INTERNAL MEDICINE

□ CASE REPORT □

Vasculitic Neuropathy Following Exposure to a Glyphosate-based Herbicide

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Abstract

We herein report a case of peripheral neuropathy following exposure to large amounts of glyphosate-based herbicide. A 70-year-old man suffered from pain and purpura in the left sole following exposure to glyphosate-based herbicide. Pain and purpura spread to the opposite side and increased in severity. Mild weakness of the lower limbs was also observed. A sural nerve biopsy revealed the infiltration of lymphocytes around small vessels in the epineurium with numerous eosinophils, deposition of hemosiderins and focal axonal degeneration, compatible with findings of vasculitic neuropathy. Glyphosate-based herbicides should be recognized as a causative agent of vasculitic neuropathy.

Key words: glyphosate-based herbicides, vasculitic neuropathy, cutaneous vasculitis, systemic vasculitis

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Introduction

Glyphosate is one of the most popular herbicides, and its use is likely to increase further because its effects are thought to be specific to plants and safe for humans when appropriately used (1). Glyphosate is classified by the United States Environmental Protection Agency in the least toxic category (IV). Although cases of acute intoxication due to glyphosate-based herbicides have been reported, with some fatal, these cases were due to the ingestion of large amounts for suicidal purposes or by accident (1, 2). Renal, hepatic, gastrointestinal, cardiovascular and respiratory dysfunctions have been reported in cases of acute intoxication (2-5). In contrast, adverse effects following daily use have rarely been reported. To date, only one case of cutaneous lesions has been reported in the Japanese literature (6).

We herein report a patient with vasculitic neuropathy thought to be caused by a glyphosate-based herbicide.

Case Report

A 70-year-old man was admitted to our hospital with complaints of moderate numbness and mild weakness in the distal portion of all extremities. He had a history of paroxysmal atrial fibrillation at 67 years of age, which was treated with warfarin, and remained in good condition thereafter. He had no history of bronchial asthma and no remarkable family history of neurological diseases. He had sprayed approximately 2,000 mL of a glyphosate-based herbicide (Roundup®) on his paddy fields for several hours without wearing protective gloves or a face mask 4 months before admission to our hospital. Although he had previously used glyphosate-based herbicide several times, that had been the first time he had handled such a large amount without the protection of gloves or a face mask. The following day, pain in the left sole suddenly developed, subsequently spreading to the opposite side and increasing in severity. Numbness of the distal portion of the lower limbs appeared. At that time, purpura was found on the bilateral soles. Numbness in the lower limbs progressed to proximal areas within a few days, and muscle weakness in the bilateral feet appeared, predominantly in the right side. Numbness of the bilateral hands appeared approximately two weeks from the onset of pain in the left sole and gradually ascended. He lost the ability to walk alone and began to use a wheelchair one month later. Liver and kidney damage were noted in another hospital, and he received symptomatic treatment for these

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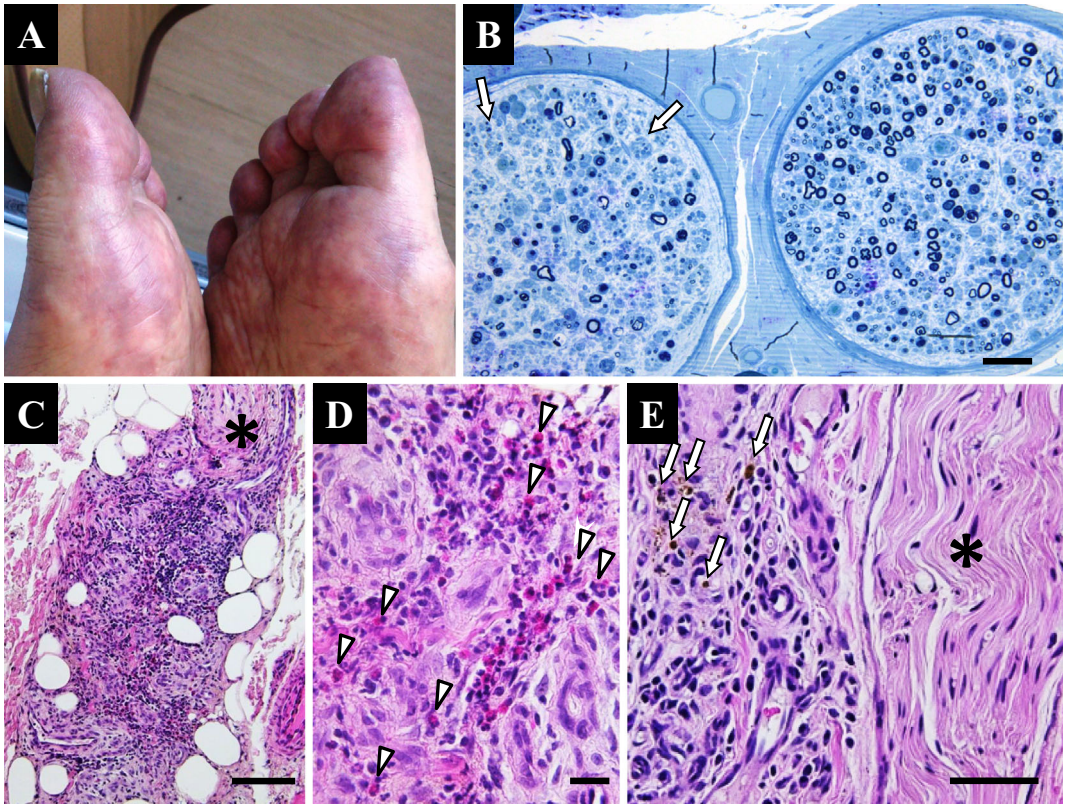

