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Nicolau Syndrome: A Review of the Literature

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Abstract: Nicolau Syndrome, first described in the 1920's in patients treated with bismuth salts for syphilis, is a rare adverse reaction at the site of intramuscular drug injection. It is clinically characterized by severe pain immediately after injection, and rapid development of blanched skin or livedoid reticular patches. Occlusion of peripheral arterial vessels is suggested to play a major pathogenic role. Since there is no specific therapy for this condition, an appropriate conservative treatment should be applied.

Keywords: Nicolau Syndrome, (NS), intramuscular drug injection

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Introduction

Nicolau Syndrome (NS) also known as livedo like dermatitis and embolia cutis medicamentosa is a rare cutaneous adverse reaction at the site of intramuscular injection of particular drugs. It is clinically characterized by severe pain immediately after the injection, followed by an erythematous, reticular patch that may result in a necrotic ulcer and scarring at the injection site.

NS was first described by Freudenthal in 1924 and Nicolau in 1925 in patients treated for syphilis with bismuth salts.¹ Nicolau suggested the term “livedoid dermatitis” for the patients with the disease.² NS has been reported with the administration of various other drugs such as penicillins,^{3,4} non-steroidal anti-inflammatory drugs,^{5–8} local anesthetics, and corticosteroids² in the literature. Table 1 summarizes causative drugs reported in the literature.

Pathogenesis

The pathogenesis of NS has not been clarified yet but in the past it was suggested to be due to accidental intraarterial injections.⁹ In 1977 Brachtel and Meinertz performed experiments on the rabbit ear lobe to clarify the pathogenesis of local skin necrosis after intramuscular injection in NS.¹⁰ Phenylbutazone solution was injected to paraarterial, intraarterial and paraarterial areas after perforation of the vessel. They detected that the drug produced violent inflammation with all kinds of application. The histological examinations of all three types of application in these cases showed massive destruction of the inner arterial wall.¹⁰ Although

several theories have been suggested in the literature, the most common hypothesis is direct trauma or irritation of the vascular structures with a compression by arterial embolism of the drug itself, crystallisation of aqueous drugs in the vessels and arteriovenous shunt development or ischemia following a paraarterial injection.¹¹ McGee and Davison reported skin necrosis following non-steroidal anti-inflammatory injection, with histopathology revealing dermal and subcutaneous necrosis with focal thrombosis and inflammation.⁷ Another suggested mechanism involves damage to an end artery, sympathetic stimulation and subsequent vascular spasm from periarterial or perineural injection. The result of all these mechanisms either singularly or acting in combination is end organ damage of the cutaneous and subcutaneous tissues and muscle. It was reported that cold application for local pain relief caused rapid skin necrosis by increasing acute local vasospastic effects in a case with NS.^{6,12,13}

Clinical Features

The typical presentation of NS is extremely severe pain around the injection site of the drug immediately after injection, followed by rapid development of erythema, livedoid reticular patch or haemorrhagic patch.⁶ Actually, this skin reaction is pathognomonic. Finally an ulcer or necrosis of skin, subcutaneous fat, and muscle tissue develops and then heals with scar formation (Fig. 1). Various neurological complications such as hypoesthesia, or paraplegia were reported in one-third of the patients.¹⁴ The necrotic ulcer usually heals in several months with an atrophic scar.

Table 1. Review of causative drugs associated with Nicolau syndrome reported in the literature.

Drug class	Examples
Non-steroidal anti-inflammatory drugs	diclofenac, ^{6,8,12,17–19} piroxicam, ¹⁴ ketoprofen, ibuprofen, ²⁰ phenylbutazone ²¹
Antibiotics	penicillin derivatives, ^{4,9,13,22–24} tetracycline, ²¹ sulfapyridine, ²¹ streptomycin, ²¹ gentamicin ²¹
Corticosteroids	dexamethasone, ²⁵ triamcinolone, ²⁵ paramethasone, ² cortivazol, ² hydrocortisone ²
Antipsychotics and antiepileptics	phenobarbital, ²¹ chlorpromazine ²¹
Vaccinations	diphtheria-tetanus-pertussis ^{26,27}
Antihistamines	diphenhydramine, ²⁵ hydroxyzine, ²⁸
Local anesthetics	lidocaine ²¹
Miscellaneous	interferon alpha, ¹³ cyanocobalamin, ²⁹ bismuth, ²⁰ vitamin K ³⁰



Figure 1. Large ulcer around the intramuscular injection site of diclofenac on the posteromedial aspect of the right buttock; two weeks after the injection.

Histopathology

Histopathological examination reveals necrosis of the epidermis, dermis, subcutaneous tissue and muscle with focal thrombosis of small and medium blood vessels in NS.⁶

Differential Diagnosis

The differential diagnosis of NS includes cutaneous cholesterol emboli, vasculitis and cutaneous embolization of cardiac myxoma. Cutaneous cholesterol embolia is a disease of elderly with severe atherosclerotic disease. Skin manifestations in patients with a left atrial myxoma are frequent, usually on acral sites and accompanied by cardiopulmonary symptoms.¹⁵

Treatment

There is no specific therapy for NS. Treatment of NS depends on the extent of the necrosis and ranges from topical to surgical. Conservative treatment with debridement, pain control (analgesics) and dressings

is the mainstay of therapy especially for limited cases. Tissue damage may be reversible in the acute phase of NS. Use of vasoactive agents such as subcutaneous heparin and oral pentoxifylline has been recognized as beneficial.¹³ Topical steroids may be worth trying. Surgical intervention is rarely required.

Prevention

Nicolau syndrome is an avoidable complication. The Z-track injection is a method of intramuscular injection into large muscle using a needle and syringe and it can minimize or prevent Nicolau syndrome.¹⁶ Health care personnel should take these precautions:^{16,17}

1. A long (enough to reach muscle) needle should be used. A 90-kg patient requires a 2 or 3-inch (5–7.5 cm) needle and a 45-kg patient requires a 1.25 or 1.45-inch needle.
2. Injection should be applied in the upper outer quadrant of the buttock.



3. Aspirating the needle before injecting the medication should be performed to be sure not to hit a blood vessel.
4. The health care personnel should never inject more than 5 ml of medication at a time when using the Z-track injection method.
5. If more than one injection or larger dose is required or ordered, different sites should be chosen.

Conclusion

Although NS is an uncommon adverse reaction, clinicians should be aware of this complication and use proper injection procedures.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author reports no conflicts of interest.

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