International Medical Case Reports Journal

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CASE SERIES

Complex Regional Pain Syndrome in Cancer Cases: Current Knowledge and Perspectives

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Background: Complex regional pain syndrome (CRPS) is a disabling painful disorder caused by many different and poorly understood mechanisms. It often affects the distal limbs and usually happens as consequence of a trauma. Its severity can remarkably affect patients' quality of life. When this painful complication happens in a cancer patient, the impact may be exponential. To date, there is limited knowledge of the surrounding circumstances of CRPS cases in this population.

Methods: We present two clinical cases of patients diagnosed with cancer-related pain presenting with symptoms and signs compatible with CRPS. In one case, CRPS was attributed to direct tumor nerve compression, and it responded successfully to an interventional pain procedure. The second case was associated with a Zoster infection in an immunocompromised cancer patient. Patient responded to multidisciplinary pain management strategies. Additionally, we conducted a literature review to investigate the coexistence of cancer pain and CRPS and suggest some pathophysiology mechanisms of action.

Results and Discussion: Literature reviewed and potential pathophysiology mechanisms are simultaneously explored in terms of classification, etiopathology, evidence, challenges, and future scientific directions.

Conclusion: Comorbid CRPS can impact negatively in cases of cancer pain by affecting their diagnosis and treatment. Further studies are necessary to elucidate how these two conditions present together and how they can be better addressed.

Keywords: causalgia, CRPS, cancer

Introduction

Complex regional pain syndrome (CRPS) is a debilitating clinical syndrome characterized by severe neuropathic pain disproportionate to the inciting event, accompanied by sensory, motor, trophic, and autonomic symptoms. This disabling disorder has an estimated incidence of 5.5–29 cases per 100,000 person-year.[1–3] Pain associated with CRPS has a severe negative impact on a patient's quality of life. The pathophysiology of CRPS remains poorly understood. Many peripheral and central mechanisms have been described including exaggerated inflammation, neuronal plasticity and hypersensitization, and dysfunction of the sympathetic nervous system.[4] There is consensus that its treatment must be based on active, intensive, and interdisciplinary approaches.[5,6] From a medical point of view, conventional analgesics, anti-neuropathic drugs, co-adjuvants medication and interventional options including percutaneous nerve procedures and implanted neurostimulation devices are listed as the main options.[7]

Although CRPS is classically seen after musculoskeletal benign pathologies, some patients with cancer do develop CRPS. This co-morbidity may represent a major challenge for both the patient and for the healthcare team. For the patient, cancer-related pain and frailty may be significantly increased by CRPS severe pain and functional disability.

Received: 15 December 2023
Accepted: 2 May 2024
Published: 18 May 2024

For the oncology team, CRPS poses challenges in its diagnosis and its management. CRPS is typically diagnosed by non-oncologists (eg, orthopedists, rheumatologists, physiatrists, pain physicians). The lack of early identification and delayed initiation of adequate treatment might lead to negative outcomes.[8]

There are several scenarios where cancer patients might develop CRPS, such as direct nervous injury from malignancies, paraneoplastic syndromes, cancer treatment-related neuropathy, and non-cancer origin.[6,9–11] We present two clinical examples of this coexistence along with a literature review to explore the current knowledge about CRPS in the cancer population. From the initial approach to specific treatments, our objective is to emphasize the unique and distinct aspects that must be considered in this context compared to CRPS in the general population, from the perspective of a specialized cancer pain service.

Methods and Literature Search

We report two compelling cases from the Cancer Pain Clinic, McGill University Health Center in Montreal, Canada. In these two cases, CRPS was diagnosed in patients referred for evaluation of a cancer-related pain to our clinic. Consent from both patients to report their case and use the images for publication purposes were duly obtained and documented in their charts. Institution approval was not required to publish anonymous case details.

We conducted an exhaustive literature search in PubMed, Scopus, and Embase (Elsevier) for articles and reviews published in English linking CRPS and cancer. The following terms were used: "complex regional pain syndrome", "CRPS", "reflex sympathetic dystrophy", "causalgia", *and* "cancer", "malignancy", "tumor".

