



Nicolau Syndrome Secondary to Intra-Muscular (IM) Injection

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Abstract:

Nicolau syndrome (NS) is a rare complication that can occur after intramuscular or subcutaneous injections. There is no tool/test exists for making a confirmative diagnosis of NS; it is purely based on the clinical features and their correlation with previous case history. With its rarity, correct diagnosis may be delayed, and furthermore tissue necrosis may be developed by inappropriate treatment. A 22-year-old female came to outpatient department with a complaint of lesion over right buttock. She gave the history of intense pain and bluish discoloration in her right buttock after intramuscular injection of diclofenac. She experienced severe dull pain immediately after the injection. Physical examination revealed an abnormal finding in the right buttock area with erythematous reticular rash and USG of the gluteal region revealed large area of diffuse subcutaneous hemorrhage in right gluteal region. Though the conservative treatment was given, patient condition got worsened and seen with tissue necrosis. As case came to the notice of clinical pharmacist, the current symptoms were compared with the literature survey of similar cases and provisionally assumed to be Nicolau syndrome. Then it was brought to the notice of medical team where it was discussed in detail & finally diagnosed with NS. Then necrotized tissue was removed with surgical debridement & advised with daily dressings. NS awareness among the health care professionals could help to diagnose the disease at its early stage and may restrict further progression of the disease.

Key words: Intramuscular injection, Erythematous reticular rash-surgical debridement, Nicolau syndrome

Introduction

Intramuscular injection for administering drugs are common procedures because they are effective and offer rapid response and sometimes may induce some complications such as injection pain, hematoma and infection around an injection area.^{1,2} Nicolau syndrome is a sporadic, iatrogenic syndrome, which was firstly reported by Freudenthal and Nicolau in 1924 and 1925, respectively, following the intramuscular injections of Bismuth to treat syphilis.² Nicolau's syndrome, also known as Embolia Cutis Medicamentosa (ECM) and Livedo-Like Dermatitis (LLD), is a rare complication or adverse drug reaction that can occur after intramuscular, intra-articular or subcutaneous injections.^{2,3} It is characterized by immediate intense pain at the injection site followed by erythema and a hemorrhagic patch with a livedoid reticular pattern after injections of non-steroidal anti-inflammatory drugs (NSAIDs), antiepileptics, antibiotics, antihistaminics, corticosteroids, etc.⁷ The incidence of complications of intramuscular injections varies between 0.4% and 19.3%.³ The development of acute vasospasm following intra-arterial or peri-arterial injection is the most widely accepted hypothesis in its pathogenesis.⁴ The reason for this complication has not been established yet; however, intra/periarterial injections and their consequent complications such as ischemia and spasms are known as the possible contributing factors.^{2,4} With its rarity, correct diagnosis may be delayed, and furthermore tissue necrosis may be worsened by inappropriate treatment.¹

Case Presentation

A 22-year-old female came to outpatient department (dermatology) with C/O lesion over right buttock since 7 days. And patient gave a history of intense pain and bluish discoloration in her right buttock (Fig.1) after 2 days of intramuscular injection of diclofenac. Her symptoms developed about 2 hours after injection of 2cc Diclofenac for headache and body pain. She experienced severe dull pain immediately after the injection. She had neither specific past illness nor previous medication issues. Her vital signs were within normal limits. Complete blood count, coagulation profile, urine examination, renal and liver function tests were also in normal limits. Physical examination revealed an abnormal finding in the right buttock area with erythematous reticular rash and USG of the gluteal region revealed large area of diffuse subcutaneous hemorrhage in right gluteal region (Fig.3). She was prescribed with conservative managements including ice bag application, pain control agents, oral antibiotics and some topical agents like T-bact ointment and Flutivate cream. But, with that treatment patient condition not got improved and day by day it got worsened (Fig-4 to 7) and there was a tissue necrosis.



Fig.-1: One Day After Taking Injection



Fig.-2: 7 Days After Taking Injection



Fig.-3: USG of Gluteal Region



Fig.-4: 15 Days After Taking Injection



Fig.-5: After 25 days



Fig.-6: After 1 month



Fig.-7: Surgical Removal of Necrotized Tissue



Fig.-8: Formation dead skin over the wound



Fig.-9: 15 Days after Second Surgery Growth of Dead Skin

Then she went to the OPD of surgery where, she treated with surgical debridement, sterile dressings, non-steroidal anti-inflammatory agents, analgesics and she was advised with daily dressings, after few days there was development of dead skin over the wound (Fig-8) so that again surgery was performed to remove dead skin and prescribed with some oral antibiotics and analgesics and advised for daily dressing. After few days there was pus from the wound (Fig-9) which was foul smelling, culture test was done which was detected with the E. coli bacteria then she has been prescribed with the Amoxicillin and Clavulanic acid.

