Abstract

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A strange case of isolated distal deep vein thrombosis: not as benign as it may seem

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Background

CANOMAD (chronic ataxic neuropathy, ophthalmoplegia, immunoglobulin M Para protein, cold agglutinins, and disialosyl antibodies) is a rare syndrome characterized by chronic neuropathy with sensory ataxia, ocular, and/or bulbar motor weakness in the presence of a monoclonal Ig M reacting against gangliosides containing disialosyl epitopes. These patients have serum monoclonal IgM gammopathy, with overt hematologic malignancies in approximately 30-40% of them. The most frequent one is Waldenstrom macroglobulinemia (about 20%). Auto reactive IgM most frequently recognizes Myelin-associated glycoprotein (MAG), but gangliosides can also be targeted. This latter activity can be responsible for CANOMAD, since such gangliosides are notably localized in the neurons of dorsal root ganglia and within the oculomotor nerves.

Case history

a 59-year-old man suffering from diplopia since about one year and oral dryness associated with eating difficulty and weight loss, presented to our Angiology Department for calf pain. A lower limb ecocolordoppler was performed and a distal deep vein thrombosis was detected, localized in right sural vein. In his medical history HCV related disease (successfully treated with alfa-interferon) and thyroid goiter. He started anticoagulant therapy with low molecular weight heparin and was hospitalized because of the detection of a monoclonal Ig M-| peak. Hereditary thrombophilia was tested, and we found an heterozygosis for the G20210A mutation of prothrombin gene. Electrophysiological studies showed both axonal and demyelinating patterns. Brain and spinal cord contrast enhanced MRI was normal. Peripheral blood immunophenotyping showed a lymph proliferative B cell clone CD19+ CD20+ CD22+ CD200+ CD10dim+ with monoclonality. Osteomodillary biopsy was performed with a diagnosis of Waldenstrom Macroglobulinemia.

Discussion: monoclonal gammopathies associated with peripheral neuropathy are more commonly immunoglobulin M (IgM) than IgG or IgA. The presence of a monoclonal component, especially IgM, causes hyper viscosity syndrome that was one of the cause of the clinical presentation with calf thrombosis. Other causes include the Cytokine secretion of tumoral cell. Pathophysiologic mechanism that link gammopathy and neuropathy include (1) specific autoantibody activity of the IgM against different components of the nerve, (2) specific properties of circulating IgM, leading to cryoglobulinemic neuropathy, amyloid or endoneurial IgM deposits and (3) nerve infiltration and nerve damage mediated by cytokine. The auto reactive activity against gangliosides can be responsible of CANOMAD syndrome. As some of the symptoms defining CANOMAD are not observed in all patients, this acronym may be restrictive and the term CANDA (chronic ataxic neuropathy with disialosyl antibodies) has also been proposed. In our case, the clinical pattern was dominated by ophtalmoplegia, symmetric sensory polyneuropathy of the leg and motor impairment. In classic CANOMAD, symptoms are dominated by progressive chronic neuropathy with marked sensory ataxia that can lead to severe disability. There is actually no consensus for treatment. Corticosteroids and immunosuppressive drugs are often ineffectively. Intravenous immunoglobulin's (VIg) and rituximab-based regimens are the most effective therapies.