ABSTRACT

Introduction: Complex Regional Pain Syndrome (CRPS) is a chronic disabling painful pathological condition that persists long after the initial injury to the affected limb, triggering characterized by constant pain, allodynia, hyperalgesia, edema, trophic changes, vasomotor dysregulation, and motor deficiency. Usually, the cause is a physical, chemical, or mechanical injury; other times no apparent cause can be identified that could justify the disease. Aspecific continuing pain is the symptomatology, which is not specific and appears disproportionate to any inciting the initial traumatic event.

Case presentation: A 36-year-old woman with a history of dysphagia, heartburn, abdominal pain and persistent cough underwent to EGDS with the suspect of a hiatal hernia. During the induction phase of anesthesia by intravenous administration of Propofol, an intravenous anesthetic agent, the extravasation of this drug occurred in the upper right limb tissue. Ten months later further EMG/NCS showed an antalgic reduction of the voluntary recruitment pattern lacking peripheral neuropathy signs. Continuing pain disproportionate to the incidental event, allodynia, temperature asymmetry and alteration of the skin color at the right arm lacking evidence of nerve lesions, confirmed the diagnosis of complex regional pain syndrome type 2.

Conclusion: In case of CPRS, the forensic pathologist has to determine the cause in order to prevent a medical malpractice claim, and also it is useful to well known the clinical features to evaluate a state of permanent invalidity. Difficult diagnosis plays a crucial role in the onset of the high disability that the disease causes if it is not recognized on time. The causes of CPRS may be the consequences of a medical error (in the specific case the extravasation of an irritant substance, Propofol) and from subsequent diagnostic delay a very debilitating morbid picture can occurs. For medico-legal purposes, it becomes essential to know the syndrome, and especially to diagnose it in a short time.

Keywords: Complex Regional Pain Syndrome, Causalgia, Reflex Sympathetic Dystrophy, Medico-legal evaluation.

DOI: 10.19193/0393-6384_2018_2_58

Received November 30, 2017; Accepted January 20, 2018
thermoregulatory blood flow to the limb leaves it colder than its counterpart\textsuperscript{(1,2)}. This differentiation, according to some authors, may be useful in understanding the physiopathology. The triggering event consists, in 50-75\% of cases, on minor to moderate tissue injury. The real impact of CPRS is unknown given the inconsistency trauma of any entity or nature. Other times the pathological picture evolves as a result of mechanical, chemical and/or physical insults. Given the intrinsic difficulty in diagnosing and the continuous updating of the diagnostic criteria and no consensus, a definitive epidemiological estimate of CRPS does not seem possible at the moment. Despite this, it has been noted that, regarding recovery.

The general population-based studies showed an incidence ranging from 5.5\textsuperscript{(3)} to 26.2 per 100,000 person-years\textsuperscript{(4)}, and 3-4 times more women than men are affected\textsuperscript{(5)}. The upper limbs are usually affected (i.e., classic example is the fracture of the radius, which in some cases can evolve into chronic and disproportionate pains), and the incidence peak is between 50 and 70 years; in addition to fractures, also distortions, bruises, crushing injuries, and some particular surgical interventions, can be considered as triggering factors\textsuperscript{(4)}. The authors present a case of CRPS from Propofol's extravasation in a 36-year-old woman who showed a CRPS due to propofol extravasation by the intravenous administration, during the induction phase of anesthesia for esophagogastroduodenoscopy (EGDS) procedure.

**Case Presentation**

A 36-year-old woman with a history of dysphagia, heartburn, abdominal pain and persistent cough underwent to EGDS with the suspect of a hiatal hernia. During the induction phase of anesthesia by intravenous administration of propofol, an intravenous anesthetic agent, the extravasation of this drug occurred in the upper right limb tissue. Severe and continuing local pain was followed by functional impotence. Since the patient was evaluated in the Emergency Room.

Specifically, color Doppler ultrasonography was performed and diagnosis of initial thrombosis of the right upper extremity of cephalic vein was made. Therefore subcutaneous low molecular weight heparin (nadroparin calcium 3800 IU per day) and non-steroid anti-inflammatory drugs (NSAIDs) (diclofenac 200 mg/day) were started. Few days later pharmacotherapy with Seleparin and painkillers was prescribed. The patient began to complain hyperemia, swelling glossy skin of the right arm. The patient underwent a phlebological evaluation without remarkable findings. In addition colorultrasonographic examination showed the recanalization of the cephalic vein phlebitis. After few days she started gabapentin (300 mg tid), a structural analogue of the inhibitory neurotransmitter \(\gamma\)-aminobutyric acid (GABA) commonly used in the managing of acute and chronic pain syndromes, especially neuropathic pain. After 2-3 months allodynia with non-painful stimuli evoking pain, motor and trophic symptoms (muscle tremors, weakness) were prominent. The patient underwent a neurological examination that showed, an initial muscle hypotrophy and tone reduction. One month later the electromyographic (EMG) and nerve conduction studies (NCS) did not show any alteration. After few weeks hyperemia, swelling and glossy skin edema worsened. Another phlebological evaluation confirmed arterial and venous patency in the right upper limb. Despite pharmacological treatment, pain was so severe to completely abolish arm movements, while the condition of hypomiotrophy was becoming more and more evident.

Ten months later further EMG/NCS showed an antalgic reduction of the voluntary recruitment pattern lacking peripheral neuropathy signs. Continuing pain disproportionate to the incidental event, allodynia, temperature asymmetry and alteration of the skin color at the right arm lacking evidence of nerve lesions, confirmed the diagnosis of complex regional pain syndrome type 2. Tricyclic antidepressant (amitriptyline), opioids (tramadol) and local amidic anesthetics (bupivacaine), and physiotherapy were discontinued after 3 months due to lack of efficacy. However a second neurological examination started duloxetine (60 mg/die) and tapentadole (100 mg bid) and further physical therapy. One-year follow-up continued. Despite pharmacological and physical therapy only a partial improvement of the clinical picture occurred.

