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Breast Surgery

Case Report

A Case Report of Nicolau Syndrome After Aesthetic Breast Surgery: A Review of the Literature and Introduction to a New Treatment Modality

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Abstract

Nicolau syndrome (NS) is a rare iatrogenic syndrome usually following intramuscular (IM) injection of various described medications. The typical presentation involves immediate injection site pain and development of a livedoid reticular patch, which can progress to muscle necrosis requiring surgical debridement. The pathophysiology is unclear, although vasoconstrictive etiologies have been implicated. Treatment ranges from supportive care to surgical debridement. The authors present a case report of this syndrome as well as a review of the literature and introduction to a new treatment modality. NS in a 52-year-old woman following IM injection of Demerol and Phenergan to address pain and nausea before discharge is reported. This occurred in the post-anesthesia care unit after aesthetic breast surgery in an ambulatory surgery center. Our patient had immediate injection site pain and a hemorrhagic patch was evident on her physical examination the following day. With local care and hyperbaric oxygen therapy, her lesion improved in appearance. However, she continued to have debilitating pain and was referred to a specialist for osteopathic manipulative therapy (OMT), which had the greatest impact on her pain level. After multi-modal therapy was initiated, the syndrome ultimately resolved without the need for surgical debridement. However, she continues to experience pain and ambulates with a limp due to muscle atrophy. NS is a rare diagnosis that can have devastating complications that can be averted by early recognition and initiation of treatment modalities. In this case, the authors introduced OMT as a new treatment modality, with the potential to improve the progression of this syndrome.

Level of Evidence: 5

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Nicolau syndrome (NS) was first described in the 1920s following intramuscular injection of bismuth salts for the treatment of syphilis.[1] Since then, there have been about a hundred case reports written describing this iatrogenic complication. It is a rare syndrome following intramuscular, subcutaneous, intravenous, as well as intra-articular injection of multiple different drugs leading to ischemic necrosis of the skin, soft tissue, and muscle, which arises locoregionally at the injection site.[1]

The pathophysiology is not well understood and so treatment and prevention are not well elucidated.[1] Here, we

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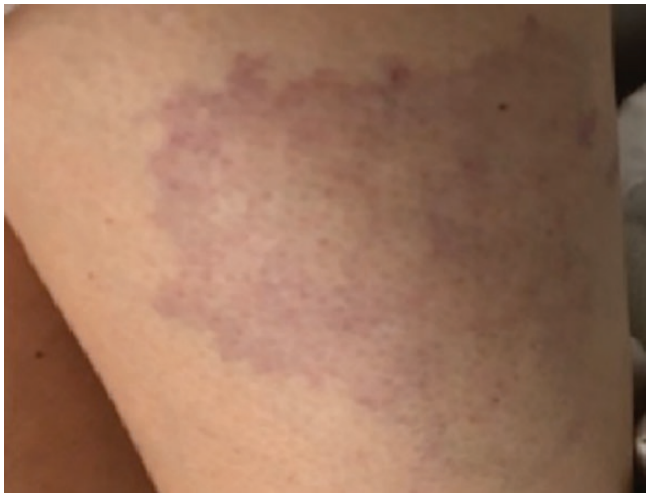

Figure 1. A 52-year-old female with a classic pattern of livedoid reticular patch to left lateral thigh seen on post-operative day 1.

