Complex Regional Pain Syndrome Type I in Cancer Patients

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Complex regional pain syndrome type I (CRPS-I) is infrequently associated with various malignancies, and may lead to severe pain in already debilitated patients. The causal relationship between CRPS-I and paraneoplastic syndrome, controversies in diagnosis and treatment, and new treatment modalities are presented.

Complex regional pain syndrome type I is infrequently associated with various types of underlying malignancies. When present it can cause significant pain, tenderness, and swelling, as well as limitation of motion and trophic changes [1]. CRPS-I may present itself much earlier than any evidence of neoplastic growth, or it may appear as a complication of advanced malignancy, leading to severe pain in an already debilitated patient. Indeed, patients with malignancy may already have significant cancer pain that requires numerous treatment modalities, including nonpharmacologic techniques and nonopioid and opioid analgesics, which may further complicate the presentation, diagnosis, and treatment of CRPS-I.

In this article we review the available literature related to CRPS-I in patients with malignant tumors, explain how CRPS-I may represent a part of paraneoplastic syndrome with certain types of malignancies, and discuss the controversies related to the diagnosis and treatment of CRPS-I. Moreover, we review new therapies and present information on our experience with some new treatment modalities.

Complex Regional Pain Syndrome Type I

Over the past decades, CRPS-I has been known under many different names, including Sudeck's dystrophy, algoneurodystrophy, shoulder-hand syndrome, and reflex sympathetic dystrophy, without well-established diagnostic criteria. The names introduced recently to describe two painful syndromes formerly known as reflex sympathetic dystrophy and causalgia are CRPS type I and II, respectively [2]. In the case of reflex sympathetic dystrophy, the need for a new taxonomy was obvious because, in most instances, the name reflex sympathetic dystrophy lacks any degree of accuracy because there is neither reflex nor dystrophy present. Moreover, the relationship to the sympathetic nervous system is not consistent. Therefore, 25 pain management authorities met as a consensus conference to establish a new descriptive name as well as specific diagnostic criteria (Table 1) [2]. CRPS-I is defined as a painful condition that appears regionally after an initiating noxious event (Fig. 1). Pain always exceeds the inciting event in magnitude and duration and results in significant impairment of sensory and motor functions. In patients with undiagnosed malignancies the initiating noxious event may not be obvious for a longer time period and this may somewhat delay the diagnosis of CRPS-I. Validation of established criteria for diagnosis of CRPS-I and some important revisions were recently introduced [3–5].

Whereas the majority of the CRPS-I cases have been associated with surgical and nonsurgical trauma, ischemic heart disease, cervical spine or spinal cord disorders, and cerebrovascular disease, malignancy is an infrequent underlying cause. Females are three times more likely to be affected than males [6,7], and it is also more common in Caucasians [7].

The mechanism of this syndrome of sensory, motor, and autonomic dysfunction is unclear, but several theories were proposed in attempts to explain its complicated clinical picture. The sympathetic nervous system hyperactivity and the inflammatory process theories fail to explain CRPS-I in a satisfactory way. Contributory factors, including abnormal neuroendocrine response, psychological dysfunction, and stressful life events (such as dealing with malignancy) [8] were shown to predispose certain patient populations to CRPS-I. Discussion on the exact pathophysiology of CRPS-I—whether it is the central [9] or peripheral [10] mechanism, or both—is still unsettled. At the periphery, major pathologic change in CRPS-I is the development of sensitivity of peripheral nonciceptors to sympathetic stimulation. Noradrenaline released from sympathetic postganglionic neurons stimulates the release of prostaglandins. There is strong evidence that ATP acts as a co-transmitter with noradrenaline and neuropeptide Y in the sympathetic system toward the generation of pain and inducing prostaglandin synthesis. ATP is also released directly from tumor cells [11].

Table 1. Diagnostic Criteria: Complex Regional Pain Syndrome (CRPS)*

CRPS Type I (RSD)
1. Type I is a syndrome that develops after an initiating noxious event.
2. Spontaneous pain or allodynia/hyperalgesia occurs, is not limited to the territory of a single peripheral nerve, and is disproportionate to the inciting event.
3. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

CRPS Type II (causalgia)
1. Type II is a syndrome that develops after a nerve injury.
2. Spontaneous pain or allodynia/hyperalgesia occurs and is not necessarily limited to the territory of the injured nerve.
3. There is or has been evidence of edema, skin blood flow abnormality, or abnormal sudomotor activity in the region of the pain since the inciting event.
4. This diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction.

*A term describing a variety of painful conditions following injury, which appears regionally having a distal predominance of abnormal findings, exceeding in both magnitude and duration the expected clinical course of the inciting event often resulting in significant impairment of motor function, and showing variable progression over time.
RSD—reflex sympathetic dystrophy.
(*From* Stanton-Hicks *et al.* [2]; with permission.)

