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**Nicolau Syndrome Caused by Penicillin Injection a Report From Iran.**

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**Abstract:**

Introduction: Nicolau syndrome also known as livedo-like dermatitis or embolia cutis medicamentosa is a rare adverse reaction of a still largely unidentified pathogenesis at the site of intramuscular and intra-articular drug injection.

Case report: herein we report a 7-year-old boy, a known case of cerebral palsy received a penicillin injection in the left buttock due to upper respiratory tract infection and one day later developed an echymotic, ischemic and necrotic area in the site of injection which extended to the left leg, thigh and foot gradually. Nicolau syndrome was diagnosed and the patient received prednisolone, pentoxifyllin and was heparinized. In the follow up, the lesion began to improve.

Discussion: There is no specific therapy for Nicolau syndrome other than prevention. Correct Intramuscular injections may prevent these conditions. This case is the second report of Nicolau syndrome from Iran after the case of Beheshti-rooy et al.

**Keywords: Nicolau Syndrome – Penicillin - Intramuscular Injection- I**

**Introduction:**

Nicolau syndrome also known as livedo-like dermatitis or embolia cutis medicamentosa is a rare adverse reaction of a still largely unidentified pathogenesis at the site of intramuscular and intra-articular drug injection.<sup>(1-7)</sup> The typical presentation is pain

around the injection site soon after injection, followed by erythema, livedoid patch, haemorrhagic patch, and finally necrosis of skin, subcutaneous fat, and muscle tissue.<sup>(1, 5)</sup>

The cases were described by Nicolau occurred in association with injections of oily bismuth suspensions in 1920. In 1970s and

1980s, some cases of the disorder occurred with delayed-action penicillin suspensions injected intramuscularly.<sup>(1)</sup> Typically, the injection is followed immediately by excruciating pain in the buttock, sometimes with syncope. Cyanotic patches and a livedoid pattern develop. Rapid resolution of the pain and slower clearing of the skin changes occur in most patients.<sup>(1-5)</sup>

The phenomenon has been related to the administration of a variety of drugs, including non-steroidal anti-inflammatory drugs, corticosteroids, penicillin G<sup>(6, 7)</sup>, intra-articular injection<sup>(7)</sup> and DTP vaccine.

#### **Case Presentation:**

A 7 year old boy, a known case of cerebral palsy was transferred to a general physician due to upper respiratory tract infection. He received a penicillin injection in the left buttock.

From the day of penicillin injection, the patient developed an echymotic, painful, ischemic and necrotic lesion in the site of injection which extended to the left leg, thigh foot and fingers gradually. The patient referred to our center for better evaluations.

The color Doppler sonography of the lower extremity includes, common femoral artery, superficial femoral, popliteal, dorsalis pedis and posterior tibialis arteries showed increased diastolic flow representing vasodilation which may be due to hyperemia and inflammation. In the laboratory evaluations inflammatory factors increased, kidney and liver function test was within normal range. Histological examination of the necrotic sites revealed necrosis of the glands with thrombosis of small-sized vessels in the dermis, but no sign of vasculitis was detected.

Nicolau syndrome was diagnosed according to history, radiologic, histologic and laboratory evaluations and the patient received intravenous immunoglobulin (IVIG) (2 g/kg) and pentoxifyllin. The patient was heparinized and after 12 days he was discharged from the ward in a good general condition. In the follow up, the lesion began to improve.

#### **Discussion:**

Livedoid dermatitis (LD) (Nicolau's syndrome) is a rare condition with an acute and severe pain and a localized erythematous rash during intramuscular injection leading shortly to cutaneous, subcutaneous and even muscular necrosis. For the first time it was recognized as an adverse effect of bismuth salts routinely used for the treatment of syphilis in 1920.<sup>(1-5)</sup>

Subsequently, many different drugs have been reported to cause this rare condition.<sup>(6, 7)</sup> Initially, the patient felt intense pain with pallor due to local reflex vasospasm around the injection site. The site developed an erythematous macule which evolved into a livedoid violaceous patch, and then it became hemorrhagic and ulcerated, and eventually healed with an atrophic scar and followed by necrosis and a sharply demarcated pale lesion. Signs of bacterial secondary infection may also occur.<sup>(1-5)</sup>

The skin reaction is pathognomonic, as exemplified by its synonym "embolia cutis medicamentosa".<sup>(1)</sup>

In these situations Histological examinations show necrosis of the eccrine glands of dermis and also extensive thrombosis of medium- and small-sized vessels of the reticular dermis without any vasculitis.

The ultimate event is emboli or vessel damage and occlusion of the peripheral arteries. The hypothesis of an allergic and immunologic origin or the role of physical and chemical factors such as injection technique and solution pH has been discontinued by experimental studies. However, reinjection in the same patient of the same drug has not induced a recurrence.<sup>(7)</sup>

The neurologic change like hypoesthesia, paraplegia, and sphincter incompetence occurred in some patients. Elevation of the hepatic enzyme and creatinine phosphokinase were previously described. There has been a report of a variant of Nicolau syndrome presented with isolated myonecrosis without skin change.<sup>(4)</sup>

Differential diagnosis of Nicolau syndrome includes cholesterol emboli, the left atrial myxoma emboli, and Hoigne syndrome. Cholesterol emboli usually occurs in the elderly patients with severe atherosclerotic disease and after endovascular manipulation and/or anticoagulation. Left atrial myxomas can cause cutaneous emboli, usually to the acral sites and accompanied by cardiopulmonary symptoms such as chest pain and dyspnea. Hoigne syndrome is a German term for an acute direct intravenous injection.<sup>(1)</sup>

There is no specific therapy for Nicolau syndrome other than prevention. Intramuscular injections should be performed only after aspirating with the syringe in order to ensure extra-vascular injection of the drug. The preferred site for the injection is the upper outer quadrant of the gluteal region, with fewer large blood vessels. Tissue damage has not been found to be reversible; however, plexus block, anticoagulant ther-

apy (heparin), arteriotomy and extraction of the clot, and local care have been discussed. Vasoactive medications were used in some patients and they had a rapid response to treatment with complete healing and no scarring or functional impairment during 4 weeks.<sup>(1-5)</sup> In this patient due to more extensive necrosis, IVIG and methyl prednisolon were used with favorable results.

This case is the second report of Nicolau syndrome from Iran after the case of Beheshti-rooy et al.<sup>(8)</sup>

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