Figure. **(A) The patient's distal portion of the lower extremities. Livedo reticularis in the bilateral sole was observed. (B) A transverse section of the sural nerve biopsy stained with toluidine blue exhibited focal myelinated fiber loss (arrows). (C-E) Hematoxylin and Eosin staining. Infiltration of lymphocytes around the small vessels (C), including numerous eosinophils (arrowheads) (D). Deposition of hemosiderins (arrows) in the epineurium (E). The asterisks indicate the profile of small vessels in C and the endoneurium in E. Scale bar=(B) 50 μm; (C) 100 μm; (D) 20 μm; (E) 50 μm.**

complaints. Although purpura on the bilateral soles gradually improved, the numbness and muscle weakness remained unchanged. He lost 12 kg of body weight in 4 months over the course of the disease.

On admission, a physical examination revealed livedo reticularis of the skin in the bilateral soles (Figure A) and pitting edema of the lower limbs. A neurological examination revealed severe sensory disturbance of all modalities in the bilateral hands and distal portion of the lower limbs. The superficial sensation of the right lower limb was particularly strongly affected. Mild weakness in the lower extremities was observed, predominantly on the right side, but no muscle atrophy was observed. The deep tendon reflexes were normal, except for absent bilateral Achilles tendon reflexes. The plantar responses were flexor on both sides. There were no abnormalities in the cranial nerves or the autonomic nervous system.

A laboratory examination revealed mild elevation of the white blood cell count (9,900/mm^3), of which 3% were eosinophils. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were 71 mm/h and 10.28 mg/dL, respectively. Serum levels of aspartate aminotransferase and alanine aminotransferase were within the normal range (12 and 9, respectively). The levels of blood urea nitrogen and creatinine were slightly elevated (19 and 1.39 mg/dL, respectively). The serological tests for cryoglobulins, immunoglobulins, complement (C3 and C4), rheumatoid factor, myeloperoxidase- and proteinase 3-antineutrophil cytoplasmic antibodies (ANCA), antinuclear antibodies, anti-SS-A and SS-B antibodies, angiotensin-converting enzyme, hepatitis B and C, human immunodeficiency virus serology, and tumor markers, including CEA and CA19-9, were all normal. HbA1c was 5.8% (less than 6.2% was normal range). A urine analysis indicated mild protein content but no white or red blood cells. The level of protein in the pooled urine was high (64 mg/dL; normal range, 0-10 mg/dL). Hyaline and epithelial casts were positive. The cerebrospinal fluid protein levels and cell counts were within the normal range. Chest and abdominal computed tomography and gallium scintigraphic tests revealed no significant findings of interstitial pneumonia or malignancies.

Nerve conduction studies were performed using a standard method. Although the motor nerve conduction velocities (MCVs) in the right median and ulnar nerves were in the normal range of 48 and 51 m/s, respectively, the compound muscle action potentials (CMAPs) in the median nerve were decreased to 2.9 mV, whereas that of the ulnar nerve was normal at 8.3 mV. Prolonged distal latencies of

the median and ulnar nerves were observed at 5.4 and 3.2 ms, respectively. The MCV in the left tibial nerve was preserved (40 m/s), but the CMAPs were markedly low (0.1 mV). CMAPs in the right tibial nerve were not elicited. The sensory nerve conduction velocity and sensory nerve action potentials in the right ulnar nerve were 41 m/s and 5.4 μV, respectively, whereas the sensory nerve action potentials in the right median and bilateral sural nerves were not elicited. The findings of the nerve conduction studies indicated axonal neuropathy compatible with multiple mononeuropathy.

