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Connective Tissue Diseases

Eosinophilia-Myalgia Syndrome

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Introduction

Background

Eosinophilia-myalgia syndrome (EMS) was first recognized in 1989 in New Mexico in 3 patients who had an illness with a unique array of symptoms, including peripheral blood eosinophilia and severe myalgias. All 3 patients had ingested sleeping aids containing L-tryptophan. In the ensuing weeks, a nationwide epidemic of EMS became apparent; this epidemic was correlated with the use of over-the-counter compounds containing L-tryptophan. In response, the US Food and Drug Administration ordered a recall of all single-entity products containing L-tryptophan.

In 1989, the Centers for Disease Control and Prevention (CDC) issued the following case definition for EMS: (1) a peripheral eosinophil count of at least 1.0×10^9 cells/L, (2) a generalized myalgia at some point during the illness that is severe enough to affect the patient's ability to perform his or her usual daily activities, and (3) no evidence of infection or neoplasm that could explain either the eosinophilia or the myalgia.

EMS may be related to the toxic oil syndrome in Spain. They are linked by a common toxic metabolite (4-aminophenol) and may be further associated by the concomitant release of potentially hazardous carbonyl species.[1]

The eMedicine Rheumatology article Eosinophilia-Myalgia Syndrome may be helpful.

Pathophysiology

EMS is an illness characterized by pruritus, cutaneous lesions, edema, sclerodermoid changes, and joint pain, in addition to dramatic myalgia and eosinophilia. In the early phase of the disease, most patients have muscle aches; cough; dyspnea; macules, papules, or urticarial skin lesions; intense pruritus; constitutional symptoms, such as fatigue, fever, and weight loss; and persistent, incapacitating myalgias. This phase lasts weeks to months and is followed by a chronic phase characterized by sclerodermoid skin changes, neuropathy, neurocognitive deficits, continued myalgia, and muscle cramps. Other less common chronic manifestations involve the pulmonary, cardiac, and gastrointestinal systems.

The exact cause of EMS remains unknown; however, its histopathologic pattern is well described. The most prominent pathogenic feature of the disease is the widespread inflammatory reaction. Besides the marked

eosinophilia, a considerable accumulation of inflammatory mediators is present in the tissues; these mediators include cytokines, lymphocytes, mononuclear cells, and eosinophils. This cell-mediated immune response is ultimately responsible for the widespread tissue injury, in addition to the fibrosis of the skin and the connective tissue that pervades muscles, nerves, and other organs. In fact, examination of muscle biopsy specimens reveals a dramatic inflammatory infiltrate that is predominantly composed of mononuclear cells and activated T cells.

Cytokines are implicated in several aspects of the disease. Three cytokines, granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin 3 (IL-3), and interleukin 5 (IL-5) have been shown to promote the growth and the maturation of eosinophils and to induce the conversion of normal eosinophils to hypodense eosinophils. Hypodense eosinophils are activated cells with increased survival and an increased capacity for cytotoxicity, and their release of inflammatory mediators, such as leukotrienes, is increased. In particular, IL-5 activity is shown to be elevated in sera from patients with EMS. Therefore, in EMS, IL-5 may play a substantial role in the growth and the stimulation of eosinophils and in their conversion to the hypodense, cytotoxic form.

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The exact cause of EMS remains unknown; however, its histopathologic pattern is well described. The most prominent pathogenic feature of the disease is the widespread inflammatory reaction. Besides the marked eosinophilia, a considerable accumulation of inflammatory mediators is present in the tissues; these mediators include cytokines, lymphocytes, mononuclear cells, and eosinophils. This cell-mediated immune response is ultimately responsible for the widespread tissue injury, in addition to the fibrosis of the skin and the connective tissue that pervades muscles, nerves, and other organs. In fact, examination of muscle biopsy specimens reveals a dramatic inflammatory infiltrate that is predominantly composed of mononuclear cells and activated T cells.

