CASE REPORT

Peripheral neuropathy associated to cryoglobulinemia in patient with hepatitis C. Case report and literature review*

Neuropatia periférica associada à crioglobulinemia em paciente com hepatite C. Relato de caso e revisão da literatura

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ABSTRACT

BACKGROUND AND OBJECTIVES: Hepatitis C is an infectious disease affecting approximately 170 million people worldwide. In addition to the liver disease, the virus causes extra-liver manifestations, such as peripheral neuropathy and essential mixed cryoglobulinemia. This study aimed at presenting a case of a patient with hepatitis C virus who developed cryoglobulinemia associated to peripheral neuropathy.

CASE REPORT: Male patient, 62 years old, with hepatitis C subtype 1 diagnosed more than 10 years ago, with possible contamination after right knee surgical procedure. He presented initially "shock"-type pain episodes followed by hands and feet continuous paresthesia in boot-glove pattern, associated to Raynaud phenomenon and lower limbs petechiae. He evolved along the years with motor deficit in left fibular nerve leading to foot-drop. Plasma cryoglobulines test was positive. Pain became continuous, severe, symmetric, located in the distal third and lateral face of lower limbs. When the evaluation of the multidisciplinary pain and rehabilitation team was asked, tramadol (50 mg) every 6 hours and gabapentin (900 mg/day) were prescribed in association to pulse therapy with total resolution of pain in some weeks. Orthosis and daily rehabilitation were needed for several months.

CONCLUSION: As early as possible, multimodal treatment with different classes of drugs associated to adequate rehabilitation is directly associated to a better prognosis for this type of neuropathy.

Keywords: Cryoglobulinemia, Hepatitis C, Neuropathic pain, Rehabilitation.

RESUMO

JUSTIFICATIVA E OBJETIVOS: A hepatite C é uma doença infecciosa que afeta cerca de 170 milhões de pessoas no mundo. Além da doença hepática, o vírus causa manifestações extra-hepáticas como a neuropatia periférica e a crioglobulinemia mista essencial. O objetivo deste estudo foi apresentar o caso de um paciente portador do vírus da hepatite C que desenvolveu no curso da doença um quadro de crioglobulinemia associado à neuropatia periférica.

RELATO DO CASO: Paciente do sexo masculino, 62 anos, portador de hepatite C subtipo 1b, diagnosticada há mais de 10 anos, com provável contágio após procedimento cirúrgico em joelho direito. Apresentou inicialmente episódios de dor tipo "choque" acompanhado de parestesias em mãos e pés com padrão bota-luva, contínua, associado à fenômeno de Raynaud e petéquias em membros inferiores. Evoluiu ao longo dos anos com déficit motor em nervo fibular esquerdo levando a quadro de pé caído. A pesquisa de crioglobulinas plasmáticas foi positiva. A dor se tornou contínua, intensa, simétrica, localizada no terço distal e face lateral dos membros inferiores. Quando foi solicitada avaliação pela equipe multidisciplinar de dor e reabilitação, associado à pulsoterapia foi prescrito tramadol (50 mg) a cada 6h e gabapentina (900 mg/dia) com resolução total do quadro doloroso em algumas semanas. Foram necessários o uso de órtese e reabilitação diária por vários meses.

CONCLUSÃO: O tratamento multimodal com diferentes classes de fármacos associado à reabilitação adequada realizados o mais precocemente possível está diretamente relacionado à melhor prognóstico deste tipo de neuropatia.

Descritores: Crioglobulinemia, Dor neuropática, Hepatite C, Reabilitação.

INTRODUCTION

Hepatitis C is an infectious disease affecting approximately 170 million people worldwide[1]. In Brazil, the most frequent are 1, 2 and 3 (viral hepatitis A, B and C)[2].

Major clinical manifestation is hepatitis and some level of fibrosis, followed by nonspecific symptoms such as fatigue. In addition, hepatitis C virus infection (HCV) may impair quality of life even in the absence of severe disease[3-5]. The prevalence of HCV in Brazil is not exactly known; there are reports from several areas which suggest that mean prevalence is between 1% and 2% of general population[2].

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A search of the Brazilian Society of Hepatology has revealed that from 1,173,406 evaluated blood donors, 14,527 (1.23%) were reactive to anti-HCV[6]. Higher prevalence rates were observed in the northern region of Brazil (2.12%). The southern region, on the other hand, has shown low prevalence of positivity for anti-HCV (0.65%). Midwest, northeastern and southeastern regions had intermediate rates (1.04%, 1.19% and 1.43%, respectively).

