Case Report

Nicolau Syndrome

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Abstract

A 23-year-old man was admitted to the hospital with chief complaints of pain, edema and spasm of the left lower limb, as well as mottling of dorsal and plantar aspects of the foot. One week before the current admission, he was treated with oral co–amoxiclav and intramuscular penicillin 6.3.3. Immediately after the third injection, he experienced burning and yellowish discoloration at the site of the injection which then progressed to his leg and foot. Pain, significant edema, spasm and mottling occurred within 30 minutes of the injection. The patient was referred to the hospital after 36 hours from the beginning of symptoms. Color Doppler sonography revealed no impairment in the lower extremity flow and the common femoral artery, superficial femoral, popliteal, *dorsalis pedis* and *posterior tibialis* arteries were normal. Superficial probe sonography detected mild effusion in the left ankle without collection.

Keywords: Intramuscular injection, Nicolua syndrome, penicillin

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Introduction

Nicolau syndrome (NS) is an uncommon injection site reaction following intramuscular (IM) injection of drugs. It can cause different degrees of skin and soft tissue damage. This reaction has been also described as *embolia cutis medicamentosa* and livedo-like dermatitis.[1–4] NS is marked by development of acute, intense pain, immediately after drug injection followed by rapid skin erythema, a livedoid reticular or a hemorrhagic patch. On pathologic examination of the lesions, necrosis and ulceration of the skin, muscle tissue, and subcutaneous fat have been described. These skin lesions are pathognomonic for the diagnosis of NS.[1–8] In this report, we describe a 23-year-old man with a diagnosis of NS after intramuscular injection of penicillin 6.3.3.

Case Report

A 23-year-old man was admitted to the emergency department of the Imam Khomeini hospital, Tehran, Iran, with chief complaints of pain, edema and spasm of the left lower limb, as well as mottling of the dorsal and plantar aspects of his foot. His past medical history was positive diabetes mellitus type 1 for 12 years and sinusitis. One week before the current admission, he was treated with oral co–amoxiclav tablet and intramuscular penicillin 6.3.3 (600,000 PNC G benzathine, 300,000 PNC G procaine, 300,000 PNC G potassium). The first IM injection of penicillin was administered 4 days before the admission. The first and third injections were performed in the left buttock and the second dose of penicillin was injected in his right buttock. Immediately after the third injection, he experienced burning and yellowish discoloration at the site of injection (*quadriceps femoris* muscle) which progressed to his leg and foot. Pain, significant edema, spasm and mottling occurred within 30 minutes of the injection. The patient was referred to the hospital after 36 h from the beginning of symptoms. On physical examination, the patient's vital signs were stable and the left gastrocnemius muscle was cold and tense. The popliteal, *dorsalis pedis*, and posterior tibial pulses were attenuated. The patient's laboratory data on admission are summarized in Table 1.

Before pharmacotherapy consults, local ice compress was applied according to the recommendation of the orthopedics service in order to reduce the probable complications of compartment syndrome

Following pain exacerbation and pharmacotherapy note, ice compression was discontinued.

Color Doppler Sonography revealed no impairment in the lower extremity flow. Common femoral artery, superficial femoral, popliteal, *dorsalis pedis* and *posterior tibialis* arteries were normal. Superficial probe sonography detected mild effusion in the left ankle without collection.

According to the Naranjo and WHO causality assessment scale, the likelihood of NS following penicillin injection is categorized as probable. Subcutaneous heparin (5000 IU/ TDS), pentoxifyllin tablet (400 mg/TDS), systemic glucocorticoid (methylprednisolone succinate 500 mg/daily for 3 days), amlodipine Tab (5 mg/BD), pregabalin (75 mg/BD), morphine sulfate (5 mg as IV injection PRN), pantoprazole (40 mg/day) and complete bed rest were started for the patient within the first 12 hours of admission. After 24 hours, all of the patient's symptoms improved significantly. The treatment regimen was continued

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Table 1. Laboratory data of the patient on admission

WBC	13.9	**PT**	14.1
Lymph (%)	4.3	**INR**	1.3
Neut (%)	93.8	**LDH**	1587
HGB	17.1	**CPK**	62
MCV	87.1	**ESR**	14
PLT	250,000	**CRP**	5.7
Na	137	**Albumin**	4.1
K	40	**Ca**	9.1
BS	240	**P**	3.3
Urea	36	**ALP**	384
Cr	1.2		

WBC: white blood cell; Lymph: lymphocyte; Neut: neutrophil; HGB: hemoglobin; MCV: mean corpuscular volume; PLT: platelet; Na: sodium; Ca: calcium; K: potassium; BS: blood sugar; Cr: creatinine; PT: prothrombin time; INR: international normalized ratio; LDH: lactate dehydrogenase; CPK: creatine phosphokinase; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Ca: calcium; P: phosphorus; ALP: alkaline phosphatase.

