Hyperacute Paraplegia and Neurovascular (Immuno Vasculotoxic) Catastrophe of Nicolau Syndrome: Primum Non nocere

Bhaskara P. Shelley, Prasanth Prasad[1], Malla M. Manjunath[2], Shrijeet Chakraborti[3]

Departments of Neurology, [1]Medicine and [2]Dermatology, Yenepoya Medical College, Mangalore, Yenepoya (Deemed to be) University, [3]Department of Pathology, Kasturba Medical College (Manipal University), Mangalore, Karnataka, India

Abstract

A case of Nicolau syndrome (NS) in a 36-year-old adult taking an unusual and devastating hyperacute irreversible paraplegia after an intramuscular injection of benzathine penicillin as a part of routine chemoprophylaxis of her rheumatic heart disease is reported. Although this syndrome is a considerably rare, iatrogenic and underappreciated dermatologic entity, we reiterate in this report, its extracutaneous systemic potential for a catastrophic neurovascular phenomenon and morbidity as well as its possible preventive measures. The apoplectiform onset of T10 flaccid areflexic paraplegia, with the cutaneous hallmark of "embolia cutis medicamentosa" was corroborated by magnetic resonance imaging evidence of centromedullary complete cord involvement from T10 to conus medullaris. Combination therapy with pulse methylprednisolone, low-molecular-weight heparin, and pentoxifylline infusion proved unsuccessful. The skin biopsy and direct immunofluorescence revealed features were consistent with NS with overlap features of leukocytoclastic vasculitis, hitherto not reported. The literature of this preventable and iatrogenic disorder is reviewed, and plausible etiology is discussed.

Keywords: Embolia cutis medicamentosa, hyperacute paraplegia, intramuscular, leukocytoclastic vasculitis, myelopathy, Nicolau syndrome, paraplegia, vasculitis, immuno-vasculo-toxic

Introduction

While acknowledging typical adverse drug reactions, such as the purple glove syndrome and the Red neck syndrome from phenytoin and vancomycin, respectively, and Hoigne's syndrome and Nicolau syndrome (NS), are uncommon and underappreciated. In the dermatological literature, NS with its distinctive cutaneous hallmark of embolia cutis medicamentosa (ECM) has been ascribed to the accidental, inadvertent intra-arterial injection of intramuscular (IM) insoluble, viscous, lipophilic, or microcrystal particulate substances such as bismuth treatment of syphilis and mercury antibiotic preparations,[1] yet a whole host of offending drugs have been described in the published literature [Table 1]. Animal experimental studies using arteriography have explicated the pathogenesis of an obstructive vasculopathy, nonfilling and marked vascular stasis in the superior gluteal artery and adjacent arterial vasculature. The catastrophic immune-allergic vasculopathy due to the toxic angiopathy or crystalline drugs and the antecedent iatrogenic ischemic necrosis of the skin and deeper tissue termed.

ECM was first described by Juliusberg, Freudenthal, and Nicolau between 1924 and 1928.[1] NS in literature is portrayed as a "benign" dermatologic entity with its protean ECM at the injection site. The impetus of the article is to foster a greater interspecialty awareness and more importantly to allude to the more catastrophic and underreported neurological manifestations of NS [Table 2].

Case Report

A 36-year-old immunocompetent female without any medical comorbidity, vascular risk factors, or drug allergy presented to the emergency department with a history of hyperacute onset of flaccid paraplegia with double sphincteric incontinence of a day's duration. She stated that she attended a hospital for her routine monthly injection of 12 lakh units of benzathine penicillin for her rheumatic heart disease. She did the report of rheumatic fever at the age of 3 years and had been diagnosed with moderate mitral stenosis, mild aortic stenosis with mild aortic regurgitation since the age of 12 years and has been on benzathine penicillin prophylaxis without any untoward events in the past.

