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Multiple neurological syndromes during Hodgkin lymphoma remission

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Abstract

We report a young patient who developed a stiff man syndrome (SMS) long after remission of Hodgkin lymphoma. This patient is remarkable because he has had several other potentially autoimmune or paraneoplastic neurological syndromes including limbic encephalitis and demyelinating polyneuropathy which also occurred years after remission from Hodgkin disease.

Key words : Stiff man syndrome ; chronic inflammatory demyelinating polyneuropathy ; Hodgkin lymphoma ; limbic encephalitis ; paraneoplastic syndrome ; Guillain-Barré syndrome.

Introduction

Hodgkin lymphoma is sometimes associated with neurological paraneoplastic diseases. In general, paraneoplastic neurological syndromes parallel the course or are the presenting sign of an underlying neoplasm (Voltz *et al.*, 2002 ; Dropcho *et al.*, 1998). Rarely these syndromes develop years after remission from Hodgkin disease. Hammack *et al.*, however, reported six cases of paraneoplastic cerebellar degeneration one to 54 months after remission form Hodgkin disease (Hammack *et al.*, 1992). We present a patient who is remarkable because of the combination of several autoimmune or paraneoplastic neurological syndromes emerging long after total remission of Hodgkin disease. He consecutively developed an episode of limbic encephalitis, demyelinating polyneuropathy and stiff man syndrome (SMS). The development of these syndromes during remission of Hodgkin lymphoma has not been reported yet.

Case report

A 38-year-old man of Indian origin is known with non insulin dependent diabetes mellitus since 1997. In 1998, he presents with a swollen inguinal lymph node, night sweats, fever of unknown origin and fatigue. Hodgkin lymphoma grade IIB is diagnosed with involvement of inguinal and pelvic lymph nodes. He is treated with an adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) regimen of combination chemotherapy once every two weeks for 12 cycles. The patient is in total remission since 1999.

In 1999, the patient is admitted to another hospital with a history of seizures, hallucinations and disorientation. He has a persisting amnesia for about six months of this episode. Thyroid tests and thyreoglobulin and thyreoperoxidase antibodies are normal. The CSF shows lymphocytic pleocytosis (258 white blood cells/mm^3 : 85% lymphocytes, 13% segments, 2% monocytes), elevated protein levels (74 mg/dl ; normal < 50 mg/dl) but no oligoclonal bands on immunoelectrofocusing. The EEG is diffusely slowed with high-voltage delta activity predominantly over the left temporal and occipital lobe. MRI T2 images show a non contrast enhancing lesion at the anterior pole of the left temporal lobe. The past history of cancer, the clinical picture, CSF analysis, MRI and EEG findings are suggestive for the diagnosis of limbic encephalitis. Serology testing for VGKC antibodies was done in a serum sample collected in 2004, but these antibodies turned out to be absent. The patient is treated with valproate resulting in a complete recovery of the seizures and disorientation.

In 2001, the patient presents to our hospital with paresthesias at his fingertips and forefeet, and an asymmetric bilateral facial paresis of the peripheral type, both sub-acute in onset. Deep tendon reflexes are absent. Blood tests including viral serology are normal. The CSF shows an elevated protein content (144 mg/dl). The EMG shows a demyelinating sensory and motor polyneuropathy in all limbs. MRI of the brain is normal. The diagnosis of sub-acute Guillain-Barré syndrome is made and treatment with oral prednisolon (1 mg/kg) is initiated during three months. The facial paresis recovers partially and the paresthesias become less intense.

In 2002, the patient consults for disabling cramps and stiffness of the lower limbs and back. Walking is slow and awkward especially on initiation of the movements. Clinical investigation shows hypertonia of the lower limbs with areflexia. There are no Babinski signs. The Romberg test is unstable. Finger-nose test is normal. There are still

sequellae of his polyneuropathy. The diagnosis of sub-acute Guillain-Barré syndrome is corrected to chronic inflammatory demyelinating polyneuropathy (CIDP).

