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Nicolau Syndrome, an Iatrogenic Drug Reaction Caused by Bupivacaine Injection as Spinal Anaesthesia: A Description of Two instances and Literature Review

Vishal Kumar [a*], Pramod Kumar Manjhi [b#] and Amol Raj [c++]

[a] Department of Pharmacy Practice, Teerthanker Mahaveer College of Pharmacy, Moradabad, Uttar Pradesh- 244001, India.
[b] Department of Pharmacology, All India Institute of Medical Science, Patna, Bihar– 801507, India.
[c] Department of Materiovigilance Programme of India (MvPI), Indian Pharmacopoeia Commission (IPC), Ghaziabad, Uttar Pradesh, 201002, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

An uncommon side effect of administering medications parenterally is Nicolau syndrome. Pain will first manifest, followed by edema and erythema, and finally, a necrotic plaque will be seen. An uncommon side effect of parenteral medication administration is Nicolau syndrome. It is characterized by the initial manifestation of pain, followed by edema, erythema, and ultimately the

[#]Associate Professor and Head of Department;
[++] Pharmacopoeia;
**Corresponding author: E-mail: Vishal4321gupta@gmail.com;*

formation of a necrotic plaque. In this report, we present two exceptional cases of female patients who developed Nicolau syndrome after receiving a spinal anesthetic injection of bupivacaine. Their therapeutic regimen included the use of pentoxifylline, Omnacortil, cetirizine tablets, flucidine H cream, and Calasoft AF lotion, applied in a 1:1 combination for topical application.

Keywords: Nicolau syndrome; livedoid dermatitis; bupivacaine injection; Embolia cutis medicamentosa.

1. INTRODUCTION

An uncommon condition linked to the parenteral administration of several medications is known as Nicolaou syndrome. A burning sensation that is followed by edema and erythema, as well as acute and intense pain, is frequently present. Additionally, the erythema tends to develop into the livedoid reticular and necrotic plaque quite quickly. Nicolaus syndrome (NS), also known as Embolia cutis medicamentosa, was first identified in 1924 following an intramuscular injection of bismuth salts for the treatment of syphilis. Subsequently, reports of similar symptoms following IM injections of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, penicillin, or local anaesthetic agents have been found in several reports [1,2]. One hypothesis holds that NS develops when an intramuscular drug is accidentally injected straight into an artery lumen or wall, causing vascular thrombosis and necrosis of the subcutaneous tissues and muscles [3]. Excruciating pain and significant inflammation frequently accompany the symptoms of skin discoloration [4]. Necrosis often appears after hyperemia, skin pigmentation, livedoid dermatitis, and the development of hemorrhagic patches at the injection site [4]. A fast clinical course and mortality may occur in severe situations [5]. There is no known precise pathophysiology [6]. The most plausible hypothesis is that it has a vascular origin. The primary mechanisms are acute vasospasm, arterial inflammation, and thromboembolic occlusion of the arteriole [7]. The research studies suggest that injections of cytotoxic drugs can also result in perivascular inflammation and ischemia necrosis. A fat embolism can be brought on by a lipophilic drug that clogs the arteries after it enters them. Necrosis of the sweat glands has also been reported in various research on the Nicolaus syndrome [8]. Here, we provide Two instances of bupivacaine-induced Nicolaus syndrome as spinal anesthesia are given here.

2. CASE PRESENTATIONS

2.1 Case - 1

A 42-year-old woman (P5L5) who had a low-grade fever and dysmenorrhea for two years visited the gynaecology outpatient department. Additionally, the patient reported vaginal discharge for one to two years that has a bad odour and was not cyclical or associated with itching. She also reported having lower abdominal discomfort for a year, which was dull in nature, made worse by weightlifting, and made better by medicine (no record is accessible). Additionally, the patient reported having dyspareunia for a year that was accompanied by post-coitus bleeding.

