

Nicolau Syndrome: A Rare Event Following Intramuscular Diclofenac

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Abstract

Nicolau Syndrome (Embolia cutis medicamentosa) is a rare complication occurs after parenteral administration of drugs. It has been reported in association with intramuscular, intravenous or rarely subcutaneous injections. We hereby report a case of Nicolau Syndrome in a 60-year-old male patient.

Key Words

Nicolau Syndrome, Embolia cutis medicamentosa, Parental administration

Introduction

Nicolau Syndrome is a rare cutaneous adverse reaction which occurs at the site of injection (intramuscular, intravenous, or rarely subcutaneous) of certain drugs (*Table 1*) that may lead to ischemic necrosis of skin, soft and muscular tissues (1). Nicolau Syndrome is characterised by immediate intense pain post injection at the site and significant red to purplish discoloration of the overlying skin with or without a reticulate pattern. Although the skin necrosis heals with time and supportive care it leaves permanent disfiguring scar. Despite many hypothesis was proposed, the exact pathophysiology of this rare condition is still unknown. Of such hypothesis: Vasospasm secondary to needle prick (Angiospasm), embolization due to injected material (Embolism) or mechanical pressure exerted by the material placed around the blood vessel (Thrombosis) were well elucidated(2).

Case Report

We present here a case of 60-year-old male patient who was admitted to in-patient ward of Department of Orthopaedics at JSS Medical College Hospital, Mysuru which is an 1800 bedded tertiary care teaching hospital, with the complaints of severe pain in the right gluteal

region. On examination patient gives a history of generalised body ache for which he was administered with 2mL (75mg) diclofenac through intramuscular at an unknown local clinic. Following this injection patient developed severe pain at injection site which was characterised as sudden in onset radiating towards right lower limb, continuous and moderate in intensity. Patient also complained that he had difficulty in walking ever since then. The intensity of the pain was 9 on 10 with VAS (Visual Analog Scale) (3). Within eight hours of injection, swelling, pallor and bluish black discoloration of skin were noticed. As symptomatic treatment, the patient was prescribed with Ceftriaxone (1000mg) + Sulbactam (500mg) for infection, Pregabalin (75mg) + Methylcobalamine (750mg) for radiculopathy, Injection tramadol (100mg) SOS, Injection paracetamol (100mg) and topical gel for pain.

The reaction of the injected site on day 1 is shown in *Figure 1*. On the second day the patient complained that the pain has extended upto the left ankle. On third day, the injection site turned dark red with a visible haemorrhagic patch which is shown in *Figure 2*. The patient was continued with the same treatment. By day five, erythematic area reduced however leaving a

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Table 1: List of Drugs that are known to cause Nicolau Syndrome with different routes of administration of injections (5)

Route of administration of injection	Medication injected
Intramuscular	Vitamin K
	NSAIDs
	Hydroxyzine
	Vaccination
	Bismuth
	Penicillin G
	Benzathine penicillin
Intravenous	Polidocanol
Intra-articular	Glucocorticoid
Subcutaneous	Pegylated interferon-alpha.



Figure 2



Figure 1



Figure 3

progressive dark discoloration of skin which is shown in *Figure 3*. On the note of patient's past medical history, he had received anti tubercular medications for a year four years back. No history of trauma, type 2 diabetes mellitus or hypertension.

On physical examination upon admission, the patient had tenderness on the right gluteal region extending to femoral region. However, there was no rise in temperature and swelling. In a vain attempt of aspiration of swollen site, 18 G needle was employed and no aspirate was aspirated. The patient was continued to be afebrile throughout of hospital stay.

The patient was checked for complete blood count, erythrocyte sedimentation rate and CRP for any infection. Based on the laboratory reports Erythrocyte sedimentation rate was high (40mm in 1hr) which indicates there is inflammation at the injection site. He was also suggested for Ultrasound Surface Scan which gave the impression

of mildly bulky and edematous right gluteus Maximus muscle.

Discussion

It was first described by Freudenthal and Nicolau in 1924 as "Nicolau syndrome presents with pallor, owing a local reflex vasospasm, and pain, rapidly followed by erythema, haemorrhagic patch, blistering and variable degree of necrosis" (4). Nicolau syndrome has been reported with the administration of various other drugs ... *Table 1* which were found in the literature (5). It is commonly seen in paediatric population, in whom the phenomenon of arterial embolization is more likely to occur owing to smaller size of vascular segments.

Injection Diclofenac is a Non-Steroidal Anti-Inflammatory Drug (NSAIDs) that reduces pain, decrease fever, prevent blood clots and in higher doses, decrease inflammation. NSAIDs act by inhibiting cyclo-

oxygenase (COX)-1 and COX-2, thereby inhibiting prostaglandin synthesis and it may also inhibit neutrophil aggregation/activation, inhibit chemotaxis, decrease pro inflammatory cytokine level (6). As a part of altered mechanism if COX-2 is blocked there are chances of inflammation due to COX-1; but this does not explain the necrosis of tissues which occurred in this patient. The most commonly described differential diagnoses for NS are cutaneous cholesterol emboli, which usually occur in the elderly with a history of atherosclerosis (7).

A well-defined standard therapy for Nicolau syndrome was not found and treatment can vary from supportive care for pain management to extensive surgical debridement based on severity of necrosis. Administration of appropriate antibiotic regimen may be considered when there is evidence of infection. Since cell damage may be reversible in the acute phase of Nicolau syndrome, starting early supportive care prevents tissue damage. CT scan or MRI are helpful to determine the extent of damage to recognize the degree of fat necrosis to prevent inadequate debridement and poor wound healing (8).

To minimize the risk of Nicolau syndrome, the following recommendations may be helpful:

- To minimize or prevent subcutaneous irritation, Z-track IM injection of irritant medications is suggested;
- Sufficiently long needle should be used to reach the muscle for IM injection. A 2 or 3 and 1.25- or 1.45-inch needle is recommended for a 90 kg and 45 kg patient, respectively;
- The upper outer quadrant of the buttock is the best site for IM Injection (fewer large blood vessels);
- To protect the blood vessels, aspirate the needle before IM injection;
- The volume of each IM injection should never be more than 5 mL in Z-track injection;
- Rotate the injection site for the patient requiring repeated or multiple injections (3-5).

There are cases of Nicolau syndrome in which buttocks are involved, it has also been described in the shoulder, thigh, knee and ankle. In this case Nicolau syndrome occurred immediately after IM injection of Diclofenac and presented as sudden pain radiation towards lower limb, swelling, pallor and bluish black discoloration of skin was noticed. Patient was conservatively managed. The initial diagnosis of this allergic reaction was made as gluteal abscess which later on was confirmed as Nicolau syndrome.

Conclusion

Nicolau Syndrome is a very rare condition caused by improper administration of parental drugs or injectables. Hence to prevent such lethal condition the health care professionals should be educated and aware of injection techniques. According to the literature the etiopathogenesis of this condition is idiopathic and there are lacunae in the evidence-based management of such rare condition, where systemic antibiotics, surgical debridement and cosmetic surgery are the only choice in the management. However, all the health care professionals should be cautious on administering injectables to prevent such adverse unwanted reactions which compromise patient's safety.

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