



Eosinophilia-myalgia syndrome

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■ The eosinophilia-myalgia syndrome is a newly described disease associated with ingestion of a contaminant or byproduct of the amino acid L-tryptophan. Patients typically present with intense myalgias, especially of the extremities, and commonly suffer from skin and subcutaneous manifestations (edema and induration of the skin, morphea-like lesions, pruritus). Less frequent findings are cardiorespiratory involvement (cough, dyspnea, pulmonary infiltrates) and neurologic disease (ascending polyneuropathy). Laboratory findings include blood eosinophilia (greater than 10^9 cells per liter), normal to slightly elevated serum aldolase levels, and negative studies for connective tissue diseases (normal erythrocyte sedimentation rate, negative antinuclear antibodies). Tissue damage in eosinophilia-myalgia syndrome is likely related to infiltration by eosinophils with subsequent release of toxic molecules such as major basic protein. Management in severely ill patients includes administration of corticosteroids.

□ INDEX TERMS: EOSINOPHILIA; MYALGIA □ CLEVE CLIN J MED 1991; 58:267-270

WHEN FIRST DESCRIBED in 1989,¹ eosinophilia-myalgia syndrome (EMS) generated a great deal of publicity in both the medical and lay literatures. The syndrome, characterized by intense, rapid-onset myalgias and various skin and subcutaneous lesions, was linked to L-tryptophan, an amino acid used in over-the-counter preparations for the treatment of insomnia, premenstrual syndrome, and depression. Since that first report, more than 1,500 cases of EMS (including 23 related fatalities) have been reported from

all areas of the United States.

The incidence of EMS has decreased since January 1989, when the Food and Drug Administration recalled tryptophan preparations containing more than 100 mg per daily dose. Yet the need for physician awareness persists due to the potential for serious complications associated with the use of this preparation. The purposes of this review are to describe the major clinical manifestations and diagnostic features of EMS, its possible pathogenesis, and future directions in clinical and basic research that may help improve management of EMS and related illnesses.

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EMS: DEFINITION AND BACKGROUND

All of the initial and subsequently reported cases of EMS in the United States, Canada,^{3,4} and western Europe⁵ have been associated with ingestion of L-tryptophan, a non-prescription preparation self-administered for treatment of insomnia, premenstrual

syndrome, or depression, or taken by body builders to enhance muscle mass. More than 75% of cases have been reported in women. The doses of L-tryptophan associated with development of EMS have varied widely, ranging from less than 100 mg to more than 1.5 g per day. The duration of exposure prior to onset of clinical symptoms also has a broad range, from approximately 1 month to several years. Some patients have reported discontinuation of L-tryptophan weeks to months before the onset of symptoms.

The case surveillance definition of EMS requires fulfillment of the following three criteria:² (1) a total eosinophil count exceeding 1×10^9 cells per liter of blood; (2) generalized myalgias severe enough to limit daily activity; and (3) exclusion of infectious or neoplastic diseases that might be associated with eosinophilia.

CLINICAL AND LABORATORY FEATURES

EMS is characterized by the rapid onset (usually 1 to 2 weeks) of intense myalgias and signs and symptoms attributable to a pathologic process involving primarily the skin and subcutaneous tissues. In several cases with a fatal outcome, neurologic (eg, ascending polyneuropathy) and pulmonary involvement (eg, dyspnea, arterial hypoxemia, and occasionally pulmonary infiltrates) have been noted. The severity of these signs and symptoms may wax and wane in an individual patient and may persist despite discontinuation of L-tryptophan ingestion.

Skin and subcutaneous findings are the most consistent objective findings reported. Edema, induration of the skin, and maculopapular or urticarial rashes may develop, especially during the early phases of the illness. Alopecia and morphea-like skin lesions similar to those seen in scleroderma occur in some individuals. Skin lesions most frequently involve the extremities and tend to spare the hands and feet. Severe pruritus, myalgias, weakness, and paresthesias suggest that both peripheral sensory and motor neurons are involved. Some patients with EMS have noted arthralgias, although joint swelling or effusions are not a consistent finding.