There was no history of thyroid disease, hypertension, diabetes mellitus, cardiovascular disease, stroke, or burning urination. Four years ago, the patient had extrapulmonary TB, for which they had six months of anti-tuberculosis treatment. Additionally, she had undergone a cholecystectomy seven years prior. On examination, there was pallor, and the abdomen was soft and non-tender. On local inspection, the cervix was hypertrophied, and an endovaginal polyp measuring 2*7 cm in length was found along with mucous secretion. The patient was identified as having P5L5 with secondary dysmenorrhea, cervical polyps, and pelvic inflammatory disease (PID) based on the patient's medical history and physical examination.

Blood parameters, including liver function, blood sugar, renal function, serum electrolytes, coagulation profile, and serological markers, from the patient's lab test results were all normal; however, the haemoglobin count has reduced to 9.6 g/dl (the usual range is 12.0–15.0 g/dl). The patient's chest X-ray impression shows a bilateral costophrenic angle, with the left hilum being predominant, raising the possibility of lymphadenopathy. Her USG findings include an endometrial thickness of 6 to 7 mm, a polypoidal

structure with a stalk that likely arises from the anterior endocervical canal, and intramural forms (9.3 * 6.4) of complicated left ovarian cysts that resemble endoluminal. Her ECG is within normal ranges.

The doctor proposes TLH (total laparoscopic hysterectomy) surgery based on patient history and lab results. The patient is examined by a group of anesthesiologists for general anaesthesia prior to the TLH operation, and BUPIVACAINE injection is administered as general anesthesia while following all aseptic precautions. The patient was taken up for TLH surgery after receiving anesthetic clearance. During the procedure of the operation, the operative findings were that the left ovary had an endometrial cyst (also known as a chocolate cyst) present, whereas the right ovary and fallopian tube both seemed normal.

The patient's procedure went well, and it was done with all the necessary aseptic precautions. 8mL of epidural anaesthesia top-up was administered. A 0.125% BUPIVACAINE injection was softly given over ten minutes after a negative aspiration was indicated and advised for the monitor vitals. After two days of epidural top-up anaesthesia, the patient complained of a blackish lesion across the lower back that had been stinging and burning for two days. However, upon examination, a well-defined erythematous to hyperpigmented patch measuring around 2*3–5*6 cm was seen. Following an examination, the patient's dermatologist verified the NICOLAU SYNDROME diagnosis brought on by epidural anaesthesia at the site of injection.

The main goals of therapy are to relieve the erythematous, burning feeling and to provide supportive medical care. Tabs. Cetirizine 10 mg PO HS and pentoxifylline 400 mg BD via oral. For local application, combine Mometasone Cream and Calasoft AF Lotion in a 1:1 ratio of TDS. Among the medications, the doctor suggested are some of these: in order to treat Nicolau syndrome.

2.2 Case – 2

A 26-year-old primigravida female complained of lower abdomen pain that moved to the back and was seen at the gynaecology department at 37 + 6 weeks into her pregnancy. She also had a good awareness of foetal movement.

After two months of amenorrhoea, the patient confirmed her pregnancy in the first trimester, and there were no complaints of blood pressure fluctuations. In the second trimester, the patient felt quickening at 20 weeks, there were no complaints of vaginal discharge or spotting, and she had a history of consuming iron and calcium tablets. When the patient is in the third trimester, she feels well enough to perceive foetal movement. There has been no history of headaches, blurred vision, or spotting PV, and the patient previously took DUVADILAN infusions (no documentation is provided).

The patient is found to have significant pallor, bilateral pedal edema, a breech-position baby, and oligohydramnios.

Her blood parameters were abnormal, including her liver and kidney functions. Based on lab testing, the patient was also found to have HCV positivity and to have thrombocytosis, and leucocytosis. Her platelet count was 5 lakh/cumm (normal range: 1.5-4.5 lakh/cumm), and her TLC count was 15840 cells/cumm (normal range: 4000-11000).

There were no cases of asthma, thyroid disease, diabetes mellitus, or tuberculosis.

The patient's vital signs were steady. Her clinical impression was that she was a first-time mother who was 37+6 weeks POG, in breech position, in the latent phase of labor, and had oligohydramnios.

Based on the physical examination and laboratory analysis, the doctor advises doing an emergency LSCS (lower segment cesarean section).

