Inflammatory neuropathy in homosexual men with lymphadenopathy

Article abstract—Twelve homosexual men had peripheral neuropathy with fever, night sweats, and lymphadenopathy. Sensory symptoms predominated, but there was also weakness and cranial nerve dysfunction. Manifestations were multifocal in nine and distal and symmetric in three. CSF was abnormal in all eight patients examined. Sural nerve in five patients showed axonal degeneration, accompanied in two by segmental demyelination. Four patients had epineurial and endoneurial perivascular chronic inflammatory cells without evidence of vasculitis. Neuropathy remitted spontaneously in six patients. Four patients received steroids without clinical response, although one later responded to plasmapheresis-lymphocytapheresis. Four patients later progressed to AIDS.

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A syndrome characterized by fever, night sweats, malaise, and generalized lymphadenopathy has been described in homosexual men and may presage the appearance of the acquired immunodeficiency syndrome (AIDS) by months or years.[1-3] We report 12 men who had peripheral neuropathy with this syndrome.

Case reports. For 6 months, patient 5, a 31-year-old homosexual man, had fever, night sweats, weight loss, and lymphadenopathy. For 4 months, he had patches of numbness and burning on the trunk and limbs. New areas of sensory involvement appeared during a 2-week course of prednisone therapy (60 mg daily). Two months later, he had horizontal and vertical diplopia that did not respond to a second 2-week course of prednisone. Examination revealed diffuse lymphadenopathy, oral candidiasis, right superior oblique palsy, multiple areas of sensory loss and weakness in both radicular and peripheral nerve distributions, and normal tendon and plantar reflexes. A right peripheral facial palsy and numbness in the distribution of the third division of the left trigeminal nerve appeared. CSF pressure was 110 mm water with 42 white blood cells per mm^3, protein 42 mg/dl, glucose 51 mg/dl, IgG 5.71 mg/dl (normal range, 0.90 to 5.7 mg/dl), IgG/Albumin index 0.96 (normal range, 0.29 to 0.59), and three oligoclonal bands. CSF cultures, cytology, VDRL, and cryptococcal antigen were negative. EMG was consistent with multifocal axonal degeneration with some evidence of demyelination. Sural nerve biopsy showed severe chronic and active axonal degeneration, segmental demyelination, marked endoneurial edema, and endoneurial and epineurial perivascular inflammatory cells (figure, a and b). Alternate-day plasmapheresis-lymphocytapheresis was started, exchanging one plasma volume and removing 9×10^9 lymphocytes per treatment. New areas of sensory disturbance developed in the first week of therapy, but not thereafter. After 3 weeks of therapy, treatment frequency was reduced to twice weekly. After 3 months, there was complete resolution of right superior oblique palsy and improvement of the right facial palsy and sensory and motor deficits. He was given one treatment weekly for 1 month. Two weeks after the last treatment, new areas of sensory disturbance appeared. CSF pressure was 150 mm of water with 6 white blood cells per mm^3, protein 61 mg/dl, glucose 40 mg/dl, IgG 8.6 mg/dl, and IgG/Albumin index 1.25. Therapy was reinstituted with one treatment

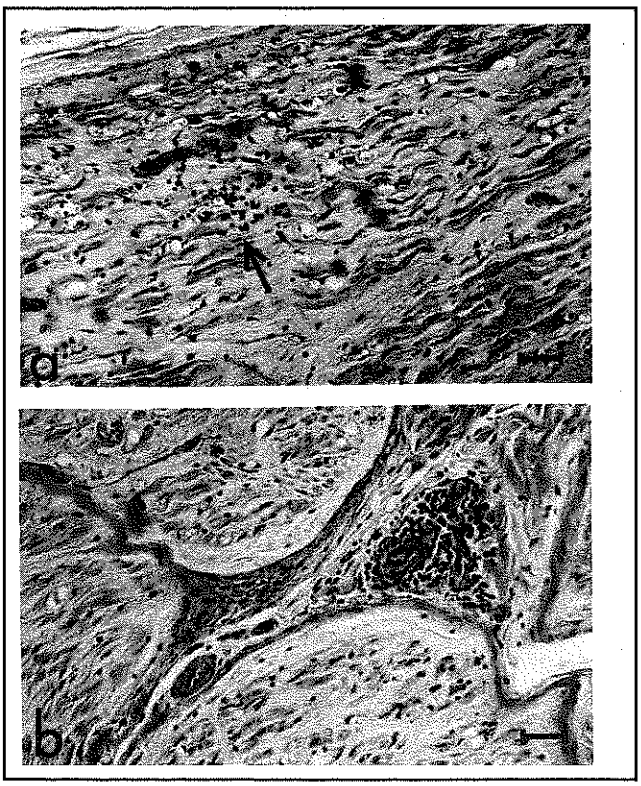

Figure. Photomicrographs of the sural nerve from a patient with mononeuropathy multiplex. (a) Longitudinal section of a fascicle with axonal degeneration and a mononuclear cell infiltrate (arrow). (b) Transverse section showing an endoneurial arteriole with a perivascular mononuclear cell collection. Bar = 50 μm.

