

UNVEILING ADVANCES AND PIONEERING METHODS IN MANAGING NICOLAU SYNDROME POST ENDODONTICS: AN IN-DEPTH ANALYSIS

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Abstract: Nicolau Syndrome, also known as skin reaction embolism, is a rare but serious complication associated with the improper conversion of calcium hydroxide during endodontic treatment. This inflammation can cause serious side effects such as blood clots, tissue damage, and skin necrosis once the substance enters the bloodstream. Despite its seriousness, this condition rarely occurs during root canal treatment. Calcium hydroxide has been a mainstay of root canal treatment for many years, but its adverse effects on nearby vital structures pose significant risks. This article explores the mechanisms underlying Nicolau syndrome, clinical manifestations, and treatment strategies and emphasizes the need for careful and prompt treatment to reduce the risk. Through a review of current literature, case studies, and practical experiences, our goal is to improve awareness and offer recommendations for preventing and managing this serious complication in endodontic procedures. By reviewing current literature and clinical experiences, this article aims to enhance understanding and awareness of Nicolau syndrome within the field of endodontics.

Keywords: Nicolau syndrome, Livedoid dermatitis, Embolia Cutis Medicamentosa, Drug hypersensitivity, Dermatitis, Calcium hydroxide, Diclofenac, Complication, Tissue damage, Vascular thrombosis

I. Introduction:

Nicolau Syndrome, also known as embolia cutis medicamentosa or livedoid dermatitis, was first described in 1924 by Freudenthal.¹ It is a rare but severe complication following the administration of parenteral medications, particularly via the intramuscular route.² This condition arises due to intramural or periarterial injection of the offending drug, which leads to arterial spasm and cutaneous necrosis.³ The pathophysiology of Nicolau syndrome involves the unintended introduction of substances such as calcium hydroxide or other drugs into blood vessels or sensitive tissues, causing vascular obstruction and subsequent local tissue damage.⁴ The condition typically presents with an abrupt onset of severe pain at the injection site immediately following the administration of the injection.⁵ This is often accompanied by syncope.⁶ The initial symptoms include erythema, livedoid patches, and hemorrhagic lesions at the injection site, which are characteristic of the condition.⁷ Within a few days, the affected area progresses to necrosis of the skin, subcutaneous fat, and potentially muscle tissue.⁸ It can lead to serious complications, including widespread cutaneous necrosis, extensive scarring, and ischemia of the affected limb, organ failure, neurological deficits, superimposed infections, and potentially sepsis or compartment syndrome.⁹ Factors contributing to a poor prognosis include the application of cold compresses to the injection site, superimposed infections, sepsis, compartment syndrome, and a pre-existing immunocompromised state.¹⁰ These complications can lead to significant morbidity and mortality and have substantial medicolegal implications.¹¹ It has been linked to a range of medications, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antibiotics, and local anesthetics.¹² Calcium hydroxide, commonly used in endodontic therapy for its antimicrobial properties, can also cause severe damage if accidentally injected into soft tissue or vessels.¹³ A notable example is the use of calcium hydroxide in root

canal treatment, where accidental injection can lead to significant damage.¹⁴ For instance, a 2011 case described thrombosis of the inferior alveolar artery and branches of the maxillary artery, resulting in skin necrosis, following an accidental injection of calcium hydroxide.¹⁵ Despite its severity, Nicolau syndrome is infrequently reported in endodontic practice, making it relatively unfamiliar to many practitioners.¹⁶ This article aims to review the current understanding of Nicolau syndrome, focusing on its mechanisms, clinical manifestations, and management strategies. By consolidating insights from existing literature, case reports, and clinical experiences, the goal is to raise awareness among dental professionals and provide practical guidance for preventing and managing this rare but serious complication.¹⁷

