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Nicolau syndrome, embolia cutis medicamentosa, an iatrogenic consequence of intramuscular injections: a case report and literature review with a synthesis of case studies

Abstract

Introduction: Nicolau syndrome (NS) was first described in 1924 by Freudental and Nicolau in a syphilis patient that was treated with injections of bismuth. NS is characterized by skin necrosis secondary to vascular occlusion caused by intramuscular drug injections. Recent literature has shown that livedoid dermatitis and embolia cutis medicamentosa are symptoms of Nicolau syndrome, which develop into a hemorrhagic bullae. The bullae then progress to necrotic ulcerations that may lead to infection, ischemia and even limb loss.

Purpose: To describe Nicolau Syndrome and the life-altering effects it can have on patients.

Methodology & procedure: A systematic review of studies published in the Medline database from January 2018 through July 2022 was conducted to identify articles that evaluated the causes and symptoms of Nicolau Syndrome. The systematic review was conducted following the PRISMA guidelines with an inclusion criteria of Nicolau syndrome diagnosis with no exclusion criteria. Summary tables were generated from the included studies for case specific indications of the intramuscular injection(s), sequence of symptomology, any treatment(s) administered and outcome of the syndrome for each case.

Results: 36 Cases of NS were reported in the last 5 years from our literature search. The PRISMA flow diagram will show the reported cases, sex, age, what the injection consisted of, the number of recorded injections in the past 3 and 5 years and treatments (if rendered) with outcomes, if data is available. Spontaneous resolution was seen in a few select cases, although most ended up with some type of debridement/amputation.

Case description: Our patient was a 47-year-old female with a long history of corticosteroid injections including the neck, back and upper extremities, with her most recent injection for plantar fasciitis of her left foot. After the injection she was prescribed oral Cephalexin that she took for two days before presenting to the emergency department with a small lesion that had dermatological changes consistent with bruising/contusion. Over the course of the month, the patient's lesion continued to deteriorate despite several treatment attempts from a multidisciplinary limb salvage team. Ultimately, she underwent a left lower extremity below-knee amputation.

Discussion: Use of intramuscular injections across all fields of medicine is commonplace and it would appear physicians overlook or are unaware of the risks of Nicolau Syndrome. Although the pathogenesis is still debated, researchers have theorized that sympathetic activation results in vasoconstriction, embolic occlusion of microcirculation, and prostaglandin synthesis inhibition.

Volume 14 Issue 1 - 2024

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Received: March 09, 2024 | **Published:** March 22, 2024

Introduction

Nicolau syndrome (NS) was first described in 1924 by Freudental and Nicolau in a syphilis patient that was treated with injections of bismuth.[1] NS is characterized by skin necrosis secondary to vascular occlusion caused by intramuscular drug injections. It is characterized by skin blanching and acute injection site pain subsequent to intramuscular injection. This skin blanching progresses to a violaceous livedoid dermatitis; which proceeds into a hemorrhagic bullae followed by a necrotic ulceration.[1,2] The necrotic ulceration may be a nidus for infection, further ischemia or may even progress to an amputation.[2] A variety of theories have been proposed in regards to the pathophysiology of this disease, however, the current consensus appears to be that NS develops from vascular occlusion due to the trauma of the injection and/or the crystallization of the drug within the blood vessel(s).[3] Our aim is to educate our colleagues on the life-altering pathology of Nicolau Syndrome, an associated complication of intramuscular injections.

Methodology & procedure for synthesis of case studies

A systematic review of studies published in the Medline database from January 2018 through July 2022 was conducted to identify articles that evaluated the causes and symptoms of Nicolau Syndrome. The systematic review was conducted following the PRISMA guidelines. Studies including the upper extremities and animal models were excluded. Summary tables were generated from the included studies for case specific indications of the intramuscular injection(s), if any drug(s) was utilized during injection, sequence of symptomology, any treatment(s) administered and outcome of the syndrome for each case

Background

36 Cases of NS were reported in the last 5 years from our literature search. 2 studies were excluded due to lack of outcome/treatment reporting. Table 1 illustrates the included cases (n=34), patient outcomes and location of the initial site on injection. Complete resolution was seen in 27 reported cases. Of the 26 reported complete resolutions: 13 initial sites of injection occurred in an extremity of the patient, 8 initial sites of injection occurred in the gluteal region, 4 initial sites of injections occurred in the torso, 2 initial sites of injection occurred in the head. 6 cases resulted in amputation of extremity. 1 case resulted in expiration of the patient secondary to sepsis acquired from infection of the wound site. Table 2 illustrates the contents of reported injections. 10 injections consisted of Penicillin G Benzathine, 5 injections consisted of Diclofenac, 5 injections consisted of Glatiramer acetate, 1 injection consisted of each of the following: Lidocaine, Buprenorphine, Dicyclomine, Terlipressin, Cyclizine, Paracetamol, Cloxacillin and Dexamethasone, Vitamin K, Demerol and Phenergan, 0.9% Saline, Calcium Hydroxide, mRNA-1273 COVID-19 vaccine, secondary to trauma from a sewing needle.