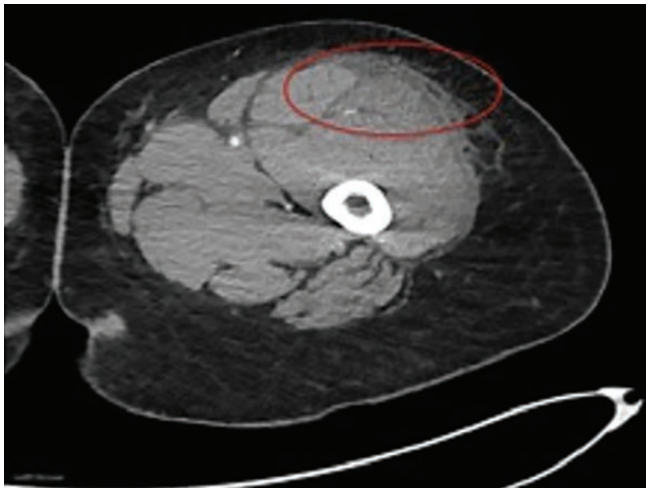

Figure 2. Computed tomography (CT) scan of the left lower extremity (LLE) with contrast done on post-operative day 1 with reactive changes noted to *vastus lateralis* muscle (circled in red above).

present a case report as well as a review of the literature of this rare syndrome following intramuscular injection of Phenergan and Demerol postoperatively after an outpatient aesthetic breast surgery procedure. From this, we hope to increase awareness of NS and to suggest the utility of hyperbaric oxygen (HBO) and introduce osteopathic manipulative treatment (OMT) as a useful treatment for this rare syndrome.

CASE REPORT

A 52-year-old female underwent bilateral breast implant exchange and mastopexy on July 9, 2018 by the senior author (K.M.) at an outpatient surgery center without adverse events from her procedure. After discontinuation of her intravenous access, she was given an intramuscular injection of 12.5 mg of Demerol and 12.5 mg of Phenergan to address pain and nausea for outpatient control before discharge. The injection was made with a 25 gauge needle, 3 cm in length, and was placed at her left anterolateral thigh. She immediately experienced severe injection site pain as well as noted a violaceous patch at the site. Along with pain, she had left lower extremity swelling, but no parasthesias. She was seen in the clinic the following day and the purplish patch appeared less pronounced and appeared ecchymotic with slight induration beneath the skin, along with swelling of her left lower extremity and pain over the lesion (Figure 1). As her pain continued to worsen, she was evaluated in the emergency room later that day. A computed tomography (CT) scan with contrast of her left lower extremity was done and revealed interfascial fluid in the anterior compartment of her proximal thigh and hypodensity within the *vastus lateralis* and some soft tissue swelling (Figure 2). Labs drawn that same day showed a mild white blood cell count elevation of 13.8 and the complete metabolic panel was within normal limits. She was discharged home under the assumption that this was an extravasation injury. She was encouraged to keep her lower extremity elevated and apply heat or ice for comfort. On postoperative day 2, she was evaluated by dermatology and was treated expectantly for suspected NS and told she should not apply ice to the lesion. Her pain continued to worsen, and she required hospital admission for pain control and expectant management of NS on post-operative day 4. Magnetic resonance imaging obtained in the hospital showed concern for myositis and necrosis in the *vastus lateralis* and to a lesser degree in the *rectus femoris* and *vastus medialis*. All her bloodwork including complete metabolic panel and complete blood count were within normal limits. While in the hospital, an ultrasound-assisted muscle biopsy was also performed, and final pathology showed viable skeletal muscle with focal granulation tissue and limited muscle fiber injury. Microbiology of the specimen showed no growth. She was discharged from the hospital on postoperative day 7 on a pain regimen to include narcotics, nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and Lyrica along with antibiotics. As the lesion became increasingly hemorrhagic, violaceous and ischemic appearing with less blanching, it was thought she would benefit from HBO treatment. Thus, on postoperative day 8, she was started on HBO twice daily for a total of 10 treatments (Figure 3). There was an immediate and dramatic improvement in the lesion's appearance as well as a decrease in size upon initiation of HBO therapy. At her 2-week postoperative visit, the lesion was noted to be shrinking and epidermolysis was noted.

