

CLINICAL VIGNETTE

Nicolau Syndrome: A Rare Injection Site Reaction

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Introduction

Nicolau syndrome (NS) is a rare complication of intramuscular, intra-articular, or subcutaneous injection of a medication leading to ischemic necrosis of the skin, soft tissue, and muscular tissue.¹ This uncommon reaction has also been described as "embolia cutis medicamentosa" and "livedoid dermatitis".^{2,3} NS is characterized by intense pain at the injection site, hyperemia, skin discoloration or purplish discoloration of the overlying skin, with or without a reticulate pattern, redness, abscess formation, and local ischemic necrosis involving the skin and adipose tissue. The pathogenesis is unknown but the prevalent hypothesis is initial vascular injury with local inflammation, reflex arterial spasm, local arterial thrombosis, and vascular occlusion by microemboli.⁴ NS complications may range from reversible skin reactions to gangrene of extremities that can lead to amputation, paralysis of lower extremities, sciatic nerve damage, compartment syndrome, renal failure, and possible death. We report a 76-year-old male with Nicolau syndrome following an intramuscular injection of naltrexone for alcohol use disorder.

Case Report

The patient is a 76-year-old male with a history of chronic alcohol use disorder, cognitive impairment, hypertension, and hyperlipidemia presenting with a chief complaint of right lateral buttock and hip pain radiating down his right leg. The pain started earlier in the day, after he received an intramuscular (IM) injection of naltrexone in the affected area. This was the patient's first injection of naltrexone. Shortly after the injection he developed abnormal skin changes and severe pain which persisted throughout the day. Pain was significant at rest, worsened with weight bearing, and he was unable to find a comfortable position due to pain and restlessness. His daughter, who was at bedside, also reported that he was more confused on the day of admission compared to his baseline. He did not have a history of hip or leg pain and was ambulating without difficulty prior to receiving this injection. He denied any recent illnesses, and he had been in his usual state of health. He denied fevers, chills, nausea, vomiting, diarrhea, abdominal pain, chest pain, shortness of breath, vision changes, headache, urinary symptoms, or numbness or tingling. His daughter reported they were advised by his doctor to present for evaluation after they were told that necrosis is a possible side effect of IM naltrexone.

The patient's chronic medications included amlodipine, atorvastatin, bupropion, and methylphenidate. His geriatrician

recently ordered naltrexone 380mg IM injection every week for alcohol use disorder, with the first injection given earlier on the day of admission. On exam, patient was slow and confused, but alert and oriented to person, place and time. Other pertinent exam findings included erythematous to violaceous reticular patches on his right buttocks (Figure 1). Gait was antalgic. Laboratory analysis was most significant for a Creatinine Kinase (CK) elevated to 29,972, as well as leukocytosis to 10.8. Aspartate Aminotransferase (AST) was elevated to 666 and Alanine Aminotransferase (ALT) was elevated to 229. CRP and ESR were within normal range. His urinalysis showed 3+ blood, 1+ ketones, and 1+ protein. Pertinent labs and trends are summarized in Table 1. Imaging studies included a CT abdomen/pelvis with contrast which showed no radiologic evidence of acute pathology in the abdomen or pelvis. A 2-view right hip x-ray revealed advanced degenerative disease of the lower lumbar spine without any acute bony findings.

The patient was admitted for further management and pain control. He was initially treated with intravenous fluids and pain medications. The CK level was trended and electrolytes and creatinine were closely monitored. Dermatology was consulted and recommended starting aspirin 81 mg daily and pentoxifylline 400mg daily as part of treatment for Nicolau Syndrome. Dermatology offered biopsy to confirm diagnosis, but family declined. His CK downtrended to 21,995 by hospital day 2. On hospital day 2, pentoxifylline was increased to twice daily per Dermatology recommendation. The patient's pain had improved and mental status was at baseline. We continued to monitor the patient to ensure that the rash did not progress and that necrosis or ulceration did not develop. Abdominal ultrasound was done in context of abnormal liver function tests, which revealed a normal liver without any focal lesions, gallstones, or biliary dilatation. All laboratory values ultimately improved. Given swelling and bruising, a right lower extremity duplex ultra-sound was performed and was negative for deep venous thrombosis. Aspirin was stopped due to the significant bruising. There was no clinical evidence of compartment syndrome, and he was able to ambulate steadily with a walker. Throughout admission he displayed no signs of alcohol withdrawal. He was eventually discharged home on hospital day 7 with continued course of pentoxifylline, home health services, and scheduled outpatient follow-up.