Table 1 Illustrates the included cases (n=34), patient outcomes and location of injection site

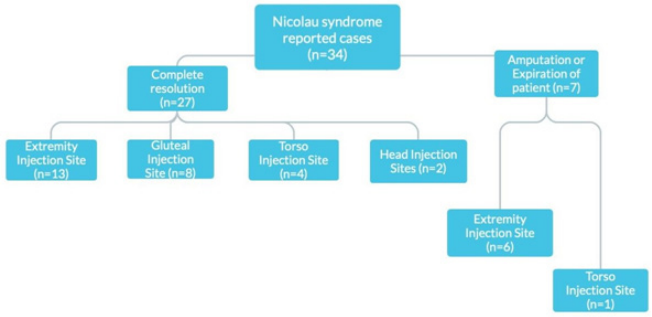
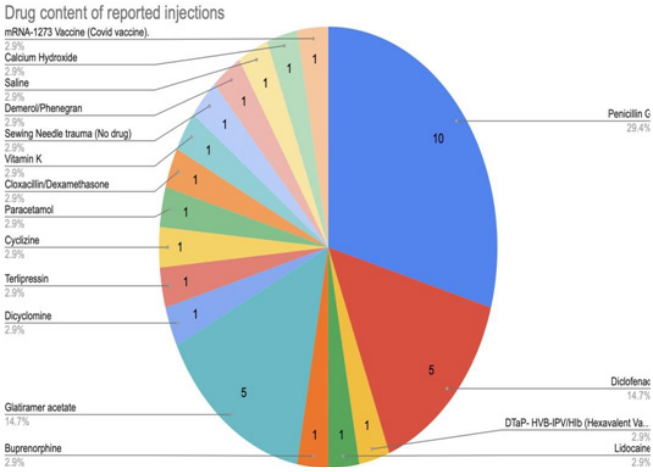


Table 2 Distribution of drug content to disease progression



The authors noted the variety of treatments utilized between each case. Of the 12 complete resolution cases in the extremity: 3 noted no treatments rendered, 3 used topical antibiotics/outpatient wound care dressing changes and serial debridement's, 2 cases underwent surgical debridement, 2 cases solely used intravenous antibiotics, 1 case carried out a fasciotomy on the extremity and 1 case used hyperbaric oxygen therapy.

Of the 8 cases of complete resolution within a gluteal site of injection: 1 case rendered no treatment, 1 used oral antibiotics and analgesics, 1 used intravenous steroids alone, 1 used oral Diclofenac, 1 case used electrophysical therapy, 3 cases underwent surgical debridement. Of the 4 cases of complete resolution where the torso was the initial site of injection: 1 case used topical Mupirocin, 1 case used IV Heparin, 1 case used topical betamethasone and 1 case rendered no treatment. Of the 2 cases of complete resolution where a region of the head was the initial site of injection: 1 case carried out surgical debridement and split thickness skin graft with chondral cartilage graft and 1 case used oral antibiotics with analgesics followed by endodontic revisional surgery. Treatments utilized for the 6 cases of limb amputation consisted of: 1 fasciotomy, 4 serial debridement's and no treatment rendered in 1 case. 1 patient with an injection site that was in the torso expired secondary to sepsis that was acquired from the wound site.

Case report

Our patient is a 47-year-old Caucasian female, 5'0 and 210lbs, who presented to the emergency department with left lower extremity (LLE) cellulitis. PMH significant for Type II Diabetes, PAD, COPD, and an elevated BMI of 41. Patient reported serial corticosteroid injections in many other locations including but not limited to her neck, back, gluteal region, upper extremities, with the most recent injection in her left foot for chronic plantar fasciitis. Patient reported that the injection was mixed with a corticosteroid at a local Podiatrist's private office (unable to obtain documentation regarding the mixture), which was administered on 10/1/21.

Patient reported pain and erythema at the injection site the days following injection and was prescribed PO Cephalexin 500 mg BID (10/4/21) by the podiatrist who administered the injection. Patient presented to the emergency department on 10/6/21 with worsening symptoms and more proximal erythema of the LLE, despite taking oral antibiotics (Figure 1). Palpable pedal pulses were appreciated bilaterally upon initial evaluation in the ED. On 10/11/21, an incision and drainage (I&D) of the left foot was performed into the subcutaneous tissue of the calcaneal fat pad and was found to be necrotic with no bleeding or viable tissue (Figure 2).

