Luo et al., J Clin Case Rep 2019, 9:4
DOI: 10.4172/2165-7920.10001235

Journal of Clinical Case Reports

Case Report Open Access

Coincidence of Nicolau Syndrome and Rhabdomyolysis after Intramuscular Benzathine Penicillin Injection: A Case Report

Luo Q, Peng J and Dai L*

Department of Surgery, The Second Affiliated Hospital of Kunming Medical University, P.R. China

Abstract

Nicolau syndrome (NS) is a rare but well-known complication of intramuscular Benzathine Penicillin (BP) injection, manifesting by symptoms of livedoid discoloration of the skin, edema, as well as classical clinical features of myalgia, muscle weakness and pigmenturia immediately after intramuscular. NS or embolia cutis medicamentosa was first described in 1925 by Nicolau and Freudenthal following intramuscular injection of bismuth salt for the treatment of syphilis. Since then, a few cases have been reported both in adult and children.

Keywords: Nicolau syndrome; Rhabdomyolysis; Benzathine penicillin; Intramuscular injection

Introduction

Numerous medications have been reported to be related with NS, including penicillin, pyrazolone derivates, diclofenac, glucocorticoids, ibuprofen, vitamin B complex, antibiotics, recombinant interferon-a and a mixture of sedatives [1-3]. The major pathology histopathology is destruction of the inner arterial wall resulting from vessel spasm and arterial embolism, as well as reveal dermal and subcutaneous necrosis with focal thrombosis and inflammation [1-5]. Thus, the symptoms manifest extremely severe pain around the injection site with skin ulcer or necrosis. There are several complications of NS, including infections, rhabdomyolysis (RM), renal failure, and various concurrent neurological disorders, all of them are closely related to the prognosis of NS. If these complications are controlled well, skin lesions will heal completely, with only scars left [5-7].

This case is an example presenting two concurrent rare complications, NS and RM, after intramuscular BP injection, aiming to share our experience of managing adverse reactions following medical interventions.

Case Presentation

A 12-year-old male patient was admitted with complaints of diffuse pain, swelling, red discoloration, patchy ecchymosis in his right lower extremity, he was unable to walk due to the right lower limb weakness. These symptoms appeared within 15 minutes after an intramuscular injection of 1,200,000 UI Benzathine Penicillin (BP) in his upper outer quadrant of the right buttock, and he had severe pain around the injection area, which became ecchymosis, livedoid skin lesions and diffuse swelling within several hours. Then, the patient began to vomit, diarrhea, hematochezia, oliguria, as well as tea-colored urine. Within 6 hours after the injection, the symptoms deteriorated, soft tissue necrosis was observed, with that he was referred to Emergency Department of Kunming Children's Hospital, a tertiary care center.

In the initial physical examination, his general condition was good and vital signs were stable, cardiovascular and respiratory responses were normal ranges. But he complained of severe pain in right buttock and lower extremity. An acute violaceous edematous plaque measuring 10 cm × 8 cm on the right buttock was noticed, which was warm and tender to palpation, pulses of both lower limbs were normal and symmetrical. Sensory loss and muscle strength could not be evaluated accurately because of the pain and his in-cooperation. Dynamic changes of laboratory assessment showed prominent leukocytosis and increased C-reactive protein (Table 1). Serum biochemistry revealed extremely elevated levels of liver enzymes (glutamate transaminase, alanine transaminase), lactate dehydrogenase, creatine kinase, urea nitrogen and uric acid (Table 2). D-dimer and active partial thromboplastin time were also very high (Table 3). Value of myoglobin was significantly

Characteristic	Initial diagnosis	Day 1	Day 2	Day 3	Day 25
white blood cell count N=3.50-9.59	21.31	14.6	12.48	12.77	5.48
X–reactin protein N<10	121.23	81.37	116.82	69.03	2.07

Table 1: Blood count and C-reactin protein.

Characteristic	Initial diagnosis	Day 1	Day 2	Day 3	Day 25
glutamate transaminase N=5-40 U/L	399.4	434.8	425.8	412.5	55
alanine transaminase N=8-40 U/L	1157	1246.2	1209.8	1120.1	50
lactate dehydrogenase N=109-245 U/L	2749.6	2481.5	2161.2	1995.1	405
creatine kinase N=38-174 U/L	73390	59914	43761	39297	1330
Creatinekinase isoenzyme N<25 U/L	6831.9	2052	1247	1042	56
urea nitrogen N=3.10-8.00 mmol/L	16.5	15.4	12.8	9.4	4.13
uric acid N=208-428 μmol/L	395.4	331.2	371.1	396.3	243

Table 2: Serum biochemistry examination.

***Corresponding author:** Dai L, Department of Surgery, The Second Affiliated Hospital of Kunming Medical University, P.R. China, Tel: 13759576780; E-mail: dailifenkm@sina.com

Received April 11, 2019; **Accepted** April 18, 2019; **Published** April 25, 2019

Citation: Luo Q, Peng J, Dai L (2019) Coincidence of Nicolau Syndrome and Rhabdomyolysis after Intramuscular Benzathine Penicillin Injection: A Case Report. J Clin Case Rep 9: 1235. doi: 10.4172/2165-7920.10001235

increased (Table 4). Serum electrolyte levels and other biochemical parameters were within normal ranges. Arterial and venous Doppler ultrasound showed no signs of occlusion.

