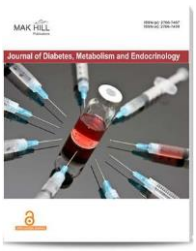

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Case Report

Nicolau Syndrome Following Intravenous Diclofenac Injection: A Case Report.

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Abstract: Background: Nicolau syndrome (NS), also known as embolia cutis medicamentosa, is a rare and potentially severe complication of injectable medications characterized by acute pain, vascular compromise, skin necrosis, and, in severe cases, tissue loss. Diclofenac is among the drugs most frequently implicated. Although the condition is usually reported following intramuscular injections, it can rarely occur following intravenous administration. ***Case Report:*** A 26-year-old woman presented with rapidly progressive blackish discoloration of the left forearm and distal fingers associated with severe pain and intermittent fever for one week. She had received an intravenous injection of diclofenac in the left cubital region for low backache. Approximately two hours after injection, she developed local skin changes that progressively evolved into extensive necrosis. Examination revealed patchy to diffuse necrotic areas with sharply demarcated, irregular, angulated and geographic margins over the outer aspect of the left forearm, with intervening areas of apparently normal skin. Similar lesions were present over the dorsum of the hand and distal fingers. The affected fingers showed distal narrowing, while the thumb was spared. Peripheral pulses were palpable with normal volume. Routine hematological, biochemical and coagulation investigations were within normal limits. Blood, urine and pus cultures showed no bacterial growth. Doppler ultrasonography and CT angiography demonstrated normal arterial flow without significant luminal narrowing. A diagnosis of Nicolau syndrome secondary to intravenous diclofenac was made. The patient was treated with cilostazol, pentoxifylline and aspirin, along with debridement of the necrotic tissue. At one-month follow-up, distal gangrenous portions of three fingers required amputation. ***Conclusion:*** Nicolau syndrome should be considered when acute, painful skin discoloration and necrosis develop shortly after administration of an injectable drug, even when distal arterial pulses and major-vessel imaging are normal. Early recognition and appropriate management may limit tissue loss and associated morbidity.

Keywords: Nicolau syndrome, embolia cutis medicamentosa, diclofenac, skin.

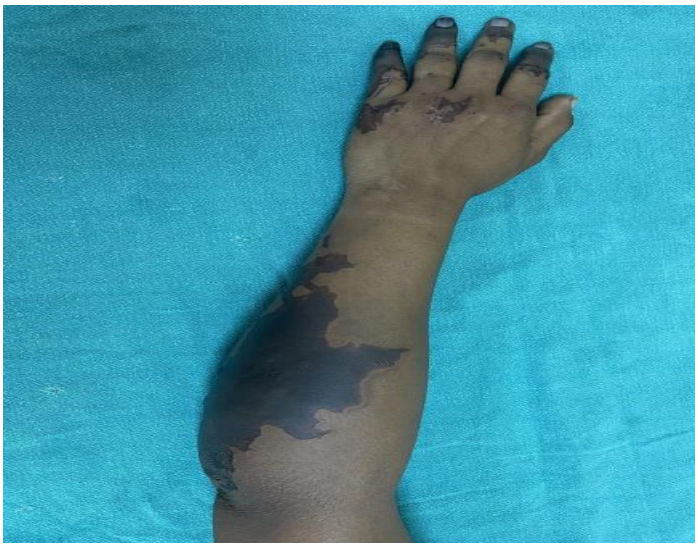
INTRODUCTION

Nicolau syndrome (NS), also termed embolia cutis medicamentosa or livedoid dermatitis, is an uncommon and potentially devastating adverse reaction following injection of various medications. It was initially described in patients receiving bismuth preparations for syphilis and has subsequently been reported after administration of several drugs, including non-steroidal anti-inflammatory drugs (NSAIDs), penicillin, corticosteroids, antihistamines, local anesthetics and other injectable agents.[1–3]

The characteristic clinical evolution consists of severe pain soon after injection, followed by pallor or erythema, a livedoid or reticular discoloration, hemorrhagic changes and progressive tissue necrosis. The process may extend from the skin and subcutaneous tissue to deeper structures, including muscle.[1–3] Diclofenac is one of the commonly reported offending drugs, particularly following intramuscular administration.[4,5]

The exact mechanism of Nicolau syndrome remains uncertain. Proposed mechanisms include inadvertent intra-arterial or periarterial injection, intense arterial vasospasm, vascular thrombosis, embolization of the injected drug and direct vascular injury. NSAIDs may additionally contribute through inhibition of prostaglandin synthesis, thereby promoting vasoconstriction and ischemia.[4–6] Importantly, major arterial imaging may remain normal because the pathological process can involve small vessels and transient vasospasm rather than persistent occlusion.

CASE REPORT



A 26-year-old woman presented with a one-week history of sudden-onset and progressively increasing blackish discoloration over the left forearm and distal portions of the fingers of the left hand. The lesions were associated with severe local pain and intermittent fever. There was no history of diabetes mellitus, vascular disease, coagulation disorder or any other known comorbidity.

One week before presentation, the patient had received an intravenous injection of diclofenac in the left cubital region for low backache. Approximately two hours after administration, she noticed the development of skin discoloration at the injection site. The discoloration progressively increased in extent and was followed by severe pain and tissue necrosis. There was no history of administration of any other medication during this period.

