DOI: 10.7860/JCDR/2025/80595.21490

Case Series

Dermatology Section

Embolia Cutis Medicamentosa Secondary to Commonly used Drugs: A Series of Four Cases

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ABSTRACT

Nicolau syndrome, also referred to as Embolia Cutis Medicamentosa, is a rare iatrogenic complication typically following intramuscular, subcutaneous, or intra-articular drug administration. It is characterised by the sudden onset of severe pain, followed by erythema, violaceous discoloration, and skin necrosis at the injection site. This report presents a case series of four patients aged 13, 30, 43, and 56 years, who developed Nicolau syndrome after intramuscular injections of commonly used drugs such as Deriphyllin, Diclofenac, Tramadol, and Betamethasone. The clinical presentation in all cases involved acute pain followed by ulceration or necrosis over the gluteal region. Diagnosis was primarily clinical, supported by normal laboratory parameters and ultrasonographic findings showing subcutaneous tissue changes. Management included conservative approaches such as wound care with topical antibiotics, systemic analgesics, and oral antibiotics as needed. All patients recovered with residual scarring and post-inflammatory hyperpigmentation. This case series emphasises the importance of correct injection techniques, including appropriate site selection (upper outer quadrant of the buttock), using the Z-track method, aspirating before injection, and employing appropriate needle lengths to minimise risk. Given that Embolia Cutis Medicamentosa is preventable, reporting such cases is crucial to raise awareness among healthcare professionals. Early diagnosis and appropriate intervention can significantly reduce the complications and morbidity associated with this condition.

Keywords: Deriphyllin, Intramuscular injection, Livedoid dermatitis, Non-steroidal anti-inflammatory drug, Tissue necrosis

INTRODUCTION

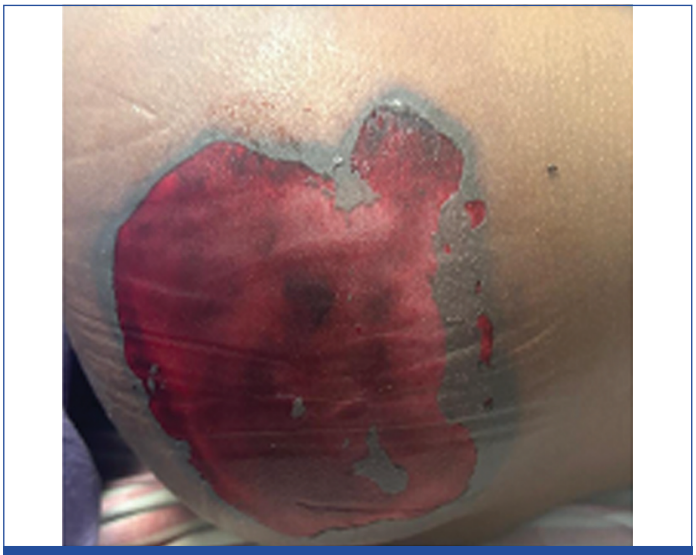
Embolia Cutis Medicamentosa, also known as Nicolau syndrome, Livedoid Dermatitis, or drug-induced embolic dermatosis, was initially identified by Nicolau in the early 1920s as a side effect of administering intramuscular injections of bismuth salts to treat syphilis [1]. Nicolau syndrome is commonly seen in patients following intramuscular, intra-articular, or subcutaneous injections of non-steroidal anti-inflammatory drugs, antiepileptics, antipsychotics, antibiotics, antihistamines, and corticosteroids. Nicolau syndrome typically presents in three phases, as summarised by Kim KK and Chae DS [2]:

1. Initial phase: Patients experience intense pain at the injection site, which is then accompanied by erythema or a bluish tint on the skin above, characterised by clear boundaries. At times, a reticulate or haemorrhagic patch may also appear.
2. Acute phase: This develops within 24 hours to three days. The lesion evolves into an erythematous, non-necrotic lesion, which may present as an indurated, painful, livedoid plaque with violaceous borders.
3. Necrotic phase: Ulceration and necrosis affect the involved skin, as well as the underlying subcutaneous tissue and muscle layers. It usually takes several months for the ulcer to heal, and complications such as scarring, contracture, and hypoesthesia often result from it [3].

