

Nicolau Syndrome Following Intramuscular Penicillin Injection

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ABSTRACT

Nicolau Syndrome (NS) is a rare but severe localized adverse reaction at the site of intramuscular drug injection. The typical presentation is intense pain around the injection site soon after injection, followed by erythema, purplish network discolouration of the skin, haemorrhagic patch, and finally tissue necrosis. Here in, we report a 9 years old boy, the third Nicolau Syndrome (NS) reported from Iran after a single intramuscular injection of penicillin.

Key words: Nicolau syndrome (NS). Penicillin. Adverse drug reaction. Intramuscular injection.

INTRODUCTION

Almost all drug administrations are potentially associated with some minor or even major side effects. Injectable medicines have some known adverse effects, but most of them are self limited. Local pain, abscess formation, nerve injury and systemic allergic reaction are among the frequently observed adverse reaction to injections. On the other hand, extensive tissue necrosis is very rare finding after intramuscular injections. It is supposed that intra-arterial embolization of the medicine seems to be the possible mechanism.¹ The first description of this condition (also known as livedoid dermatitis, embolia cutis medicamentosa) was made by Freudenthal and Nicolau in 1924 and 1925.¹ Development of skin, subcutaneous, and even muscle tissue necrosis are less commonly observed complications of the intramuscular penicillin injection.^{2,3} We report a case of NS following an intramuscular injection of penicillin.

CASE REPORT

A 9 years old boy was subject to an intramuscular injection of benzathine penicillin on his right buttock in a primary health care centre following symptoms of pharyngitis on March 2011. He showed intense deep pain of his right thigh and buttock a few minutes after injection followed by inability to move his right lower limb.

Three hours later the patient complained of swelling all over the buttock and discolouration of the gluteal area which progressed to lower part of back and upper part of posterior thigh. He was referred to our centre and admitted to the department of paediatrics. On physical

examination, he revealed a violaceous discolouration and livedoid pattern of the right gluteal region upto lower back and the right scrotum with swelling and severe tenderness around the injection site (Figure 1). Some areas were subject to superficial skin gangrene. No crepitation was palpable despite a very tender and sensitive injection site. Vital signs were normal and distal arterial pulses were palpated normally. Other physical examination including neurologic examination was normal.

The blood tests revealed increased serum levels of creatine phosphokinase to 30040 U/L (normal range: 25-195) and lactate dehydrogenase to 1434 U/L (normal range: 225-500) but, other tests were normal.

He was treated initially with non-steroidal anti-inflammatory agents, and full dose oral acetaminophen was given for pain relief. Initial MRI showed severe soft tissue swelling along with increased volume and signal intensity of gluteus maximus and medius muscles on the right side on T2 weighted sequences (Figure 2). T1 weighted sequences showed a focal area of infarct in gluteus maximus muscle. His Doppler ultrasound did not show femoral artery obliteration. The follow-up MRI after 10 days showed marked improvement in muscular and soft tissue swelling and signal changes.



Figure 1: Ischaemic changes in the right buttock showing a livedoid pattern.



Figure 2: T2W MRI images of pelvis showing severe swelling and abnormal signal in right gluteal muscles.

After establishment of diagnosis of NS following a comprehensive literature search and multidisciplinary joint clinic, we prescribed a single pulse of 100 mg

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intravenous Methylprednisolone, oral Pentoxifylline 400 mg tid and Cephazolin 650 mg/q6 hrs intravenously based on beneficial results from anecdotal reports in medical literature.

Three days after admission, patient developed a transient sciatic pain for 2 days. On the third day of admission Diltilazem 15 mg/q8h orally, Enoxaparin 25 mg/q12h subcutaneously, and Imipenem 400 mg/ q6hr were started for next ten days after stopping Cephazolin.

The right buttock pain, swelling and discolouration improved slightly and the patient was discharged after 13 days of hospitalization.

His follow-up after 14 days showed moderately improvement in skin lesions and gluteal swelling. He was able to walk a few meters for the first time after this complication. A rehabilitative program was started.

DISCUSSION

NS is a rare adverse reaction following intramuscular injection of various drugs. Silva *et al.* reported case of NS induced by intra-articular glucocorticoid injections.⁴ In our case soon after injection the patient suffered from severe pain and 3 hours later, skin, subcutaneous, and even muscle tissue damage developed at the site of intramuscular drug injection. It is looks like the frequency of NS seems not to be very low but lack of knowing this condition among most clinicians leads to under-diagnosis and poorer outcome. This condition should be differentiated from cellulitis and necrotizing fasciitis. Compartment syndrome of gluteus muscles are reported as rare differential diagnosis of NS.

The mechanism of NS is not fully understood, but one hypothesis is damage to the end-arteries by cytotoxic effects following intra-arterial embolism of the particular drug, followed by arterial vasospasm (probably secondary to release of some vasoactive mediators) and tissue necrosis. Other hypothesis is extra-arterial compression of the supplying artery by the injected volume. But none of these hypotheses justify occurrence of NS after other routes of administration of drugs such as intra-articular injections. In general, NS is a catastrophic vascular phenomenon that could be differentiated from nerve injury or local pure immunologic reactions secondary to injected materials. NS has been related to the administration of wide variety of medicines, including non-steroidal anti-inflammatory drugs and Etanercept, corticosteroids and penicillin.²⁻⁶ So NS could not be attributed to intramuscular injection of penicillin alone.

There is no published standard of care for NS and treatment used ranges from local care to extensive surgical debridement. Alyasin *et al.* reported a 7-year-old boy with NS treated with intravenous immunoglobulin (IVIG) (2 g/kg) and Pentoxifylline. They reported that the patient was heparinized and after 12 days, he was

discharged in a good general condition.⁷ Yildiz *et al.* used hyperbaric oxygen in the late treatment of NS in a 3-year-old boy to prevent the progression of the necrosis and therefore, limit the amputation level.⁸ Application of a cold compress was considered as an aggravating factor.⁹

In spite of reports of urgent need for wide surgical debridement by some authors,¹⁰ we believe that judicious use of oxygen along with heparin and broad spectrum antibiotics should be the mainstay of therapy. A watchful management with step-wise fashion based on individual clinical setting and serial MRI imaging could be a reasonable manner to minimize morbidity. Rehabilitation would be crucial in restoring muscle strength.

For preventing adverse injection reactions, health care providers should be informed of proper method of intramuscular injection such as Z-track method of injection, aspiration before injection, holding injection immediately if the patient complains of unusual excruciating pain on injection site. Needle must be long enough to reach the muscle. When multiple injections have to be given, different sites should be chosen.

In conclusion, clinicians should be aware of NS, a serious complication of the intramuscular injection of common agents such as penicillin for early institution of heparin and antibiotics. Minimizing prescription of injectable drugs could minimize global rate of NS.

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