Leukoencephalopathy after Levamisole for the Treatment of Verrucae

Yu-Chen Cheng, Helen L. Po

Abstract-

Purpose: Levamisole is an antihelmintic and immunomodulator used as a dewormer and in combination with other forms of chemotherapy to treat colon cancer, melanoma, and head and neck cancer. It has also been used for treating dermatologic disorders such as verrucae. However, its benefits remain controversial and serious side effects such as central nervous system toxicity are unexpected.

Case Report: Multifocal leukoencephalopathy developed in a 26-year-old man after levamisole treatment for verrucae. He recovered completely after discontinuation of the offending drug and treatment with steroid and plasmapheresis.

Conclusion: Clinicians should be aware of this neurotoxicity in order to provide early diagnosis and treatment and thereby improve outcome.

Key Words: levamisole, leukoencephalopathy, encephalopathy, verrucae

Acta Neurol Taiwan 2011;20:262-266

INTRODUCTION

Synthesized in 1966, levamisole was initially used as an anthelmintic agent[1]. In the past decades, its immunomodulating properties have been exploited for the treatment of colon cancer[2]. It is also useful in a wide range of dermatologic disorders[3-5]. Levamisole-induced leukoencephalopathy (LIL) can occur when levamisole is used in combination with 5-fluorouracil[6-8] or alone[9,10]. Cases of LIL have been reported in patients treated with levamisole for recurrent aphthous ulcers[4]. Herein, we report a case of LIL in a patient treated for verrucae.

CASE REPORT

A 26-year-old man visited our dermatologic clinic for skin lesions on the scalp. Verrucae were diagnosed and he received levamisole 150 mg daily. However, he stopped taking the levamisole after 4 days because of dizziness.

Six weeks after the initial dose of levamisole, the patient felt numbness on the right lower half of his face, right thumb, and right index finger. He had trouble speaking and found it awkward to use his computer keyboard over the following 3 days. One week after symptom onset, he choked while drinking. He was then

From the Department of Neurology, Mackay Memorial Hospital, Taipei, Taiwan.
Received January 20, 2011. Revised January 28, 2011
Accepted March 7, 2011.

Correspondence to: Yu-Chen Cheng, MD. Department of Neurology, Mackay Memorial Hospital, No. 92, Sec. 2, Zhongshan N. Rd., Zhongshan Dist., Taipei City 10449, Taiwan.
E-mail: vattmo@gmail.com

admitted to our hospital.

Neurologic examination showed mild cognitive dysfunction (acalculia), partial motor aphasia, mild dysarthria, dysphagia, right facial palsy, right-sided brachiofacial hemiparesis, and sensory impairment (insensitivity to light touch and pinpricks). Brain computed tomography (CT) (Figure 1A) showed severe ill-defined, various-sized hypodense white matter lesions in the bilateral frontal and parietal lobes with moderate contrast enhancement. Magnetic resonance imaging (MRI) (Figure 1B & C) showed multifocal, oval or round, asymmetric lesions with peripheral rim enhancement in the bilateral frontal, parietal, centrum semiovale and periventricular areas. The results of blood studies including cytological and biochemical examination, autoimmune profiles, and bacterial and fungal cultures, were normal or negative. Analysis of the cerebrospinal fluid (CSF) found only a mild increase in protein level (55 mg/dL). CSF bacterial, fungal, and viral cultures, cryptococcal antigen titer, and cytological findings were negative. HIV antibody, immunofixation electrophoresis (IFE) for Bence Jones protein, and IgG index were also negative. The findings suggested a demyelinating disease, but multiple sclerosis and similar leukoencephalopathies were excluded. The favored clinical diagnosis was LIL. Intravenous methylprednisolone 1 gram daily was administered for 5 days but failed to produce clinical improvement. However, 5 sessions of double filtration plasmapheresis (DFPP) therapy were given subsequently and led to improvement in right hemiparesis. He was discharged, received rehabilitation as an outpatient, and ultimately recovered without sequelae.

DISCUSSION

Levamisole is a synthetic phenylimidazolthiazole originally used as an anthelmintic agent[1]. Current studies suggest it could boost cell-mediated immunity by shifting the T helper-1 (Th1) cell/ T helper-2 (Th2) cell balance, consequently up-regulating expression of interleukins (ILs) IL-2 and IL-12 and down-regulating expression of IL-4, IL-5, and IL-10[5,11].

