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Case Report

Paediatrics Section

Nicolau Syndrome in a Child Caused by Penicillin Injection

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ABSTRACT

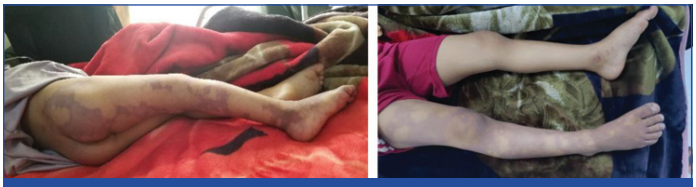
A wide range of side effects can occur during drug administration. Nicolau Syndrome (NS) is a rare iatrogenic side effect of medications injected Intramuscularly (i.m.). The clinical manifestations range from localised pain and erythema to total necrosis requiring amputation. The present report is about a five-year-old boy, who developed NS after receiving an i.m. injection of benzathine penicillin for treatment of pharyngitis. He developed symptoms minutes after the injection including intense pain at the site of injection followed by progressive discolouration and impairment of movement of the affected limb. The patient was treated with pentoxifylline, methylprednisolone, heparin and antibiotics in a hospital and after one month, complete improvement was noticed.

Keywords: Benzathine, Intramuscular, Livedo reticularis, Pentoxifylline

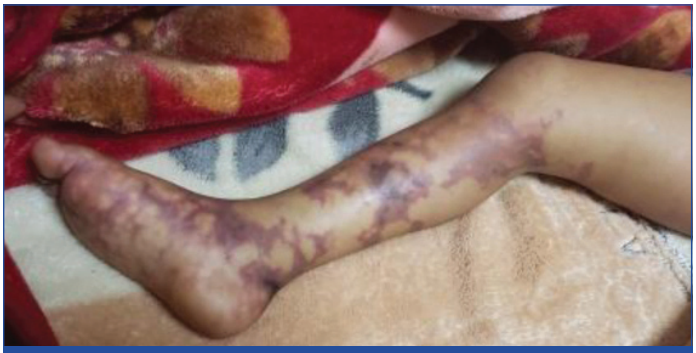
CASE REPORT

A five-year-old boy presented to the Emergency Department with history of severe pain in the right lower limb within minutes of i.m. benzathine penicillin in the right buttock. The injection was administered in a primary healthcare clinic for treatment of pharyngitis. Few hours later, the patient suffered from impairment of voluntary movement of the affected limb and skin discolouration over the gluteal area which progressed to the whole limb and lower back. There was no history of allergy or medical illness.

Physical examination on the day of admission revealed multiple blue-purple ecchymotic patches, with livedoid pattern involving the right gluteal area, lower back and extending to the entire limb [Table/Fig-1]. Four days later, discolouration became darker, and superficial skin gangrene appeared in some areas. Moreover, there was severe tenderness, high temperature and mild swelling of the affected limb [Table/Fig-2]. Except for intact sensory examination, neurological examination of the affected limb was difficult because of severe pain and tenderness. On day eight, the swelling of the affected limb worsened and extended to the scrotum. Bilateral lower limbs (femoral, popliteal, anterior tibial and dorsalis pedis arteries) pulsations were intact. Vital signs demonstrated that the patient was febrile (38.5°C), had tachycardia (140 beats per minute) and tachypnoea (30 breaths/min) but normal blood pressure (100/60 mmHg). Other physical examinations, including chest, heart, and abdomen, were normal.



[Table/Fig-1]: Clinical findings on day of admission. Note the multiple blue-purple discolouration patches, with livedoid pattern involving the right gluteal area, and extending to the foot.



[Table/Fig-2]: Picture after four days revealed a darker skin discolouration, swelling and superficial skin gangrene in some areas.