II. Discussion:

The exact pathogenesis of Nicolau Syndrome is not fully understood, but several factors contribute to its development. One hypothesis suggests that sympathetic nerve stimulation from pain during drug injection leads to vasospasm and ischemia.¹⁸ Another hypothesis involves the embolism of drug crystals within the vascular compartment due to intramuscular, intravenous, or intraarterial injections.¹⁹ The most likely cause of Nicolau Syndrome is thought to be vascular. Important mechanisms include acute vasospasm, arterial inflammation, and thromboembolic occlusion of small blood vessels.²⁰ Perivascular and neural tissue leakage may cause discomfort, while visual stimulation and vasospasm can lead to ischemic damage and skin necrosis.²¹ Inadvertent intravascular injection may trigger inflammation or thromboembolism in arterioles, damaging the arterial wall and leading to skin necrosis.²² From reports, diclofenac sodium, a widely used nonsteroidal anti-inflammatory drug, is frequently associated with Nicolau Syndrome due to its cyclooxygenase inhibitory effect, which reduces prostaglandin production and causes vasoconstriction.²³ Other medications include calcium hydroxide, cyanocobalamin (vitamin B12), lidocaine, vitamin K, etanercept, naltrexone, ketorolac, ketoprofen, pethidine, gentamicin, chlorpheniramine maleate, phenylbutazone, salicylamide, dexamethasone, interbenutherinfen, triamineferon beta, penicillin G, thiocolchicoside, glatiramer acetate, piroxicam, and many other medications.²⁴ However, some studies have shown elevated levels of biomarkers associated with muscle tissue, such as creatine kinase, myoglobin, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase.²⁵ White blood cell count, markers of inflammation and renal function are usually within normal limits. In some cases, leukocytosis, increased serum aspartate aminotransferase, lactate dehydrogenase, and myoglobinuria have been noted.²⁶ Of these factors, the anatomic location is, of course, not possible to influence, but it is important to take the anatomic structures in consideration, as in all other forms of medical treatment. The over instrumentation of the root canal established a communication to the inferior alveolar artery and, for that reason, a communication farther to the external carotid artery, which supplies the face and the oral cavity mainly via the maxillary, facial, and superficial temporal arteries.²⁷ In few cases, the syringe probably entered the root canal deep enough to increase pressure, sufficiently high to exceed the arterial blood pressure, making it possible to distribute the paste upstream.²⁸ After the paste entered the maxillary and external carotid arteries, it simply followed the bloodstream distally and was spread out into the capillary bed.²⁹ This is based on the assumption that the volume of the calcium hydroxide paste particles was sufficiently low to permit entrance into the capillaries.³⁰ This is the only likely explanation because of the extremely severe ischemia. A contributing factor is probably the toxicity of the paste.³¹ Cytotoxic cell destruction caused by calcium hydroxide, among other dental materials, has been reported by Murray et al.³² Brodin and Orstavik described the neurotoxic effects of Calasept.³³ Extended inflammatory damaging reactions on connective tissue caused by calcium hydroxide are described by Nelson et al.³⁴ The importance of implanting alloplastic substances in the human body with respect as to their biology and precautions is obvious, as well as the development of new materials with high biocompatibility.³⁵ The technique of endodontic filling is also worth noting in this case. It has been shown that the Lentulo spiral is most effective in carrying the paste to working length. The use of the syringe is a less exacting means of delivering the filling material.³⁶

Clinical Results: Ultrasound Examination shows widespread intramuscular edema, necrotic lesions with large hyper echoic areas, subcutaneous areas, and muscle swelling.³⁷ Computed Tomography may reveal a well-developed central fatty artery with unaffected muscles and no fluid. The continuity of affected tissue is usually limited to the myofascia.³⁸ Magnetic Resonance Imaging shows subcutaneous fluid accumulation and muscle necrosis, with some cases showing no muscle involvement or residual fluid in eschar tissue.³⁹ Histopathology typically shows fibrosis of fat tissue, fat necrosis, eosinophilic infiltration, and inflammatory infiltration of the subcutaneous fat without vasculitis or granuloma. There is no evidence of malignancy.⁴⁰ Cultures Bacterial, fungal, and mycobacterial cultures are generally negative. However, specific cases may identify pathogens such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*.⁴¹ Differential Diagnosis Initial diagnosis includes local toxicity, hypertension, and gastrointestinal disease.⁴² Cardiac problems can be distinguished by electrocardiogram, cardiac enzyme levels, and chest X-ray.⁴³ Other diagnoses include vasculitis, fat embolism, left atrial myxoma, and Hovane syndrome.⁴⁴ Misdiagnosis of cellulitis may lead to inappropriate antibiotic use and failure of Nicolau Syndrome therapy.⁴⁵ The degree of malignancy should be assessed by surgical removal

