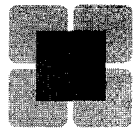

Eosinophilia-myalgia syndrome: the Cleveland Clinic experience

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■ Eosinophilia-myalgia syndrome is a recently described clinical syndrome caused by a suspected contaminant of L-tryptophan, an essential amino acid that was manufactured and sold as a nutritional supplement. This study reports the clinical and pathological findings of 22 cases of eosinophilia-myalgia syndrome evaluated at the Cleveland Clinic and includes data for up to 1 year of follow-up (for the epidemic cases). Nineteen of the 22 cases were evaluated and followed prospectively in the time period from November 1989 to November 1990. Two of the 22 represented nonepidemic forms of the syndrome which occurred prior to the 1989 epidemic. During a review of all cases of biopsy-proven diffuse fasciitis with eosinophilia at the Cleveland Clinic since 1978, one of the 22 was retrospectively identified as having an epidemic form of the syndrome, with onset in July 1989. In this study, adverse prognosticating factors in eosinophilia-myalgia syndrome included nerve and muscle involvement, fasciitis, and weight loss. Eosinophilia-myalgia syndrome is striking in its severity and diversity, and its features are similar to those of two other unusual illnesses—toxic oil syndrome and diffuse fasciitis with eosinophilia. With the recent purification of the suspected contaminant, it is hoped that further clues to the etiology of this syndrome and similar syndromes will be uncovered.

□ INDEX TERMS: EOSINOPHILIA; TRYPTOPHAN; PAIN; MUSCULAR DISEASES □ CLEVE CLIN J MED 1991; 58:400–408

In October 1989, an apparently new clinical entity called "eosinophilia-myalgia syndrome" (EMS) was first described by a group of clinicians in New Mexico[1] in patients whose common denominator was the ingestion of L-tryptophan, an essential amino acid sold as a nutritional supplement. Information was disseminated quickly by the Centers for Disease Control (CDC) [2] and the lay media. The CDC surveillance case definition of EMS is as follows: (A) an absolute eosinophil count greater than 1,000 cells/mm^3; (B) generalized myalgias affecting activities of daily living; and (C) exclusion of other causes. This paper describes the Cleveland Clinic Foundation experience with 22 patients whose illness is compatible with EMS.

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BACKGROUND

EMS resembles two other unusual clinical syndromes associated with eosinophilia: the toxic oil syndrome,[3] and diffuse fasciitis with eosinophilia (Shulman's syndrome), which was first described in 1974.[4] Recent epidemiologic evidence has linked EMS to batches of L-tryptophan fermented at a particular Japanese company.[5] The putative contaminant or possible marker for the contaminant has recently been identified as a di-L-tryptophan aminal of acetaldehyde,[6] and experimental studies are underway to see if this identified substance causes EMS in laboratory rats.[7] Host factors are

presumed to be important, since not all exposed persons develop clinical illness; however, these factors are not yet fully understood.

Prior to its recall by the US Food and Drug Administration (FDA) in November 1989, L-tryptophan was sold as a nutritional supplement and was used by bodybuilders and persons seeking relief from a variety of common symptoms, such as insomnia, depression, fibromyalgia, stress, and premenstrual molimina. According to one estimate, approximately 2% of the population of Minnesota was ingesting L-tryptophan.[8]

