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Case Report

Nicolau's Syndrome Following Metamizole and Penicillin Injection: A Case Report

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Abstract

Introduction: Nicolau's syndrome, embolism cutis or livedoid dermatitis, is an uncommon pathology that occurs as a complication of an intramuscular, intra-arterial, or subcutaneous injection.

Case Presentation: A1-year-10-month infant who was admitted to the Hospital para el Niño Poblano, after the intramuscular application of metamizole and ampicillin, with the appearance of purplish color changes that doesn't disappear with acupressure in the left buttock, with progression to the rest of the left pelvic extremity. Initially, it was managed with conservative treatment, without improvement, advanced airway management was performed, as well as various surgical procedures for complications with adequate evolution, a biopsy was taken with a report of necrosis of skin and subcutaneous soft tissues associated with vascular and venous thrombosis.

Discussion: Nicolau's syndrome is characterized by severe pain at the application site, followed by cutaneous and/or neurological changes usually within 24 hours, with purplish livedoid macula/plaque being the most common manifestation, which may progress to skin necrosis; the diagnosis is clinically associated with the history of intramuscular drug application, mainly, and the prognosis depends on the treatment and timely diagnosis.

Conclusion: As it is a condition with a rare occurrence, the diagnosis can be delayed and incorrect. For this reason, it is concluded that Nicolau´s Syndrome, being an infrequent pathology in which clinical presentation and the duration of the condition influence it's a prognosis, underscores the critical importance of timely diagnosis and multidisciplinary management to reduce morbidity and mortality.

Keywords: *Case Report; Nicolau's Syndrome; Intramuscular Injection*

Introduction

Nicolau´s syndrome, also known as embolism cutis medicamentosa or livedoid dermatitis, is an uncommon pathology that occurs as a complication of an intramuscular, intra-arterial or subcutaneous injection of multiple medications: antibiotics, local anesthetics, steroids, non-steroidal anti-inflammatory drugs, hyaluronic acid, vaccines and vitamins, among others, which causes variable degrees of tissue injury, including necrosis of the skin and soft tissues [1,3]. Nicolau´s syndrome, was first described by Freudenthal and Nicolau in 1924 and 1925, respectively, after intramuscular injection of bismuth salts in syphilis patients [2].

Case Presentation

A 1-year-10-month-old infant who, on February 26, 2023, presented decreased consistency of evacuations, progressing from pasty to liquid, without mucus or blood. The child visited a doctor who recommended symptomatic management and Plan A for dehydration. On February 27, 2023, the child developed an unspecified fever and difficulty walking. The child visited a doctor who advised continuing the established treatment. Due to the lack of improvement, on February 28, 2023, the child visited a new doctor who administered intramuscular metamizole and ampicillin in the left buttock. After the injection, the mother reports persistent bluish discoloration that does not disappear with finger pressure on the left buttock, with progression to the rest of the left pelvic limb. On March 1, 2023, the child experienced decreased walking ability; on March 2, 2023, there was an inability to walk and loss of mobility in the lower limbs.

The patient came to the Hospital para el Niño Poblano on March 4, 2034, with impaired gait, no pelvic limb mobility, minimal thoracic limb mobility, and unaffected breathing and speech. He presented changes in skin coloration in the buttocks and left leg (Figure 1).

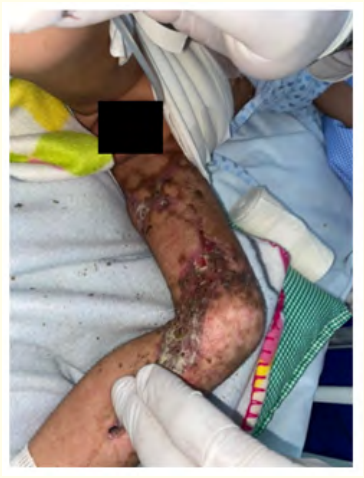

Figure 1: *A lesion with diffuse and blackish edges, produced by ischemia and tissue necrosis, disseminated lesion in the left leg.*

Laboratory studies: Lumbar puncture with a report of sanguineous cerebrospinal fluid (+), negative fibrin network, WBC count 1 cell, negative India ink, negative Gram stain, glucose 60 mg/dl, proteins 63 mg/dl, chloride 120 mmol/l, negative VDRL.