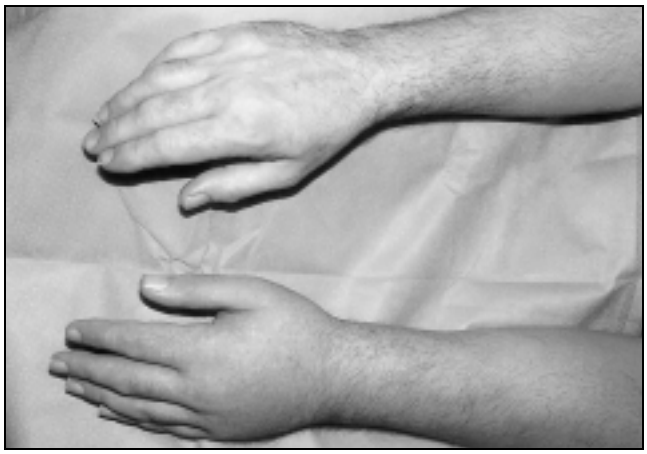

Figure 1. CRPS-I of the left hand. Notice the swelling of the left hand, fingers, and forearm as compared with the right. This patient experienced significant allodynia. CRPS—complex regional pain syndrome.

Release of the ATP directly from tumor cells may be a contributory factor for pain development in CRPS-I during the early stages of malignant growth. ATP released from sympathetic nerve endings or from tumor cells is believed to act on purinergic nociceptive sensory endings, thereby contributing to the pain in CRPS-I. In support of this hypothesis are the facts that surgical sympathectomy, sympathetic ganglion blockers, and guanethidine (which prevents the release of co-transmitters) are more effective than adrenoceptor agonists or reserpine (which depletes noradrenaline but not ATP from sympathetic nerve terminals) in preventing sympathetic-maintained pain [12]. Central mechanisms include central sensitization and decreased pain threshold mediated via wide-dynamic range neurons in the dorsal horn [13].

CRPS-I and Malignancy

The relationship between malignancy and CRPS-I was first noted approximately 60 years ago [14]. Since that time, 85 cases of CRPS-I in patients with various types of cancer were described in the literature. The majority of these cases had upper extremity CRPS-I [15].

In many of these cases in which malignancy was associated with CRPS-I, periods of 4 to 6 months were recorded from the onset of CRPS-I to actual diagnosis of cancer [16–18]. Therefore, occult malignancy must be considered when CRPS-I presents itself in the absence of an obvious explanation, especially in patients with a high risk of developing cancer.

There are numerous reports of CRPS-I involving gynecologic malignancies. Cervical and vulvar carcinomas may cause CRPS-I of the lower extremities, whereas ovarian carcinomas can frequently precipitate upper extremity CRPS-I (shoulder-hand syndrome). The appearance of the CRPS-I may be a part of the paraneoplastic syndrome caused by ovarian carcinoma [19]. Additionally, it also appears that this paraneoplastic syndrome is not only associated with ovarian carcinomas but also with other types of malignant tumors, such as hemangioendothelioma, pancreatic and other cancers [15,16,20,21]. However, considering the small number of described single cases and rather anecdotal descriptions of this possible syndrome, it is difficult to substantiate its existence.

Some patients with ovarian and cervical carcinoma may present with bilateral rather than unilateral CRPS-I of the upper extremities [22,23]. They may also have other rheumatic problems associated with cancer, including frequent inflammatory arthropathy of the large joints such as knees [19,22].

Findings of severe inflammatory changes and severe arthropathy are not confined to patients with ovarian carcinomas. Severe fasciitis and contractures have been described with other malignancies, including pancreatic [21] or lung carcinomas [24], in patients with CRPS-I. These subintimal proliferative changes [19] may be preceded by perivascular infiltrates in dermal vessels [21].

Pancoast tumors are adenocarcinomas or squamous cell tumors of the pulmonary apex that cause Pancoast Syndrome [25], which includes destruction of surrounding bone, Horner's syndrome, and involvement of the brachial plexus (C8,T1), stellate ganglion, or sympathetic chain. CRPS-I is manifested in these patients as hyperesthesia, pain, swelling, dystrophic skin changes, and vasomotor

Table 2. Proposed Modified Research Diagnostic Criteria for Complex Regional Pain Syndrome

1. Continuing pain that is disproportionate to any inciting event
2. Must report at least one symptom in each of the four following categories:
   - Sensory: reports of hyperesthesia
   - Vasomotor: reports of temperature asymmetry or skin color changes or skin color asymmetry
   - Sudomotor/edema: reports of edema or sweating changes or sweating asymmetry
   - Motor/trophic: reports of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)
3. Must display at least one sign in two or more of the following categories:
   - Sensory: evidence of hyperalgesia (to pinprick) or allodynia (to light touch)
   - Vasomotor: evidence of temperature asymmetry or skin color changes or asymmetry
   - Sudomotor/edema: evidence of edema or sweating changes or sweating asymmetry
   - Motor/trophic: evidence of decreased range of motion or motor dysfunction (weakness, tremor, dystonia) or trophic changes (hair, nail, skin)

(*From* Bruehl *et al.* [3]; with permission.)

disturbances of the upper extremities [24,26,27]. When the tumor is at a relatively early stage [24], CRPS-I may be the only initial finding in the absence of other symptomatology. In these patients it would be prudent to search for underlying malignancy if other possible causes of CRPS-I are unclear. Cases of CRPS with Pancoast tumor were described in which apical chest opacity during chest radiograph examination was the only abnormality at the time of diagnosis of CRPS [26,27].

