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Pain management in cryoglobulinaemic syndrome

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A B S T R A C T

Cryoglobulinaemic syndrome (CS) includes clinical signs and symptoms that range from the classic triad of Meltzer and Franklin (purpura, weakness and arthralgias) to multiple organ involvement, and it may be characterised by nociceptive or neuropathic pain. Both types of pain use the same pathways and neurotransmitters, but nociceptive pain has an adaptive system and biological function whereas neuropathic pain does not. Managing CS means dealing with often very different clinical patterns, activity and severity with the aim of preventing irreversible organ damage, reducing pain, improving the patients' quality of life and reducing social costs. However, treatment is still largely empirical, and it is often delayed. The Italian Group for the Study of Cryoglobulinaemia (GISC) strongly recommended a low-antigen-content diet and colchicine for all symptomatic CS patients. Patients with mild–moderate symptoms (such as purpura, weakness, arthralgia and initial neuropathy) have been treated with low or medium doses of steroids, and, in the presence of chronic hepatitis

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C virus (HCV)-related hepatitis, an attempt has been made to eradicate HCV with pegylated interferon plus ribavirin. In the case of severe or rapidly progressive disease (glomerulonephritis, neuropathy, leg ulcers, widespread vasculitis or hyperviscosity syndrome), more aggressive treatment should be used (e.g., high doses of corticosteroids, plasma exchange plus cyclophosphamide or rituximab). Pain management in CS therefore depends on the type of pain (nociceptive, neuropathic or mixed), the characteristics of the patients and their co-morbidities. Drug therapy should be carefully monitored in order to obtain prompt and beneficial results.

Introduction

Cryoglobulinaemic syndrome (CS) includes clinical signs and symptoms that range from the classic triad of Meltzer and Franklin (purpura, weakness and arthralgias) to multiple organ involvement (see Table 1), and it may be characterised by nociceptive or neuropathic pain [1,2]. Some of these symptoms, such as arthralgias/arthritis and peripheral neuropathy, are the preliminary classification criteria of cryoglobulinaemic vasculitis [2], and more than one mechanism involved in the chronic pain associated with CS may be responsible for different symptoms that act differently and show different changes over time from patient to patient.

Inflammation, which plays a role in nociceptive pain (e.g., articular involvement), can be expressed as 'somatic pain' activating bone, joint, muscle and connective tissue nociceptors, or 'visceral pain' when it stimulates afferent receptors in the deep organs. Neuropathic pain can be caused by a lesion in the peripheral nervous system (PNS): the damaged peripheral nerves are infiltrated by mast cells, granulocytes, macrophages and T lymphocytes, which contribute to the origin of neuropathic pain by secreting inflammatory mediators [3]. Furthermore, some inflammatory mechanisms and other

Table 1
Prevalence of clinical manifestations of cryoglobulinaemic syndrome.

Clinical manifestations	Prevalence
Purpura	73–100%
Weakness[a,b]	10–100%
Arthralgias[a]	33–91%
Non-erosive arthritis[a]	8%
Raynaud's phenomenon	7–40%
Sicca syndrome	10–51%
Peripheral neuropathy[b]	2–81%
Autonomic neuropathy[b]	Rare
Central nervous system involvement[b]	Rare
Nephropathy	8–54%
Endocrinological disorders	Rare
Liver damage	9–88%
Lung involvement	Rare
Visceral vasculitis[a]	Rare
Cardiovascular involvement	Rare
Leg ulcers[a]	4–30%
Spleen enlargement	4–50%
Lymphoadenopathy	16%
B cell lymphoma	11%
HCC (*Hepatocellular carcinoma*)	3%

[a] Nociceptive patterns of pain.
[b] Neuropathic patterns of pain.