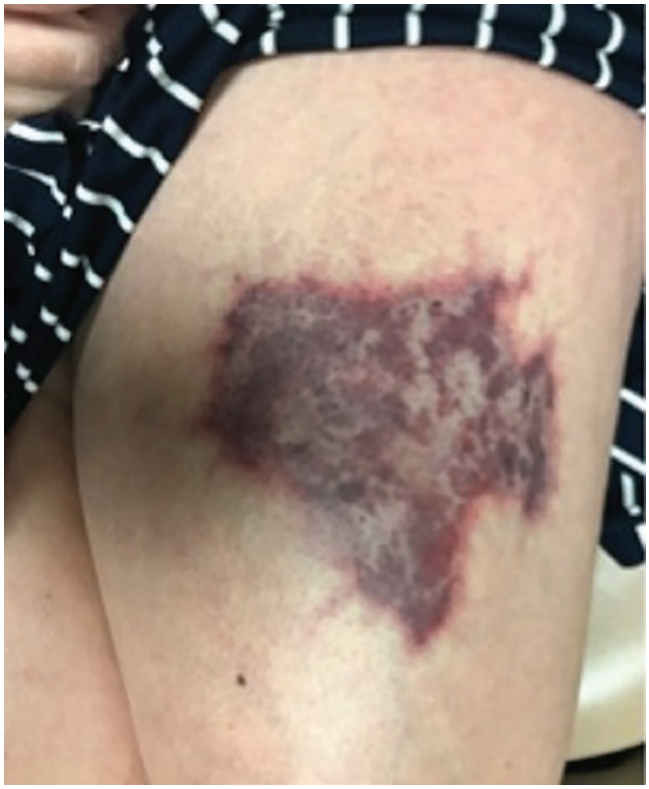

Figure 3. Appearance of lesion before hyperbaric oxygen treatment (post-operative day 8).

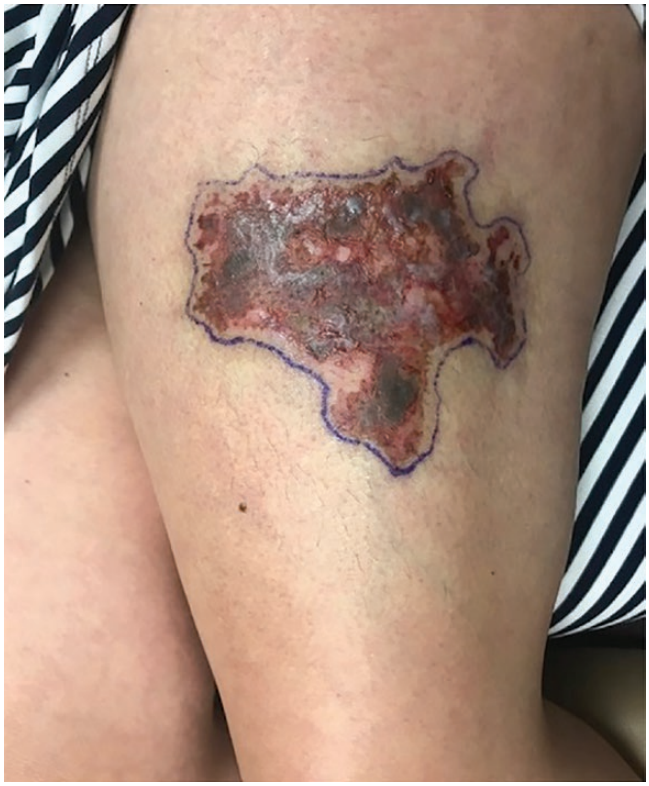

Figure 4. Appearance of lesion before initiation of osteopathic manipulative therapy (post-operative day 17).

There was only superficial desquamation of the skin. At her 2.5-week visit, after completion of 10 HBO treatments, her left thigh lesion was noted to be even smaller with continued epidermolysis and decreased ischemic patches (Figure 4). Although the lesion continued to improve in appearance, she continued to have exquisite, debilitating pain at the site.

At this point, she was referred to an osteopathic physician for further pain management. Our patient's pain likely stemmed from the initial injection producing a strong enough afferent autonomic pain signal to trigger a very strong efferent sympathetic nervous system (SNS) response causing spasm in one or more arterioles surrounding the injection site in her thigh. The ensuing hypoxic tissue damage produced enough additional pain to perpetuate the strong autonomic response in a vicious cycle of hyper sympathetic activity. Essentially, this is reflex sympathetic dystrophy or complex regional pain syndrome but acted out on a more focal level.