We designed a blinded peer-review selection process to identify studies related to topics using Rayyan®. Following title and abstract screening, the blind was turned off, and any disagreements between reviewers were resolved through discussion. The inclusion criteria encompassed studies involving CRPS in the cancer population, including case reports, case series, or conference abstracts. Articles were excluded if they were duplicated or written in languages other than English.

The information recorded for each publication included author and publication year, study type, number of cases reported, initial presentation and affected organ, disease course, cancer type, the association between cancer and CRPS, as well as the outcomes.

Case 1

A 50-year-old female patient diagnosed with stage IV left-sided Pancoast tumor syndrome presented to our cancer pain clinic with severe neuropathic pain in her left arm and hand. The pain extended from the left hand throughout the entire forearm in a non-dermatomal distribution. The patient also reported severe pain upon light touch and with movements of the left hand. Upon inspection, the ipsilateral arm appeared paler and colder than the right arm. Severe restriction in the movement of the left hand, wrist and elbow was evident, significantly impacting the patient's performance status, general physical activity, and quality of life. During examination, we observed left hand pallor, spontaneous tremor, mild muscle and skin atrophy, and decreased temperature (Figure 1). Brush allodynia and hyperalgesia were present over the five fingers, dorsal and ventral hand, and forearm. Additionally, the patient presented with a left-sided Horner's syndrome.

The team diagnosed her with a Pancoast syndrome featuring pain at her ipsilateral upper limb fulfilling the Budapest criteria[12] for CRPS type II. Before our consultation, the patient had received methadone, oxycodone, pregabalin and carbamazepine yet the pain remained poorly managed.

We performed an ipsilateral T2 sympathetic chemo-neurolysis with phenol as adjunct to drug therapy (Figure 2). One week after the procedure, the patient reported a reduction in pain exceeding 80%, which persisted for several months. Consequently, she was able to discontinue her breakthrough analgesics. In conjunction with intensive individualized physiotherapy, her hand movement and quality of life had significantly improved.

This case represents an example of CRPS type II resulting from direct tumor invasion of nerve structures. Successful multidisciplinary pain management was achieved through the integration of pharmacological treatment, interventional pain management and individualized physiotherapy.

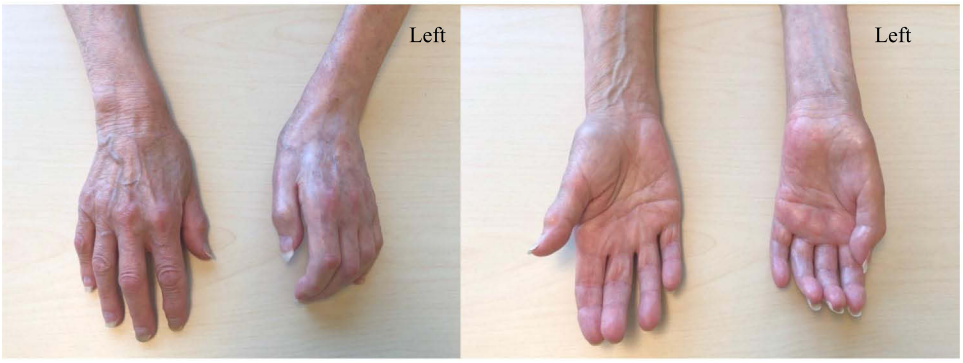

Figure 1 Left hand presenting with trophic changes of skin.