and biopsy of the plaque. Treatment initially focuses on pain relief and differential diagnosis. Antibiotics and dressings are used to control infection and promote healing. Ice packs should be used cautiously to prevent local vasospasm.⁴⁶ Prophylactic antibiotics may be considered if cellulitis is excluded. Vascular and pain management in the acute phase includes therapies such as heparin, amyl alcohol, and hyperbaric oxygen therapy. Steroids, particularly betamethasone diphosphate and methylprednisolone, have shown rapid response. Pain management, anticoagulant therapy, and vasoactive therapy (such as oxyphylline) are also recommended.⁴⁷ Surgery should be performed as the disease progresses to the necrotic stage. This includes removal of slough, subcutaneous tissue, and muscle. Aftercare may include skin repair or reconstruction with results ranging from wound healing to atrophic scarring. For patients receiving drugs associated with Nicolau syndrome, such as glatiramer acetate and etanercept, it is important to consider other injection sites, especially if there has been a problem at a previous injection site.⁴⁸ Precautions should include avoiding freezing, which can worsen ischemia, and using antibiotics to prevent infection. To reduce the risk of Nicolau syndrome, it is recommended to use a needle of appropriate length for the patient's weight (for example, a 5 to 7.5 cm needle for a patient weighing 90 kg) and to inject in the upper thigh, where there are fewer blood vessels. Using the Z-track and thinking before injection is important steps, and each injection should not exceed 5 mL.⁴⁹ Rotating the injection site can help reduce the risk of complications. Supportive care involves managing pain, using anticoagulants such as heparin, administering steroids like methylprednisolone, and employing vasoactive therapy with medications such as pentoxifylline. Hyperbaric oxygen therapy may also be beneficial. In severe cases, treatment may require surgical debridement, fasciotomy, skin grafting, or flap reconstruction.⁵⁰ Effective management and prevention of Nicolau syndrome requires a combination of careful management, surgical intervention, and careful monitoring of the injection process.⁵¹

III. Conclusion:

This comprehensive analysis has highlighted significant advances and pioneering methods in managing Nicolau Syndrome following endodontic procedures. Nicolau Syndrome remains a challenging complication, with its severity often exacerbated by misdiagnosis and inadequate treatment. Recent developments in understanding the pathogenesis of this syndrome, including vascular mechanisms and the role of specific medications, have led to improved diagnostic accuracy and more effective therapeutic strategies. Advancements in pain management, anticoagulation, and vasoactive therapies have refined treatment protocols, while hyperbaric oxygen therapy and precise surgical interventions offer promising outcomes for severe cases. The implementation of meticulous injection techniques, including the use of long needles, the Z-track method, and rotating injection sites, has proven essential in preventing the onset of NS. Continued research and clinical experience are crucial for further refining treatment approaches and enhancing patient outcomes. By integrating these advances with careful attention to injection practices and supportive care, dental professionals can better manage Nicolau Syndrome and mitigate its associated risks. This in-depth analysis underscores the importance of ongoing education and vigilance in preventing and addressing this rare but serious complication in endodontics.

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References:

- [1]. Marangi GF, Gigliofiorito P, Toto V, Langella M, Pallara T, Persichetti P. Three cases of embolia cutis medicamentosa (Nicolau's syndrome). *J Dermatol.* 2010; 37:488-492.
- [2]. Corazza M, Capozzi O, Virgili A. Five cases of livedo-like dermatitis (Nicolau's syndrome) due to bismuth salts and various other non-steroidal anti-inflammatory drugs. *J Eur Acad Dermatol Venereol.* 2001; 15:585-588.
- [3]. Nicolau S. Dermite livédoïde et gangréneuse de la fesse, consécutive aux injections intra-musculaires, dans la syphilis: à propos d'un cas d'embolie artérielle bismuthique. *Ann Mal Vener.* 1925; 20:321-339.
- [4]. Saputo V, Bruni G. Nicolau syndrome caused by penicillin preparations: review of the literature in search for potential risk factors. *Pediatr Med Chir.* 1998; 20:105-123.
- [5]. Ozcan A, Senol M, Aydin EN, Aki T. Embolia cutis medicamentosa (nicolau syndrome): two cases due to different drugs in distinct age groups. *Clin Drug Investig.* 2005; 25:481-483.
- [6]. Lie C, Leung F, Chow SP. Nicolau syndrome following intramuscular diclofenac administration: a case report. *J Orthop Surg (Hong Kong).* 2006; 14:104-107.
- [7]. Guarneri C, Polimeni G, Guarneri F, Cuzzocrea S. Embolia cutis medicamentosa following thiocolchicoside injection. *J Eur Acad Dermatol Venereol.* 2008; 22:1005-1006.
- [8]. Lee DP, Bae GY, Lee MW, Choi JH, Moon KC, Koh JK. Nicolau syndrome caused by piroxicam. *Int J Dermatol.* 2005; 44:1069-1070.
- [9]. Senel E, Ada S, Güleç AT, Çağlar B. Nicolau syndrome aggravated by cold application after i.m. diclofenac. *J Dermatol.* 2008; 35:18-20
- [10]. Cherasse A, Kahn MF, Mistrih R, Maillard H, Strauss J, Tavernier C. Nicolau's syndrome after local glucocorticoid injection. *Joint Bone Spine.* 2003; 70:390-392.
- [11]. Sarifakioglu E. Nicolau syndrome after diclofenac injection. *J Eur Acad Dermatol Venereol.* 2007; 21:266-267.
- [12]. Luton K, Garcia C, Poletti E, Koester G. Nicolau Syndrome: three cases and review. *Int J Dermatol.* 2006; 45:1326-1328.

