Case report

Efficacy of intramuscular clodronate in Complex Regional Pain Syndrome type I: description of a case located in the astragalus in a patient with psoriatic arthritis

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Abstract. Reflex sympathetic dystrophy or Complex Regional Pain Syndrome type I (CRPS I) is a painful regional disease with non-metameric topography, which shows extreme pathomorphological variability, from forms in which pain is the only clinical manifestation, to "pseudo-purulent" forms characterized by impressive local manifestations. The use of high doses of bisphosphonates in the treatment of CRPS I is confirmed in different publications which associate their efficacy with their specific biological properties and multiple actions at local level. This case report describes a case of CRPS I in the astragalus of a patient with psoriatic arthritis, successfully treated with intramuscular clodronate. (www.actabiomedica.it)

Key words: CRPS I, bisphosphonates, clodronate, psoriatic arthritis, Reflex Sympathetic Distrophy

Introduction

Reflex sympathetic dystrophy or *Complex Regional Pain Syndrome type I* (CRPS I) (1) is a painful regional disease with non-metameric topography, which can be associated with a series of local manifestations during its course, such as oedema, vasomotor and sudomotor changes, articular rigidity and osteoporosis, with dystrophic and atrophic changes as a possible outcome.

As a matter of fact, CRPS I shows extreme pathomorphological variability, from forms in which pain is the only clinical manifestation, to "pseudo-purulent" forms characterized by impressive local manifestations (2).

This syndrome is more frequent in the middle age group, between 40 and 60 years, with a higher incidence amongst females in a ratio which varies between 2:1 and 4:1 in different case histories. However, no age group appears to be exempt, including the paediatric one.

With regard to the incidence and prevalence of CRPS I, only a few data are available in the literature and not all are in agreement. One USA study revealed an annual incidence of 5.4/100,000 with a prevalence of 20.5/100.000 (3). Recently, data collected in the Netherlands revealed, however, an incidence of 26.2/100,000 persons per year (4) which is 5 times higher than that of the American study.

The latter study also reported a spontaneous resolution rate of 74% of cases even if this datum is rather controversial because recovery is very infrequent in patients who reach clinical observation.

Approximately half of the CRPS I cases refer to a trauma as the causing factor (3, 5). Other clinical situations can also be causing factors, such as myocardial infarction, hemiplegic syndromes and diabetes mellitus. However it is not possible to identify any related or causing factor or pathology in a percentage which varies between 10 and 26% of cases (6).

Uncertainties regarding the aetiology and consequently the pathogenesis of CRPS I are reflected in

the therapeutic approach. Indeed, there are around 60 different treatments proposed in the literature and biphosphonates are certainly some of the most studied drugs and appear to offer the best guarantees (7-18).

This case report describes a case of CRPS I in the astragalus of a patient with psoriatic arthritis, successfully treated with intramuscular clodronate.

It seemed useful to share this experience as it appears that no therapy with intramuscular bisphosphonate in CRPS I has ever been completely reported in the literature.

Clinical aspects

CRPS I has been known from long time. In 1766, Hunter identified its long-term complications and, in 1864, Mitchell gave it an accurate description, defining it as "causalgia". Lastly, Südeck described the radiographic aspects in 1900. Several different synonyms were coined over the years until in 1994 the IASP (International Association for the Study of Pain) defined it as "Complex Regional Pain Syndrome", divided into type I (referring to the classic reflex sympathetic dystrofy) and type II (incorporating causalgia) (1). The diagnostic criteria were defined at the same time and were subsequently revised and validated by Bruehl et al in 1999 (19).

The *"classic" or "complete" form* of CRPS I, despite being less frequent, shows typical clinical signs which are not always revealed in the "incomplete" forms, and which therefore require instrumental diagnostic supports in order to be confirmed.

The *typical form,* which most frequently affects the hands or feet, is usually differentiated into 3 stages, although not all authors agree on this classification (5):

- *first stage*: pain and swelling with marked functional impotence associated with changes in the skin trophism and adnexa and signs of vasomotor instability (pallor, erythrosis, subcyanosis); the oedema is subcutaneous, the skin is taut, thickened and shiny; the piliferous follicles tend to become sparse;
- *second stage* (from 3 to 6 months): the dystrophic changes prevail, with cold, shiny, hypoelastic skin, functional limitation with a loss of elasticity in the articular capsules and tendon sheaths; muscle contracture and hypotrophy are present;
- *third stage:* the atrophic aspects of the skin, subcutaneous tissue, muscles and capsules prevail, with irreversible changes.

