvy and Fossoul, 2019; Yapo et al., 2021). This condition seems common with glucocorticoids frequently most often linked to a technical fault in injection, delay in diagnosis and avoidable vital and functional prognosis (Bouvy and Fossoul, 2019). Also, in our context of overload of activity, the evolution is often severe. The objective of this case report was to demonstrate the preventable and disabling nature of iatrogenic complications following
intramuscular injection of glucocorticoids in order to raise awareness among health professionals.

**CLINICAL CASES**

Two clinical pharmacovigilance observations were reported by the pediatric surgery department of the University Hospital Center (CHU) in March 2023. Case No. 1: Patient KAB IS, aged 2 years, with no particular history and unknown vaccination status, was admitted on 03/11/2023 to the pediatric surgery department for painful swelling of the right thigh.

He presented with post-traumatic pain in the left knee for which an intramuscular injection (anterior surface of the right thigh) of dexamethasone (dose not specified) was administered for analgesic purposes. Approximately ten hours after the injection (03/08/2023), painful swelling of the ipsilateral thigh occurred. On physical examination, the patient was conscious with apparent good general condition. Locally, there was swelling of the right lower limb, predominantly the thigh, with exquisite pain on palpation. The adjacent skin was slightly erythematous with skin necrosis of the leg and foot. The sensitivity and motor skills of the limb were abolished as were the popliteal, posterior tibial and pedal pulses.

Biological assessment revealed hyperleukocytosis at 22,000 elements/mm³ with a predominance of polymorphonuclear neutrophils (75%). The sedimentation rate was accelerated in the 1st and 2nd h by 34 and 45 mm, respectively. The C-reactive protein (CRP) increased to 48 mg/L. A collapse in prothrombin time (55%) and normal blood sugar (0.80 g/L or 4.44 mmol/L) were observed. Renal assessment was normal. Doppler ultrasound of the arteries of the right lower limb showed abolition of flow in the popliteal artery. The diagnosis of dry gangrene complicating Nicolau syndrome was made.

A transfemoral amputation (upper 1/3 and middle 1/3 junction) was carried out as well as antibiotic therapy consisting of ceftriaxone 1 g × 2/day via DIV, metronidazole 250 mg × 3/day, antitetanus serotherapy 750 IU subcutaneously, and Perfalgan® (paracetamol) 400 mg × 3/day infusion. The postoperative course was uneventful. The French imputability method found scores I5 (C2S3), B2, and NI2.

Case No. 2: Patient CIS SE, aged 6 years, with no particular history and unknown vaccination status, was admitted on 03/28/2023 to the pediatric surgery department for painful swelling of the right foot. He presented with chickenpox in the state for which an intramuscular injection (anterior surface of the right thigh) of dexamethasone (dose not specified) was administered for anti-allergic purposes. Approximately eight hours after the injection (03/25/2023), painful swelling of the ipsilateral thigh occurred with relative functional impotence of the limb. On physical examination, the patient was conscious with apparent good general condition. There was swelling of the right thigh with exquisite pain on palpation. The adjacent skin was warm with cyanosis of the leg and foot. The sensitivity and motor skills of the leg as well as the pedal and posterior tibial pulses were abolished. The biological assessment revealed leukocytosis of 15,000 elements/mm³ with a predominance of neutrophils (97%). Renal assessment, blood ionogram, blood sugar (0.95 g/L or 5.3 mmol/L), and prothrombin (PT) level were normal. Doppler ultrasound of the limb arteries revealed abolition of arterial flow from the lower 2/3 of the tibial arteries. The diagnosis of dry gangrene complicating Nicolau syndrome was made. A transtibial amputation was carried out as well as antibiotic therapy consisting of ceftriaxone 1 g × 2/day via DIV, metronidazole 250 mg × 3/day, antitetanus serotherapy 750 IU subcutaneously, and Perfalgan® (paracetamol) 400 mg × 3-day infusion. The postoperative course was uneventful. The French imputability method found scores I5 (C2S3), B2, and NI2.