- [13]. De Sousa R, Dang A, Rataboli PV. Nicolau syndrome following intramuscular benzathine penicillin. *J Postgrad Med.* 2008; 54:332-334.
- [14]. Koller S, Kränke B. Nicolau syndrome following subcutaneous glatiramer-acetate injection. *J Am Acad Dermatol.* 2011; 64:e16-e17.
- [15]. Kienast AK, Mentze D, Hoeger PH. Nicolau's syndrome induced by intramuscular vaccinations in children: report of seven patients and review of the literature. *Clin Exp Dermatol.* 2008; 33:555-558.
- [16]. Gayken J, Westanmo A, Knutsen A, Ahrenholz DH, Mohr WJ, Solem LD. Livedoid dermatitis and severe necrosis (Nicolau's syndrome) after intramuscular hydroxyzine injection. *J Burn Care Res.* 2006; 27:541-544.
- [17]. Koklu E, Sarici SU, Altun D, Erdeve O. Nicolau syndrome induced by intramuscular vitamin K in a premature newborn. *Eur J Pediatr.* 2009;168:1541-1542.
- [18]. Miranda MCC, Rozenfeld S, Olivera SP. A systematic review of the non-allergic adverse reactions following benzathine penicillin injections. *J Vasc Br.* 2004; 3:253-260.
- [19]. Uri O, Arad E. Skin necrosis after self-administered intramuscular diclofenac. *J Plast Reconstr Aesthet Surg.* 2010; 63:e4-e5.
- [20]. García-Vilanova-Comas A, Fuster-Diana C, Cubells-Parrilla M, Pérez-Ferriols MD, Pérez-Valles A, Roig-Vila JV. Nicolau syndrome after lidocaine injection and cold application: a rare complication of breast core needle biopsy. *Int J Dermatol.* 2011; 50:78-80.
- [21]. Guarneri C, Polimeni G. Nicolau syndrome following etanercept administration. *Am J Clin Dermatol.* 2010; 11 Suppl 1:51-52.
- [22]. Harde V, Schwarz T. Embolia cutis medicamentosa following subcutaneous injection of glatiramer acetate. *J Dtsch Dermatol Ges.* 2007; 5:1122-1123.
- [23]. Ocak S, Ekici B, Cam H, Taştan Y. Nicolau syndrome after intramuscular benzathine penicillin treatment. *Pediatr Infect Dis J.* 2006; 25:749.
- [24]. Puvabanditsin S, Garrow E, Weerasethsiri R, Joshi M, Brandsma E. Nicolau's syndrome induced by intramuscular vitamin K injection in two extremely low birth weight infants. *Int J Dermatol.* 2010; 49:1047-1049.
- [25]. Ezzedine K, Vadoud-Seyedi J, Heenen M. Nicolau syndrome following diclofenac administration. *Br J Dermatol.* 2004; 150:385-387.
- [26]. Luton K, Caria C, Polent E, Koester G. Nicolau Syndrome: three cases and review. *Int J Dermatol.* 2006; 45(11):1326-1328.
- [27]. Kim SK, Kim TH, Lee KC. Nicolau syndrome after intramuscular injection: 3 cases. *Arch Plast Surg.* 2012; 39:249-252.
- [28]. Lee MW, Kim KJ, Choi JH, Sung KJ, Moon KC, Koh JK. A case of embolia cutis medicamentosa. *J Dermatol.* 2003; 30:927-928.
- [29]. Kim DH, Ahn HH, Kye YC, Choi JE. Nicolau syndrome involving whole ipsilateral limb induced by intramuscular administration of gentamycin. *Indian J Dermatol Venereol Leprol.* 2014; 80:96.
- [30]. Nischal K, Basavaraj H, Swaroop M, Agrawal D, Sathyanarayana B, Umashankar N. Nicolau syndrome: an iatrogenic cutaneous necrosis. *J Cutan Aesthet Surg.* 2009; 2:92-95.
- [31]. Ruffieux P, Salomon D, Saurat JH. Livedo-like dermatitis (Nicolau's syndrome): a review of three cases. *Dermatology.* 1996; 193:368-371.