Imaging tests: Doppler ultrasound that reports no alteration data in vascular perfusion.

Treatments (Medical/Surgical): In the presence of suspected deep vein thrombosis, heparin was administered. Treatment was initiated with ceftriaxone and clindamycin, and on the same day, a transition was made to piperacillin/tazobactam and vancomycin. Immunoglobulin therapy was also started due to suspicion of Guillain Barre syndrome.

Clinical evolution

On March 5, 2023, the patient presented speech impairment, leading to the decision for orotracheal intubation until March 30, 2023. He was assessed by the plastic surgery service, which reported necrosis in the thigh and gluteal region requiring surgical management and changes in coloration in the mesogastrium (Figure 2), warranting a diversion colostomy, performed on March 14, 2023 (Figure 3).

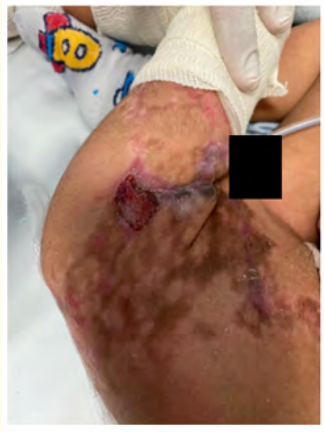

Figure 2: *Changes in coloration at the mesogastrium level, with irregular borders, involving tissues and skin.*

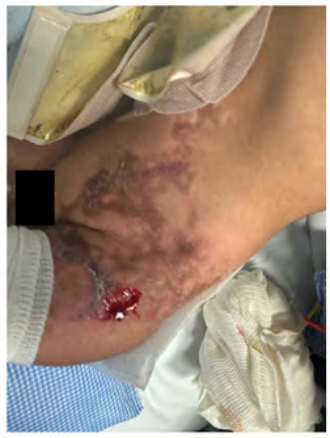

Figure 3: *Patient undergoing diversion colostomy.*

On March 16, 2023, we carried out a surgical wound irrigation and a tenotomy of the extensor muscles of the first, second, third, fourth, and fifth toes due to necrosis and neurovascular compromise in the left foot. Additionally, deperiostization of the first metatarsal to the fifth in the dorsal and plantar regions and osteotomy of the first to the fifth toe at a 30-degree angle with a smaller base in the plantar region were performed (Figure 4).

The patient required multiple surgical wound irrigations in the gluteal region, left leg, and stump of the left foot on 03.7.23, 03.22.23, and 03.28.23. In the latest surgical wound irrigation, the following was reported: necrosis of the greater gluteus, necrosis in the abdominal wall near the left umbilicus, and necrosis at the edge of the stump of the left foot (Figure 5).

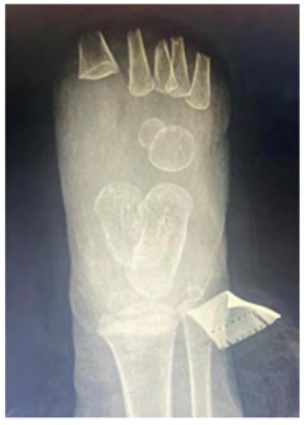

Figure 4: *X-ray showing an osteotomy from the first to the fifth toe.*

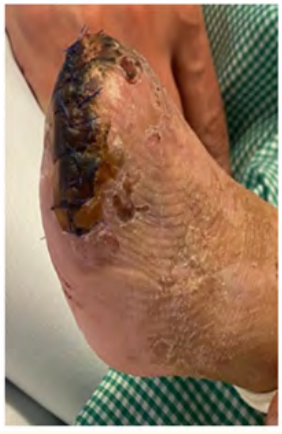

Figure 5: *Necrosis at the edge of the left foot stump.*

On March 30, 2023, the dressing was removed, revealing the presence of necrosis in the middle gluteus and adipose tissue and a hematoma in the wound near the upper left paraumbilical region of the abdomen. Partial debridement of necrotic tissue from the gluteal muscle and left leg was performed (Figure 6 and 7).

