Late development of Nicolau syndrome - Case report

Síndrome de Nicolau de desenvolvimento tardio - Relato de caso

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Abstract: Nicolau syndrome also known as Embolia cutis medicamentosa and Livedoid dermatitis is a rare complication characterized by tissue necrosis that occurs after injection of medicines. We describe a case of late development of Nicolau syndrome following intra-articular infiltration with corticosteroid.
Keywords: Adrenal Cortex Hormones; Dermatitis; Necrosis; Seepage

Resumo: A Síndrome de Nicolau, também conhecida como Embolia Cutis Medicamentosa e Dermatite Livedóide, é uma rara complicação caracterizada por necrose tecidual que ocorre após a injeção de medicamentos. Descrevemos um caso de Síndrome de Nicolau de curso tardio, posterior à infiltração intra-articular com corticóide.
Palavras-chave: Corticosteróides; Dermatite; Infiltração; Necrose

INTRODUCTION

Injection of glucocorticoids is one of the most common procedures in rheumatology. Although steroids cause a range of local or systemic adverse effects the procedure is considered safe.[1,2]

The injections of local glucocorticoids are largely used in the treatment of patients with muscoskeletal diseases. The infectious complications are the main source of concern although they still remain unusual.[3]

Two cases of Nicolau syndrome after intra-articular injection of glucocorticoids were described.[3] According to Cherasse et al (2003), the development of this syndrome in these situations is rare. However, studies about the needle position during injections supposedly intra-articular show that the needle is commonly localized completely or partially outside the joint space. [3]

We report a case of a patient who had had two intra-articular injections of glucocorticoids that evolved into a late condition of Nicolau syndrome.

CASE REPORT

Female patient, aged 47, hypertensive, sprained her left ankle, grade 3, in November, 2008 that evolved into intense and painful swelling on the lateral side of the ankle leading to functional inability to walk, limitation of mobility and extensive local erythema.

She immediately sought for orthopedic care and MRI (magnetic resonance imaging) was performed and diagnosed a partial rupture of the talofibular ligament and tenosynovitis of the peroneus with a small partial rupture of the peroneus brevis and marked fluid distension of its synovial sheath. Analgesic and anti-inflammatory medicines were prescribed, without joint immobilization.

As the swelling and pain remained after 5 months, the patient underwent 2 procedures of injection of the peroneal sheath with the incision of the extensor retinaculum percutaneously, within an interval of 7 days between them. The condition evolved with improvement of the edema but the pain remained.

After one week, the patient developed an intense burning pain, on the site of the injection, with no mitigating or aggravating factors, associated with the appearance of circumscribed necrotic area on the left lateral malleolus region, measuring, approximate-

Received on 18.09.2009.
Approved by the Advisory Board and accepted for publication on 07.03.2010.
* Work carried out at Faculdade Brasileira (UNIVIX) – Vitória (ES), Brazil.
Conflict of interest: None / *Conflito de interesse: Nenhum*
Financial funding: None / *Suporte financeiro: Nenhum*

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ly, 2 cm of diameter (Figure 1A). The patient sought for medical care in the emergency unit where she was medicated with painkillers and monitored hemodynamically.

About 72 hours later, the condition evolved with extension of the necrosis that acquired irregular borders, erythematous rash in the affected limb with the presence of a halo of erythema around the lesion and pain was worsening. She was, then, admitted to the Vila Velha Hospital where she had a normal Ecodoppler evaluation of the lower limbs. It was diagnosed Nicolau syndrome and she was medicated with ciprofloxacin, enoxaparin and pentoxifylline.

Later, surgical debridement of the devitalized tissue was performed, with tendon exposure. (Figure 1B). The injury evolved favorably, with development of atrophic scar 3 months after the surgery. (Figure 1C).