One day earlier, she attended her hospital for benzathine penicillin prophylaxis and was given the IM injection at 3 PM. Although she did not notice any difficulties during the IM

Address for correspondence: Prof. Bhaskara P. Shelley, Department of Neurology, Yenepoya Medical College, Yenepoya (Deemed to be) University, Mangalore, Karnataka, India.
E-mail: drbpshelley@gmail.com

DOI: 10.4103/aian.AIAN_298_18

Table 1: Drugs implicated in Nicolau syndrome (1924-2018)

Mercury
Bismuth
Rolitetracycline
Penicillin aluminum monostearate
Benzathine penicillin G
Antibiotics-
Antibiotics
Gentamycin, streptomycin, tetracycline
Cyanocobalamine, and Vitamin B complexes
NSAIDs
Diclofenac sodium, piroxicam, ketoprofen, ketorolac, ibuprofen, phenylbutazone, and etofenamate
Local anesthetics-lidocaine
Thiocolchicoside injection
Antihistamines
Diphenhydramine
Corticosteroids
Dexamethasone, triamcinolone, and hydrocortisone
Intra-articular injections of glucocorticoids
Antipsychotics
Chlorpromazine
Miscellaneous
Vitamin K
Phenobarbitone
Intramuscular oxytocin
Meperidine, buprenorphine, and naltrexone hyaluronic acid
Vaccines
Diphtheria, tetanus, and pertussis
PEG-modified interferon-α-2b; β interferon
Etanercept and bortezomib
Glatiramer acetate

NSAID=Nonsteroidal anti-inflammatory drugs, PEG=Polyethylene-glycol

Table 2: Neurological manifestations in Nicolau syndrome

Transverse myelopathy-acute flaccid paraplegia
Ischemic plexopathies involving (1) the lumbar plexus or its femoral branch or (2) the lumbar and sacral plexus or (3) the lumbosacral plexus including some lumbosacral nerve roots due to involvement to toxic angiopathy of iliac artery branches
Lumbosacral plexopathy-toxic endarteritis with spasms and thrombosis, with spread to the epineural and perineural blood vessels and cause segmental infarction
Flaccid crural monoplegia (involvement of ipsilateral iliac arteries, affecting lumbar or lumbosacral plexus)
Mononeuropathies-femoral nerve palsy obturator nerve palsy
Sciatic/common perineal neuropathy due to the involvement of inferior gluteal artery
Necrotizing fasciitis and compartmental syndrome with neuropraxias

injection to her right gluteal region, within few minutes (5 min), as she was stepping out of the hospital entrance, she experienced a sudden burning, stinging sensation at the site of injection that progressed to the periumbilical region, followed by an almost abrupt ascending numbness in both lower limbs to her hip level, only to buckle and collapse to the floor. She was fully conscious with no features of anaphylaxis and realized that she had complete weakness of both lower limbs, developed urinary retention and had to be catheterized. While in bed, due to the pain at the injection, her daughter noticed a bluish mottled discoloration on her right gluteal region.

The clinical examination during her presentation to our hospital 18 hours after the onset of the neurological catastrophe revealed an alert, conscious patient with normal vital signs. Her femoral, popliteal, tibial, and dorsalis pedis pulses were palpable with no evidence of skin lesions over the limbs or perineal region; no gangrene of the toes; and no evidence of rectal bleeding.

Initial neurological examination revealed Grade 0/5 Medical Research Council paraplegia, with flaccidity, areflexia, bilateral Babinski sign with a nondissociated pan-sensory level at T6, and double-sphincteric incontinence without flexor spasm or other evidence of multifocal neurological or meningeal deficits. The skin over the site of her IM injection revealed nonblanching, nonindurated, area of mottled erythemato-violaceous patches without a "palpable purpura" over the right superior gluteal distribution, with a reticulate pattern extending to the lateral aspect of the thigh and right lumbar paraspinal area, and with satellite lesions; the maximum diameter measuring 23 cm ×18 cm [Figure 1] which the patient had corroborated to have coalesced and increased in size.

In view of the apoplectiform "stroke-like" paraplegia in a young female patient and unaware of "*a priori*" NS, especially in view of having had her regular benzathine penicillin prophylaxis, we did reexplore her medical history for vasculitis, vascular risk factors, thrombophilia, connective-tissue disorders, history of optic neuritis, or opticospinal neurological deficits in an attempt to exclude other plausible and treatable etiologies of the "unexpected" hyperacute paraplegia.

