CASE REPORT

NICOLAU SYNDROME: A CASE REPORT OF A RARE DEBILITATING COMPLICATION FOLLOWING INTRAMUSCULAR INJECTION OF PENICILLIN

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Summary

Objective: Nicolau Syndrome is a rare, debilitating and sometimes fatal complication resulting from the administration of parenteral medication. It is associated with administration of a variety of medications. It causes a local aseptic ischaemic necrosis of the muscles, subcutaneous tissues and skin. It may be associated with neurological deficits and organ failure. The administration of parenteral medication is common in our health institutions, but this complication seems to be unknown. We would like to increase awareness about its existence and the preventive measures to take in order to minimize its occurrence as it can be associated with significant morbidity and even mortality.

Case report and interventions: A young man presented with sudden onset of severe pain in the right buttock and the whole right lower limb with associated paralysis after an intramuscular injection of penicillin. He developed a darkened patch of skin at the site of the injection on the right buttock and also on the right leg anteriorly. This progressed to necrosis of the skin, subcutaneous tissue and muscles and osteomyelitis of the right tibia. He also presented with acute renal failure. After serial debridement, wound dressing and antibiotic treatment the wound healed with extensive scarring, the osteomyelitis resolved and the neurological deficit improved leaving a foot drop. His renal function normalized after several sessions of haemodialysis.

Conclusion: Administration of parenteral medication can be complicated by debilitating conditions such as Nicolau Syndrome. No specific treatment exists, so it is best prevented by taking the necessary precautions during administration of parenteral medication when indicated.

Key Words: Nicolau Syndrome, Intramuscular injections, prevention

Introduction

Parenteral medications are very frequently administered in our health facilities, but they can be associated with complications. Nicolau Syndrome, also known as embolia cutis medicamentosa or livedoid dermatitis, was first described in the 1920's. It is a rare debilitating complication following administration of parenteral medication, particularly via the intramuscular route. It is a local aseptic cutaneous, soft tissue and sometimes muscular ischaemic necrosis at the site of administration of parenteral medication. It may have devastating complications such as paralysis, limb gangrene, neurological deficits, sepsis, organ failure and even death. Therefore it has significant morbidity, mortality and medicolegal implications. We present a case of a young man with Nicolau Syndrome following intramuscular injection (IM) injection of penicillin. This was complicated with osteomyelitis of the tibia, a neurological deficit of foot drop, and acute renal failure.

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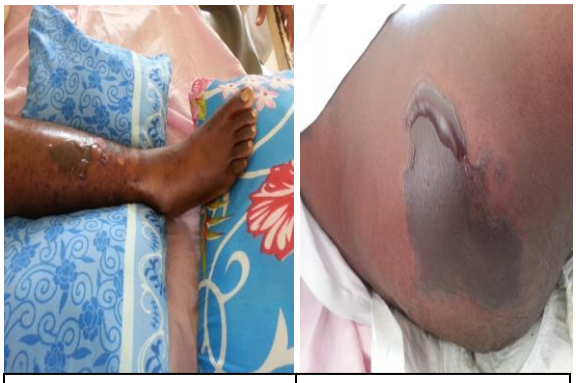
Case Report

A 27-year old male was referred to the surgical emergency unit with a 5-day history of a swollen painful right buttock and lower limb with inability to walk. He had presented to a private clinic 5 days prior to presentation at the surgical emergency unit and had been given an IM injection of penicillin on account of a diagnosis of syphilis. This diagnosis was made based on a 1-month history of recurrent urethral discharge and 1-week history of oral ulcers and dysuria. His Venereal Disease Research Laboratory (VDRL) test and Treponema Pallidum hemagglutination assay (TPHA) were both positive. He developed severe pain immediately after the injection was given into the right buttock. This was associated with paralysis of the limb almost immediately necessitating subsequent admission at the clinic on that same day. He was found to have developed a darkened patch of skin with blisters at the injection site and on the leg a few days later, and so was referred to our facility on the 5th day after the incident. On presentation to the surgical emergency unit five days after the onset of the symptoms, he was acutely ill, moderately pale and afebrile. His cardiovascular system was stable, chest was clinically clear and abdomen was unremarkable. His right buttock and entire right lower limb was

