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Nicolau syndrome associated with fluphenazine depot: A case report

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Abstract

Nicolau syndrome is a rare condition characterized by severe pain at the site of injection, leading to ulceration and necrosis of the local tissues. Its presentation is usually acute. Nicolau syndrome is commonly seen in patients after intramuscular, intra-articular, or subcutaneous injections of non-steroidal anti-inflammatory drugs, antiepileptics, antipsychotics, antibiotics, antihistamines, and corticosteroids. Immediate diagnosis and management of this syndrome are of great importance. We herein report a rare presentation of Nicolau syndrome in a 36-year-old married male who suffered from paranoid schizophrenia for the past 3 years. The patient presented with dull pain, mild swelling, and necrotic ulceration over the injection site after receiving intramuscular fluphenazine. The patient underwent wound debridement and was given prophylactic antibiotics. Despite a wide range of therapeutic options for the management of Nicolau syndrome described in the literature, there exist limited guidelines for its management.

Keywords

Case report, depot antipsychotics, injection site ulceration, adverse reaction, fluphenazine, Nicolau syndrome

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Introduction

Nicolau syndrome, also known as livedoid dermatitis or embolia cutis medicamentosa,[1] is a rare and potentially serious complication that can occur after injecting medication into the skin or subcutaneous tissue. It can be caused by intramuscular, intravascular, intra-articular, or subcutaneous injections.[2,3] Nicolau syndrome following intramuscular injection is most commonly seen following penicillin and non-steroidal anti-inflammatory drugs (NSAID) injections.[2] Intravascular injections have also been commonly incriminated.[2–4] The symptoms of Nicolau syndrome typically develop within 24–48 h after injection and may include pain, localized edema, tenderness on palpation, and skin discoloration at the injection site. In severe cases, the affected skin may become necrotic and slough off and may be accompanied by fever, chills, and malaise. In such cases, surgical intervention may be needed to remove the necrotic tissue and prevent further tissue damage. Although the pathogenesis of tissue necrosis is not well understood, it is believed that it is induced by direct vascular injury, perivascular inflammation, and vascular constriction.[5] The diagnosis of Nicolau syndrome is typically made based on the clinical presentation and history of medication injection. It is important to differentiate Nicolau syndrome from other conditions that can cause similar symptoms, such as cellulitis or abscess, as the treatment and management of these conditions can be different.[6] Prevention of Nicolau syndrome involves ensuring proper technique when administering injections, including avoiding injecting medications into arteries or arterioles and using appropriate injection sites and needles. It is also

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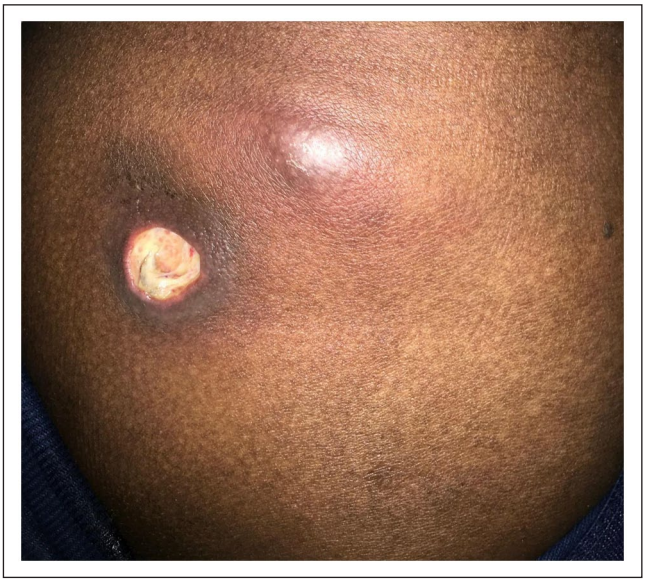

Figure 1. Injection site ulceration along with a lump over the right gluteal region.

important to follow the recommended dosing and frequency of medication use, as excessive use of certain medications, such as NSAIDs, can increase the risk of developing Nicolau syndrome.[6]

The literature on the occurrence of Nicolau syndrome after intramuscular antipsychotic injection is scarce. Here we discuss a case of Nicolau syndrome in a 36-year-old male patient with a significant past medical history of paranoid schizophrenia caused by intramuscular fluphenazine.