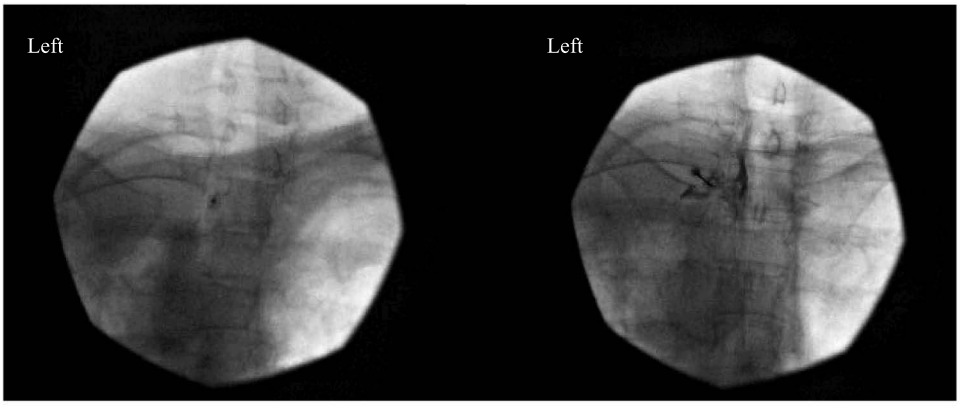

Figure 2 Left-sided T2 sympathetic neurolysis. On the left side, an antero-posterior view of the fluoroscopically guided procedure to place the tip of a 22G spinal needle onto the ventrolateral aspect of the T2 vertebral body. On the right side, an injection of 1mL of contrast media confirmed the lack of spread into intra-spinal structure and intravascular uptake. 3mL of 0.25% bupivacaine and 3mL of 8% phenol were injected.

Case 2

A 43-year-old male, treated with immunotherapy and status post-autologous stem cell transplantation for multiple myeloma, was referred to our cancer pain clinic with pain in his left hand. One month prior to consulting our cancer pain clinic, the patient had been diagnosed with disseminated herpes zoster infection, which manifested with skin lesions at multiple sites across the body. Upon initial interview, the patient complained with constant severe pain in the left hand and arm corresponding to the C8-T1 dermatomes. The pain was described in clear neuropathic terms (DN4+) and was accompanied by severe tactile allodynia, abnormal sweating, swelling and warmth in the affected limb. Physical examination revealed edema, increased temperature, and decreased range of motion of the left hand and arm. Additionally, allodynia to brush and spontaneous tremor were observed in the affected limb. These symptoms and signs satisfied the Budapest criteria for diagnosing CRPS, probably of type II.

The patient was on 600 mg/day of pregabalin with limited benefit. He agreed to a trial of adding night-time 50 mg nortriptyline, along with tramadol 37.5 mg plus acetaminophen 325 mg as breakthrough medication. Interventional options including selective nerve root block and stellate ganglion block were offered, but the patient declined. The patient accepted a referral for intensive physiotherapy. Two months later, the pain had improved with reduced severity, but mild numbness and stiffness persisted in his left arm and hand. Analgesics remained unchanged, alongside individualized physiotherapy. Eight months after initial consultation, the pain had completely disappeared, all analgesics had been discontinued, and the patient had regained full function of the left arm.

Literature Search Results

Only case reports were found from our literature search and none of them were presented as case-control study. Table 1 presents the literature from our search.

Due to the low quality and methodological heterogeneity found in existing literature, no quantitative analyses were performed. Cases reported were presented, not by evidence level but by how CRPS and cancer were intertwined.

The different themes we identified included 1. Cancer directly causing CRPS; 2. CRPS as a complication of cancer treatment; and 3. CRPS impacting cancer diagnosis (Table 1). Figure 3 illustrates the interconnection between CRPS and cancer within each theme.