Increased vasodilatation possibly caused by local cytokine release (such as prostaglandins) results in increased specificity and sensitivity of the triple-phase scintigraphy, which may then be used as an additional diagnostic tool to establish the diagnosis of CRPS-I [26,28]. There are reports that do confirm a causal relationship between apical lung tumor and CRPS-I, demonstrating immediate improvement in pain after tumor removal [24].

Approximately 5% of patients with brain tumors develop CRPS-I, especially in the upper extremities, which is referred to as shoulder-hand syndrome. Clinical signs include edema, erythema, and contractures with severe pain. Interestingly, one group of patients with brain tumors who were treated with phenobarbital have had a higher incidence of shoulder-hand syndrome (12% compared with 5%) [29]. Phenobarbital is often used to control tumor-induced seizures when patients are allergic to phenytoin. The most typical initial presentation of CRPS-I in patients using phenobarbital is painful limitation of movements in both shoulders [29], with bilateral symptoms occurring more frequently than in patients not using phenobarbital [30,31]. There is evidence that symptoms may disappear at approximately 2 months after barbiturate withdrawal [30]. The precise mechanism of how phenobarbital precipitates CRPS-I remains unclear.

Other causes of upper extremity CRPS-I include lymphoma, recurrent breast carcinoma [17], and pancreatic and bladder carcinoma [15]. CRPS-I was also described in association with some very rare malignancies, such as epitheloid hemangioendothelioma [20]. In addition, CRPS-I may occur as a consequence of the spread of peripheral metastatic disease [32,33]. An interesting situation is described when malignancy involves the sympathetic nervous system. Although most neoplasms that involve the sympathetic nervous system lead to sympathetic denervation, some neoplasms may manifest themselves in the same manner as CRPS-I [34]. Excision of such a tumor may then result in all signs and symptoms of sympathectomy as well as relief of CRPS-I–induced pain [35].

Diagnosis of CRPS-I in Cancer Patients

In the absence of a single reliable test to establish a diagnosis of CRPS-I, a comprehensive history and physical examination and the patient's response to sympathetic nerve blocks are of great importance. Diagnosis of CRPS-I is generally established on clinical grounds after excluding the existence of other conditions that would account for the degree of pain and dysfunction present [2]. Moreover, recently proposed modified diagnostic criteria increased diagnostic specificity by requiring at least two positive categories of signs and four categories of symptoms. This is elaborated on in Table 2 [3].

Swelling, pain, decreased skin temperature, and skin color change, as well as restricted range of motion, are usually present in an area much larger than and distal to the tumor site. Symptoms are also aggravated by activity involving the affected extremity [6]. A significant decrease of the active range of motion is present in almost every patient with CRPS-I (96%). In addition, decreased muscle strength and tremor are also frequently seen [36].

Description of the pain is similar in the vast majority of cases. Although initially burning and continuous, there may be a fluctuation in intensity. Pain can be exacerbated by movement, stimulation, or stress [37]. Pain is also regional, nondermatomal and diffuse, extends distally and usually involves an extremity. It is severe and out of proportion with other presenting clinical signs. These pain characteristics as well as the allodynia are of great impor-

tance for the diagnosis of CRPS-I [38]. In a study by Sandroni *et al.* [38], most of the patients had dull pain, or other burning or sharp pain. Initially, pain was usually described as burning and distal, while later it became more aching and diffuse [13]. Most patients who suffer from CRPS-I less than a year describe pain as tiring and troublesome [1]. The contribution of sympathetically maintained pain to overall pain may vary significantly in two different patients or in the same patient at different points of disease progression [2]. The presence of cancer-related pain usually complicates the picture in the assessment of CRPS-I. Moreover, those patients may already be receiving various pharmacologic and radiation treatments. It is therefore important to identify the nature of pain complaints in patients with advanced cancer.

Allodynia and hyperalgesia are not limited to the territory of a single nerve but rather present at disproportionally expanded areas. Hyperalgesia appears to be dynamic in nature, suggesting a central rather than peripheral contribution in the early stages of CRPS-I [9].

Assessment of peripheral sympathetic nerve function is of great importance. Edema either localized or sometimes generalized may be present from 50% [13] to almost 90% of patients [36]. When upper extremities are involved, edema usually spreads over the dorsal areas of the hands and forearms [36]. Attention should be also directed toward changes in skin color and hair, and nail growth alteration. Those changes, as well as the presence of contractures, are nonspecific changes but present in numerous patients with CRPS-I.