Case report

The patient was a 36-year-old married male, a farmer by occupation. He had been suffering from paranoid schizophrenia for the past 3 years, with partial improvement of psychotic symptoms while treated with oral medication: tablets risperidone 6 mg/day and trihexyphenidyl 4 mg/day. The patient was found to have poor compliance. Hence, fluphenazine (25 mg), intramuscular long-acting (LA) injection, was initiated fortnightly along with existing oral medications, as previous multiple attempts to improve adherence failed. The patient used to come for follow-ups every month on an outpatient basis. He used to receive the depot injection from a psychiatric nurse near his place. On follow-up after 1 month, the patient complained of dull pain over the injection site. On local physical examination, mild swelling was noticed and this was managed by a brief course of analgesics: diclofenac 50 mg two times per day for 5 days. On the second follow-up, the pain increased in severity with high-level discomfort in movement. The injection site was examined by the resident. A 4-cm × 4-cm deep-seated necrotic ulceration (Figure 1), along with two other lumps over the previous injection sites, was noticed. In view of the above complication, a further dose of fluphenazine was stopped and the patient was immediately referred to general surgery consultation for evaluation and management. Wound debridement along with wide excision of margins was done by the surgeon and a course of prophylactic antibiotics (cephazolin 2 g intravenous for 5 days) was given. It took another 2 months for the wound to heal.

Discussion

Patient adherence to antipsychotics is essential for successful treatment of schizophrenia.[7] With regard to medication adherence, long-acting intramuscular antipsychotics (LAIAs) provide therapeutic benefits and are often used in schizophrenia. LAIAs increase adherence and reduce relapse rates in schizophrenia.[2,8]

LAIAs have the same side effects as oral formulations, except for an added risk of rare injection site reactions[3,8] which have been scarcely reported in the published literature (Table 1). Small sample sizes limit identification of such serious side effects in controlled clinical drug trials.[8] High drug doses, frequency, volume, and lipophilic drug delivery medium increase the risk of injection site reactions.[8,15] However, a meta-analysis by Ting et al.[16] revealed that different injection frequencies of the same depot antipsychotic at equivalent doses did not lead to differences in adverse events such as injection site pain.

Fluphenazine decanoate is a cost-effective and widely used depot antipsychotic in developing countries. Few cases of necrotic and inflammatory injection site reactions with first-generation LAIAs have been documented in the literature.[8,14] However, there were no occurrences of Nicolau syndrome, a severe type of injection site reaction, associated with fluphenazine decanoate depot injections.

LAIAs have increased adherence to therapy, but first-generation antipsychotics, especially oil-based formulations such as fluphenazine decanoate and haloperidol decanoate, are mostly linked to painful and severe necrotic injection site reactions.[8,14] However, second-generation long-acting injectables such as paliperidone palmitate, aripiprazole monohydrate, risperidone, and olanzapine pamoate have limited injection site responses, which were mostly mild and inflammatory in nature.[6,8,13,14,16] Second-generation injectables use hydrophilic aqueous-based formulations, resulting in fewer injection site responses than first-generation LAIAs.[8,14]

Haloperidol decanoate and fluphenazine decanoate LA injectables utilize a lipophilic sesame oil vehicle.[6] Decanoate drugs have a 20% incidence of injection site reactions over a 12-month period.[6,11] Jones et al.[11] found that 15% of patients treated with fluphenazine decanoate developed clinically significant depot site reactions. These reactions to lipophilic formulations can lead to non-adherence to treatment and relapse of schizophrenia. Reactions to lipophilic formulations have included bleeding, pain, lumps, indurations, nodules, muscle granulomas, fibrosis, abscess, accumulation of oil, and scar tissue formation.[6,8,9,11]

Table 1. Studies presenting antipsychotic-induced injection site reactions.