Toxic reaction to levamisole is usually mild[12]. Common reactions include gastrointestinal dysfunction, mucocutaneous symptoms, and reversible hematologic damage. A wide range of neurologic symptoms, with frequency around 1.3-5%[6,12], have been reported, including headache, dizziness, vertigo, vomiting, impaired coordination, impaired thinking, motor aphasia, blurred vision, diplopia, cramps, and weakness[9,13].

Leukoencephalopathy due to levamisole combined with fluorouracil for colon cancer was first reported in 1992[6,7]. Leukoencephalopathy due to levamisole alone was also described in patients under treatment for malignant melanoma and hepatitis C[9,10]. The pathogenesis of this problem remains unclear. Disseminated perivascular

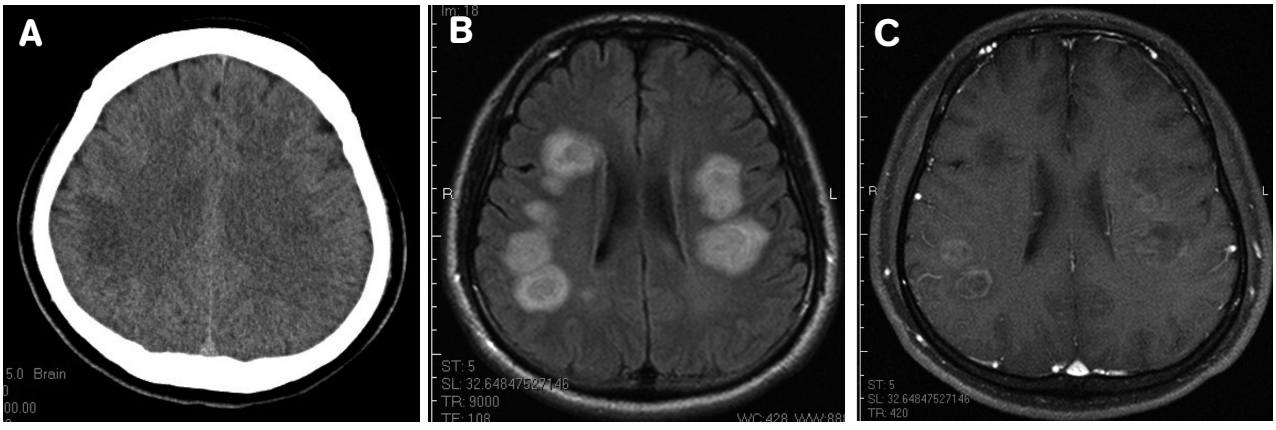

Figure 1. (A)CT: ill-b hypodense matter. (B)MRI: attenuated recovery (FLAIR) image shows oval the matter. (C)MRI: T1 shows hypoattenuated.

cuffing with mononuclear cells throughout the brain and meninges has been noted in levamisole-treated dogs[14]. Levamisole is not considered to be toxic to myelin, because no inflammation or demyelination are noted after levamisole administration in normal mice. On the other hand, demyelination and inflammation are augmented by levamisole administration in mice infected with a demyelinating strain of virus. Thus, the most likely explanation for levamisole-induced leukoencephalopathy in susceptible persons is demyelination due to stimulation of a destructive immune response to a novel antigen that persists without causing symptoms[15]. This scenario may also explain why the onset is subacute and the clinical course is progressive rather than abrupt.

Ten cases of LIL have been reported in Taiwan since 2002[4,16,17]. and only 3 have been noted in western countries[9,10,18]. All these cases in Taiwan (Table 1) occurred after treatment of recurrent aphthous ulcers and pamphigus vulgaris. The onset was subacute, and symptoms became apparent 2-20 weeks after the levamisole treatment. The total dosage (700-5400 mg) and duration of treatment (around 1 week to 6 months) varied. There were no dose-dependent clinical patterns (symptoms or brain lesions), which may suggest the idiosyncratic nature of levamisole-induced leukoencephalopathy. In our case, the total dosage needed to induce leukoencephalopathy (600 mg) was smaller and the treatment duration (4 days) was shorter than in these previous cases.

