Intravascular lymphomatosis presenting as an ascending cauda equina: conus medullaris syndrome: remission after biweekly CHOP therapy

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Abstract
A 63 year old man developed dysaesthesia in the legs followed by a subacute ascending flaccid paraparesis with sacral sensory and autonomic involvement. Intravascular lymphomatosis (IVL) was favoured by the presence of low grade fever and raised serum C reactive protein, CSF pleocytosis, raised lymphoma markers (serum LDH, soluble IL-2 receptor), and steroid responsiveness. Only muscle, among several organ biopsies, confirmed IVL. A cytogenetic study of the bone marrow showed chromosome 6 monosomy, as previously reported. The monosomy of chromosome 19, which bears the intercellular cell adhesion molecule-1, newly found in this case, may be related to the unique tumour embolisation of IVL. The CHOP regimen (six courses in 12 weeks) using granulocyte colony stimulating factor (G-CSF) led to gradual resolution of myeloradiculoapathy and laboratory supported remission lasting for more than 13 months. The biweekly CHOP with G-CSF support may be a choice of chemotherapy in averting rapidly fatal IVL.

Keywords: intravascular lymphomatosis; angiotropic large cell lymphoma; chemotherapy; muscle biopsy

Intravascular lymphomatosis (IVL), or angiotropic large cell lymphoma, is a special form of lymphoma, in which lymphoma cells lodge in the systemic vasculature, but it usually lacks lymphadenopathy.1,2 Tumour embolisation with secondary haemostasis, thrombosis, and vasculitis in small vessels presents preferentially with vascular syndromes of the brain, spinal cord, and nerve roots.2 Inflammatory signs, steroid responsiveness, pancytopenia, and cutaneous manifestations may often complete the clinical picture. Thus IVL is often a diagnostic challenge, as it mimics strokes, cerebral angitis, multiple sclerosis, polyradiculoneuritis, and systemic vasculitic disorders.1,4

As this form of lymphoma is potentially treatable and even curable when chemotherapy is initiated early, histopathological diagnosis is mandatory.

Here, we report a patient with IVL presenting with a progressive cauda equina-conus medullaris syndrome. Despite some delay in diagnosis, we were able to induce a complete remission by intense chemotherapy, the second case ever reported of the successful chemotherapy for paraplegic IVL.4

Case report
A 63 year old man, whose father had died of malignant lymphoma, experienced lancinating pains in the lateral part of his right thigh, followed by dysaesthesia of both legs, causing insomnia over a period of 1 month. Spinal x ray films, CT, and a myelogram at another hospital were unremarkable. Because of unstable walking, urinary hesitancy, and dysesthesia that extended to both thighs, he was transferred to our hospital. Thereafter, subacutely ascending flaccid paraparesis together with urinary retention made him bedridden by 2 months. Low grade fever, exaggerated erythrocyte sedimentation rate, serum C reactive protein, and a high LDH of 3444 mg/dl (reference<400 mg/dl) were noted, but spinal MRI was negative. Examination of CSF after lumbar puncture showed a total protein of 169 mg/dl, pleocytosis of 32 /ml (lymphoid cells 97%), equally dominant CD4 and CD8 positive cells, and no plasma cells or malignant cells, and higher β2-microglobulin of 2.8 µg/ml than that in serum (2.4 µg/ml, reference <1.9 µg/ml). These findings suggested intrathecal lymphoma infiltration. After intravenous methylprednisolone (1000 mg daily for 3 days), he became ambulatory for 2 weeks and then deteriorated. Lymphadenopathy or mass lesions were not found by whole body CT or endoscopy of the gastrointestinal tract. Gallium scanning and spinal Gd-MRI did not disclose any abnormalities. IVL was suspected because it often lacks lymphadenopathy and preferentially involves the lower spinal region. However, biopsies of the thyroid, gastric mucosa, a colonic polyp, bone marrow, and prostate were all negative. When transferred to our neurology service 3 months after the onset, he showed symmetric flaccid paraplegia with mild muscle atrophy from the iliopsoas down to the anal sphincters, all modality sensory loss below the mid-thighs including the sacral area,
ataxic bladder, and Lasegue signs; plantar stimulation provoked no response. Electromyography of the leg muscles disclosed active denervation. Raised serum soluble IL-2 receptor concentrations (2350 U/ml, reference <750 U/ml) with persistently increased LDH were noted. Ultimately, biopsy of a paralytic quadriceps femoris muscle showed the presence of IVL (figure); lymphoid cells with large pleomorphic nuclei, prominent nucleoli, and mitoses were seen mainly in perimysial venules without extravasation. Most of the neoplastic cells were CD 20+ and CD3−, indicating the B cell lineage. Despite irradiation at a total dose of 25 Gy to the lower spine, the sensory level ascended to the lower thoracic dermatomes and paraplegia worsened with painful tonic spasms and spinal automatism. Then, cardiopulmonary failure, anasarca, hepatosplenomegaly, and pancytopenia gradually developed. A bone marrow aspirate was normal in cell counts but culture showed 45, XY, add (1)(p13), -6, der (8;15)(q10;q10), add (11)(q13), -19, add (21)(p11), +2 mar besides normal karyotype in 13 cells, which was against a congenital abnormality. Chemotherapy with 750 mg/m² cyclophosphamide, 50 mg/m² doxorubicin, 1.4 mg/m² vincristine on day 1, and 50 mg/m² prednisolone on days 1–5) was started; 2 µg/kg G- CSF (lenograstim) was used on days 3–13 or longer, until white blood cells were greater than 2000/µl and platelets were greater than 50 000/µl. The paraplegia started to improve in a week after the first course and LDH and soluble IL-2 receptor became normal after two courses. In 12 weeks, six courses were completed. He was still wheelchair bound but neurologically improving steadily 13 months after the therapy. Immunoglobulin gene rearrangements in the peripheral blood and repeated muscle biopsy were negative but only a subclinical adrenal nodule on CT suggested that remission was not complete.