A sural nerve biopsy revealed infiltration of lymphocytes with numerous eosinophils around the small vessels in the epineurium (Figure C, D). Granulomas were not observed. Deposition of hemosiderins in the epineurium was also observed (Figure E). Epoxy resin-embedded specimens exhibited focal myelinated fiber loss with ballooning of myelinated fibers and myelin ovoids (Figure B). Although we performed immunofluorescent studies, the deposition of C3d and C5b-9 was not detected. In teased fiber preparations, axonal degeneration was prominent (56%), and segmental demyelination was not present. Amyloid deposition in the endoneurium was not detected by Congo red staining.

Following admission, oral prednisolone was administered at a dosage of 30 mg/day for 1 month and tapered at the rate of 5 mg every 2 weeks. Following prednisolone treatment, the patient's numbness and muscle weakness gradually improved. Laboratory results, including the CRP levels, ESR, and urinalysis, were also improved. The level of creatinine was 1.24 mg/dL after treatment.

Distal muscles in both lower legs improved to nearly normal muscle strength. Prior to oral prednisolone treatment, the patient was unable to walk alone and required a wheelchair; however, he was able to leave the hospital walking with a cane following treatment. Weakness, numbness, and laboratory results were not exacerbated despite the tapering of prednisolone.

Discussion

The toxicokinetics of glyphosate or its surfactant in humans have not been well established, and most of the current knowledge has been derived from animal studies (7, 8). In addition to the toxicity of glyphosate itself, the effect of ingredients, particularly surfactants, should also be considered as possible causes of intoxication of glyphosate-based herbicides if a large amount is ingested. Despite the widespread use of glyphosate-based herbicides, reports of adverse effects with daily use are extremely rare. Other than nonspecific symptoms such as nausea and oral discomfort, only one case report describes cutaneous reactions associated with glyphosate (6).

The present case was characterized by subacute, progressive multiple mononeuropathy after exposure to a glyphosate-based herbicide. The nerve biopsy findings, such as infiltration of lymphocytes around the small vessels in the epineurium, deposition of hemosiderins, and focal axonal degeneration, indicated the presence of vasculitis (9). Although drug-induced lymphocyte stimulation test or a patch test was not performed for confirmation, the presence of numerous eosinophils suggests that an allergic process may have contributed to vasculitis in the present case. As cutaneous lesions and transient hepatic and renal abnormalities were also present, the patient would have suffered from systemic vasculitis.

Vasculitic neuropathy can occur in isolation as nonsystemic vasculitic neuropathy (10, 11); however, it more commonly evolves in the setting of primary systemic vasculitis or secondary vasculitis, which is related to connective tissue disorders, infections, drugs, or malignancy (12, 13). Vasculitis resulting from drug use, such as antibiotics, nonsteroidal anti-inflammatory drugs, diuretics, herbicides, insecticide, chemical agents, and toxins, includes a wide variety of clinical and pathologic conditions, which have been empirically defined (14-17). According to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Systemic Vasculitides, drug-induced vasculitis may be classified into "drug-associated immune complex vasculitis", "drug-associated ANCA-associated vasculitis", or "others" under the category of "vasculitis associated with probable etiology" (18). The absence of complement deposition and ANCA suggest that our case may fall under the "others" classification. Clinical manifestations of drug-induced vasculitis are typically limited to the skin; however, systemic manifestations such as renal, neurological, gastrointestinal, and pulmonary lesions may occur, and a protracted chronic course has been occasionally described (19-22). Due to the wide spectrum of causative agents and variety of symptoms, the diagnosis and determination of a therapeutic strategy are difficult in some cases (15, 20, 21).

In conclusion, exposure to a large quantity of glyphosate-based herbicide in a short time through transcutaneous or inhalation pathways without protection may cause vasculitis, not only in the peripheral nervous system but also in other organs. Glyphosate-based herbicides should be recognized as a causative agent of vasculitis, with or without other systemic involvement.

The authors state that they have no Conflict of Interest (COI).

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