A complete blood count (hemogram) revealed neutrophilic leukocytosis, raised erythrocyte sedimentation rate of 62 mm/1st h with a normal coagulation profile (Coombs test, antiphospholipid, and anticardiolipin antibodies), and urine examinations. Her chest X-ray, electrocardiography, blood urea, serum electrolytes, serum creatinine, and creatine kinase were normal. Tissue destruction was indicated by elevated transaminases with serum glutamic-oxaloacetic transaminase (aspartate aminotransferase [AST]) of 1018 units, serum glutamic pyruvic transaminase (alanine aminotransferase [ALT]) of 413, and serum lactate dehydrogenase of 1075 units. The results of her Venereal disease research laboratory (VDRL) and Human immunodeficiency virus (HIV)-1 and HIV-2 tests were negative. Her arterial Doppler studies in the extremities were normal. Antinuclear antibody profile, cytoplasmic and perinuclear antineutrophil cytoplasmic antibodies, rheumatoid factor anti-cyclic citrullinated peptide, and serologies (Leptospira IgM, Dengue NS1 antigen, malarial parasite, HbsAg, and HCV) were unremarkable. The cerebrospinal fluid examination was normal with no oligoclonal bands. Her nerve conduction studies were unremarkable. Magnetic resonance imaging (MRI) revealed

a longitudinally extensive, centromedullary cord involvement with altered signal intensity from T7 level to conus level in T2, fluid-attenuated inversion recovery, and short tau inversion recovery sequences without contrast enhancement with normal brain and optic nerve MRI sequences [Figure 2].

Sections of the skin biopsy [Figure 3a-f] revealed epidermal and papillary dermis infarction, with edema and extravasation of erythrocytes, the vessel walls showed fibrinoid necrosis and thrombotic occlusion of the vessel lumina with progression of vascular and perivascular necrosis, neutrophilic exocytosis, apoptotic nuclei, perivascular and transmural neutrophilic, and lymphocytic infiltrate associated with karyorrhexis in the dermal vessels all of which was consistent with leukocytoclastic vasculitis (LCV). LCV is the most common form of vasculitis of the skin and usually results from the deposition of immune complexes at the vessel wall, which was partially evident in the direct immunofluorescence (DIF) microscopy in this patient. We reiterate that a diagnosis of LCV should not be made solely on the presence of positive DIF findings nor should the diagnosis be excluded with a negative DIF test. The findings of DIF should be interpreted along with clinical, microscopic, and other laboratory findings.[2,3] It is prudent to recognize that the DIF result may be negative in a significant number of cases especially when samples are taken more than 7 days after the onset of lesions.

She was initiated on combination therapy with 1 g pulse methylprednisolone for 5 days (followed by tapering short course of 1 mg/kg/day of prednisolone), 40 mg enoxaparin s/c Q12 h, and pentoxifylline infusion for 2 weeks after 48 h

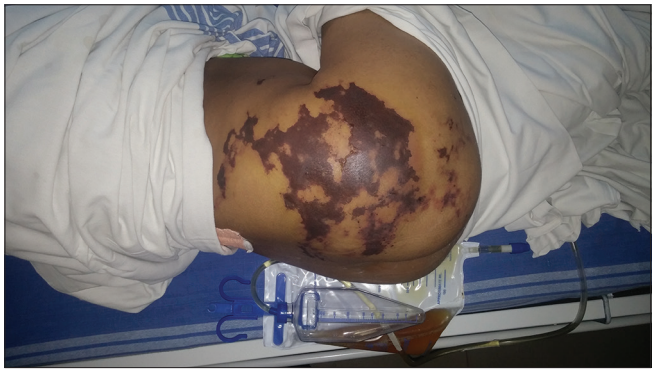

Figure 1: Embolia cutis medicamentosa. A reticulate, nonblasnching, nonindurated, coalesced areas of mottled erythemato-violaceous patches over the right superior gluteal distribution with extension to the lateral aspect of the thigh, and right lumbar paraspinal area, with satellite lesions measuring in its maximum diameter 23 cm × 18 cm

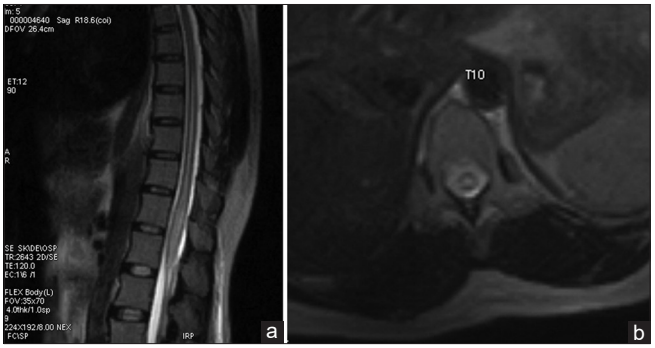

Figure 2: Magnetic resonance imaging. (a) T2-weighted sagittal spine magnetic resonance imaging revealed a longitudinally extensive altered signal intensity from T7 level to conus level with (b) (T2-weighted axial magnetic resonance imaging at T10 level) centromedullary cord involvement