TABLE 1
L-TRYPTOPHAN USE IN 22 PATIENTS: DEMOGRAPHIC INFORMATION

Pt #	Sex	Age	Daily dose of L-T	Duration	Reason for use of L-T	Antidepressant taken concurrently	L-T discontinued	Onset of EMS
1	M	67	3,000 mg	5 years	Insomnia, depression	Doxepin	11/89	10/89
2	F	56	30 mg	3 months	Fibromyalgia	None	3/90	2/90
3	F	39	2,500 mg	6 months	Insomnia	None	11/89	11/89
4	F	51	1,000 mg	9 months	Insomnia	Doxepin	11/89	11/89
5	F	58	2,000 mg	3 years	Fibromyalgia	Desipramine	9/89	11/89
6	F	47	1,500 mg	3 years	Fibromyalgia	Nortriptyline	11/89	7/89
7*	F	63	6,000 mg	4 years	Fibromyalgia, depression	Nortriptyline	1/90	12/89
8	F	47	1,000 mg	2 months	Insomnia	None	11/89	10/89
9	F	38	500 mg	1 month	Weight loss aid	None	6/84	6/84†
10*	F	53	1,500 mg	1 year	Depression	Trazodone	12/86	12/86†
11	F	51	1,000 mg	6 months	Fibromyalgia	Doxepin	11/89	11/89
12*	F	36	2,000 mg	1 month	Insomnia, fibromyalgia	None	11/89	11/89
13*	F	49	500 mg	1 month	Alcohol rehabilitation	None	5/89	7/89
14	M	46	1,500 mg	1 month	Nutritional aid	None	9/89	12/89
15*	M	27	1,500 mg	3 years	Insomnia	None	11/89	11/89
16	F	67	1,000 mg	8 years	Insomnia, depression	Nortriptyline	11/89	2/90
17	F	54	3,000 mg	1 year	Insomnia	None	11/89	10/89
18	F	34	4,500 mg	5 years	Insomnia, depression	Doxepin	11/89	11/89
19	F	29	1,000 mg	14 days	Insomnia	None	11/89	11/89
20*	M	56	500 mg	1.5 years	Depression	Fluoxetine	12/89	10/89
21	F	49	500 mg	1.5 years	Insomnia	None	6/89	8/89
22*	M	54	500 mg	10 months	Depression	Phenelzine	8/89	9/89

*Severely affected patients † Pre-epidemic

Use of L-tryptophan was promoted in the lay media; however, it was occasionally prescribed by physicians in the hope of improving central serotonin levels. L-tryptophan was not approved or recommended by the FDA for medicinal purposes because of the lack of definitive evidence for efficacy. A possible underlying reason for L-tryptophan's growth in popularity is that a portion of it is metabolized to 5-hydroxy-tryptamine, also known as serotonin. Serotonin was serendipitously discovered in 1948 by investigators at the Cleveland Clinic who were trying to identify angiotensin.[9] Later work by many different investigators established the role of serotonin in the central nervous system (CNS) in mediating restorative sleep, mood, and perception of pain. Consequently, the majority of people who ingested L-tryptophan did so to enhance their sense of well-being with respect to sleep, mood, and perception of pain. However, the sense of well-being paradoxically worsened in those afflicted with EMS.

MATERIAL AND METHODS

Twenty-two patients were examined and followed at the Cleveland Clinic; 19 of the 22 were followed prospectively (between November 2, 1989 and November 8, 1990). Three of the 22 patients in this series were evaluated prior to the publicized November 1989 epidemic. These 3 patients were retrospectively identified as having EMS after all biopsy-proven cases of diffuse fasciitis with eosinophilia (25 total cases) evaluated at the Cleveland Clinic from June 1978 to May 1990 were retrospectively reviewed. Two of the 3 patients were classified as nonepidemic, and the other, with onset of illness in July of 1989, was classified as epidemic.

Epidemic patients were defined as those with onset in 1989 associated with the suspected ingestion of "hot lots" of manufactured L-tryptophan produced from January 1989 through June 1989 by a single Japanese company.[5] Although the CDC surveillance case definition requires an absolute eosinophil count of greater than 1,000 cells/mm^3, 5 of 22 patients had typical clinical features of EMS with only a mild eosinophilia, and they were included because of their clinical findings and a history of L-tryptophan ingestion.

There was no evidence of infection, allergy, neoplasm, or known hypersensitivity disorder to explain the presenting clinical features in these 22 cases. Each patient was systematically evaluated with at least a complete history and physical and routine laboratory testing. Full-thickness skin, fascia, and muscle biopsies were obtained in patients with indications. Nerve biopsy, nerve conduction studies, and electromyography (EMG) were performed selectively on patients with neurologic and muscular symptoms. One-year follow-up information was collected for 11 of 20 patients

