MULTIPLE SCLEROSIS INDUCED FROM LEVAMISOLE: A CASE REPORT

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Abstract

Cerebral demyelization was formed in a patient after levamisole therapy for occult tumor. This patient had no evidence of previous neurologic diseases. Levamisole was administered eight months before admission. Over a period of several days, double vision and weakness over left-side extremities were observed. Cerebral magnetic resonance imaging (MRI) with gadolinium enhancement demonstrated multiple enhancing inflammatory plaques. A meticulous systemic work -up including positron emission tomography (PET) was arranged but failed to uncover any systemic occult tumor or distant cerebral metastases. Multifocal inflammatory leukoencephalopathy (MIL) was impressed according to published literature. The patient’s conditions were improved after the discontinuation of levamisole treatment and a short course of corticosteroid therapy. Despite simulation of drug-induced MIL newly formed lesions were observed in followed-up cerebral MRI four months after his discharge. Based on the aforementioned clinical manifestations, laboratory findings and correlated imaging studies, it is our proposal that levamisole could be a triggering factor in developing multiple sclerosis. It is therefore imperative for frontline clinicians to be aware of such malady and further avoidance in the susceptible.

Key words: Levamisole, Magnetic resonance imaging, Multifocal inflammatory leukoencephalopathy, Corticosteroid, Multiple sclerosis

Introduction

Multifocal inflammatory leukoencephalopathy (MIL) is a disorder of the central nervous system assted with idiosyncratic side effect of levamisole. It is often developed acutely tooia subacutely with a demyelinating process having uncertain pathogenesis. Levamisole, the isomer of tetrarmisole, was initially used as an antihelminthic agent but later recognized as an adjuvant chemotherapeutic medication due to its powerful immunomodulatory capacity. Rarely MIL has evolved into multiple sclerosis. We herein report a case of suspected multiple sclerosis induced from levamisole.

Case report

A 49-year-old Taiwanese male came to our
neurology clinic on account of double vision and numbness over left-side extremities. A cerebrovascular event was speculated because of rather abrupt onset. He was a victim of right-side parotid gland tumor diagnosed by an otolaryngologist and partial resection was done fifteen years ago. Pathological proof indicated adeno-squamous carcinoma and he had had regular follow-ups in Department of Onco-radiology for more than ten years with several courses of radiotherapy. Adjunctive chemotherapy, levimasole, was launched eight months before admission. No concomitant infection or vaccination was noted during this period. Upon admission, cranial nerve exam disclosed right-side gazing palsy.

Sensory testing revealed left-side impaired pinprick and light touch modalities. The remainder of neurological and physical examinations was unremarkable. There had been no optic disc blurring or optic neuritis observed in fundoscopy. Routine laboratory work-ups, tumor marker survey and serum rheumatologic testing were all within normal limits. Gadolinium-enhanced cranial magnetic resonance imaging studies (MRI) delineated multiple cerebral hemispheric inflammatory plaques (Fig.1) and right-side infratentorial lesions (Fig. 2A, 2B). Neurophysiologic study showed delayed P40 bilaterally and mild delayed pick-up in left-side P100. MRI of cervical spine exposed nothing in particular. In an attempt to rule out any possible brain metastatic tumor or demyelinating disease, we performed whole-body FDG-proton emission tomography (PET) and cerebrospinal fluid testing (CSF). The result of PET was normal. Cerebrospinal fluid showed slightly elevated protein at 78 (normal value: 10-45 mg/dL). All bacterial, fungal, viral and cytologic findings were negative. CSF serology for mumps virus, measles, herpes simplex virus was also negative. IgG index was normal at 0.75 (normal, 0.0-0.77). CSF tumor marker survey including carcinogen embryonic antigen and alpha fetal protein was set within normal values. Chemotherapy was therefore suspended. We administered low-dose dexamethasone at 10 mg three times daily for two weeks. His neurological focal signs received satisfactory recovery. Before he was discharged for outpatient follow-ups, the dose was tapered to 5 mg once daily. No fresh neurologic defects were notified except mild fatigue. We followed up our patient by arranging a second MRI four months after his discharge. Newly formed lesions were detected (Fig. 2C, 2D).

**Discussion**

Multifocal inflammatory leuкоencephalopathy (MIL) is an inflammatory demyelinating disorder of the central nervous system. The most notorious cause is linked with the use of levamisole. Pathogenesis is suspected to be an autoimmune response to myelin. Other neurological demyelinating diseases such as multiple sclerosis and acute disseminated encephalomyelitis, thus, need to be differentiated.

Predilection of acute disseminated encephalomyelitis is in children. Occurrences are often preceded by respiratory tract infections. Its course is relatively benign and its process monophonic.
By contrast, afflictions from multiple sclerosis occur in adult groups. Its course is relapsing and remitting in most people. Premorbid symptoms vary and prognoses usually lead to long-term debilitation.