Table 1 List of Publication on Complex Regional Pain Syndrome in Cancer Patient

Author (Year)	Type of Article	N. of Patients	Affected Organ	Type of Cancer	Association	Outcome
1. Cancer directly causing CRPS						
Derbekyan et al 1993,[11]	Case report	1	Unilateral upper extremity	Pancoast tumor	from tumor invasion was the initial symptom of cancer	Complete resolution after cancer treatment
Bertrand et al 2004,[13]						No data on outcome
Olson W.1993,[14]		2		Pancoast tumor;[1] Neuroectodermal cancer[2]		No data on outcome;[1] improved after radiation therapy[2]
Inoue et al 2021,[15]		1		Metastatic breast cancer		Pain improved after rehabilitation
Gofiță et al 2019,[9]			Bilateral upper extremities	Metastatic basal cell carcinoma	CRPS as a paraneoplastic syndrome	Pain improved after initiation of analgesics
2. CRPS as a complication of cancer treatment						
Massard et al 2009,[10]	Case report	4	Unilateral lower extremity	Metastatic renal cancer	CRPS from systemic treatment	Complete resolution despite continuation of cancer treatment
Perez de Amezaga et al 2022,[16]		1		Neuroendocrine tumor with hepatic metastasis		Pain improved with analgesic medication and discontinuation of cancer treatment
Magnol et al 2019,[17]				Metastatic renal cancer		Complete resolution despite continuation of cancer treatment
Meeks et al 2022,[18]				Acute lymphoblastic leukemia		Complete resolution after multimodal analgesic medication
Chi et al 2016,[19]				Endometrial cancer and Lynch syndrome	CRPS from surgery for cancer	Pain improved after spinal cord stimulation
3. CRPS impacting cancer diagnosis						
Beytemur et al 2019,[20]	Case report	1	Unilateral lower extremity	Osteoblastoma of talus	CRPS was the presenting symptom of tumor	Complete resolution after cancer treatment
Ku et al 1996,[21]		2	Unilateral upper extremity	Breast cancer;[1] Lymphoma[2]	CRPS was the first symptom of metastasis;[1] CRPS was the symptom of new malignancy[2]	Improvement of hand and shoulder function after cancer treatment
Soliz et al 2016,[22]		1		Prostate cancer	CRPS led to the diagnosis of widespread metastatic cancer	Initial response to sympathetic block
Nazemi et al 2022,[23]		1	Unilateral lower extremity	Glomus tumor and Myxofibrosarcoma	Misdiagnosed tumor as CRPS	Pain improved after tumor decompression

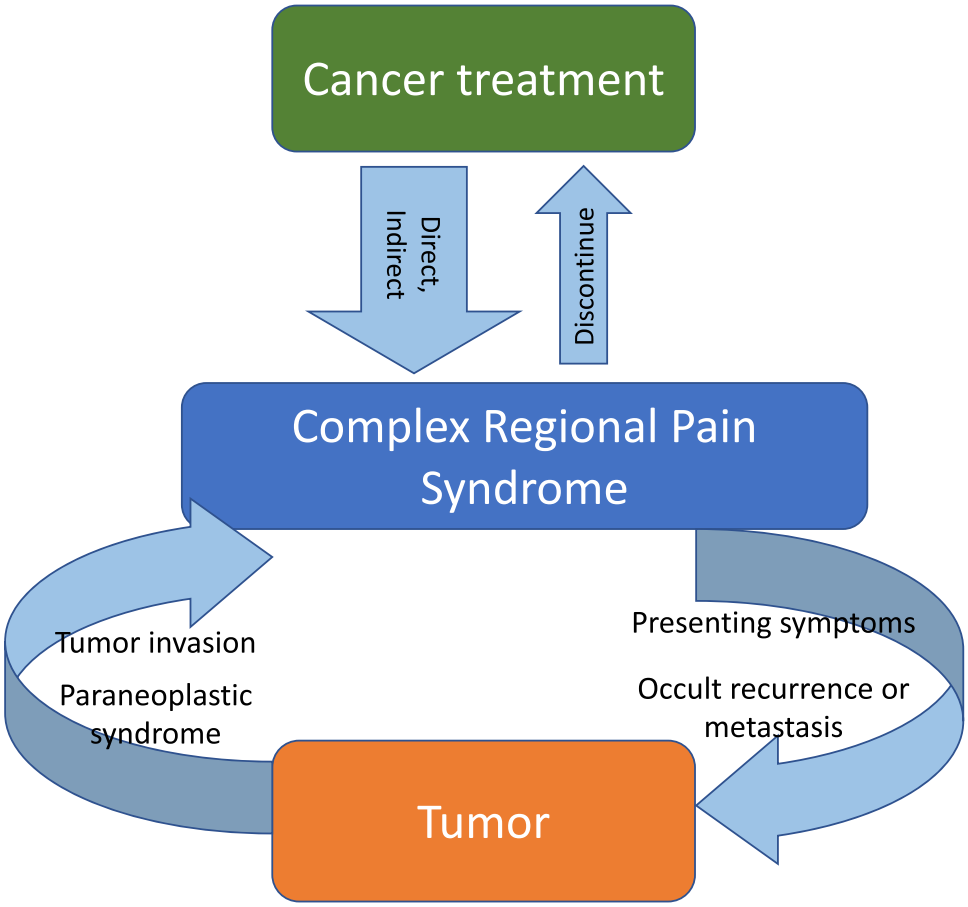

Figure 3 Impact of CRPS on cancer population.

