INTRODUCTION

Nicolau syndrome (NS), also known as embolia cutis medicamentosa or livedoid dermatitis, is a rare cutaneous adverse drug reaction seen at the site of injection of some particular drugs. It was first reported by Freudenthal in 1924 and Nicolau in 1925 as an adverse effect of bismuth salts used in syphilis. Typically, this syndrome is clinically manifested by intense burning or stabbing pain at the site of injection and retiform hemorrhagic patches with or without vesiculations and ulceration with a variable degree of tissue necrosis. To the best of our knowledge, <50 cases of Nicolau syndrome have been reported in medical literature which occurred following intramuscular administration of diclofenac sodium. Here, we report a 26-year-old female typically presenting with pathognomic signs and symptoms of NS after taking intramuscular injection of diclofenac.

CASE REPORT

A 26-year-old female patient presented with intensely painful, well-defined bluish-black and hemorrhagic patches with few vesiculations, and denuded erythematous skin at some sites over the right gluteal region since two days. On probing into the detailed history, it was noted that four days back, she was given an intramuscular injection of diclofenac sodium into the right gluteal region for generalized body ache followed by local massage by a local health worker. On the next day, she felt pain along with reticular rashes and induration over the injection site. After 2 days, patient noticed multiple hemorrhagic patches associated with increasing burning pain. By the time, patient got admitted in the emergency department; lesions were extending to the intergluteal cleft and left buttock. Vesicles along with peeling of skin were also evident.

There was no history of trauma, snake bite, other medications, spontaneous bleeding from the gingiva or mucosa, or any other systemic illness. Local cutaneous examination revealed large well-defined, tender, necrotic purple hemorrhagic patches with vesiculations, peeling of skin, and impending ulceration on the right buttock extending into the sacrococcygeal region [Figure 1]. By the 6th postinjection day, cutaneous and subcutaneous tissue necrosis was evident, and color of skin turned black, however new vesicular eruptions ceased [Figure 2].

Rest of the cutaneous and mucosal examination was normal. There was no regional or generalized lymphadenopathy. All routine laboratory parameters including bleeding time and clotting time were within normal limits except slightly raised total leukocyte count (12,500 cells/µl) and mild neutrophilia. Serology for HIV 1 and 2, venereal disease research laboratory (VDRL), malarial parasite, and dengue virus were also nonreactive. General physical and systemic examination was unremarkable with all the vitals stable.
Considering the typical history, characteristic clinical presentation and the temporal association between administration of injectable drug and development of such characteristic cutaneous lesions, a diagnosis of “NS” was made. The condition was managed conservatively with surgical debridement and sterile dressings, and patient was kept on oral analgesics and antibiotics (cefuroxime and linezolid) for 7 days. The patient and his attendant were counseled about this condition and its course.

**DISCUSSION**

NS is a rarely seen iatrogenic fatal injection site cutaneous reaction characteristically manifested by pallor followed by pain, erythema, hemorrhagic patch, blistering, and variable degree of necrosis of dermis, subcutaneous tissue, and muscle.\(^3\) Apart from its historical description in syphilitic patients taking bismuth salts, it was also reported with many other drugs such as phenylbutazone, diclofenac, ibuprofen, Vitamins K and B complex, sulfapyridine, tetracycline, streptomycin, sulfonamide, lidocaine, phenobarbital, chlorpromazine, dexamethasone, trimethadione, diphenhydramine, interferon alfa, gentamicin, ketoprofen, influenza and diphtheria pertussis toxin vaccination after intramuscular, subcutaneous, intravenous, or intra-articular injections.\(^3\) Children younger than 3 years are more prone due to the smaller caliber of the vessels.\(^4\) Its etiopathogenesis is still unknown, but presumably, three factors may be responsible for NS: first is vasospasms leading to ischemia caused by sympathetic stimulation from the intra-arterial or periarterial injection of drugs. Second is due to inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory drugs induced cyclooxygenase inhibition. Third is the embolic occlusion caused by intra-arterially injected drug, especially lipophilic drugs.\(^5\)

Clinically, patients experience intense pain of burning or throbbing in character at the injection site followed by the development of well-defined purplish/bluish discoloration of the skin with angulated margins sometimes referred to as noninflammatory retiform purpura or livedoid rash.\(^1\)\(^-\)\(^3\)\(^-\)\(^6\) With progression, it may lead to the variable degree of necrosis of deeper tissues including muscles. Transient paralysis of the lower extremities has also been reported in one-third of the cases due to embolization of the medication, mainly due to ischemia of sciatic nerve.\(^6\)\(^-\)\(^7\) Sometimes, cold application for local pain relief may also facilitate the event of skin necrosis. The necrotic ulcer usually heals within few months with an atrophic scar. Ultrasonography of the skin and magnetic resonance imaging help in delineating the extent of damage. Late complications include contractures and deformities.

The differential diagnosis of NS chiefly includes cutaneous cholesterol emboli, vasculitis, and necrotizing fasciitis. Cutaneous cholesterol emboli are usually associated with severe atherosclerotic disease in the elderly patients, and vasculitis can be ruled out by its clinical course, systemic associations, autoantibody profile, and biopsy. Necrotizing fasciitis is the only entity which closely simulates NS and must be ruled out. Necrotizing fasciitis is a rapidly spreading postsurgical or traumatic infection of the subcutis and fascia due to anaerobes and symptoms are out of proportion to clinical signs with anesthesia of the involved region.\(^6\)\(^-\)\(^7\)

NS is an avoidable complication, and its management relies on the extent of the necrosis and early institution of nonsurgical conservative intervention. Wound debridement, dressings, analgesics, and antibiotics are a therapeutic mainstay.\(^6\)\(^-\)\(^8\) Skin grafting and flap reconstruction may be needed in cases with extensive tissue destructions. In the early stages, process of tissue necrosis can be averted by adding vasodilators such as pentoxifylline, hyperbaric oxygen, intravenous alprostadil, and heparin.\(^9\) To avoid this fatal condition, following precautions should be taken during injection:\(^9\)\(^-\)\(^10\)
1. A long (enough to reach muscle) needle should be used. A 90 kg patient requires a 2- or 3 inch (5–7.5 cm) needle and a 45 kg patient requires a 1.25 or 1.45 inch needle.

2. Injection should be applied in the upper outer quadrant of the buttock.

3. Aspirating the needle before injecting the medication should be performed, to ensure that no blood vessel is hit.

4. The health-care personnel should never inject more than 5 ml of medication at a time when using the Z-track injection method.

5. If more than one injection or larger dose is required or ordered, different sites should be chosen.

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Conflicts of interest
There are no conflicts of interest.

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