Discussion

Nicolau syndrome is a rarely described injection site reaction. NS was first described by Freudental and Nicolau as an adverse cutaneous reaction to intramuscular injection of bismuth in patients treated for syphilis in 1925.^{1,4,5} Substances reported to cause the syndrome include local anesthetics, antihistamines, the vitamin B complex, non-steroidal anti-inflammatories, antibiotics, antipsychotics, anti-epileptics, vitamin K, corticosteroids, diphtheria, tetanus and pertussis vaccines, and meperidine.^{3,4,6-8} Naltrexone is an FDA-approved treatment for alcohol use disorder in the outpatient setting for those who are unable to abstain from alcohol use.^{9,10} Naltrexone reduces alcohol consumption by decreasing mesolimbic opioidergic activity and thereby toning down the dopamine-mediated rewarding effects of alcohol.¹¹ Common adverse effects of naltrexone include somnolence, nausea, vomiting, insomnia, dizziness, abdominal pain, decreased appetite, and injection site reactions.^{9,12}

The pathogenesis of NS is not very well understood. The proposed mechanisms include localized sympathetic reactive vasospasm following intra-arterial or perivascular injection, arterial embolism caused by intra-arterial injection of microcrystals, and ischemia caused by microvascular thrombosis.¹³ The etiology of NS seems to be related to the physical injection itself rather than from the medication being injected, although it remains unclear.⁵ The syndrome typically manifests with intense pain and pallor at the injection site due to local reflex vasospasm, progressing to an erythematous macule, and after approximately 24 hours evolving into a livedoid violaceous patch with dendritic extensions with both hemorrhagic and necrotic components.^{4,14} The livedoid rash developing immediately after an intramuscular injection is particularly consistent with a diagnosis of Nicolau syndrome.⁵

There is no specific treatment for NS.^{1,4,5,15} Administration of anticoagulants, intravenous corticosteroids, and vasoactive therapy (i.e. pentoxifylline) are reported to support the clinical improvement of patients.¹⁵ Other treatments include antibiotics, wound dressings, skin grafting, and flap reconstruction.^{16,17} Although the majority of lesions in Nicolau syndrome are confined to the injection site, the skin changes (ecchymosis and rash) in our patient spread from his right gluteal area down his right leg. He had a favorable outcome as he had no signs of deep ulceration at the lesion sites, evidence of necrosis, or compartment syndrome, which was monitored for closely while he was in the hospital.

In conclusion, although NS is a rare adverse reaction that affects injections sites, it can be seen in patients who receive intramuscular, intravenous, subcutaneous, or other routes of parenteral drug administration. Healthcare providers should be aware of this complication when administering injections. Prevention is key and accomplished by avoiding accidental intra-arterial or perivascular injection. Clinicians must ensure that their medical staff are properly trained in the correct method of intramuscular injection, the correct Z-track injection

method, appropriate needle length selection, injection site rotation, and aspiration before injection. Early recognition of these signs and symptoms can help facilitate prompt initiation of specific therapy. This may prevent adverse outcomes, which include loss of a limb due to tissue necrosis or serious infection that could lead to death. Due to rarity of NS, clinicians may not always associate the development of the necrotic skin changes with a history of injections at these sites. As always, a detailed history is paramount to the comprehensive evaluation of a patient.

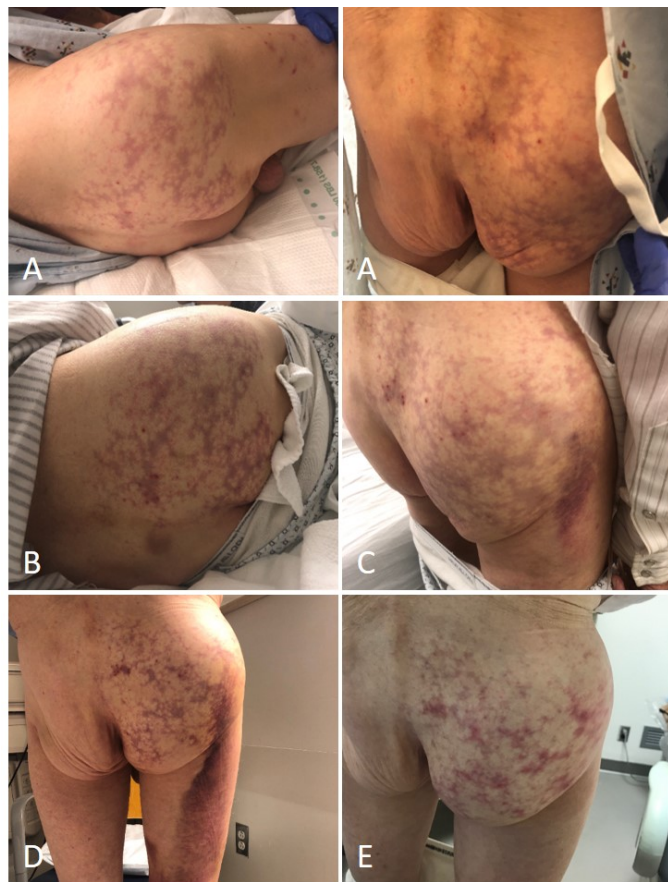


Figure 1. Pictures demonstrating patient's rash and its evolution. A: Hospital Day 1. B: Hospital Day 2. C: Hospital 3. D: Hospital Day 6. E: Approximately 2 weeks from initial presentation.

Lab	Admission	Hospital 2	Discharge
WBC	10.88	8.46	5.8
Hgb	13.8	12.6	11.9
Plt	198	169	198
AST	666	690	388
ALT	229	265	264
CK	29,972	21,995	6,902

Table 1. Pertinent lab values and trends

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