Amongst the *incomplete or regional forms, transient osteoporosis of the hip, regional migratory osteoporosis and post-traumatic and non-traumatic bone marrow oedema syndrome* should be mentioned. These conditions, which share the finding of bone marrow oedema through MRI, do not correspond to the IASP diagnostic criteria and present clinical characteristics which distinguish them from classic CRPS I.

Pathogenesis

The pathogenesis, which over time has seen several hypotheses, does not recognize an universally accepted model. Over the years, the hypothesis of a hyperactivation of the sympathetic nervous system as the *primum movens* of CRPS I has declined, because it lacks neurophysiological confirmation, but apparently there is clinical evidence of a secondary activation of the sympathetic system (20, 21). However, the "*neurogenic phlogistic theory*", which suggests a direct sensitization of the nociceptors and the low-threshold mechanoreceptors by vasoactive substances released by the same peripheral endings, currently appears more credible (22). This would determine an increase in the permeability of the microcirculation, the prerequisite of both bone marrow oedema and subcutaneous oedema. This was supported by the detection, in the disease locations, of a high concentration of neuromediators and cytokines related to these events (23).

The sympathetic-mediated involvement and the vasoconstriction would however be reserved for the later phase of the disease (the "cold" phase). The "ultra-sensitivity" of the sympathetic nervous system could however be involved, according to some Authors, in maintaining the CRPS I (21).

In response to the insult, the tissue hypoxia would then induce a change in the capillary permeability followed by bone marrow oedema and the activation of

monocytes-macrophages capable of releasing local mediators which extend the changes in the microcirculation and the hyperalgesia. The hypoxic phenomena would then be responsible for the so-called "extra-osteoclastic" re-absorption mediated by the disintegration of the hydroxyapatite crystals due to the acid microenvironment and to the enzymatic lysis of the organic osseous component. The current hypothesis also states that CRPS represents a change in the central nervous system as well as at peripheral level and in this context, it has been demonstrated that a protracted peripheral change can alter the central nervous system response to pain (20, 24-28).

Table 1. Ways of administration and efficacy of bisphosphonates in algodystrophy

Devogelaer JP.	1988	Pamidronate	i.v.	Effective
Adami S.	1992	Clodronate	i.v., i.m., os	Equally effective
Adami S.	1997	Alendronate	i.v.	Effective
Varenna M.	2000	Clodronate	i.v.	Effective
Kubalek I.	2001	Pamidronate	i.v.	Effective
Muratore M.	2004	Clodronate vs neridronate	i.v.	Equally effective
Robinson JN.	2004	Pamidronate	i.v.	Effective
Varenna M.	2004	Neridronate	i.v.	Effective
Manicourt DH.	2004	Alendronate	x os	Effective
Gremaux V.	2007	Pamidronate	i.v.	Effective
Breuer B.	2008	Ibandronate	i.v.	Effective

Bisphosphonates and algodystrophy

The use of high doses of bisphosphonates in the treatment of algodystrophy is confirmed in different publications which associate their efficacy with their specific biological properties and multiple actions at local level.

Bisphosphonates would also have a contributing therapeutic in bone marrow oedema and pain, as well as in other joint diseases such as spondylarthritis and rheumatoid arthritis (29, 30).

Their mechanism of action in CRPS I, however, is still controversial (31) and different mechanisms have been suggested, such as a possible inhibitory effect on the disintegration of the hydroxyapatite crystals due to acidosis (32), a direct cytotoxic action on the medullary cell populations (inhibition of anaerobic metabolism, reduction of lactic acid, reduction of the pH-mediated nociceptive stimulation) (33), as well as blocking the release of the mediators of osteoclastic reabsorption by the monocytes-macrophages (34, 35). Clodronate, whose mechanism of action is clearly distinct from that of the aminobisphosphonates, could have a significant role in the treatment of CRPS (13).

Several publications demonstrating the efficacy of bisphosphonates have appeared in the literature over the years, some of which were meeting abstracts. Clodronate (36, 37), pamidronate (38-42), alendronate (43), neridronate (37, 44) and ibandronate (45) all seem to have a considerable efficacy and a good tolerability profile. A recent study with oral alendronate has also given encouraging results (Table 1) (46).

