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Nicolau syndrome: a review of case studies

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Abstract

Nicolau syndrome, although it is quite rare, often occurs following intramuscular injections of different medications, especially diclofenac and penicillins. Accordingly, its symptoms usually begin with severe pain during injection, leading to ulceration and necrosis of the local tissue over time. Immediate diagnosis and treatment in the case of this syndrome, are of great importance. There are no established criteria for Nicolau's diagnosis, and preferably, these can be achieved by examining the patient's symptoms and eliminating differential diagnoses. The proposed treatments are primarily symptomatic therapy and measures such as fasciotomy, debridement, and plastic surgery provided in the affected area. The exact cause of this syndrome has not been determined yet. However, since vasospasm, thrombosis, and embolism have been observed in majority of Nicolau syndrome cases, so any intra-arterial/para-arterial injection or any other factor leading to these three conditions could be hypothetically regarded as the cause of this problem. This review aims to provide a comprehensive overview of Nicolau's symptoms, diagnosis, treatment methods, and prevention. It also investigates the association between the incidence of this disease and some factors such as gender, age, injection method, and causative drugs, in order to widen our understanding on this syndrome and help practitioners with a much faster diagnosis method and step-by-step approach to Nicolau syndrome.

Keywords: Injections, Necrosis, Nicolau syndrome, Pain, Review

Introduction

Nicolau syndrome is a sporadic, iatrogenic syndrome, which was firstly reported by Freudenthal and Nicolau in 1924 and 1925, respectively, following the intramuscular injections of bismuth to treat syphilis. This syndrome is also known as Embolia Cutis Medicamentosa (ECM) and Livedo-Like Dermatitis (LLD). In addition, the syndrome often occurs as a sudden and severe local pain following skin reaction and neurovascular phenomenon in the injection site, to which it is usually confined. This syndrome in most cases have taken place after intramuscular injection of the following drugs: penicillin, non-steroidal anti-inflammatory drugs (NSAIDs), topical anesthetics

(lidocaine), vaccines, corticosteroids, vitamin K, antihistamines, polidocanol, and pegylated interferon-alpha.[1,2] Although this syndrome has been found to be usually associated with intramuscular injection, several researchers in their studies have related it to subcutaneous, intravenous, and intra-articular injections of some drugs.[3-6] The reason of this complication has not been established yet; however, intra/periarterial injections and its consequent complications such as ischemia and spasms are known as the possible contributing factors.[7] It was indicated that injecting cytotoxic drugs can also lead to perivascular inflammation and ischemic necrosis.[7] A lipophilic drug can penetrate and block the vessels, resulting in fat embolism. As well, Sweat gland necrosis has been reported in some studies on Nicolau syndrome.[8-10] Management and treatment strategies proposed for this disease vary from one case to another, which usually are supportive and symptomatic.[11] The consequences of Nicolau syndrome convince the practitioners to implement many precautions like syringe aspiration before injection, in order to ensure no intravascular infusion, use of the Z-track technique, the accurate preparation of the injection site, prevention of high dose injections in one site, and regularly changing the injection site in case of multiple injections.[12]

This study aimed to search the literature and review all clinical aspects of Nicolau syndrome, i.e., symptoms, etiology, diagnosis, treatment methods, and prevention with all offending agents causing this syndrome.

Overview of Case Studies

Data collection

The search was conducted for English articles published up to April 1, 2021, in some electronic databases, including PubMed, Medline, Scopus, Web of Science, Science Direct, and Google Scholar using the heading terms Nicolau syndrome, OR Embolia Cutis Medicamentosa (ECM), OR Livedo-Like Dermatitis (LLD). Thereafter, demographic data, clinical characteristics, offending agent(s), route of administration, symptoms, and type of treatments were assessed in the included articles.

Findings

Some articles did not mention a number of details such as length of hospitalization, injection method, and gender. In total, 150 cases obtained from different databases were reviewed, and the final analysis was only performed based on the available articles, the results of which were mentioned.

Analysis

Demographic characteristics

Analysis of those articles that had taken patients' gender into account (133 cases) indicated that the incidence of Nicolau syndrome is higher in women (n= 83; 62.40%). As well, the patients' age had been addressed in 135 cases, as shown in table 1. Evaluating different age groups showed that the highest incidence rate of Nicolau syndrome is among adults aged between 30 and 40 years old and children aged up to 10 years old with 20% and 19.26%, respectively.

