Case Report

Amputation of phalanges as an adverse effect of benzathine penicillin injection

Amputação de falanges como efeito adverso da injeção de penicilina benzatina

Alexandre Sacchetti Bezerra[1,2,3]*
Thais Dante Correia Rocha[2]
Xu Xue Quing[2,3]
Daniela dos Santos Ferreira[4]
João Antonio Correa[2]
Domenico Monetta Neto[4,5]

[1] Hospital Israelita Albert Einstein, Vascular Surgery - São Paulo - SP - Brazil.
[2] Faculdade de Medicina do ABC, Vascular Surgery - Santo André - SP - Brazil.
[3] Rede D'Or, Vascular Surgery - São Paulo - SP - Brazil.
[4] Faculdade de Medicina do ABC, Pedriatrician - Santo André - SP - Brazil.
[5] Santa Casa de Misericórdia de São Paulo, Pedriatrician - São Paulo - SP - Brazil.

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***Corresponding Author:**
Alexandre Sacchetti Bezerra
E-mail: alexandre.bezerra@einstein.br

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ABSTRACT

Nicolau syndrome is a rare adverse effect of a few types of intramuscular medications. We report a case of a 13-month-old child treated at the emergency room who had been medicated with benzathine penicillin for pharyngitis less than 24 hours before. The child developed critical lower limb ischemia homolateral to the gluteal region where the drug was administered, and although fasciotomy aiming to mitigate the compartment syndrome was performed at an early stage, the child developed mummification and spontaneous amputation of the phalanges. Nicolau syndrome is a complication of intramuscular antibiotic administration, and owing to its high morbidity rate, should be diagnosed and treated early.

Headings: Nicolau Syndrome; Penicillin G Benzathine; Amputees; Fasciotomy; Compartment Syndromes; Case Report.

RESUMO

A síndrome de Nicolau é um efeito adverso raro decorrente do uso de alguns medicamentos intramusculares. Relatamos o caso de uma criança de 13 meses que foi atendida no pronto-socorro após ter recebido, menos de 24 horas antes, uma injeção de penicilina benzatina para tratar uma faringite. A criança desenvolveu isquemia grave no membro inferior, no mesmo lado da aplicação no glúteo, e, apesar de uma fasciotomia precoce para mitigar a síndrome compartimental, evoluiu com mumificação e amputação espontânea de falanges. A síndrome de Nicolau é uma complicação possível da administração de antibióticos por via intramuscular e, devido à sua alta morbidade, deve ser diagnosticada e tratada precocemente.

Descritores: Síndrome de Nicolau; Penicilina G Benzatina; Amputação; Fasciotomia; Síndromes Compartimentais; Relato de caso.

INTRODUCTION

The World Health Organization (WHO) defines an adverse drug reaction as any noxious, unintended, and undesired effect of a drug that occurs at doses normally used in humans for prophylaxis, diagnosis, or treatment[1].

Nicolau syndrome (NS) or embolia cutis medicamentosa was described in 1925 as a complication of using bismuth salts for syphilis treatment[2,3]. This diagnosis was later assigned to numerous patients who presented with lower limb ischemia associated with compartment syndrome (CS) caused by intramuscular administration of drugs such as glucocorticoids[4], anti-inflammatory drugs[3,5], vaccines (such as the triple vaccine for measles, rubella, and mumps)[6], hyaluronic acid (used

for aesthetic fillers)[7], and benzathine penicillin (BP), especially in children[8].

This case report illustrates the evolution of NS in a child who had been medicated less than 24 hours before with BP, who developed severe ischemia of the leg and consequent necrosis with spontaneous amputation of the phalanges.