Dysfunction of the autonomic system may be evaluated using thermographic imaging. In this method thermal emission is measured, possible abnormal distal thermal gradients identified, and response to cold water autonomic stress testing analyzed. Sensitivity of the test was found to be 93% for detecting CRPS-I and specificity as high as 89%. In addition, it may assist in earlier recognition and early treatment of disease, which is of greatest importance for CRPS outcome [39,40].

The quantitative sudomotor axon reflex test (QSART) is a valuable quantitative test of sudomotor activity in limited skin area. Differences in the humidity over certain areas of the skin measured by two hygrometers in the oxygen-constant stream can help measure cutaneous evaporation. Additional sweating then can be induced iontophoretically by a 5% to 10% solution of acetylcholine. The typical response to stimulus on the QSART curve is measured by sweat volume and latency of the response [41]. Very short latency and large differences in sweat volume are considered abnormal secondary to increased somatosympathetic response, and together with other symptomatology may suggest CRPS [38].

Scintigraphy may be useful in assisting diagnosis of CRPS-I. In general, periarticular hyperemia and increased radiotracer uptake of the affected extremity are usual findings [42]. The osseous, or third phase of the triple-phase scintigraphy, has been reported initially to have as high as 96% sensitivity and 98% specificity in detecting CRPS-I. Later those numbers were shown to be significantly lower and rather closer to 50% in sensitivity [7,13]. Using diffuse increase of the tracer uptake in delayed images, diagnosis of CRPS-I may be established [28]. The actual disease stage is important as hemovelocity, blood pool, and bone fixation differ at three different stages of disease [43]. Unfortunately, scanning at different stages of the disease may actually decrease specificity to very low levels [13]. Variability of the tracer uptake in children precludes effective use of the three-phase bone scan in pediatric patients [44].

Plain radiographs may be used for comparison with the unaffected extremity. The presence of osteoporosis at the affected side may be helpful in establishing diagnosis. Psychiatric symptoms coexisting with CRPS-I have been well described, and major depressive disorders as well as personality disorders (such as obsessive-compulsive and self-defeating personalities) are most frequent [45,46•].

Therapy for Cancer Patients with CRPS-I

Sympathetic block remains the major component of the therapy for CRPS-I. Effective sympathetic blockade of the extremity is usually confirmed by an increase in skin temperature, suppression of sudomotor activity at the site of the stimulation, and the onset of Horner's syndrome [47]. Sympathetic blockade of the upper extremity is performed at the stellate ganglion, whereas blockade of the lower extremity is performed at the lumbar sympathetic chain. In patients with malignancies whose prognosis is poor, the primary goal when sympathetic blocks are used is to relieve pain from CRPS-I. However, the early use of sympathetic blocks will also improve the long-term outcome of CRPS-I in patients with a fair-to-good prognosis [48]. When local anesthetics are used for sympathetic ganglion blocks, longer pain relief lasting up to several days may be achieved, which is significantly longer than the use of a saline control [49]. Opioids, including morphine [50], fentanyl [51], and sufentanil [52], have been used for sympathetic blockade without clear evidence of efficacy and a limited knowledge of mechanism of action.

Intravenous regional blocks may be used in addition to other therapeutic interventions. They are performed by the intravenous injection of a variety of therapeutic medications after the tourniquet is placed to minimize further spread of the agent. Bretylium [53], ketanserin [54], and ketorolac [55] demonstrated some efficacy in pain inhibition when given regionally.

More recently, subcutaneous lidocaine infusion has been used for the treatment of patients with CRPS-I, resulting in significant pain relief and a decrease of other related symptoms. Subcutaneous infusion may be beneficial as stable blood levels may be achieved. However, patients with seizure disorders, brain tumors, cardiac problems, or drug allergies may not be able to tolerate lidocaine therapy [56].