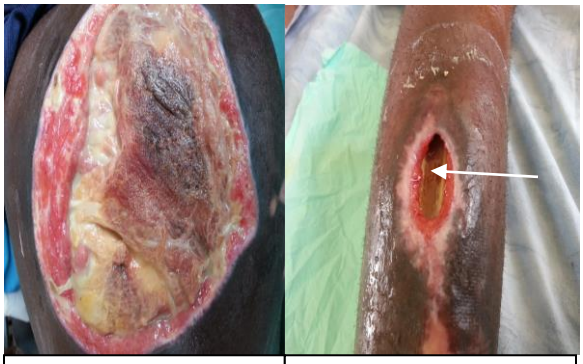
swollen, moderately tense and had differential warmth. There was a darkened patch of skin with blisters over the leg anteriorly (figure 1a), and another of about 10 by 8 cm, with blisters over the posterolateral aspect of the right buttock (figure 1b). Power in the right lower limb was 1/5 with associated right foot drop and loss of sensation. Peripheral pulses were not palpable probably due to the edema but capillary refill was less than 2 seconds. Initial diagnoses entertained included intraarterial injection with ischaemia, compartment syndrome, sciatic nerve injury and cellulitis.



a. Well defined dark patch with blisters on the shin of the right leg distant from the site of injection	b. Well defined dark patch with blistering on the right buttock, the site of injection

Figure: 1a & 1b

On admission, he was noticed to be passing dark urine but in adequate volumes of more than 1L over 24hours. His haemoglobin count was 7.0g/dl, white blood cell count 14.68 x 10^9/L and platelets 88 x 10^9. His sodium level was 127 mmol/l, potassium 5.3 mmol/l, urea 42.5 mmol/l and creatinine 819 mmol/l. His liver function tests and clotting profile were normal. His Human Immunodeficiency Virus (HIV) test was negative. Doppler ultrasound of the right lower limb showed heterogenous echopattern with loss of muscle fibres with normal venous system. He was started on intravenous fluids, intravenous penicillin and cloxacillin and subcutaneous enoxaparine. He had 2 sessions of haemodialysis on account of deteriorating renal function. As the differential diagnoses did not all fit the patient's presentation, a literature search was done and the diagnosis of Nicolau Syndrome arrived at. Over the next few days, the pain and swelling reduced, and power improved, but he had a residual foot drop for which he had physiotherapy and was fitted with a foot brace. The renal function also improved. X-rays of the tibia and fibula showed localized osteomyelitis of the tibia for which he was treated with clindamycin for 6 weeks. The darkened patches over the gluteal region and leg became necrotic. He therefore had serial debridement of the necrotic tissues (figure 2), with wound dressing. He was referred for plastic surgery assessment for grafting of the skin defect, but declined to have the procedure and eventually the wound healed by secondary intention (figure 3) in 3 months.



a. Extensive myonecrosis of the underlying gluteus muscles after debridement of the dead skin	b. Extensive necrosis involving the underlying tibia. Arrow pointing to the involved bone

Figure: 2a & 2b

Healed gluteal ulcer with scarring	Healed ulcer on the shin of the right leg

Figure: 3a & 3b

Discussion

Nicolau Syndrome, also known as *embolia cutis medicamentosa or livedoid dermatitis*, was first described in 1924 by Freudenthal[1] and has since been reported worldwide in association with administration of a wide variety of parenteral medications particularly intramuscular medications[2,3,4] . More than 25 different drugs have been reported as causing this syndrome1. Table 1 shows some reported causes of Nicolau Syndrome[3-23]. Cases have also been reported in association with intra or periarticular injections17 of steroids as well as intravenous[22] and subcutaneous injections[23].

It is a local aseptic cutaneous, soft tissue and sometimes muscular ischaemic necrosis. Pathogenesis

of Nicolau Syndrome is unclear but is likely to be of vascular origin[1, 2]. Intra-arterial, peri-arterial or peri-neural injections can result in occlusion of peripheral arterial vessels either from vasospasm, vessel damage or embolization of the administered medication. Subcutaneous injections with injury to cutaneous arteries may contribute to the occurrence of this syndrome[3, 5, 8]. Application of cold compress for pain relief may accelerate progression of the features and worsen outcome[6, 7, 18]. Also, the mechanism of injury seems to be related solely to the process of administering the injection as injections of the same agents after an episode of Nicolau Syndrome have not been associated with recurrence of the syndrome[3, 23]. However, another school of thought proposes that the role of physical and chemical factors such as injection technique and solution pH may not have any bearing on the occurrence of Nicolau syndrome [13].

