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Successful Limb Salvage in Pediatric Nicolau Syndrome Following Intramuscular Benzathine Penicillin: A Case Report

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ABSTRACT

Nicolau syndrome, also known as emboli cutis medicamentosa, is a rare but potentially severe complication of parenteral drug administration that may lead to acute pain, livedoid discoloration, and cutaneous or subcutaneous necrosis. We report the case of a 4-year-old boy who developed Nicolau syndrome shortly after intramuscular administration of benzathine penicillin for streptococcal pharyngitis. He presented with sudden severe pain, pallor, mottling, and livedoid changes involving the injected limb and adjacent regions. Prompt recognition and multidisciplinary conservative management, including anticoagulation, topical vasodilator therapy, corticosteroids, limb elevation, and intensive monitoring, were associated with progressive clinical improvement and preservation of limb function. This case highlights the importance of early diagnosis and timely supportive intervention in preventing severe ischemic complications of Nicolau syndrome.

Introduction

Nicolau syndrome is a rare iatrogenic complication most commonly associated with intramuscular injections, although it has also been reported after subcutaneous, intravenous, and intra-articular drug administration [1]. First described in 1925, the syndrome typically begins with immediate severe pain at the injection site, followed by blanching, livedoid discoloration, and, in severe cases, cutaneous necrosis and deeper soft tissue ischemia. The exact pathophysiology remains unclear. Proposed mechanisms include inadvertent intra-arterial injection, arterial embolization, intense vasospasm, and direct vascular injury with subsequent tissue ischemia. Because the clinical course may progress rapidly, early recognition and intervention are critical [2]. We report a pediatric case of Nicolau syndrome after intramuscular benzathine penicillin injection with a favorable outcome following conservative management.

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Case Presentation

A 4-year-old boy, weighing 16 kg, presented to the emergency department approximately 20 minutes after receiving an intramuscular injection of benzathine penicillin G (dose: 1,200,000 IU) in the upper outer quadrant of the right gluteal region. This medication had been administered at an outpatient clinic prior to hospital presentation. It is noteworthy that for a child weighing 16 kg, this dose (1,200,000 IU) exceeds the standard pediatric weight-based recommendation, which is typically 600,000 IU for children weighing less than 27 kg. Shortly after the injection, the patient experienced excruciating pain at the injection site (rated 8/10 on the analog scale), followed by the rapid development of pallor and livedoid, mottled discoloration.

The patient had no significant medical history, no known drug allergies, and no prior exposure to penicillin. The injection was administered to empirically treat suspected streptococcal pharyngitis, following symptoms of upper respiratory infection (URI), including cough, fever, and sore throat, in the absence of throat culture or rapid antigen testing. Prior to administration, aspiration was performed and was negative for blood, although the rapid onset of symptoms following the injection strongly suggested an adverse vascular event.

Shortly after the injection, the patient experienced excruciating pain at the injection site (rated 8/10 on the analog scale), followed by the rapid development of pallor and livedoid, mottled discoloration spreading over the lateral aspect of the right thigh and extending down to the ankle. Clinical findings were highly suggestive of Nicolau syndrome (NS). Upon initial assessment, the patient was alert but in significant distress. Vital signs were stable: heart rate 110 bpm, respiratory rate 24/min, blood pressure 95/60 mmHg, and temperature 37.0°C. The affected right lower limb exhibited marked coolness and cyanosis distal to the injection site, with a characteristic livedoid, purpuric appearance.

A thorough neurovascular assessment revealed that distal pulses (dorsalis pedis and posterior tibial) were not palpable. Capillary refill time in the toes exceeded 5 seconds. Motor function was significantly impaired, with the patient unable to actively dorsiflex or plantarflex his foot. Sensation appeared diminished to light touch in the distribution of the superficial peroneal nerve. Doppler ultrasound was not immediately available for further vascular assessment at the bedside at that moment. Crucially, during the injection administration, aspiration was performed prior to injecting the medication, and it was negative for blood, making inadvertent intravascular injection less likely, though not entirely dismissible given the rapid onset and severity of symptoms. The abrupt onset of severe pain and ischemic changes after injection is in keeping with the typical clinical pattern of NS.

Initial laboratory investigations were performed to assess for systemic involvement and tissue injury. Serum lactate dehydrogenase (LDH) was significantly elevated at 1269 U/L, consistent with potential muscle or tissue injury. Renal function was within normal limits, with blood urea nitrogen (BUN) at 16 mg/dL and creatinine at 0.5 mg/dL. Electrolytes remained stable (Na^+ 134 mEq/L, K^+ 4.3 mEq/L, Ca^{2+} 9.3 mg/dL, and P 3.8 mg/dL). Urinalysis revealed hematuria (blood 3+) and proteinuria (protein 2+), with the urine appearing red and semi-translucent (specific gravity: 1.018, pH: 6). Additionally, glucosuria was noted (glucose 2+), while ketones were negative.

A computed tomography angiography (CTA) of the lower extremity was performed, demonstrating segmental, irregular narrowing and a distal cut-off of the right anterior tibial artery. There was also evidence of irregular filling in the peroneal artery. Despite these findings, the CTA showed diminished but preserved distal perfusion in the distal portions of the foot, suggesting collateral flow. No definitive thrombus was visualized, leaning the interpretation towards severe vasospasm and intimal injury rather than complete arterial thrombosis. An orthopedic surgery consultation was obtained due to concerns for potential compartment syndrome. The orthopedic team performed a detailed clinical assessment, including evaluation of pain out of proportion to visible injury, palpation of compartment tension, and reassessment of distal neurovascular status. Based on the absence of tense compartments and preserved, albeit diminished, distal perfusion on CTA, clinical evidence of compartment syndrome was deemed absent.