TABLE 2
DERMATOLOGIC MANIFESTATIONS OF EMS

Pt #	Pruritis	Alopecia	Skin dimpling	Rash description	Skin biopsy
1	Yes	No	Yes	Hyperpigmentation, livedo retic.	Mucinosis
2	No	Mild	No	Annular erythema	Not done
3	Yes	Mild	No	None	Not done
4	Yes	Mild	No	Initial hives, granuloma annulare	Necrobiotic granuloma c/w granuloma annulare
5	Yes	No	No	Slight skin thickening	Not done
6	Yes	Mild	Yes	c/w eosinophilic fasciitis	Fibrous septa in SQ tissue
7*	Yes	Mild	No	Slight skin thickening	Not done
8	Yes	Moderate	No	Urticarial	Not done
9	Yes	Mild	Yes	Hyperpigmentation	Deep fibrous SQ inflammation
10*	Yes	Mild	Yes	Patches of skin thickening	c/w early eosinophilic fasciitis
11	No	Moderate	No	None	Not done
12*	Yes	Moderate	No	Urticarial, target lesions	Reactive fibrosis
13*	Yes	Moderate	Yes	c/w eosinophilic fasciitis	Chronic II in fascia
14	Yes	No	No	Brittle nails	Not done
15*	Yes	No	No	Skin thickening	Chronic fasciitis
16	Yes	Mild	No	Brawny edema	Not done
17	No	No	Yes	Patches of induration	Dermal fibrosis, no II
18	Yes	Mild	Yes	c/w eosinophilic fasciitis	II in fascia, fibrous septae
19	No	None	No	Urticarial, malar erythema	Not done
20*	No	None	Yes	c/w eosinophilic fasciitis	II in fascia
21	No	Moderate	Yes	c/w eosinophilic fasciitis	Not done
22*	Yes	Moderate	No	Pruritic papules (from scabies)	Not done, but skin scraped

*Severely affected patients
c/w = consistent with; II = inflammatory infiltrate; SQ = subcutaneous

in this series with the epidemic form of EMS, and 4 and 6 years of follow-up is available in the 2 nonepidemic cases identified through retrospective case finding.

During the study period, four patients presented to the Cleveland Clinic with a chief complaint of self-diagnosed EMS without any historical, clinical, or pathologic evidence of EMS; these patients are briefly described as well.

RESULTS

Our series of 22 patients with EMS consisted of 17 women and 5 men, ages 29 to 67 (*Table 1*). Ingestion of L-tryptophan ranged from 30 mg to 6,000 mg per day (mean, 1,660 mg per day). For most patients, a combination of insomnia, fibromyalgia, and depression was the reason for taking L-tryptophan. One patient was prescribed L-tryptophan during an admission for alcohol withdrawal. One patient was using L-tryptophan as a supplement for bodybuilding. No definite association between the dose of L-tryptophan and the severity of illness was found, and a definite time course from ingestion of L-tryptophan to onset of illness could not be determined: some patients had ingested L-tryptophan for years, whereas others had only ingested a few tablets. Eleven of 22 patients were taking antidepressants concurrently at the time of the onset of illness.

The clinical and pathological findings were diverse and included myalgias, eosinophilia, skin changes, weight changes, and muscle weakness. Fourteen of the 22 patients (60%) in this series were hospitalized, 7 either frequently or for extended periods of time. These 7 patients were classified as "severely affected" by EMS and are indicated by an asterisk in the accompanying *Tables*.

Myalgias

Twenty-one of the 22 patients had intense myalgias that affected activities of daily living. The one patient who did not suffer from intense myalgia was a male (patient 22) who had poliomyelitis as a child and, as a consequence, was almost totally quadriplegic. He did suffer some pain in a thumb, which interestingly was one of the few parts of his body with some remaining motor function. He also had a sensory neuropathy and Guillain-Barré syndrome.

Eosinophilia

The maximum absolute eosinophil count was 18,630 cells/mm^3, with the minimum recorded as 231 (mean 4,200). Twelve of 22 patients tested (54%) had low creatine phosphokinase (CPK) levels, with the rest being normal. Low-normal CPK levels are defined as ≤40 IU/L. Seven of 16 tested (44%) had modestly elevated serum aldolase levels. Five of 11 tested (45%) had elevated C-reactive protein levels. Twelve of 17 tested (70%) had positive antinuclear antibody tests; however, only 4 patients (23%) who tested positive had significant titers of 1:160 or greater. Eight of 21 tested (38%) had low albumin levels which were usually associated with elevated lactate dehydrogenase values and a degree of nonspecific inflammation. Three of 20 patients (15%) had elevated transaminase levels. Scleroderma antibodies were negative in the 6 patients who were tested.