The need for a treatment easier than an intravenous therapy necessarily performed in a hospital setting, together with the substantial equivalence in terms of the bioavailability of intramuscular or intravenous administration of clodronate (47, 51) represented, along with the conviction that in the short/medium term the cumulative dose represents the critical factor, the rationale for this treatment proposal.

Clinical case

V.B. came to our attention in May, 2003 in a non-hospital based outpatient clinic for pain in the left ankle which was causing considerable limitations in his work as a forest ranger.

He referred two previous episodes, in May 2001 and December 2002, of fleeting pain in the right ankle which both resolved without therapies. In December, 2002, the patient noticed the onset of persistent, invalidating pain in the left ankle, accompanied with swelling. For work reasons, he continued to carry out his activities for some time, despite the pain. In April 2003, when admitted to a Rheumatology division, changes were noticed in the inflammatory markers (ESR 33 mm, CRP 10.4 mg/L) without changes in the parameters of skeletal remodelling. Whole-body

multiphase bone scintigraphy with anterior and posterior projections revealed a "distinct hyperactivity of the distal segment of the left tibia and the tibiotarsal joint" (Figure 1). However, a MRI scan showed an "evenness of the capsular and ligamentous structures with a thickening of the synovial component in the fatty area of the sinus tarsi; marked and widespread signal changes at the spongey bone of the astragalus with relative sparing of the head due to hyperemia and oedema; the sheath of the long flexor tendon of the hallux is distended with fluid" (Figure 2).

The patient was then discharged with a diagnosis of "probable psoriatic arthropathy and algodystrophy of the astragalus" and treated with anti-inflammatory drugs and low-dose steroids (4 mg/day of 6-methyl-prednisolone for two months). Two articular steroid injections were also performed in the left ankle with satisfactory results in terms of swelling and functional limitation, but not pain however.

Subsequently, at the time of the visit at our outpatient clinic, no remarkable facts was noticed in the medical history and the general physical examination was substantially within the normal values but an onicopathy of the feet was present. The left ankle joint was hot, swollen, with ruddy, almost cyanotic skin; passive flexion/extension was normal, with no pain, whereas elective pressure on the astragalus produced a sharp pain. The clinical data were compatible with the diagnosis of CRPS I (first stage) according to IASP criteria (19) and the instrumental tests supported this diagnosis.

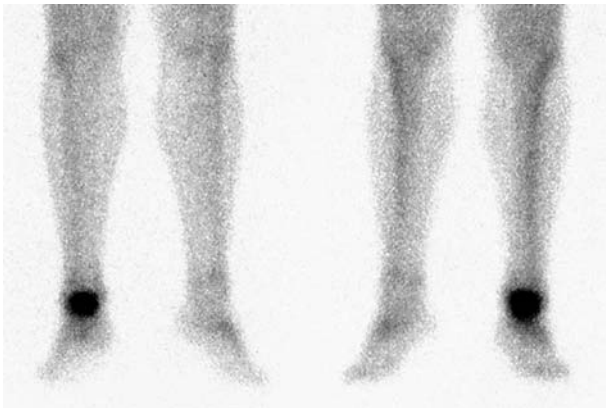

Figure 1. Whole-body multiphase bone scintigraphy with anterior and posterior projections

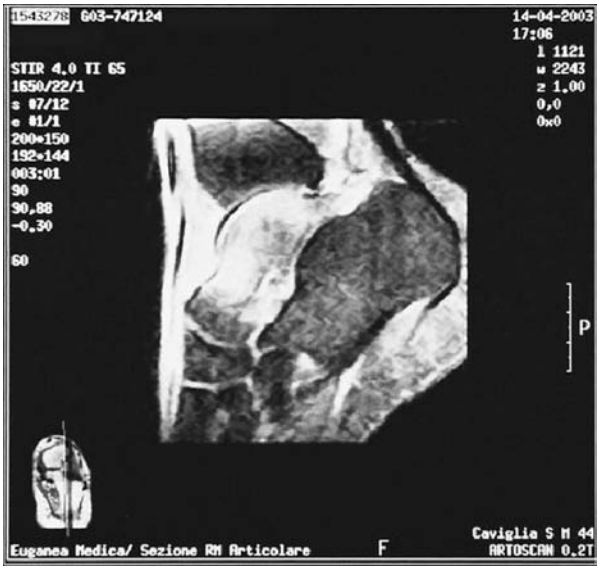

Figure 2. First MRI scan

Treatment with 6-methyl-prednisolone 8 mg/day was started, gradually reducing over 40 days to the maintenance dose of 4 mg/day, together with celecoxib 200 mg twice daily and acetaminophen 500 mg three times a day.