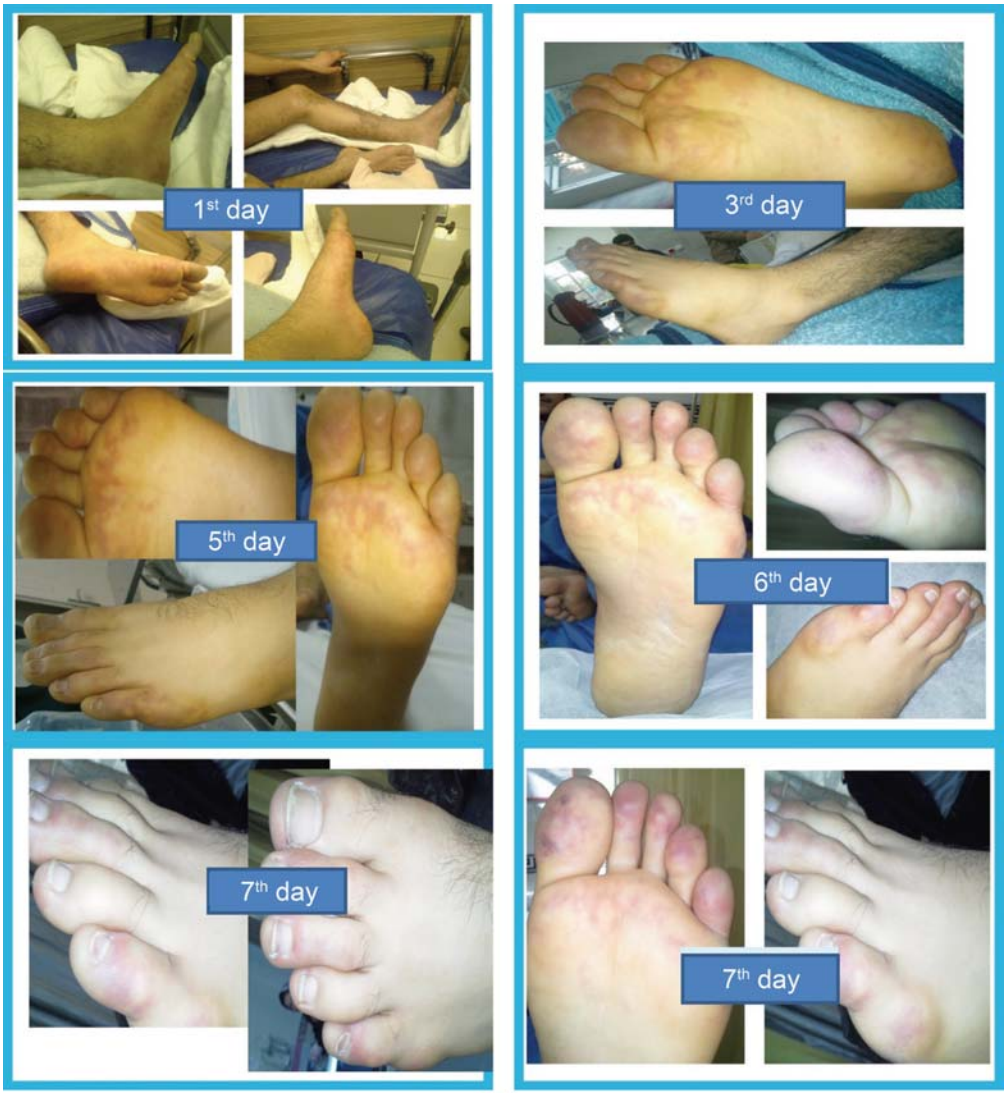

Figure 1. The patient's lower limb conditions on days 1, 3, 5, 6 and 7

and the patient was finally discharged on the 7th day of admission while pain, edema and spasm were completely resolved, and slight mottling remained. On the follow–up visit on day 14, all the symptoms had disappeared completely and the patient walked without any complaints. The patient's conditions on days 1, 3, 5, 6 and 7 of hospital admission are shown in Figure 1.