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Table. Patient data

Pt	Age	Systemic prodrome/ duration	Neurologic manifestations	Clinical course	CSF
1. DC	31	LAS/3 months	Headache, MM (CN 5, 7 involvement)	No response to high-dose oral steroids. Neuropathy resolved at 2 months. Stable at 4 months.	WBCs 3/mm^3 Pro 58 mg/dl Glu 54 mg/dl
2. CF	42	LAS/2 years	MM	Neuropathy resolved 2 weeks. Stable at 8 months.	NA
3. JG	30	LAS/<1 year	MM	Neuropathy resolved 1 month. Stable at 8 months.	NA
4. ES	41	LAS, ATP, oral *Candida*/ <1 year	MM (CN 5 involvement)	Received high-dose oral steroids for ATP without effect on neuropathy. Neuropathy resolved 4 months. ATP stable on steroids 5 months.	NA
5. MS	31	LAS, oral *Candida*/ 3 months	MM (CN 4, 5, 7 involvement)	No response to two courses of high-dose oral steroids. Neuropathy stabilized with plasmapheresis-lymphocytapheresis.	WBCs 42/mm^3 Pro 44 mg/dl Glu 51 mg/dl IgG 5.71 mg/dl IgG/Alb index 0.96 OCB - 3
6. CB	31	LAS/3 weeks	Headache, meningismus, MM (CN 5, 7 involvement), extensor plantars	Mild distal weakness, sensory deficit at 18 months.	WBCs 40/mm^3 Pro 1,400 mg/dl Glu 70 mg/dl IgG 131 mg/dl IgG/Alb index 19.5
7. JAL	51	LAS/2 years	MM, extensor plantars	No response to high-dose oral steroids. Neuropathy stabilized 4 months. Lost to follow-up at 6 months.	WBCs 8/mm^3 Pro 31 mg/dl Glu 47 mg/dl IgG 8.6 mg/dl IgG/Alb index 0.76
8. JS	25	LAS/4 months	MM	Lost to follow-up at 2 months.	WBCs 8/mm^3 Pro 31 mg/dl Glu 63 mg/dl
9. JL	34	LAS/3 months; oral *Candida*	DSPN, extensor plantars	Indolent progression of neuropathy. Plasmapheresis-lymphocytapheresis initiated at 5 months.	WBCs 13/mm^3 Pro 65 mg/dl Glu 51 mg/dl IgG 9.6 mg/dl IgG/Alb index 0.91 OCB - 3
10. AO	36	LAS, pancytopenia/ 4 months; diarrhea, oral *Candida*	DSPN, extensor plantars	Indolent progression of neuropathy. Died of PCP at 5 months.	WBCs 0/mm^3 Pro 36 mg/dl Glu 48 mg/dl IgG 6.1 mg/dl OCB - 0
11. TO	30	LAS/6 weeks; oral *Candida*	Headache, meningismus, MM (CN 5 involvement)	Neuropathy resolved 2 weeks. Diagnosed with PCP at 5 months. Stable at 7 months.	WBCs 27/mm^3 Pro 94 mg/dl Glu 49 mg/dl IgG 10.3 IgG/Alb index 0.73
12. CA	31	LAS/1 year; oral *Candida*	DSPN	Indolent progression of neuropathy. Diagnosed with KS at 1 month, MAI at 6 months. Stable at 7 months.	NA

LAS Lymphadenopathy syndrome.
ATP Autoimmune thrombocytopenic purpura.
DSPN Distal symmetric polyneuropathy.
MM Mononeuropathy multiplex.
PCP Pneumocystis carinii pneumonia.
KS Kaposi's sarcoma.
MAI Mycobacterium avium-intracellulare.
CN Cranial nerve.
Pro Protein.
Glu Glucose.
OCB Oligoclonal bands.
NA Not available.