Discussion

Nicolau syndrome (NS) is defined as a local aseptic tissue necrosis, and characterized by intractable pain, distinct skin lesions, and various degrees of tissue destruction at the injection site.¹ Nicolau syndrome was first described in the early 1920s by Freudenthal and Nicolau as an adverse effect of using intramuscular injections of Bismuth salts in the treatment of syphilis.⁷ It is a rare condition caused by intramuscular or intra-articular injection of various medications. Penicillin, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), corticosteroids, and local anesthetics have been reported as the causative agents of NS.³

Clinical features of various patients suffering from NS are divided in to three steps; initial, acute and necrotic phases.^{2,6} Initial phase of NS is presented by intense pain immediately or soon after the injection with a bluish discoloration. Acute phase occurs 24 h to 3 days later. In this phase, erythematous lesion develop at the injection site or indurated painful livedoid plaque with the border of the violaceous and reticular plaque develop. That is non necrotic plaque or patch. Necrotic phase as a final stage reveals that the injection site progress to violaceous, necrotic, crusted, indurated plaque. The lesion is progressing to erythema, swelling and tender induration with central necrosis.^{2,3,6,7} And all these phases are observed in our patient.

The exact pathogenesis of NS is not known but the following hypotheses have been suggested: (1) inflammation caused by vascular or perivascular injection, which induces arterial wall destruction and subsequent tissue necrosis, (2) embolism caused by intra-arterial injection, causing occlusion of small vessels, (3) periarterial injection associated with arterial wall perforation, leading to thrombosis and necrosis, (4) sympathetic stimuli caused by intra-arterial injection, resulting in vasospasm, (5) direct trauma provoked by the needle.¹⁻⁵ Crystallisation of aqueous drugs in the vessels and arteriovenous shunt development are other proposed causes.⁸

No tool or test exists for making a confirmative diagnosis of Nicolau syndrome; it is based purely on the clinical features and their correlation with previous case reports. One report suggests that laboratory tests reveal creatine kinase and myoglobin as well as other markers of muscle damage, but author thought that a mere increase in

creatinase kinase and myoglobin does not automatically mean necrosis with muscle involvement.¹⁰ In this case there was a delay in recognizing the syndrome as it was a rare condition and there is no particular diagnostic tests for this disease. After it has been come to the notice of clinical pharmacist, where present symptoms were compared with the previous literatures & other case reports of similar types & provisionally assumed to be a Nicolau syndrome. Then it was brought into the notice of medical team where it was discussed in detail and finally diagnosed with the NS.

NS has no definitive treatment. During the early stage of the disease, the main goal of therapy is to prevent the development of necrosis. Conservative management with pain control is the mainstay of therapy. However, surgical debridement should be performed in the case of necrosis. Necrosis and secondary infection of the skin and underlying muscle may follow, often requiring extensive debridement and with significant morbidity.⁸ Several studies have shown the occurrence of secondary infections following NS⁴. Necrotic ulcers usually heal in several months, leaving an atrophic scar. In this case with the conservative therapy patient condition was not improved, there was a progressive development of the necrotized tissue and surgical debridement was performed to remove the necrotized tissue. And After few days secondary infection was developed and wound was treated with oral antibiotics.

Conclusion

Although NS is a rare reaction, the symptoms are extremely dangerous so, healthcare professionals must be aware of this clinical entity and know how to avoid it by taking preventive measures, since intramuscular, intra-articular and subcutaneous injections are all common procedures.³ And as there is no specific therapy for Nicolau syndrome exists other than prevention. Finally, physicians should consider Nicolau syndrome as a diagnostic possibility for anyone presenting with severe localized pain following an intramuscular injection of any substance. Nicolau syndrome can be avoided by precautions such as aspirating the needle before injecting to check for blood, use of Z-track injection technique, proper site of injection, avoiding large doses at a single site, and regular change of sites if multiple injections are to be given.^{3,10}

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interest None declared.

Patient consent for publication Patient consent obtained

Provenance and peer review not commissioned; externally peer reviewed.

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