35 y/o man complains of diffuse burning pain in the left arm and hand for the last 6 months. He recalls spraining his left wrist while playing volleyball. His left hand feels colder than the right and his fingertips are blue. He is a recently divorced high-profile executive.

Questions:

What is the differential diagnosis of pain in this patient?

Pain accompanied by burning and temperature change in this patient is most likely due to complex regional pain syndrome (CRPS). The differential diagnosis may also include the following:
1. Peripheral neuropathy
2. Soft tissue injury
3. Vascular insufficiency (Raynaud's disease)
4. Nerve entrapment syndrome (carpal tunnel syndrome)
5. Brachial plexopathy

Over the years, CRPS has been referred to as reflex sympathetic dystrophy (RSD), causalgia, sympathetically maintained pain (SMP), and chronic peripheral pain syndrome. The term CRPS was introduced in 1994 by the International Association for the Study of Pain subcommittee on taxonomy. It is subdivided into CRPS type I (formerly described as RSD) and CRPS type IT (formerly described as causalgia).


What is complex regional pain syndrome (CRPS)?

CRPS is characterized by pain with sudomotor or vasomotor instability. CRPS is triggered by noxious stimuli (type I) or by nerve injury (type II). It is not limited to the distribution of a single peripheral nerve and is disproportionate to the inciting event.

Reflex sympathetic dystrophy (RSD), causalgia, algodystrophy, Sudeck’s atrophy, and various other conditions are all grouped under CRPS. This diagnosis is better descriptive of the wide range of clinical signs and symptoms and the complexity of the pathophysiology responsible for the clinical picture.


Define alldynia, hyperalgesia, hyperesthesia, and dysesthesia.

Allodynia - Pain caused by a stimulus that normally does not provoke pain (i.e., touching with a cotton swab)

Hyperalgesia - An increased response to a stimulus that is normally painful (i.e., increased response to pinprick)

Hyperesthesia - Increased sensitivity to a stimulus either due to a diminished threshold or an increased response to stimuli that are normally recognized. Hyperesthesia includes both alldynia and hyperalgesia

Dysesthesia - An abnormal sensation that is unpleasant to the patient. It may be either spontaneous or evoked (i.e., lumbar radiculopathy)

What are the possible etiologies of CRPS?

CRPS may follow relatively minor trauma with or without nerve injury. Causes leading to CRPS include the following:

- Injuries to peripheral tissues (e.g., fractures, dislocations, and postoperative state)
- Inflammatory conditions (e.g., fasciitis, tendonitis, bursitis, and arthritis)
- Immobilization as a result of injury or cast application
- Peripheral nerve injury resulting from direct compression or ischemia (e.g., brachial plexopathy, postherpetic neuralgia, and nerve root injury)
- Central nervous system insults (e.g., head injury, ischemia, and brain tumor)
- Spinal cord lesions
- Idiopathic


Explain the pathophysiology of the development of CRPS.

Several hypotheses have been postulated but none can explain all the findings and the varying responses to treatment in these patients. These hypotheses include the following:

- Abnormal discharges in sympathetic and nociceptive afferents produced by trauma
- Sensitization of peripheral sensory receptors produced by sympathetic hyperactivity
- Formation of ephapses (artificial synapses) after peripheral nerve injury
- Spontaneous neuronal ectopy at the site of demyelination or axonal injury
- Central reorganization of pain processing
More than one sequence of events likely take place in a patient, giving rise to a mixed clinical picture. Finally, the psychologic component and neuromodulation cannot be discernibly separated.


**Define sympathetically maintained pain (SMP) and sympathetically independent pain (SIP).**

The pain that is maintained by sympathetic innervation or circulating catecholamines is defined as SMP. It describes a pain mechanism, rather than clinical syndrome. Therefore, by definition, patients with complex regional pain syndrome (CRPS) who report pain relief after a sympathetic block (e.g., stellate ganglion block) have SMP. Conversely, pain conditions that show features of sympathetic overactivity, yet fail to respond to sympathetic blocks, are described as SIP.


What is central pain? How will you differentiate central pain from CRPS?

Central pain is regional pain initiated or caused by a primary lesion or dysfunction in the central nervous system, usually associated with abnormal sensitivity to temperature and to noxious stimulus. Central pain, also referred to as deafferentation pain, is a difficult pain syndrome to treat because the pathophysiology is not well understood. Regional pain not relieved by peripheral nerve blocks, either sympathetic or somatic, is more likely to be central pain. Central pain may be associated with various neurologic symptoms and signs such as monoparesis, hemiparesis, or paraparesis.


Is the social history of this patient relevant to the development of chronic pain?