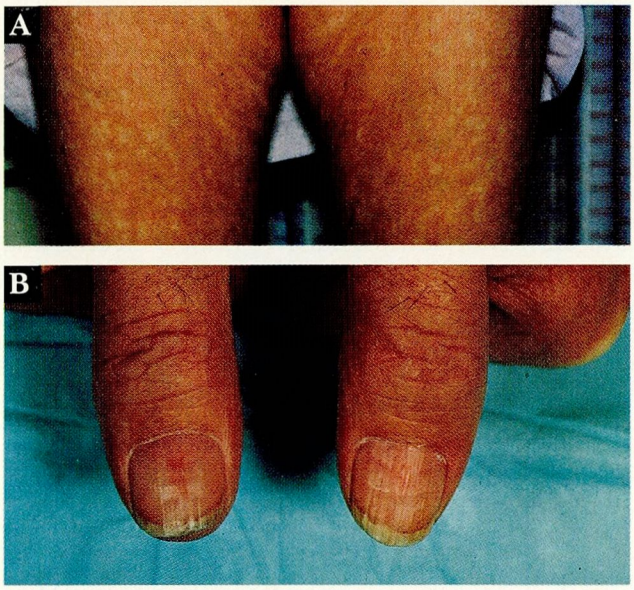

Figure 1. Skin findings in EMS include dimpling of the skin (*A*) characteristic of diffuse fascitis with eosinophilia. Unusual nail findings (*B*) include transparency and apparent lack of the lunulae.

Skin manifestations

After eosinophilia and myalgia, skin involvement was next in frequency of occurrence (*Table 2*). Eighteen of 22 patients (82%) had documented skin involvement. Skin manifestations were protean, but most commonly involved complaints of heightened skin sensitivity and pruritus. Transient urticaria was noted during the acute phase of the illness in a few of the patients. Both skin thickening and fasciitis ranging from a doughy induration to dimpling of the skin to classic peau d'orange was noted in 9 of 22 patients (40%). Skin biopsies showed focal mucinosis, which has been reported elsewhere,[10] diffuse patchy hyperpigmentation, and frank fasciitis. One case of granuloma annulare was noted. Fasciitis was noted pathologically in 6 of 22 patients (27%), 9 of 22 (40%) showed skin dimpling (*Figure 1*).

Two patients were noted to have translucent nails, both grossly and by capillaroscopy, with apparent absence of the lunulae. The skin of the fingers and nails was said to be transparent by the examining physician. No patient examined by capillaroscopy had nailbed evidence of vessel changes characteristic of progressive systemic sclerosis. The lack of nailbed evidence for progressive systemic sclerosis has been reported elsewhere in a series of four patients.[11] Raynaud's phenomenon was notably absent in this Cleveland Clinic series of patients.

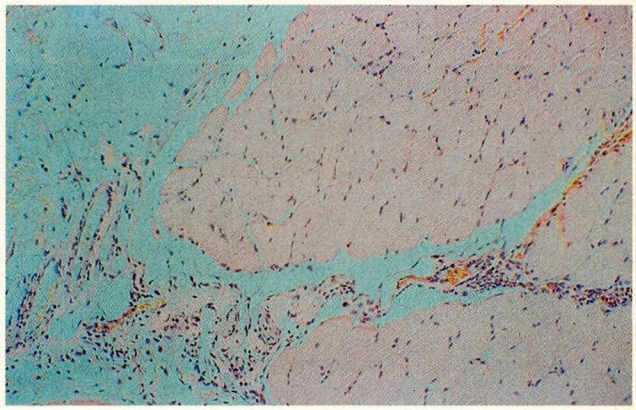

Figure 2. Photomicrograph of muscle showing perimysial lymphocytic infiltrates and perivascular lymphocytic cuffing (hematoxylin-eosin, × 30).

Some patients whose skin texture was initially described as normal by the consulting dermatologist later developed obvious induration and thickening in a pattern clinically consistent with Shulman's syndrome. This pattern of diffuse fasciitis with eosinophilia is different from the pattern seen in patients with progressive systemic sclerosis: that is, whereas the fingers and hands are affected in progressive systemic sclerosis, patients in this series who had EMS with diffuse fasciitis had no sclerosis of the fingers and hands. A mild to moderate alopecia, thought to be the telogen effluvium type, was noted in 15 of 22 patients (68%).

