Can hepatocellular carcinoma cause complex regional pain syndrome?

Volkan Yilmaz¹, Taner Dandinoglu², Ozgur Dandin³, Murat Karadeniz⁴, Uygar Teomete⁵

¹Mevki Military Hospital, Department of Physical Medicine and Rehabilitation, Ankara, Turkey
²Bursa Military Hospital, Department of Physical Medicine and Rehabilitation, Bursa, Turkey
³Bursa Military Hospital, Department of General Surgery, Bursa, Turkey
⁴Çorlu Military Hospital, Department of Physical Medicine and Rehabilitation, Tekirdağ, Turkey
⁵University of Miami, Department of Radiology, Miami, Florida, USA

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Abstract

Complex regional pain syndrome (CRPS) is a disorder which has variable clinical manifestations. CRPS type I is characterized by an initiating noxious situation, like a crush or soft tissue injury; or by immobilization, such as a tight cast. CRPS type II is characterized by the existence of a defined nerve damage. Among widespread causative factors soft tissue traumas and fractures had been reported as the most common reason of CRPS. Primary pathologies of the central nervous system and malignancies would also be seen as a causative factor. Because of complex presentations in cancer patients, signs of CRPS may be unrecognised or misdiagnosed. These cases may present before malignancy or as a complication of primary neoplasia. In this report an unusual and different CRPS patient associated with hepatocellular carcinoma is presented.

Keywords: Complex regional pain syndrome, malignancy, carcinoma, hepatocellular

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Introduction

Complex regional pain syndrome (CRPS) is a painful condition associated with motor, sensory, autonomic and bone abnormalities [1]. The most common reasons of CRPS are accepted as tissue trauma, fractures and surgery [2]. Nevertheless CRPS is not only related with these factors.

CRPS is diagnosed using diagnostic Budapest criteria requiring both symptoms and observed informations regarding sensory, vasomotor, motor, sudomotor and motortrophic disturbances. Additional diagnostic tools (laboratory or radiological) provide insufficient basis for the diagnosis of CRPS, but these tools are still used to exclude other pathologies (infection or unresolved fracture etc.). Pain, limited joint movement and sympathetic dysfunction are the main findings which suggest the presence of CRPS [3,4]. Punctate radiographic lucencies in the affected areas on X-ray, and increased activity in bone scintigraphy with Tc 99m-MDP (Technetium-99m Methylene Diphosphonate) supports the diagnosis of CRPS [5]. Because of disease’s complex nature a combined interdisciplinary and personalized management is recommended. The primary aim of disease’s treatment includes reducing pain, preserving or restoring function, and improving patient’s quality of life [6]. Anti-inflammatory therapy and increasing motor function by physiotherapy may be used for reducing inflammation. Normalisation of motor and vasomotor function, pain reduction and psychological interventions might also be needed. In this report an unusual and different CRPS patient associated with hepatocellular carcinoma is reported. Similar reports related with malignancies like cases with colon carcinoma [7], lung carcinoma [8], pancreas carcinoma [9], lymphoma [10] and ovarian carcinoma [11] were previously presented but to the best of our knowledge, this is the first work that presents a CRPS patient associated with hepatocellular carcinoma.

Case

A 68-year-old male patient was admitted to the outpatient clinic with 2 months history of pain, swelling and numbness in the left foot which have become apparent nearly one month before the diagnosis of upper gastrointestinal bleeding due to hepatocellular carcinoma. In addition to alcoholic cirrhosis and upper gastrointestinal system bleeding, medical records revealed chronic obstructive lung disease and hypertension besides daily alcohol consumption for nearly 40 years (given up 6 months ago). There was no history of any trauma or other