**Discussion**

To our knowledge this is the first report of CPRS induced by extravasation of the anesthetic agent Propofol. Although CPRS pathogenesis is still unknown, various mechanisms have been proposed such as inflammation, neurogenic inflammation and maladaptive alterations in perception of pain at CNS level\textsuperscript{(9)}. 
Since several minor or moderate mechanical, chemical or physical insults leading to a CPRS were described, pathogenesis is still puzzling and debated\(^6\). Our patient developed CPRS type 2 after a mild chemical thrombosis of cephalic vein in right upper extremity. The symptoms satisfied the Budapest Clinical Criteria\(^6\). Budapest Diagnostic criteria for CPRS are continuing pain, which is disproportionate to any inciting event and at least one symptom in three of the following categories: hyperesthesia or allodynia (sensory), temperature asymmetry, skin color changes, or skin color asymmetry (vasomotor), edema, sweating changes, or sweating asymmetry (sudomotor or edema); decreased range of motion, motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin) (motor and trophic). In addition the CPRS patients should display at least one sign at time of diagnosis in two or more of the following categories: hyperalgesia (to pinprick) or allodynia (to light touch, deep somatic pressure, or joint movement) (Sensory); temperature asymmetry, skin color changes or asymmetry (Vasomotor); edema, sweating changes, or sweating asymmetry; decreased range of motion, or motor dysfunction (weakness, tremor, or dystonia), or trophic changes (hair, nails, or skin).

Finally, no other diagnosis better explains this signs and symptoms\(^6\). Often, the inciting event leading to a CPRS could be a mechanical, chemical or physical insult\(^6\). Due to the many predisposing factors and the complex physiopathological aspects, the CPRS diagnosis is complex and is based primarily on established clinical criteria, including allodynia, hyperthermia and skin alterations, edema, motor dysfunction and muscle tropism alterations\(^4,7-9\). The main differential diagnoses are: infection of skin, muscle, joint or bone, compartment syndrome, peripheral vascular disease, deep vein thrombosis, peripheral neuropathy, vascular thoracic outlet syndrome, rheumatoid arthritis, erythromelalgia, conversion disorder or factitious disorder. Diagnosis is made clinically after the rigorous elimination of other possible causes, and 3-phase bone scintigraphy can be a useful tool for confirming CPRS during initial phase.

The clinical course of CPRS progresses through three phases: acute inflammation followed by dystrophy, eventually leading to structural atrophy. However, these phases may overlap and be less distinct, or be missing\(^6\). In the first phase, all signs and symptoms of classical inflammation (burning, throbbing pain, diffuse and uncomfortable aching, sensitivity to touch or cold and localized edema) are present. During the second phase, which lasts from three to six months, there is progression of edema, thickening of the skin and articular soft tissues, muscle wasting and development of brownish skin. The last stage is characterized by a severe limitation of movement\(^10\). Despite the severity of clinical symptoms, the diagnostic process to allow the demonstration of the lack of other causes better explain clinical picture, may represent the main reason of the delayed diagnosis.

In addition, the lack of awareness of a CPRS among both general practitioners and neurologist specialists may represent a further critical issue\(^12\). Although there is not an established treatment, physicians should start early and include NSAIDs, anticonvulsants (i.e. gabapentin or pregabalin), tricyclic antidepressants, bisphosphonates, lidocaine or topical capsaicin, nasal calcitonin, oral glucocorticoids or other drugs such as opioid or intravenous immunoglobulin; patient education (physical and occupational therapy; psychosocial and behavioral management)\(^13,14\).

Although a single case does not allow any generalization, we describe a CPRS induced by the extravasation of a propofol solution resulting in a mild chemical tissue injury during the induction phase of anesthesia for EGDS procedure. Rare cases of CRPS following extravasation of irritant solutions have been described in the literature (i.e. dextrose)\(^9\). The extravasation caused an inflammatory response resulting in edema, redness, and pain, triggering the onset of CPRS. It is important also for the medico-legal physician to know and report such a pathology that may arise from a technical error (in the specific case of incorrect execution of Propofol’s infusion) and at the same time be at the center of actions for professional responsibility in case of failed or delayed diagnosis that leads to a greater disability of the subject.

Particularly, Propofol’s initial extravasation and subsequent diagnostic delay resulted in a clinical picture characterized by chronic “neuropathic” pain, functional impotence to the upper right limb and, consequently, a post-traumatic disorder from stress with depressive and anxious symptomatology.

Our case seems to confirm that the pathophysiology of CRPS is multifactorial in nature and is characterized by an aberrant host response to tissue injury. We suggest that individual susceptibility
may be the main risk factor of CPRS independently from severity or type of tissue injury.

Conclusions

CPRS is a pathological condition often limiting autonomy. Difficult diagnosis plays a crucial role in the onset of the high disability that the disease causes if it is not recognized on time. The triggering factor in some circumstances results from a medical error (in the specific case the extravasation of an irritant substance, Propofol); from this and from subsequent diagnostic delay, a very debilitating morbid picture for the patient followed. Therefore, also for medico-legal purposes, it becomes essential to know the syndrome, and especially to diagnose it in a short time.

References

3) PD Drummond Sensory disturbances in complex regional pain syndrome: clinical observations, autonomic interactions, and possible mechanisms Pain Med, 11 (2010), 153-161

Corresponding Author:
GIAN LUCA MARELLA
Department of Experimental Medicine and Surgery
Section of Legal Medicine, University of Rome Tor Vergata
via Montpellier, 1
00133, Rome
Email glmarella@gmail.com
(Italy)