Neurolymphomatosis Associated With Sézary Syndrome

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Background: Mycosis fungoides and Sézary syndrome are cutaneous T-cell lymphomas characterized by the epidermotropism of tumor cells. Neuropathic disease is rare during mycosis fungoides and Sézary syndrome and usually results from a central nervous system involvement in late stages. Neurolymphomatosis is defined as the infiltration of the peripheral nerves by tumor lymphocytes. It has been described in patients with aggressive systemic lymphomas but, to our knowledge, not in patients with mycosis fungoides or Sézary syndrome. We report the first case of neurolymphomatosis in a patient with Sézary syndrome and the partial efficacy of high-dose methotrexate sodium in treating this usually refractory complication.

Observation: A 73-year-old woman with newly diagnosed Sézary syndrome rapidly developed severe peripheral neuropathic disease with multiple paralyses. Biopsy specimens were taken from a clinically affected nerve and the adjacent muscle; they revealed a neural infiltration by Sézary cells with secondary muscular atrophy. Partial response and major neurologic recovery occurred and persisted under high doses of intravenous methotrexate until the patient died 14 months after the Sézary syndrome diagnosis from a pericarditis of uncertain origin.

Conclusion: This unusual and demonstrative case report highlights the possible neurotropism of malignant cells in Sézary syndrome and suggests the effectiveness of high doses of intravenous methotrexate in this rare and fatal disorder.


Neurolymphomatosis is a rare neurologic manifestation of systemic lymphomas due to infiltration of peripheral nerves by tumor cells. The diagnosis of neurolymphomatosis is difficult and often delayed because it ideally requires a biopsy specimen of an involved nerve. Cutaneous T-cell lymphomas (CTCLs) are a heterogeneous group of lymphoproliferative disorders caused by clonally derived, skin-invasive T cells. Mycosis fungoides (MF) and Sézary syndrome (SS), the most common types of CTCLs, are characterized by the epidermotropism of tumor cells. Sézary syndrome is a leukemic form of the disease, in which erythroderma is classically associated with generalized lymphadenopathic disease and the presence of neoplastic T cells (Sézary cells) in skin, lymph nodes, and peripheral blood. Although an extracutaneous spread is not uncommon in advanced stages of MF and SS, neurologic complications are rare and generally result from leptomeningeal or central nervous system involvement. We report, to our knowledge, the first case of epidermotropic CTCL (ie, MF or SS) with severe neurolymphomatosis proven by histologic examination. In addition, we emphasize the major diagnostic and therapeutic difficulties encountered in this exceptional situation and provide preliminary data on the efficacy and tolerance of high doses of methotrexate.

Report of a Case

A 73-year-old woman was hospitalized for right hemiparesis. She reported a recent access of atrial fibrillation and a 3-year history of diffuse skin dryness and erythema. The results of computed tomography of the head were normal, and her headaches improved spontaneously. She was therefore referred to our department for evaluation of her skin condition. Clinical examination revealed an erythroderma with widespread lymphadenopathic disease. Histologic findings in skin and nodal biopsy specimens were those of an epidermotropic CTCL with node involvement. Peripheral blood analyses revealed moderate leukocytosis and lymphocytosis, with a Sézary cell count of 3400/µL, a CD4/CD8 ratio greater than 20, and less than 7% T cells that expressed CD7. The same clonal amplification of T cells was demonstrated by T-cell receptor gene analysis in skin, blood, and lymph nodes. The diagnosis of SS was established according to...
previously published criteria from the International Society for Cutaneous Lymphomas.3 The patient informed physicians that she was experiencing gradual weakness, which affected several regions, including the right facial nerve which had a typical Bell palsy (Figure 1), the left third cranial nerve, the right lower leg, and the right upper limb. She began to require the use of a wheelchair. A lymphomatous leptomeningeal involvement was ruled out by normal or negative results of cerebral, spinal, and cranial magnetic resonance imaging; bone scintigraphy; and subsequent cerebrospinal fluid analyses. Human T-lymphotropic virus 1, human immunodeficiency virus, and Borrelia burgdorferi serologic test results were negative. The electromyogram showed a polyneuropathy with axonal radiculoneuropathy and low motor potential amplitudes, mostly affecting external and internal popliteal sciatic nerves. Three cycles of chemotherapy with cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, and prednisone (CHOP), associated with a methylprednisolone bolus, followed by oral prednisone (1 mg/kg/d) and chlorambucil improved cutaneous lesions and decreased the Sézary blood cell count, but the patient’s motor condition worsened. A biopsy of the right superficial peroneal nerve and the adjacent muscle was performed. Histologic examination showed a neurogenic muscular atrophy and a decreased number of myelinated fibers with major Wallerian degeneration. The wall of an epineurial artery and the endoneurium were infiltrated by large atypical cells with mitoses and convoluted nuclei (Figure 2). The diagnosis of axonal neuropathy secondary to a neural infiltration by Sézary cells was established.