[Corresponding Author: Taner Dandinoglu, Bursa Military Hospital, Department of Physical Medicine and Rehabilitation, Bursa, Turkey]
possible reasons of CRPS. Physical examination revealed allodynia, hyperpathia, edema and bright skin color which is evident in left ankle and dorsum of the left foot, temperature of the skin was warm on the left side. The left ankle range of motion was reduced due to severe pain. His general and systemic examination including the abdomen was unremarkable with no sign of chronic liver disease. LANSS (Leeds Assessment of Neuropathic Symptoms and Signs) scale score which is frequently used to determine which mechanisms (neuropathic and/or nociceptive) dominantly contribute to pain was 20 (LANSS score ≥ 12 means neuropathic mechanisms are likely to be contributing to the patient’s pain). Reflexes were intact. Serum total protein, albumin, gamma-glutamyl transferase, lactate dehydrogenase, alkaline phosphatase, total bilirubin, haemoglobin, platelet, high sensitive C reactive protein were as follows: 4.47 gr/dl (6.4-8.3 gr/dl), 2.35 gr/dl (3.5-5.5 gr/dl), 102 U/L(10-49 U/L), 261 U/L (0-248 U/L), 184 U/L (30-120 U/L), 1.25 gr/dl (0.2-1 gr/dl), 7.8 gr/dl (13.6-17.2 gr/dl), 80000/microL(156000-373000/microL), 42.57U/L (0-3 U/L), respectively. Other laboratory tests were in normal range. The X-ray of the left foot exposed slight punctate osteoporosis (fig. 1a). Results of nerve conduction study performed in bilateral lower extremities were all normal range. The arterial and venous doppler examination of the lower extremities was also normal. There were multiple masses located in right, left and caudate lobes of the liver (fig. 1b). The three phase bone scanning with technetium 99m revealed increased activity in left foot (fig. 1c). MRI imaging of the affected limb revealed skin thickening and effusion of adjacent joints. According to Budapest criteria patient was diagnosed with CRPS, after excluding other reasons including metastasis of bone due to hepatocellular carcinoma. To normalize sensation, minimize edema caused by CRPS and increase patient’s independence, after treatment including chemotherapy followed by complete surgical resection of tumoral lesions, an early physical therapy program was performed. Oral tramadol/paracetamol (37.5/325 mg tablet) combination that was given after a gastroenterologist consultation (two times daily), provided adequate responses for the neuropathic complaints and decreased spontaneous exacerbations. After 3 weeks of tramadol/paracetamol regime, the drug was stopped for successful control of neuropathic complaints. A considerable reduce in edema and pain was observed after 2 months of physical therapy including desensitisation, passive stretching, isometric exercises, mild active isotonic exercises, mild strength training and whirlpool. LANSS scale score was only 2 after therapy.

**Discussion**

Different CRPS cases associated with malignancies have previously been reported primarily involving the upper extremity. It has been thought that CRPS may present as a paraneoplastic syndrome in some malignancies. CRPS has also found to be associated with meningiomas, primary and metastatic cerebral tumors, pancreatic carcinoma, and pancoast tumors of the lung [12-19].

For decades sympathetic nerve hyperactivity is thought to be responsible for most of the clinical findings in CRPS and exact mechanism for the pathogenesis is still not clearly understood. Multiple factors including inflammation, dysfunction within sympathetic and somatosensory nervous system and cortical factors are thought to be responsible for the generation and continuation of symptoms [20]. Locally released neuropeptides and vasoactive amines were found to be effective on skin color and temperature changes [21]. Autonomic dysregulation may be an important factor for CRPS, noradrenaline release from sympathetic nerve terminals was found to be responsible for the generation of inflammatory mediators studied in a rat tibial fracture model [22]. Otherwise in the acute phase, reduced sympathetic outflow to skin vasoconstrictors was found to be responsible for the warm and swollen limb. Also cold skin observed in chronic phase was associated with
increased sympathetic nervous system (SNS) receptor sensitivity rather than an increase in sympathetic activity [23].

The pathogenesis of malignancy associated CRPS may slightly be different from other cases. Circulating humoral factors may also contribute to the sensitive nature of progress. Humoral factors produced by tumor cells may act as a stimulating factor and rearrange the activity of SNS [15]. Noradrenaline release from postganglionic sympathetic neurons stimulates the release of prostaglandins and it has been claimed that neoplasia induced adenosine triphosphate (ATP) outflow may act as a co-transmitter with noradrenaline. Besides its effects on prostaglandins, noradrenaline also decreases the threshold of peripheral mechanoreceptors and enhances abnormal firing in peripheral sensory nerves which is possibly responsible for formation of spontaneous pain and hyperaesthesia observed in malignancy associated CRPS[24-26]. ATP release directly from tumor cells may take part in generation of pain, via this complex mechanisms [27, 28]. Recent studies suggested that tumor cells can directly influence monocyte/macrophage–osteoclast differentiation through the release of soluble factors which promote osteoclastogenesis. Osteoclastic activation and osteoclast cell generation modulated by the receptor activator of nuclear factor-kappaB ligand-osteoprotegerin (RANK-RANKL-OPG) system (induced by humoral mediators) may also contribute to malignancy associated CRPS pathogenesis and osteolysis [29-31]. RANKL/RANK signaling organizes the scheme of osteoclasts from their precursors as well as their activation and survival in normal bone remodeling and in a variety of pathologic conditions. OPG preserves the bone from increased bone resorption by binding to RANKL [32]. Two challenging part of the disease; pain and punctate osteoporosis in malignancy related CRPS may strongly be associated with these factors and their dramatic effects. Exact pathogenesis is still unclear and further studies are required for demonstrating the real mechanisms underlying malignancy related CPRS.

In this report, we want to emphasize and highlight an uncommon cause of CRPS and tried to raise awareness about malignancy associated CPRS. Malignancy associated cases may present before malignancy or as a complication of a neoplasia [28]. Spontaneous development of prolonged or excessive pain, color, temperature changes and swelling in the affected area should remind the possibility of CRPS in patient with suspected malignancy symptoms. Every patient should be assessed carefully and if needed further evaluated for the exclusion of other possible underlying pathologies. An early physical therapy program planned right after diagnosis may prevent patient from challenging complications caused by CRPS. Also in uncertain malignancy patients an early identification of CRPS without a meaningful predisposing factor can support diagnosis of primary disease.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