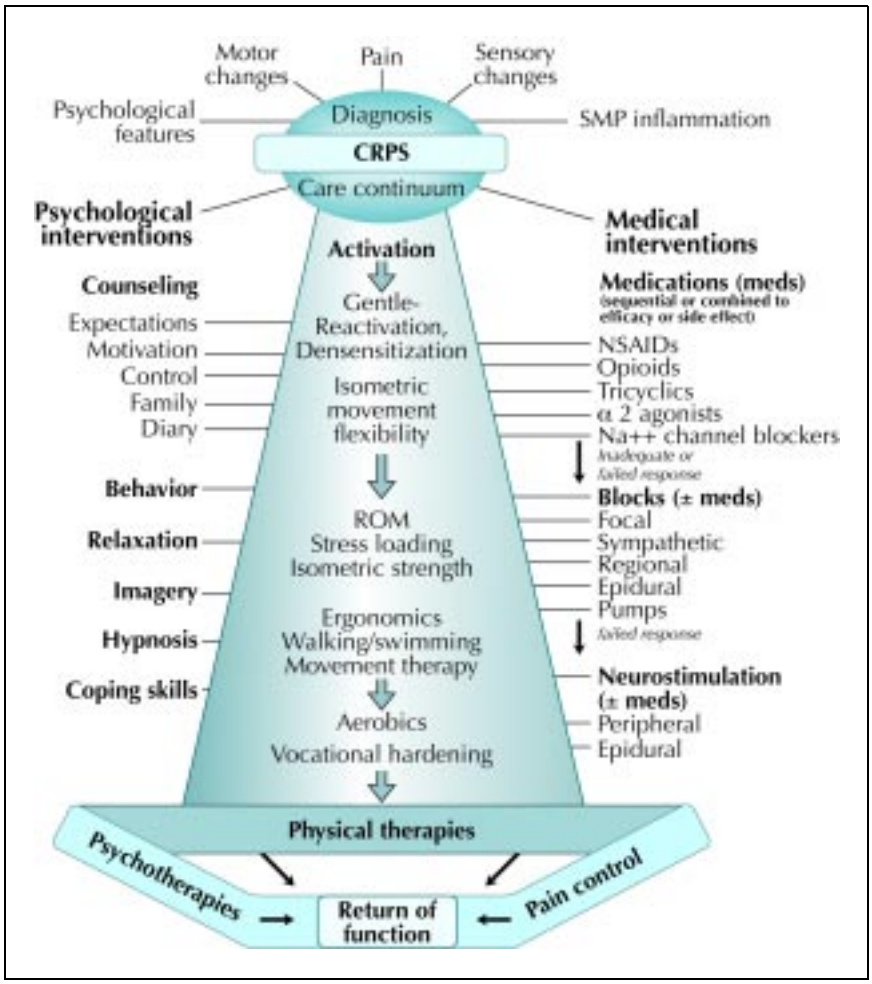

Figure 2. Essential levels of physical therapy governed by progress that is limited only by the degree of pain and successful treatment of pain by using the different pharmacologic or interventional modalities. CRPS—complex regional pain syndrome; NSAIDs—nonsteroidal anti-inflammatory drugs; ROM—range of motion; SMP—sympathetic-maintained pain. (*From* Stanton-Hicks *et al.* [57•]; with permission.)

For intractable, severe pain, epidural infusions may be of greater help. Epidural catheters are implanted to be used for longer time periods under strict sterile conditions, and usually are placed under fluoroscopy. A combination of local anesthetic with opioid is used for infusion. Stanton-Hicks *et al.* [57•] selected bupivacaine as a longer-acting local anesthetic to be used in combination with fentanyl/morphine epidurally. Controlled, randomized trials are still needed to demonstrate efficacy.

Early initiation of physical therapy is of great importance, starting with gentle reactivation and movement of the extremity, and elimination of the phobia from the movement. Immobilization of the extremity may contribute significantly to the pathogenesis of CRPS-I [7]. Isometric strengthening, then achievement of good range of motion and isotonic strengthening are essential. Later, aerobic conditioning and movement therapies with normalization of use of the extremity are a goal of physical therapy [58] (Fig. 2).

Pharmacologic agents, although frequently used alone, failed to demonstrate consistent usefulness in the treatment of CRPS-I. Of the anticonvulsants and membrane stabilizers, phenytoin may be of benefit [59], gabapentin may be a promising agent [60], and mexiletine is an oral lidocaine analogue that has demonstrated significant inhibition of neuropathic pain [61].

Nifedipine and other calcium channel blockers have been shown to be promising but were studied in small groups of patients with CRPS-I [62]. Tricyclic antidepressants and selective serotonin reuptake inhibitors are effective in CRPS-I; the former may have some effectiveness in chronic cases [57•]. Tricyclics were recommended for use as first-line agents for most of the neuropathic pain syndromes, including CRPS-I [63]. Other medications used are corticosteroids, capsaicin, calcitonin, alpha-adrenergic drugs, nonsteroidal anti-inflammatory drugs, and opioids with variable success [13,57•].

Neuromodulation is a good additional therapy for the late stages of CRPS-I (Fig. 3). Calvillo *et al.* [63] measured pain intensity 36 months after implantation of either spinal cord or peripheral nerve stimulator and found significant decrease in pain intensity when compared with controls. In addition, consumption of analgesics decreased an average of 50% [63]. Others also found good pain relief using either of those two techniques [64]. Results from our center confirmed significant improvement of quality of life measures (Mekhail NA *et al.*, Paper presented at the 9th World Congress on Pain in Vienna, Austria, 1999) and in