**DISCUSSION**

Both observations report a rare complication following an intramuscular injection of dexamethasone, a glucocorticoid, in two children with no previous history. These were two cases of Nicolau syndrome, characterized by the complication of dry gangrene requiring amputations of the affected limbs. The delay in diagnosis could explain this evolution towards necrosis (Yapo et al., 2021). The importance of diagnostic delay is highlighted in several other syndromes and diseases such as Ixemark syndrome (Jamila et al., 2015), fetal alcohol syndrome (Palmer and Paley, 2024), shaken baby syndrome (Laurent-Vannier, 2018), and aganglionicism (Hidouri et al., 2017). The positive diagnosis of Nicolau syndrome is essentially clinical, based on questioning, evolving in 3 phases (initial, acute, and necrotic) with a notion of recent injection and the normality of serological and coagulation assessments (Bouvy and Fossole, 2019). Histopathology reveals ischemia, necrosis, inflammation, intraluminal microthrombi, or even hemorrhagic areas (Bouvy and Fossole, 2019). This syndrome is more common in the pediatric population, mainly in children under 3 years old (Kýlić et al., 2014). The gluteal region is frequently affected, and lesions of the shoulder, thigh, ankle, knee, thorax, and abdomen have also been described (Yapo et al., 2021). In our case, the location is the lower limb. Another common and striking point of these incidents is the misuse of dexamethasone in its indication and in the way of its administration. Indeed, this medication was used in our cases respectively for their analgesic and anti-allergic effect. These indications are specific to corticosteroids, to which are added the immunomodulatory properties (Claire, 2012).

However, in acute pain, it would be recommended to use paracetamol or non-steroidal anti-inflammatory drugs...
by the digestive route (oral or rectal) at medium doses in the absence of contraindications such as peptic ulcer, asthma, severe hepatocellular or renal failure, or infection (Claire, 2012).

As chickenpox is a viral infection, corticosteroids were contraindicated in our context (Karabinta et al., 2018). In addition to this locoregional complication, high-dose or long-term corticosteroids promote the occurrence of shingles in the immediate aftermath of chickenpox through immunosuppression (Karabinta et al., 2018). The classic absolute contraindications are in particular, all progressive infectious conditions not controlled by treatment, especially certain viruses (hepatitis, herpes, chickenpox, shingles), and psychotic conditions (Muster, 2005). Corticosteroids are symptomatic medications and in no case provide etiological treatment (Muster, 2005).

Before any prescription of an anti-inflammatory, a careful and individualized analysis of the benefit/risk ratio is desirable. Also, the efficacy of oral and intravenous forms is comparable, even in traumatic emergencies and in anesthesiology (Qinquin et al., 2022); this would have enabled enteral forms to be preferred. Corticosteroids should be prescribed in accordance with the indications given in the summary of product characteristics, taking into account the patient's condition and terrain. These prescriptions outside of marketing authorization (AMM) could be linked to difficulties in access or availability of oral forms in rural areas and for concerns about good compliance. The analysis of the causes of avoidable iatrogenics made it possible to specify that 22% of the 334 errors were due to a lack of knowledge about the drug (interactions, precautions for use, compatibility, rate of administration) and 14% were due to a lack of knowledge of patient data (history, allergy, etc.) (Ankri, 2002). In order to reduce these technical defects, capacity building should be organized by health authorities for healthcare providers. Also, it would also be necessary to provide oral forms of essential drugs of first necessity in hospital pharmacies or drug sales depots in rural areas.