Discussion

To our knowledge, this is only the second report of lasting remission of paraplegic IVL,5 in which devastating brain involvement commonly follows. G-CSF was of great help in treatment as it shortens the course interval, and thus the dose intensity is increased. This is perhaps the reason that the complete remission rate in malignant lymphomas has been improved by the current treatment regimen. Moreover, biweekly CHOP with G-CSF support seems safe even when there is pancytopenia, a common accompaniment of IVL.2,7

To improve the outcome of this particular form of lymphoma, chemotherapy has to be initiated early. IVL is a diagnostic challenge as it only rarely shows nodal or extranodal mass lesions, although pituitary, hepatic, splenic, and adrenal sinusoids are often filled with lymphoma cells. Therefore, imaging methods are not always revealing, as in the present patient. Thus a high rate of suspicion has to be generated by the finding of inflammatory signs and serum markers of lymphomas. A raised serum LDH, predominant in LDH 2, 3, and 4 isozymes, is probably due to the lymphoma load and pulmonary involvement.26 Raised serum soluble IL-2 receptor produced by normal T cells and lymphoma cells is suggestive of IVL but autoimmune disorders need to be ruled out.8

A literature review2 showed that two thirds of patients with IVL had one or more of four neurological presentations: progressive multifocal cerebrovascular events (76%), spinal cord and nerve root vascular syndromes (38%), subacute encephalopathy (27%), and peripheral or cranial neuropathies (21%). The patient described here showed a cauda equina-conus medullaris syndrome with subacutely ascending sensorimotor deficits and spinal involvements.2,9–13 Intravascular lymphomatosis has been confirmed by biopsy of symptomatic or swollen tissues,7 although occasional deterioration or death has been described after brain or spinal cord biopsy.14 To our knowledge muscle biopsy has been diagnostic in 13 out of 18 patients (72%);2,5–7,9,12,13,15–22 most positive cases had neurogenic weakness in the legs (table) whereas myalgia or creatine kinase increases were rarely detected. In our patient
Table: Skeletal muscle/nerve biopsy in intravascular lymphomatosis

<table>
<thead>
<tr>
<th>No</th>
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<th>Paralysis</th>
<th>EMG</th>
<th>Neurogenic</th>
<th>Diagnostic biopsy muscle/nerve</th>
<th>Therapy</th>
<th>Outcome term after onset</th>
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<td>+/-/ND</td>
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<td>+</td>
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<td>ND</td>
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ND=not described, paralysis=+ weakness, ++ paralysis, *terms after therapy, **=terms after diagnosis.
Ara-c=cytosine arabinoside; CPA=cyclophosphamide; DXR=doxorubicin; EP=etoposide; MTX=methotrexate; VCR=vincristine; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisolone; COPP=cyclophosphamide, vincristine, procarbazine, prednisolone; VEPA-M=vincristine, cyclophosphamide, prednisolone, doxorubicin, methotrexate.

Haemostasis caused by flaccid paralysis may have predisposed to lymphoma cell nesting. Therefore, muscle biopsy seems a safe and useful alternative to CNS biopsy in neurological IVL.

There has been a controversy as to the type of lymphoma cells, which is confined to the vascular lumina in this particular condition. Reduced expression of αLβ2 integrin (LFA-1, CD11a/CD18), a cell adhesion molecule related to invasivity, has been found once,23 but its relevance remains controversial.24 This is the third report to look into the cytogenetic abnormality of IVL,19 as it may be a clue to the unique phenomenon of lymphoma cell invasion. The chromosomes 16 and 21 bearing αLβ2 integrin genes were normal in our patient. The monosomy of chromosome 6 carrying the HLA gene shares the same abnormality as a previous reported case. The monosomy of chromosome 19 bearing the intercellular cell adhesion molecule-1 gene was found only in the present patient, although the relevance of this abnormality has yet to be studied.

Patients with IVL are prone to multiple organ failures and the disease is fatal after a few months.2 Only antilymphoma combination chemotherapies seem rational for the hematogenous metastases—for example, focal irradiation—seems ineffective as systemic haematogenous spread of lymphoma cells presumably occurs. However, induction chemotherapy has been largely unsuccessful.2 This may be due to multifocal infarction by intravascular lymphoma cell lodging and secondary thrombosis in this particular form, but chemotherapy related events may complicate the problem—for example, infection or bleeding by myelo-suppression, seizures provoked by tumour lysis syndrome, adrenal insufficiency, and potentiated neurotoxicity due to a compromised blood-brain barrier. Interestingly, thrombolytic therapy was reported to lead to successful chemotherapy in a patient with neurological IVL.25 Support with G-CSF may be of benefit in reducing some risk in chemotherapy and to raise dose intensity, a crucial factor for remission yield.

Thus early diagnosis using clinical pathological measures, vigorous treatment to alleviate ischaemic organ failures, and revised chemotherapy protocol may be of benefit to improve IVL outcome.

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References