

Nicolau syndrome following intramuscular benzathine penicillin

De Sousa R, Dang A, Rataboli PV

Department of Surgery, Goa Medical College, Bambolim, Goa - 403 202, India

Correspondence:

Dr. Reuben De Sousa
E-mail: reuben_ds@yahoo.co.in

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ABSTRACT

Nicolau syndrome (NS) is a rare complication of an intramuscular injection characterized by severe pain, skin discoloration, and varying levels of tissue necrosis. The case outcomes vary from atrophic ulcers and severe pain to sepsis and limb amputation. We describe a case of a seven-year-old boy with diagnosis of NS after intramuscular benzathine penicillin injection to the ventrolateral aspect of the left thigh. Characteristic violaceous discoloration of skin and immediate injection site pain identified it as a case of NS. The case was complicated by rapid progression of compartment syndrome of the lower limb, proceeding to acute renal failure and death. Associated compartment syndrome can be postulated as a poor prognostic factor for NS.

KEY WORDS: Benzathine penicillin, embolia cutis medicamentosa, livedoid dermatitis, Nicolau syndrome

Nicolau syndrome (NS) is a rare injection site reaction, following intramuscular administration of drugs, with varying degrees of tissue damage.^[1] It is synonymously described as embolia cutis medicamentosa and livedoid dermatitis. NS is characterized by development of an acute, severe pain, and a localized erythematous reticular rash. Subsequently, it results in cutaneous, subcutaneous, and even muscular necrosis with a pale marble-like livedoid pattern.

Case Report

A seven-year-old boy presented to the emergency room of a tertiary referral center with acute onset pain and paralysis of left lower limb. The boy was a patient of rheumatic heart disease and gave history of receiving benzathine penicillin a day prior at a rural health center.

A detailed history revealed that immediately following the injection, there was severe pain in the thigh and buttock, followed by inability to move the left lower limb and discoloration of the limb which progressed to involve the abdomen. This was also accompanied by decreased urinary output and altered sensorium for 6 h prior to admission.

On examination, the patient was stuporous, afebrile with stable vital signs (pulse - 110/min, blood pressure - 120/80 mm Hg, respiratory rate - 24/min). Cardiovascular examination revealed a Grade 3 mid-diastolic murmur with no signs of cardiac failure. Abdominal examination showed marked tenderness in the hypogastrium with no organomegaly. A violaceous livedoid pattern discoloration of the left lower limb, left gluteal region, genitalia, perineum, and lower abdomen was present [Figure 1].

Left leg pulsations distal to femoral artery were absent and the limb was cold compared to the right one. Extensor compartment of thigh and flexor compartment of leg were tense. Pinprick sensations could not be evaluated due to lack of cooperation. Paralysis of left hip, knee, ankle, and toe joints was detected.

Laboratory assessment showed deranged renal functions tests (blood urea - 80 mg%, serum creatinine - 1.3 mg%). Urine examination showed traces of myoglobin with gross hematuria. Arterial blood gas evaluation revealed metabolic acidosis with compensatory respiratory alkalosis. Electrocardiogram showed tall peaked T waves indicating hyperkalemia.

Abdominal ultrasound showed increased echogenicity of both kidneys with normal corticomedullary differentiation suggestive of acute medical renal disease. On soft tissue ultrasound, left lower limb and lower anterior abdominal wall muscles were bulky and echogenic, resembling intramuscular hemorrhage. Arterial and venous Doppler of left limb were normal.

The patient was given age and weight-adjusted doses of linezolid (150 mg i.v.), aztreonam (900 mg i.v.), metronidazole (300 mg i.v.), and tetanus immunoglobulin (250 units i.m.). After preoperative correction for hyperkalemia and with the diagnosis of necrotising fascitis, release incisions were given. The operative findings showed a left gluteus maximus muscle hematoma with edema of underlying gluteus medius and pouting muscle bellies in all compartments of the left thigh and leg. Postoperatively, the boy had generalized tonic clonic seizures and expired with cardiorespiratory arrest 3 h later.

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Figure 1: Violaceous livedoid pattern discoloration of the left lower limb, left gluteal region, genitalia, perineum and lower abdomen 36 hours following the benzathine penicillin injection

Analysis of muscle tissue fluid later revealed numerous neutrophils with no organisms suggestive of acute inflammation. Sections from gluteus muscle biopsy revealed muscle congestion and hemorrhage [Figure 2]. As per Naranjo causality algorithm, the case was classified as a probable adverse drug reaction with score of six.