There are several extra-hepatic manifestations of HCV infection associated to liver diseases. Among them one may mention peripheral neuropathy, which affects 40% to 75% of infected patients[4,5,7]. Several of those syndromes are related to autoimmune or lymphoproliferative diseases, having as pathological substrate the HCV replication inside lymphoid cells, inducing an abnormal immune response, with the formation of immunocomplexes and inducing an inflammatory process with further development of vasculitis by the activation of the complement system[8]. Among such manifestations there are polyneuritis and vasculitis secondary to cryoglobulinemia[9]. This study aimed at describing the case of HCV patient who developed cryoglobulinemia associated to peripheral neuropathy in the course of the disease.

CASE REPORT

Male patient, 62 years old, Caucasian with hepatitis C, subtype 1b, diagnosed in 1998 when submitted to screening tests to donate blood. He reports possible infection after surgical procedure in right knee ("spiritual surgery" – Dr. Fritz). In regular follow up he used daily ribavirin and interferon-α (IFN) three times a week with progressive decrease of his viral load until the year 2000, when the treatment was interrupted due to intolerance to side-effects, in spite of the non negativation of viral load levels count.

In 2005, he started having episodes of "shock" pain followed by hands and feet paresthesia with boot-glove pattern, continuous, associated to Reynaud's phenomenon and lower limbs (LLll) petechiae. By this time he looked for medical assistance when lab tests were requested, among them search for cryoglobulines which was positive. Patient was referred to the infectologist to evaluate hepatitis C retreatment, however he considered such approach unnecessary.

In 2006, due to worsening of pain predominantly in LLll, color doppler was performed of LLll veins, which has not revealed major changes, and electroneuromyography, which has shown a residual neurogenic pattern caused by asymmetric, sensory-motor and predominantly sensory axonal polyneuropathy.

In this same year he suffered an ischemic stroke (IS), remaining hospitalized during this period for evaluation. During hospital stay, he evolved with bilateral, intermittent moderate stabbing pain in plantar region which would worsen when he put his feet on the ground and would improve at rest. Patient was submitted to a cycle of pulsetherapy with cyclophosphamide with remission of symptoms and was discharged without sequelae.

In the following year his LLll pain has again worsened with continuous and severe paresthesias. Sural nerve biopsy was requested and revealed: perivascular inflammatory infiltrates; occluded arteries and neoformation of epineural arterioles; loss of large and small myelinated fibers within fascicles; few axonal degeneration images and lack of regeneration images, confirming the diagnosis of peripheral nervous system (PNS) vasculitis associated to hepatitis C. By the time, cyclophosphamide was again prescribed as pulsetherapy, however treatment was not immediate. He restarted hepatitis C treatment with pegylated IFN and ribavirin, with negativation of HCV-RNA titles after six months of treatment.

One year later he evolved with arthralgia, LLll palpable purpura, motor deficit of left fibular nerve leading to drop foot, right foot and hands paresthesias, in addition to laboratorial impairment of liver function and positive rheumatoid factor. He started pulsetherapy with cyclophosphamide and methylprednisolone (Solu-Medrol®) and was submitted to new electroneuromyography which has evidenced: multiple mononeuritis with myelin predominance and secondary axonal involvement, impairing common peroneal nerves, more markedly to the left and sural nerve to the right. He has partially improved with the treatment.

One year and four months later, he entered the first aid unit with history of chest pain to the left with progressive worsening, in addition to fever for approximately one week. By that time he reported history of hospitalization in the previous week due to myalgia and fever. Chest angiotomography (Angio-CT) has revealed secondary vessel occlusion in right lower segment, confirming the diagnosis of pulmonary thromboembolism (PTE). Patient remained in the intensive care unit (ICU) where full heparinization and plasmapheresis were performed with remission of symptoms and improvement of pain. After discharge he started presenting loss of muscle strength and LLll anesthesia, which has intensified his existing difficulty to ambulate due to "drop foot" to the left, and numbness-type, pain continuous, symmetric and localized in LLll distal and lateral faces. Due to this, we requested evaluation by the pain and rehabilitation multidisciplinary team.

