Abstract

We report two cases of intravascular malignant lymphomatosis (IML) with a clinical expression limited to the central nervous system. The first patient presented with signs of cerebral, cerebellar and spinal cord involvement. The second had an isolated involvement of the spinal cord. In both cases the diagnosis was made at post-mortem examination; pre-mortem examination of biops tissue from peripheral nerve and muscle in the first case, spleen and liver in the second were unhelpful for the diagnosis of lymphoma. We review the published literature on IML, its ante-mortem diagnosis and treatment.

Key words: Intravascular malignant lymphomatosis; lymphoma; chemotherapy; myelopathy.

Introduction

Intravascular malignant lymphomatosis is an uncommon neoplastic disorder, which often involves the central and peripheral nervous system in the setting of a relentless multisystemic disease: clinical presentations restricted to the nervous system are rare but they represent a difficult diagnostic challenge.

We report two cases of intravascular malignant lymphomatosis presenting with clinical signs restricted to the nervous system. The first patient presented with cerebral, cerebellar and spinal cord signs, the second with an isolated myelopathy. Both cases were diagnosed at post-mortem examination; pre-mortem examination of neuromuscular biopsy in the first patient and of splenic and hepatic biopsies in the second patient were unhelpful for diagnosing this lymphoma.

Clinical presentation

Patient 1

A 54 year-old-man was admitted to the hospital in July 1996 for gait disturbance with asymmetrical lower limb weakness (left > right), urinary retention, and diffuse headache. He had experienced lower limb thrombophlebitis one week earlier.

His previous medical history included severe osteoporosis, prostatic hypertrophy, gastric ulcer, hypertension and Menière’s disease. He was treated with bisoprolol, betahistine, terazosin and cimetidine.

Clinical examination revealed a paresis of the left upper limb and lower limbs. Tendon jerks were brisk with a bilateral Babinski and a right Hoffmann’s sign. Cerebellar signs predominated on the right side with moderate ataxia, hypermetry and dysdiadokokinesia. Sensory testing showed distal hypoesthesia of the lower limbs. The patient improved initially under methylprednisone 64 mg/d but after a few days he developed asthenia, anorexia, dizziness and confusion.

The only laboratory abnormalities were increased levels of SGPT and gamma-GT. Immunological and serological studies were negative. CSF examination showed increased protein (82 mg/dl on admission; 114 mg/dl one week later; 44 mg/dl after 1 month); mild lymphocytosis (10 cells/mm³) and oligoclonal banding on isoelectrofusing in two out of three CSF samples. Brain CT-scan showed a cortico-subcortical parietal low density lesion. Brain MRI showed multiple aspecific lesions (hypertense on T2- and hypointense on T1-weighted images) of the left middle cerebellar pedunculus, the corpus callosum and the right hemispheric white matter. Thoraco-lumbar MRI was unremarkable. Abdominal CT-scan and ultrasonography were normal. Thoracic CT-scan was suggestive of bilateral segmental emboli. On EMG there was mild denervation in multiple lumbo-sacral radicular territories suggestive of a cauda equina lesion. Transcranial magnetic stimulation revealed slowing of central motor conduction between C5 and C7 on the left side. A neuromuscular biopsy sampling a distal sensitive branch of the musculocutaneous nerve and peroneal muscle showed mild axonal loss in nerve fascicles and changes of acute denervation in the muscle.

The patient deteriorated gradually and died less than two months after onset of the first symptoms. At autopsy, the fixed brain weighed 1360 gr and showed moderate symmetrical edema of both hemispheres. Coronal sections showed numerous
Intravascular malignant lymphomatosis (IML) was first described in 1959 by Pfleger and Tappeiner, as “angioendotheliomatosis proliferans systemisata”. It has been reported in the literature under a variety of names including malignant or systemic angioendotheliomatosis, endothelioma, angiotropic large-cell lymphoma and intravascular lymphoma.

Its histological feature is proliferation of large, atypical lymphoid cells within the lumen of capillaries, small veins and arteries (Wick et Stacey 1991). The histogenesis of IML cells has been variously described as endothelial (Pfleger and Tappeiner 1959) or lymphocytic (Mori et al. 1989). Immunohistochemical and genetic studies indicate that the malignant cells have lymphoid origin and that in most cases, such
FIG. 1. — Autopsy results:
Case 1:
(a-b) numerous ill-defined areas of haemorrhagic and ischaemic changes are present in the centrum semi-ovale and corpus callosum (coronal sections);
(c-d) large lymphoma cells with centroblastic or immunoblastic features (arrows) investing the small vessels in the hemispheric white matter (c : He, 100 X) and in a lumbar dorsal root ganglia (c : HE, 400 X).
Case 2:
(e-f) sequellae of spinal cord infarction (arrows) at the cervico-thoracic junction (HE, 100 X) ; CD20+ lymphoma cells are seen in the vasa nervorum of a neighbouring dorsal spinal root (immunostaining with anti-CD20, 400 X).
as in ours, they have a B-cell immunophenotype (Otrakji et al. 1988, Stroup et al. 1990, Wick et al., 1991, Demirer et al., 1994). IML is considered to be a rare, high-grade, extranodal non-Hodgkinian lymphoma with a tropism for the endothelium. The affinity of tumor cells for capillary endothelium may be explained by lymphocyte receptors for endothelial membrane antigens (Demirer et al., 1994, Shanks et al., 1997).