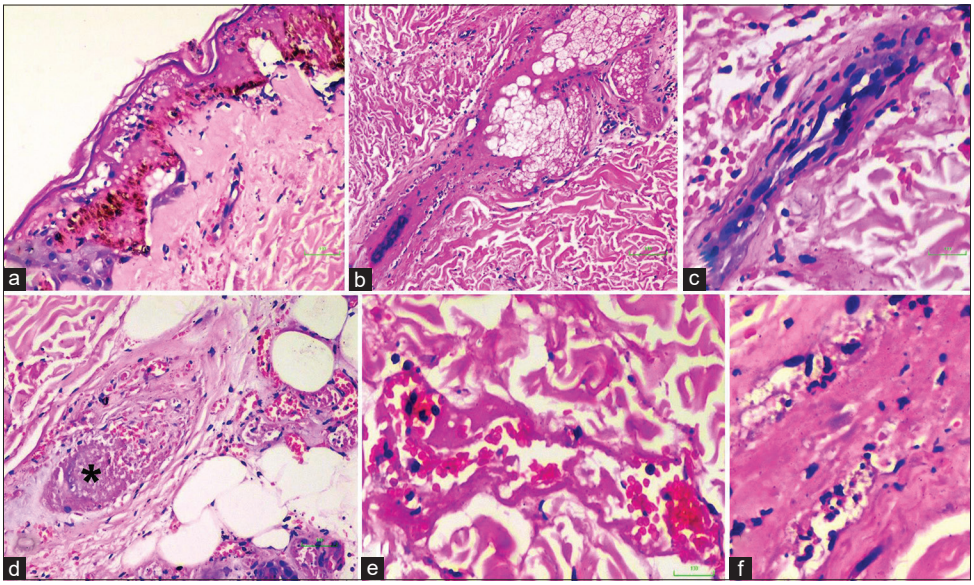

Figure 3: Leukocytoclastic vasculitis. (a) Epidermal infarction and subepidermal blister with inflammatory cells (H and E, ×100). (b) Infarcted pilosebaceous unit (H and E, ×100). (c) Perivascular and transmural neutrophilic and lymphocytic infiltrate and RBC extravasation (H and E, ×200). (d) Fibrin thrombi (asterisk), destruction of vessel wall, inflammatory infiltrate, and leukocytoclasis (H and E, ×100). (e) Fibrin deposition along the blood vessel wall (H and E, ×400). (f) Transmural inflammatory infiltrate and leukocytoclasis (H and E, ×400)

of onset of her neurological complication. However, she did not make any improvement in her neurological status and was discharged home after 3 weeks of hospital admission.

Discussion

To the best of our knowledge and review of the published literature, there are about 80 cases of NS reiterating the fact that this dermatologic entity is uncommon. It is intriguing to recognize that the neurological sequela of NS is underappreciated as there are less than 30 cases in PubMed till date.

Our report highlights noteworthy clinical pearls and clinical takeaway features, i.e., (i) the awareness of the treating neurologist of this iatrogenic dermatologic entity related to the accidental intra-arterial injection of benzathine penicillin to produce the distinctive ECM, a cutaneous thrombotic vasculopathy, at the IM injection site would obviate an expensive and unnecessary "excludogram" clinical investigation for hyperacute vascular myelopathy; (ii) diagnosis is essentially clinical taking cognizance of the temporal relation of IM drug administration and the severe pain at the injection site with ominous and pathognomonic appearance of ECM; (iii) the skin biopsy and immunofluorescence features of LCV in this patient does warrant exclusion of other plausible and treatable etiologies; and (iv) first report of documented immune and/or hapten-mediated vasculitis in NS. To the best of our informed knowledge, an immune-mediated or hapten-mediated immune vasculitis (leukocytoclastic vasculitis as in our case) in skin pathology of NS has not been reported.

Finally, the neurologic complications of NS should be preventable and abide by "primum non nocere" through the education of health professionals on appropriate IM injection techniques as per the article by Dietrich *et al*.[4] A noteworthy clinical pearl is that immediate discontinuation of the injection is recommended if pain occurs during the injection.