Table 1. age distribution of 135 cases addressed in the final articles.

Age group (years old)	**Number of cases out of 135**	**percentage**
0-10	26	19.26%
10-20	11	8.15%
20-30	15	11.11%
30-40	27	20%
40-50	15	11.11%
50-60	14	10.37%
60-70	14	10.37%
70-80	12	8.89%
80-90	1	0.74%

Route of administration

Examining the articles that referred the injection route as the leading cause of Nicolau syndrome (105 articles), indicated that this complication occurs more frequently with intramuscular injection (83 articles, 79.05%). Moreover, other administration methods that gave rise to Nicolau syndrome

were subcutaneous injection (12 articles, 11.43%) and intra-arterial injection (4 articles, 3.81%). Notably, intravenous injection, intradermal injection, and intra-articular injection all share the same proportion of 1.90% (2 articles each).

Medication inducing Nicolau syndrome

Reviewing those articles dealing with drugs (145 articles) revealed that the most common causes of the syndrome are diclofenac (35 articles, 24.14%) and penicillins (32 articles, 22.07%). Table 2 presents the incidence of Nicolau syndrome reported by the reviewed articles.

Table 2. The incidence of Nicolau syndrome associated with different drugs

Offending agent	**Number of cases out of 145 cases**	**Percentage**	**Reference**
Diclofenac	35	24.14%	1,7,8,12-37
Penicillin derivatives	32	22.07%	11,13,17,38-56
Glatiramer acetate	7	4.82%	57,58
Hyaluronic acid	6	4.14%	1,39,59-63
DTP (Diphtheria- Tetanus- Pertussis)	4	2.76%	64-68
Bismuth salicylate	3	2.07%	
Lidocaine	3	2.07%	8,17,69,70
Piroxicam	3	2.07%	
Dexamethasone	2	1.38%	
Ibuprofen	2	1.38%	
Interferon alpha	2	1.38%	
Oxytocin	2	1.38%	5,18,70-78
Polidocanol	2	1.38%	
Thiocolchicoside	2	1.38%	
Triamcinolone acetonide	2	1.38%	

Acetaminophen (Paracetamol), Anti-flu vaccine, B complex vitamin, Bortezomib, Buprenorphine, Calcium hydroxide, Ceftriaxone, Chlorpheniramine maleate, Chlorpromazine, Cortivazol, Cyanocobalamin (Vitamin B12), Cyclizine, Dicyclomine, Diphenhydramine, Epinephrine, Etanercept, Etofenamate, Gentamicin, Hydrocortisone, Hydroxyzine, Interferon Beta, Ketoprofen, Ketorolac, Meperidine, Methylprednisolone, Naltrexone, Paramethasone, Phenobarbital, Phenylbutazone, Pneumococcal vaccine, Sodium tetradecyl sulfate, Streptomycin, Sulfapyridine, Sulfonamide, Terlipressin, Tetracycline, Varicella vaccine, Vitamin K	1*	0.69%*	1,4,8,11,13,17,18,26,31,40,61,72,79-98

* The frequency of each one of these drugs is one case.

Symptoms

In general, the onset of Nicolau syndrome in about 90% of the affected cases was accompanied with severe pain during injection. After several hours, this was followed by livedoid, discoloration of the affected area, and ulceration in the injection site. By passing several days, about 55% of the cases developed necrosis in the affected area and necessitated debridement.

In most of the cases, post-injection symptoms (including tissue discoloration, livedoid, ulcer, and necrosis) were confined to the injection site. In contrast, in approximately 25% of the cases, these were observed in other organs such as hands, thighs, feet, and fingers. Of note, more than half of these cases were children. Subsequently, Blood tests and vital signs were examined, which were relatively standard in most cases, but neutrophils and leukocytes, alanine transaminase (ALT) and aspartate transaminase (AST), and lactate dehydrogenase and creatine kinase increased in few cases. Given that Nicolau syndrome has different phases, it can occasionally be hazardous and also entail irreparable consequences and can even cause death. About 4.5% of the reported cases had ended in mortality.

Treatment

The most frequent treatments performed in the reviewed cases were pharmacotherapy and debridement of necrotic tissue (Table 3).