At bedside evaluation he presented muscle strength decrease degree 1 for left foot extension and degree 2 for flexion, degree 3 for left knee extension with abolished Achilles and patella reflexes in this same limb. Right foot had muscle strength degree 2 for extension and flexion and knee degree 3 for flexion and extension. Deep sensitivity was normal, but superficially it presented hypoesthesia on distal third lateral medial face of right lower limb and medial face of left lower limb, in addition to anesthesia on lateral face of left lower limb.

Patient was submitted to LLll arterial ultrasound (Duplex-Scan) which revealed mid third posterior tibial artery occlusion; upper stenosis at 50% of anterior proximal tibial artery and diffuse atheromatosis in right lower limb artery, without signs of acute thrombosis. Left lower limb also had mid third posterior tibial artery occlusion and diffuse atheromatosis in. LLll deep vein exam has shown a pervious system without signs of acute thrombosis.

After evaluation, the pain and rehabilitation multidisciplinary team concluded that it was a neuropathic pain probably secondary to nervous and vascular lesion induced by cryoglobulinemia or hepatitis C. Associated to new pulsetherapy, tramadol (50 mg) every 6 hours and gabapentin (900 mg/day) were prescribed with total resolution of pain in a few weeks.

The team has also recommended physical therapy at bedside aiming at strengthening sural triceps, quadriceps and ischiotibial muscles, has prescribed a bilateral, articulated, suropodalic orthosis and daily walks. With pulsetherapy, patient recovered LLll muscle strength,

but maintained decreased sural triceps strength. He completed one and a half year of treatment with resolution of "drop foot". One month after daily rehabilitation, suropodalic orthosis was replaced by an anti-equine strip which allowed patient to walk with more freedom without risk of falls.

Currently, patient has muscle strength degree 4 for right foot inversion, eversion, flexion and extension and muscle strength degree 3 for left foot flexion and extension, in addition to muscle strength degree 2 for hallux extension. Patient ambulates without the anti-equine strip and has intermittent low intensity pain associated to LLll paresthesias.

DISCUSSION

A broad spectrum of extra-hepatic manifestations has been attributed to HCV. Cryoglobulinemia is the most common extra-hepatic manifestation. Almost 100% of essential cryoglobulinemia patients have positive HCV and almost half of them have association with cryoglobulinemia. The high prevalence of cryoglobulinemia among patients infected by HCV has been confirmed by several studies[9-15].

Our patient had HCV genotype 1, which is the most frequent genotype in Brazil and is most associated to cryoglobylinemia[16]. With regard to different HCV genotypes, types 1b and 2a are more often associated to cryoglobulinemia, however patients with types 1b and 3 have more neurological involvement than those with types 2a and 2a/c[16].

In most cases, cryoglobulinemia is asymptomatic. Only 13%-30% of patients are symptomatic and its clinical presentation varies from mild vasculitis (Raynaud's phenomenon) (20%-50%), arthralgia (20%), weakness (65%) and purpura (10%), to severe vasculitis (peripheral neuropathy) (15%-25%), membranoproliferative glomerulonephritis (30%-50%) and systemic vasculitis (8%)[17-19]. The reason for symptoms variation and organ involvement is not totally understood[20].

Patient was asymptomatic for some time, when "shock" pain started followed by continuous hands and feet paresthesias associated to Raynaud's phenomenon and LLll petechiae. These symptoms were compatible with typical essential mixed cryoglobulinemia cutaneous manifestations which depend on the season (cold seasons)[21,22]. The so-called "purpura to cold" presents as hemorrhagic petechiae in areas exposed to cold, especially hands and feet, or as large bruises[12]. There may be clinical presentation similar to pernius erythema, forcing the differential diagnosis. There may be hives to cold, Raynaud's phenomenon, skin ulceration, livedo racemosa, acrocyanosis and arthralgia[12,13].

The incidence of neurological changes in HCV patients with mixed cryoglobulinemia may exceed 60%[22]. Peripheral neuropathy manifests as severe pain and asymmetric paresthesia which later may evolve to symmetric and, finally, there is motor deficit[20], all symptoms especially in LLll[21]. Neuropathological data show axonal degeneration, signs of demyelization, loss of axonal fascicular differentiation and small vessels vasculitis, with perivascular infiltrate of mononuclear cells[20,23]. These findings are compatible with the biopsies of this case. Central nervous system (CNS) involvement is not frequent, manifesting as dysarthria and hemiplegia, being even more uncommon the state of mental confusion. Our patient had ischemic stroke.