Multiple sclerosis can be difficult to diagnose since its signs and symptoms may be similar to other medical problems. Medical organizations have created diagnostic criteria to ease and standardize the diagnostic process for practicing physicians, especially in the first stages of the disease. Currently, the McDonald criteria focus on a demonstration with clinical, laboratory and radiologic data of the dissemination of MS lesions in time and space. Clinical data alone may be sufficient for a diagnosis of MS if an individual has suffered separate episodes of neurologic symptoms characteristic of MS. Since some people seek medical attention after only one attack, other testing may hasten and ease the diagnosis. The most commonly used diagnostic tools are neuroimaging, analysis of cerebrospinal fluid and evoked potentials.1-3

Magnetic resonance imaging of the brain and spine shows areas of demyelination (lesions or plaques). Gadolinium can be administered intravenously as a contrast to highlight active plaques and, by elimination, demonstrate the existence of historical lesions not associated with symptoms at the moment of the evaluation. Testing of cerebrospinal fluid obtained from a lumbar puncture can provide evidence of chronic inflam-

Fig. 2. Initial axial FLAIR images (A and B) shows hyperintense lesions in right dorsal pons and right cerebellum. On follow-up FLAIR images (C and D), the right pontine lesion becomes smaller and the right cerebellar lesion disappears but a newly developed lesion is found in left lateral pons. (Arrows)
mation of the central nervous system. The cerebrospinal fluid is tested for oligoclonal bands of IgG on electrophoresis, which are an inflammation marker found in 75-85% of people with MS.\textsuperscript{2,3} The nervous system of a person with MS responds less actively to stimulation of the optic nerve and sensory nerves due to demyelination of such pathways. These brain responses can be examined using visual and sensory evoked potentials. The McDonald criteria are diagnostic criteria for multiple sclerosis (MS). They discourage the previously used terms such as “clinically definite” and “probable MS”, and propose as diagnostic either “MS”, “possible MS”, or “not MS.” The McDonald criteria for the diagnosis of multiple sclerosis were revised in 2005 to clarify exactly what is meant by an “attack,” “dissemination,” a “positive MRI.” Currently, McDonald criteria is regarded as the gold standard for MS diagnosis.

Levamisole is well known to have an immune modulating effect and is originally used as an anti-thelminthieetic or anti-cancer agent.\textsuperscript{1} Levamisole alone, or its combination with 5-fluorouracil, has been reported to play a major factor in developing multifocal inflammatory leukoencephalopathy.\textsuperscript{2,3}

Lesions of MIL presented in MRI images mimic the presentation of multiple sclerosis and are symmetric in bilateral cerebral hemispheres. Involvements include following up the course of subependymal vein but lesions located at basal ganglia or corpus callosum are seldom observed.

From the perspective of immunology, the effect of levamisole is not unequivocal and it seems to have a twofold function in terms of suppressing or enhancing immuno-modulation. In animal models, Spreafico et al.\textsuperscript{4} demonstrated that levamisole could elevate T-cell mediated immune activity leading to decreased number of cancer cells. Dau et al.\textsuperscript{5} reported patients with multiple sclerosis who were treated with levamisole had a prominent level of lymphocyte stimulation response toward virus-associated antigens and delayed hypersensitivity of skin test antigens. Other scientific experiments hinted that levamisole might give rise to increased E-rosettes formation in immunocompromised patients leading to T cell function or amounts, in which cell-mediated immunity is to play a role in its regard.\textsuperscript{8} Though levamisole-induced systemic reaction toward immune activity was elevated, the outcome of their experiment that capitulated multiple sclerosis patients had otherwise deteriorating conditions.

Tracking back published literature, it is suggested brain metastasis is better monitored by SPECT imaging. However, we used PET\textsuperscript{7} to follow our case in an attempt to survey if there existed any systemic occult tumors or distant brain metastases. Fortunately, the result with our patient showed no increased uptake or cold activity in cranial region.

Our initial diagnosis with MIL was overturned by the following MRI. The result was highly indicative of multiple sclerosis based on revised diagnostic Macdonald criteria. Other possible differential diagnoses such as brain metastasis or acute demeylinating encephalomyelitis were ruled out by means of PET and detailed history taking.

Our patient represents a clinically isolated syndrome with ensuing asymptomatic flare-up. Since those with multiple sclerosis have similar neurological aggravation in imaging studies, scholars propose that this drug-induced MIL might, at least to a certain extent, reflect the unmasking of previously silent or subclinical multiple sclerosis.\textsuperscript{8}

Though rare, a similar phenomenon is emerging in Taiwan. Lin et al.\textsuperscript{9} collected 50 patients with acute disseminated encephalomyelitis. One adult with previous use of levamisole evolved into multiple sclerosis of relapsing-remitting type. To confer MIL standing as an established entity or a variant of multiple sclerosis is still under investigation. Further cohort studies on patients with levamisole use are crucial to substantiate the relationship between levamisole and the development of multiple sclerosis.

Our patient’s clinical course is compatible with the documented literature which manifests itself in relapsing and remitting manner (each
episodes lasted more than 24 hours and interval between episodes is greater than three months’ time).

In conclusion, levamisole could be a triggering factor in multiple sclerosis. Avoiding it from the susceptible or proven multiple sclerosis is of utmost significance. Frontline clinicians should be aware of the discrepancy and resemblance over these neurological disorders. To abate clinical symptoms, corticosteroid is able to serve as a competent and timely therapy.

Disclosure

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References


Levamisole 引發之多發性硬化症：一病例討論

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摘要

多發性硬化症引發之原因很多。Levamisole 誘發之案例很少見。一個 49 歲的中年人，因 cancer 服用 levamisole。數月後發生了腦部病變。多發性硬化症之診斷依據其臨床表現及影像診斷其中之病理及生理均有探討。

關鍵詞：多發性硬化症，Levamisole，腦部病變