The delay in treatment linked to a delay in diagnosis could be explained by this evolution towards serious forms of gangrene or even superinfection and septicemia. Suspicion of sepsis with a cutaneous portal of entry was raised in our patients by the inflammatory syndrome (Casado-Flores, 2003). This would be linked to insufficient aseptic measures at the injection site and/or to a reduction in cellular and humoral immunity caused by the drug. The frequency of staphylococcal and streptococcal germs is high. In this context, secondary staphylococcal infections are effectively treated with antibiotics (Kylýç et al., 2014). Rapid administration of anticoagulant (low molecular weight heparin), phosphodiesterase inhibitor (cilostazol), and vasodilator could improve functional prognosis (Bouvy and Fossooul, 2019).

Amputation was necessary given the severity and evolving stage of the clinical picture (Yapo et al., 2021; Ramin et al., 2023). This therapeutic approach is essential to avoid rapid progression to serious complications such as septic shock and death (Yapo et al., 2021; Ramin et al., 2023). Aseptic measures must be strictly respected when injecting parenteral products. Skin superinfection justified the implementation of dual antibiotic therapy in therapeutic management (Kylýç et al., 2014). The diagnosis of this drug-induced iatrogenicity is based on pharmacovigilance accountability. Referring to the updated French method (Armon et al., 2011), the chronological criteria were in favor of the drug in view of the rapid onset of the syndrome after the injection, the evolution being irreversible. There was no readministration of the product.

From a semiological point of view, the symptomatology is suggestive of the role of the drug due to its pharmacological properties. Corticosteroids inhibit prostaglandin synthesis by inhibiting cyclooxygenase. Ischemic necrosis occurs after vasospasm is induced by the suppression of prostaglandin by the drug (Luton et al., 2006; Bouvy and Fossoul, 2019; Yapo et al., 2021).

Dexamethasone was a risk factor due to its physicochemical characteristics (oily substance) (Bouvy and Fossooul, 2019). Intravenous injection of these lipophilic drugs causes physical obstruction of blood vessels. Nicolau syndrome has also been reported with the administration of various other medications such as penicillins, local anesthetics, antipsychotics, vaccines, corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) in the literature (Tabor et al., 2017; Bouvy and Fossooul, 2019). In our case, only normal blood sugar levels and the absence of elevated blood pressure figures make it possible to rule out a non-drug cause, and the biopsy can guide the diagnosis. However, carrying out a thrombophilia assessment (activators and inhibitors of coagulation), D-dimer, hemoglobin electrophoresis, and lipid profile would have made it possible to rule out pre-existing blood disease or peripheral arterial disease (atherosclerosis). Although a causal link has been established between the use of corticosteroids and Nicolau syndrome, it is also possible that the paramedical act was responsible for the event, given the homolateral location of the lesion. This adverse event associated with care (AEAS) could be linked to poor execution of the injection technique due to error or lack of experience. The pathophysiology of Nicolau syndrome is unclear. However, several theories of the pathogenesis of the condition have been suggested, including the notion of necrosis due to vasospasm induced by stimulation of the sympathetic nerve, inadvertent injection into an artery, responsible for thromboembolic occlusion of the blood vessel, and vascular or perivascular injection producing marked inflammation and progressive necrosis of the intima leading to destruction of the arterial wall and
subsequent necrosis (Kylįč et al., 2014; Bouvy and Fossoul, 2019). In our observations, Nicolau syndrome was a potentially avoidable complication. Prevention aimed at evaluating the injection technique must be the mainstay of treatment. Z-track injection (tracking and subsequent release of the skin to prevent reflux of the drug into the skin), use of long needles (to reach the muscle) or an auto-injector (to control the depth of the needle), choosing the outer upper quadrant of the buttocks (fewer blood vessels), and aspiration before injection (to ensure the needle tip is not in a vessel) have been recommended (Tabor et al., 2017). Where possible, alternative ways of administration such as oral or rectal administration should be considered.

Conclusion

This report highlights Nicolau syndrome evolving into gangrene of the lower limb, ultimately leading to amputation. This rare condition was preventable and is linked to misuse and a delay in diagnosis. Knowledge of this condition and preventive measures can considerably avoid this iatrogenic complication.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

REFERENCES