In patients with complex regional pain syndrome (CRPS), the disproportionate pain and dysfunction, and the absence of clear pathogenesis and pathophysiology have led to examination of potential psychologic etiology. Also noted is the fact that as the CRPS progresses, patients' personality measures such as Minnesota Multiphasic Personality Inventory (MMPI) profiles tend to resemble those of patients experiencing chronic pain and psychologic distress as evidenced by hypochondriasis, depression, and hysteria scales. Certainly, stress has been implicated in increasing sympathetic outflow. The literature suggests that the presence of psychologic disorders, particularly anxiety and depression, may predispose the patient to the development of CRPS.


How will you work up CRPSs type I and II?

CRPS is diagnosed clinically with a detailed history and physical examination. As it is a clinical diagnosis of exclusion, other specific conditions that could account for the degree of pain and dysfunction must be ruled out. Objective signs are variable but almost universally include loss of function of the affected part due to pain. Allodynia and hyperalgesia are extremely common. Change in temperature and sweating may vary depending on the stage of the disease. Several diagnostic studies may aid in the diagnosis of CRPS but are seldom pathognomonic.

Quantitative sweat test may show excessive sweating, and thermography may demonstrate abnormal heat regulation and disparity in temperature between affected and normal regions. Radiologic studies may reveal patchy osteoporosis in early stages. Triple-phase bone scan using technetium Tc 99m may show increased periarticular uptake in the affected extremity. However, negative triple-phase bone scan results do not rule out CRPS. Thermographic, radiologic, or scintigraphic findings can be nonspecific and should be correlated with the clinical findings. Positive diagnostic sympathetic blocks can confirm the sympathetically mediated component of CRPS.


Where is the stellate ganglion located? What are the anatomic landmarks used in the stellate ganglion block?

The stellate ganglion is formed by the fusion of the inferior cervical and the first thoracic ganglia. It usually measures 2.5 by 1.5 by 0.5 cm and lies between the base of the transverse process of the seventh cervical vertebra and the neck of the first rib. It is situated behind the carotid sheath, ventral to the longus colli muscle, behind the vertebral artery, and lateral to the body of the vertebra. The vertebral.
subclavian, inferior thyroid, and the first intercostals arteries are in close proximity to the ganglion and so is the recurrent laryngeal nerve. The left pleura is 1 to 2 cm below it, whereas the right pleura is in closer proximity.

The landmarks used in the stellate ganglion block are the jugular notch of the sternum, the sternocleidomastoid muscle, the cricoid cartilage, and Chassaignac tubercle. In a supine patient with neck extended, a mark placed approximately 3.5 cm from the midline along the jugular notch and the same distance above the clavicle should overlie the transverse process of the seventh vertebra and the medial border of the sternocleidomastoid muscle. This marking is further confirmed by palpating the cricoid cartilage, which lies at the level of the sixth cervical vertebra, and the anterior tubercle on the vertebral transverse process, which is the most prominent tubercle in the neck (Chassaignac tubercle).


**What is the pharmacologic management of CRPS?**

Sympathetically maintained pain (SMP) of CRPS is treated with the drugs that deplete norepinephrine from the sympathetic nerve terminals. Oral sympatholytic agents include phenoxybenzamine, prazosin, and terazosin. Topical clonidine, a selective a-2 agonist, has been successfully used to treat SMP. Tricyclic antidepressants have been effective in approximately half the number of patients and have been recommended as first-line agents. Other drugs that have been successfully used to treat CRPS are anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine, and topiramate), local anesthetics such as lidocaine and mexiletine, calcitonin, corticosteroids, and high-dose opioids. Anecdotal reports suggest that methadone (opioid with anti-N-methyl-D-aspartate receptor effect) has been more effective than other opioids. Long-term intrathecal morphine has been reported to produce analgesic effects in CRPS. Nonsteroidal antiinflammatory drugs have also been used successfully.


**What is the role of intravenous regional block (Bier method) in diagnosis and treatment of CRPS?**

Intravenous regional block (Bier method) with guanethidine, reserpine, bretylium, and phentolamine has been used to achieve temporary sympatholytic effect and relieve sympathetically maintained pain (SMP) of CRPS. Intravenous guanethidine and reserpine have been reported to relieve pain in more than 50% of patients as compared with a control group in one study. However, guanethidine and reserpine are not commercially available in the United States. The combination of bretylium and lidocaine is more effective than lidocaine alone. a-adrenergic blockade with intravenous phentolamine is a sensitive test to identify patients with SMP. Phentolamine has been used as a predictor agent before more invasive sympathetic blocks.


**What is the role of spinal cord stimulation (SCS) and surgical sympathectomy?**
Surgical, chemical, or radiofrequency sympathectomy produces short-term pain relief but long-failure of sympathectomy may be due to regeneration of ipsilateral nerves or reinnervation from the contralateral sympathetic nerves. SCS is an effective treatment for the pain of complex regional pain syndrome (CRPS), including recurrent pain after surgical or radio frequency sympatholysis. Epidural SCS is a simple procedure and carries low morbidity.