The emphasis of this report is to highlight the potentially devastating neurological manifestations that would alert specialists the pleiotropic features beyond the confines of a pure dermatologic entity. The neurological involvement with lower limb paralysis may be explained by drug embolism. The embolization of the lumbar branch of iliolumbar artery would explain the hyperacute transverse myelopathy.[5-8] Although the pathophysiologic mechanisms are unclear in the literature, it was Freudenthal in 1924 who proposed that the plausible pathomechanisms. The viscous penicillin solutions are difficult to inject through the needle and must therefore be given forcefully with inadvertent injection into branches of the superior gluteal artery located in the upper outer quadrant.[9] Some other authors hypothesized that penicillin suspension injected into the superior gluteal artery under high pressure could flow retrograde into the internal iliac artery and then to the aorta, leading to the obstruction of the lumbar spinal arteries.[6,10,11] In the thoracolumbar region, all of the blood supply to the spinal cord is derived from a single artery from the aorta, the artery of Adamkiewicz. The retrograde flow could extent further up the aorta to the level of the artery of Adamkiewicz. Extensive vasculotoxic injury with resultant occlusive peripheral arterial stenosis may be mediated through true microemboli, through extensive vascular injury, sympathetic vasospasm, toxic endarteritis with retrograde propagation of spasm, and/or vaso-occlusive thrombosis with resultant myelopathy.

However, there is no published literature on the presence of "hypersensitivity vasculitis" or LCV triggered by a reaction to a drug in NS as was reported in our skin biopsy. We speculate a plausible vasculitic process to be involved, leading to a necrotic process as evident by the results of the DIF skin microscopy study. We reiterate that the clinician should also look for following clinical features that will give additional clues to the extra-dermatologic accompaniments of NS. This will include the absence of lower pulses, gangrene of toes, and distal foot; gangrene of buttocks, perineum, vulva, scrotum, and penis due to the involvement of internal iliac arteries; granular proctitis, rectal bleeding secondary to vasospasm of middle and inferior rectal arteries; homolateral lumbosacral plexus ischemic damage; and embolization of the lumbar branch of iliolumbar artery-spinal artery leading to paraplegia with sphincteric involvement as in our reported case.

Conclusion

This case report does reiterate the occurrence of catastrophic neurologic complications in NS which is well beyond the confines of the protean "benign" dermatologic NS. The extracutaneous systemic potential of NS to evoke a catastrophic neurovascular phenomenon and morbidity does certainly underscore the need for awareness and to exercise utmost care during the administration of any parenteral injections by health workers. The skin biopsy and DIF in this patient revealed characteristic features that were consistent with NS with overlap features of LCV, hitherto not reported in the published literature. The clinical correlation of the temporal time relationship of the IM drug administration and the appearance of the distinctive ECM will be the quintessential clue for the correct diagnostic decison-making thus obviating an unnecessary shot-gun "excludogram" approach for the myelopathic workup.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initial will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Freudenthal W. Lokales embolisches bismugenol-exanthem. Arch Fiur Dermatol Syphc 1924;147:155-60.
2. Nandeesh B, Tirumalae R. Direct immunofluorescence in cutaneous vasculitis: Experience from a referral hospital in India. Indian J Dermatol 2013;58:22-5.
3. Kumar V, Beutner E, Chorzelski T. Immunopathology of blood vessels: Immunopathology of vasculitis. In: Immunopathology of the Skin. 3rd ed. New York: Wiley; 1987. p. 745-55.
4. Dietrich T, Runta NV, Holman J. Intramuscular injection. In: Nursing Procedure. 3rd ed. Pennsylvania: Springhouse; 2000. p. 243-9.
5. Shaw EB. Transverse myelitis from injection of penicillin. Am J Dis Child 1966;111:548-51.
6. Tesio L, Bassi L, Strada L. Spinal cord lesion after penicillin gluteal injection. Paraplegia 1992;30:442-4.
7. Cohen SM. Accidental intra-arterial injection of drugs. Lancet 1948;2:409-17.
8. Cohen M. Accidental intra-arterial injection of drugs. Dangers of therapeutic or diagnostic intra-arterial injections. Lancet 1948;2:409-16.
9. Gordon W, Dove J. Complications of accidental intra-arterial long-acting penicillin injections. S Afr Med J 1972;46:1833-6.
10. Wynne JM, Williams GL, Ellman BA. Accidental intra-arterial injection. Arch Dis Child 1978;53:396-400
11. Stöhr M, Dichgans J, Dörstelmann D. Ischaemic neuropathy of the lumbosacral plexus following intragluteal injection. J Neurol Neurosurg Psychiatry 1980;43:489-94.