The patient was given OMT using gentle indirect soft tissue techniques to reduce spasm both locally (in the cutaneous and subcutaneous tissues at and around the lesion site, and in the underlying muscle tissues), regionally (in the upper leg, hip, and pelvis), and more centrally at the involved levels of the spinal cord. Her perceived pain reduced immediately after the first treatment and decreased more markedly over the next 2 treatments. This was accompanied by a significant improvement in vascular perfusion of the lesion area, as evidenced by the rapid reduction in her perceived pain and by observation of improved changes in skin perfusion made at her second osteopathic visit 5 days later (Figure 5). She was recommended further osteopathic treatments; however, she stopped going after her third treatment session (Figure 6).

Ultimately, on her most recent postoperative visit on postoperative month (POM) 9, her pain was significantly improved but she continues to experience a constant ache. On physical examination, she continues to have contour irregularities and hyperpigmentation at the site of her lesion (Figure 7). She no longer requires ambulatory assistance but continues to walk with a slight limp. She is continuing to see physical therapy and a pain specialist and remains on daily Lyrica and oxycontin for pain.

DISCUSSION

First described by Freudenthal in 1924 and subsequently by Nicolau in 1925, NS (also known as embolia cutis medicamentosa, livedo-like dermatitis) is a rare complication most commonly following intramuscular injection of a drug.[2-4] While intramuscular injection is the most

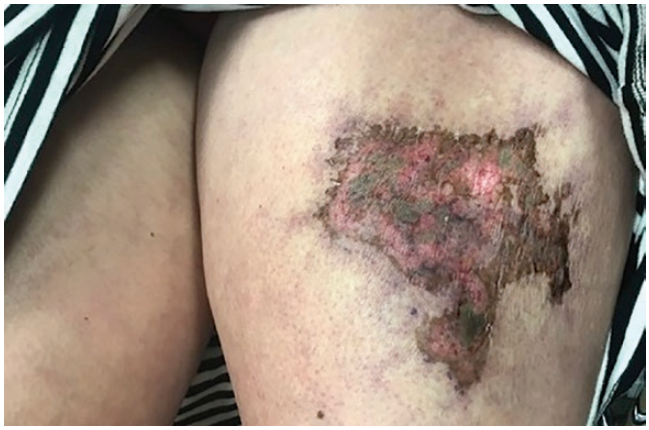

Figure 5. Appearance of lesion 5 days after first osteopathic manipulative therapy visit (postoperative day 22).

frequent underlying event, it has also been reported after other parenteral routes of administration, such as subcutaneous, intravenous, intra-articular, subacromial, and even intramatricial.[2,5] Along with various routes of administration, multiple drugs have been associated with this syndrome, most notably, NSAIDs, antibacterials, antihistamines, local anesthetics, corticosteroids, antipsychotics, interferons, and even vaccinations.[2,6]

Although the pathophysiology of NS remains unclear, there are several theories connecting the syndrome to ischemia caused by thromboembolic occlusion or vascular injury and compression followed by occlusion after injection.[2] One theory poses that after peri-arterial or intra-arterial injection, the sympathetic nerve stimulation due to pain leads to vasospasm and ischemia.[7,8] Another theory, specific to NSAIDs, depicts vasospasm and ischemia due to blockade of prostaglandin synthesis.[9-12] A third theory is based around accidental intra-arterial injection leading to embolic occlusion.[13,14] A fourth theory emphasizes perivascular inflammation due to cytotoxic reaction from the injected medication.[1,11] Finally, a fifth theory postulates physical obstruction of blood vessels due to lipophilic drugs, which inadvertently penetrated the vessel.[9,11,15] Since the pathophysiology is not well understood and the route of administration as well as the drug administered has no apparent correlation, it seems that the injection itself is the common variable leading to this syndrome.[2]