Further excisional debridement was carried down until healthy bleeding was reached at the level of the lateral midfoot and posterior-superior aspect of the calcaneus. Figure 3 illustrates the wound had plateaued 3 days post-operatively (10/14/21) and as such, a subsequent I&D was carried out on 10/21/21 with application of negative pressure wound therapy (Figure 4). On 10/26/21 another repeat I&D was performed due to the appearance of the left heel, which revealed distal midfoot purulence and minimal bleeding (Figure 5). All devitalized tissue was removed down to and including the level of bone. A deep wound culture and bone biopsy were taken of the calcaneus with minimal bleeding; which revealed growth of Vancomycin Resistant Enterococcus faecium, confirming acute osteomyelitis of the left calcaneus.

On 11/4/21 Vascular Surgery was consulted and determined there were no options for re- vascularization as there were occlusions of the posterior tibial and peroneal arteries at the level of the left mid-calf. Patient was offered a below knee amputation (BKA) as there was no viable treatment alternatives. During this time, there was a resurgence in COVID-19 which led to a restricted visitation policy for inpatients. Patient reported they needed additional time to make a treatment decision as she was dealing with concurrent marital and psychological issues. On 11/17/21, a left BKA was performed by Vascular Surgery (Figure 6) and appeared to be healing uneventfully as she was discharged to a short-term rehab facility on 11/30/21.

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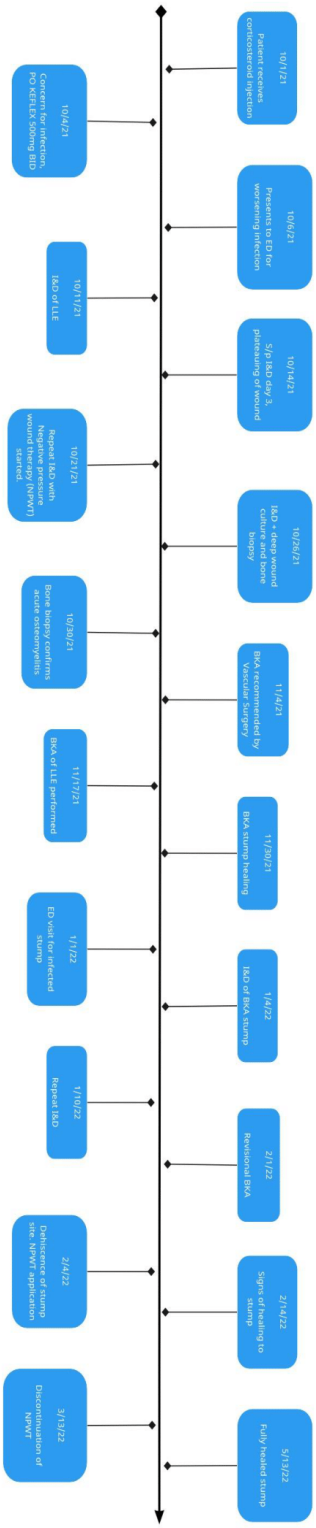
Unfortunately, our patient returned to the emergency department on 1/1/22 with an infected left BKA stump necessitating multiple debridement's by Vascular Surgery over the next month including a revisional BKA with negative pressure wound therapy (2/4/22). Local wound care was carried out until the stump was completely healed (5/13/22) and has been ulcer free since with no further hospitalizations or complications, to our knowledge (Table 3).