The differential diagnosis of multifocal leukoencephalopathy includes acute disseminated encephalitis (ADEM), multiple sclerosis, metastasis, multicentric

Table 1. Multifocal leukoencephalopathy related to levamisole in Taiwan

	Age/sex	Levamisole (mg)/duration	Underlying disease	Clinical characteristics	Treatment
1	26/M	600/4 days	Verrucae	Mental decline, aphasia, dysarthria, R hemiparesis	Steroid, plasmapheresis
2	1/70/F[4,16]	2100/2 wk	RAU	Mental decline, ataxia, aphasia, dizziness	Steroid
3	2/43/M[4,16]	2100/2 wk	RAU	Ataxia, urinary incontinence, coma	Steroid, plasma exchange
4	3/62/F[4,16]	2550/5 wk	RAU	Progressive weakness, ataxia	Steroid
5	4/50/F[4,16]	3150/4 wk	RAU	R hemiparesis, dizziness, lethargy; weakness, aphasia, ataxia	Steroid
6	5/51/M[4,16]	NA	RAU/ Ankylosing spondylosis	Dizziness, nausea, dysarthria, R leg numbness	Steroid
7	6/65/M[4,16]	5250/5 wk	RAU/ Pemphigus vulgaris	Mutism, progressive weakness, urinary incontinence	Steroid
8	7/24/F[4,16]	NA	RAU	Dysarthria, dizziness, nausea, lethargy	Steroid
9	8/26/F[4,16]	1050/1wk	RAU	Mutism, ataxia, general malaise	Steroid, plasma exchange
10	9/66/F[4,16]	2100/2 wk	RAU	Nausea, vomiting, speech disturbance, mental decline	Steroid, plasma exchange, intravenous immunoglobulin
11	24/F[17]	5400/6 mo	RAU	Dysarthria, gait ataxia, hemiparesis, defecation/ urination incontinence	Steroid

R, right; RAU, recurrent aphthous ulcers.

gliomas, and lymphoma of the central nervous system. Negative cytological findings exclude the malignancies. The absence viral, bacterial, parasitic infection, or vaccine injection in the history exclude ADEM. The brain imaging had no evidence of subcortical or periventricular lesions, while the Barkoffs criteria was not fulfilled. The lack of recurrent attacks, optic tract and spinal cord lesions, elevated CSF IgG index and CSF oligoclonal bands exclude multiple sclerosis. First episode of tumefactive multiple sclerosis should be considered, but mass effect and edema should be seen in brain MRI[19,20].

In LIL, brain CT shows multiple hypoattenuating lesions, while T2-weighted MRI shows multifocal, disseminated round or oval hyperintense subcortical white matter lesions. Most lesions are located in frontal, parietal, basal ganglion, and periventricular areas. Ring-like gadolinium-enhancement may occur in some cases[4,16]. Liu et al. described two patterns of initial MRI abnormalities[4]. Pattern 1 consisted of oval or round asymmetric confluent lesions in the white matter with a tumor-like appearance and mass effect. Pattern 2 consisted of bilateral, small, and symmetric white matter lesions perpendicular to the lateral ventricular wall, mimicking the pattern seen in multiple sclerosis (MS). In our case, multiple sclerosis was excluded by pattern 1 on MRI, the monophasic presentation of the disorder, and progressive recovery.

The treatment of LIL is aimed at suppression of immune-mediated demyelination in the central nervous system. Steroid pulse therapy (the most common therapy for ADEM[21]) has been used successfully to treat LIL[9,10]. In all 11 cases in Taiwan, steroid pulse therapy was used[4,16,17] (Table 1) but in 36.3% (4/11) of cases, LIL was resistant. Consequently three of these patients received additional plasma exchange or plasmapheresis and one received additional plasma exchange and intravenous immunoglobulin[16]. Clinical improvement, even good recovery, was achieved in all cases. Plasmapheresis has been used effectively to treat acute demyelinating diseases[22,23]. It may remove antibodies and cytokines that mediate inflammatory processes within the perivascular spaces of the brain[16]. In cases resistant to steroid therapy, early plasmapheresis or plasma exchange may be an alternative strategy to improve prognosis[16].

Our case confirmed that levamisole alone can cause multifocal inflammatory leukoencephalopathy. The common side effects of levamisole are mostly mild and reversible. But neurologic toxicity, such as LIL, can occur in a dose-independent and idiosyncratic manner and can be triggered by even low dose and short duration of treatment. LIL occurs more frequently in Asians than in westerners, which may be related to genetic differences. Clinicians should pay prompt attention to neurologic symptoms for early diagnosis and treatment of this severe and unpredictable adverse effect.