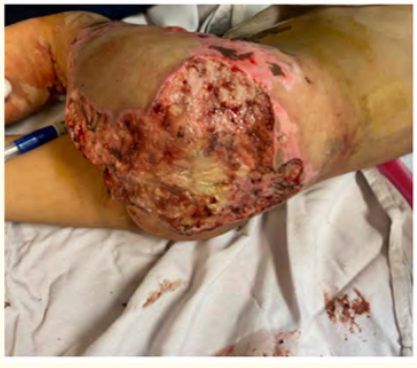

Figure 6: *Partial debridement of necrotic tissue from the gluteal muscle.*

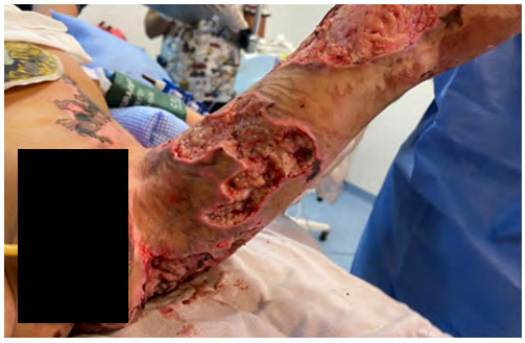

Figure 7: *Debridement of necrotic tissue from the left leg.*

On April 3, 2023, the dressing was removed, silver sulfadiazine was applied to surgical wound areas, and the lesions were covered. Multiple surgical wound irrigations were performed (April 5, 2023, April 12, 2023), with proper clinical progress (Figure 8).

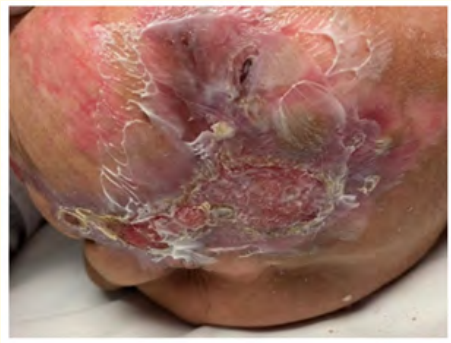

Figure 8: *Application of silver sulfadiazine in surgical wound areas.*

On April 27, 2023, we received a pathology report. The macroscopic description indicated a 6 x 5.5 cm transmetatarsal amputation of the left foot, noting diaphyseal spindles, as well as muscular and adipose tissue at the surgical end. The five toes were purplish, while the remaining skin appeared reddish-brown. The microscopic description showed sloughed stratum lucidum, epidermis with ischemic changes and difficulty in observing its layers, papillary dermis with mixed inflammatory infiltrate and cellular debris, and reticular dermis and subcutaneous cellular tissue with necrosis and thrombosis in multiple foci. The diagnosis was necrosis of the skin and subcutaneous soft tissues associated with vascular and venous thrombosis.

On April 18, 2023, a graft was taken from the anterior thigh and mosaic-placed in open lesions. On May 2, 2023, 100% graft integration was reported. On May 9, 2023, re-epithelialization was identified in 90% of open lesions of the left lower extremity, with complete graft lysis in the gluteal region and hypertrophic granulation tissue throughout the area (Figure 9-11).