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The exact role of the eosinophils in the pathogenesis of EMS is uncertain, but products of the activated eosinophils, particularly the toxic granule proteins (ie, major basic protein, eosinophil-derived neurotoxin), are implicated in tissue injury. The serum and urine levels of both major basic protein and eosinophil-derived neurotoxin are dramatically increased in patients with EMS; these findings are evidence of continuous eosinophil degranulation. Also, eosinophils themselves, along with major basic protein, probably contribute to the debilitating fibrosis in EMS because they stimulate fibroblast-activating agonists, such as transforming growth factor-beta (TGF-b).

TGF-b is a powerful inducer of collagen synthesis and is implicated in the pathogenesis of several fibrotic conditions, including EMS. Fibroblasts isolated from patients with EMS demonstrate elevated expression of TGF-b, along with other genes that code for extracellular matrix components. In fact, skin and fascia from patients with EMS demonstrate excessive deposition of collagen, fibronectin, and other extracellular matrix components.

In addition to the striking fibrosis of the integument, the perimysium, and the perineurium, fibrosis and inflammation of the blood vessels lead to occlusive microangiopathy. The occlusion of the blood vessels may lead to tissue ischemia, which may also contribute to the tissue injury seen in EMS.

Although the precise etiologic agent remains unknown, evidence suggests that either a chemical contaminant or a toxic metabolite of L-tryptophan is responsible for the inflammation seen in EMS (see Causes). Ultimately, the tissue injury in EMS appears to be related to a combination of factors: eosinophil-derived toxins, microangiopathy-related ischemia, fibrosis, and direct injury due to inflammatory mediators.

By applying the CDC case definition, 191 cases of EMS were retrospectively identified as pre-epidemic cases, that is, cases identified prior to July 1989.

Early epidemiological evidence linked EMS and microimpurities of L-tryptophan–containing dietary supplements. Reliance on a finite impurity from one manufacturer has been challenged as both unnecessary and insufficient to explain the etiology of EMS.[2] Excessive histamine activity has been postulated because it induces blood eosinophilia and myalgia. Correlations have been made between histamine degradation, eosinophilia, and this myopathy.[3]

Frequency

United States

From October 30, 1989, to January 31, 1993, a total of 1,512 cases of EMS were reported. However, only 1,345 of those fulfilled the CDC's surveillance case definition for EMS. An overwhelming majority of the cases of EMS occurred in the United States.

International

Other countries reporting cases of EMS include Germany (100 cases), Canada (12 cases), and the United Kingdom (11 cases).

Mortality/Morbidity

From October 1989 to January 1993, a total of 1,512 cases of EMS were reported. Approximately one third of patients in these cases required hospitalization, and 35 deaths were recorded.

Race

A CDC study of 1,117 patients showed that 1,046 (94%) of patients were non-Hispanic white, 19 (2%) were Hispanic, 12 (1%) were black, and 40 (4%) were from other or unknown racial or ethnic groups.

Sex

Of the 1,117 subjects in the CDC study, 927 (83%) of patients were female.

Age

The CDC study of 1,117 patients showed that patients with EMS were aged 4-85 years, with a median age of 48 years.

Clinical

History

The case definition of EMS is useful to identify patients with suspected EMS; however, to ensure a more accurate diagnosis, a more stringent set of criteria must be applied. One set of proposed classification criteria includes 4 axes: (1) the presence of a distinct acute episode with the typical signs and symptoms; (2) major physical findings, including typical involvement of organs, such as the skin, the muscles, the lungs, and

the nerves; (3) characteristic laboratory values, including an eosinophil count greater than 1.0×10^9 cells/L; and (4) characteristic histopathologic features.