The patient was managed through a multidisciplinary, conservative approach. To address potential inflammation, edema, and vasospasm, a systemic corticosteroid regimen of methylprednisolone (2 mg/kg/day) was initiated. Broad-spectrum antibiotic therapy was administered to prevent secondary soft tissue infection, consisting of vancomycin (20 mg/kg/dose every 6 hours) and meropenem (10 mg/kg/dose every 8 hours). To mitigate thromboembolic risks, enoxaparin (1 mg/kg/dose twice daily) was administered. Local perfusion was supported using topical nitroglycerin ointment applied twice daily to the affected areas, alongside limb elevation. Pain management was provided with apotel (paracetamol) as needed. The patient was maintained on intravenous

KVO (keep vein open) fluids and oral nutrition.

Over the following 72 hours, the patient's pain gradually subsided, and the livedoid discoloration transitioned into a petechial and subsequently an ecchymotic pattern. The limb remained slightly edematous but showed improving capillary refill. AST, ALT, and LDH levels progressively declined. The heparin therapy was transitioned to subcutaneous enoxaparin for a total duration of 10 days. Systemic corticosteroids were tapered over a 2-week period. The patient was discharged on post-injection day 5 with full restoration of limb mobility and sensation. At the 3-month follow-up, the patient had regained full functional use of the right leg, with only residual hyperpigmentation at the initial lesion site. Anticoagulation was guided by serial anti-Xa monitoring, with treatment targets set at 0.2–0.5 IU/mL. Measured anti-Xa values during therapy were compared against this range and remained therapeutic after dose titration. Topical 2% nitroglycerin ointment, applied every 4 hours, was used as a vasodilatory adjunct in an attempt to improve regional blood flow.

Discussion

Nicolau syndrome (NS), also known as embolia cutis medicamentosa, is a rare but potentially devastating complication of parenteral drug administration characterized by acute pain, livedoid discoloration, and tissue ischemia. Although its pathophysiological mechanisms remain incompletely understood, the management of NS, particularly in pediatric populations, remains challenging due to the limited evidence base [3]. This report details a case of pediatric NS managed successfully with a conservative, multidisciplinary approach. Proposed mechanisms include inadvertent intra-arterial injection, embolic occlusion, and intense vasospasm. In our case, CT angiography demonstrated segmental narrowing of the anterior tibial artery without complete thrombosis. The preservation of distal perfusion and rapid clinical recovery suggest that vasospasm and endothelial injury played a significant role. Vascular imaging findings are rarely reported in pediatric NS, making our observation particularly noteworthy.

Regarding the pathogenesis, Nicolau syndrome is primarily considered an injection-related vascular complication rather than a dose-dependent pharmacological adverse effect. The core mechanism involves accidental intra-arterial or peri-arterial injection, leading to immediate vasospasm, embolic occlusion by the drug suspension, or direct intimal injury. While the syndrome itself is not dose-dependent, the administration of a higher-than-recommended dose (1,200,000 IU in this 16-kg child) may have played a contributory role. A larger volume of the insoluble penicillin suspension can increase local hydrostatic pressure and mechanical compression of the microvasculature, potentially exacerbating the ischemic process triggered by the initial vascular insult [5].

The diagnosis of NS is primarily clinical. In our patient, the abrupt onset of symptoms following intramuscular benzathine penicillin injection, characteristic livedoid discoloration, and angiographic findings strongly supported the diagnosis over differentials such as compartment syndrome or necrotizing fasciitis [6]. Currently, no standardized guidelines exist for NS. Our patient was managed with a multidisciplinary conservative strategy including anticoagulation, topical nitroglycerin, and systemic corticosteroids. Anticoagulation was used due to concerns regarding microvascular thrombosis [4]. Topical nitroglycerin was administered to improve regional blood flow, and corticosteroids were used to reduce inflammation. Although the individual contribution of each intervention cannot be determined, this approach was associated with a favorable clinical course. Broad-spectrum antibiotics were also used prophylactically [5]. Unlike some previously reported cases that progressed to necrosis or limb loss, our patient demonstrated complete recovery without surgical intervention, likely due to exceptionally early recognition and prompt therapy [2].

This case contributes to the literature by documenting angiographic evidence of arterial involvement and successful limb salvage in a pediatric patient. While a single case report cannot establish the efficacy of specific interventions, it provides valuable clinical insights for managing this rare complication.

Conclusion

Nicolau syndrome should be considered in any child presenting with severe pain and livedoid skin changes immediately after intramuscular injection. While this single case report suggests that early diagnosis, prompt vascular assessment, and multidisciplinary conservative management may play a role in preventing irreversible ischemic injury and facilitating functional recovery, further research is needed to establish definitive treatment protocols. The findings in this case may indicate the potential value of CT angiography in evaluating vascular involvement and support the consideration of aggressive early supportive treatment as a potential limb-salvaging strategy in similar situations.

Learning Points

- Early clinical suspicion of Nicolau syndrome in pediatric patients presenting with post-injection ischemic skin changes is vital for timely intervention.
- Vascular imaging, particularly CT angiography, provides essential insights into the degree of arterial compromise.
- A prompt, multidisciplinary conservative strategy should be considered as a primary approach to prevent limb loss and promote functional recovery.

Ethical Considerations

Ethics Statement

Written informed consent was obtained from the patient's parents for the publication of this case report and any accompanying images. The management of the patient adhered to the ethical principles outlined in the Declaration of Helsinki.

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Conflict of Interests

The authors have no conflict of interest to declare.

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