Clodronate 100 mg i.m. was also prescribed according to the following protocol: one vial per day for the first week, one vial per day on alternate days for the second week, one vial every 3 days for the third week, two vials every 4 days for the fourth week and lastly, one vial per week for two months, making a total dose of 1500 mg at the first month of treatment (Table 2).

A rapid and progressive improvement was found at the outpatient check-up after three months of therapy, with an almost complete disappearance of the painful symptoms which only reappeared when the patient started walking again. On this occasion the dose of celecoxib was reduced to 200 mg/day, the acetaminophen was discontinued and, the following month, the dosage of 6-methyl-prednisolone was reduced to 4 mg on alternate days. At this point, the blood tests showed that the inflammatory markers, calcemia and alkaline phosphatase values were normal. Slight changes in gamma-glutamyltranspeptidase, triglycerides and cholesterolemia remained, but these were likely due to incorrect non-essential eating habits. On this occasion HLA ABC (MHC I) assess-

Table 2. Timing for the treatment with intramuscular clodronate

Week	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
1	X	X	X	X	X	X	X
2		X		X		X	
3		X			X		
4	X				X		

ment was performed which emphasized the following: A1-23, B8-44, Cw4-7 (Cw7 frequently occurs in psoriatic arthropathies). A "disease modifying" therapy was therefore started with hydroxychloroquine 400 mg/day and the therapy with clodronate 100 mg i.m./week was continued.

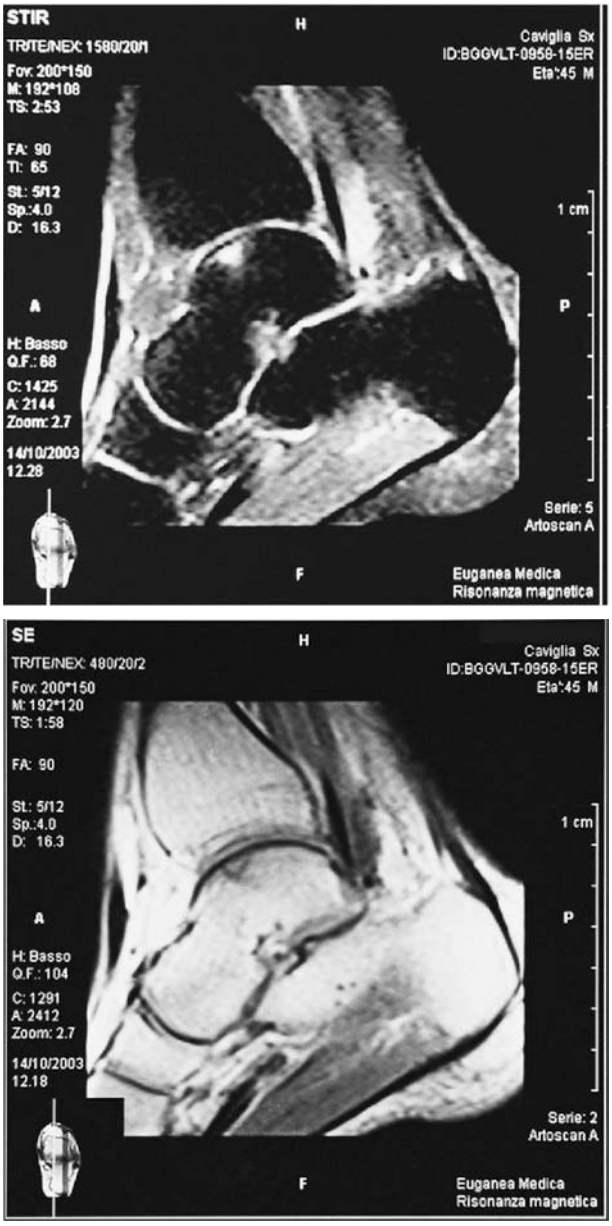

Figure 3. Second MRI scan

A subsequent outpatient assessment approximately six months later, confirmed that the pain symptoms were under control and, at the same time, a MRI scan demonstrated the "resolution of the signal changes at the astragalus due to the bone oedema; a change in the osteochondral limit appeared at its medial edge, corresponding to the area of greater uptake previously seen at the coronal section, the appearance of a change in the osteochondral border with a subcortical fluid component and its initial depression in a segment extending to about 8 mm, less bordered on the spongey side by hypointense rings, due to an osteochondral lesion which is probably a result of osteonecrosis; unchanged distension of the long flexor tendon of the hallux" (Figure 3).

