

## Nicolau Syndrome Due to Benzathine Penicillin Injection: (A Case Report)

Faghihi G<sup>1</sup>, Moosavi A<sup>1\*</sup> and Radan<sup>2</sup>

<sup>1</sup>Department of dermatology, skin diseases and leishmaniasis research center, Isfahan University of medical sciences, Isfahan, Iran

<sup>2</sup>Medical student, Isfahan medical school, Isfahan University of medical sciences, Isfahan, Iran

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### 1. Abstract

Nicolau Syndrome(NS) is a rare complication of intramuscular injections, which is manifested by pain, edema, and livedoid discoloration of the skin immediately after injection. The pathophysiology of the disease is uncertain, but some studies have suggested, reasons such as embolic vessel occlusion, sympathetic nerve stimulation, inflammation, or mechanical injury. In this paper we report a case of NS following penicillin Injection.

### 2. Key words

Nicolau Syndrome; Pathophysiology; Penicillins

### 3. Introduction

Every year an estimated 12 billion injections are performed by health care workers [1] Intramuscular injection is used as a technique of choice for application of drugs in many treatment protocols in order to achieve effective and quick response. The best-known and most severe complication of this procedure is sciatic nerve injury; however, an abscess and/or tissue necrosis may also develop at the injection site [2-6].

Nicolau syndrome (livedoid dermatitis, embolia cutis medicamentosa) is a rare complication of intramuscular injection that usually presents with pain at the injection site, hyperemia, skin redness, discoloration, abscess formation, and local ischemic necrosis involving the skin and adipose tissue. The pathogenesis is not yet clearly understood, but is thought to involve direct vascular damage, perivascular inflammation, and vascular constriction following the injection [2-6].

The drugs most commonly causing tissue necrosis include phenylbutazone, local anesthetics, antihistamines, anti-inflammatory agents, corticosteroids, and penicillins [6-15].

De Sousa et al. have reported a death following Nicolau syndrome [13-16]. In this report, we describe a 48-year-old male with a diagnosis of the Nicolau Syndrome (NS) after intramuscular benzathine penicillin injection.

### 4. Case Presentation

A 48-year- male was admitted to the emergency department with a complain of swelling and skin lesions on the left lower limb in Isfahan, Iran, in September 2019. The problem had started since 1 day

ago after he received an injection of benzathine penicillin (120000 IU) to the left buttock, for fever and signs and symptoms of an upper respiratory infection. About half an hour after the injection, the left lower extremity became pale and mottled, and edema and coldness developed a few minutes later.

He was nervous and agitated. The vital signs were stable and he did not have fever. The left leg was tender to touch so he did not allow proper exam of his left lower limb and could not bear weight on the same side. On inspection there were mottled ,dark purplish patches on buttock ,gluteal region and upper part of left thigh .There were some bulla formation, intradermal hemorrhagic areas and skin necrosis on the above-mentioned patches (Figure 1, 2) .The examinations of the abdomen, heart, respiratory system, and head and neck or other extremities (except the affected limb) were normal. The pulses of both lower limbs (dorsalis pedis, popliteal, and femoral) were symmetrical and normal on palpation, though the left leg and foot were colder. Complete Blood Cells Count (CBC), erythrocyte sedimentation rate, Aspartate Aminotransferase (AST) , Alanine Aminotransferase (ALT), Prothrombin Time(PT), Partial Thromboplastin Time(PTT), Serum Creatinine(Cr), Blood Urea Nitrogen(BUN) Creatinine Phosphokinase Kinase (CPK), lactate dehydrogenase and C-reactive protein levels were within normal ranges. Color Doppler ultrasonography of lower limb arteries and veins were normal. During the admission, the patient's irritability improved and the mottled purple patches faded. For this patient, supportive treatment was started and oral corticosteroids (0.5 mg/kg/day prednisolone) along with analgesics were administered. After a week the patient had been well discharged and the lesions healed nearly completely.

\*Corresponding Author (s): Azam Moosavi, Department of dermatology, skin diseases and leishmaniasis research center, Isfahan University of medical sciences, Isfahan, Iran. E-mail: Dr.azam.mosavi@gmail.com

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**Figure 1:** Close up view of left gluteal skin lesions , areas of hemorrhagic bullae superimposed on purplish livedoid patches.



**Figure 2:** Distribution of tender ,cool, mottled areas over left flank, buttock and upper thigh.

## 5. Discussion

Nicolau syndrome (also known as livedoid dermatitis) is a rare complication of intramuscular injection, which is manifested by pain, edema, and livedoid discoloration of the skin immediately after injection. It was first described in 1925 by Nicolau following intramuscular injection of bismuth salt, but it also has been reported after intramuscular or subcutaneous injection of numerous drugs [3].

Nicolau Syndrome has been reported with intramuscular injections of non-steroidal anti-inflammatory drugs (diclofenac, piroxicam, ketoprofen, ibuprofen, phenylbutazone), corticosteroids (dexamethasone, triamcinolone, paramethasone, cortivazol, hydrocortisone), antibiotics (penicillin derivatives, tetracycline, sulfapyridine, streptomycin, gentamicin), antipsychotics and anti-epileptics (phenobarbital, chlorpromazine), Vaccinations (diphtheria-tetanus-pertussis), antihistamines (diphenhydramine, hydroxyzine), local anesthetics (lidocaine), cyanocobalamin, interferon alpha , bismuth and vitamin K. [18-19].

One theory explains, that NS happens when an intramuscular drug is injected into an artery and causes thrombosis and muscle and subcutaneous necrosis. However the pathogenesis of NS is unknown [11].

One important clinical element is the sudden onset with regard to the injection, often with no lesion at the injection site. The signs of

NS are skin discoloration, intense pain, and inflammation. Necrosis usually comes after hyperemia, discoloration of skin, formation of hemorrhagic patch at the site of injection, and livedoid dermatitis. Local vasospasm causes pallor. One-third of the patients may experience neurologic complications (usually transitional) which are most frequently hypoesthesia and paraplegia. NS has also been reported to cause compartment syndrome of the limb, hyperkalemia, renal failure, and death. Paralysis of the lower limb can happen and can be explained by medication embolism. Embolus in the vessels of gluteal muscle can reach the internal iliac artery and then vertebral canal by retrograde flow. This arterial stenosis can result in peripheral nerve disturbance and lower limb paralysis [20].

There is no published standard of care for NS and treatment used ranges from local care to extensive surgical debridement. Alyasin et al. reported a 7-year-old boy with NS treated with intravenous immunoglobulin (IVIG) (2 g/kg) and Pentoxifylline. They reported that the patient was heparinized and after 12 days, he was discharged in a good general condition. Yildiz et al. used hyperbaric oxygen in the late treatment of NS in a 3-year-old boy to prevent the progression of the necrosis and therefore, limiting the amputation level. Application of a cold compress was considered as an aggravating factor [21].

For preventing adverse injection reactions, health care providers should be informed of proper method of intramuscular injection such as Z-track method of injection, aspiration before injection, holding injection immediately if the patient complains of unusual excruciating pain on injection site. Needle must be long enough to reach the muscle. When multiple injections have to be given, different sites should be chosen [21].

Fortunately we did not see terrible complications such as acute hyperkalemia, renal failure, limb amputation, or disfiguring features in our patient and recovered by Supportive treatment measures in quite short period of time.

This issue shows the importance of proper administration of medication and appropriate injection method by doctors.

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