

Extensive Nicolau Syndrome Following Intramuscular Injection of Paracetamol in a Patient Who Is HIV Positive

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Abstract

Nicolau syndrome (NS) is a type of adverse skin reaction occurring after parenteral drug injection. In certain conditions, it can cause ischemic necrosis of the skin and the underlying adipose tissue. The actual cause of NS is not clear though inflammation, vasospasm, and thromboembolic occlusion of blood vessels have been proposed. In this case presentation, we report an interesting case of a 30-year-old man who turned out to be human immunodeficiency virus (HIV) positive on investigations, developed extensive purpuric lesions of his skin on left buttock and then spread to the trunk and shoulders after receiving intramuscular injection of paracetamol. With a suggestive history and further supported by clinical examination, a diagnosis of NS following injection of paracetamol was made. Though NS is considered to be rare, at times it can be devastating. Being a common procedure in the life of a health-care professional, the awareness regarding this entity is very essential. Despite intense medical literature search in, we could not find a single report of NS after intramuscular injection of paracetamol in a patient who is HIV positive, thus obliging this communication.

Keywords: Intramuscular injection, Nicolau syndrome, paracetamol, purpura

INTRODUCTION

Nicolau syndrome (NS) is a rare complication arising from an inadvertent parenteral drug injection. The first case of NS was published in 1925 in a patient who was suffering from syphilis and who received injection of bismuth via intramuscular (IM) route in the gluteal region.^[1] The sequence of events, which usually occurs during NS, includes pain and redness at the site of injection followed by a purpuric patch and in some cases necrosis of skin and subcutaneous tissue.^[2] Within a few days, the skin becomes hemorrhagic and forms a necrotic eschar and eventually heals leaving behind an atrophic scar. The exact mechanism leading to NS is unknown; however, an inadvertent drug injection into an artery, which causes the spasm of the injected artery and the consequent formation of emboli have been suggested as the pathophysiological events.^[3] The various drugs that have been implicated in the causation of NS include nonsteroidal anti-inflammatory drugs, corticosteroids, local anesthetics, antibiotics, recombinant interferons, sedatives, vaccines, tumor necrosis factor-alpha antagonists, and immunomodulators.^[4,5] In

this article, we present a unique case of NS developing after IM injection of paracetamol in a patient who is human immunodeficiency virus (HIV) positive.

CASE REPORT

A 30-year-old man presented us with chief complaint of reddish-blue discoloration on the left buttock and trunk after receiving IM injection of paracetamol. He experienced pain while the injection was being administered and the pain continued after the injection, after which it regressed and was managed with the use of analgesics. The patient had a history of fever for the last 10 days for which he had taken some oral drugs, and an injection of paracetamol was prescribed to him by the local practitioner. Two days after receiving IM paracetamol in the left buttock, the patient developed

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Access this article online

Quick Response Code:



Website:
www.jcasonline.com

DOI:
10.4103/JCAS.JCAS_53_18

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How to cite this article: Arif T, Dorjay K. Extensive Nicolau syndrome following intramuscular injection of paracetamol in a patient who is HIV positive. *J Cutan Aesthet Surg* 2018;11:136-9.

reddish discoloration at the injection site, which in a span of 2 days changed to reddish-blue color and spread to the left side of trunk, shoulder, and right shoulder and arm. History of any spontaneous bleeding from any orifice was not reported. History of any joint swelling or any episode of unconsciousness or abnormal body movements was not reported. On physical examination, his vitals were stable. Systemic examination was unremarkable. Cutaneous examination revealed large areas of nonpalpable ecchymotic patches involving left buttock reaching up to the right buttock, left side of trunk, shoulder, and arm and right shoulder, neck, and anterior chest [Figure 1]. On diascopy, the bluish discoloration persisted, confirming the purpura. Laboratory investigations revealed positive enzyme-linked immunosorbent assay for HIV, which was an incidental finding. Rest of his laboratory tests including platelet count and bleeding, clotting, and prothrombin

times were unremarkable. He was advised skin biopsy for histopathological examination in view of the extensive purpuric lesions with some lesions distant from the main site of injection and separated by areas of normal skin. However, consent for biopsy was not given. On the basis of history and a suggestive clinical examination, a diagnosis of NS secondary to IM injection of paracetamol was made. He was managed conservatively with oral diclofenac and topical histocalamine lotion. He was referred to HIV medicine department for further management of HIV. As no necrosis occurred in our case, the patient recovered fully in 4 weeks without any complication.

DISCUSSION

NS, which is also known by other terms such as “livedo-like dermatitis” and “embolia cutis medicamentosa,” is a



Figure 1: (A) Extensive purpuric patches over left thigh, buttock, left half of trunk, shoulder, and reaching up to the right buttock. (B) Purpuric patches over right shoulder, anterior chest, and neck. (C) Purpuric patches involving left side of abdomen

rare type of adverse reaction that occurs after parenteral (intra-arterial, IM, or rarely subcutaneous route) drug injection. Usually, the patients complain of pain around the injection site soon after injection. This is followed by the appearance of redness at the site of injection. Later, a bluish discoloration appears forming a hemorrhagic patch, which can break down leading to necrosis and ulceration.^[2] However, in our case, there were extensive purpuric lesions but fortunately no necrosis and ulceration occurred.