IML may affect a wide range of age groups with a high incidence in the seventh decade. There is no clear gender difference in incidence. In up to one-half of cases, IML presents clinically with skin lesions characterized by prominent, hyperpigmented, or hypervascular plaques or nodules, located preferentially over the abdomen and the thighs. Up to two-thirds of patients have neurological symptoms with more frequently diffuse cerebral signs and dementia or focal cerebral signs including stroke-like episodes, partial or generalized seizures (Pellat et al. 1993, Liszka et al. 1994). Other neurological involvements include peripheral neuropathy, polyradiculopathy, myopathy and myelopathy (Levin et Lutz 1996).

In this report, patient 2 presented with spinal cord symptoms for the first eight months of the disease course, after which he developed diffuse CNS symptoms. Similar cases of isolated myelopathy lasting for many months have been reported in IML (Hamada et al. 1991). However, in most reports of IML cases with initial spinal symptoms, the disorder remained limited to the spinal cord for no more than three months (Bots 1974, Dolman et al. 1979, Ojeda 1983, Dubas et al. 1990). As in our cases, repeated MRI of the spinal cord did not reveal any medullary lesions.

Infiltration by IML of lungs, kidneys, adrenal glands and prostate is frequent. All organs may be involved, individually or in combination, but liver, spleen, lymph nodes and bone marrow are relatively spared until late in the disease course. Patients may also present with general symptoms (“B-symptoms”) such as fever of unknown origin (Kuvliev et al. 1999), night sweats, chills, weight loss and malaise (Saacson et Norton 1994). Thrombophilia has commonly been reported in IML (Wick et al. 1986, Stroup et al. 1990, Stahl et al. 1991, Curtis et al. 1991), which may also have favoured the thrombophilebitis in patient 1 as well as pulmonary embolism in both cases. A more unusual presentation is disseminated intravascular coagulation (Stahl et al. 1991).

Common laboratory abnormalities include mild anemia, elevated erythrocyte sedimentation rate and markedly elevated serum lactate dehydrogenase levels (Otrakji et al. 1988, Croisile et al. 1990). Usually, there are no detectable circulating lymphoma cells in blood and CSF, but the latter is frequently characterized by moderate pleiocytosis and elevated protein levels.

| 1. Progressive, multifocal cerebrovascular events | 78% |
| 2. Spinal cord and nerve root vascular syndromes | 38% |
| 3. Subacute encephalopathy | 27% |
| 4. Peripheral or cranial neuropathies | 21% |

(Glass et al., Cancer 1993).

Brain MRI may reveal aspecific lesions mostly located in the white matter. However, Liow et al reported two cases with linear, punctate, and patchy enhancement on brain MRI (Liow et al. 2000). In these two cases, the pattern of enhancement was correlated with T2 abnormalities (the more pronounced the T2 abnormality, the more patchy/confuent the enhancement). They concluded that careful interpretation of cerebral MRI findings including T2/FLAIR and T1 postgadolinium sequences could allow clinicians and neuroradiologists to make timely diagnosis. Spinal MRI is generally normal even in cases presenting with spinal cord signs (Hamada et al. 1991, Nakahara et al. 1999, Waring et al. 1999, Bequet et al. 2000). The diagnosis is made post-mortem in most (> 60%) cases. Sometimes, it may be provided by biopsies of the brain, skin or other involved organs (Liszka et al. 1994, Nakahara et al. 1999, Vieren et al. 1999, Baumann et al. 2000, Bequet et al. 2000). When there is neurogenic weakness in the legs, muscle biopsy has been diagnostic in 14 out of 19 patients (74%) (Petito et al. 1978, Sparling et al. 1979, Krieger et al. 1982, Shibuya et al. 1983, Vital et al. 1989, Molina et al. 1990, Stroup et al. 1990, Stahl et al. 1991, Lacomis et al. 1992, Glass et al. 1993, Harris et al. 1994, Sleater et al. 1994, Roux et al. 1995, Levin et Lutz 1996, Pryason 1996, Butori et al. 1997, Suzuki et Koizumi 1997, Kuvliev et al. 1999, Nakahara et al. 1999). Cerebral biopsies may be falsely negative in neurological cases in which the diagnosis was confirmed post-mortem (Bille et al. 1995).

IML with CNS involvement has an extremely poor prognosis. Most patients survive no more than 1 year after the diagnosis has been made (Willemze et al. 1987, Levin & Lutz 1996). Transient improvement has been reported with steroids, radiation therapy, plasmapheresis and chemotherapy (Domizio et al. 1989, Stroup et al. 1990, Beal & Fischer 1982, Nakahara et al. 1999). Chemotherapy regimens directed at intermediate and high-grade lymphomas seem to be the most efficient treatments (Di Giuseppe et al. 1994, Nakahara et al. 1999, Vieren et al. 1999). In patients receiving CHOP chemotherapy (cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone), 6 (55%) of 11 went into complete remission (Demirer et al. 1994). In cases of retractive...
IML, a second-line therapy can be performed followed by autologous bone marrow transplantation (Rose et al. 1999).

To summarize, IML should be considered in the differential diagnosis of unexplained myelopathy, meningo-encephalitis, acute confusional state, dementia or stroke-like syndromes. Diagnostic work-up should include biopsy of organs known to be frequently involved in IML, such as skin, kidneys, adrenal glands, liver and lungs. Biopsy of peripheral organs may lead to diagnosis avoiding the need for a cerebral biopsy and allowing appropriate treatment to be started. CHOP chemotherapy eventually with G-CSF support is the most effective treatment.

REFERENCES


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