CASE REPORT

A 13-month-old patient was treated at a municipal hospital emergency department for pain and cyanosis of the leg. The child had history of an intramuscular injection of 600,000 U of BP in the right gluteal region less than 24 hours before for empirical treatment of pharyngitis. On physical examination, the child had symmetrical pulses in the lower limbs without clinical signs of sepsis or rhabdomyolysis. She was referred to the pediatric intensive care unit and received intravenous corticosteroids (methylprednisolone succinate at a dose of 2.5 mg/kg/day) and anticoagulant treatment (enoxaparin sodium at a dose of 2 mg/kg/day, every 12 hours, subcutaneously). However, on the second day of hospitalization, the dorsalis pedis and posterior tibial pulses of the right leg were no longer palpable. This finding along with worsening pain and swelling, defined the clinical diagnosis of CS. Although the patient was clinically stable, laboratory tests revealed high serum creatine phosphokinase levels (32,911 U/L; normal laboratory reference: 30–200 U/L) and lactate dehydrogenase levels (3,006 U/L; normal laboratory reference: 230 U/L), with no changes in leukogram or urea/creatinine ratio. We opted for early fasciotomy (Figure 1), broad-spectrum antibiotic therapy (maintained for 21 days), and daily sessions of hyperbaric oxygen therapy, with the mother's consent and monitoring. Good clinical progress, reduction in edema, and improved perfusion in the leg allowed the skin incisions to be closed on the 21st day (Figure 2). The patient was discharged on the 27th day of hospitalization for weekly outpatient follow-up, and gradual delimitation of the distal necrosis sites was observed (Figure 3). Additionally, the child underwent regular outpatient motor physiotherapy sessions to prevent ankylosis of the ankle. On the 77th day after fasciotomy, complete resolution of the necrotic condition was observed with spontaneous amputation of the distal phalanges, showing the underlying scar tissue (Figure 4). There were no motor sequelae.

DISCUSSION

BP is an antibiotic on the WHO list of essential medicines[9], and BP is still widely used for the treatment of streptococcal tonsillitis and cellulitis as well as recommended for the prophylaxis of rheumatic fever and the treatment of syphilis (with the exception of congenital and neurosyphilis)[9]. It is classified as a beta-lactam antibiotic with a bactericidal action due to its enzymatic inhibition of transpeptidation[10], and it is still one of the most used antibiotics globally. Nearly a century after its discovery in 1928, society faces environmental problems related to the universal dispensation of BP, and its clinical use remains associated with serious adverse effects[11,12].

BP is available as a 4 ml vial of solution (concentration of 150,000 or 300,000 U/mL) that can be injected exclusively intramuscularly, and adverse reactions are common, ranging from the well-known hypersensitivity reactions (potentially serious) to laboratory alterations, such as proteinuria and hemolytic anemia[11]. Complications such as pain, edema, and hematoma related to the injection site are also common, with NS being one of these locoregional disorders, albeit rarer and more challenging[2,8,11]. Considering the severity of NS, we believe that all patients with limb ischemia, after the administration of intramuscular medications, should be considered as having NS.

A wrong anatomical puncture site cannot be considered the cause of NS, since the majority of patients with this adverse reaction to BP has received the intramuscular injection in ventrogluteal rather than anterolateral topography[13]. An inadvertent puncture of blood vessels during an intramuscular injection of any medication also does not explain, on its own, the development of the syndrome.

Although its pathophysiology is not entirely understood, NS involves type I hypersensitivity reactions in the acute phase (mediated by immunoglobulin E) and type IV hypersensitivity (mediated by T cells) in later phases[11,14]. These phenomena justify the use of corticosteroids in the initial treatment (as in the case reported herein), aiming to reduce the inflammation by reversing the increase in capillary permeability and suppressing the migration of polymorphonuclear leukocytes[11]. Although there is no consensus in literature, the prescription of corticosteroids and full anticoagulation in NS (unless contraindicated) are standard procedures in our department.

The clinical observation that NS follows a certain cutaneous pattern in children is another concept adopted by our team. Figure 5 exemplifies the vertical delimitation of cyanosis in the midline and the horizontal delimitation near the umbilical scar of another child (newborn) who also had NS after receiving BP, but not CS, and was treated conservatively; in this case there was complete resolution of cyanosis without the need for a surgical approach[14,15].

Cyanosis manifested in NS does not follow the historical (and current) Langer's lines based on collagen