Other findings

Eleven of 22 patients (50%) lost from 10 to 30 lb, with one patient losing 50 lb. Six of seven patients (85%) classified as severely affected lost weight. A few patients gained weight transiently due to fluid gain from associated inflammation and resultant hypoalbuminemia.

All 22 patients had muscle pain, while 15 (68%) had actual muscle weakness. Ten of the 15 patients (66%) with muscle weakness had proximal muscle weakness, and 5 (33%) had both proximal and distal weakness. No definite CNS involvement and no cranial nerve palsies were identified in this series. Five of 22 patients (23%) had pleural effusions at the time of onset of illness. Many patients complained of transient pulmonary symptoms with cough and shortness of breath during the acute onset of illness. No pulmonary hypertension has been identified to date. Be-

TABLE 3
MUSCLE AND FASCIA BIOPSY RESULTS

Pt #	Pathologic description
1	Minimal neurogenic atrophy
2	Not done
3	Not done
4	Not done
5	Moderate interstitial infiltrates, mild neurogenic atrophy
6	Perivascular and perineural lymphocytic inflammation
7*	Marked interstitial lymphocytic infiltration, inflammatory myopathy
8	Not done
9	Question of early diffuse fasciitis vs inflammatory morphea
10*	Lymphocytic vasculitis of the sural nerve, lymphocytic vasculitis with perimysial and endomysial fibrosis
11	Focal perivascular lymphocytic infiltration
12*	Polymyositis, nerve with vasculopathy and expansion of vessel wall
13*	Minimal focal endomysial inflammation, focal phlebitis, perivascular lymphocytic infiltration
14	Moderate interstitial and perivascular inflammation
15*	Denervation atrophy, mild endoneurial fibrosis
16	Not done
17	Perivascular, endomysial, and fascial lymphocytic inflammation
18	Polymyositis, granuloma formation, endomysial and perivascular infiltrates
19	Normal full-thickness biopsy
20*	Neurogenic atrophy, interstitial infiltration
21	Inflammatory reaction in the endomysium and perimysium
22*	Not done

*Severely affected patients

cause of intermittent complaints of acute dyspnea, one patient (patient 20) underwent pulmonary angiography, but the results were normal.

An interesting and unusual complaint of many patients was spontaneous carpopedal and truncal muscle spasms. True tetany was absent, and electrolyte levels in these patients were repeatedly normal. The truncal muscle spasms appeared to exacerbate the patients' sensation of dyspnea. One patient had intense jaw muscle spasms that caused a fracture of a tooth.

Biopsy, nerve conduction studies, and EMG showed a wide spectrum of muscle and nerve involvement. Muscle abnormalities ranged from necrotizing myopathy to noninflammatory myopathy. An ascending polyradiculopathy similar to Guillain-Barré syndrome was seen in some severely affected patients, including the one patient with the history of poliomyelitis. Clinically, 9 of 22 patients (40%) in this series had neuropathy, and most of these had myopathic features as well.

Eleven of 22 patients were evaluated by nerve conduction studies and EMG. Two of these had essentially normal studies. Two had a "necrotizing myopathy" on EMG (both of these patients were severely ill). Two patients had a demyelinating neuropathy. One patient (patient 20) had features of both demyelinating and axonal neuropathy. The electrical findings were noted to be both diverse and complicated in the severely affected cases. Five of nine patients tested (56%) were classified as having a polyradiculopathy.

Fifteen of the 22 patients in this study underwent muscle, fascia, and/or nerve biopsy (*Table 3*, *Figure 2*). Muscle abnormalities ranged from a necrotizing myopathy to noninflammatory myopathy. A perivascular and perimysial inflammatory infiltrate with lymphocytes was commonly observed.

Follow-up findings

Seven of 22 patients (32%) were judged to be severely affected by EMS, with repeated or prolonged hospitalizations. Fourteen of 22 patients (64%) were hospitalized at some time during the course of their illness. Follow-up has ranged from 1 month to 12 months (mean, 8 months) in the epidemic cases. Most patients remain symptomatic. In three patients, the syndrome has entirely resolved. One patient improved, only to relapse with sclerosing skin manifestations 1 month later. One female patient (patient 7), who had significant neuromuscular involvement, expired due to arteriosclerotic heart disease and the debilitated state from the neuromuscular involvement.

