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MINIREVIEWS

Nicolau syndrome: A literature review

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Abstract

Nicolau syndrome (NS) is a rare cutaneous adverse reaction after intra-muscular or intra-articular injection. Clinical features of NS are presented by three typical phases (initial, acute and necrotic phases). The cause of NS is acute vasospasm, inflammation of arteries and thromboembolic occlusion of arteriole related various drugs. Many results of laboratory test, imaging studies and histopathology are reported and are associated with disease status. Three phase treatment is recommended for the patients with NS. Initially pain control and rule out differential diagnosis and in acute phase steroid therapy, heparin and pentoxifylline are useful. In necrotic phase, surgical treatment is needed depending on size of the affected site. NS is not well understood so far, however three phase treatment could lead to good result on basis of literature review.

Key words: Nicolau syndrome; Livedoid dermatitis; Embolia Cutis Medicamentosa; Drug hypersensitivity; Dermatitis; Diclofenac

Core tip: To our knowledge, there is no literature review of nicolau syndrome (NS) and we report this review article for understanding NS.

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INTRODUCTION

Nicolau syndrome (NS) (Embolia Cutis Medicamentosa or Livedoid dermatitis) is an uncommon cutaneous adverse reaction after intra-muscular or intra-articular injection of various drugs. NS was first reported in 1925 after the muscular injection of bismuth for the syphilis in the gluteal area[1,2]. The usual characteristics of the injected lesion are pain immediately after injection, subsequently erythematous lesion, livedoid and hemorrhagic patch, and NS leads to necrosis of skin, adipose and muscle layers. The syndrome has been related to the injection of various drugs, including non-steroidal anti-inflammatory drugs

Table 1 Clinical features and three phase treatment of nicolau syndrome

Phase	Clinical features	Treatment
Initial	Intense pain	Analgesics
	Erythema	Systemic antibiotics[1]
	Radiating pain	No ice pack
	Faintness, syncope	
Acute	Livedoid plaque	Systemic steroid
	Violaceous patch	Anticoagulant agent
	Non-necrotic	
Necrotic	Necrotic indurated plaque	Surgical debridement
	Ulceration with necrosis	Plastic surgery

[1]Systemic antibiotics: Until rule out cellulitis.

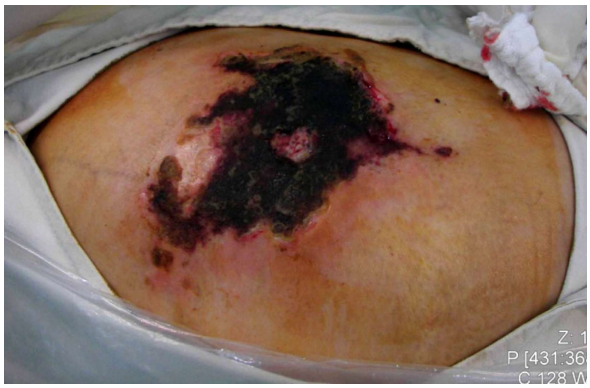

Figure 1 Photography of right gluteal lesion three weeks post injection illustrating the nature and extent of the eschar.

(NSAIDs), etancercpt, pethidine, antibacterial agents, chlorpheniramine maleate, corticosteroids, vitamin, sulphonamide, lidocaine, phenobarbital, chlorpromazine, thiocolchicoside and vaccines. To our knowledge, there were no literature review of NS and we report this review article for understanding NS.

RESEARCH

Literature search and selection criteria

The expansion of the search for this review was conducting during the last week of August 2014 using the MEDLINE (December 1966 to August 2014). The following medical terms were searched: "Nicolau syndrome", "Embolia Cutis Medicamentosa", "Embolic Cutis Medicamentosa", and "Livedoid dermatitis". Results were limited to human subjects, written in English (except one which is first described report by France), and published in peer-reviewed journals. There is one review article that is limited to children cases[3]. And 80 cases less than 12 years old was reported in Italian[4].

Clinical features

Clinical features of various patients suffering from NS are divided to three steps; initial, acute and necrotic phases (Table 1).

Initial phase of NS is presented by intense pain immediately or soon after the injection with a bluish discoloration[5]. Some patient complaints radiating pain to affected extremity or neurologic symptom such as peroneal neuropathy[6-9]. Faintness or syncope may occur[10]. Pain at the injection site is first sign subsequently erythema or hemorrhagic lesion and cutaneous necrosis or soft tissue and of the muscle develop eventually.

Acute phase occurs 24 h to 3 d later. In this phase, erythematous lesion develop at the injection site[11] or indurated painful livedoid plaque with the border of the violaceous and reticular plaque[12] develop. That is non-necrotic plaque or patch.

Necrotic phase as a final stage reveals that the injection site progress to violaceous, necrotic, crusted, indurated plaque. The lesion is progressing to erythema, swelling and tender induration with central necrosis. Finally necrotic phase comes 5 d to 2 wk. A painful indurated erythematous plaque with black necrosis[11,13] or a large necrotic skin patch with ulceration over the injection site is observed[6] (Figure 1).

The most common sites are the buttocks however NS also has been reported on the shoulder[10], thigh[14-19], knee, ankle, breast[20] and abdomen[21,22]. In some complicated cases, critical complications such as extensive skin necrosis, transient or persisting ischemic changes of the ipsilateral limb and several neurological deficit may occur.