Discussion

Nicolau syndrome (NS) has been introduced as a rare but serious complication of IM injection, characterized by severe pain,

edema, and skin changes immediately after injection.

The first case of NS was reported following IM injection of bismuth salt for treating syphilis in a patient.[1,2] Although most cases of NS occur following IM injection, some of them are related to local injection of medications.[3] Penicillins are the most common agents causing NS, followed by nonsteroidal anti–inflammatory drugs (NSAIDs), local anesthetics, and corticosteroids.[2–8]

The pathogenesis of NS is not well defined. It may occur after accidental intra–arterial injection of a chemical agent.[9] The pathogenesis of local skin necrosis after IM injection was described in an animal model by Brachtel, et al. Phenylbutazone solution was injected in the para–arterial and intra–arterial sites on rabbit ear lobes in this experimental study. The drug caused serious inflammation following both routes of injection. Histological findings showed significant damage of the inner arterial wall.[10] Direct injury to vessels or vascular compression following arterial embolism of drug, vasospasm (secondary to release of some vasoactive mediators), crystallization of aqueous drug in blood vessels and arteriovenous shunt progression or ischemia after para–arterial injection are available evidences related to NS pathogenesis.[11] Based on the proposed pathogenesis, cold compression may exacerbate the symptoms of NS.[6,12,13]

The most common clinical feature of NS is severe pain around the site of injection, followed by erythema, *livedo reticularis* (purplish network discoloration of the skin) or hemorrhagic patch immediately after injection.[6] Along with these superficial complications, involvement of the deeper tissues including necrosis and ulceration of the skin, muscle tissue, and subcutaneous fat may also occur. In one third of the patients, neurological symptoms such as hypoesthesia, paraplegia, and sphincter incompetence have been reported.[14]

The most commonly described differential diagnoses for NS are cutaneous cholesterol emboli, which usually occur in the elderly with a history of atherosclerosis following endovascular interventions, cutaneous presentations of cardiac myxoma, vasculitis, cellulitis, necrotizing fasciitis and compartment syndrome of gluteus muscle, as well as Hoigne syndrome; a German term for an acute direct intravenous injection[15,16].

There is no well-defined standard therapy for NS and treatment can vary from supportive care for pain management to extensive surgical debridement, based on necrosis severity. Administration of vasoactive agents such as subcutaneous heparin and oral pentoxifylline has been reported to be helpful.[13] Also, some studies have suggested hyperbaric oxygen, as well as systemic and topical steroids for ameliorating complications of NS.[17] It should be remembered that cold compression can deteriorate ischemia phenomena due to vasoconstriction in NS.[6,12,13]

Administration of appropriate antibiotic regimen may be considered when there is evidence of infection. Since cell damage may be reversible in the acute phase of NS, starting early supportive care saves tissues.[17] CT scan or MRI are helpful to determine the extent of damage to recognize the degree of fat necrosis to prevent inadequate debridement and poor wound healing.[18]

To minimize the risk of NS, the following recommendations may be helpful:

a. To minimize or prevent subcutaneous irritation, Z–track IM injection of irritant medications is suggested.

b. Sufficiently long needles should be used to reach the muscle for IM injection. A 2 or 3 and 1.25 or 1.45–inch needle is recommended for a 90kg and 45kg patient, respectively.

c. The upper outer quadrant of the buttock is the best site for IM Injection (fewer large blood vessels).

d. To protect the blood vessels, aspirate the needle before IM injection.

e. The volume of each IM injection should never be more than 5 mL in Z–track injection

f. Rotate the injection site for the patient requiring repeated or multiple injections.[19–21]

The first case of NS was described in 1925 by Nicola following IM injection of bismuth salt. Later, it has been reported following the IM or subcutaneous injection of a wide range of other medications.[22–24] Although in most cases of NS, the buttocks are involved, it has also been described in the shoulder, thigh, knee, and ankle.[6] In our case, NS occurred immediately after IM injection of penicillin benzatine and presented as pain, significant swelling, spasm and mottling in the patient's leg and foot.