Discussion

Nicolau´s syndrome (NS) is a rare clinical entity described as early as the 1920's in the setting of intramuscular bismuth injections for the treatment of syphilis. Fewer than 240 cases have been described in reported studies. Since the first report describing NS, several

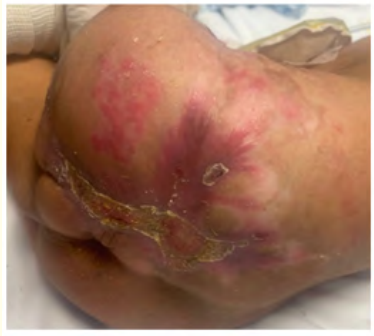

Figure 9: *90% reepithelialization of the graft.*

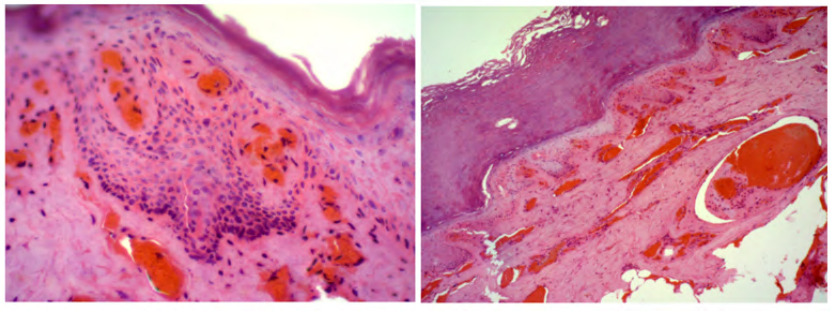

Figure 10 and 11: *Epidermis with internal ischemic and necrotic changes, multiple thrombi in venous and arterial capillaries.*

other drugs have been implicated in the development of this condition, including nonsteroidal anti-inflammatory drugs (e.g. piroxicam, ibuprofen, diclofenac, ketoprofen, ketorolac), antibiotics (penicillin G, gentamicin), cobalamin, vitamin K, corticosteroids, and local anesthetics (lidocaine) [4].

The pathophysiological mechanism is not clear so far, three hypotheses have been generated based on the findings observed in the tissue biopsy: 1) inflammation caused by the perivascular injection of the administered medication, induces arterial lesions, that lead to necrosis of the skin; 2) periarterial or perineural injection leading to severe pain can overactivate the sympathetic system, producing vasospasm and circulatory compromise; 3) Intra-arterial injection causes embolic occlusion of the cutaneous arteries with necrosis tissue [3].

Clinically, it begins with severe pain at the site of application, followed by cutaneous or neurological manifestations in general within 24 hours. The most common cutaneous manifestation is a purplish livedoid macula/plaque, which may progress to cutaneous necrosis. It can be associated with neurological manifestations such as sensory or motor deficits (Table 1 and 2) [5].

The diagnosis is mainly clinical and is associated with a history of intramuscular drug administration. The complementary tests to be requested are laboratory studies that include muscle and liver enzymes, blood count with platelets, coagulation profile, ultrasound of the soft tissues and skin biopsy. In the skin biopsy, observations may include areas of necrosis in the epidermis, in the papillary dermis

Mercury	
Bismuth	
Rolitetracycline	
Penicillin aluminum monostearate	
Benzathine penicillin G	
Antibiotics	Gentamycin, streptomycin, tetracycline
	Cyanocobalamine, and Vitamin B complexes
NSAIDs	Diclofenac sodium, piroxicam, ketoprofen, ketorolac, ibuprofen
	Phenylbutazone, and etofenamate
	Local anestheticslidocaine
	Thiocolchicoside injection
Antihistamines	Diphenhydramine
Corticosteroids	Dexamethasone, triamcinolone, and hydrocortisone
	Intraarticular injections of glucocorticoids
Antipsychotics	Chlorpromazine
Miscellaneous	Vitamin K
	Phenobarbitone
	Intramuscular oxytocin
	Meperidine, buprenorphine, and naltrexone hyaluronic acid
Vaccines	Diphtheria, tetanus, and pertussis
	PEGmodified interferonα2b; β interferon
	Etanercept and bortezomib
	Glatiramer acetate

Table 1: *Drugs implicated in Nicolau´s syndrome (1924 2018). Source: 10. Shelley, Bhaskara P., et al. "Hyperacute Paraplegia and Neurovascular (Immuno Vasculotoxic) Catastrophe of Nicolau´s syndrome: Primum Non Nocere." Annals of Indian Academy of Neurology vol. 22,1 (2019): 104-108. doi: 10.4103/aian.AIAN_298_18.*

NSAID: Nonsteroidal Anti Inflammatory Drugs; PEG: Polyethylene Glycol.