Lesion mechanism is probably multifactorial and it is believed that it is associated to the formation of immunocomplexes, complement activation and presence of cryoglobulines. PNS symptoms are attributed to vasa nervorum vasculitis and axonal degeneration. CNS manifestations are related to intracranial vasculitis leading to well defined ischemic symptoms or leukoencephalopathy, the latter probably due to white matter micro-infarctions with slow and progressive evolution. In a case of progressive encephalomyelitis with generalized rigidity, viral RNA was found in brain tissue after necropsy, showing trophism for CNS[21]. This may mean a lesion mechanism independent of inflammatory and vascular lesions of HCV in CNS, as primary virus effect, especially in degenerative diseases[23].

There are many studies evaluating the association between peripheral neuropathy in HCV patients and mixed cryoglobulinemia, although peripheral neuropathy may also be found in patients not developing cryoglobulinemia[5,7]. The presence of serum cryoglobulinemia is predictive of more severe and generalized neuropathic complication[22,24]. Sensory or motor peripheral neuropathy was found in up to 9% of patients with chronic HCV infection[25].

In patients infected by HCV however without cryoglobulinemia, most common neurological manifestations are mononeuropathy and multiple mononeuropathy[22,24]. A Japanese study has retrospectively evaluated 55 HCV patients with neuropathic symptoms and prospectively evaluated 11 control group patients with chronic HCV infection without neuropathic symptoms. The study has shown the presence of several types of neuropathies in HCV patients, such as multiple mononeuropathy, polyneuropathy and Guillain-Barré syndrome. Multiple mononeuropathy was the most common, with or without mixed cryoglobulinemia, being HCV responsible for the modulation of several neurological manifestations in other viral infections. Subclinical neuropathy may also be present in patients infected by HCV without neurological symptoms[4,5,7].

Sensory neuropathy may affect A-delta myelinated thin fibers and demyelinated C fibers. Studies indicate that this is the most common condition of painful sensory neuropathy in patients above 50 years of age. Other neuropathies associated to pain are those affecting A-beta and A-alpha thick fibers. These fibers are responsible for proprioception, vibratory sensation, muscle reflexes and muscle strength. The differentiation between these two groups of sensory neuropathic pain is not common since it is more frequently identified when both thick and thin fibers are involved[26].

Typical symptoms of neuropathic pain related to thin fibers are numbness, stabbing or stinging pain localized in fingers, toes or feet. Pain from peripheral nervous involvement is described as pricking, numbness or grip and weight sensation. Peripheral neuropathy pain is often exacerbated at night, but some patients refer worsening when standing up or walking, as it was described by the patient of this case[26].

In disorders with exclusive predominance of thin fibers there is a considerable similarity between symptoms and neurological deficits. This disorder is more predominant in males, with abnormal loss of sensitivity to finger pressure and which centripetally extends to the knee, but seldom above it. Superficial sensitivity to touch is also decreased, although other forms of sensitivity are preserved. In pain-

ful sensory neuropathies affecting both thin and thick fibers, there is decreased proprioception, loss of muscle reflexes and of muscle strength reflecting the impairment of thick fibers. The lack of vibration sensation on feet may be normal in elderly people, but it is abnormal when it extends to the ankle[26,27].

Electroneuromyography is requested at baseline evaluation, unless the diagnosis is well defined, such as a diabetes patient with peripheral vasculopathy. Electrodiagnostic studies are useful for patients with painful sensory neuropathy to identify mononeuropathy, to differentiate multiple mononeuropathy (characteristic of peripheral nervous vasculopathy) from polyneuropathy (which is symmetric); and to distinguish between axonal neuropathy (e.g., diabetic neuropathy) from demyelinating neuropathy. Studies showing normal electroneuromyography results are consistent with isolated thin fibers neuropathy[26,27]. It is worth stressing the importance of the electrophysiological study even for patients without typical peripheral neuropathy symptoms, since many of such results may be underestimated by not performing the exam[4].

A multicentric Italian study has observed the importance of electroneuromyography to detect subclinical peripheral neuropathy in HCV patients with or without cryoglobulinemia and its statistical analysis has shown that the presence of cryoglobulinemia was not a risk factor for the development of peripheral neuropathy, although the incidence of neuropathy increases with age[4].

There are no definite guidelines to treat HCV associated to neurological manifestations. Some therapeutic options are immunosuppressive agents, such as steroids, or immunomodulatory agents, such as IFN and ribavirin[27]. Other studies have also shown clinical improvement of acute inflammatory processes after treatment with steroids and cyclophosphamide[27-29].