The anesthesiologist team delivered 13.0 mg of bupivacaine in the L2-L3 area under spinal anaesthesia under all aseptic settings before the LSCS surgery when the patient arrived in the operating room.

An abdominal Pfannenstiel incision was made, the abdomen was opened layer by layer, a loose flap of peritoneum was found and removed, the uterus was exposed by a little nick, and the amniotic fluid was nil. The baby was born alive, weighing 2.2 kg, and began crying shortly after delivery. 800 mcg of misoprostol per rectal tablet is retained.

Antibiotics (metronidazole, ceftriaxone 1gm TDS, and amikacin 500mg IV BD), antiemetics (injection emset 1 ampoule IV BD), and injection voveran aqua 3 cc in TDS are some of the medications the doctor may give following procedures.

The patient complained of an itchy, burning lesion across his lower back after just one day of LSCS. For more investigation, the patient was referred to the dermatology department. Two days earlier, spinal anaesthesia was noted in patient histories.

Dermatologists examined the patient and found a solitary, well-defined erythematous to the hyperpigmented area over the lower back, just above the gluteal region, measuring around 3 by 8 cm with interspersed erosion of approximately 1 cm in diameter. A dermatologist identified NICOLAU syndrome with spinal anaesthesia based on the examination.

Doctors recommend the following medications to treat Nicolau syndrome: pentoxifylline 400 mg oral tablet, Omnacortil 20 mg oral tablet, cetirizine 10 mg oral tablet, flucidine H cream, and Calasoft AF lotion, and used as a mixture of 1:1 for locally applied TDS.

3. DISCUSSION

Freudenthal and Nicolau initially noticed these cutaneous phenomena in syphilis patients who had intramuscular injections of bismuth salts for their treatment in 1925. This condition is also known as Embolia cutis medicamentosa or livedoid dermatitis [9]. It describes an uncommon adverse reaction to intramuscular (IM), subcutaneous (sometimes), and intra-articular (occasionally) injections of certain medications, that is characterised by the development of an initial acute inflammatory response in the skin and subcutaneous tissues followed by necrosis, lesions, and eschar formation [10]. The lesions start to appear soon after the medication is administered intramuscularly. Acute-onset local vasospasm causes excruciating pain and pallor at the injection site. As the condition worsens, the skin develops erythematous indurated macules, livedoid patches, and branching patterns. The next stage is the appearance of blisters, which burst to reveal an ulcerated surface that is later covered with eschar. If the eschar is tiny, it gradually sloughs off along with the ulcer that develops consequently. The ulcer eventually leads to an atrophic scar [11]. Necrosis occasionally progresses into the deeper muscle layers and becomes worsened by an additional bacterial infection. Nicolau syndrome has been linked to the injection of a variety of medications, including corticosteroids (triamcinolone), antibiotics (particularly sulphonamide and benzathine penicillin), NSAIDs (diclofenac sodium, ketoprofen, and piroxicam), sedatives (chlorpromazine and phenobarbital), interferons, coumarin, sclerosing agents, and many others [12,13].

Since the vascular segments implicated in this syndrome are smaller, children under three are more prone to experience it, this condition is more common in the paediatric population [14].

The cause of the disease's pathophysiology is unknown; however, there are several theories that have been put out, including sympathetic nerve stimulation, embolic occlusions, perivascular inflammation brought on by a cytotoxic medication reaction, and physically produced occlusions [15]. By stimulating sympathetic nerves, subsequent vasospastic processes are triggered, resulting in ischemia and ultimately necrosis [16].

As demonstrated by evidence of intra-arterial bismuth deposits identified in biopsy specimens of patients described by Nicolau, intravascular viscosity drug deposits further worsen the illness by embolic occluding the veins [17,18]. The endothelium lining is harmed by extra-inflammatory infiltrates, which also cause thrombosis [10]. The use of NSAIDs particularly exacerbates ischemia by preventing the generation of prostaglandins by cyclooxygenase [19].