EMG	Pathology
Normal	NA
NA	NA
NA	NA
NA	NA
Severe multifocal axonal and demyelinating neuropathy.	Severe axonal and demyelinating neuropathy, marked endoneurial edema; Epineurial and endoneurial perivascular inflammation.
Severe multifocal axonal and demyelinating polyneuropathy.	Severe axonal and demyelinating neuropathy, marked endoneurial edema. Epineurial and endoneurial perivascular inflammation.
Axonal polyneuropathy.	Moderate axonal neuropathy, epineurial and endoneurial perivascular inflammation.
Axonal polyneuropathy.	Normal.
Axonal polyneuropathy.	Mild axonal neuropathy, epineurial and endoneurial perivascular inflammation.
Severe multifocal axonal polyneuropathy.	Multifocal axonal neuropathy.
NA	NA
Axonal polyneuropathy.	NA

weekly, with no change in symptoms or signs over the next 7 months.

For 2 months, patient 9, a 34-year-old homosexual man, had fever, night sweats, weight loss, and lymphadenopathy. For 6 weeks, he had burning paresthesias in hands and feet. Examination revealed diffuse lymphadenopathy, hepatosplenomegaly, and oral candidiasis. The intrinsic foot muscles were wasted, but gait was normal. Position sense was intact and vibration sense reduced in the toes. Pinprick, temperature, and light touch were reduced below the knees and in the fingertips. Tendon reflexes were overactive, and there were bilateral Babinski signs. CSF pressure was 100 mm of water with 12 white blood cells per mm^3, protein 65 mg/dl, glucose 51 mg/dl, IgG 9.6 mg/dl, and IgG/Albumin index 0.91. CSF cultures, cytology, VDRL, and cryptococcal antigen were negative. EMG was consistent with mild axonal degeneration. Sural nerve biopsy showed mild axonal degeneration and endoneurial and epineurial perivascular inflammation. The pain responded to amitriptyline and acetaminophen, but neuropathy progressed. After 6 months of neurologic illness, treatment with plasmapheresis-lymphocytapheresis was given.

Clinical features (table). The patients were homosexual men, aged 25 to 51 years. Six were members of a 200-patient study cohort of homosexual men with unexplained diffuse lymphadenopathy, followed since November 1981. A seventh patient (patient 10, table) had been followed for 4 months for unexplained diffuse lymphadenopathy, but was not a part of the 200-patient study cohort. Five patients came to medical attention primarily because of neurologic symptoms. All had fever, night sweats, malaise, and lymphadenopathy for 2 to 3 years before onset of neuropathy. All patients underwent general medical evaluation according to guidelines established in our AIDS clinic.[3] Six patients had oral candidiasis, one had pancytopenia, and another had autoimmune thrombocytopenia, but none had neoplasia, life-threatening opportunistic infection, recent neurotoxin exposure, or family history of neuropathy. All were referred for evaluation of sensory symptoms, but some also had focal weakness. Nine patients had mononeuropathy multiplex with involvement of cutaneous nerves, mixed nerves, and nerve roots. Three patients had distal symmetric neuropathy. One of these had multifocal axonal degeneration at autopsy. Signs developed or remitted in days or weeks. No patient had abrupt onset of neuropathy or a saltatory course. In several patients, the neuropathy was accompanied by upper motor neuron signs (table).

Laboratory investigations (table). Peripheral blood lymphocytes were studied in 10 patients. All had a reduced percentage of OKT_4+ cells and a reduced OKT_4+/OKT_8+ ratio. CSF was abnormal in all eight patients studied. CSF glucose was normal, and CSF cultures, cytology, cryptococcal antigen, and VDRL were negative. Brain CT was normal in the four patients with Babinski signs.

Nine patients had EMG examination (three patients with distal symmetric neuropathy, six patients with mononeuropathy multiplex). The three patients with distal symmetric neuropathy had low-amplitude sensory and motor compound action potentials and mildly reduced nerve conduction velocities consistent with axonal degeneration. Three patients with mononeuropathy multiplex had low-amplitude sensory and motor compound action potentials and evidence of denervation. Two patients had evidence of both axonal degeneration and segmental demyelination (marked reduction in nerve conduction velocities or conduction block). One patient with mononeuropathy multiplex involving cranial nerves and sensory spinal nerve roots had a normal study.