The routine laboratory tests show normal haematological findings and biochemical findings compatible with diabetes mellitus type II. ELISA testing shows elevated serum levels of anti-GAD65 (Glutamic Acid Decarboxylase) antibodies (14% bound ; normal value < 2.6% bound). Serology for anti-nuclear (ANA), anti-neutrophile cytoplasmic (ANCA), anti-mitochondrial, anti-cyclic citrullinated peptide (CCP), anti-cardiolipin, anti-gastric parietal cell, anti-cryoglobulin, anti-Hu, anti-Yo en anti-Ri autoantibodies are negative. Serum anti-amphiphysine antibodies have been determined in 2004, but were negative. CSF analysis is normal with no oligoclonal IgG bands. MRI of the cervical spine and brain is normal. The diagnosis of stiff man syndrome is made, and the patient is treated with diazepam and intravenous immunoglobulins (IVIg). There is a partial response to the IVIg therapy with diminished abdominal spasms. Diazepam is not tolerated in therapeutic dosages.

Discussion

The consecutive development of several autoimmune or paraneoplastic syndromes after remission of neoplastic disease is a rare observation.

Limbic encephalitis is a paraneoplastic neurological syndrome often associated with small cell lung carcinoma (50%), testicular (20%), breast (8%) and other tumours (Gultekin *et al.*, 2000). Limbic encephalitis has been described earlier in association with Hodgkin disease (Bernard *et al.*, 2003). Limbic encephalitis causes short-term memory loss, confusion and behavioural changes, but seizures can also occur. CSF often contains elevated protein combined with mild mononuclear pleocytosis. Sometimes oligoclonal bands can be detected in CSF (Gultekin *et al.*, 2000 ; Vincent *et al.*, 2004). MRI scan usually shows hyperintense T2 lesions in both amygdala and hippocampus. These lesions in the temporal lobe happen to be transient during the course of the disease (Dirr *et al.*, 1990). Our patient did have T2 lesions at the anterior temporal lobe, but these lesions disappeared during follow-up MRI. Thyroid function should be analysed to rule out the possibility of Hashimoto encephalopathy, a condition also characterised by seizures, stupor and psychosis (Ferracci *et al.*, 2003). Recently the presence of voltage-gated potassium channel (VGKC) antibodies was demonstrated in some cases of limbic encephalitis. These antibodies do not discriminate between idiopathic or paraneoplastic limbic encephalitis but probably indicate a good response to immunotherapy (Pozo-Rosich *et al.*, 2003 ; Vincent *et al.*, 2004). No residual anti-VGKC antibodies could be detected in 2004 (courtesy Prof. A. Vincent, Oxford University, UK). The five year delay between the limbic encephalitis manifestations and the test could be the reason for the negative results.

Peripheral nervous system abnormalities occur in five percent of patients with lymphoma (Hughes *et al.*, 1994 ; Mallecourt *et al.*, 2000). Demyelinating polyneuropathies such as Guillain-Barré syndrome and CIDP have been reported in association with lymphoma (Maslovsky *et al.*, 2001). Our patient developed a demyelinating neuropathy that is best classified as CIDP. Vinca alkaloids such as vinblastine are the only drugs used in lymphoma which commonly cause neuropathy of the sensorimotor axonal type (Hughes *et al.*, 1994).

Stiff man syndrome is characterised by muscular rigidity and spasms of predominantly axial and proximal limb muscles. Emotional or audiovisual stimuli can elicit spasms of the legs and trunk. Stiffness and spasms fluctuate throughout the day and lessen or even disappear during sleep or narcosis (Meinck *et al.*, 2002). An autoimmune pathogenesis is suspected. About 70 percent of all patients have serum and CSF anti-GAD65 antibodies (Dalakas *et al.*, 2001). GABA is one of the most important inhibitory neurotransmitters in the brain and spinal cord. Anti-GAD65 antibodies are an excellent marker for SPS, but following their titers has no value in monitoring the disease nor is there a relationship between the antibody titer and disease severity (Rakocevic *et al.*, 2004). Given the history of Hodgkin lymphoma and the presence of anti-GAD65 antibodies, the SMS in our patient may be an auto-immune complication of the lymphoma. SMS rarely has a paraneoplastic etiology. If so, the tumour most commonly involved is breast cancer in association with anti-amphiphysine antibodies (Bataller *et al.*, 2003). Serum analysis in 2004 showed no anti-amphiphysine antibodies. This patient developed a SMS 4 years after remission of the lymphoma while paraneoplastic syndromes normally parallel the course of a malignancy or are the presenting sign of an occult cancer. Intravenous immunoglobulins have been successful in some cases (Dalakas *et al.*, 2001). Our patient responds only partially to the IVIg therapy with diminished abdominal spasms and improved gait.

In conclusion, this case demonstrates that Hodgkin disease can cause multiple delayed neurological syndromes long after remission of the lymphoma.

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