The patient was then treated with high doses of intravenous methotrexate (1.5 g/m²) every 2 weeks. A partial response with major motor improvement was observed after 3 cycles, but every attempt to space out subsequent infusions led to rapid worsening of her neurologic condition. Maintenance therapy with methotrexate, 2 g/m² every 4 weeks, was therefore continued until a total of 11 cycles and a cumulative dose of 18.5 g/m². The patient partially recovered and was able to walk without assistance. However, her condition suddenly worsened 14 months after diagnosis, and she was readmitted for severe acute heart failure. A pericarditis with major pericardial effusion was diagnosed, which rapidly led to the patient’s death despite her admission to a cardiology intensive care unit. No autopsy was performed.

Both MF and SS rarely involve the nervous system. The literature on this topic mainly consists of individual case reports of patients with large cell transformation of MF and either neoplastic meningitis or cerebral tumors.4-7 In a retrospective study8 of 187 patients with CTCL, 2.7% had neurologic complications, with 1.6% due to direct involvement of the nervous system. Meningeal infiltration was the most frequent feature. Most patients had a
transformed MF with a poor prognosis (median survival time, 12 weeks).\(^8\)

In contrast with previous reports, our patient had a severe peripheral neuropathy without central nervous system involvement. Histologic examination of a muscle and nerve biopsy specimen showed neurogenic muscle atrophy and an axonal neuropathy secondary to an epineurial and endoneurial infiltration by Sézary cells. This is, to our knowledge, the first reported case of SS with neurolymphomatosis proven by histologic examination.

Patients with neurolymphomatosis usually present with widespread systemic multiorgan involvement by noncutaneous, non-Hodgkin lymphomas. The clinical presentation is a painful or painless, asymmetrical sensorimotor polyneuropathy that affects cranial and/or spinal roots or nerves. Neurolymphomatosis should be distinguished from leptomeningeal involvement, which can mimic a peripheral neuropathy.\(^1\) A nerve biopsy is required to confirm the diagnosis. The most suggestive pathologic finding is an infiltration by lymphoma cells of all compartments of involved nerves, especially the endoneurium, as observed in our patient. Neurolymphomatosis is characterized by a rapid and fatal progression in most patients. This may be explained by the intrinsic biology of tumor cells, the difficulties and delays in establishing the diagnosis, and the inability of most chemotherapies to penetrate through the blood-nerve barrier into the peripheral nervous system. Only rare patients with neurolymphomatosis experience significant responses to intensive chemotherapy regimens.\(^9,10\) In one report,\(^11\) a patient with a stage IVB nodal diffuse large B-cell lymphoma and neurolymphomatosis achieved a 6-month complete response to high doses of methotrexate followed by intensive polychemotherapy and autologous hematopoietic stem cell transplantation.\(^10\)

Because our patient’s paralyses rapidly worsened with conventional treatments of SS, including 3 cycles of CHOP, she was subsequently treated with high doses of methotrexate. This regimen was chosen on the basis of reported success in patients with lymphomatous central nervous system involvement, using concomitant intrathecal and high-dose systemic methotrexate.\(^11\) However, this treatment had not been evaluated previously in SS. Our patient experienced a rapid initial improvement of both her SS and the associated neurolymphomatosis. Partial remission persisted for 10 months under maintenance therapy without hematologic, hepatic, or renal toxic effects. However, she eventually died from a pericardial effusion. Pericarditis has been reported as a rare adverse effect in patients treated with low doses of methotrexate for various benign conditions\(^12-15\) but not, to our knowledge, with high doses in aggressive lymphomas. Because no autopsy was performed on our patient, it remains unclear whether this pericardial effusion had a neoplastic or toxic origin or was secondary to a pericardial lymphomatous involvement. Finally, this unusual and demonstrative case report highlights the possible neurotropism of malignant cells in cutaneous lymphomas and particularly in erythrodermic forms of CTCL. Many patients with erythrodermic MF or SS have unusual pains with a neuropathic component or unexplained minor neurologic symptoms. Whether these symptoms could result from previously unrecognized infiltrations of peripheral nerves by neoplastic malignant T cells should be evaluated in prospective studies, combining careful clinical evaluations, electromyograms, and targeted biopsies for accurate histologic examination.

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