Table 1. Causes of some reported cases of Nicolau Syndrome

Drug	Route of administration	Site of administration
Diclofenac[3,5-13]	IM	Buttock, Thigh
Ketoprofen [8,10]	IM	Thigh, Buttock
Piroxicam[14]	IA	Ankle
Ketorolac[15]	IM	Buttock
Gluco-corticoid[16]	IA	Ankle
Para-methasone[17]	IA	Shoulder
Cortivazol[17]	IA	Shoulder
Hydro-cortisone[17]	IA	Shoulder
Penicillin[13,18-21]	IM	Thigh, Buttock
Meperidine [10]	IM	Buttock
Cyano-cobalamin [13]	IM	Buttock
Polido-chanol [22]	IV	Achilles tendon
Glatiramer acetate [23]	SC	Buttock
Hexavalent vaccine [4]	IM	Thigh, arm,
DTP [4]	IM	Thigh

IM – intramuscular, IA –intraarticular, IV – intravenous, SC – subcutaneous
DTP – diphtheria/tetanus/pertussis vaccine

Nicolau Syndrome usually presents with sudden onset of excruciating pain at the site of the injection immediately after administration of the injection. Syncope may occur[17]. It is then followed by erythema, livedoid patch and hemorrhagic patch of skin at the injection site[6]. This skin reaction is pathognomonic of Nicolau Syndrome[1, 2]. Ultimately, necrosis of skin, subcutaneous fat and / or muscles occurs over 1 – 2 weeks. Sequelae of this syndrome include: widespread cutaneous necrosis, extensive scarring, ischaemia of ipsilateral limb, organ failure, neurological deficits, superimposed infections, sepsis and compartment syndrome[1, 2, 5, 7,9,19]. Factors that result in poor prognosis include use of cold compress on the injection site[6,7,18], superimposed infection[5,6,8,9], sepsis[18,19] compartment syndrome[19] and prior immunocompromised state of the patient[5,6,8,9] . These can result in significant morbidity[9, 19] and mortality[9,19,24]. It therefore has significant medicolegal implications14.

No confirmatory diagnostic tests for Nicolau Syndrome exists[2]. Diagnosis is purely clinical with correlation to previous case reports[3]. Investigations however should be done to rule out other differentials and assess for complications of the syndrome. Tests[5,18,19,25] to be done include full blood count (FBC) to rule out an infection and anemia from intravascular hemolysis; blood urea, electrolytes and creatinine (BUE and CR) to identify any associated renal impairment; creatinine kinase to detect muscle damage; arterial blood gases (ABG) to assess metabolic derangements; urinalysis to detect myoglobinuria resulting from muscle necrosis; cultures from the ulcers to detect superimposed infection; electrocardiogram (ECG) to rule out any hyperkalemia from renal failure and duplex scan of the vessels of the affected limb to rule out a deep vein thrombosis and arterial occlusion. Computed tomogram (CT) scan or magnetic resonance imaging (MRI) can help to define the extent of the lesion, and also exclude compartment syndrome. Tissue biopsy shows necrosis of dermis and subcutaneous tissue with focal vascular thrombosis and inflammation in the muscles in the acute phase.

There is no specific treatment for Nicolau Syndrome, but patients are managed symptomatically depending on the extent of the lesion and its complications[1,2.] Tissue damage may however be reversible in the acute phase [1]. Treatment involves pain control[1, 2], topical[1, 19] or oral steroids[25] for the

inflammation, antibiotics for superimposed infections[5,6,8], vasoactive agents e.g. pentoxyphylline[18] to counteract the vasospasm, anticoagulants e.g. heparin[18] and hyperbaric oxygen[18] which have been found to be helpful. Wound debridement and dressing are done[1]. The wounds usually heal over several months resulting in an atrophic scar[1, 2, 3]. Skin grafting or flaps if required can be done. Physiotherapy is also employed.

Prevention is essential as no specific treatment exists. Steps to be taken to avoid Nicolau Syndrome include[5, 7,21,26,27]:

1. Using a long enough needle to reach the muscles when giving IM injections so as to avoid subcutaneous injections of intramuscular preparations. Recommended length of needle for a 90kg patient is 5 -7.5cm and for a 45kg patient 3 -4cm.
2. Injections on the buttock should be given in the upper outer quadrant to avoid injury to the sciatic nerve.
3. Aspiration should always be done before medication is injected into the muscle to avoid intravascular injections.
4. The Z-track method of giving injections should be used where the skin and subcutaneous tissues are retracted from the site of the injection. This de-aligns them from the underlying muscle. The needle is inserted at 90 degrees, the injection is given and the needle withdrawn slowly and smoothly at a 90-degree angle. The finger is then released to trap the medication inside the muscle and minimize subcutaneous injection by blocking the tract.
5. Volumes larger than 5 mls to be injected using the Z-track method should be divided and administered at different sites.
6. Repeated injections at the same site should be avoided
7. Cold compress application after IM injection should be avoided.
8. IM injections should be avoided in obese patients if possible
9. Injections should be stopped if patient complains of excessive unexpected pain during the procedure

Conclusion

Administration of parenteral medication particularly via the IM route can lead to debilitating complications and hence unnecessary injections should be avoided. Awareness of Nicolau Syndrome among health care practitioners should be raised. As no specific treatment exists, the necessary steps to prevent its occurrence should be taken especially when IM injections are administered.

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