As well, Pharmacotherapy was mainly applied through systemic antibiotics, anticoagulants, systemic corticosteroids, blood viscosity reducers, antibiotics, topical corticosteroids, and various analgesics, including NSAIDs and opioids. Generally, in most of the reviewed studies, therapy was started by symptomatic treatment of pain, bruising, swelling, and inflammation of the injection site. In symptoms exacerbation or necrotic lesions (reported in approximately 55% of the included studies), some measures such as fasciotomy, necrotic tissue debridement, and plastic surgery (even amputation in case of extensive necrosis) were adopted. Accordingly, fasciotomy was performed often successfully in most cases, when the blood flow to the injection site or its surrounding area could not be detected or when it had been interrupted.

Depending on the severity of the tissue damage and the speed, the patients were provided with a correct diagnosis and appropriate treatment. In this regard, the treatment courses mostly ranged from one to two months. However, these occasionally lasted from one week to nine months.

Table 3. Frequency of the therapeutic measures implemented for Nicolau syndrome

Intervention	**Percentage**
Debridement	12%
Plastic surgery and skin graft	5%
Fasciotomy	4%
Amputation	2%
Hemodialysis	0.5%
Pharmacotherapy	76.5%
Systemic Antibiotic therapy (Amikacin- Amoxicillin- Aztreonam- Cefazolin- Cefotaxime- Ceftriaxone- Cephalexin- Ciprofloxacin- Clindamycin- Gentamycin- Imipenem- Linezolid- Meropenem- Metronidazole- Piperacillin- Tazobactam- Ticarcillin)	16.5%
Anti-coagulants (Enoxaparin - Heparin)	11.5%
Systemic corticosteroid	9%
Blood viscosity reducer agent (Pentoxifylline)	6.5%
Topical antibiotic (Mupirocin)	6%
NSAIDs	5%

Antiplatelet (Aspirin- Clopidogrel- Dipyridamole)	3.5%
Topical corticosteroids	3.5%
Opioid analgesics (Morphine- Pethidine)	2.5%
CCB (Amlodipine- Diltiazem- Nifedipine)	2.5%
Vasodilator (Alprostadil- Nitroglycerin transdermal)	2.5%
Hyperbaric Oxygen therapy (HBOT)	2.5%
Hyaluronic acid	1.5%
Pregabalin	1%
Post therapeutic neurology (Amitriptyline- Gabapentin)	1%
Probenecid	0.5%
Epinephrine	0.5%
Albuterol	0.5%

Discussion

Symptoms

Symptoms of Nicolau syndrome vary depending on its three phases. The primary symptoms could be dermatological, neurological, and cardiovascular signs alone or simultaneously. Severe pain and discoloration of the injection site occurring immediately after injection, livedo reticularis (net-like purplish discoloration), and hemorrhagic lesion are known as usual symptoms of this complication. In addition to these symptoms, which mainly occur on the skin's surface, secondary problems such as necrosis, infection, and scarring may also be presented in muscle tissue and subcutaneous fat.

Neurological signs are the vast proportion of the symptoms that could lead to unilateral or bilateral sensory and motor disorders.[38,70] Accordingly, these seem to occur due to axonopathy, secondary to vascular problems such as embolism and vascular occlusions. Moreover, these are ranged from burning and numbness, starting from the initial phase, to dystonia, paresthesia, paraplegia, and sensitivity. Due to axonopathy and injury in one or more nerves at the injection site, symptoms can even spread to other organs occasionally such as the shoulder, thigh, knee, and ankle.[14,56] Additionally, dizziness, fainting, loss of consciousness or cognitive changes have been reported in some cases.[56,99,100] As well, it was observed that due to the location and extent of the damaged

nerve, some normal functions could be disrupted, which can consequently lead to nausea, vomiting, loss of bladder or bowel control, renal failure, and even death.[40,56,61]

Dermatological manifestations usually appear from the beginning of the initial phase. Correspondingly, these contain paleness, erythema, and livedoid violaceous patch at the injection site, as well as hemorrhagic lesion, contributing to cutaneous necrosis.[7,27]

In terms of cardiovascular signs, the coldness of the injection site and the absence of pulses in the area have been observed in some cases.[38,43,44]

Table 4 summarizes all the symptoms of three phases of Nicolau syndrome and the treatments used for the studied patients.