Discussion

CRPS Caused by the Tumor

In our first case report, the patient developed CRPS due to direct neurovascular invasion of a Pancoast tumor. The pain was successfully managed following medical management and a sympathetic plexus neurolysis. Our case is comparable to most of reported cases linking cancer and CRPS. Pancoast syndromes are commonly associated with CRPS.[11,13,14] A Pancoast tumor, also known as a superior pulmonary sulcus tumor, can cause CRPS by directly damaging the ipsilateral cervical and upper thoracic neurovascular bundle, as well as the cervico-thoracic sympathetic chain.[11] As a result, patients may develop CRPS either as a complication of direct tumor invasion following a cancer diagnosis or as a presenting symptom indicating undiagnosed cancer, occult recurrence, or metastasis, or even as a complication following tumor surgery in the cervico-thoracic area.[11,13,14] Olson W[14] reported a patient developed CRPS in the right upper extremity following surgery for a Pancoast tumor. Histological study revealed infiltration of the Pancoast tumor into the right stellate ganglion. Subsequently, pain was significantly alleviated after a right stellate ganglionectomy. CRPS can also result from a tumor invading somatic nerve structures, as reported by Inoue R et al.[15] In their study, a patient diagnosed with metastatic breast cancer developed CRPS type II due to metastases to subclavian lymph nodes infiltrating the adjacent brachial plexus.

In addition to direct tumor invasion, CRPS can also be an indirect consequence of tumors through paraneoplastic syndrome. Gofita CE et al[9] described a case of a patient diagnosed with bilateral CRPS type I as a result of paraneoplastic syndrome associated with metatypical basal cell carcinoma in upper back with pulmonary metastasis.

CRPS Caused by Anti-Cancer Treatment

In our second case report, we depicted the development of CRPS as a consequent of anti-neoplastic treatment. In this case, the patient developed immunocompromised state due to systemic anti-neoplastic treatment, which led to the reactivation of a Zoster infection. Herpes virus reactivation is a common occurrence among patients receiving systemic anti-neoplastic treatment.[24] The uniqueness of this case lies in the patient presenting with features consistent with CRPS following herpes zoster infection. Several case reports have been published the association between CRPS and herpes zoster infection since 1901.[25,26] Berry et al[26] conducted a prospective observational study on patients diagnosed with herpes zoster infection and concluded that CRPS is not uncommon in these individuals, particularly when the distal extremity is involved. However, the underlying pathophysiology remains uncertain and specific treatment is not well demonstrated. In our second case, we can explain why the patient developed a zoster infection after becoming immunocompromised, but we have yet to understand why this postherpetic neuralgia progressed into full-blown CRPS.

Furthermore, CRPS can arise as a direct consequence of systematic anti-neoplastic treatment. The use of Everolimus has been suggested as a risk factor.[10,16,17] The reason why Everolimus can trigger CRPS remains unclear.[17] Similar cases of CRPS have been observed in patients receiving Sirolimus, another mTOR inhibitor, in renal transplant patients.[27] Several hypotheses have been proposed, including metabolic side effects such as hyperglycemia and dyslipidemia, as well as potential bone marrow injury leading to osteoporosis, which may triggering CRPS.[10,16,17]

In cases where the association between CRPS and systemic anti-neoplastic treatment has been established, discontinuation of the anti-neoplastic therapy resulted in amelioration of CRPS symptoms, potentially hindering and impeding the successful outcome of anti-cancer therapy.[16,17]

CRPS can also be a consequence of direct nerve damage from surgery and/or radiation therapy required to treat localized cancers. A surgical trigger is not uncommon in cases of CRPS diagnosed in the general population;[12] therefore, it is not unlikely to assume that oncological surgery can also lead to this complication.[19,28]

Impact of CRPS on Tumor Diagnosis

CRPS can lead to the diagnosis of cancer, relapse and/or metastatic disease.[20,21] Any tumor invading neural structures may potentially cause symptoms compatible with CRPS. Ku A et al[21] reported two cases of patients with a history of breast cancer and thyroid cancer in clinical remission who presented to their clinic with clinical upper extremity CRPS. These patients were eventually diagnosed with recurrent metastatic breast cancer and secondary primary lymphoma after undergoing prolonged misguided treatment and hospitalization for CRPS. Soliz L et al[22] also reported a similar case where a patient admitted to a rehabilitation unit developed symptoms of CRPS type I, ultimately leading to the diagnosis of occult wide spread metastatic prostate cancer.