Study	Nature of study	Country; year of study	Drug(s) administered	Treatment administered
Hay[9]	Cross-sectional	UK; 1995	Haloperidol, zuclopenthixol, fluphenazine, flupenthixol	Not reported
Faucher and Marcoux[10]	Case report	Canada; 1995	Meperidine hydrochloride 12.5 mg, promethazine hydrochloride 3.25 mg, and chlorpromazine hydrochloride 3.25 mg	Conservative management involving local disinfectant, topical antibiotic ointment (mupirocin), sterile petrolatum gauze, and dry dressings
Jones et al.[11]	Cross-sectional	UK; 1998	Haloperidol, flupenthixol	Not reported
Andrade[12]	Case report	Australia; 2002	Flupenthixol decanoate	Not reported
Lindenmayer et al.[13]	Analysis report of two randomized clinical trials	USA; 2005	Risperidone	Not reported
Atkins et al.[14]	Meta-analysis	USA; 2014	Olanzapine	Cefalexin was given to five patients for diverse events (two patients with abscesses, two with injection site reactions, and one with a mass), amoxicillin was given to one patient with an injection site reaction, and betamethasone was given to one patient with a rash.
Leung et al.[6]	Case report	USA; 2015	Paliperidone palmitate	Norepinephrine, phenylephrine, levofloxacin, piperacillin/tazobactam, and vancomycin
Tan et al.[15]	Case report	USA; 2015	IM paliperidone	10-day treatment of daptomycin and 7 weeks of wound care.
Kern Sliwa et al.[8]	Phase 3, randomized, double-blinded, parallel-group, multicenter, noninferiority study	UK; 2018	Paliperidone palmitate	Not reported
Ting et al.[16]	Systematic review and meta-analyses	Australia; 2019	Risperidone, paliperidone, olanzapine, fluphenazine, aripiprazole	Not reported
Present study	Case report	Australia; 2023	Fluphenazine	Wound debridement along with wide excision of margins was done by the surgeon and a course of prophylactic antibiotics (cephazolin 2 g) was given.

IM: intramuscular.

Possible explanations for Nicolau syndrome have been suggested, such as an acute vasospastic reaction to the needle injection, vaso-occlusion, or local pressure around vessels by the injected substance, causing direct vascular injury, perivascular inflammation, and local, aseptic tissue necrosis.[6,8,17] Drug leakage around neurovascular tissue has been suggested as a cause of pain.[17] Sympathetic nerve stimulation causing vasospasm has also been suggested to play a role, leading to ischemia and necrosis.[17] Obesity (body mass index (BMI) of more than 30) can be a risk factor for Nicolau syndrome due to inadvertent injection of drugs into subcutaneous fat.[3,12] This could also be linked to the negative effect of obesity on tissue microcirculation, increasing the likelihood of tissue ischemia.[18]

Nicolau syndrome typically presents in three phases, as summarized by Kim and Chae[17]:

- Initial phase: Patients experience excruciating pain at the injection site, followed by erythema or bluish discoloration of overlying skin with distinct margins, and occasionally a reticulate or hemorrhagic patch.
- Acute phase: Occurs after 24 h to 3 days. The lesion develops into an erythematous non-necrotic lesion which can be an indurated, painful, livedoid plaque with violaceous borders.
- Necrotic phase: Ulceration and necrosis of the involved skin, underlying subcutaneous tissue, and muscular layers. The ulcer usually takes several months to heal,

often resulting in complications such as scarring, contracture, and hypoesthesia.[2,3]

Nicolau syndrome is clinically diagnosed, but investigations can help rule out differential diagnoses. Blood tests are usually unremarkable.[17] A focal lesion or area of inflammation can be seen during imaging tests, such as ultrasonograms, computed tomography, or magnetic resonance imaging.[6,15,17] During the necrotic phase, histopathology can show eosinophilic infiltration, necrosis of adipose tissue, and inflammation of the subcutaneous tissue.[17] Blood and specimen cultures are usually negative or revealing of resident flora.[6,15,17]

Currently, there is no consensus for treatment. Kim and Chae[17] proposed a three-phase treatment regimen, using conservative therapy with analgesics, wound dressing, and surgical debridement.

- In the initial phase, analgesics are recommended for pain. Systemic antibiotics help prevent secondary infection and are recommended empirically until cellulitis has been ruled out. Local ice packs should be avoided to prevent vasospasm.[17]
- In the acute phase, the main focus is improvement in local circulation with drugs such as pentoxifylline, hyperbaric oxygen treatment, intravenous alprostadil, and heparin thrombolysis.[2,3,17,19] Warm intermittent compression is also recommended.[10] Reduction of local inflammation can also be a mode of treatment using intralesional or systemic corticosteroids.[2,17,19] Early treatment initiation can halt or reverse tissue damage.[2,3]
- Once necrosis sets in, surgical debridement is indicated, which prevents further infection and hastens healing.[3,17]
- When lesions are complicated by abscess formation, incision and drainage is necessary.[9] Sepsis can also be a complication, which needs to be managed accordingly with fluids, antibiotics, and vasopressors.[6,15]