Table 4. Clinical symptoms in different phases of Nicolau syndrome and their respective treatments.

Phase	**Symptoms**	**Probability**	**Approximate treatment (most used)**	**Usual duration**
Initial	Intense pain	Common	Analgesics	1-3 days
	Paleness of injection site	Uncommon	Rest Warm compress Avoid cold compress Hyperbaric oxygen	
	Paresthesia	Uncommon		
	Bluish discoloration	Common		
	Erythema	Common		
	Livedo-like dermatitis	Common		
	Maybe syncope (fainting)	Rare		
Acute	Tenderness on the site of injection Hemorrhagic lesion	Common Uncommon	Analgesics Corticosteroids	5-10 days
	Swelling	Common	Corticosteroids	
	Fever	Uncommon	NSAIDs Acetaminophen	
	Spasm and coldness and mottling of the limb	Uncommon	Warm compress	
	Discoloration and purplish livedoid in the injection site	Common	Vasoactive agents Anticoagulants	
	Erythematous lesion Livedoid violaceous plaque	Common Common	Antibiotics Vasoactive agents Anticoagulants	
	Urosepsis and soft tissue infection	Rare	Antibiotics	
	Vomiting	Rare	Antiemetic	

	Absence of pulses	Uncommon	Fasciotomy	
Necrotic	Necrotic, crusted, and indurated plaque Injection site or limb necrosis	Uncommon Uncommon	Debridement Skin graft Corticosteroids IV/Topical	5 days - 2 weeks
	Infection	Uncommon	Antibiotic therapy	

Etiology

The etiology of this syndrome is not well-known yet, so microscopic and biopsy studies suggesting ischemic tissue necrosis have put forth several hypotheses that could mainly be classified into the following three theories: inadvertent intra/peri-arterial injection, leading to embolism and vascular occlusion; vasospasm due to the needle prick of the injected drug; and applying a cold compress to the lesion site.[101] There is an evidence demonstrating primary or secondary vascular thrombosis of the reticular dermis with no vasculitis.[13] In addition, no convincing evidence exist to explain the mechanisms of inflammation and cell damage in Nicolau syndrome. In all the examined cases, microbial culture was reported as negative; therefore, sterility non-compliance has been generally eliminated from the list of the possible causes in this regard.

Histological studies conducted on most of the cases suggest that microemboli obstruction in skin arteries and tissues can be considered as a significant concept during the development of syndrome. Moreover, neurologic disorders of the extremities and lower limb paralysis can be justified by a drug embolism.[102] Accordingly, this is a fact that no vasculitis or malignancy exists in the affected area's tissue.[12]

Saputo and Bruni in a study reported the majority of Nicolau syndrome cases in children under the age of five years old. They attributed it to the smaller size of vessels and the higher probability rate of arterial embolism in this age group.[103] Conversely, Senel et al. in their study noted the higher incidence of this syndrome among adults.[14] As well, another possible cause of the embolism occurring following benzathine penicillin G injection, including condensed, viscose, and opaque suspensions, can hinder aspirated blood from being detected in the syringe. As a result, aspiration is not performed accurately or the clots might subsequently result in microemboli. In case of any inadvertent intra-arterial injection, this can persist in the narrowed arteries of the lower extremities and skin of the affected area and then trigger embolism.[11,39,40] In an animal study performed by

Brachtel et al., it was reported that both para-arterial and intra-arterial injections of phenylbutazone to rabbit ears led to severe inflammation and necrosis in the affected area and caused severe damage to the inner arterial wall. The results of this study partially support the above-mentioned theory stating that the leading cause of Nicolau syndrome is a pre-arterial or intra-arterial injection.[104]

It is mostly probable that a combination consisting of vasospasm, thrombosis, and embolism mechanisms is involved in developing the final lesion. In this regard, Embolism and thrombosis have been previously reported to occur following the inadvertent intravascular injection. Vasospasm can be resulted from many factors (including compression of the artery, direct vascular injury by the needle prick or localized immune-allergic reaction), which leads to necrosis. Drug molecules can be identified as haptens and then trigger the body's immune responses, followed by thrombosis leading to necrosis.[105] Blood tests of most of the Nicolau syndrome cases have revealed no cellulitis, and they were normal.[17,19] Meanwhile, it was indicated that several cell-damaging factors such as lactate dehydrogenase, creatine kinase, and myoglobin have intensified in some patients with Nicolau syndrome.[20,38,49,53]