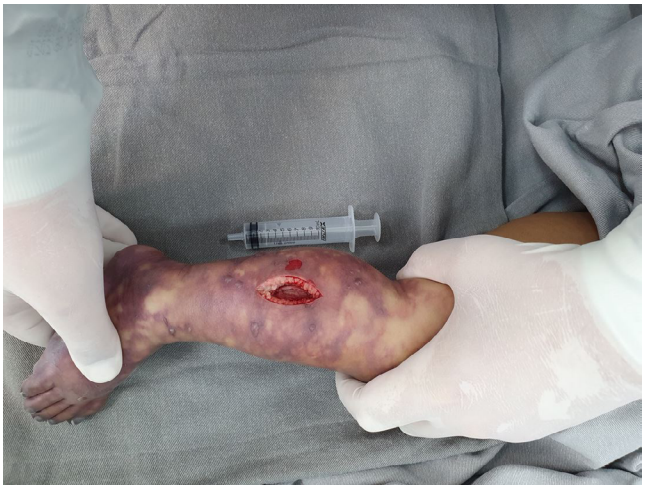

Figure 1. Cutaneous incision on the lateral aspect of the right leg (fasciotomy of the lateral and anterior compartments). Presence of flictena caused by ischemia.

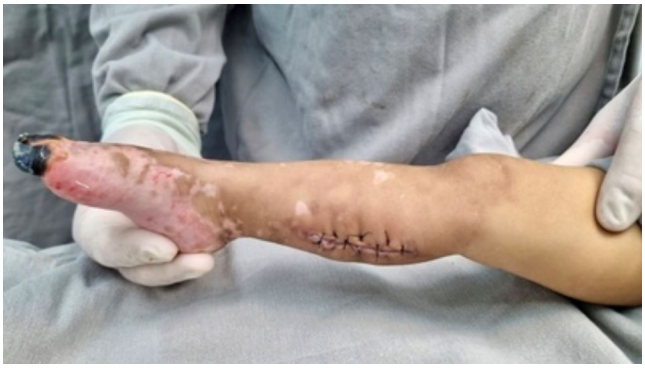

Figure 2. Skin suture on the medial side of the right leg (access to the posterior compartment fasciotomy).

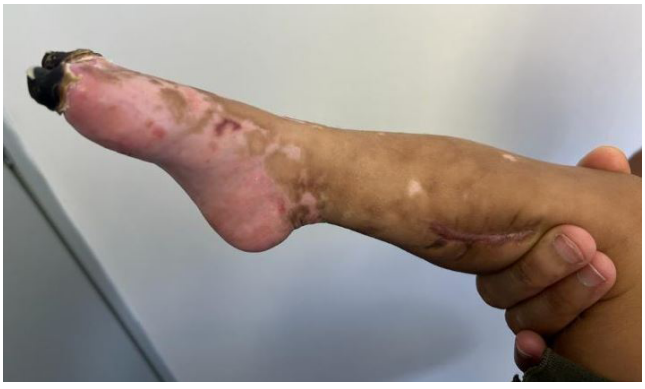

Figure 3. Delineation of the distal necrosis with complete healing of the skin incision on the right leg.

distribution and skin tension[16,17]. Even with the expansion of Blaschko's theories and his imaginary and invisible skin lines following the embryonic route of melanocytes[18,19], it also cannot be said that the swirls and chimeras in the midst of cyanosis follow this pattern or that they are associated with the usual angiosomes or dermatomes.

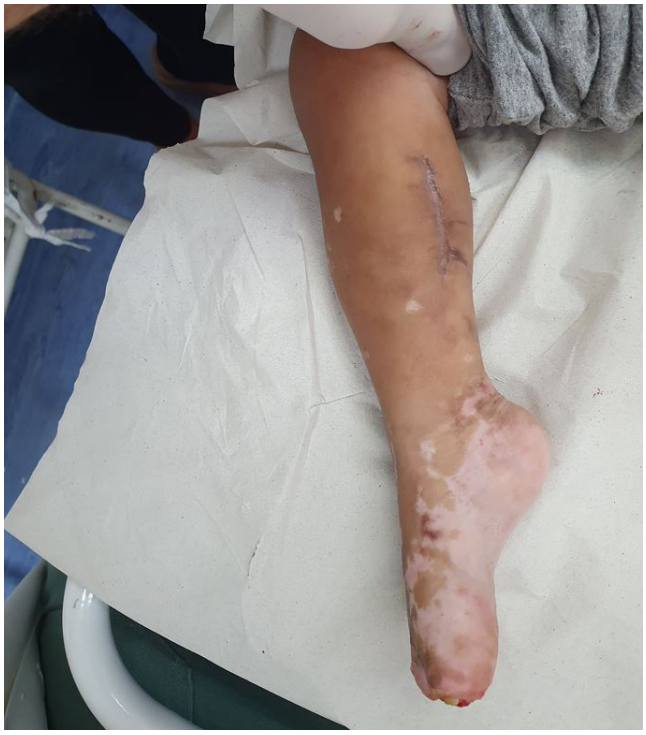

Figure 4. Absence of necrosis during an outpatient visit on the 77th day after surgery.