With respect to host factors, one patient (patient 2) developed EMS, whereas her husband, who took the same L-tryptophan, did not. One patient with a long history of infertility (patient 19) unexpectedly became pregnant and has had an unremarkable prenatal and postnatal course. One male patient (patient 1) with a history of asbestos exposure has since developed a pleural mesothelioma and has undergone partial pleural decortication. No cases of lymphoreticular malignancy have yet been identified, though it has been reported in some series of Shulman's syndrome patients.[12]

Treatment of the syndrome has been limited. Three of the most severely affected patients underwent plasmapheresis (*Table 4*). Glucocorticoids have improved some patients' skin manifestations; however, the vexing muscle cramps and neurological sequelae do not seem to be as responsive to various empirical treatments of glucocorticoids and nonsteroidal anti-inflammatory medications. There is not enough data from this study to comment on the efficacy of plasmapheresis; however, two of the three patients who underwent plasmapheresis appeared to stabilize within 2 months. Patient 22, who refused plasmapheresis, remained ventilator-dependent for 6 months and is now extubated

and in stable condition. Some of the patients with persistent myalgias have disturbed sleep patterns and appear to clinically respond to reinstitution of antidepressants such as doxepin. Limited use of cytotoxic agents appears to allow reduction in the dosage of glucocorticoids for the treatment of fasciitis in this series of patients. Mechlorethamine (nitrogen mustard, HN_2) was administered to three patients, and one patient underwent treatment with the blood-tryptophan removal device.

Because of the clinical link between EMS and diffuse fasciitis with eosinophilia, all cases of diffuse fasciitis with eosinophilia diagnosed by biopsy at the Cleveland Clinic were reviewed from the time period of June 1978 to May 1990 for case-finding purposes. A total of 25 biopsy-proven cases of diffuse fasciitis with eosinophilia were identified. Eight of the 25 were associated with L-tryptophan use, and 6 of the 8 were epidemic EMS cases from 1989. Out of 25 biopsy-proven cases, 13 retrospectively denied any ingestion of L-tryptophan when contacted by phone. Four of the 25 biopsy-proven cases have unknown ingestion histories: 1 died from complications of the diffuse fasciitis, and the other 3 could not be contacted.

TABLE 4
TREATMENT AND CLINICAL STATUS IN 22 EMS PATIENTS

Pt #	Maximal dose of corticoid used	Plasmapheresis	Other tx	Hospitalized	Clinical status/follow-up time period	
1	Prednisone 20 mg	No	No	Yes	Unchanged, newly diagnosed mesothelioma	1 year
2	Prednisone 20 mg	No	No	Yes	Improved, nonspecific inflammation on SBB	9 months
3	Medrol dose pack	No	No	No	Resolved	1 month
4	None	No	No	No	Improved	9 months
5	Prednisone 20 mg	No	No	No	Improved	9 months
6	Prednisone 20 mg	No	No	Yes	Unchanged	5 months
7*	Prednisone 50 mg	Yes	HN_2/BTD	Yes	Expired after long hospitalization	5 months
8	Prednisone 20 mg	No	No	Yes	Resolved	1 year
9	Prednisone 20 mg	No	Hydroxy-chloroquine	No	Unchanged stable morphea	6 years
10*	Prednisone 30 mg	No	Hydroxy-chloroquine	Yes	Dramatically improved	4 years
11	Triamcinolone 40 mg IM	No	No	No	Improved	3 months
12*	Prednisone 80 mg	Yes	HN_2	Yes	Sent to rehabilitation hospital, unchanged	3 months
13*	Prednisone 80 mg	No	Hydroxy-chloroquine	Yes	Relapsing course with fasciitis	1 year
14	Prednisone 20 mg	No	No	Yes	Improved	3 months
15*	Prednisone 60 mg	No	No	Yes	Slight improvement	4 months
16	None	No	No	Yes	Slight improvement	4 months
17	Prednisone 20 mg	No	No	No	Relapsing skin manifestations	1 year
18	Prednisone 20 mg	No	No	No	Improved but not resolved	4 months
19	Prednisone 60 mg	No	No	No	Resolved, now pregnant	1 year
20*	Prednisone 60 mg	Yes	HN_2	Yes	Improved, returned home from rehabilitation	1 year
21	Prednisone 60 mg	No	Methotrexate	Yes	Relapsing course, but improved	1 year
22*	Prednisone 60 mg	No	No	Yes	Slow improvement, 6 months on ventilator	1 year