The clinical presentation and history of drug injections are typically used to establish the diagnosis of Nicolau syndrome. Presented below are four cases of Embolia Cutis Medicamentosa following intramuscular injections of commonly used drugs.

Case 1

A 13-year-old female patient presented with bluish-black skin discolouration over her left buttock, accompanied by pain at the site that had been present for five days. Initially, she developed swelling and redness, which progressed to form a necrotic plaque [Table/Fig-1]. Five days earlier, she had been treated for fever and cough with an intramuscular injection of Deriphyllin at a local hospital, administered in the left buttock. Within two hours of the injection, she experienced dull, aching pain at the site, which later developed into a raw, ulcerated area. There was no history of trauma, topical medication use, or any other precipitating factors.



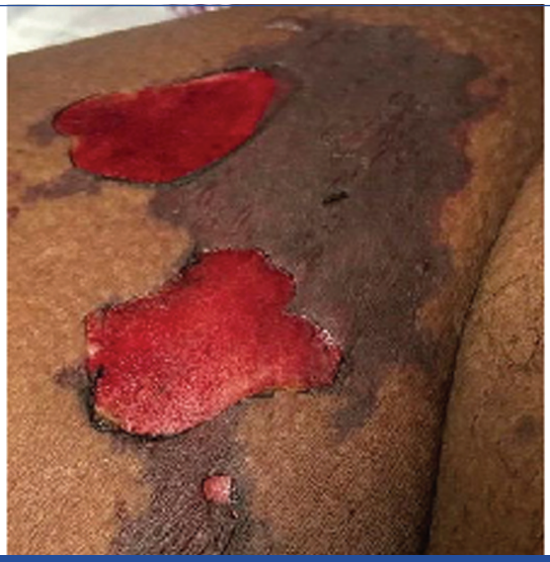
[Table/Fig-1]: A well-defined, necrotic violaceous erosion of size 12 cm × 10 cm with surrounding sharp violaceous margins present over the upper lateral quadrant of left buttock.

Over the following days, the lesion worsened and became necrotic. Her family and past medical history were unremarkable. Laboratory investigations, including complete blood count, bleeding time, clotting time, renal and liver function tests, creatine kinase, and urine analysis, were all within normal limits. The patient was informed about the progression of skin and soft tissue necrosis, which commonly leads to ulcer formation and scarring. A diagnosis of Nicolau syndrome was primarily made based on the clinical

features and history. Treatment included intravenous paracetamol, oral amoxicillin-clavulanic acid 625 mg twice daily for five days, and Bactigras dressings. She was advised to return for follow-up after one week. The lesion eventually healed, leaving behind post-inflammatory hyperpigmentation.

Case 2

A 30-year-old male presented to the emergency department with a painful raw area over his right buttock. He had received an intramuscular injection of Diclofenac at an unknown local clinic for severe back pain following a fall. Soon after the injection, he experienced intense pain at the site, which later developed into a blister and erosion. There was no significant medical or family history. On skin examination, an irregular, tender, violaceous necrotic patch with superficial erosions was observed over the gluteal area [Table/Fig-2]. There was no lymphadenopathy, and the systemic examination was unremarkable.

