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Review Article

Nicolau Syndrome – "Penalty for the Pain Killer:" A Review Article

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Abstract

Nicolau syndrome, also called embolia cutis medicamentosa (ECM), is an infrequent complication following intramuscular and intra-articular injection of various drugs. This rare entity is characterized by severe pain and erythematous-ecchymotic reticular lesions, which in many cases lead to necrotic ulcers and scarring. Clinicians must be cautious in the use of proper injection procedures, including appropriate needle length, to minimize complications.

Key words: Diclofenac, Intramuscular injections, Necrosis, Nicolau syndrome

INTRODUCTION

Nicolau syndrome, also called embolia cutis medicamentosa, consists of necrosis of the skin with a livedoid pattern following injections of several drugs, such as local anesthesia, antihistamine (promethazine), Vitamin B complexes, diclofenac sodium, ketoprofen, piroxicam, corticosteroids, diphtheria, tetanus, pertussis vaccine, and meperidine-phenylbutazone, corticosteroids, local anesthetics, and antibiotics. It is due to intramural or periarterial injection of the offending drug with subsequent arterial spasm and cutaneous necrosis. While the injection is being administered, there are burning and stabbing pain. The first visible sign is pallor, followed by bluish-red, net-like erythema. Within a few days, the area becomes hemorrhagic and forms a necrotic eschar. Eventually, the ulcer heals leaving behind an atrophic scar.

CASE REPORT

A 69-year-old male patient who is a known case of COPD came with the complaints of pain and purplish discoloration over left gluteal (3 × 4 cm), left iliac fossa (12 × 8 cm) following intramuscular injection of diclofenac for joints pain from a general practitioner 1 week back. On examination, peripheral pulses of lower limbs were feeble and arterial Doppler showed diffuse atherosclerosis. Blood investigations showed severe anemia (Hb – 5%) for which blood transfusion was done, leukocytosis (20,100 cells/cumm). Debridement was done and tissue was sent for culture and sensitivity, HPE. The patient was treated with appropriate iv antibiotics and analgesics.

After 3 days of admission, the patient developed one more purplish discoloration over left anterior aspect of upper leg measuring 8 × 6 cm. Nicolau syndrome was suspected for which dermatologist opinion taken and followed their advice. Later, debridement and bone drill were done.

Bacteriological culture showed pseudomonas species which was sensitive to imipenem and was changed accordingly. Histology of the tissue showed fat necrosis and non-specific inflammation, mainly in the subcutaneous layer. Multiple surgical debridements (4 in total) and regular dressings were performed [Figures 1-4].

DISCUSSION

Nicolau syndrome is a rare adverse reaction involving skin, subcutaneous, and even muscle tissue necrosis. It was first described in the 1920s as an adverse effect of bismuth salts routinely used for the treatment of syphilis. The phenomenon has been related to the administration of a variety of drugs, such as local anesthesia, antihistamine (promethazine), Vitamin B

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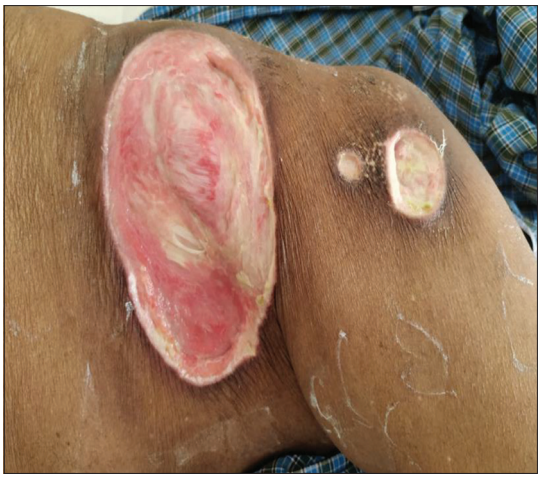

Figure 1: Ulcer over left gluteal and left iliac fossa after debridement

Figure 2: Newly developed purplish discoloration over left upper leg after 3 days of admission.

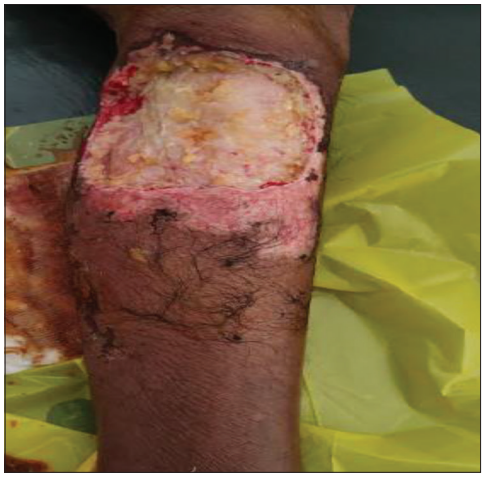

Figure 3: Debrided necrotic tissue over left upper leg

complexes, diclofenac sodium, ketoprofen, piroxicam, corticosteroids, diphtheria, tetanus, pertussis vaccine,

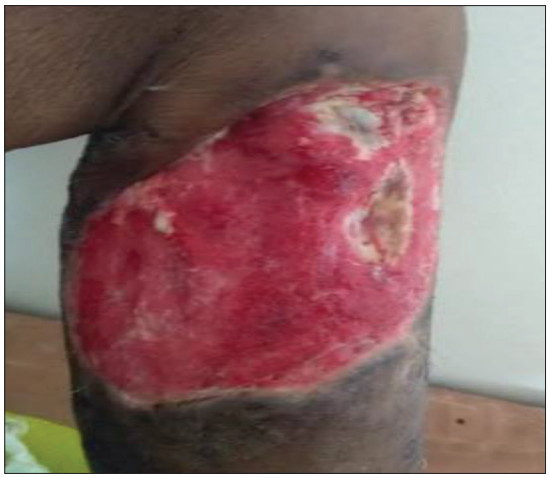

Figure 4: Ulcer over left upper leg after 3 weeks of regular dressing

and meperidine-phenylbutazone, corticosteroids, local anesthetics, and antibiotics.