Pathogenesis and etiology

Pathogenesis of NS is not clear but a vascular origin is the most reasonable hypothesis. Acute vasospasm, inflammation of arteries and thromboembolic occlusion of arteriole are the key mechanisms[12]. The leakage of around artery and neural space has been suggested as cause of intense pain. Moreover, sympathetic nerve stimulation and vasospasm lead to ischemic change and skin necrosis. Unintended intravascular injection of drugs also has been proposed as causing inflammation or thromboembolic occlusion of the arterioles. These may cause arterial intimal necrosis, destructure the arterial membrane and induced subsequently cutaneous necrosis[12,23]. Few patients with NS after intramuscular injection of diclofenac have been reported even though which is a commonly used NSAIDs. Diclofenac as a cyclo-oxygenase inhibitor inhibits prostaglandin synthesis and causes vasoconstriction. Therefore, a vasospastic effect of diclofenac is the suggested pathogenetic mechanism of NS[24].

Many drugs (Table 2) related to NS have been reported such as cyanocobalamin (vitamin B_{12})[12], lidocaine[20], vitamin K[17,18], etanercept[21], naltrexone[25], ketorolac[26], ketoprofen[27,28], meperidine[27], gentamycin[29], chlorpheniramine maleate[30], Trabit (phenylbutazone, salicylamide, dexamethasone and lidocaine)[31], triamcinolone[31], benzathine penicillin[23,31,32], salicylate bismuth[2], ibuprofen[2], Interferon β[5], penicillin G[12], thiocolchicoside[7], glatiramer acetate[22,33], piroxicam[8], DPT(diphtheria-tetanus-pertussis)[15], DTP-polio-Hib[14],

Table 2 Drug list related to nicolau syndrome

Drug	Target disease or symptom of using drug	Ref.	Duration of necrosis	Affected site
Naltrexone	Alcohol dependency	Perli *et al*[25]	Over 7 d	Buttock
Etanercept	Psoriatic arthritis	Guarneri *et al*[21]	10 d	Abdomen
Ketorolac	NS	Marangi *et al*[26]	2 wk	Buttock
Ketoprofen	Knee pain	Kim *et al*[27]	NS	Buttock
	COM	Lee *et al*[28]		
Meperidine	Operation site pain	Kim *et al*[27]		Buttock
Gentamycin	Elbow sprain	Kim *et al*[29]		Buttock
Chlorpheniramine maleate	Pruritus	Nischal *et al*[30]	7 d	Arm
Trabit	Back pain	Ruffieux *et al*[31]		Buttock
Triamcinolone acetonide	Lichen planus of scalp	Ruffieux *et al*[31]		Buttock
Salicylate bismuth	Syphilis	Corazza *et al*[2]	A few days	Buttock, thigh
Ibuprofen	Coxarthrosis	Corazza *et al*[2]		Buttock
Interferon β		Ozcan *et al*[5]	3 d	Arm
Benzathine penicillin	Cellulitis	Ruffieux *et al*[31]		Buttock,
	NS	De Sousa *et al*[32]	1 d	L/Ext.
		Ocak *et al*[23]		
Penicillin G	Fever and cough	Luton *et al*[12]	2 d	Buttock, L/Ext.
Cyanocobalamin		Luton *et al*[12]		Buttock
Thiocolchicoside	Back pain	Guarneri *et al*[7]	2	Buttock
Glatiramer acetate	Multiple sclerosis	Harde *et al*[22]	2 d	Lower
		Koller *et al*[33]		abdomen
Piroxicam	Ankle sprain	Lee *et al*[8]		Ankle
DPT	Vaccination	Erkek *et al*[15]	2 wk	Thigh
DTP-polio-Hib	Vaccination	Bégin *et al*[14]	2 wk	Thigh
Hydroxyzine	Itching	Gayken *et al*[16]		Thigh
Calcium hydroxide	Bleeding in the distal root canal	Willbrand *et al*[34]		Cheek
Lidocaine	Core needle biopsy on breast	García-Vilanova-Comas *et al*[20]		Breast
Vitamin K	Prematurity	Puvabanditsin *et al*[18]	2 wk	Thigh
Mesotherapy injections	Tendinopathy	Zaragoza *et al*[35]	3 wk	Knee

NS: Non-specific; COM: Chronic otitis media; Trabit: Phenylbutazone, salicylamide, dexamethasone and lidocaine; L/Ext: Lower extremity; DPT: Diphtheria-tetanus-pertussis.

hydroxyzine[16], calcium hydroxide[34] and mesotherapy injections[35]. However, diclofenac sodium is the major drug of NS.

Laboratory test

Blood result is unremarkable[6]. Initially there was no evidence of cellulitis. Some studies reported that The biologic markers suggesting muscle damage such as creatine kinase, myoglobin, aspartate transaminase, alanine transaminase and lactate dehydrogenase are elevated although white cell count, inflammatory markers and renal function were unremarkable[36]. Otherwise leukocytosis, increased serum glutamic oxalacetic transaminase, lactic dehydrogenase and myoglobinuria were found[12].

Imaging studies

Ultrasonography do not identify any definite abscess or sign of fluid collection[19,25] but shows an evidence of an area of diffuse edema within the muscles[2]. Necrotic lesion reveals a diffuse hyperechogenic area with inflammation involving the subcutaneous area and the muscles[11].

Computed tomography reveals a well-defined lesion of the diffuse adipose inflammation with central gas collection[25,37] However the muscle tissue is uninvolved and there is no liquid collection[24]. Extension of involved lesion is usually limited out of the muscular fascia[13,37].

Magnetic resonance imaging reveals a subcutaneous liquid collection up to the fascia and muscle tissue appears uninvolved[11] or only diffuse change of signal intensity in the adipose layer at the injection site showing extensive edema in the subcutaneous fat[36] in acute phase. Progressing to necrotic phase, MRI reveals focal muscle necrosis and the residual muscle edema[36] however the muscle is spared and there is no liquid collected under the eschar tissue in some case[38].

Histopathology

Histopathologic findings are mainly reported in necrotic