Nicolau Syndrome: A Rare Adverse Effect of Intravenous Diclofenac Sodium Injection

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ABSTRACT

Nicolau syndrome (embolia cutis medicamentosa) is an uncommon complication of intramuscular injection leading to necrosis of skin and underlying tissue to a variable extent. I am reporting one such case who developed this complication after intravenous injection of diclofenac sodium. The aim of reporting this case is to create awareness among our colleagues and staff to exercise precautions during parental injection administration.

Keywords: Embolia cutis medicamentosa, Nicolau syndrome, Parenteral injection.

The Journal of Medical Sciences (2020): 10.5005/jp-journals-10045-00143

INTRODUCTION

Nicolau syndrome (NS) or embolia cutis medicamentosa (ECM) is a rare complication arising from an incorrect local injection of various drugs.¹ Nicolau syndrome was previously credited to immunological mechanisms, injection technique, pH, or other chemical–physical properties of the administered drug. However, experimental studies controverted this hypothesis.² Inadvertent perivascular injection, which can lead to vessel damage, acute arterial thrombosis, and subsequent necrosis, is a widely accepted hypothesis in the pathogenesis. Diagnosis is mainly based on clinical presentation variable amount of skin and tissue necrosis with pain and purple discoloration of skin at the injection site. Usually, the skin heals with scarring and deformity; therefore, all medical personnel should be aware of this iatrogenic complication and its management. Skin biopsy shows necrotic changes caused by ischemia. Ultrasonography (USG) and magnetic resonance imaging (MRI) may help determine the extent of the damage. The early start of treatment has been reported beneficial to this condition. The course of the disease is unpredictable and may at times end up with complications like myositis, abscess, nerve palsies, muscle atrophy, and, rarely, myonecrosis.

Treatment should be aimed at improving vascular flow. In severe cases, surgical debridement may be required. Systemic antibiotics have a significant place in the management of this syndrome.^{3,4}

CASE DESCRIPTION

A 43-year-old female patient of Indian origin visited the outpatient department of dermatology with cutaneous necrosis associated with moderate pain at the injection site of the left arm. As per the history given by the patient, she met a road traffic accident a week before and had a mild injury with moderate traumatic pain. She was brought to the emergency department of the hospital where minor scratches were cleaned and dressing is done. She was then administered inj. diclofenac sodium 75 mg intravenous in the left arm for pain and was discharged from hospital on the same day. After 3–4 hours, the patient had inflammation over the injection site and the next morning she observed black discoloration with pain over the injection site. She then developed swelling all over her upper limb and a pit-like appearance over (left) cubital fossa

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How to cite this article: Kumawat K, Rafi M, Namdeo C, *et al.* Nicolau Syndrome: A Rare Adverse Effect of Intravenous Diclofenac Sodium Injection. *J Med Sci* 2020;6(2):32–33.

Source of support: Nil

Conflict of interest: None

(injection site) associated with pain (Fig. 1). She was diagnosed by the dermatologist with NS to intravenous diclofenac sodium injection. For this reaction, she has prescribed a tab. Azithromycin 500 mg once a day for 5 days and cream fusidic acid twice a day for topical application. She was advised to follow-up after a week. On follow-up, there was a mild improvement and the patient was much worried about the pit/hollow that had developed at the injection site. Cream fusidic acid was continued and the patient was advised for the next follow-up after 2 weeks. It was after 2 months of therapy, the necrosed area recovered completely leaving a slight scar. Afterward, the treatment was discontinued.

DISCUSSION

Clinically, when a patient develops this complication of NS they complain of severe pain at the site of injection followed by bluish discoloration of the skin which is usually well defined with sharp and angulated margins and sometimes, it may have a reticular pattern which is called non-inflammatory retiform purpura,⁵ livedo-like dermatitis,⁶ and livedoid dermatitis. This discoloration of the skin may be followed by necrosis and ulceration which can go deep into the subcutaneous tissue and muscles. Even paraplegia has

Fig. 1: Pit-like appearance over (left) cubital fossa (injection site) associated with pain

been reported following ischemia of the sciatic nerve due to the embolization of drug into the internal iliac arteries.

The exact etiopathogenesis of this condition is not well known but it has been hypothesized that it is ischemic necrosis of the skin and deeper tissue which is responsible for this complication, embolization of the ejected drug or mechanical pressure by the drug around the vessel has been supposed to be responsible for this problem.⁷ Diagnosis is primarily clinical; USG and MRI can be used to see the extent of pathology. Treatment is usually medical with antibiotics which are the mainstay of the treatment, also pentoxifylline, hyperbaric oxygen, thrombolysis with heparin, and even intraluminal steroids have been used to treat the condition.⁸ Rarely, the patients who develop scars and contracture may need surgery. Aspiration before injecting drugs has been used to prevent NS but how effective it is in view of vasospasm and vasocompression is doubtful, NS has to be differentiated from necrotizing fasciitis which is a much more rapidly spreading infection due to aerobic and anaerobic bacteria.

On searching WHO-UMCs open global adverse drug reaction (ADR) database "Vigiaccess", hitherto, there were 83 reports of ECM with diclofenac from its member countries⁹

There might be some more similar reports from India too after which a regulatory order by Indian regulatory body CDSCO dated 24.07.2019 was issued for marketing authorization holders (MAHs) based on recommendations of NCC-PvPI, IPC for the incorporation of NS as an ADR inpatient/prescription information leaflet of the drug diclofenac sodium injection marketed in India.

The United States FDA Adverse Events Reporting System (FAERS) public dashboard updated till June 30, 2020 showed 370 reports of ECM from the U.S. (2003–2020) out of which 368 were serious and included 08 deaths. Out of these 370 reports, diclofenac accounted for 106 (28.6%) reports followed by 63 reports (17%) each of glatiramer acetate and diclofenac sodium (17%), penicillin

G benzathine 26 (7%), lidocaine 13 (3.5%), lidocaine hydrochloride 11 (2.9%), etc.¹⁰ Hence, our healthcare professionals should be well aware in diagnosing such events timely which will certainly lead to proper and prompt treatment of these patients, thus reducing mortality due to NS.

CONCLUSION

Nicolau syndrome is an uncommon complication of parental drug administration, which should always be kept in mind and in case it develops needs immediate intervention with antibiotics, debridement and may require corrective surgery at a later stage. As a rule, cold compresses should never be applied.

ACKNOWLEDGMENTS

We are thankful to Dr Kailash Bhatia, Dr Rajesh Kataria, and all other residents of our dermatology department for timely reporting adverse reactions to the ADR monitoring center of our hospital. We also wish to acknowledge the National Coordinating Center—Pharmacovigilance Programmer of India (PvPI) under the aegis of the Indian Pharmacopoeia Commission, Ghaziabad for expanding the network of ADR monitoring centers throughout the country.

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