Life-threatening complications have been reported in several series of case reports. An ascending polyneuropathy reminiscent of Guillain-Barré syndrome may result in respiratory failure,⁶ the most common cause of death in EMS. With respect to cardiorespiratory symptoms, dyspnea and a non-productive cough may occur. These symptoms are associated with a moderate reduction in arterial

oxygen tension in a minority of patients. Although the chest radiograph frequently is normal, interstitial infiltrates and pleural effusions have been described in several cases.⁷ Even less frequent are findings consistent with pulmonary hypertension (tricuspid insufficiency, right ventricular strain).⁸ Invasive or non-invasive studies to determine if these abnormalities exist to a less severe degree in other EMS patients without clinically overt cardiorespiratory symptoms have not been reported.

Signs or symptoms attributable to involvement of the central nervous system, kidneys, liver, gastrointestinal tract, or endocrine system have not been prominent among the reported cases. However, it should be stressed that only one third of patients with EMS have been hospitalized, and the extent of diagnostic tests is variable among the series of reported cases. The major laboratory test abnormality is peripheral blood eosinophilia of greater than 1×10^9 cells per liter. Because automated counters may not accurately enumerate hypodense or degranulated eosinophils, quantification of eosinophils is optimized by performing an absolute count with a specific stain such as Discombe's solution. A generalized blood dyscrasia is not evident, since other blood cell elements (eg, hematocrit, neutrophil, basophil, mononuclear cell, and platelet count) are normal. Abnormalities in procoagulant activity and platelet function have not been reported.

Although the intense myalgias commonly associated with EMS suggest elevations in muscle enzymes, serum creatine kinase levels are usually not higher than normal. Aldolase levels are moderately elevated (two to three times the normal) in approximately 50% of patients. Liver enzymes may be slightly increased and albumin decreased. No consistent abnormality is seen in the level or profile of serum immunoglobulins (Ig). Total serum IgE is higher than normal in 10% of cases in which it was measured.² Serologic tests for connective tissue diseases (eg, antinuclear antibodies, rheumatoid factor) are within normal limits. The erythrocyte sedimentation rate is not elevated.

CLUES TO PATHOGENESIS

Histologic examination of the skin and subcutaneous tissues of patients with EMS demonstrates accumulation of lymphocytes, mononuclear cells, and eosinophils with a perivascular distribution.⁹ Accumulation of collagen and increased gene expression

of type I collagen have also been described in four patients with EMS who had fasciitis as a prominent feature of their illness.¹¹ Biopsies of muscle, intestines, and the vagina revealed similar histologic changes in these organs. On the basis of the finding of tissue deposition of major basic protein, elevated serum levels of eosinophil neurotoxin,⁸ and abundant eosinophil granule components, some have suggested that end-organ damage in EMS is secondary to release of these or similar eosinophil proteins with cytotoxic properties.¹⁰ Eosinophil-specific proteins such as major basic protein have an extremely high isoelectric point ($pI > 10.0$) and bind avidly to negatively charged surface membranes of surrounding target tissues. Major basic protein has been shown to kill helminthic parasites¹² and damage mammalian tissues, including epithelium of the respiratory tract.¹³ It is also likely that reduced oxygen products generated by eosinophils upon contact with a non-phagocytosable target also contribute directly to the toxic properties of these cells.¹⁴

Failure to locate eosinophils in biopsy specimens of affected tissues does not exclude a role for eosinophil products in tissue damage. Eosinophils rapidly degranulate and lose their characteristic histologic features after infiltrating tissues. Relative to cells of healthy individuals with normal absolute eosinophil counts, eosinophils of persons with a variety of underlying causes of eosinophilia are also functionally more active than normal, as evidenced by an increased propensity to release their granules and produce greater amounts of toxic oxygen molecules such as hydrogen peroxide.¹⁵ Eosinophilia-associated eosinophils also release increased amounts of sulfidopeptide leukotrienes (leukotrienes C4 and D4) relative to eosinophils of persons without eosinophilia.¹⁶ These lipid mediators may attract and activate incoming eosinophils from the peripheral blood. In addition, they may induce vasoconstriction and alterations of capillary function that alter delivery of nutrients and oxygen to tissue.