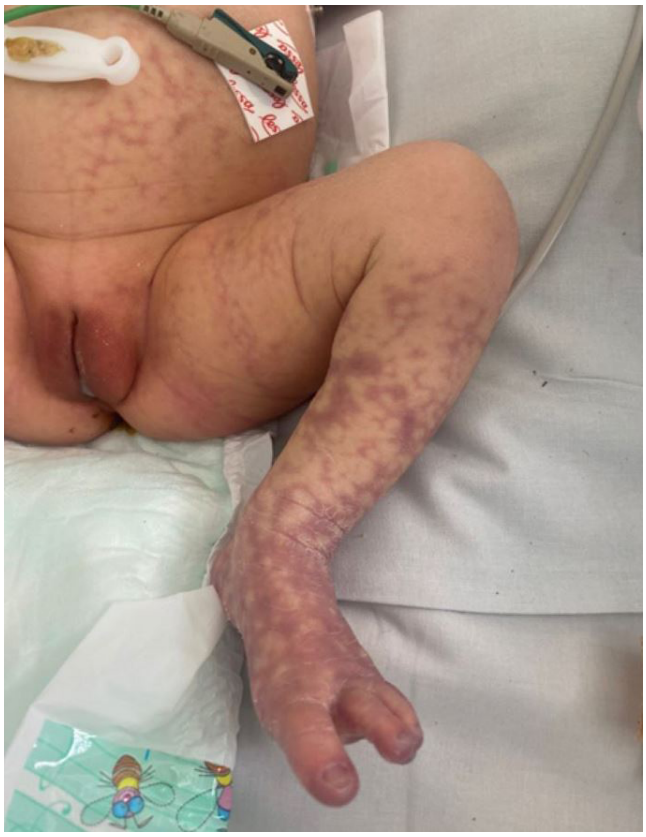

Figure 5. Vertical skin delineation of cyanosis in the midline and horizontal limits near the umbilical scar of another newborn child, with the right hemibody standing out without cyanosis. Source: Author's personal archive (ASB).

Similarly, diagnostic criteria and evolution of NS are not compatible with primary vasculitis. NS may be considered a vasculopathy secondary to BP use, but is unrelated to the pathophysiology of other entities such as livedoid vasculopathy (LV). Regardless of having similar characteristics to LV, such as thrombosis of dermal vessels, NS has livedo reticularis (different from livedo racemosa) and involvement of deep compartments (in addition to the skin), but this is not related to thrombophilia[6,20].

CS can be diagnosed and monitored using devices such as MY01 (NXTSENS, Montreal, Canada) or Stryker 295-1 (Kalamazoo, Michigan, USA). In the absence of these resources, however, the diagnosis can and should be established through physical examination. Thus, multidisciplinary efforts from medical teams are paramount in defining the diagnosis of NS, assessing CS, and indicating early fasciotomy, thus preventing the patient from suffering further complications due to rhabdomyolysis and renal failure[2,11,15].

In regards to hyperbaric oxygen therapy, it is a procedure of recognized value and positive impact on treatment of chronic wounds, such as in the diabetes-related feet[21]. Other reports have also attested to its complementary role in the treatment of NS[22] and contribution to good results, as in our case. Notably, the logistics of using hyperbaric chambers for treating children are not simple, as they depend on the availability and active participation of parents, besides exposing healthy individuals to the risks and side effects of the hyperbaric environment[21,22].

CONCLUSION

Although the clinical outcome of our case was favorable, the child progressed with phalangeal amputation, a result that highlights the high morbidity and potential severity of NS.

BP injection as a trigger for NS should not be a focus of recrimination, but it does serve as a warning not to underestimate the potential complications related to administering this antibiotic and other substances intramuscularly.

"This case report deserved an official declaration of acknowledgement and ethical approval by its institution of origin and was peer-reviewed before publication, whilst the authors declare no fundings nor any conflicts of interest concerning this paper. It is noteworthy that case reports provide a valuable learning resource for the scientific community but should not be used in isolation to guide diagnostic or treatment choices in practical care or health policies.

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