After multidisciplinary consultation, patient was treated with vasodilator and anticoagulant therapy, completed bed rest and continuous extremity elevation, intravenous standard heparin (given at 25-60 units/kg/h), dopamine plus Regitine (continuous infusion 4 ug/kg/min). At the same time, Oral Methylprednisolone Tablets (40 mg/day) and Intravenous glucose-insulin-potassium (GIK) 100 ml were started based on a diagnosis of reactive vasospasm and suspicious heart failure. Dopamine plus Regitine were stopped at the second day, heparin was stopped at the end of second week. Treatment lasted for 25 days, by the third week of follow-up, there was only superficial desquamation with erythema on the skin of the buttock, without tissue loss (Figure 1). Most of the parameters were back to normal except value of creatine kinase. At the end of the fourth week, the patient recovered and could be able to walk independently. For the tenth month follow-up, his hip extension and hip abduction muscle strength were slightly decreased, with a few scar tissues on his right buttock (Figure 2). Electromyography study indicated sciatic nerve axon partial lesion (common peroneal nerve and tibial nerve less than a fourth of CMAP amplitude comparing with other health side), myogenic damages of gluteus maximum and gluteus medius muscle.

Characteristic	Initial diagnosis	Day 1	Day 2	Day 3	Day 25
activated partial thromboplastin time N=28.0-43.5 S	36	31.8	32.3	35.6	41.5
X–dimer N=0.00-0.50 μg/ml	2.1	9.0			

Table 3: Coagulation parameters d-dimer and active partial thromboplastin time.

Characteristic	Initial diagnosis	Day 1	Day 2	Day 3	Day 25
Myoglobin N=28.0-72.0 ng/ml	3000	3000	2485	594.2	67.37
cardiac troponin T N<0.014 ng/ml	56.51	88.78	32.77	7.07	6.34

Table 4: Diagnostic value of cardiac troponin T and myoglobin.

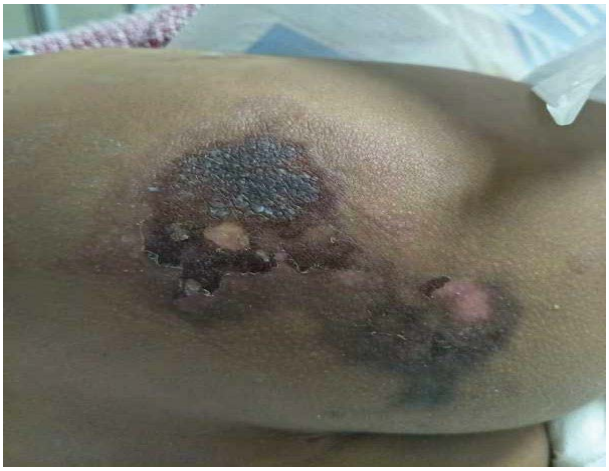

Figure 1: Superficial desquamation with erythema on the skin of the buttock, without tissue loss.

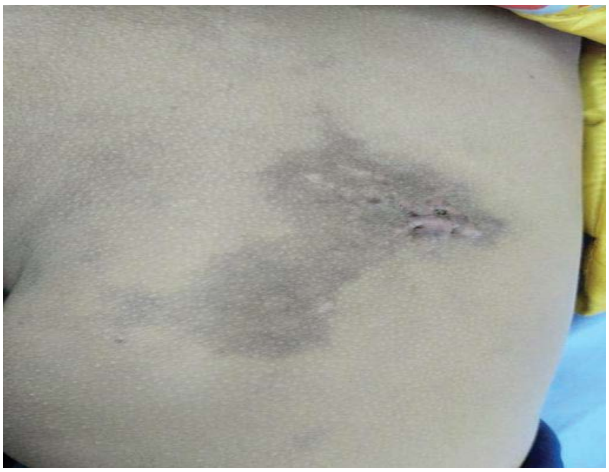

Figure 2: Hip extension and hip abduction muscle strength were slightly decreased, with a few scar tissues on his right buttock.

Discussion

Coincidence of NS and RM is a rare complication that occurs mostly after intramuscular BP injection. Here, we report a 12-year-old case, the patient had symptoms of upper respiratory tract suspected of streptococcus infection with minimal risk of rheumatic fever, who was treated with intramuscular BP injection in the upper outer quadrant of the right buttock in a local rural health center, immediately occurred NS coincidence of RM.

