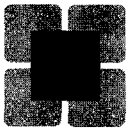

Eosinophilia-myalgia syndrome: CDC update

SOON AFTER the first identified cluster of the eosinophilia-myalgia syndrome (EMS) associated with the use of L-tryptophan-containing products (LTCPs) was reported from New Mexico in November 1989,[1-3] investigators recognized that the syndrome was occurring nationwide.[4] Subsequently, reports from the national surveillance system of the Centers for Disease Control (CDC),[5-8] several hospital-based case series,[9-13] and numerous other case reports have been published. As of December 7, 1990, 1,541 cases had been reported. Because the national surveillance system is a passive system, depending on physicians or patients to take the initiative to report to their state health department, the actual number of EMS cases meeting the strict CDC surveillance case definition is probably several times this number.

Twenty-eight deaths have been reported and confirmed as being associated directly with the EMS disease process. After the Food and Drug Administration recalled LTCPs on November 21, 1989, a dramatic decline in the number of reported new EMS cases occurred. Only eight cases have been reported with an onset of illness after January 31, 1990, the most recent having an onset of illness in May 1990. These most recent cases involved use of LTCPs up until the onset of illness, despite product recalls and public warnings to discontinue use of such products. This suggests that these cases were not the result of prolonged latency.

ROLE OF CONTAMINATION STUDIED

Even at the time of the initial reports, the epidemiologic pattern suggested that EMS was not caused by L-tryptophan per se, but was probably due to a contaminant.[8] Further research has linked LTCPs ingested by EMS case-patients to specific lots of a single manufacturer of bulk L-tryptophan.[14,15] Case-control studies involving chemical analysis of LTCPs have shown a strong statistical association with the presence of the chemical di-L-tryptophan aminal of acetaldehyde in trace amounts in the case-associated LTCPs.[16,17] Whether this is the actual etiologic agent of EMS, a necessary but not sufficient cofactor, or just a marker for some other compound cannot be determined until the substance has been purified and the syndrome reproduced in an acceptable animal model.[18]

The L-tryptophan in various LTCPs marketed in the United States came from six manufacturers in Japan. Most of these manufacturers used a fermentation process, with various bacterial strains that had been selected and/or "bioengineered" to produce large amounts of L-tryptophan when grown with specific precursors under specific conditions. The initial fermentation product then underwent several different modifying and purification steps before being shipped as raw bulk L-tryptophan.

Though results of case-control studies have shown an association between outbreak period EMS cases and particular lots of L-tryptophan from one manufacturer produced during a 6-month period in late 1988 and early 1989, researchers still have not identified the exact step in the manufacturing process at which the etiologic agent is either produced or not removed by purification. Since several manufacturing conditions changed about the time when the affected lots were produced, the specific change(s) that led to production of the contaminated lots is uncertain. Furthermore, some LTCP-associated EMS cases predate the epidemic and the manufacturing changes, suggesting that the etiologic contaminant can be present, perhaps less consistently or in lower amounts, when other bacterial strains or other manufacturing conditions are used.

LTCPs were marketed in the United States as food supplements. However, they were promoted and used by many individuals for pharmacologic purposes—most commonly for treating sleep disturbances, premenstrual syndrome, and depression. Other less fre-

quently cited reasons for their use include body-building, weight control, and drug rehabilitation.

CAVEATS FOR THE CLINICIAN

EMS is truly a syndrome. The signs and symptoms are highly variable, which results in a spectrum of types and severity of illness; no diagnostic test is specific. The CDC case definition—eosinophilia ≥ 1000 cells/mm^3; generalized myalgia at some point during the illness severe enough to affect the ability to perform usual daily activity; and the absence of any infection or neoplasm that could account for the first and second features—was developed for epidemiologic and surveillance purposes. Physicians should not use this case definition to the exclusion of clinical judgment. Many people who took LTCPs had no illness. Others who used these products developed illnesses that did not meet the strict CDC case definition because they had (1) asymptomatic eosinophilia; (2) focal and/or mild myalgia; (3) incapacitating myalgia without documentation of a sufficiently elevated eosinophil count; or (4) other symptoms such as fasciitis, neuropathy, or lung disease without sufficient myalgia or eosinophilia. Clinicians need to bear in mind these facts as they evaluate, diagnose, and treat potential or suspected cases of EMS.