On local examination, patchy to diffuse areas of cutaneous necrosis were observed over the outer aspect of the left forearm. The lesions had sharply defined, irregular, angulated and geographic margins, with areas of apparently normal skin interspersed between the necrotic areas (Figure 1). There was associated swelling of the underlying skin and marked tenderness. Similar necrotic changes were noted over the distal dorsum of the left hand and fingers. The distal portions of the involved fingers appeared narrowed, while the thumb was spared.

Despite the extensive cutaneous changes, all peripheral pulses in the affected limb were palpable and of normal volume. There was no clinically appreciable regional lymphadenopathy.

Routine investigations, including complete blood count, liver function tests, renal function tests and coagulation profile, were within normal limits. Blood, urine and pus cultures did not demonstrate bacterial growth. Doppler ultrasonography of the affected limb showed no significant luminal narrowing. CT angiography demonstrated normal opacification and blood flow in the left radial and ulnar arteries without evidence of arterial occlusion.

Based on the characteristic temporal relationship with diclofenac injection, severe pain, rapidly progressive livedoid-to-necrotic changes and absence of significant arterial occlusion or infection, a clinical diagnosis of Nicolau syndrome secondary to intravenous diclofenac was established.

The patient was managed with supportive vascular therapy consisting of cilostazol, pentoxifylline and aspirin. Necrotic tissue was surgically debrided and the wound was managed with appropriate local care. During follow-up, the necrotic changes gradually demarcated. At one month, persistent distal gangrene involving three fingers necessitated amputation of the gangrenous distal portions

DISCUSSION

Nicolau syndrome is a rare injection-related complication that can produce extensive tissue injury despite the apparently uncomplicated administration of a medication. Although it was originally described after intramuscular administration of bismuth salts, subsequent reports have implicated several classes of injectable drugs. NSAIDs, particularly diclofenac, are among the frequently reported causative agents.[1–5]

The usual clinical presentation begins with intense pain immediately or shortly after injection. This may be followed by pallor, erythema, livedoid or reticular discoloration, hemorrhagic changes and ultimately skin and soft-tissue necrosis. The characteristic irregular and geographic appearance of the lesions is consistent with the clinical spectrum described in previous reports.[3–5]

The pathogenesis of Nicolau syndrome is not completely established. Several mechanisms may act simultaneously. One proposed mechanism is inadvertent intra-arterial injection, resulting in embolic obstruction and tissue ischemia. Another possibility is periarterial injection with direct vascular irritation and intense sympathetic-mediated vasospasm. Mechanical vascular trauma, thrombosis and inflammatory injury have also been proposed.[4–6] In the case of NSAIDs, inhibition of cyclooxygenase and reduced prostaglandin synthesis may further promote vasoconstriction and ischemia.[6] Recent literature continues to support a multifactorial mechanism involving vasospasm, vascular injury, thrombosis and embolic phenomena rather than a single pathological pathway.

The present case is noteworthy because the injection was administered intravenously, whereas most reported cases involve intramuscular administration. Nicolau syndrome has nevertheless been described following different injection routes, supporting the concept that the reaction is not restricted to a particular route of administration.

Another important feature in our patient was preservation of distal arterial pulses despite extensive necrosis. Doppler ultrasonography and CT angiography also demonstrated normal flow through the radial and ulnar arteries. This observation suggests that the tissue injury may have resulted from transient vasospasm, microvascular compromise or localized vascular injury rather than persistent occlusion of the major arteries. Similar observations have contributed to the hypothesis that small-vessel involvement and vasospasm play an important role in Nicolau syndrome.[4,6]

The differential diagnosis includes necrotizing fasciitis, vasculitis, thrombotic or embolic disorders, purpura fulminans and other causes of cutaneous gangrene. Necrotizing fasciitis is generally accompanied by progressive infection and systemic toxicity, while microbiological investigations and imaging may provide supportive evidence. In our patient, normal laboratory investigations, negative cultures, preserved arterial flow and the close temporal relationship between diclofenac administration and onset of symptoms favored Nicolau syndrome.

There is currently no universally accepted diagnostic test or standardized treatment protocol for Nicolau syndrome. Diagnosis remains primarily clinical, with laboratory investigations, vascular imaging and, when indicated, histopathology used to exclude alternative causes and determine the extent of tissue injury. Management depends on the severity and stage of the disease and may include analgesia, wound care, vasoactive or antithrombotic therapy, antibiotics when secondary infection is present, debridement and reconstructive procedures. Hyperbaric oxygen therapy has also been reported in selected cases, although evidence remains limited.

The prognosis varies according to the extent and depth of tissue injury and the promptness of treatment. Severe cases can progress to extensive gangrene and may require repeated debridement, skin grafting or amputation. Previous reports have documented substantial tissue loss following diclofenac-associated Nicolau syndrome, emphasizing the importance of early recognition.

In the present case, the development of extensive necrosis despite palpable peripheral pulses highlights the possibility of transient vasospasm or microvascular injury. The normal angiographic findings suggest that the major arterial circulation remained intact, while the distal tissue injury progressed because of localized vascular compromise. This clinical observation may be useful in understanding the pathophysiology of Nicolau syndrome and warrants further investigation.

CONCLUSION

Nicolau syndrome is a rare but serious complication of injectable medications that can result in extensive skin and soft-tissue necrosis. Although diclofenac is commonly associated with the condition after intramuscular injection, clinicians should recognize that it may also occur following intravenous administration. The presence of normal peripheral pulses and normal major-vessel imaging does not exclude the diagnosis. Early recognition, close monitoring, appropriate wound management and timely surgical intervention are essential to minimize tissue loss. Greater awareness among healthcare professionals regarding this potentially preventable adverse reaction may help reduce its morbidity.

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