Table 3 Timeline of our case report



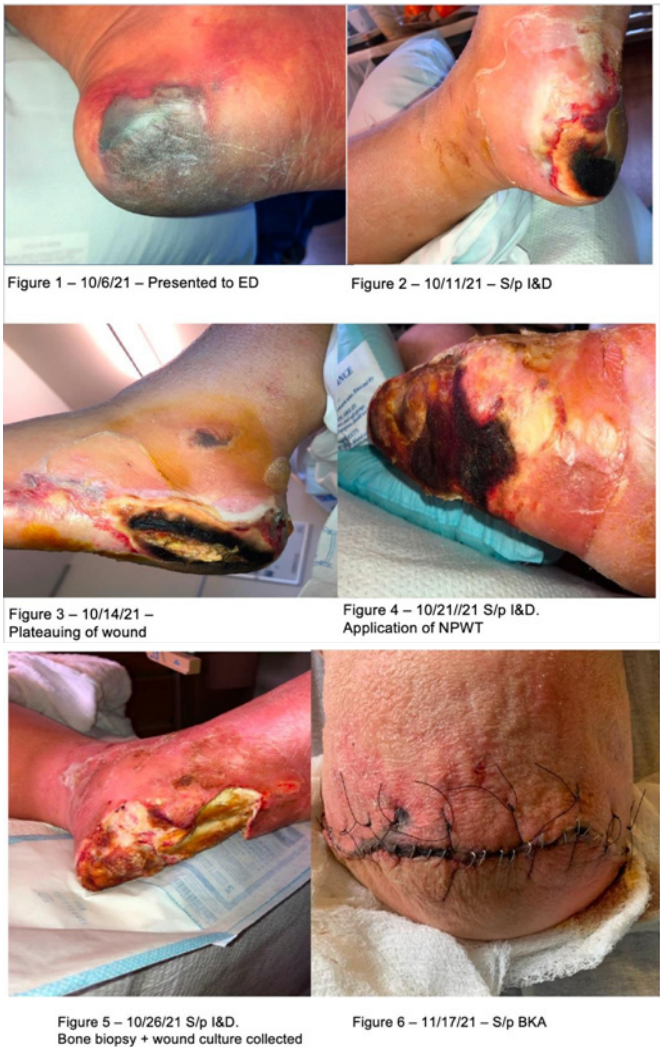


Figure 1-6

Discussion

The use of intramuscular injections is commonplace in the field of medicine and although injections carry relatively minor risks, we must take a minute to appreciate the very real complications that can occur after an injection. After a literature review, it was found that surgical intervention is rarely required and three hypotheses are given for the pathophysiology of said disease.

Hypotheses for this syndrome:

a. An accidental intra-arterial injection of crystalloid drugs may produce embolic obstruction of the small and medium size cutaneous arteries by microcyrtsals that produce subsequent tissue necrosis.[3]

b. Damage to an end artery due to a periarterial injection or a perineural injection may produce intense local pain with secondary sympathetic overstimulation that triggers extensive vascular spasm and compromised circulation.[4]

c. Perivascular injection may produce inflammation, tissue necrosis and damage to the walls of the cutaneous arteries. Arterial damage leads to skin necrosis.[5]

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As illustrated in a case report published in 2020 by Tougouma et al., even the standard of care of intramuscular penicillin injections demonstrates devastating aftermath if not approached with caution.[2] In another case report, a 5-year old patient received an intramuscular injection of penicillin that developed into a bullae at the injection site, progressed to necrotic lesions and ultimately resulted in an above knee amputation.[6] Marcus et al. published a case report in 2019 which further conveys the danger of intramuscular injections; a 21-year old patient required administration of penicillin intramuscular injection for the management of a sexually transmitted infection. Within the span of a few days the patients' injection site developed skin discoloration, extreme pain and myonecrosis.[5] The patient needed an above knee amputation in order to prevent the myonecrosis from progressing more proximally.

Currently there is no standard of care for patients that develop Nicolau Syndrome[1,2,4-6] which further highlights the unpredictability of this dangerous pathology. A total of 34 cases of Nicolau syndrome have been reported on Pubmed database in the past 5 years that matched our inclusion criteria. 27 of these cases cite the use of a monitoring/conservative approach for management of NS. Use of IV/PO antibiotics was commonplace to curtail infection of said lesion(s). If these measures fail to control the migrating necrosis, then removal of all devitalized tissue and even an amputation of limb may be required. 7/34 cases reported immediate use of amputation. Although the literature illustrates this pathology as rare, one must contemplate if the loss of limb and (or) life outweighs the benefits of injection. Our case report is not intended to dissuade the use of IM injections, but rather to remind us to be judicious with them in the medical field. A physician may see a plantar fasciitis corticosteroid injection as innocuous, however, we should consider any injection as potentially life-altering. Further research focusing on an effective standard of care for NS is necessary, as well as to understand the pathophysiology of the disease. Proper patient education of the risks and benefits of each injection administered combined with meticulous technique may help with preventing cases of Nicolau Syndrome.

Conclusion

As highlighted in the authors' case report: although IM injections may seem innocuous initially, they hold the ability to cause life-altering consequences for any patient. Despite our best efforts of limb salvage, our patient's limb had to be amputated, below the knee. Based upon current literature, there is no standard of care or guidelines on treating Nicolau Syndrome, which leaves practitioners in a peculiar position of having to treat the dermatological lesion based on their experience or what they may have encountered historically. Although Nicolau Syndrome is a rare complication of intramuscular injections, the aim of the author's are to urge all physicians and health care professionals to remain judicious with administration of any form of injections, as an injection is a procedure in and of itself and as such carries associated risks and complications.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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