The therapy with injectable clodronate was therefore discontinued and an intra-articular injection in the tibiotarsal sinus was performed with 20 mg of triamcinolone acetonide, providing a slow but progressive benefit.

One year later the patient presented with worsening of the arthritis in several joints, so a therapy with methotrexate 7.5 mg/week was added for 15 months, leading to a progressive resolution of the clinical picture. The patient, still being followed-up for the psoriatic arthritis, having lost weight under strict dietary control, now complained of pain in the left ankle only when overloading.

Discussion

To some extent, CRPS I is still a vague syndrome, and its clinical management is still challeng-

ing. The uncertain aetiology, the controversies concerning the sensitive, motor and autonomic involvement, together with the extreme variability of both the clinical picture and its evolution over time, has led to a various therapeutic approach. Clinical and instrumental monitoring, in a certain sense imprecise and articulated, has also contributed to this (15).

This is reflected in the yet unsatisfactory results of the treatment for which complete remission is reported in about 20% of patients, a partial stabilization (improvement in functionality but persistence of the pain) in 50% of cases, but no response in the remaining 30% (14).

In spite of this, by now it is ascertained that the optimal treatment at the moment is interdisciplinary and its purpose is to reduce the algic symptoms and restore *quod ante* functionality and quality of life. There is also agreement on the fact that the results differ on the basis of the stage of the disease and that, consequently, the precocity of the intervention is a critical factor for the possibilities of its success.

Amongst the commonly used treatments, besides drugs, we also find rehabilitation and nerve blocks but the clinical evidence for these interventions is still limited (7) also because, in many cases, the choice is based on analogies relating to efficacy in other types of neuropathic pain rather than on specific clinical evidence. Moreover, randomized controlled trials are extremely rare and many of them have inadequate number of patients or consist of non-verifiable abstracts presented at meetings. In this respect, the lack of homogeneity in the diagnosis should not be overlooked, particularly in papers published before the implementation of the IASP criteria.

The used drugs have therefore been widely varied: anti-epileptic drugs (gabapentin, pregabalin, carbamazepine), antidepressants (tricyclic, SSRI, SNRI), opioids, anti-inflammatory drugs (NSAIDs and corticosteroids), calcitonin, bisphosphonates (clodronate, alendronate, ibandronate, neridronate, pamidronate), anaesthetics (lidocaine, mexiletine, ketamine), adrenergic drugs, thalidomide, analgesics such as capsaicin and many others (16).

Bisphosphonates in particular are the drugs for which we have the most data, especially in terms of clinical studies (mainly initial stage CRPS I) in which they have been shown to be efficacious in open-label studies (41, 52, 53) as well as in controlled studies (36, 39, 40, 43, 46).

The specific inhibition that bisphosphonates have on osteoclastic activity appears to be essential for their efficacy in CRPS I, which is characterized precisely by high "in loco" reabsorption of osteoclasts, particularly in the early stages of the disease (36, 54). It should also be emphasized that, compared to many other proposed therapies, bisphosphonates are associated with good tolerability and a negligible incidence of side effects. Apart from a study with oral alendronate (46), bisphosphonates are always administered through intravenous injection and in much higher doses than those commonly used for osteoporosis. There is also a lack of comparison studies between the different bisphosphonates, on the basis of how to make the choice of therapy.

The use of injectable bisphosphonates was recently associated with an increased risk of osteonecrosis of the mandible (55-57), but the dosages and the clinical characteristics of the patients in whom these events were reported do not in fact correspond to those of CRPS; it remains the usual caution in respect of the prevention of hypocalcemia and their use in patients with a serious impairment of renal function (58-60).

The clodronate used in this case report is distinguished from the aminobisphosphonates for its lower relative strength and, above all, for its different mechanism of action.