Transverse myelopathyacute flaccid paraplegia
Ischemic plexopathies involving (1) the lumbar plexus or its femoral branch or (2) the lumbar and sacral plexus or (3) the lumbosacral plexus including some lumbosacral nerve roots due to involvement to toxic angiopathy of iliac artery branches
Lumbosacral plexopathytoxic endarteritis with spasms and thrombosis, with spread to the epineural and perineural blood vessels and cause segmental infarction
Flaccid crural monoplegia (involvement of ipsilateral iliac arteries, affecting lumbar or lumbosacral plexus)
Mononeuropathiesfemoral nerve palsy obturator nerve palsy
Sciatic/common perineal neuropathy due to the involvement of inferior gluteal artery
Necrotizing fasciitis and compartmental syndrome with neuropraxias

Table 2: *Neurological manifestations in Nicolau´s syndrome. Source: Shelley, Bhaskara P., et al. "Hyperacute Paraplegia and Neurovascular (Immuno Vasculotoxic) Catastrophe of Nicolau´s syndrome: Primum Non Nocere". Annals of Indian Academy of Neurology vol. 22,1 (2019): 104-108. doi: 10.4103/aian.AIAN_298_18.*

lymphocyte infiltrate of perivascular disposition and hemorrhagic foci in the reticular dermis without features of vasculitis. As for differential diagnoses should be considered, cholesterol embolisms, necrotizing fasciitis, and vasculitis, among others [6].

Timely treatment is key to mitigate the complications derived from this syndrome, pain management, corticosteroids, heparin, peripheral vasodilators, and antibiotic therapy are fundamental adjuvants [2]; however, should be determined by the severity of the neurological deficits, with most patients treated using a conservative approach (i.e. physiotherapy and analgesics). Surgical exploration has been recommended for patients without functional improvement within 3 - 6 months after injury or earlier in the case of severe pain and debilitation [4].

Complications range from skin scarring to death. Myositis, secondary infections, muscle atrophy, myonecrosis, acute renal failure, compartment syndrome, ischemia of the genitals, perineum and rectum, and neurological lesions such as paraplegia, sensory deficits and sphincter disorders have been described [8].

Conclusion

Nicolau´s syndrome refers to an iatrogenic scenario that arises because of the administration of various drugs, primarily through intramuscular injection. Although NS is a complication with low frequency and incidence, it is important to adequately understand its pathophysiology, the signs, and symptoms it presents, which enables us to initiate appropriate treatment early and in a timely manner, with the aim of preventing serious complications, as it occurred in the presented case. Since it had been evolving for several days without a prompt diagnosis and treatment, it resulted in various complications with systemic effects that adversely affected the individual's quality life.

Several drugs are associated with the appearance of NS, such as penicillin, being one of the first antibiotics associated with this syndrome, and although it is a drug with very frequent use, the administration technique must be adequate for prevention. The risk is associated with the injection site, frequency of drug administration, and application technique [9].

There are several predisposing factors to develop this syndrome, such as age (being more frequent in children under 3 years of age), in which the phenomenon of arterial embolism is more likely to occur due to the smaller size of the vascular segments involved, a decrease in muscle mass, and defense movement against the application of the various drugs [8].

As it is an infrequently condition, the diagnosis can be delayed and erroneous. For this reason, it is concluded that Nicolau´s syndrome is a rare pathology in which its clinical presentation and time of evolution condition its prognosis, a timely diagnosis and multidisciplinary management are of utmost importance to reduce morbidity and mortality. Continuously highlighting the importance of following the established guidelines and having trained personnel when administering intramuscular injections as a preventive measure to minimize complications as much as possible, such as the one mentioned in this case [10].

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