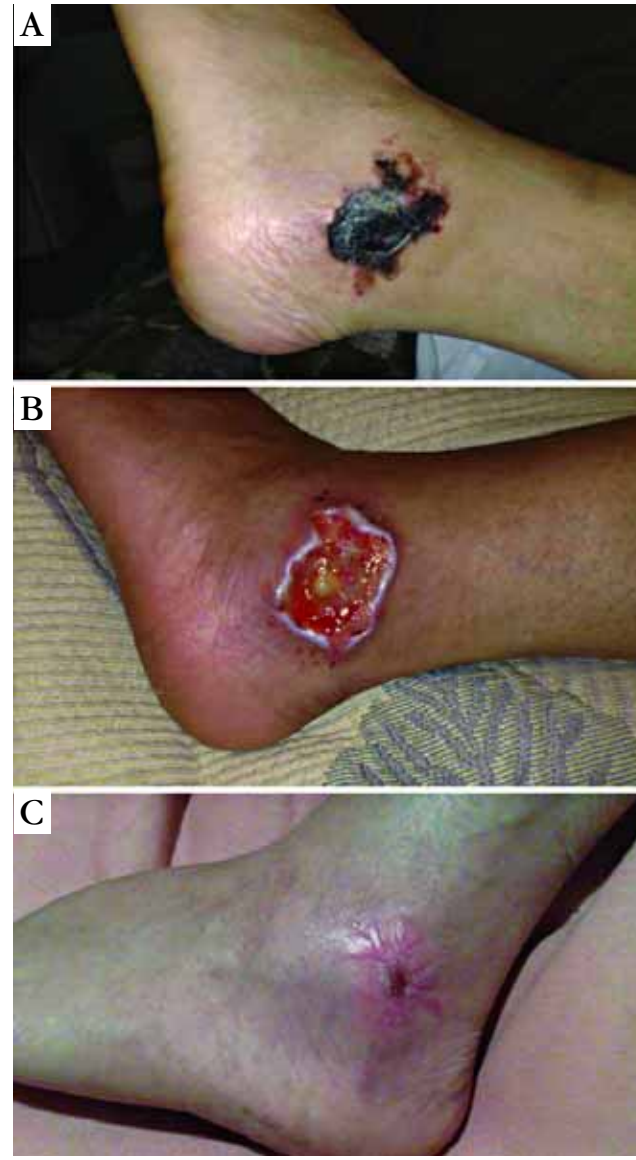

Figure 1: A. Circumscribed area of necrosis in the left malleolar region; **B.** Lesion after surgical debridement, with exposure of tendon; **C.** Atrophic scar

DISCUSSION

Nicolau syndrome or Embolia Cutis Medicamentosa, was first described by Juliusberg, Freudenthal and Nicolau between 1924 and 1928.[3,4,5,6] The first descriptions refer to patients under treatment of syphilis that were given injections of bismuth salts.[4,5]

It is well described in the dermatological literature as a rare adverse reaction characterized by dermatitis livedoid[3,4,5,7] that occurs after intramuscular injection of insoluble substances.[4,7,8,9]

However, the emergence of the syndrome is related to the pharmaceutical form of the drug and the way the remedy is applied and not with its pharmacodynamic properties and, therefore, there is not an specific group responsible for its complication potential. Systematic review showed predisposing factors such as aqueous micro-suspension in contrast with oily vehicle suggesting a prevalent genesis of embolism syndrome. [10]

Nicolau syndrome has already been described in medical literature caused by the injection of any of the following drugs: penicillin benzathine, penicillin, NSAIDs (non-steroidal anti-inflammatory drugs), local anesthetics, antihistamines and corticosteroids. [5]

According to Saputo & Bruni (1998), the syndrome is more frequent in the pediatric population, mainly in children who are younger than 3 years old, in which the phenomena of artery embolism may be more likely to happen due to the smaller size of the vascular segments involved.[10] However, according to Senel et al (2008), the majority of the cases reported refer to adults.[5]

Although the buttock is the most affected site it was also described on the shoulder, thigh, knee and ankle.[5]

The mechanism of inflammation and cell destruction is uncertain but it is known that there is a micro embolic obstruction of the arterial supply of the dermis. [4,10,11] Current data, however, suggest that embolism is not the only factor involved . The final lesion would result from three factors: angiospasm, thrombosis and embolism.[11] Embolism and thrombosis would be caused by the injection of the medicine within the vascular lumen while angiopasm could be caused by a series of factors such as vessel compression (by the injected liquid or by hematoma), by direct lesion of the vessel by the needle or by the arterio-arterial or veno-arterial reflex.[7,11]

There are still authors that believe in an immuno-allergic origin to explain the necrosis. [10,11] According to them, the drug in question would act

like an hapten, triggering a reaction of vasculitis, with deposition of immune complexes, complement activation and neutrophil chemotaxis. The result of such alterations would be a thrombosis that would manifest itself clinically as a necrosis.[11]

Clinical manifestations can be local or systemic. Initially, the patient presents severe and acute pain after the injection.[3,5,7,8,10] After that, developing a erythematous rash on the injection site, with formation of a halo of pallor around the area,[10] with a livedoid pattern [3,5,12] that slowly evolves into skin, subcutaneous and ,sometimes muscular necrosis. [10,13] In some patients it can progress to bullae in the site of the injection. Secondary infection might occur.[3,5,7]

The necrotic area in a few cases, extends to the articulation causing permanent or transient ischemia that sometimes leading to amputation.[10]

There are neurological complications, usually transitional in one third of the patients (varying from some hours to many weeks), represented by hypoesthesia and paraplegia.[10,13]

Tissue injury is reversible and quick therapy with vasoactive substances like subcutaneous heparin could be beneficial. [14] Vasospasm can be relieved by the inhibitory action of phosphodiesterase provided by pentoxifylline.[10] Corroborating data, according to Uri & Arad (2009), various studies mentioned clinical improvement of patient that had being treated with anticoagulants (e.g. heparin), intravenous steroids (e.g. betamethasone, dexamethasone or intravenous methylprednisolones) and vasoactive therapy (e.g. pentoxifylline).[14]

According to Murthy, Siddalingappa & Suresh (2007), conservative treatment with debridement and pain control is the main therapy. [14]

Considering the fact that there is no set standard for the treatment of the Nicolau syndrome it is important that the use of a correct technique for injection to minimize the risk factors. Prior aspiration is important to ensure an extra-articular injection. However, there is not a specific guideline.[15] ❑

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How to cite this article/*Como citar este artigo*: Silva AMM, Ton A, Loureiro TF, Agrizzi BL. Late development of Nicolau syndrome - Case report. An Bras Dermatol. 2011;86(1):157-9.