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STIFF-MAN SYNDROME IN A PATIENT WITH HODGKIN'S DISEASE. AN UNUSUAL PARANEOPLASTIC SYNDROME

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A case of stiff-man syndrome (SMS), a rare and dramatic CNS disease characterized by continuous muscle activity and painful spasms resembling a chronic form of tetanus, occurring in a patient with Hodgkin's disease (HD) is reported. The patient developed the clinical features of SMS at the same time as the HD relapse. A satisfactory improvement was obtained with diazepam, but the complete recovery from stiffness was achieved only after chemotherapy was started. Cerebellar autoantibodies were found in the serum of the patient. With chemotherapy the patient achieved a second complete remission (CR). Eighteen months later the patient developed a second HD relapse, and at that time no signs of SMS were detected.

KEY WORDS: Stiff-man syndrome, Hodgkin's disease, paraneoplastic syndromes.

The stiff-man syndrome (SMS) is an unusual and dramatic central nervous system (CNS) disease characterized by muscle rigidity and painful spasms, resembling a chronic form of tetanus. The disease was first described by Moersch and Woltman in 1956 [1], and several observations of sporadic cases have been reported since then [2-6]. The origin of this disorder is unknown, but it has been associated with diabetes, other endocrine diseases, and tumors. Recently autoantibodies to glutamic acid decarboxylase have been found in a patient with SMS, suggesting the possible autoimmune pathogenesis of this disease [6].

We describe a patient with Hodgkin's disease (HD) who developed the clinical features of SMS at the same time as the HD relapse, as an unusual paraneoplastic syndrome.

CASE REPORT

A 31-year-old man was in good health until 1984, when he noted the enlargement of the right cervical lymphnodes. The patient was then hospitalized and a diagnosis of HD, mixed cellularity sub-type, was made. The staging procedures stated that it was stage III A with cervical, hilar and mediastinal, para-aortic, celiac and retrocaval node involvement. Laparotomy with splenectomy was not performed because of the positive findings of the bipedal lymphangiography. The bone marrow biopsy revealed no HD involvement, so that the disease was classified in clinical stage III A. Two cycles of MOPP chemotherapy followed by subtotal nodal irradiation (40 Gy) were administered to the patient, and a complete remission (CR) was achieved. The patient was in CR for 18 months. In November, 1987, the patient suffered painful cramps and stiffness of the left foot. In the following days the stiffness extended to both legs and then to the lower back, accompanied by episodes of painful spasms. His physician administered gangliosides, without any improvement in the stiffness. The stiffness worsened with acute urine retention and severe constipation. The patient was then admitted to our division. At neurological examination the tone and consistency of muscles were considerably increased in both legs and in the left arm. Facial, neck and trunk muscles had normal tone and consistency. No muscular atrophy or weakness were present. The deep tendon reflexes were brisk, but symmetrical. Deep and superficial sensations were normal. The cranial nerves were spared. No cerebellar or extrapyramidal signs were noted. The patient was unable to stand for the severe spasticity; sensory stimuli aggravated the stiffness and provoked painful spasms. Bladder and bowel dysfunction were also present. CSF examination exhibited normal parameters.

Visual and somatosensory evoked potentials, electroencephalography (EEG), computed tomography (CT) scan, magnetic resonance imaging (MRI), and myelography gave normal pictures. Concentric-needle electromyography (EMG) showed continuous motor activity in the left tibialis anterior muscle. A sural nerve biopsy showed endoneural and perivascular accumulation of lymphocytes; there was a reduction in the number of myelinated fibers of all sizes, especially at the periphery of the fascicles. The picture was compatible with a subclinical inflammatory demyelinating peripheral neuropathy.

A search for serum autoantibody activity against cerebellar structures containing glutamic acid decarboxylase (GAD) [6], using immunohistochemistry of fixed rat brain tissue sections, showed a mild reactivity, likely directed against glial fibrillary acidic protein (GFAP) (Figure 1).

The laboratory study showed: ESR 85, hemoglobin 11.9 g/dl, WBC 5.9×10^9/l, LDH 269 UI/L (normal values <320 UI/L), serum iron 31 μg/dl, and serum copper 222 μg/dl. Other standard tests were normal.

The diagnosis of SMS was suggested and diazepam (30

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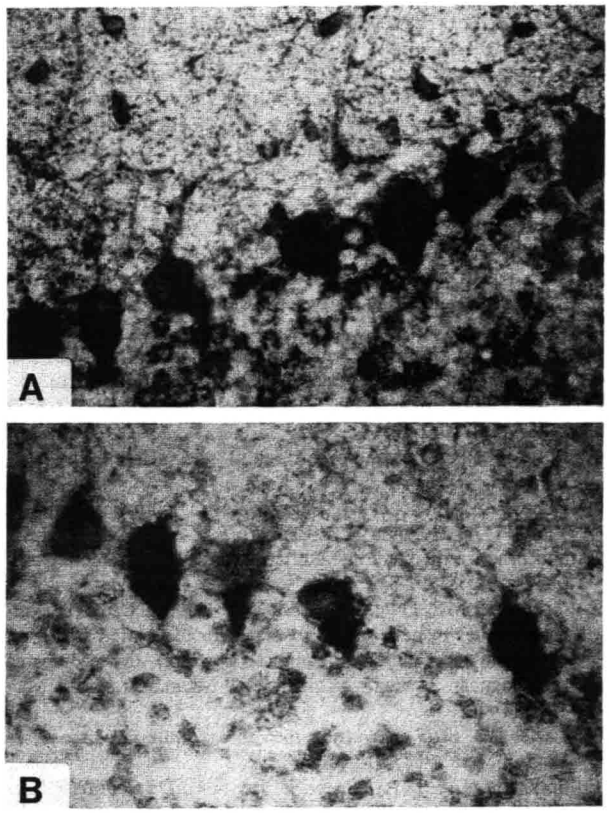