Uncertain mechanisms

A major unresolved issue in EMS is the mechanism by which a contaminant of L-tryptophan elicits eosinophilia and tissue infiltration by these cells. Several clues have been provided by comparison to other diseases characterized by eosinophilia. Eosinophilia with diffuse fasciitis was initially described in 1974,^{17,18} 1 year after L-tryptophan was released for use in the United States. Surveys of patients with this disease indicate that a large proportion had been taking L-tryptophan. The myalgias,

eosinophilia, and neuropathy of EMS are also similar to the signs and symptoms reported in many individuals with the toxic oil syndrome that occurred in Spain in 1981.¹⁹ Epidemiologic investigations indicate that a contaminant in cooking oil was responsible for the outbreak of toxic oil syndrome. Aniline or a related derivative is suspected but has not been unequivocally identified as the causative agent of toxic oil syndrome. By analogy, a byproduct of the process by which the offending batches of L-tryptophan were prepared would seem likely to be at least partly responsible for the development of EMS; however, this has not yet been proven.

It is also possible that abnormalities in L-tryptophan metabolism may contribute to the propensity to develop EMS and related illnesses such as eosinophilic fasciitis. Increased plasma levels of L-kynurenine and quinolinic acid metabolites of L-tryptophan have been found in several cases of EMS.²⁰ In addition, a scleroderma-like illness with eosinophilia has been described in a patient given L-5-hydroxytryptophan and carbidopa.²¹ The plasma of this individual contained elevated amounts of serotonin and L-kynurenine, both of which are products of tryptophan metabolism. Additional support for the notion that an abnormality in tryptophan metabolism accounts for development of EMS is the observation that elevated plasma levels of L-kynurenine and quinolinic acid were observed in four subjects with active disease and eosinophilia but not in three patients following resolution of eosinophilia or in healthy persons.²¹ Several patients with EMS have reported taking benzodiazepines or antidepressants in conjunction with L-tryptophan. Examination of the effect of the former drugs on tryptophan breakdown may provide additional clues to the role of this metabolic pathway in the induction of eosinophilia in EMS.

Unequivocal identification of the putative toxic contaminant that causes EMS and its mechanism of action will require its isolation and demonstration of biologic activity in experimental animals. Because the cytokine interleukin-5 (IL-5) is likely a major regulatory factor in the pathogenesis of eosinophilia,²² demonstrating the capacity of such a compound to upregulate production of IL-5 and/or its receptor will be important.

DIAGNOSIS AND MANAGEMENT

The diagnosis of EMS is based on eosinophilia, the presence of myalgias and signs and symptoms described

above, and the exclusion of other causes of eosinophilia. Helminthic infections and idiopathic hypereosinophilic syndrome are the major considerations in the differential diagnosis of EMS. In the United States, infection by the helminth *Trichinella spiralis* is most likely to cause eosinophilia and myalgias. Trichinosis is diagnosed on the basis of a history of eating poorly cooked meat that contains viable larvae (eg, pork, wild bear), positive serology, and occasionally by muscle biopsy.²³ Most cases of trichinosis occur in outbreaks and become symptomatic 1 to 4 weeks after ingestion of larvae. Other intestinal helminthic infections that may cause eosinophilia (*Strongyloides stercoralis* infection) may be excluded by examination of stools for ova and parasites. Several features of idiopathic hypereosinophilic syndrome distinguish it from EMS. These include most notably cardiac manifestations (especially thrombi detectable by echocardiogram), peripheral neuropathy, lack of female predominance, and hemorrhagic or thrombotic

diathesis.²⁴ Neoplasms such as lymphomas and carcinomas of the lung, uterus, and liver may also be associated with eosinophilia. A number of drugs (eg, diphenylhydantoin, penicillin, sulfa drugs) may induce eosinophilia. Their use should be discontinued when possible, as in any idiosyncratic drug reaction.

Management of patients with EMS includes discontinuation of L-tryptophan use and administration of corticosteroids if, in the physician's opinion, the severity of symptoms warrants it.²⁵ However, these recommendations are not based on controlled trials or an understanding of etiology. As such they should be considered preliminary and likely to change. In patients with neurologic or other life-threatening manifestations of EMS, appropriate supportive care is obviously indicated. Because the frequency of these complications does not appear to correlate directly the degree of eosinophilia, cytotoxic agents such as hydroxyurea do not appear useful at present.

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