The impact of CRPS on tumor diagnosis is particularly important among cancer survivors. Epidemiological studies recommend that clinicians should avoid excessive screening in patients with a history of low risk of cancer. However, cancer survivors who spontaneously develop CRPS should be investigated carefully with suspicion of the growth of a new primary tumor or relapse of previous cancer.[29,30]

We believe that neoplasm should be considered as a potential differential diagnosis, particularly in cases of CRPS type I with atypical clinical presentations, such as the absence of a clear inciting event, bilateral symptoms, or symptoms predominantly affecting proximal organs.[9,23,29]

Providing the Appropriate CRPS Treatment in the Oncological Population

Poorly managed pain is linked with poor health outcomes, particularly in the cancer population.[31] Our literature review revealed significant heterogeneity in CRPS treatment approaches within this population (Table 1), suggesting the need for further studies addressing specific approaches for cancer patient with CRPS.

Our second case report is an exemplary illustration of effective multidisciplinary CRPS management, underscoring the importance of clinical recommendations for CRPS management. Several studies have shown better outcome in CRPS management with a multidisciplinary approach to address every aspect of biopsychosocial nature of pain.[32,33] However, several limitations in cancer patients can impede the multidisciplinary management of CRPS. For example, cancer

patients often suffer from other non-pain symptoms such as nausea and vomiting, shortness of breath, cachexia, fatigue, and higher psychological distress such as depression, fear, and anxiety.[28,34]

This excellent outcome in our second case report also emphasizes the importance of early detection and management of CRPS, with the prognosis showing a resolution rate of 74% in the first year, decreasing to 36% after 6 years.[35]

Cancer patients may be followed by multiple different specialists, including but not limited to oncologists, surgeons, physiatrists, and palliative care physicians. Therefore, it is paramount that each professional involved in the care of cancer patient is aware of this unique painful syndrome and provides early diagnosis and prompt management, including referral to a specialized pain clinic.[36,37]

In selected cases, CRPS can be the first presentation of undiagnosed, recurrence or metastatic disease.[22] From this perspective, an early diagnosis could significantly impact prognosis and decision-making in cancer treatment.[22] Malignancy should always be excluded in a patient presenting with atypical symptoms of CRPS or in patients with a history of cancer or other constitutional red-flag symptoms.

Another important consideration when managing CRPS in cancer patients is the possibility of drug interactions with anti-neoplastic treatments. The pharmacological treatment of CRPS sometimes requires discussion with the oncology team, as some recommended options may adversely affect cancer outcomes and the morbidity associated with cancer treatment. For example, prednisone and bisphosphonates are pharmacological options for acute CRPS.[38,39] It is advisable to discuss these options with the oncology team, given the controversial interaction between corticosteroids and immunotherapy, and the possibility that bisphosphonate may already be part of the oncology systemic therapy.[40] This emphasizes the importance of multidisciplinary management of CRPS in oncology patients.

Sympathetically Independent Pain

We could not find any evidence on the prevalence of CRPS types I and II in the cancer population, likely due to the ambiguity in making a clear diagnosis whether there is neural structure damage and the scarcity of reports on this condition. However, the clinical differentiation may not be relevant when constructing the treatment plan. The presence of clinical signs suggesting abnormal activation of the sympathetic nervous system can be more significant. Diagnosis of sympathetically maintained pain may prompt the indication of percutaneous procedures, such as sympathetic block, to interrupt it.[36]

When considering interventional treatment for cancer patients, it is important to carefully assess the indication, as the prognosis and other non-pain symptoms may significantly predominate and influence clinical decision-making. These patients may also have absolute or relative contraindications for such procedures, including patient refusal, coagulation disorders, receiving anticoagulation treatment, and severe frailty.[41,42] This is particularly important since cancer patients are commonly on anticoagulants and/or may be too frail. These factors could make sympathetic block or other interventions more challenging and, if the pain is sympathetically independent, potentially less or not effective.

