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Case Report

Undetected Myxofibrosarcoma in a Patient Diagnosed with Long Standing Complex Regional Pain Syndrome; A Case Report

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ABSTRACT

Case presentation: A 61-year-old woman diagnosed with long standing, therapy resistant CRPS-1 fourteen years prior was referred to our center for assessment on her wish to have her limb amputated, due to recent worsening of the symptoms. A soft tissue lesion was detected on the affected limb and she was sent back to her primary hospital for further study of this lesion and exclusion of an alternative diagnosis. The biopsies were inconclusive, and no underlying causes were determined for her symptoms in her primary hospital. Thus, back at our center, elective amputation of the affected limb was carried out.

Results: Post-operative histology of the amputated limb revealed a myxofibrosarcoma, a rare malignant tumor. Corresponding dissemination study, follow-up and treatment was conducted. The patient died from metastatic complications 17 months post-amputation.

Conclusion: This case exemplifies how various confusing factors can lead to misdiagnosis of a malignant tumor. Low incidence of sarcomas, a previous CRPS-1 diagnosis of 14 years and inconclusive biopsies conducted in a primary hospital led to this misdiagnosis. Primary amputation was appropriate due to a dysfunctional limb, and size and local invasion degree of the tumor. The most important take away lessons in this case report are the importance of never discarding a neoplasm in presence of a growing mass even in the case of other possible causes and the fact that it merits a thorough diagnostic procedure, as well as the recommendation to conduct diagnostic tests in reference hospitals specialized in the relevant techniques.

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Introduction

Complex Regional Pain Syndrome type I (CRPS-I) is characterized by pain disproportionate to any inciting and sensory, vasomotor, sudomotor, and motor/trophic changes [1]. It may develop after a trauma or spontaneously. The pain can be invalidating and sometimes the affected limb becomes nonfunctional [2]. Diagnosis is based on patient history and physical examination, according to Budapest criteria [1, 3]. It is a diagnosis of exclusion. The mean age at onset is 37.5 years and the duration of the syndrome ranges from 1 month to 46 years [2, 4]. Two years after onset of CRPS-1 64% of patients still fulfill the diagnostic criteria [5]. Treatment of CRPS-1 is multidisciplinary,

including exercise therapy, psychological support and regional pain management [4]. Amputation of the affected limb is arising as last resort treatment, although controversial [2, 6]. This case report focuses on the discovery of myxofibrosarcoma (MFS) in the amputated limb of a woman diagnosed with long standing, therapy resistant CRPS-I.

Case Report

A 61-year-old Caucasian woman, diagnosed with CRPS-1 of her right calf, was referred to the University Medical Centre Groningen (UMCG) by her rehabilitation physician for a second opinion on her wish to have her limb amputated. The pain started 14 years before, after an ankle sprain, followed by immobilization. Pain was disabling and unyielding

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to treatment. When assessed at the UMCG, the patient claimed that in the last 7 months pain had worsened following an episode of inflammation and erythema in the calf. She reported pain reaching 9/10 on Visual Analogue Scale and needed walking aids for ambulation. In her medical history rheumatoid arthritis and a knee arthroscopy stood out. In our hospital she was evaluated by a multidisciplinary group (physiotherapist, psychologist, anesthesiologist, vascular surgeon and rehabilitation physician) experienced in elective amputation for long standing therapy resistant CRPS-I [7, 8].

Physical examination revealed a grade II-III lymphedema from toes to the knee. A soft tissue lesion, 2 cm diameter, solid, well demarcated, ulcerated in the center and surrounded by a halo of dark skin was found in the mid-third of the calf (Figure 1.1, 1.2, 1.3). Allodynia was present distal of midcalf. Severely limited ROM of ankle and foot, hyperhidrosis, warm skin and abnormal nail growth were present. The previously diagnosed CRPS-I was doubted based on the lesion. The patient was sent to her primary hospital to rule out underlying causes for her symptoms. An excision biopsy was conducted at that hospital. The pathological report showed “mostly ulceration with granulation tissue” and “vital tissue was insufficient for adequate diagnostics”, but it didn’t specify whether the site of the biopsy was the ulcer or the mass. Based on this report the CRPS-I diagnosis was accepted, and an elective amputation was considered a suitable option. Together with the patient, the decision-making process was carried out, and with her informed consent a transfemoral amputation was performed [7, 8].



Figure :1.1

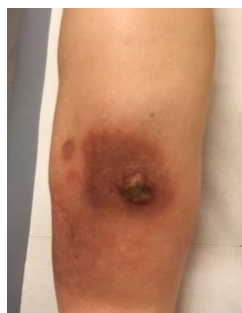


Figure: 1.2



Figure: 1.3

Figures 1.1, 1.2, 1.3: The affected limb at the time of the consultation with the team in UMCG. There is a noticeable skin lesion and distal lymphedema.

Results

The pathologic analysis of the limb revealed a tumor, a grade 2 MFS with invasion of muscle and bone tissue, with a maximum diameter of 7cm. Additionally “findings typical for CPRS-I such as skin orthokeratosis, dermis and subcutaneous fat edema and chronic muscle

atrophy” were present [9]. Surgical resection margins were free by 10 cm. Tumor dissemination was investigated, using chest CT and abdomen MRI. No distant metastases were found initially and radiotherapy wasn’t deemed necessary. Shortly after, the patient was fitted with a prosthesis and walking in the community. Five months after the amputation the patient reported pain in the residual limb that prevented her from using the prosthesis. One month later a groin, jaw and chest CT revealed metastases in all these locations. Together with the patient and her family it was decided to have radiotherapy as palliative treatment. The patient continued receiving palliative care until her death, 17 months after the anatomopathological diagnosis of the MFS.