*Severely affected patients
HN_2= nitrogen mustard; BTD = blood-tryptophan removal device; SBB = small-bowel biopsy

Two of the above 25 patients were retrospectively diagnosed as having nonepidemic forms of EMS. One case occurred in 1984 with histologic changes consistent with early eosinophilic fasciitis. This patient had associated myalgias and was ingesting a combination of amino acids at the time of onset of illness. She did not have documented eosinophilia but is included in the series because of clinical similarities. This patient is stable but continues to complain of fibromyalgia and stable, unchanged morphea. The second patient developed eosinophilia (absolute count, 2,376 cells/mm^3), a demyelinating neuropathy, and a lymphocytic vasculitis with perimysial and endomysial fibrosis while ingesting L-tryptophan (1,500 mg/day) for depression in 1986. This patient is reported to be much improved and is now ambulatory.

This series does not include enough nonepidemic cases of EMS to compare and contrast with the epidemic cases of EMS for prognosticating purposes. Whether these nonepidemic cases represent the same pathophysiologic process remains to be defined. It is possible that a low level of contamination of manufactured L-tryptophan occurred prior to the epidemic of contaminated L-tryptophan in 1989. However, it is also quite plausible that EMS represents a clinical syndrome that has different etiologic mechanisms and triggers.

The four patients who presented to the author with a chief complaint of self-diagnosed EMS that could not be clinically or pathologically confirmed were diagnosed with the following: a long history of somatization disorder with secondary psychological gain issues; generalized anxiety disorder with minor cardiac

dysrhythmia; depression with secondary gain factors; and longstanding fibromyalgia (which was stable and unchanged).

DISCUSSION

The reported series of 22 patients is similar to the few other reported series in the literature. There is a consistent but varied skin, muscle, and nerve involvement in these reported cases.[13–21] Notably absent in this series is reported pulmonary hypertension, thromboembolic phenomenon, immune thrombocytopenia, or CNS involvement reported in other series.[13] A slightly higher proportion of patients with demyelinating neuropathy is reported in this series, in contrast to one report on the neurological manifestations and results of nerve conduction and EMG studies of EMS patients, which showed axonal degeneration to be more typical than demyelination.[22]

A recent report from France discussed 24 cases of fasciitis and myositis with eosinophilia and described muscle, nerve, and fascia involvement.[23] This French series did not mention L-tryptophan ingestion, presumably because the report was accepted for publication prior to the reported epidemic. Many of the pathological descriptions are quite similar to the Cleveland Clinic patients with EMS.

The consistent and curious finding of low-normal CPK values with modest elevations in the aldolase is not explained. A recent report indicated this was not due to a CPK inhibitor.[15] This pattern of low CPK and elevated aldolase has been reported in patients with progressive systemic sclerosis with myopathy.[24] The muscle cramps are also not yet explained from a pathophysiologic mechanism. It is notable and perhaps revealing that the patient in this series with a history of polio and resultant widespread muscle atrophy did not experience myalgia to any significant degree. Perhaps this is because atrophied myofibrils do not cramp and thus are not painful.

A recent review article on muscle cramps[25] described two different mechanisms by which muscle cramps occur. First, an increased frequency of muscle action potential due to motor neuron hyperactivity causes a sustained muscle spasm. This event is electrically active and is often preceded by repetitive contractions of isolated motor units, evident clinically by repetitive muscle twitches or fasciculations. Second, when muscle adenosine triphosphate becomes depleted, cytosolic accumulation of calcium prevents muscle relaxation. This electrically silent event is also called a contracture. I suspect that patients with EMS have at least both of these mechanisms that account for the baseline myalgia and intermittent cramps. EMS is another condition added to a list of conditions associated with muscle cramps.

The proportion of patients hospitalized in this series is somewhat higher than what has been reported by the CDC and most likely reflects the tertiary care referral patterns of the Cleveland Clinic. Six of the 22 patients (27%) reported in this series are from states other than Ohio.