- Acute episode
  - The acute episode is characterized by shortness of breath; cough; fever; debilitating fatigue; arthralgias; paresthesias; severe weakness; muscle cramps; periorbital and peripheral edema; skin hypersensitivity; and a generalized erythematous, maculopapular, or blotchy erythematous rash.
  - After this acute episode, most patients have more chronic symptoms that involve several organ systems.
- Cutaneous involvement
  - Cutaneous involvement occurs in 60% of patients with EMS. After the initial symptoms, this is the most prominent feature of the disease.
  - In the acute phase of the disease, patients often have a diffuse eruption with pruritus and swelling.
  - Later in the disease, patients may experience skin tightening, which reflects sclerodermoid changes. However, unlike scleroderma, the fingers and the toes are almost always spared, and the Raynaud phenomenon is usually absent.
  - Patients may note an inability to tolerate even light touch. This finding tends to be more pronounced in the lower extremities than elsewhere.
  - Alopecia is also noted in more than one quarter of patients.
- Muscular involvement
  - By definition, patients must have myalgia. This condition usually begins in the proximal muscle groups, such as those in the shoulders, the buttocks, and the thighs; then, myalgia becomes incapacitating.
  - Patients may have stiffness and aches in the affected muscles, as well as muscle cramps, particularly during exercise.
  - Patients also complain of weakness and muscle wasting that limit their ability to walk or lift heavy objects.
  - Myalgia in the jaw can lead to pain in the facial muscle or the jaw.
- Nervous system involvement
  - Central nervous system and peripheral nervous system involvement is seen in 27% of patients, in whom disorders of these systems are the presenting features.
  - Patients may have decreased sensation, particularly in the hands, or hyperesthesia in the back and the extremities.
  - Patients may present with weakness, cognitive deficits, or bladder dysfunction.
- Pulmonary involvement
  - Pulmonary symptoms are the major presenting complaints in the acute phase of EMS.
  - Patients report rapidly progressive shortness of breath associated with a nonproductive cough and other symptoms related to upper respiratory tract infections.
  - Patients may have chest tightness, pleuritic chest pain, or dyspnea on exertion.
- Cardiac involvement
  - Most patients do not have heart problems; however, pericarditis, myocarditis, and cardiac arrhythmias are known complications of the disease.
  - Patients with arrhythmias may have palpitations.
- Gastrointestinal involvement
  - Gastrointestinal problems are not common problems in this disease.
  - Some patients experience abdominal pain, nausea, vomiting, diarrhea, and weight loss.
- Rheumatologic involvement
  - About 73% of patients have joint pain.
  - This pain can be located in the wrist, the knees, the ankles, the shoulders, the hips, the spine, or the interphalangeal and metacarpophalangeal joints.

Physical

- Cutaneous manifestations
  - A diffuse eruption consisting of erythematous macules and papules often develops over the trunk and the extremities. The skin may have a mottled appearance and occasionally appears ecchymotic. No palpable purpura is evident.

- Four weeks to 4 months after the onset of myalgias, a progressive peau d'orange–type induration may develop. This process tends to start in the distal part of the lower and upper extremities and gradually moves proximally. The digits are characteristically spared. The skin classically appears firm, shiny, and hide-bound.
        - Sometimes, venous furrowing of the uplifted arm is observed.
- Neuromuscular manifestations
        - Neuromuscular examination of patients with EMS reveals weakness and paresthesias. Some patients have cutaneous hyperesthesia (the inability to tolerate touch). This finding tends to be more pronounced in the lower extremities.
        - Muscles are often tender to palpation.

Causes

Although the consumption of L-tryptophan is not part of the definition of EMS, it is described in more than 96% of patients with EMS. Tryptophan is an essential amino acid that is present in many foods and is part of various remedies. It is used to treat insomnia, anxiety, premenstrual syndrome, and obesity. In fact, prior to 1989, millions of Americans had been ingesting products containing L-tryptophan for many years. Therefore, any hypothesis about the association between L-tryptophan consumption and EMS must address why some individuals had the syndrome while others did not. During the peak of the epidemic, 2 theories emerged: the toxic metabolite hypothesis and the contaminant hypothesis.