The mechanism of inflammation and cell destruction in NS is not well defined. Micro-embolic obstruction of the arterial supply of the dermis is suggested as a probable mechanism.[25–27] The neurological involvement with lower limb paralysis can be explained by drug embolism.[28] As there is no confirmatory test, the diagnosis of NS is based on patients' past medical history and the clinical manifestations. Therefore, NS should be considered as a possible diagnosis for anyone who presents with severe localized pain following an intramuscular injection. NS cases have been described following IM injections of penicillins and NSAIDs.[5,7,16,29–31] In these patients, necrosis and secondary infection of the skin and underlying muscle have been reported. Debridement of necrotic tissues improved the patients' conditions.[5,29] Subcutaneous fat and skin necrosis following SC injection also has been reported by Okan, et al.[24]

Initially, clinical improvement in NS symptoms was observed following resting the affected limb, and administration of corticosteroids, antibiotics, low molecular weight or UF heparin, as well as oral pentoxifylline and oral CCB. Anti–inflammatory, vasodilatation, improving blood rheology and preventing infection are possible beneficial effects of these agents.

However, the potential benefits of these agents have not been approved yet. Resting the affected limb is important and any activity or pressure can aggravate the conditions of the patient. NS should be differentiated from cellulitis, necrotizing fasciitis and compartment syndrome of gluteus muscles, cutaneous cholesterol emboli, cutaneous presentations of cardiac myxoma, vasculitis, and Hoigne syndrome.

While the exact pathogenesis of NS has not been understood yet, clinicians should remember this uncommon and serious complication of IM injection of common medications such as NSAIDs and penicillins. Silva, et al. reported a case of NS induced by intra–articular glucocorticoid injections.[32] It is important to emphasize that the use of a correct technique for injection can minimize the risk factors. The injection should be administered in the upper outer quadrant of the buttock with aspirating the needle before injecting to ensure that no inadvertent intra-arterial injection occurs; however, there is no specific guideline.[33]

For prevention of adverse injection reactions, health care providers should be informed of the proper method of intramuscular injection such as Z–track method of injection, aspiration before injection and holding the injection site immediately after the

Table 2. Characteristics of the Iranian cases with diagnosis of NS

Case NO	Authors Name	Publication date	Age(y/o)	Sex	Causative agent	Route of administration	Injection site	Past medical history	Cause of recent medication administration	Medical intervention	Surgical ntervention	improvement	Duration of hospitalition
1	Alyasin S, Sharifian M	2010	7	Male	penicillin		Left buttock	Cerebral palsy	URI	IVIG(2g/kg) Pentoxifylline heparin	---	+	12
2	Mehran Karimi, Mohamma Bagher Owlia	2011	9	Male	benzathine penicillin	IM	Right buttock	---	Pharyngitis	NSAIDs Full dose of oral acetaminophen Methylprednisolone (IV) Oral pentoxifylline 400 mg tds Cephazolin 650 mg qid Diltazem 15 mg tds Enoxaparin 25 mg bd Imipenem 400 mg qid	---	+	13
3	Khakshour A, Bonyad iB, Sedaghat M	2013	7	Male	benzathine penicillin	IM	Right gluteal muscles	---	Sore throat	Acetaminophen codeine NSAIDs IV hydrocortisone Heparin Clindamycin Vancomycin	---	+	14
4	Morteza Noaparast, Rasoul Mirsharifi Fezzeh Elyasinia Reza Parsaei Hessam Kondori Sara Farifteh	2014	3	Male	benzathine penicillin	IM	Upper outer quadrant of the right buttock	---	URI	IV heparin, pentoxifylline , systemic C/S	fasciotomy of the calf	+	10
5	Fateme Shamekhi Amiri, Alireza Foroughi	2014	39	Female	diclofenac	IM	---	Type 2 DM	Fever, chills, nausea, vomiting and right flank pain (Pyelonephritis)	empiric i.v. piperacillin/ tazobactam, vancomycin and amphotericin B.	incision and drainage of the left buttock	+	

patient complains of unusual excruciating pain on the injection site. The needle must be long enough to reach the muscle. Different sites should be chosen when multiple injections need to be given. The characteristics of Iranian cases with a diagnosis of NS are summarized in Table 2.

Benzathine penicillin was mentioned as the most common causative agent and all cases were male except one. This female was treated with diclofenac. The age range was between 3 to 39 years; it seems that NS is more prevalent in children and adolescent. Two cases were diabetic and this may be considered as a predisposing factor for NS. In all cases, the method of injection was IM. Since vasospasm is one of the mechanisms involved in the pathogenesis of NS, calcium channel blockers may be helpful in management of this condition. The diltiazem tablet was used in the 3rd case in table 2.

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