The pathology of EMS includes a multiple organ system vasculitis or perivasculitis and an inflammatory response at the site of the affected tissue. (Interestingly, the kidneys are spared.) The pathogenesis probably includes both direct toxic effects from the eosinophils and effects from a "turned-on" cellular immune system (eg, T-cells, monocytes, and fibroblasts). Clinically, EMS is a potentially chronic progressive illness that may wax and wane on a daily or weekly basis, but that can progress over months despite stopping the L-tryptophan exposure. Furthermore, resolution of the eosinophilia does not necessarily mean that the disease process has stopped.

Major features

The predominant acute problems include myalgias and edema, often with concurrent mild respiratory symptoms. The most common severe chronic problems are fasciitis, alopecia, and the muscle weakness, spasms, myoclonus, and paresthesias usually associated with neuropathy. Less frequent severe chronic problems include pulmonary disease with progression marked by chronic inflammatory changes, fibrosis, or, rarely, pulmonary hypertension. The neuropathy is most commonly of the peripheral motor type, occasionally taking the form of an ascending polyneuropathy. Varying combinations of motor, sensory, radicular, and, less frequently, central nervous system involvement may be present.

Cardiac involvement

Unlike the previously described idiopathic hypereosinophilic syndrome, cardiac involvement is relatively rare in EMS. When it does occur, the problem is usually a mild arrhythmia, often an atrial tachycardia, which may be the result of an autonomic neuropathy. There are a small number of cases with more severe arrhythmias or myocarditis with failure.

DIFFERENTIAL DIAGNOSIS

The fasciitis associated with this syndrome obviously overlaps with the previously described entity of eosinophilic fasciitis or Shulman's syndrome.[19] Indeed, before the outbreak of EMS associated with the use of LTCPs was recognized, many patients were diagnosed as having Shulman's syndrome. In retrospect, it seems likely that many of the patients diagnosed as having Shulman's syndrome in recent years had LTCP-associated EMS. However, Shulman's original description did not include some of the signs and symptoms commonly found in EMS patients, such as neuropathy or pulmonary disease, and they usually recovered. Some patients whose disease process is limited to a strict pathological diagnosis of eosinophilic fasciitis have neither these other findings nor a history of antecedent LTCP use. In addition, some laboratory findings are different for EMS and Shulman's syndrome.[20,21] The similarities between EMS, toxic oil syndrome, eosinophilic fasciitis, and other idiopathic hypereosinophilic syndromes could be due to similar underlying etiologies, common pathophysiologic responses to different triggers, or some combination of these factors. EMS may provide a useful model for studying similar diseases of unknown etiology, especially if the etiologic contaminant in LTCPs is confirmed.

PROGRESSION AND PROGNOSIS

Many patients with mild EMS (or EMS-like disease that does not meet the strict surveillance definition) have already fully recovered. Others have stabilized at various levels of severity; some are showing slow improvement; and others show chronic progression. Of course, the severely ill patients have received the most attention. Most of these patients have been given systemic glucocorticoids, with variable success. Other

modalities have been tried, including cyclophosphamide, cyclosporine, hydroxychloroquine, hydroxyurea, mercaptopurine, methotrexate, penicillamine, retinoids, vincristine, and various plasmapheresis protocols. Patients with EMS may benefit from physical therapy, and this adjunct should not be ignored. The best therapy, the appropriate degree of therapeutic aggressiveness, and the risk/benefit ratios of current therapies are not known.

From our limited knowledge of EMS based on published reports and studies in progress, and by extrapolating from the similarity between EMS and the Spanish toxic oil syndrome,22 we believe that even patients with significant functional impairment 6 months to 2 years after the illness began may continue to improve over time.

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