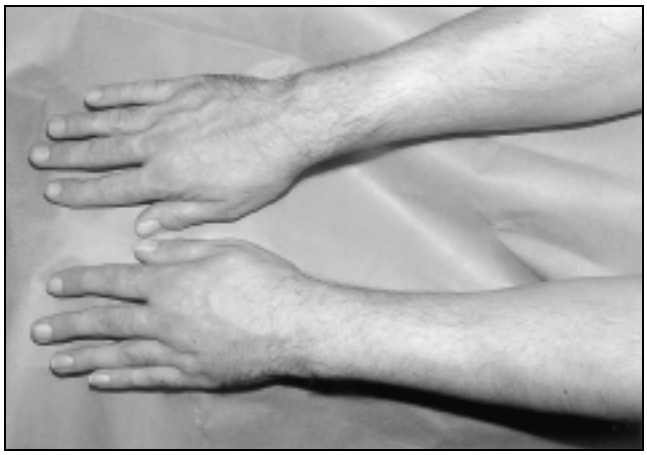

Figure 3. Same patient as in Figure 1, after spinal cord stimulator implantation in the cervical epidural space. Notice the left hand and forearm are normal as compared with the right.

activities of daily living (Stanton-Hicks M *et al.*, Paper presented at the 9th World Congress on Pain in Vienna, Austria, 1999) in more than half of the patients treated with either spinal cord or peripheral nerve stimulation.

Conclusions

Complex regional pain syndrome type I is infrequently associated with a variety of malignant conditions. It might represent a part of paraneoplastic syndrome. Careful evaluation for overt malignancy is warranted in patients with CRPS who have no evident inciting trauma or illness that explained the CRPS phenomenon. Diagnosis of CRPS is based primarily on the clinical picture and response to sympathetic blockade. A multidisciplinary approach to treat CRPS is mandatory to achieve both pain relief and functional restoration. Main elements of treatment include physical therapy and rehabilitation, behavioral therapy, and measures to relieve pain that include mainly sympathetic blocks, continuous infusion analgesia, and spinal cord stimulation. Other adjuvant medications include clonidine, calcium channel blockers, tricyclic antidepressants, and anticonvulsants. The prognosis of CRPS is very favorable if the multidisciplinary treatment is applied as early as possible.

References and Recommended Reading

Recently published papers of particular interest are highlighted as:

- • Of special interest
- •• Of outstanding interest

1. Orlemans HM, Oostendorp RAB, deBoo T, *et al.*: **Signs and symptoms in complex regional pain syndrome type 1/Reflex sympathetic dystrophy: judgment of the physician versus objective measurement.** *Clin J Pain* 1999, **15:**224–232.
2. Stanton-Hicks M, Janig W, Hassenbusch S, *et al.*: **Reflex sympathetic dystrophy: changing concepts and taxonomy.** *Pain* 1995, **63:**127–133.
3. Bruehl S, Harden RN, Galer BS, *et al.*: **External validation of IASP diagnostic criteria for complex regional pain syndrome and proposed research diagnostic criteria.** *Pain* 1999, **81:**147–154.
4. Galer BS, Bruehl S, Harden N: **IASP diagnostic criteria for complex regional pain syndrome: a preliminary empirical validation study.** *Clin J Pain* 1998, **14:**48–54.
5. Harden RN, Bruehl S, Galer BS, *et al.*: **Complex regional pain syndrome: are the IASP diagnostic criteria valid and sufficiently comprehensive.** *Pain* 1999, **83:**211–219.
6. Veldman PHJM, Reynen HM, Arntz IE, Goris RJA: **Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients.** *Lancet* 1993, **342:**1012–1016.
7. Allen G, Galer BS, Schwartz L: **Epidemiology of complex regional pain syndrome: a retrospective chart review of 134 patients.** *Pain* 1999, **80:**539–544.
8. Geertzen JHB, deBruijn-Kofman AT, deBrujin HP, *et al.*: **Stressful life events and psychological dysfunction in complex regional pain syndrome type 1.** *Clin J Pain* 1998, **14:**143–147.
9. Sieweke N, Birklein F, Riedl B, *et al.*: **Patterns of hyperalgesia in complex regional pain syndrome.** *Pain* 1999, **80:**171–177.
10. Cline MA, Ochoa J, Torebjork E: **Chronic hyperalgesia and skin warming caused by sensitized C nonciceptors.** *Brain* 1989, **112:**288–296.
11. Burnstock G: **A unifying purinergic hypothesis for the initiation of pain.** *Lancet* 1996, **347:**1604–1605.
12. Yasuda JM: **Guanithidine for reflex sympathetic dystrophy.** *Ann Pharmacother* 1994, **28:**338–341.
13. Walker SM, Cousins MJ: **Complex regional pain syndromes: including "Reflex Sympathetic Dystrophy" and "Causalgia."** *Anesth Intensive Care* 1997, **25:**113–125.
14. Oppenheimer A: **The swollen atrophic hand.** *Surg Gynecol Obstet* 1938, **67:**446–454.
15. Michaels R, Sorber JA: **Reflex sympathetic dystrophy as a probable paraneoplastic syndrome: case report and literature review.** *Arthritis Rheum* 1984, **27:**1183–1185.
16. Goldberg E, Dobransky R, Gill R: **Reflex sympathetic dystrophy associated with malignancy.** *Arthritis Rheum* 1985, **28:**1079–1080.
17. Ku A, Lachmann E, Tunkel R, Nagler W: **Upper limb sympathetic dystrophy associated with occult malignancy.** *Arch Phys Med Rehabil* 1996, **77:**726–728.
18. Bremer C: **Shoulder-hand syndrome: a case of unusual ethiology.** *Ann Phys Med* 1966, **9:**168–171.
19. Medsger TA, Dixon JA, Garwood VF: **Palmar fasciitis and polyarthritis associated with ovarian carcinoma.** *Ann Intern Med* 1982, **96:**424–431.
20. Malane SL, Sau P, Benson PM: **Epitheloid hemangioendothelioma associated with reflex sympathetic dystrophy.** *J Am Acad Dermatol* 1992, **26:**325–328.
21. Baer AN, Phillips RM: **Pancreatic carcinoma and palmar fasciitis [letter].** *Ann Intern Med* 1983, **99:**411–412.
22. Taggart AJ, Iveson MI, Wright V: **Shoulder-hand syndrome and symmetrical arthralgia in patients with tubo-ovarian carcinoma.** *Ann Rheum Dis* 1984, **43:**391–393.
23. Amin R: **Bilateral pancoast's syndrome in a patient with carcinoma of the cervix.** *Gynecol Oncol* 1986, **24:**126–128.
24. Prowse M, Higgs CMB, Forrester-Wood C, McHugh N: **Reflex sympathetic dystrophy associated with squamous cell carcinoma of the lung.** *Ann Rheum Dis* 1989, **48:**339–341.
25. Pancoast HK: **Superior pulmonary sulcus tumour.** *JAMA* 1932, **99:**1391–1396.
26. Derbekyan V, Novales-Dias J, Lisbona R: **Pancoast tumor as a cause of reflex sympathetic dystrophy.** *J Nucl Med* 1993, **34:**1992–1994.
27. Regan M, Foley-Nolan D, McCarthy G, Coughlan RJ: **Reflex sympathetic dystrophy associated with large cell lung carcinoma [abstract].** *Ann Rheum Dis* 1989, **48:**1031.
28. Mackinnon SE, Holder LE: **The use of three-phase radionuclide bone scanning in the diagnosis of reflex sympathetic dystrophy.** *J Hand Surg* 1984, **9A:**556–563.