A complete blood count showed leukocytosis (14600 cells/mm^3) with neutrophilia (84%), thrombocytosis (585000/mm^3) and normal haemoglobin (13.1 g/dL). Erythrocyte sedimentation rate (3 mm/hr.) and C-reactive protein (3 mg/dL). There was elevation in Creatine Phosphokinase (CPK) (7193 U/L), Lactate Dehydrogenase (LDH) (710 U/L) and Aspartate Aminotransferase (AST) (106 U/L). The coagulation profile (prothrombin time: 13.1 seconds, international normalisation ratio: 0.96, partial thromboplastin time: 24.9 seconds) and renal function tests (creatinine: 0.6 mg/dL, blood urea nitrogen: 15 mg/dL) were within normal limits. Urine examination showed a positive blood test on a urine dipstick. Right lower limb doppler and Computed Tomography Angiography (CTA) revealed intact arteries and veins. At this stage, differential diagnoses were NS, compartment syndrome and cellulitis.

A few days later, the patient's condition worsened as the discolouration became darker with gangrenous areas and non pitting oedema, and the CPK level (59390 U/L) was markedly elevated. A plastic and vascular surgeon was consulted, and it was advised to undergo medical treatment and no surgical intervention was necessary for the patient. Pentoxifylline 180 mg oral every 8 hour for seven days, methylprednisolone 18 mg intravenous (i.v.) every 12 hour for five days, unfractionated heparin (loading dose: 1350 U i.v., then infusion rate: 360 International Unit (IU) per hour for seven days), and antibiotics (meropenem 350 mg (i.v.) every 8 hour and linezolid 180 mg (i.v.) every 8 hour) for 10 days were administered to the patient. Patient stayed in hospital for 12 days, then discharged on subcutaneous low molecular weight heparin 18 mg subcutaneous every 12 hour for one month and oral linezolid 180 mg oral every 8 hours for two weeks. The final diagnosis was NS based on clinical manifestations preceded by history of drug injection and exclusion of important other differential diagnosis. The patient's condition gradually improved over one month, and he recovered completely, with no cicatricial skin manifestations or neurological deficits.

DISCUSSION

The NS, also called livedoid dermatitis and embolia cutis medicamentosa, is an acute severe medical dermatological entity

that occurs after using different injectable drugs, with a wide spectrum of clinical presentations and prognosis [1]. It was first described by Freudenthal in 1924 and Nicolau in 1925 following an i.m. injection of oily bismuth used to treat syphilis [2].

Different drugs were found to cause the syndrome, but the most common causes are with diclofenac (24.14%) and penicillins (22%) [1]. Other drugs reported to cause this syndrome are antibiotics (penicillin derivatives, tetracycline, sulfapyridine, streptomycin, gentamicin), vitamins (vitamin K, vitamin B12), vaccines (diphtheria-tetanus-pertussis, polio), non steroidal anti-inflammatory drugs (piroxicam, ibuprofen, ketoprofen, phenylbutazone), corticosteroids (hydrocortisone, dexamethasone, triamcinolone, paramethasone, cortivazol), antipsychotics, antiepileptics (phenobarbital, chlorpromazine), antihistamines (ketoprofen, chlorpheniramine, diphenhydramine, hydroxyzine), local anaesthetics (lidocaine) and others (etanercept, naltrexone, ketorolac, interferon alpha, meperidine, maleate, salicylate bismuth, thiocolchicoside, glatiramer acetate) [3,4].

The pathogenesis is not well understood, but arteriolar and/or neural injuries are implicated. The vascular injury occurs due to direct end artery trauma or irritation with sympathetic stimulation and subsequent vascular spasm, compression by arterial embolism of the drug itself, crystallisation of aqueous drugs in the vessels and arteriovenous shunt development or ischaemia followed by focal thrombosis [4,5].

A perineural injection and an involvement of a nerve's perfusing artery result in an end-organ damage of the cutaneous and subcutaneous tissues and muscles [4-6]. Histopathologically, there is focal vascular thrombosis and inflammatory infiltration with necrosis of the dermis and subcutaneous tissue [7]. The type of drug significantly affects the pathogenesis of NS, where cytotoxic drugs lead to perivascular inflammation and ischaemia necrosis while lipophilic drugs penetrate and block the vessels due to fat embolism [1]. The NS occurs more frequently after i.m. injections (80%), less commonly after subcutaneous injections (11.4%) and intra-arterial injections (3.8%), and rarely after intravenous, intradermal and intra-articular injections [1]. It has been reported among children aged ≤10 years elsewhere [2,5,7-11]. It is noteworthy that the incidence rate of NS among children of this age group can be as high as 19.3% [1]. The buttock is the most commonly affected area [3,8,9], but NS has also been reported on the shoulder, thigh, knee, ankle, breast, and abdomen [3].