REFERENCES

1. Lionel ND, Mirando EH, Nanayakkara JC, Soysa PE. Levamisole in the treatment of ascariasis in children. Br Med J 1969;4:340-341.
2. Gill S, Loprinzi CL, Sargent DJ, Thome SD, Alberts SR, Haller DG, Benedetti J, Francini G, Shepherd LE, Francois Seitz J, Labianca R, Chen W, Cha SS, Heldebrant MP, Goldberg RM. Pooled analysis of fluorouracil-based adjuvant therapy for stage II and III colon cancer: who benefits and by how much? J Clin Oncol 2004;22:1797-1806.
3. Barrons RW. Treatment strategies for recurrent oral aphthous ulcers. Am J Health Syst Pharm 2001;58:41-50;quiz 1-3.
4. Liu HM, Hsieh WJ, Yang CC, Wu VC, Wu KD. Leukoencephalopathy induced by levamisole alone for the treatment of recurrent aphthous ulcers. Neurology 2006;67: 1065-1067.
5. Scheinfeld N, Rosenberg JD, Weinberg JM. Levamisole in dermatology: a review. Am J Clin Dermatol 2004;5:97-104.
6. Hook CC, Kimmel DW, Kvols LK, Scheithauer BW, Forsyth PA, Rubin J, Moertel CG, Rodriguez M. Multifocal inflammatory leukoencephalopathy with 5-fluorouracil and levamisole. Ann Neurol 1992;31:262-267.
7. Neu IS, Ober H. [Multifocal leukoencephalopathy following adjuvant therapy with fluorouracil and levamisole]. Dtsch Med Wochenschr 1992;117:1379.
8. Kimmel DW, Schutt AJ. Multifocal leukoencephalopathy: occurrence during 5-fluorouracil and levamisole therapy and resolution after discontinuation of chemotherapy. Mayo

Clin Proc 1993;68:363-365.
9. Kimmel DW, Wijdicks EF, Rodriguez M. Multifocal inflammatory leukoencephalopathy associated with levamisole therapy. Neurology 1995;45:374-376.
10. Lucia P, Pocek M, Passacantando A, Sebastiani ML, De Martinis C. Multifocal leucoencephalopathy induced by levamisole. Lancet 1996;348:1450.
11. Szeto C, Gillespie KM, Mathieson PW. Levamisole induces interleukin-18 and shifts type 1/type 2 cytokine balance. Immunology 2000;100:217-224.
12. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, Ungerleider JS, Emerson WA, Tormey DC, Glick JH, Veeder MH, Mailliard. JA. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med 1990;322:352-358.
13. Sigidin JA, Bunchuk NV. Neurological complication of levamisole. Lancet 1977;2:980.
14. Vandevelde M, Boring JG, Hoff EJ, Gingerich DA. The effect of levamisole on the canine central nervous system. J Neuropathol Exp Neurol 1978;37:165-173.
15. Lucchinetti CF, Kimmel DW, Pavelko K, Rodriguez M. 5-Fluorouracil and levamisole exacerbate demyelination in susceptible mice infected with Theiler's virus. Exp Neurol 1997;147:123-129.
16. Wu VC, Huang JW, Lien HC, Hsieh ST, Liu HM, Yang CC, Lin YH, Hwang JJ, Wu KD. Levamisole-induced multifocal inflammatory leukoencephalopathy: clinical characteristics, outcome, and impact of treatment in 31 patients. Medicine (Baltimore) 2006;85:203-213.
17. Wang C, Jeng J, Yip P. Multifocal leukoencephalopathy induced by levamisole: a case report. Acta Neurol Taiwan 2002;11:205-208.
18. Boente Mdel C, Bibas Bonet H, Primc NB. [Dermatopathy associated with levamisole-induced reversible posterior leukoencephalopathy]. Arch Argent Pediatr 2008;106:42-46.
19. Lucchinetti CF, Gavrilova RH, Metz I, Parisi JE, Scheithauer BW, Weigand S, Thomsen K, Mandrekar J, Altintas A, Erickson BJ, Konig F, Giannini C, Lassmann H, Linbo L, Pittock SJ, Bruck W. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. Brain 2008;131:1759-1775.
20. Kiriyama T, Kataoka H, Taoka T, Tonomura Y, Terashima M, Morikawa M, Tanizawa E, Kawahara M, Furiya Y, Sugie K, Kichikawa K, Ueno S. Characteristic Neuroimaging in Patients with Tumefactive Demyelinating Lesions Exceeding 30 mm. J Neuroimaging 2011;21:e69-e77.
21. Tenembaum S, Chitnis T, Ness J, Hahn JS. Acute disseminated encephalomyelitis. Neurology 2007;68:S23-S36.
22. Rodriguez M, Karnes WE, Bartleson JD, Pineda AA. Plasmapheresis in acute episodes of fulminant CNS inflammatory demyelination. Neurology 1993;43:1100-1104.
23. Kanter DS, Horensky D, Sperling RA, Kaplan JD, Malachowski ME, Churchill WH, Jr. Plasmapheresis in fulminant acute disseminated encephalomyelitis. Neurology 1995;45:824-827.