The possible two mechanisms would be involved in the pathogenesis of NS coincidence RM in this case, on the one hand, based on the pharmacology of BP, a viscous suspension of low solubility with a slow absorption rate, hence, blood will enter the syringe even if an artery is perforated and it will need considerable pressure to administrate the injection. That means, the BP could enter the blood during the injection process and evoke vessel spasm. So, for this patient, it was possible that BP got into the gluteal artery and evoked vessel spasm reaction [6-8]. Some angiography studies also proved that it is possible for cases that the superior gluteal artery was punctures during gluteus injection result in arterial spasm and longtime spasm will aggravate ischemia necrosis or arteriolar obstruction by BP particulate matter [7,8]. On the other hand, the cause of RM follows a common reason. Namely, it damages the ion channels and pumps in the skeletal muscle, as a result, direct injury to the sarcolemma or failure of energy production can cause RM. Because of the persistent arterial spasm, the shortage of energy results in pump dysfunction, such as Na/K-ATPase, Ca2+ ATPase pump, leading to increased intracellular calcium, the destruction of myofibrillar, cytoskeletal and membrane proteins thus occurred [8-10]. Meanwhile, intracellular metabolites and proteins leaking into the circulation resulted in rapidly increased level of serum creatine kinase. Considering the dysfunction of muscle energy, pump dysfunction, and suspected heart failure, in the initial treatment plan, pediatricians prescribed GIK for this child to improve cardiac muscle contraction and to provide energy for skeletal muscle [9-12].

The Diagnosis of NS is based on typical clinical features after

intramuscular injection, which includes pain, edema, livedoid erythematous or violaceous skin discoloration [6,7]. NS is totally different from vasculitis and distribution of skin lesions in the site of injection. The second diagnosis of RM is confirmed by neurological examination, measurement of serum creatine kinase and/or myoglobinuria [8-10]. The recommended golden standard of RM is muscle biopsy, but the timing of muscle biopsy is important. If the biopsy is too early, the necrotic changes of the muscle fiber may be misdiagnosed. However, our case had significantly recovery within one month, his parents refused to have this invasive procedure.

Although it is not difficult to make the diagnosis of NS and RM, however, prevention is more important. Because we still cannot totally understand the whole process of coincidence of NS and RM, so patient would have high risks of death due to kidney failure or multiple organ failure. In this case, proper first aid saved the patient's life, which also teaches us a lesson. An important way to reduce high risk of NS is to avoid using BP in patients without enough evidence for rheumatic fever. Additionally, we should try to choose oral or intravenous medications, instead of intramuscular injection antibiotic [9,10].

Conclusion

In conclusion, the cases we have observed show that early anticoagulation therapy and vasodilator therapy can effectively prevent the development of tissue and muscle necrosis. This patient had been followed up for 10 months, the sequela consisting of sciatic nerve neurogenic damages, gluteus maximum and gluteus medius muscle myogenic damage were observed, but further research is needed in order to know better about nerve damages and myogenic damage. The coincidence rate of NS and RM in children is high, so intramuscular BP should be used cautiously.

References

1. Domula M, Weissbach G, Lenk H (1972) Nicolau's syndrome following benzathine penicillin: A survey based on 5 own cases. Kinderarztl Prax 40: 437-448.
2. Brachtel R, Meinertz T (1977) Local skin necroses after intramuscular injection experimental animal studies. Arch Dermatol Res 258: 281-288.
3. Fiocchi A, Vittadini G (1978) Nicolau's syndrome (drug-induced arterial thromboembolism) caused by benzathine penicillin in children: Contribution of 6 personal cases. Minerva Pediatr 30: 591-596.
4. Saputo V, Bruni G (1998) Nicolau syndrome caused by penicillin preparations: Review of the literature in search for potential risk factors. Pediatr Med Chir 20: 105-123.
5. Gayken J, Westanmo A, Knutsen A, Ahrenholz DH, Mohr WJ, et al. (2006) Livedoid dermatitis and severe necrosis (Nicolau's syndrome) after intramuscular hydroxyzine injection. J Burn Care Res 27: 541-544.
6. Hamilton B, Fowler P, Galloway H, Popovic N (2008) Nicolau syndrome in an athlete following intra-muscular diclofenac injection. Acta Orthop Belg 74: 860-864.
7. Kim WB, Alhusayen RO (2015) Skin necrosis from intra-articular hyaluronic acid injection. J Cutan Med Surg 19: 182-184.
8. Tierce MLT, Schultz SM, Lanier BQ (2016) Tissue loss with subcutaneous immunotherapy-Nicolau syndrome. J Allergy Clin Immunol Pract 4: 154-155.
9. Vale A (2016) Rhabdomyolysis. Med 44: 93-94.
10. Miranda MCC, Rozenfeld S, Olivera SP (2004) A systematic review of the nonallergic adverse reactions following benzathine penicillin injections. J Vasc Br 3: 253-260.
11. Zutt R, Kooi VAJ, Linthorst GE, Wanders RJ, Visser MD (2014) Rhabdomyolysis: Review of the literature. Neuromuscul Disord 24: 651-659.
12. Silva AM, Ton A, Loureiro TF, Agrizzi BL (2011) Late development of Nicolau syndrome: Case report. A Bras Dermatol 86: 157-159.