In the present case, the five-year-old boy developed NS after i.m. injection of benzathine penicillin in the right gluteal area for treatment of pharyngitis. The clinical presentation of NS is variable but typically starts with a severe pain at the site of injection and its surrounding [3,4,7-12], with neurological signs as radiating pain, numbness, paraesthesia or difficulty in movement of the affected limb [3,8,10,12,13]. Initial symptoms are usually followed by erythematous patches, violaceous livedoid plaques or haemorrhagic patches [2-4,6-13]. Finally, skin gangrene, cutaneous necrosis and ulceration are seen in some cases [2-4,8-10,13]. An atypical presentation of NS following injection were bilateral lower limb weakness with temporary urinary and fecal incontinence. Multiple ecchymoses extend upto the back of the thigh without radicular pain during or after injection [5]. The index patient developed an immediate severe pain in the right lower limb followed by discolouration, swelling and difficulty of movements. Because of the non specific nature of its signs and symptoms, NS may be misdiagnosed as other illnesses such as vasculitis or infectious processes [2]. The most important differential diagnoses for NS are necrotising fasciitis, cellulitis, vasculitis and compartment syndrome [1,8]. Moreover fat embolism, Hoigne's syndrome and left atrial myxoma emboli are other differential diagnoses [1,9].

The NS is often diagnosed clinically based on history of recent injection and clinical presentation after ruling out other similar conditions [1], with no confirmatory tests or criteria for identifying this syndrome. Laboratory tests are usually done to aid in diagnosis, to predict the complications or to rule out other similar conditions [1]. For example, increased LDH, CPK and myoglobin indicate tissue damage for this syndrome [1]. The reported case was seen with very high CPK and elevated LDH as well. There are no published standard guidelines for NS. The treatment ranges from symptomatic and supportive medications to surgical interventions depending on the patient's condition [1]. Medications to treat NS usually include analgesics, corticosteroids, anticoagulants, blood viscosity reducers and antibiotics [1]. The i.v. immunoglobulin, methylprednisolone and heparin were successfully used to treat a seven-year-old child suffering from NS with extensive necrosis after i.m. penicillin [9]. Hyperbaric oxygen with heparin and pentoxifylline were effective in treating i.m. benzathine penicillin-induced NS in two, three-year-old boys [2,7]. Antibiotics are used only if the infection is confirmed [7]. Use of cold compress is well-known to aggravate NS symptoms [1]. Surgical treatments, including fasciotomy, debridement and plastic surgery, are used according to the patient's condition [1]. The index patient was successfully treated with drugs only, including pentoxifylline, methylprednisolone, heparin and antibiotics.

The prognosis is guarded in most cases, it ranges from a complete cure to total limb amputation, or even death [1,2]. Medical complications of NS include acute kidney injury, soft tissue infection and sepsis, or even death, while surgical complications include gangrene, compartment syndrome might necessitate limb amputation [1,2,10]. Neurological complication as bilateral limbs weakness with severe nerves axonopathy also recommended in another report [5]. The index patient had a complete cure without any sequalae. The most effective and preventive measures to minimise the risk of NS are choosing the correct site for injection, administering the appropriate amount of the injected drug according to age, selecting the proper needle size and using the correct injection techniques [1]. Appropriate injection techniques include aspiration before injection, changing the injection site if multiple injections have to be given, using the Z-track technique and stopping injection if the patient suffers from pain during injection [1,12].

CONCLUSION(S)

The present report is probably the first report on NS in a Yemeni child due to i.m. penicillin injection that highlights the severe complications of such injections. This necessitates avoiding the overuse of i.m. benzathine penicillin for treatment of upper respiratory tract infections by clinicians. Therefore, preventive measures and cautious use of i.m. penicillin should be considered before and during injection to avoid such complications.

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