Kim and Chae^[6] reviewed the various drugs and vaccines related to NS. These include diclofenac sodium, ibuprofen, piroxicam, salicylate, ketoprofen, ketorolac, benzathine penicillin, bismuth, interferon β , penicillin G, gentamycin, meperidine, hydroxyzine, chlorpheniramine maleate, thiocolchicoside, glatiramer acetate, etanercept, naltrexone, lidocaine, vitamin K, calcium hydroxide, triamcinolone, cyanocobalamin (vitamin B₁₂), Trabit (dexamethasone, phenylbutazone, lidocaine, and salicylamide), diphtheria-pertussis-tetanus (DPT) vaccine, mesotherapy injections, and DPT-polio-Hib vaccine. Diclofenac sodium has been considered as the major drug responsible for NS.^[6]

We believe that it is probably the first case of NS developing after paracetamol injection in a patient who is HIV positive. NS in a patient who is HIV positive after subcutaneous injection of alpha interferon was reported by Rasokat *et al.*^[7] The extensive involvement in our case may be due to the associated HIV infection. But whether it is a true association or not, needs further reports and studies. Kim *et al.*^[8] reported a case of bilateral NS after uterine artery embolization for postpartum bleeding. Similarly, in our case, lesions also spread to the opposite buttock and contralateral shoulder.

Although the exact mechanism for NS is unknown, earlier it was thought that immunologic mechanisms, pH, or other properties of the administered drug and faulty injection technique are the causative factors. However, this hypothesis does not stand now in view of various experimental studies.^[9] An inadvertent IM injection into an artery leading to arterial spasm and consequent formation of emboli has been proposed as the possible mechanism.^[3] Another widely accepted hypothesis in the pathogenesis of NS was vessel damage, acute arterial thrombosis, and subsequent necrosis following paravasal injection of drugs. This hypothesis was supported by Guarneri *et al.*^[10] in their cases of NS following IM injection of ketorolac, tromethamine, and thiocolchicoside. Hence, the physiopathology of NS can be summarized as: (1) vascular or perivascular injection causing tissue inflammation and necrosis, (2) intra-arterial injection causing embolus formation culminating in occlusion of small vessels, (3) arterial spasm because of reactive sympathetic stimuli caused by intra-arterial injection, and (4) needle-induced mechanical trauma. The

leakage of drug around artery and neural space has been suggested as the cause of intense pain. Diclofenac as a cyclooxygenase inhibitor inhibits prostaglandin synthesis and causes vasoconstriction. So, pathogenetic mechanism of diclofenac in NS is also suggested by its vasospastic effect.^[11] In our case, the patient received injection in his buttock, later he developed lesions on the left side of trunk and shoulder and right shoulder and arm. On literature review, we also found similar cases where lesions spread to distant area from the initial injection site. Alyasin and Sharifian^[12] described a case where the initial injection site was left buttock; however, lesions gradually spread to the left leg, thigh, foot, and finally fingers. Similar cases were also reported by Memarian *et al.*^[13]

The diagnosis of NS relies mainly on history and clinical findings as no specific laboratory investigations are available for it. Skin biopsy is also noncontributory as thrombosis of small- and medium-sized arteries and a nonspecific inflammatory infiltrate and necrosis are reported.^[14]

Treatment options include control of pain, use of antibiotics, and dressings depending on the severity of the condition. Surgical methods employing debridement of necrotic tissue and skin grafting may be needed in severe cases. Radical excision of necrotic tissue is important because inadequate debridement leads to poor wound healing.^[14] Hence, computerized tomography scan or magnetic resonance imaging is needed to determine the extent of tissue involvement. There is a vital role of systemic antibiotics in its management. A conservative treatment employing pain control and debridement has been considered as the main therapy by Murthy *et al.*^[3] Because of the uncommon nature of disease and lack of clinical trials, a standard treatment regimen with proven benefit cannot be referenced. Supportive treatments such as anticoagulant, pentoxifylline, hyperbaric oxygen, and steroids have been attempted besides the aforementioned conservative methods.^[15,16]

NS is a complication that can be avoided or minimized. The injection needle that is used should be long enough to reach the muscle compartment. The Z-track injection technique should be followed. This is a method of IM injection into a large muscle using a needle and syringe and it can minimize or prevent NS.^[13] This technique of injection seals the medication deeply within the muscle and allows no exit path back into the subcutaneous tissue and skin. First, this is performed by displacing the skin and subcutaneous tissue, 1–1.5 inches (2.5–3.75 cm) laterally, by the nondominant hand, before injection and releasing the tissue immediately after the injection. Second, a long needle (long enough to reach the muscle) should be used. A patient weighing 90 kg requires a 5–7.5 cm (2- or 3-inch) needle and a 45-kg patient requires a 3.18 or 3.68 cm (1.25- or 1.45-inch) needle. Third, the injection should be applied in the upper outer quadrant of the buttock.

Fourth, before injecting medication, aspiration should be performed to ensure that no blood vessel is hit. Fifth, never inject more than 5 mL of medication at a single site when using the Z-track injection technique. Finally, if a larger dose of medication is needed or more than one injection is required, different sites should be chosen by the health-care professional.^[14,17]

CONCLUSION

NS is a rare, underestimated but preventable complication of an inadvertent parenteral injection. Proper injection technique and selection of suitable site for injection can prevent this complication.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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