29. Taylor LP, Posner JB: **Phenobarbital rheumatism in patients with brain tumor.** *Ann Neurol* 1989, **25:**92–94.
30. Horton P, Gerster JC: **Reflex sympathetic dystrophy syndrome and barbiturates. A study of 25 cases treated with barbiturates compared with 124 cases treated without barbiturates.** *Clin Rheumatol* 1984, **3:**493–499.
31. Reynolds EH: **Chronic antiepileptic toxicity: a review.** *Epilepsia* 1975, **16:**319–352.
32. Summers CL, Shahi M: **Epitheloid sarcoma presenting as the reflex sympathetic dystrophy syndrome.** *Postgrad Med J* 1987, **63:**217–220.
33. Ameratunga R, Daly M, Caughey DE: **Metastatic malignancy associated with reflex sympathetic dystrophy.** *J Rheumatol* 1989, **16:**406–407.
34. Youmans JR, Ishida WY: **Tumors of peripheral and sympathetic nerves.** In *Neurologic Surgery,* edn 2. Edited by Youmans JR. Philadelphia: WB Saunders Co.; 1982:3299–3315.
35. Olson WL: **Reflex sympathetic dystrophy associated with tumor infiltration of the stellate ganglion.** *J Royal Soc Med* 1993, **86:**482–483.
36. Schurmann M, Gradl G, Andress HJ, *et al.*: **Assessment of peripheral sympathetic nervous function for diagnosing early post-traumatic regional pain syndrome type 1.** *Pain* 1999, **80:**149–159.
37. Merskey H, Bogduk N: *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of the Pain Terms,* edn 2. Seattle: IASP Press; 1994.
38. Sandroni P, Low PA, Ferrer T, *et al.*: **Complex regional pain syndrome I (CRPS I): prospective study and laboratory evaluation.** *Clin J Pain* 1998, **14:**282–289.
39. Gulevich SJ, Conwell TD, Lane J, *et al.*: **Stress infrared telethermography is useful in the diagnosis of complex regional pain syndrome, type 1 (formerly reflex sympathetic dystrophy).** *Clin J Pain* 1997, **13:**50–59.
40. Poplawski ZJ, Wiley AM, Murray JF: **Posttraumatic dystrophy of the extremities.** *J Bone Joint Surg* 1983, **65A:**642–653.
41. Riedel A, Braune S, Kerum G, *et al.*: **Quantitative sudomotor axon reflex test (QSART): a new approach for testing distal sites.** *Muscle Nerve* 1999, **22:**1257–1264.
42. Kozin F, Ryan LM, Carrerra GF, Soin JS: **The reflex sympathetic dystrophy syndrome (RSDS). III. Scintigraphic studies, further evidence for the therapeutic efficacy of systemic corticosteroids and proposed diagnostic criteria.** *Am J Med* 1981, **70:**23–30.
43. Demangeat JL, Constantinesco A, Brunot B, *et al.*: **Three-phase bone scanning in reflex sympathetic dystrophy of the hand.** *J Nucl Med* 1988, **29:**26–32.
44. Goldsmith DP, Vivino FB, Eichenfield AH, *et al.*: **Nuclear imaging and clinical features of childhood reflex neurovascular dystrophy: comparison with adults.** *Arthritis Rheum* 1989, **32:**480–485.
45. Lynch ME: **Psychological aspects of reflex sympathetic dystrophy: a review of the adult and pediatric literature.** *Pain* 1992, **49:**337–347.
46. • Monti DA, Herring CL, Schwartzmann RJ, Marchese M: **Personality assessment of patient with complex regional pain syndrome type 1.** *Clin J Pain* 1998, **14:**295–302.