Discussion

The interest of this case report lies especially in the diagnostic process, and how various confusing factors led to misdiagnosis. MFS is an unusual type of sarcoma [10]. Sarcomas are a rare group of malignant tumors which represent less than 1% of all adult malignancies. Normally MFS presents as a gradually enlarging, painless mass in soft tissues or bone, causing occasionally pain, paresthesia and edema. They frequently appear in the extremities [11, 12]. Given their rarity, they may be confused with lipomas, cysts, panniculitis or osteochondral lesions [13]. In CPRS-I, although rare, ulcers, edema or infections have been reported as complications, so it’s understandable that in the presence of a 14-year standing CRPS-I the development of a soft tissue lesion was initially interpreted as a sequelae related to CRPS-I [2, 14]. On the other hand, the lesion warranted further investigation, ideally with X-ray and MRI imaging. The biopsy should be a core needle biopsy, conducted in a reference center and evaluated by a specialized pathologist rather than in a referring institution, since in the latter a higher error rate has been detected, possibly related to the heterogeneous nature of the histology of MFS, which can lead to misdiagnosis [11, 12, 15]. In our patient, the preoperative biopsy was an incisional biopsy, interpreted by a general pathologist, in a referring center. In light of the results, it would probably have been best to request a new biopsy. No complementary imaging studies were requested since it was thought that they would have no additional value. However, an MRI could have shown a “high signal tail” phenomenon, which appears to be moderately sensitive and specific for MFS [12, 13].

Another point for debate regarding case report would be the appropriateness of the transfemoral amputation in light of the MFS diagnosis. The usual treatment for MFS is a limb salvage excision accompanied by perioperative local radiotherapy [10, 16, 17]. However, MFS exhibits an aggressive loco-regional behavior, and with the limb salvage treatment local recurrence (LR) rates are high (16-31% in 3.5 years) as well as secondary amputation for LR treatment (17-20%) [10, 12, 15]. Metastasis rates are also high (16-30%) [10, 12, 13, 16, 17]. In one study a positive margin rate of 43% was found, and microscopic tumor could be found even 29mm from the surgery margins [12]. Occasionally (8%) a primary amputation is conducted [12]. Mitotic activity and tumor necrosis are predictors for metastatic recurrence, and increasing tumor size, histologic grade, and tumor attachment to bone have been suggested as negative prognostic indicators [10, 13, 16]. Positive or close resection margins may also predict LR rates, though unclear [10,12,16]. Due to all of this, some authors suggest an aggressive initial limb salvage surgery, with surgical free margins ranging from 10-

50mm [12, 15, 16]. In the presented case, an elective transfemoral amputation was executed, with free surgical margins of 10 cm. Had a limb salvage surgery been done, there was little chance that the limb would have regained functionality because of the established lymphedema and limited ROM and allodynia.

Moreover, the tumor was large, with invasion of muscles and bone. Thus, it is quite possible that to secure free surgical margins a primary amputation would have been the chosen treatment. Even though the primary aim of this paper is not to discuss the indications of amputation as a treatment for CRPS-I, the decision deserves a brief discussion. Amputation as a treatment for longstanding therapy-resistant CRPS-1 has led to pain reduction and improvement in mobility of patients [2]. Additionally, patients with longstanding therapy-resistant CRPS-I who received an amputation had a better quality of life, had less pain and pain related disability, and were less depressed than patients with CRPS-I who had not been amputated [6, 8].

Lastly, this case poses the question as to whether the neoplasm could have been a complication of the CRPS-I. The association between CRPS-I and malignancies is unclear. Sarcomas are thought to arise de novo, but it has been suggested that chronic irritation, inflammation and lymphedema may induce development of a malignancy [11, 18]. CRPS-I is associated with an aberrant inflammatory response, with facilitation of neurogenic inflammation and up regulation of proinflammatory cytokines, which could theoretically lead to cell proliferation and tumor occurrence [18, 19]. As to the possibility of the CRPS-I being the presenting symptom of the neoplasm, it must be pointed out that some case studies describe a syndrome resembling CRPS-I as the first manifestation of a tumor [18, 20-22]. However, we hypothesize that in this particular case the CRPS-I and the neoplasm were independent events. It seems unlikely that the FMS was the initial trigger for development of CRPS-I, since the first CRPS-I symptoms dated from 14 years before the diagnosis of the FMS, which usually exhibits an aggressive loco-regional behavior with rapid growth.

Conclusion

Low incidence of sarcomas, a previous CRPS-1 diagnosis of 14 years and inconclusive biopsies led to this misdiagnosis. Primary amputation was appropriate due to a dysfunctional limb, and size and local invasion degree of the tumor. The most important take away lessons in this case report are the importance of never discarding a neoplasm in presence of a growing mass even in the case of other possible causes and the fact that it merits a thorough diagnostic procedure, as well as the recommendation to conduct diagnostic tests in reference hospitals specialized in the relevant techniques.

Competing interests

Not declared.

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Statement of Informed Consent

Informed consent was obtained from the patient for the publication of this case.

Abbreviations

CRPS-I:	Complex Regional Pain Syndrome type I
MFS:	Myxofibrosarcoma
UMCG:	University Medical Centre Groningen
ROM:	Range of movement
CT:	Computed tomography
MRI:	Magnetic resonance imaging
LR:	Local recurrence.

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