Diagnosis

There is no confirmatory test for Nicolau syndrome; therefore, its diagnosis is often performed based on medication history and clinical symptoms in patients. So, being familiar with the usual symptoms of Nicolau syndrome and considering it as a possible occurrence are crucial. Every person with severe injection-site pain immediately after injection could be subjected to this complication. In this regard, no deterministic criteria are available for identifying this syndrome, and its diagnosis is solely performed based on clinical symptoms following a recent injection and after ruling out the possibility of similar disorders.[8,13,15,16,99,106] Necrotizing fasciitis is the most important differential diagnosis used for Nicolau syndrome.[1] Moreover, other differential diagnoses of this syndrome are the followings: local toxic reaction to drugs, acute compartment syndrome, vasculitis, fat embolism, and Hoigne's syndrome.[56] Injection nerve injury diagnosis, which could lead to nerve palsy, is known as another differential that puts unqualified staff injecting into an inappropriate site. Although Nicolau syndrome almost presents dermatological symptoms, usually there are no dermatological symptoms caused by the injection nerve injury.[56,107,108] Cellulitis is another differential diagnosis whose misdiagnosis could consequently

lead to antibiotics administration and treatment failure.[109] Gas gangrene and necrotizing fasciitis are acute infections considered as other differential diagnoses for Nicolau syndrome. Correspondingly, these could quickly spread and then contribute to necrotic damage of muscle, and their symptoms are easily mistaken for Nicolau syndrome. Skin culture and imaging are essential tools, in order to cross gas gangrene out.[110-112] Ruling all differential diagnosis out from the list is possible performed by asking for a complete medical history from the patient, taking a blood test, local microbial culture, and conducting pathological examinations.

Treatment

No standard treatment is proposed for Nicola syndrome so far. Depending on the disease's phase and its symptoms, its healing procedures range from supportive local or systemic treatment for pain, swelling, erythematous lesion to surgical interventions like debridement of the necrotic tissue. Besides these symptomatic treatments, some studies have previously suggest the use of anticoagulant, antiplatelet, blood viscosity reducer agents, vasodilators, and topical or oral corticosteroids for the treatment of this syndrome.[49,50,56,113]

Some other studies have recommended hyperbaric oxygen for treating this complication. The use of cold compresses is also known to exacerbate Nicolau syndrome. In this regard, appropriate antibiotic regimens may be prescribed, usually in the second or third phase of the syndrome, for those cases in whom the lesion is infected.[14,50] In more than half of cases with this syndrome, necrosis and secondary infection of the skin and underlying muscles could be detected, and under this condition, debridement of the necrotic tissue improves the patient's status.[15,99] In addition, in those cases with the absence of pulses, fasciotomy produced favorable outcomes.[43,46]

Clinical improvement of symptoms in different phases of the disease, including initial, acute, and necrotic, has occurred after resting the injured limb and by administering the appropriate symptomatic and etiological therapies. Prevention of inflammation, vasodilation, improvement of blood flow, the increased blood dilution, and preventing the dissemination of infection and its treatment are included among these therapeutic agents' effects. Although the therapeutic effectiveness of the above-mentioned medications and approaches has not been widely confirmed yet, some of these treatments that were applied experimentally have yielded several positive outcomes (Table 4). The characteristics of all Iranian cases with Nicolau syndrome have been provided in the appendix.

Prevention

Several interventions can be utilized to prevent or minimize the side effects of Nicolau syndrome. First and foremost, choosing an appropriate site of injection is critical in this regard. for example, intramuscular injection in the buttock must be administered in the right site located in the upper-outer quadrant, in order to minimize Nicolau syndrome's risk and also to prevent the injection nerve injury, which could contribute into injection palsy.[114] Additionally, another solution is choosing correct injection techniques such as Z-track and proper needle length appropriate for the site of injection, type of injection, and patient's weight. Accordingly, for a patient weighted 90 kg, the best needle is a 2-inch one and a 1.25 to 1.45 inches needle is appropriate for a person weighted 45 kg.[12] This is especially vital in overweight or obese people with high-fat mass in the injection site (e.g., around their abdomen and buttocks), in order to ensure that the injection is intramuscular. As well, in vials containing the suspension, one must ensure uniformity of the suspension and its lack of clots. Furthermore, injection must be stopped in case of severe burning pain reported by patients.[11,115]