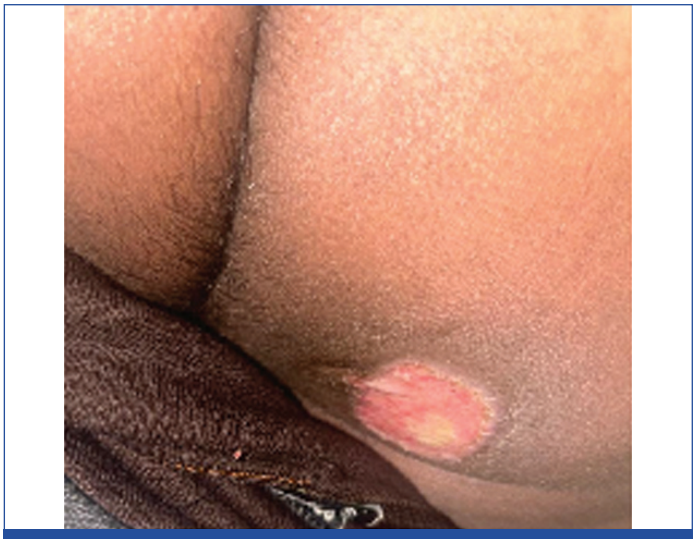


[Table/Fig-2]: Cutaneous examination showed an irregular, tender, violaceous necrotic patch with superficial erosions over gluteal region.

Laboratory investigations, including complete blood count, urine analysis, bleeding time, clotting time, liver and renal function tests, chest X-ray, and creatine kinase, were within normal limits. An ultrasound of the area showed increased echogenicity of the skin and subcutaneous tissue with no involvement of deeper structures. A diagnosis of Nicolau syndrome was made based on the history and clinical features. The patient was treated with oral cefixime 200 mg twice daily for five days, antibiotic dressings, and analgesics. He was advised to follow up after a week. The lesion healed with post-inflammatory hyperpigmentation.

Case 3

A 43-year-old male presented with a 10-day history of a painful lesion over his left gluteal region. Prior to the onset, he had received an intramuscular (intragluteal) injection of tramadol for joint pain. He reported immediate pain at the injection site, followed by the development of a bluish-red lesion, which gradually progressed into an ulcer over 10 days. On examination, there was a well-defined, round ulcer with sloping edges located over the gluteal area. The ulcer floor was covered with yellowish slough and granulation tissue, and the surrounding skin showed mild atrophy and desquamation [Table/Fig-3]. The patient had a known history of diabetes mellitus and was receiving treatment. He denied any other systemic illnesses or concurrent drug use. There was no evidence of local or generalised lymphadenopathy. Routine blood and urine tests were within normal limits, and liver and kidney function tests, creatine kinase, Venereal Disease Research Laboratory (VDRL) test, and HIV serology were all normal. Gram stain, wound culture, and sensitivity testing revealed that the organism was sensitive to ciprofloxacin. Based on the



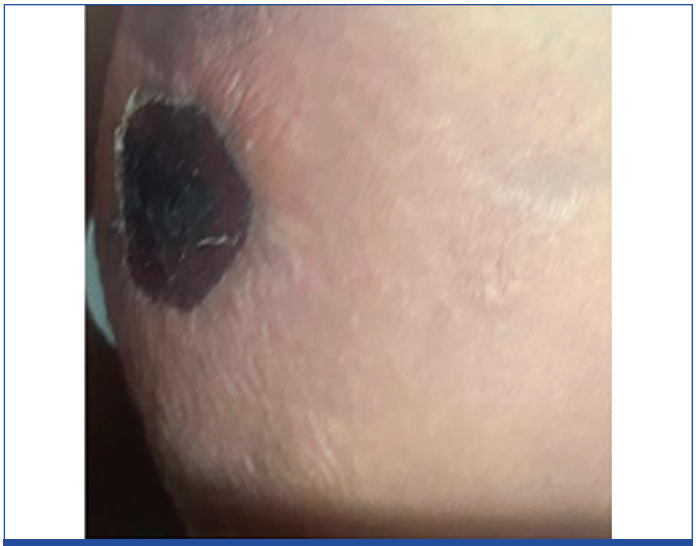
[Table/Fig-3]: A solitary, tender, ulcer of size 3×4 cms with yellowish slough present over the right gluteal region.

patient's history and clinical features, a diagnosis of Nicolau syndrome was made. The patient was counselled about the condition and its likely course. He was managed conservatively with topical fusidic acid ointment applied twice daily and oral pain relievers. A follow-up visit was scheduled for two weeks later; however, the patient did not return for further evaluation.