Sural nerve biopsy was performed in five patients, and sural and sciatic nerves were examined at autopsy in one. In

five patients there was axonal degeneration, accompanied in two by segmental demyelination. Epineurial and endoneurial perivascular chronic inflammatory cells were seen in four of these five patients (figure, a and b), but none had evidence of overt vasculitis (medial vasonecrosis or fibrosis) even when multiple sections were examined. Multifocal axonal degeneration without inflammatory cellular infiltrate was seen in the patient with distal symmetric neuropathy and pancytopenia who died with AIDS. One patient with mononeuropathy multiplex had a normal sural nerve biopsy. No nerves were cultured and no patients were studied for antiaxonal or antimyelin antibodies.

Clinical course. Neuropathy resolved spontaneously in six patients. One had mononeuropathy multiplex and developed *Pneumocystis carinii* pneumonia 4 months after the neuropathy resolved. Five were still in neurologic remission after 3 to 18 months.

Two patients had progressive neuropathy and later onset of AIDS. Both presented with distal symmetric neuropathy; in one, Kaposi's sarcoma and *Mycobacterium avium-intracellulare* appeared after 7 months. The other died of *Pneumocystis carinii* pneumonia after 5 months.

Four patients with mononeuropathy multiplex and one patient with distal symmetric neuropathy had progression of neuropathy, prompting therapeutic intervention. All four patients with mononeuropathy multiplex received steroid therapy for at least 2 weeks without benefit. One of them had spontaneous remission of his neuropathy after completing 2 weeks' steroid therapy. Another was neurologically stable after 7 months of plasmapheresis-lymphocytapheresis without progression to AIDS. Two patients with progressive mononeuropathy multiplex were lost to follow-up.

Discussion. The 12 patients in this series had peripheral neuropathy with fever, night sweats, and lymphadenopathy. Nine patients had mononeuropathy multiplex, and one patient with apparent distal symmetric neuropathy had multifocal axonal degeneration at autopsy. Multifocal nerve lesions may give rise to confluent deficits clinically indistinct from distal symmetric neuropathy,[4,5] and some of our patients who presented with mononeuropathy multiplex evolved into a clinical pattern of distal symmetric neuropathy. It may be, therefore, that all patients had multifocal nerve lesions.

Sural nerve in four patients showed epineurial and endoneurial perivascular chronic inflammatory cells without medial vasonecrosis or fibrosis. Two showed only axonal degeneration; two showed axonal degeneration and segmental demyelination with endoneurial edema. These abnormalities occur in inflammatory neuropathies and in experimental allergic neuritis, diseases presumed to be immune-mediated.[6] In one pancytopenic patient, multifocal axonal degeneration occurred without inflammatory cellular infiltrate, but high CSF IgG suggested inflammatory neuropathy. One patient with mononeuropathy multiplex had a normal sural nerve biopsy. This may have reflected sampling chance in the setting of mutifocal pathology.

Babinski signs in four patients and brisk tendon reflexes in others implied CNS lesions. Brain CT was normal.

Neither the type (mononeuropathy multiplex or distal symmetric neuropathy) nor the course of the neuropathy appeared related to risk for progression to AIDS. Three of the 12 patients developed AIDS, including one patient with transient neuropathy. Progression to AIDS has been reported to occur in 0%[3] to 17%[7] of homosexual men with unexplained diffuse lymphadenopathy. In our series of over 200 patients, 5 have developed AIDS.

Plasmapheresis-lymphocytapheresis seemed to be effective in controlling neuropathy in one patient. Oral prednisone (60 to 80 mg daily) over 2 weeks was ineffective in four patients. Immunosuppressive drugs might have been effective; yet, given the potential for life-threatening opportunistic infections in patients with oral candidiasis, we were reluctant to pursue any therapy that would cause prolonged immunosuppression.

Snider et al[8] reported eight AIDS patients with progressive distal symmetric neuropathy. CSF was normal in two of three patients, and sural nerve histopathology was normal in the one patient biopsied. The pathogenesis of neuropathy may have differed in their series, or their patients may have had confluent mononeuropathy multiplex mimicking distal symmetric neuropathy. Neither CSF IgG nor IgG/Albumin index was measured in their two patients with normal CSF studies. In our series, all patients sampled had an elevated CSF IgG or IgG/Albumin index, including one patient (patient 10, table) with normal CSF protein, glucose, and cell count.

The etiology for neuropathy in these patients is unknown. Although nerve histopathology, elevation in CSF IgG, and clinical response to plasmapheresis-lymphocytapheresis are compatible with an immune-mediated disorder, it may be that these inflammatory features reflect occult nerve infection. Identification of inflammatory neuropathy in homosexual men with lymphadenopathy and constitutional symptoms is important, given the potential response of neuropathy to therapy and because these patients may be at risk for progression to AIDS.

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