From Table 1, the most common drug causing Nicolau syndrome is diclofenac. Moreover, common presentation is painful necrotic patch over injection site.

Typical findings are pain, erythema, or a hemorrhagic lesion immediately after the injection, with eventual progression to necrosis of the skin or soft tissue and of the muscle.[1]

In most cases, the prognosis of Nicolau syndrome is healing with remaining atrophic scars or pigmentation. In rare cases, however, it can cause complications such as hypoesthesia, paraplegia, sphincter deficiency, or sepsis.[1]

The pathogenesis of Nicolau syndrome is not clear but the most reasonable hypothesis is that of a vascular origin. Histologic examination of a few cases has revealed necrosis of eccrine glands with thrombosis of medium and small sized vessels of reticular dermis without vasculitis. Several theories exist: First, an intra-arterial, periarterial, or perinervous injection may produce intense local pain and a secondary vasospasm due to sympathetic nerve stimulation, thus leading to ischemia with subsequent muscular and/or cutaneous necrosis. Second, an inadvertent intra-arterial injection of solutions intended for intramuscular use may cause embolic occlusion of small skin arteries. This assumption is based on the histologic proof of bismuth in peripheral arteries of the affected skin areas in the original cases described by Nicolau. Third, vascular or perivascular injection may produce marked inflammation and progressive necrosis of the intima, leading to destruction of the whole arterial wall and subsequent necrosis of the skin. This inflammation has been described after intra-arterial

Table 1: Review of articles on drugs causing Nicolau syndrome and there clinical presentation

Author	Cases	Age/Sex	Drug	Clinical presentation
Corazza *et al.*	Case 1	62 years/M	Salicylate bismuth	Red cyanotic arborescent reticular areas and coarse flat bullae
	Case 2	24 years/M	Bismuth salts	Wide erythematous edematous area with purplish marbling
	Case 3	71 years/F	Diclofenac	Necrotic livedoid plaque
	Case 4	76 years/M	Ibuprofen	Wide indurated painful livedoid plaque
	Case 5	62 years/F	Diclofenac	Painful ecchymotic area
Kim *et al.*	Case 1	73 years/M	Diclofenac	Pain and redness with necrotic patch
	Case 2	79 years/F	ketoprofen	Pain and hardness with necrotic patch
	Case 3	36 years/M	Meperidine	Pain and erythematous lesion
Luton *et al.*	Case 1	36 years/M	Diclofenac	Wide indurated painful livedoid plaque
	Case 2	42 years/F	Penicillin G	Urticarial itchy erythematous plaques
	Case 3	29 years/F	Cyanocobalamin	Erythematous edematous plaque with a purpuric center
Lie *et al.*	Case 1	58 years/M	Diclofenac	Pain and patch of bruising over the injection site
Yaylacl *et al.*	Case 1	30 years/M	Diclofenac	Irregular edged, ecchymotic, irregular, plaque type skin lesion

M: Male, F: Female

injection of phenylbutazone and other drugs previously reported to cause Nicolau syndrome. Fourth, experimental animal models have reproduced the syndrome when a periarterial injection perforated the arterial wall, leading to thrombosis and subsequent necrosis. Fifth, drugs injected by aqueous solution may precipitate in crystals with consequent tissue damage. Sixth, iodine sclerosing substances may cause an arteriovenous shunt at the level of the saphenofemoral juncture, thus causing subsequent skin damage.[2-4] The unifying feature of all these mechanisms is occluded peripheral "arterial" vessels, either through true emboli or through vessel damage and then occlusion.[2]

From the experience of Corazza *et al*., even prompt therapy was often inadequate as the tissue damage is not reversible and develops rapidly. The well-known Lesser's sign (to inject the drug only after having aspirated with the syringe) may not prevent Nicolau syndrome but must still be recommended as it is only sure way to avoid intravascular injection of an intramuscular drug.[4]

Adequate debridement is critical to the management of Nicolau syndrome. Computed tomographic scan or magnetic resonance imaging is helpful to define the extent of the lesion. Failure to recognize the extent of fat necrosis and poor perfusion in the wound leads to inadequate debridement and poor wound healing.[5]

Additional treatment includes antibiotics, wound dressing, skin graft, and flap reconstruction; extensive scarring is usually inevitable.

There is no specific therapy for Nicolau syndrome other than prevention. Intramuscular injections should be performed only after having aspirated with the syringe to ensure extravascular injection of the drug. Ruffieux *et al*. used vasoactive medications in two of three patients with Nicolau syndrome and noted a rapid response to treatment with complete healing and no scarring or functional impairment at 4 weeks.[3] In addition, the preferred site for the injection is the upper outer quadrant of the gluteal region, which has fewer large blood vessels.[6]

While the precise pathogenesis of Nicolau syndrome has not been determined, clinicians should be aware of such rare but serious complications of the intramuscular injection of common agents such as NSAIDs and follow proper procedures.

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