Based on our experience, we propose this flowchart (Figure 4) to enhance the multidisciplinary management of CRPS. We emphasized the importance of multimodal and interdisciplinary treatment in CRPS, especially in oncology patient. Additionally, it is crucial to rule out recurrence in cancer survivor or new metastasis in oncology patients presenting with CRPS symptoms. As discussed earlier, it is important to differentiate sympathetically maintained pain to guide potential interventions, whether sympathetic or somatic blocks. Drawing from our experience, pamidronate infusion appears to be even more effective in this population. Therefore, we suggest offering a trial of pamidronate infusion if not contraindicated. While the management depicted in the figure requires further evidence to support, it can serve as a general guide aimed at improving patient outcomes.

Limitation

The authors acknowledge the limitation arising from the absence of systematic analytic results presented in this manuscript. The narrative literature search yielded only case reports, which were not relevant to each other, rendering them insufficient to construct a homogenous data source for proper analysis.

We proposed several unique aspects of CRPS in the oncological population that require special attention. However, existing evidence is limited, necessitating further research on this topic to establish evidence-based clinical management.

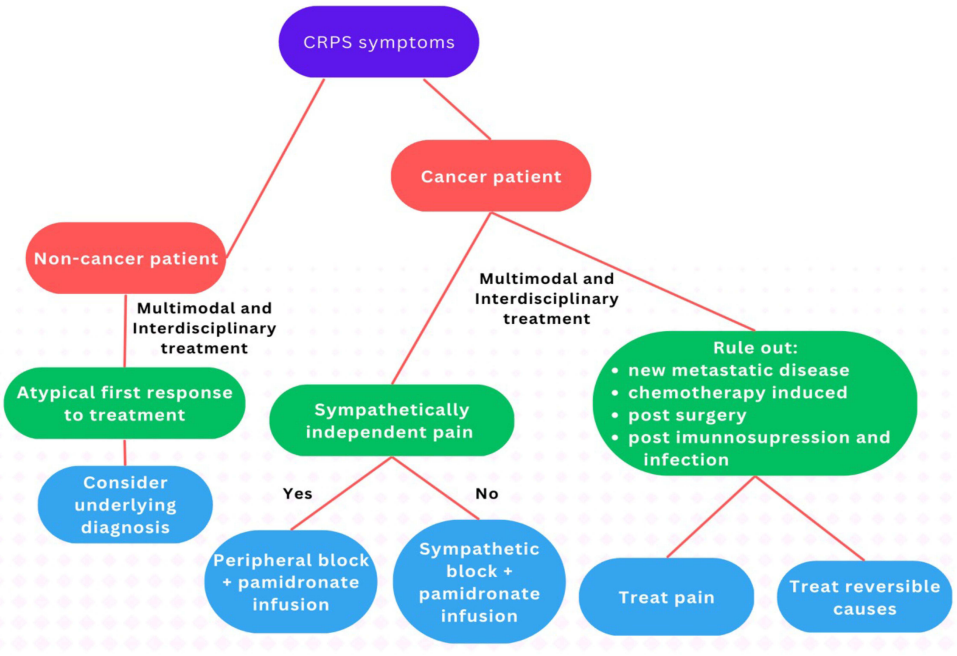

Figure 4 Proposed algorithm to manage CRPS in cancer patients.

Conclusion

CRPS is a devastating pain syndrome that imposes significant health consequences on the patient. When CRPS occurs in the context of active cancer, these consequences can become exponential. Several unique aspects differentiate CRPS in the cancer population from non-cancer population, warranting further attention. Both neoplasms and anti-neoplastic treatments can affect CRPS, and vice versa. Given the intricate nature and severity of diagnosing and treating CRPS in cancer patient, patient-centered multidisciplinary management is crucial.

Acknowledgments

Authors would like to thank the unconditional support of the Louise and Alan Edwards Foundation to all clinical, academic and research activities at the MUHC Cancer Pain Clinic.

Disclosure

The authors report no conflicts of interest in this work.

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