Good discussion on coexisting psychological and psychiatric issues in patients with CRPS.

47. Holthusen H, Stanton-Hicks M, Arndt J: **Sympathetic block does not reduce acute vascular pain in humans.** *Anesth Analg* 1998, **86:**588–590.
48. Wang JK, Kenneth AJ, Ilstrup DM: **Sympathetic blocks for reflex sympathetic dystrophy.** *Pain* 1985, **23:**13–17.
49. Price D, Long S, Wilsey B, Rafii A: **Analysis of peak magnitude and duration of analgesia produced by local anesthetic injected into sympathetic ganglia of complex regional pain syndrome patients.** *Clin J Pain* 1998, **14:**216–226.
50. Mays KS, North WC, Schnapp M: **Stellate ganglion blocks with morphine in sympathetic type pain.** *J Neurol Neurosurg Psychiatry* 1981, **44:**189–190.
51. Fine PG, Ashburn MA: **Effects of stellate ganglion block with fentanyl on post-herpetic neuralgia with a sympathetic component.** *Anesth Analg* 1988, **67:**897–899.
52. Arias LM, Bartowski R, Schwartzmann RJ, *et al.*: **Sufentanyl stellate ganglion injection in the treatment of refractory reflex sympathetic dystrophy.** *Reg Anesth* 1989, **14:**90–92.
53. Ford SR, Forrest WH, Eltherington L: **The treatment of reflex sympathetic dystrophy with intravenous regional bretylium.** *Anesthesiology* 1988, **68:**137–140.
54. Hanna MH, Peat SJ: **Ketanserin in reflex sympathetic dystrophy. A double blind placebo controlled cross-over trial.** *Pain* 1989, **38:**145–150.
55. Vanos DN, Ramamurthy S, Hoffman J: **Intravenous regional block using ketorolac: preliminary results in the treatment of reflex sympathetic dystrophy.** *Anesth Analg* 1992, **74:**139–141.
56. Linchitz RM, Raheb JC: **Subcutaneous infusion of lidocaine provides effective pain relief for CRPS patients.** *Clin J Pain* 1999, **15:**67–72.
57. • Stanton-Hicks M, Baron R, Boas R, *et al.*: **Complex regional pain syndrome: guidelines for therapy.** *Clin J Pain* 1998, **14:**155–166.

Provides a comprehensive guide in the diagnosis and management of CRPS.

58. Chaturvedi SK: **Phenytoin in reflex sympathetic dystrophy.** *Pain* 1989, **36:**379–380.
59. Mellick GA, Mellick LB: **Gabapentin in menagement of reflex sympathetic dystrophy.** *J Pain Symptom Manage* 1995, **10:**265–266.
60. Dejgard A, Petersen P, Kastrup J: **Mexilitine for treatment of chronic painful diabetic neuropathy.** *Lancet* 1988, **1:**9–11.
61. Prough DS, McLeskey CH, Poehling GG, *et al.*: **Efficacy of oral nifedipine in the treatment of reflex sympathetic dystrophy.** *Anesthesiology* 1985, **62:**796–799.
62. Galer BS: **Neuropathic pain of peripheral origin: advances in pharmacologic treatment.** *Neurology* 1995, **45:**S17–S25.
63. Calvillo O, Racz G, Didie J, Smith K: **Neuroaugmentation in the treatment of complex regional pain syndrome of the upper extremity.** *Acta Orthop Belg* 1998, **64:**57–63.
64. Stanton-Hicks M, Salamon J: **Stimulation of the central and peripheral nervous system for the control of pain.** *J Clin Neurophysiol* 1997, **14:**46–62.