The 11 patients (50%) who were taking antidepressants at the time of onset is not surprising given the reasons these persons were ingesting L-tryptophan in the first place. Whether persons who have baseline depression and/or fibromyalgia are more predisposed to developing EMS when exposed to the suspected contaminant is not answered yet. A definite association between ingestion of antidepressants and severity of illness was not identified in this series.

The varied time course from initial ingestion of L-tryptophan to onset of illness and the lack of a clear-cut association between dose and severity of illness are consistent with epidemiologic reports of variations in the suspected amount of contaminant in tainted lots of L-tryptophan. Host factors are presumed to be important, as not all persons exposed to contaminated L-tryptophan develop EMS. The various manifestations and severity of illness in these individuals are still to be explained.

CONCLUSIONS

Adverse prognosticating factors include significant nerve and muscle involvement, weight loss, and scleroderma-like thickening of the skin from diffuse fasciitis. The natural history of EMS is still being defined. In this series of patients it appears that if one survives the acute phase of the illness and stabilizes, there is hope for continued improvement. One patient with severe neuromuscular involvement with resultant near-total quadriplegia is now at home, walking with assistance. The hope for continued slow improvement is also supported by the course of the two cases of nonepidemic EMS reported in this series, as well as the clinical course of survivors of the toxic oil syndrome.[26] It is to be expected that nerve and muscle regeneration would be a slow process.

Further clinical, pathological, enzymatic, and immunological studies into this fascinating entity are needed to shed light on EMS and other poorly under-

stood clinical problems, such as diffuse fasciitis, and perhaps even the association between disturbed sleep patterns and fibromyalgia. The link between serotonin metabolism abnormalities and sclerosis has been previously noted.[27] Many substances such as 5-hydroxytryptamine with L-dopa, bleomycin, appetite suppressants, silicone implants, polyvinyl chloride, methysergide, chlorinated chemicals, and the contaminated rapeseed oil of the toxic oil syndrome are reported to be associated with sclerosis. Some cases of carcinoid syndrome have been reported to be associated with sclerosis.[28] Some of these drugs, toxins, and metabolic abnormalities appear to trigger mechanisms that lead to connective tissue abnormalities that may persist and progress long after the inciting cause is gone. It may be that many (if not all) connective tissue disorders are triggered by initial exposure to toxic or infectious agents that later lead to immunologic and nonimmunologic metabolic changes which result in connective tissue abnormalities.

The identification of the putative contaminant or contaminant marker in suspect lots of L-tryptophan took a relatively long time and was achieved by high-performance liquid chromatography. However, even though a causative agent has been identified, it should not be surprising if other substances in the environment are found to trigger similar but nonepidemic connective tissue and neuromuscular disorders that remain elusive.

The role of the eosinophil in EMS remains to be elucidated. This cell may be involved in the pathogenesis of the disorder, or it may simply be an innocent bystander that is activated incidentally. The eosinophilia uniformly subsided in this series of patients after treatment with corticosteroids, as has been reported in other referenced reports.

The preponderance of female patients (77%) in this series is similar to other referenced reports. The toxic oil syndrome had a similar preponderance of female cases in the late stages of the illness. It is known that there are estrogen receptors on the eosinophil, but how this relates to the female preponderance is unknown.

Nothing has yet been published regarding the psychological profiles of patients who ingested contaminated L-tryptophan and developed EMS compared with those who ingested it but did not develop EMS. Perhaps the biologic propensity to develop EMS is linked to the biologic propensity to have baseline neurochemical changes that lead to depression and/or fibromyalgia.

A national registry for the 2-year follow-up of patients with complicated EMS has been organized under the aegis of the Public Health Foundation, with the dual goal of (1) identifying effective strategies to treat the many facets of EMS and (2) following the natural history of the illness in patients with complications. The Cleveland Clinic is one of 23 centers following these patients. Careful clinical descriptions and pathologic correlation, along with the awaited animal model studies, will hopefully provide additional understanding of EMS and similar syndromes. Since EMS can affect a variety of organs and systems, continued collaboration among specialists in diverse fields is essential.

AUTHOR'S NOTE

Patient 13 expired in March 1991 after a protracted hospitalization for gastric perforation and sepsis.

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