Our case was a 36-year-old male patient, with a 3-year history of paranoid schizophrenia who developed Nicolau syndrome secondary to the use of intramuscular LA fluphenazine decanoate (25 mg) injected fortnightly. It was managed conservatively with analgesics, surgical debridement, and prophylactic antibiotics. Our patient's further clinical course was uncomplicated and his reaction resolved gradually over 2 months. Factors that possibly contributed to the necrotic injection site reaction were the high frequency of administration, that is, given every second week, which was reported to be a possible risk factor by Jones et al.,[11] and the lipophilic base used in the fluphenazine depot injection.[6]

Initial differential diagnoses for our patient's case were necrotizing fasciitis, abscess, cellulitis, pyomyositis, and gas gangrene. Antibiotics were given empirically, but the patient had no signs of an acute infectious etiology, and hence these were ruled out. Local toxic inflammatory reaction to the drug was ruled out due to their milder clinical course and absence of tissue ischemia or necrosis compared to Nicolau syndrome.[13,17] Other differential diagnoses for Nicolau syndrome include acute bleeding, acute compartment syndrome (lack of signs of neurovascular compression),[17] cutaneous cholesterol embolus (unusual for it to occur at the injection site and the patient lacked risk factors),[19] vasculitis,[20] and Hoigne's syndrome,[2,3,15,17] all of which seemed unlikely in our patient's case.

Although the precise mechanism by which the local ulcer developed cannot be determined, the delivery method and sterile procedures should be scrutinized.

Nicolau syndrome can be prevented by following standard protocols and good techniques for intramuscular injections:

- Sufficiently shaking the suspension followed by slow injection.[8]
- Aspirate before injection to avoid accidental intravascular injection and reduce risk of intra-arterial embolism from the administered drug.[2,3]
- Employing the Z-track method of intramuscular injection: more than 5 mL of medication must not be injected using the Z-track method.[6,8]
- The length of the needle used should correspond to the weight of the individual, which is a reflection of how deep a needle must pass to reach the muscle. A 90-kg patient requires a 5.1-cm to 7.6-cm needle and a 45-kg patient requires a 3.2- to 3.7-cm needle.[3] Short needles in obese individuals can cause inadvertent injection into subcutaneous tissue and fat leading to local irritation.[12] If short needles are used in obese individuals, they should preferentially receive depot neuroleptics in deltoid or anterolateral thigh muscles, instead of gluteal injections.[12]
- Site selection: the upper outer quadrant of the buttock has been recommended as the site for intramuscular injections in non-obese individuals, as it has fewer vessels, and thus lesser chance of unintended intravascular injection.[17]
- For cases requiring multiple injections or high doses, multiple sites of injection must be chosen.[3]

This instance serves as a reminder that all LAIAs can cause injection site reactions. Clinicians should report any such incidents at injection sites as there is little information available.

Conclusion

Nicolau syndrome is an uncommon medically induced complication of the skin and the deeper tissue. It commonly occurs following intramuscular injection and sometimes by other injection routes. A high index of clinical suspicion is required

for the diagnosis of Nicolau syndrome. Tissue diagnosis may also be done. The lesion often heals by secondary intention with scars and deformities. The pathogenesis of Nicolau syndrome is not well understood, and there are no guidelines for its management. Treatment is a multi-disciplinary approach and involves the use of systemic prophylactic antibiotics, wound debridement, and corrective plastic surgery as needed. It is important for medical personnel to be aware of this condition since it is a potentially avoidable adverse reaction if the proper injection techniques are practiced.

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Author contributions

S.D., B.R., and V.S. conceived the idea for the case report, and along with A.I., T.J. was responsible for data collection, writing the first draft, and editing. M.R. and E.M.F.C. decided the inclusion criteria, investigation, resources, and supervision and validation.

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Ethical approval

Ethical approval was not needed with respect to a case report by our institution.

Informed consent

Written informed consent was obtained from the patient for his anonymized information to be published in this article. The patient regained fair insight and judgment over the course of his treatment regime to provide written informed consent by himself.

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