Since NS is fairly rare and the pathophysiology remains unknown, there are no set diagnostic criteria. However, the common feature of the syndrome is severe injection site pain, which our patient stated she had immediately post-injection. Along with this, is pain out of proportion to physical examination findings, which was also seen in our patient.[16] Aside from pain, there is usually rapid development of edema and erythema with a livedoid reticular patch at the injection site. These patches progress to a hemorrhagic appearance with plaques that ultimately may culminate with cutaneous, subcutaneous, and possibly intramuscular necrosis.[2] Not all cases develop in this manner, and thus, clinical diagnosis is difficult. The main differential diagnosis that needs to be ruled out is necrotizing fasciitis.[2] Diagnosis is mainly based on clinical findings and early recognition is key to allow the implementation of specific therapeutic measures in order to prevent some of the dreaded complications described in the literature.

Most cases describe a somewhat benign course with a resolution with remaining atrophic scar or pigmentation. In some cases of muscular necrosis, surgical debridement is required. However, there have been reports of hypoesthesia and even paraplegia.[1] There have also been reports of compartment syndrome of the limb, hyperkalemia, renal failure, sepsis, and even death.[16]

There are many proposed treatment strategies for NS, but there is no standardized treatment protocol. Most reports utilize conservative measures to treat symptoms such as multi-modal pain control, antibiotics, dressing changes, and surgical debridement if required. Other measures include anticoagulants, intravenous or topical corticosteroids, and vasoactive therapy (such as nifedipine and pentoxifylline) to relieve vasospasm.[1,16] Some cases required fasciotomy for compartment syndrome.[10] Other measures to help improve vascularity such as HBO have also been reported. To our knowledge, the use of HBO to treat NS has been reported in 3 other cases in the literature with good results.[17-19] In our patient's case, there was a dramatic improvement in her lesion's appearance after the institution of HBO and she sustained no complications from her HBO treatments.

The therapeutic basis of HBO is based on its mechanical effect of increasing environmental pressure on gas containing spaces in the body and the physiologic changes induced by hyperoxia. Due to this hyperoxygenated state, hypoxic tissues are oxygenated, vasoconstrictive effects lessen the edema, leukocyte activation is boosted, and neoangiogenesis is started, leading to the recovery. Since NS may be due to acute vascular damage and tissue ischemia, HBO therapy may yield its effects by improving tissue oxygen tensions. Even though the mechanism of action of HBO therapy is well elucidated, since the acute vascular response in NS is still unclear, the effect of HBO therapy on patients with NS remains unclear.[17] However, based on our observation in our patient, HBO can play a role in the treatment of NS.

Finally, another modality utilized for our patient was OMT. To our knowledge, there is no previous report of using OMT as a treatment for NS. In this form of treatment, the primary goal was reducing the hyperactivity in the SNS, which was causing spasm in one or more arterioles surrounding the injection site in her thigh. At the level of the spinal SNS ganglion, sufficient nociceptive afferent

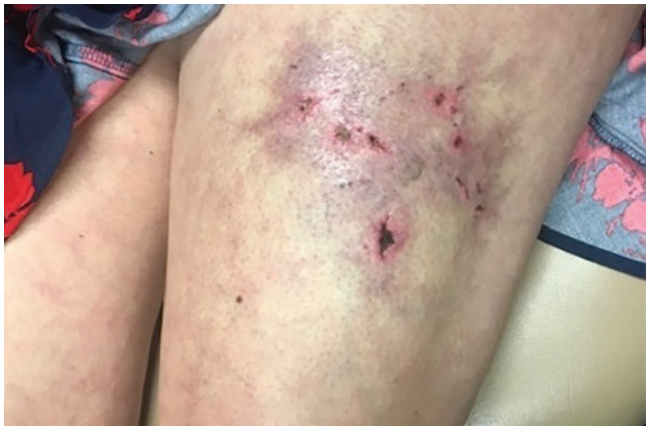

Figure 6. Appearance of lesion 12 days after third and last osteopathic manipulative therapy visit (post-operative day 35).