To ensure that the vessels are not damaged, aspiration should be performed before any injection. Besides, intramuscularly injection must never be performed more than 5 ml in one site. Finally, the rotation should be maintained if multiple injections are required at once (Table 5).[12,21,96,115]

Table 5. The effective factors on preventing Nicolau syndrome

The effective way to prevent	Explanation (s)
Ensuring drug's safety	Checking expiration date, and using an appropriate solvent
Ensuring proper drug's preparation	Preparing entirely uniformed and clot-free suspension
Choosing the right size needle	Ensuring that the needle is long enough to prevent the injection into adipose tissue, but to reach the muscle, especially in the buttock area
Selecting the correct injection site	As in the upper-outer quadrant
Ensuring the precise amount of injection	Maximum 5 mL in each injection site
Ensuring the usage of the correct injection techniques	Syringe aspiration before injection Rotation of injection site if multiple injections are required at once Using the Z-track technique

Conclusion and suggestions

Etiology and prevention

It is mainly argued that intra/peri-arterial injection, contributing to vascular thrombosis, with no vasculitis, or arterial embolism, and vascular occlusion are the primary causes of Nicolau syndrome. As well, needle prick leading to vasospasm is known as another reason. So, Nicolau syndrome is considered as an avoidable complication according to its etiology. Therefore, in order to prevent this syndrome, we can take some actions as follows: 1- choosing syringe with an standard needle size, 2- ensuring intramuscular injection, 3- aspiration and using Z-track technique, 4- providing an entirely uniform suspension, 5- choosing the right site for injection 6- considering Diclofenac and Penicillin as the two main reasons for this syndrome, and 7- limiting injection volume up to 5 mL in each injection site. Accordingly, adherence to these recommendations is even more critical in high body mass index (BMI) individuals.

Diagnosis

Based on the fact that there is no confirmatory test proposed for Nicolau syndrome diagnosis, paying attention to the history of injection as well as chief complaints of intense pain immediately after injection and other common symptoms such as livedoid dermatitis or hemorrhagic patch are essential. Therefore, by considering no history of pressure, acute compartment syndrome could be ruled out. As well, asking the patient's complete medical history is known as the best approach to omit allergic reactions. Moreover, performing some laboratory tests and pathological examinations are essential to rule out other differential diagnoses. In this regard, it was demonstrated that the pathological examination of local arteries is prone to depict thrombosis or embolism relevant to Nicolau syndrome, so vasculitis and fat embolism could be crossed out by conducting this pathological examination.

On the other hand, if neurological examinations and some tests show a local nerve damage, it could be regarded as an injection nerve injury, because of the injection performed by unqualified staff and inappropriate injection site, which leads to nerve palsy. Usually, it is not followed by any dermatological symptom. Furthermore, the negative microbial culture of skin and subcutaneous

tissues could reject necrotizing fasciitis, hoigne's syndrome, and gas gangrene. Accordingly, for the latter, the use of imaging can lead to a better diagnosis and avoiding misdiagnosis.

Symptoms and treatments

Eternal duration usually lasts from one week to nine months. Neurological, dermatological, and cardiovascular symptoms presented in this syndrome are common, which can be unilateral or bilateral that spread to limbs and other near organs. These symptoms are categorized into 3 phases based on the time of their occurrence.

The initial phase (the first phase) starts immediately after injection and lasts for 1 to 3 days. At this stage, intense pain at the injection site and paresthesia, neurological symptoms, and paleness gradually lead to bluish discoloration, and livedo-like dermatitis is known as a common symptom. In some patients with this disease, syncope has been observed. The treatments range from rest and warm compress to pharmacotherapy using analgesics and hyperbaric oxygen therapies.