Because there is significant inflammation present, serum ESR and c-reactive protein (CRP) levels are frequently elevated. Because it mostly affects the tiny arteries under the skin, these individuals typically have an unimpressive Doppler examination. A biopsy of these lesions typically reveals extensive perivascular leucocytic infiltration, thrombosis of medium- and small-sized reticular dermal vessels, extravasation of erythrocytes, and necrosis of the epidermis, along with eccrine glands and Vasculitis is not present [13,18].

When assessing these lesions, keep in consideration that there are a few potential

diagnoses. In the aftermath of surgery or penetrating injury, the disease frequently resembles necrotizing fasciitis, a potentially fatal streptococcal or mixed anaerobe infection of the subcutaneous tissue [20]. Patients with existing cardiac comorbidities or those who have acral injuries and appear with symptoms of dyspnea and chest discomfort should be suspects of cutaneous embolisation of atrial myxoma. Additionally, cutaneous cholesterol emboli can cause lesions like those described above after endovascular procedures in atherosclerotic patients. Another option is vasculitis which makes such ulcers more likely [13]. Myositis, abscesses, nerve palsy, myonecrosis, limb ischemia, and sepsis are frequent complications of Nicolau syndrome [21]. Though uncommon, compartment syndrome has been documented as a complication in a few cases, one of which ultimately necessitated a below-knee amputation [22,23]. Thankfully, none of these issues occurred with our patient.

The major focus of care continues to be Nicolau syndrome prevention. Simple safety measures and the suggested method of intramuscular medication delivery can completely rule out the likelihood of this terrible side occurrence. Due to the lack of substantial nerve bundles and arteries in this area, the upper outer quadrant of the gluteal region or the mid-lateral section of the quadriceps femoris is the optimum location for IM injections. The ideal location for subcutaneous injections is the abdominal wall [10]. The Z-track technique must be used When giving IM injections to adults. After withdrawal, the needle's track leaves a zigzag pattern, which seals the medicine in the muscle layer, prevents extravasation into the subcutaneous layers above, and reduces the likelihood of discomfort and inflammation. The skin covering the target area is pushed laterally or downward, and a perpendicular needle injection is made within. After positioning is confirmed, the medication is gently injected and the needle is then withdrawn at a 90° angle. A zigzag path is then made by releasing the stiff skin. If the aspirate contains blood, the medication and needle must be discarded, and another location must be selected. Avoid massaging the region since doing so might irritate it [24].

Anticoagulants and systemic steroids are frequently utilized. Also advised is warm, intermittent compression. If there is clinical or radiographic evidence of tissue necrosis, individuals with NS need surgical debridement of the afflicted skin, subcutaneous tissue, and muscle. When this disease is suspected, it is crucial to begin preventive antibiotics due to the high likelihood of subsequent infection associated with tissue necrosis [7,11]. Skin grafts or reconstructive surgery may be required, and an early antibiotic start has been used in certain studies to successfully treat subsequent staphylococcal infections. However, starting therapy with antibiotics without first determining the etiology may result in inadequate care and subpar clinical outcomes [25]. There is no specific therapy for Nicolau syndrome aside from prevention; a parenteral injection of any medication that may be involved should be performed after aspiration of the syringe to guarantee extra-vascular administration of the medication. Although other treatment modalities, such as plexus block, anticoagulant therapy (heparin), arteriotomy and clot extraction, and local care, have been shown to have positive outcomes due to tissue damage, Nicolau syndrome patients have shown a quick response to treatment with complete healing and no functional impairment or scarring at 4 weeks [26].

4. CONCLUSION

The goal of management is to stop NS from occurring. This can be accomplished by taking a few easy measures and adhering to suggested methods for injecting medications intramuscularly, which can dramatically reduce the likelihood of this severe side event.

It is crucial for medical professionals to be aware of this complication, which can be identified by pain, skin discoloration, and necrosis after receiving an intramuscular injection of the NSAID, diclofenac sodium, and bupivacaine as spinal anesthesia, in order to prevent giving unnecessary injections. There is no set protocol for the care of this disease because the precise etiopathogenesis is unknown. The cornerstones of therapy are systemic antibiotics, early-stage wound debridement, and late-stage corrective plastic surgery. Doctors should also consider NS as a possible diagnosis for anyone who has acute localized pain following the injection of any drug into a muscle.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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