Specifically, the reported case is a CRPS I associated to psoriatic arthropathy. The association between CRPS I and bone-marrow oedema syndrome with rheumatic diseases such as spondylarthritis, and hip and knee arthrosis and gout is not infrequent (61-64) and must therefore be taken into consideration in the presence of persistent and invalidating pain, which is not typical during arthritis. On the other hand, some clinical characteristics of arthritis and CRPS I can be superimposable, thus causing difficulty in making a differential diagnosis. Heat, reddening, swelling and pain are characteristics of arthritis and they are usually accompanied by a functional limitation of the affected joint. However, in these cases the pain is present mainly at rest, the functional limitation is constant and both improve with movement. The vasomo-

tor and trophic changes are not usually present in arthritis though (19). Moreover, pain is always present in CRPS I, or at the very least, it occurs on loading in the less full-blown forms. The colour of the skin also tends to vary from ruddy to almost cyanotic/cyanotic, whereas swelling may be present in both forms.

An essential element in making a differential diagnosis is the MRI report, with its evidence of bone-marrow oedema, not typical of arthritis, which instead shows particularly clear evidence of articular and peri-articular inflammation (soft tissues, synovial membrane and intra-articular effusion) and even sub-cortical inflammation (65-68). In spondyloarthritis (which also includes psoriatic arthritis) the characteristic inflammation of the enthesis can manifest as a combination of osteitis, hyperostosis and periostosis (69, 70).

Bone scintigraphy can also help in making a differential diagnosis due to some distinctive aspects (71).

In our case, in which the causing factor cannot be recognized with certainty, there is a temporal correlation between the onset of the arthritis and the subsequent appearance of the algodystrophic picture. It cannot therefore be excluded that the persistent overloading, perhaps related to the patient's intense physical activity which continued even after the appearance of the arthritis, could have contributed to the onset of the CRPS I.

The initial treatment with steroids would have affected the arthritic component, but not the problems connected with the overloading, so that the residual symptomatology was probably ascribed to the CRPS I for which no efficacious therapy had actually been given, seeing that in this context the steroids would probably have had to be given at higher doses (72, 73). The use of celecoxib, frequent in arthritis therapy, even in the phase after the treatment with clodronate, cannot justify the persistence of the benefits on its own, as it is known that a dosage of 200 mg per day does not have a high antalgic action.

With regard to the use of intramuscular injections of clodronate, this was based on the consolidated use of this administration route in the Italian population, the substantial equivalence of the bioavailability of intramuscular clodronate with intravenous clodronate (47-49) and its clinical efficacy in other diseases (50-51) (Table 3).

Table 3. Why to choose the treatment with intramuscular clodronate?

- Substantial equivalence of the bioavailability of intramuscular with intravenous clodronate
- Proven efficacy in other skeletal diseases
- No relevant adverse effects
- Widespread use of the i.m. home injection practice in Italy
- Good *compliance* of the patient
- Lower cost in relation to other treatments

The cumulative effective dosage turned out to be 1500 mg, roughly the same applied in Paget's disease of bone (51). This dosage turned out to be significantly lower than the 3000 mg used in a previous study (36), the procedures of which (300 mg i.v. for 10 consecutive days) would not be applicable in a non-hospital environment.

The treatment we used also reduced the risks of hypocalcemia and enabled us, at least in our case, to continue the therapy until an effective clinical remission of the symptomatology was reached. On the other hand, the extreme complexity of the clinical picture lends itself to customized treatment, so we cannot exclude that other dosages and other therapy durations could also give benefits, even in light of the possibility of frequent relapses. In all cases however, performing a MRI scan as an instrumental confirmation of therapeutic efficacy appears to be of the utmost importance before and after three months of treatment.

The protocol we used presents some clear objections relating to the singularity of the case (a single patient with two overlapping clinical pictures) but the practical utility, lower costs, the possible generalization of the treatment to domiciliary patients and the lower possibility of side effects seems exceedingly interesting (74-76).

In this specific case the non-univocal interpretation of the MRI finding of an astragalus cortical lesion in a loading point after six months remains. Our reliable interpretation however, is that it denotes an osteonecrosis which, according to some Authors, could represent a developmental phase of the CRPS I bone oedema or, alternatively, an event accompanied by a peri-lesional bone oedema (77, 78).

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