The acute phase (the second phase) starts after the initial phase, which usually lasts for 5 to 10 days. At this stage, rigidity, tenderness, and swelling of the injection site become obvious. In addition, Erythematous, hemorrhagic lesions, and livedoid violaceous plaque, usually contribute into soft tissue infection and fever. In few cases, urinary tract infections occur, which might eventually lead to urosepsis. As well, the absence of pulses sometimes happens, and following that spasm, coldness, and mottling of the limb appear. Vomiting has also been reported by few cases. Based on the symptoms, the treatment of this disease is categorized into etiological treatment and symptomatic therapy. Since the most probable etiologies for Nicolau syndrome are vascular thrombosis and arterial embolism, so its etiological therapy consists of corticosteroid, antiplatelet, anticoagulant, blood viscosity reducer agent, and vasodilator. Notably, corticosteroids could lower the blockage of arteries by reducing inflammation and swelling of adjacent tissues. Analgesics, antibiotics, antiemetics, and some surgical procedures like fasciotomy, are also included among symptomatic therapies.

The necrotic phase (the third phase) usually lasts for 5 to 14 days. In most cases, hemorrhagic lesion subsequently leads to the construction of indurated, crusted, and necrotic plaque of the skin and subcutaneous tissues. Sometimes the plaque becomes infected and rarely contributes to

mortality. In this phase, debridement and antibiotic therapy are the main treatments, followed by plastic surgery and pharmacotherapy that can be performed for pain and inflammation if necessary.

Figure 1 illustrates the stages of Nicolau syndrome after involving the predisposing factors in the injection, i.e., initial, acute, and necrotic phases. The treatment approaches consist of pharmacotherapy and surgery. In the latter, the possible outcomes are healing, amputation, and death.

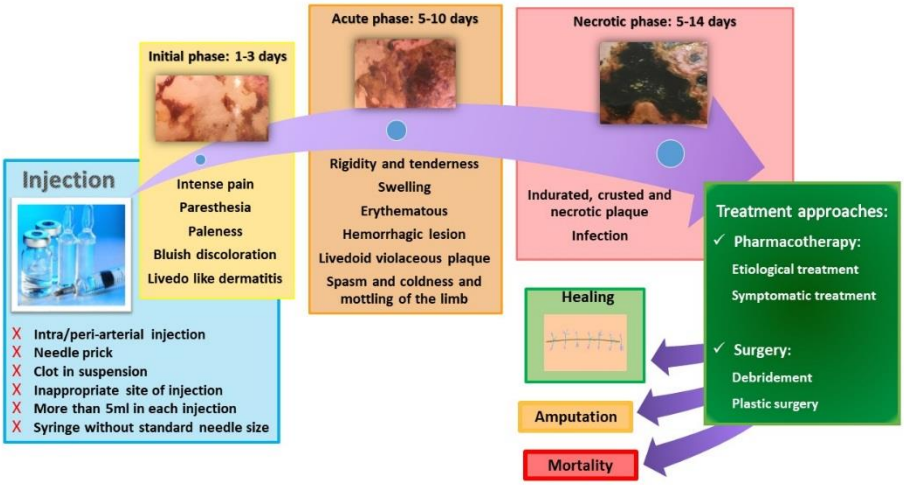

Figure 1. Development of Nicolau syndrome from the injection to the outcomes.

Suggestions

Since Nicolau syndrome still is a rare severe complication with no specific test to diagnose, so the certainty of its correct diagnosis ought to be the first and foremost priority for physicians. In most cases, corticosteroids are prescribed from the second phase of this disease, which might be the reason that most of them end up necrosis. Performing the etiological treatments like corticosteroids immediately after diagnosis and from the start of the first phase could be advisable to decrease both the duration and intensity of the symptoms and to prohibit or lower the risk of tissue necrosis. It is vital to consider that using corticosteroids can drastically exacerbate infections.

In conclusion, immediate diagnosis of Nicolau syndrome, implementing supportive and therapeutic measures as soon as possible, and administering appropriate adjunct medications are among the most critical components for preventing and treating this complication.

Authors' Contributions

The authors provide their individual contributions to this work using CRediT (Contributor Roles Taxonomy) author statement. **Paria Mojarrad:** Methodology, Formal analysis, Investigation, Data curation, Writing - Original draft preparation, and Visualization. **Hamid Mollazadeh:** Validation, Writing - Reviewing & Editing, and Visualization. **Behnaz Barikbin:** Validation, Resources, and Writing - Reviewing & Editing. **Mohammad Bagher Oghazian:** Conceptualization, Validation, Writing - Reviewing & Editing, Supervision, and Project administration. All authors read and approved the final manuscript.

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The photos used in figure 1 were selected from a collection of photos taken from our patient with Nicolau syndrome, with their informed consent.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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