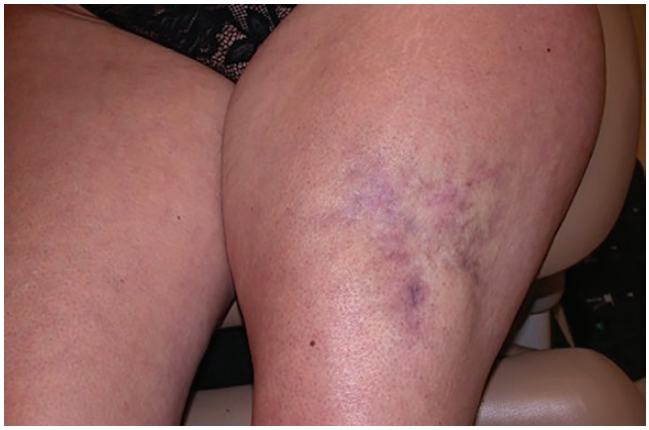

Figure 7. Appearance of lesion at most recent office visit (POM9).

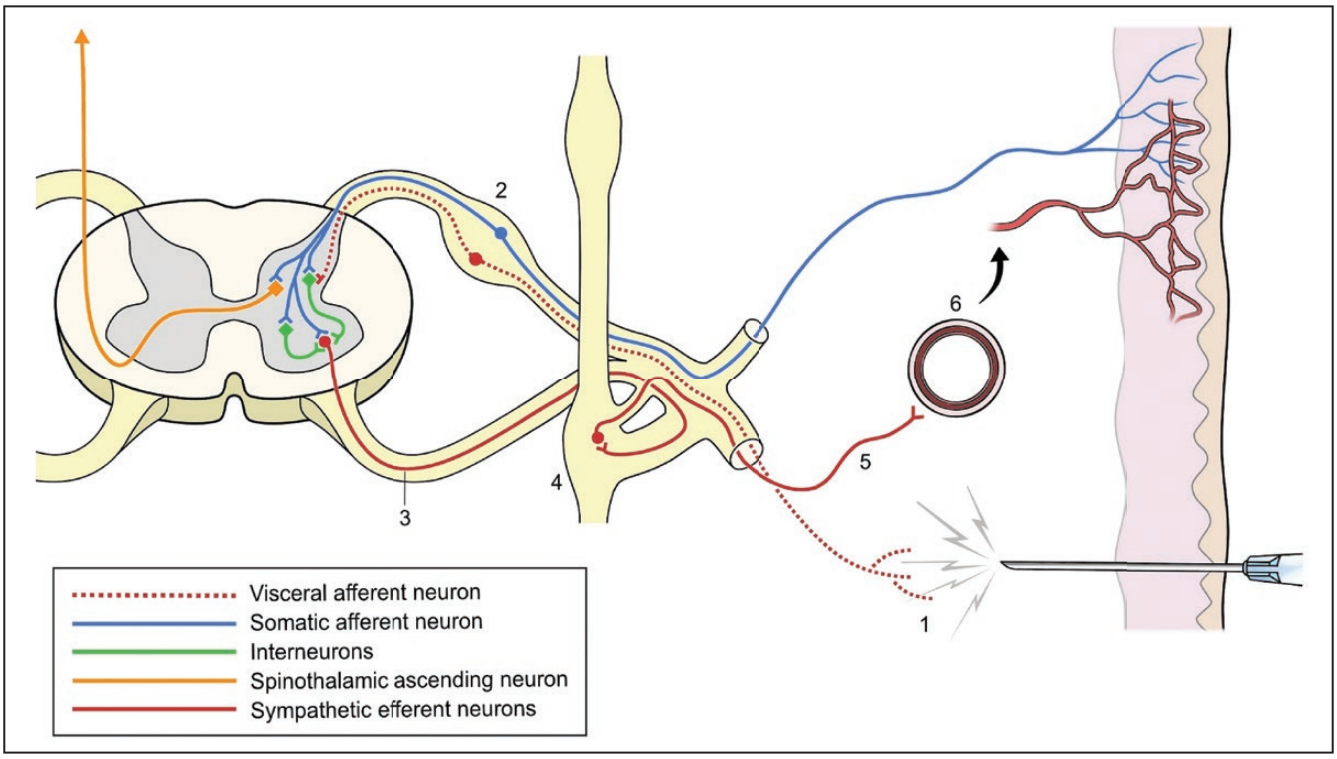

Figure 8. Target cycle of osteopathic manual medicine. (1) Visceral pain sensor, (2) dorsal root ganglion, (3) sympathetic preganglionic neuron, (4) vertebral ganglion, (5) sympathetic postganglionic neuron, (6) arteriole, and (7) somatic pain sensors.

signaling will produce a reflex efferent response that generalizes to the entire segmental autonomic distribution at that level. The vasospasm and other effects produced by a strong SNS motor output will occur in both somatic and visceral structures, and this can result in a stronger and more persistent nociceptive response, resulting in a vicious cycle of pain and spasm (Figure 8).[20]

We hypothesized that this patient's reaction to the IM injection (needle ± injected material) produced enough afferent autonomic pain signal to trigger a very strong efferent SNS motor response, which caused severe vasospasm in one or more arterioles perfusing the involved area. The ensuing hypoxic tissue damage then produced enough additional pain to perpetuate the strong autonomic response in a vicious cycle of hypersympathetic activity. Essentially, this is reflex sympathetic dystrophy or complex regional pain syndrome, but acted out on a more focal level.

In osteopathic terminology, the structural and/or physiologic changes caused by this sort of hyperactive SNS feedback loop are called "somatic dysfunction." This impaired or altered function is not simply a result of static restriction in the compliance of these structures. It is produced and actively maintained by a heightened level of SNS reflex activity at the segmental level of innervation of the involved visceral and anatomic structures.[21-29]

The osteopathic approach to treating somatic dysfunction involves working to reduce spasm in soft tissue components both locally at the site of injury and regionally at the structural level of the segmental spinal response. Reducing spasm removes some of the nociceptive input to the feedback loop and improves the flow of fluids into