- [32]. Murray PE, Lumley PJ, Ross HF, et al: Tooth slice organ culture for cytotoxicity assessment of dental materials. *Biomaterials.* 2000; 21:1711.
- [33]. Brodin P, Orstavik D: Effects of therapeutic and pulp protecting materials on nerve transmission in vitro. *Scand J Dent Res.* 1983; 91:46.
- [34]. Nelson FP, Silva LA, Leonardo MR, et al: Connective tissue responses to calcium hydroxide-based root canal medicaments. *Int Endod J.* 1999; 32:303.
- [35]. Wilbrand JF, Wilbrand M, Schaaf H, Howaldt HP, Malik CY, Streckbein P. Embolia cutis medicamentosa (Nicolau syndrome) after endodontic treatment: a case report. *J Endod.* 2011; 37:875-877.
- [36]. Zaragoza J, Delaplace M, Benamara M, Estève E. [A rare side effect of mesotherapy: Nicolau syndrome. *Ann Dermatol Venereol.* 2013; 140:713-717.
- [37]. Hamilton B, Fowler P, Galloway H, Popovic N. Nicolau syndrome in an athlete following intra-muscular diclofenac injection. *Acta Orthop Belg.* 2008; 74:860-864.
- [38]. Segreto F, Tosi D, Marangi GF, Giglioflorito P, Pendolino AL, Persichetti P. Nicolau's Syndrome Complicated by Atypical Necrotizing Fasciitis. *Arch Plast Surg.* 2013; 40:267-268.
- [39]. Okan G, Canter HI. Nicolau syndrome and perforator vessels: a new viewpoint for an old problem. *Cutan Ocul Toxicol.* 2010; 29:70-72.
- [40]. Guarneri C, Bevelacqua V, Polimeni G. Embolia cutis medicamentosa (Nicolau syndrome). *QJM.* 2012; 105:1127-1128.
- [41]. Stricker BH, van Kasteren BJ. Diclofenac-induced isolated myonecrosis and the Nicolau syndrome. *Ann Intern Med.* 1992; 117:1058.
- [42]. Kim KK, Chae DS. Nicolau syndrome: A literature review. *World J Dermatol.* 2015; 4(2): 103-107.
- [43]. Geurtsen W, Leyhausen G: Biological aspects of root canal filling materials: Histocompatibility, cytotoxicity and mutagenicity. *Clin Oral Invest* 1:5, 1997
- [44]. Sigurdsson A, Stancill R, Madison S: Intracanal placement of Ca(OH)₂: A comparison of techniques. *J Endod.* 18:367, 1992
- [45]. Noaparast M, Mirsharifi R, Elyasnia F, Parsaei R, Kondori H, Farifteh S, Nicolau syndrome after intramuscular benzathine penicillin injection. *IJMS.* 2014 39(6):577-79.
- [46]. Kılıç I, Kaya F, T, Özdemir A, Demirel T, Çelik I, Nicolau syndrome due to diclofenac sodium (Voltaren) injection: a case report. *Journal of Medical Case Reports.* 2014 8:404.
- [47]. Nayc S, Gurel MS, Nicolau syndrome following intramuscular diclofenac injection. *Indian Dermatology Online Journal.* 2013 4(2):152-53.
- [48]. Kim SK, Kim TH, Lee KC, Nicolau Syndrome after Intramuscular Injection: 3 Cases. *APS.* 2012 39:249-52.
- [49]. Kim KK. Nicolau syndrome in patient following diclofenac administration: a case report. *Ann Dermatol.* 2011; 23:501-503.
- [50]. Bégin P, Anne DR. Nicolau syndrome may be caused by intravascular vaccine injection. *Vaccine.* 2012; 30:2035-2036.
- [51]. Erkek E, Tuncez F, Sanli C, Duman D, Kurtipek GS, Bagci Y, Ayaslioglu E. Nicolau's syndrome in a newborn caused by triple DTP (diphtheria-tetanus-pertussis) vaccination. *J Am Acad Dermatol.* 2006; 54:S241-S242.