Fig. 1. - Rat cerebellum. Marked reactivity (PAP) in terminal cones of Purkinje cells, granular cell axons, and terminal synapses obtained with patient's serum (1:150) (A), and sheep polyclonal anti-GAD serum (1:2000) (B).

mg/die) and baclofen (10 mg t.i.d.) therapy was administered, resulting in decreased stiffness and lower frequency of painful spasms. The chest X-ray film and CT scan of the abdomen displayed no abnormalities; however, the bone marrow biopsy exhibited the presence of HD. A treatment alternating 3 MOPP with 3 ABVD cycles was planned. One month later, at the end of the first cycle, he had regained the full control of bladder and bowel function. Stiffness and spasms progressively disappeared over the following months.

The MOPP/ABVD chemotherapy regimen resulted in a second CR from HD. The patient was readmitted in June, 1989 for further evaluation. At that time, on physical examination he had full range motion of his arms, no lymph node enlargement and normal laboratory tests, including ESR, hemoglobin, LDH, iron, copper, and WBC counts. An EMG showed a slow peripheral motor conduction velocity for the left lower limb and limited signs of chronic denervation in the lower limb muscles, without any activity at rest. This picture was compatible with an axonal neuropathy, secondary to the treatment with vincristine he underwent several months before. Reactivity to GFAP was not found on a serum sample obtained at that time.

In December, 1989 the patient was readmitted to our division for persistent cough. The chest X-ray film showed a marked enlargement of mediastinal nodes; furthermore, CT scan of the abdomen showed marked enlargement of all retroperitoneal nodes. A thoracotomic biopsy of the mediastinal mass showed the presence of HD.

No signs of stiffness were present, and autoantibodies to GFAP were not detectable in the patient's serum at that time. A chemotherapeutic program with the MOPP/ABV/CAD hybrid protocol is in progress, with a satisfactory objective response after the first cycle.

Discussion

Although the nosological classification of the syndromes presenting with neuromuscular hyperactivity is still controversial [7], our patient's clinical picture (presenting with painful cramps associated with limb and truncal stiffness responsive to diazepam, and EMG evidence of continuous motor activity) was consistent with a diagnosis of SMS. The complete absence of other diseases responsible for the stiffness strongly supports the role of HD as causative of the following SMS.

Several months after the disappearance of his SMS, the patient presented a new relapse of HD. This time he did not feel any spasms or sense of rigidity, indicating that paraneoplastic SMS is a sporadic complication of neoplasms, a feature common to other paraneoplastic syndromes [8].

To date, several sporadic cases of SMS have been described, mostly in recent years. The disorder is usually associated with other diseases, namely endocrine disorders and/or tumors [3 6 9]. The pathogenesis of the disease is unknown and still debated. In some instances high levels of immunoglobulins were found in the cerebrospinal fluid, suggesting an inflammatory process. A few patients were found to have elevated IgG production and oligoclonal IgG bands in the cerebrospinal fluid [10]. Solimena et al [6] described a typical case of SMS, associated with epilepsy and Type I diabetes, and reported that the patient's serum and cerebrospinal fluid contained an autoantibody against structures containing the CNS enzyme glutamic acid decarboxylase (GAD). GAD is the key enzyme in the synthesis of GABA, a major inhibitory neurotransmitter, and impairment of GABA-mediated central inhibition has been proposed as the pathogenetic mechanism of SMS. A larger study by the same authors demonstrated that anti-GAD activity is neither sufficient nor necessary to cause SMS [11]. However, it is of interest to note that anti-GAD cerebellar autoantibodies were actually present in our patient's serum, indicating that anti-cerebellar antibodies may play a role in the pathogenesis of the syndrome. To date, SMS treatment is not well defined. In the past few years improvement, and sometimes complete recovery of the symptoms of SMS, has been obtained with sodium valproate [12], clonidine [13], and diazepam [2]. Diazepam and other drugs are thought to potentiate GABA-ergic transmission and have proved to be effective in the treatment of contractures in patients with SMS [2].

Recently, encouraging results were reported with the use of corticosteroids [5], suggesting the possible autoimmune

pathogenesis of the disorder. In our patient, even if a satisfactory response was obtained with diazepam, the complete recovery from stiffness was achieved only after chemotherapy (including a corticosteroid) was started. In a recent report, 3 patients with SMS had an associated neoplasia [14], hinting at a paraneoplastic origin of some cases of SMS. In the described case we think that the SMS could have been a paraneoplastic syndrome of the underlying HD, because of the close relationship between SMS and HD relapse. The immune derangement typical of most HD patients may well promote the development of autoimmune disorders.

«STIFF-MAN SYNDROME»: UNA INSOLITA SINDROME PARANEOPLASTICA IN CORSO DI MALATTIA DI HODGKIN

Viene descritto un caso di recidiva di Malattia di Hodgkin (MH) associata a «sindrome dell'uomo rigido (stiff-man syndrome)» (SMS), una rara e drammatica malattia del sistema nervoso centrale (SNC) caratterizzata da rigidità muscolare continua e spasmi dolorosi che simulano una forma cronica di tetano. La SMS è comparsa in concomitanza con una recidiva di MH, ed è regredita completamente con la terapia instaurata per la MH. Nel siero del paziente sono stati riscontrati anticorpi contro le strutture cerebellari. Dopo diciotto mesi il paziente ha presentato una seconda recidiva di HD, ma in questa occasione non sono ricomparsi sintomi riferibili alla SMS.

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