and out of the involved tissues. Better fluid movement leads to better peripheral oxygenation and allows better tissue repair and normalization of local physiology, which further reduces nociceptive input. With enough reduction in nociceptive signaling, the positive feedback is removed from the system, and reflex functions can reestablish their normal equilibriums.

After our patient was given osteopathic manipulative treatment, her perceived pain reduced immediately after the first treatment and continued to decrease over the next 2 treatments. This was correlated with a dramatic improvement in vascular perfusion of the lesion area, as noted by the healing rate of her skin lesion thereafter. Furthermore, since our patient discontinued her osteopathic manipulative treatments prematurely, before what was recommended, and was not medically stationary with regard to osteopathic medical treatment, we propose that she may well be in a significantly better shape today if she had continued to receive this form of treatment. Due to the multiple treatments utilized and their subsequent promotion of healing, it is our observation that multi-modal therapy is the key to this syndrome's resolution as treatment is mainly based on symptomatology.

Some limitations to our study are centered on the rarity of this syndrome. No direct conclusions can be made to the utility of OMT or otherwise, as this study was based on observation of a single patient and multiple modalities were used to treat our patient. Thus, since we cannot run a two-armed study with multiple patients, we can only surmise from our single patient observations.

CONCLUSION

NS is a rare iatrogenic complication due to injection of multiple drugs reported in the literature. It is important to recognize the diagnosis early, so that appropriate treatment modalities can be initiated to help prevent some of the potential dreaded outcomes of this syndrome. We introduce osteopathic manipulative treatment as a new possible treatment modality, with the potential to improve the progression of this syndrome.

Disclosures

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