IFN is a potent modulator of humoral and cellular immune response, however its action mechanism is poorly understood. Decreased viral replication rate (even without complete or permanent elimination), lymphocyte proliferation inhibition, immunoglobulins synthesis and improvement of immune complex capacity with increased macrophages activity, may be responsible for its therapeutic properties[27].

Previous studies have shown that treatment with IFN in monotherapy has resulted in improvement of vasculitis associated to decreased serum cryoglobuline levels, but with recurrence of symptoms after treatment interruption[30].

It is also known that the treatment with IFN and antiviral drugs was able to revert symptoms of chronic inflammatory demyelinating polyradiculitis and polyneuropathy associated to vasculitis and cryoglobulinemia[29,31], suggesting that virus eradication may revert symptoms.

Authors have described the case of a male patient with 40 years of age with hepatitis C and cryoglobulinemia who developed peripheral neuropathy associated to vasculitis. After treatment with IFN-α, patient improved, recovering muscle strength and with no numbness in LLll. This was the first case report described in the literature of neuropathy associated to cryoglobulinemia which has responded to IFN-α, suggesting that patients with peripheral neuropathy and cryoglobulinemia should be tested for the presence of HCV and treated this way to obtain good clinical result[27]. In our case, the patient used IFN and ribavirin in two moments. In the first moment, just to control viral load since patient was asymptomatic, and in the second moment when he was retreated for HCV due to extra-hepatic symptoms.

Therapy for patients with HCV associated to peripheral neuropathy should be based on its severity and response to treatment. Steroids or IFN plus ribavirin are the first options for patients with mild to moderate neuropathy[32]. Since chronic steroid administration was associated to increased serum cryoglobulines and CHV-RNA levels, these drugs shall be administered in low doses and stepped down as soon as possible[33].

Neuropathic pain treatment is often complex and frustrating. In addition to usually multimodal drug treatment made up of tricyclic antidepressants, local anesthetics and other drugs, such as opioids, physical and social rehabilitation measures are needed[34].

Antidepressants are knowingly effective to decrease neuropathic pain especially amitriptyline, and more recently duloxetine. Anticonvulsants, such as carbamazepine and phenytoin, are also used to treat peripheral neuropathies. However, these are drugs with significant adverse effects and not always they are first line therapy. Oxcarbamazepine, anticonvulsant with structure similar to carbamazepine, has also been used, but few studies were published with this purpose[35,36].

Gabapentin is a calcium channel antagonist anticonvulsant and has repeatedly shown its analgesic efficacy, in addition to improving mood and sleep in several published studies[35,36]. Pregabaline is within this same line of results. Other anticonvulsants, such as valproate, lamotrigine and topiramate have uncertain results[36].

Due to the limited efficacy of current treatments, the combination of different drugs results in pain relief with low doses and few side effects. Many patients have received several drugs to treat neuropathic pain, even with poor scientific evidence about them[36,37]. In our case, pain symptoms were controlled with tramadol and gabapentin in association with methylprednisolone and cyclophosphamide pulsetherapy. HCV RNA negativation was anterior with pegylated IFN plus ribavirin. It is important to stress in this case the delay of the pain and rehabilitation team intervention. Fortunately we were successful, but the delay in instituting the treatment in general courses with refractory responses[34].

Physiatric approach of a patient with peripheral nerve lesion should be similar to that dedicated to patients with other types of incapacities or deficiencies, looking for the maximum functional potential and their social reinsertion. It is necessary to know whether nervous recovery is possible or not. When the lesion will leave sequelae, patients and their families should be carefully explained about the limitations and residual potential to be explored. When there is possibility of reversion, one should work safely and in stages, depending on patients' internal structure, who may rapidly assimilate, understand and actively participate in their rehabilitation[38].

Advice, awareness, use of orthosis, gait aids, evolution, sensitivity, motor recovery and joint maintenance tests, care with hypertrophic scars are also greatly important. In sensory changes, patients should be re-educated on how to protect feet with adequate shoes and accessories to prevent mutilations, skin integrity evaluation, as well as the presence of injuries. They should also be advised about possible falls, which may add more limitations such as fractures and ligament injuries[38].

CONCLUSION

This case report stresses the association between HCV and cryoglobulinemia, being the latter responsible for vascular and peripheral neuropathy symptoms, especially neuropathic pain. The understanding of this association and its early diagnosis enable the introduction of adequa te therapy, thus decreasing sequelae and obtaining a better prognosis.

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