Case 4

A 56-year-old woman, undergoing treatment for bronchial asthma and hypothyroidism, presented with a 3-week history of blackish skin discolouration over the upper outer quadrant of her left buttock. Prior to this, she had an episode of severe coughing and wheezing, for which she received an intramuscular injection of Betnesol (betamethasone) at a local clinic. Although she felt immediate and persistent discomfort at the injection site, she initially assumed it was normal. In the following days, she developed intense redness and swelling in the area, which progressively worsened. Over time, the lesion enlarged, and she later noticed a blackish patch measuring approximately 5 cm by 5 cm, surrounded by redness [Table/Fig-4]. Laboratory investigations were normal, and the patient's vital signs remained stable. A diagnosis of Nicolau syndrome was made based on the history of the intramuscular betamethasone injection and the subsequent skin changes noted by the patient. The necrotic patch was debrided, and treatment included sterile dressings, oral antibiotics, and pain medication. The lesion eventually healed, leaving behind a scar.

A summary of all the cases is presented in [Table/Fig-5].



[Table/Fig-4]: Cutaneous examination showed a solitary large tender, non-indurated ulcer with necrotic eschar present over the left buttock.

Patient	1	2	3	4
Gender	Female	Male	Female	Female
Age	13 years	30 years	43 years	56 years
Injection side (quadrant of buttock)/ site	Left upper lateral/ Intramuscular	Right upper lateral/ Intramuscular	Right lower lateral/ Intramuscular	Left upper lateral/ Intramuscular
Drug administered	Deriphyllin	Diclofenac	Tramadol	Betamethasone
Comorbidities	None	None	Diabetes Mellitus – Type 2	Bronchial asthma and hypothyroidism

[Table/Fig-5]: Summary of cases.

DISCUSSION

Nicolau syndrome is a rare complication that can occur following parenteral drug administration. The proposed mechanisms for its pathogenesis include local arterial vasospasm due to sympathetic stimulation, arterial embolism from the intra-arterial injection of microcrystals, and ischaemia resulting from compression after vascular or perivascular injection [4]. Histopathological evaluations in the case studies by Udawatta M et al., and Kumawat K et al., revealed thrombosis of medium- and small-sized vessels, notably in the absence of accompanying vascular inflammation [5,6]. Nicolau syndrome can affect women of any age, but it primarily affects children and those between the ages of 31 and 40 years, according to Mojjarad P et al.,'s analysis of 135 cases from several databases [7].

In paediatric cases reported by Kumar V et al., patients with bupivacaine-induced Nicolau syndrome were treated with a combination of pentoxifylline, Omnacortil (corticosteroid), cetirizine, and topical steroid cream, resulting in lesion stabilisation and eventual healing [8]. A 2024 case series by Korpinar S demonstrated that adjunctive Hyperbaric Oxygen Therapy (HBOT), administered 5 to 33 days post-injection alongside standard wound care and anticoagulation, expedited healing in four Nicolau syndrome patients without complete tissue loss [9]. Because there are fewer major blood vessels in the upper outer quadrant of the buttock, this is the ideal location for intramuscular injection [10]. However, certain safety measures should be taken into account to reduce the risk of Nicolau syndrome.

Nicolau syndrome can be reduced or avoided by employing the Z-track technique, which involves injecting a needle and syringe intramuscularly into a major muscle. In order to monitor for blood return, injections should be administered gently, and aspiration should be performed beforehand. The needle length should be adequate to ensure proper intramuscular injection [11].

CONCLUSION(S)

Embolia cutis medicamentosa is an avoidable complication. Patients should be educated on the warning signs and should be properly monitored following injections. To raise awareness among medical professionals and the general public, this case series is being published.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 16, 2025
- Manual Googling: Jul 23, 2025
- iThenticate Software: Aug 02, 2025 (16%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **May 13, 2025**
Date of Peer Review: **Jun 02, 2025**
Date of Acceptance: **Aug 04, 2025**
Date of Publishing: **Sep 01, 2025**