Discussion

Nicolau syndrome (livedoid dermatitis or embolia cutis medicamentosa), first described by Freudenthal in 1924 and Nicolau in 1925, is a rare injection site reaction of an intramuscular injection. Initially seen with intramuscular bismuth salt administration in syphilis, it has now been documented with several drugs [Table 1].^[2]

The pathogenesis of NS is obscure. The mechanism may involve direct trauma or arterial embolism caused by microcrystals of crystalloid drugs or ischemia due to compression following paravascular injection. Vascular pathogenesis may involve end artery thrombosis or arterial vasospasm with resultant ischemia-mediated livedoid necrosis.^[3]

Symptoms include excruciating stabbing pain soon after injection, probably due to involvement of peripheral sensory nerves. Clinically, patients present with pallor, cyanotic patches, and later a livedoid pattern around the injection site. At times, there is local necrosis, ulceration, and subsequent scarring. There can also be necrosis of subcutaneous fat and muscle as well.

Tissue diagnosis is based on skin biopsy showing necrosis of dermis and subcutaneous tissue and muscle biopsy showing focal vascular thrombosis and inflammatory infiltrate in acute phase.

Treatment ranges from local care to surgical intervention. Antibiotic use is restricted to cases with signs and symptoms of infection. Use of vasoactive agents (pentoxifylline) together with hyperbaric oxygen may be beneficial considering the vascular pathogenesis.^[4] Vasospasm may be relieved by the

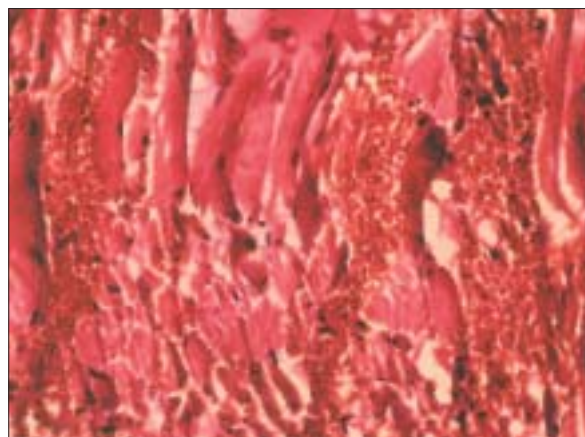


Figure 2: Gluteal muscle biopsy showing muscle bundles separated by erythrocytes suggestive of hemorrhage with neutrophilic infiltrate ($\times 40$)

Table 1: Drugs associated with Nicolau syndrome

Class of the drug	Examples
NSAIDS	Diclofenac, Ibuprofen, Ketoprofen, Piroxicam
Antiepileptics and antipsychotics	Phenobarbital, Chlorpromazine
Antibiotics	Sulfapyridine, Tetracycline, Streptomycin, Sulphonamide, Gentamicin
Steroids	Dexamethasone, Triamcinolone
Miscellaneous	DPT vaccine, Diphenhydramine, Lidocaine, Phenylbutazone

NSAIDS= Non-steroidal anti-inflammatory drugs, DPT= Diphtheria-pertussis-tetanus

phosphodiesterase inhibiting action of pentoxifylline. Topical corticosteroids are effective for acute tissue inflammation. Wound care, debridement, dressings, and flap reconstruction are ideal surgical measures. Failure to recognize the extent of fat necrosis and poor blood supply leads to inadequate debridement and poor wound healing. The patients are then prone to repetitive cycles of infection leading to extensive scarring, soft tissue indentation, and unsightly skin grafts.^[5]

A review of 102 cases of NS done by Saputo *et al.* revealed that children are at higher risk with 78.43% of cases reported to be under 12 years of age.^[6] Other postulated poor prognostic factors include cold application for local pain relief^[7] and septicemia.^[4] The present case highlights associated compartment syndrome as a poor prognostic factor for NS.

Noteworthy findings

The neurological involvement with lower limb paralysis can be explained by drug embolism. Embolus in the vessels of the buttocks (site of injection) formed due to retrograde flow, could reach the internal iliac artery with the force of the injection. It would then travel to the vertebral canal, and go to the lower limbs, causing arterial occlusion, sciatic nerve injury, and distal vasa nervosum lesion.^[8]

As the benzathine benzylpenicillin injectable suspension is viscous and opaque, it would hinder the visualization of blood on aspiration if a blood vessel was inadvertently entered. These

features would facilitate an accidental intravascular injection, mainly in the gluteal region, which has many blood vessels and is next to the sciatic nerve.^[7]

We report this case to highlight the occurrence of a fatal reaction to a widely used drug and to sensitize the clinicians to take preventive measures to avoid any such occurrences. In intramuscular injections, the needle must be long enough to reach the muscle: a 90-kg patient requires a two-inch needle whereas a 45-kg patient requires a 1.25-1.5-inch needle. The Z-track method of injecting can minimize subcutaneous irritation following intramuscular injection. When multiple injections have to be given, different sites should be chosen. Before injecting, one should always aspirate and look for blood; one should immediately stop if the patient complains of pain on injecting.^[1]

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