- Toxic metabolite hypothesis
        - L-tryptophan is metabolized through 2 separate pathways. In one pathway, L-tryptophan is broken down to serotonin. In the other pathway, L-tryptophan is degraded into kynurenine. In this pathway, kynurenine can be metabolized to quinolinic acid, which is an endogenous neurotoxin implicated in the pathogenesis of several metabolic and neurologic conditions.
        - Metabolites of both pathways are associated with connective tissue disorders.
        - Serotonin overproduction by carcinoid tumors is associated with myalgias and arthralgias in addition to sclerodermalike skin changes.
        - Patients with EMS are noted to have abnormalities in both of these pathways. However, aberrant tryptophan metabolism by itself does not provide an adequate explanation.
- Contaminant hypothesis
        - Because of the epidemic nature of the syndrome, an inherited alteration in tryptophan sensitivity or metabolism is unlikely to be the sole factor responsible for the development of EMS. Rather, a contaminant is implicated as a cause of the syndrome.
        - In fact, L-tryptophan from different brands of products used by patients with EMS was traced back to one manufacturer in Japan who had altered the manufacturing process of L-tryptophan before the epidemic.
        - High-performance liquid chromatography of EMS-associated L-tryptophan reveals several peaks that correspond to impurities. One particular peak was consistently found in case-associated lots. This substance was isolated, purified, and shown to be 1,1-ethylidenebis (tryptophan). Although 1,1-ethylidenebis may not be the etiologic agent, it may be a marker for another contaminant.

Differential Diagnoses

Dermatomyositis

Eosinophilic Fasciitis

Hypereosinophilic Syndrome

Mixed Connective Tissue Disease

Systemic Sclerosis

Other Problems to Be Considered

Toxic oil syndrome

Polymyositis

Polyarteritis nodosa

Workup

Laboratory Studies

- Complete blood count with differential
  - By definition, patients should have an eosinophil count higher than 1.0×10^9 cells/L.
  - A value of 1.5×10^9 cells/L is suggested as an alternate baseline value, with more weight given to eosinophil counts higher than 3×10^9 cells/L.
  - An elevated white blood cell count is observed in 46% of patients and is often secondary to the eosinophilia.
- Liver function tests
  - Abnormal results of liver function tests are observed in 43% of patients with EMS.
  - These abnormalities can include elevated levels of bilirubin, alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma-glutamyl transferase.
- Creatine kinase and aldolase tests: Levels are elevated in 3% of patients with EMS.
- Major basic protein and eosinophil-derived neurotoxin tests
  - Serum levels of major basic protein are 213-1352 ng/mL (reference range, 158±42), and urine levels are 9-225 ng/nL (reference range, 10±10).
  - Serum levels of eosinophil-derived neurotoxin are 10-208 ng/mL (reference range, 16±6), and urine levels are 113-10,700 ng/nL (reference range, 298±145).
- Immunologic workup
  - This set of tests is important to rule out other known rheumatologic diseases, such as scleroderma.
  - Patients with EMS may have an elevated antinuclear antibody titer, but, generally, anti-Ro, anti-La, antiribonucleoprotein (anti-RNP), anticentromere, anti-DNA, Smith antigen, and Scl-70 results are negative. One patient with EMS had elevated antimitochondrial antibody levels.

Imaging Studies

- Chest radiography
  - Chest radiographic findings may be normal, even in patients with evidence of lung function compromise.
  - Abnormal findings may include basilar interstitial opacities, lower lobe infiltrates, diffuse interstitial infiltrates, pleural effusions, and reticulonodular infiltrates.
- Head MRI
  - Head MRIs may show several areas of increased signal intensity in the white matter and the corpus callosum, particularly in the occipital region.
  - MRIs may also reveal focal areas of increased signal intensity in the parietal lobe.
- Abdominal CT
  - Abdominal CT scans may show splenomegaly in 1% of patients with EMS.
  - Hepatomegaly is found in 5% of patients with EMS.

Other Tests

- Electromyography
  - Electromyography (EMG) shows evidence of myopathy in two thirds of patients.
  - In many cases of EMS, EMG reveals evidence of polyneuropathy that is often severe. This finding is consistent with demyelination and associated axonal involvement.
- Pulmonary function tests

- - The results of pulmonary function tests (PFTs) are abnormal in patients with respiratory symptoms and in some patients without respiratory symptoms and normal chest radiographic findings.
  - PFTs demonstrate both mild-to-moderate obstructive lung disease and restrictive lung disease.
  - Forced vital capacity, forced expiratory volume in 1 second, total lung capacity, and single-breath carbon monoxide diffusing capacity values are diminished in patients with EMS.
- Electrocardiography
  - ECG findings are usually normal.
  - Reported abnormalities include atrial flutter, left-axis deviation with a pattern of right ventricular strain, minor ventricular and atrioventricular delays, right ventricular hypertrophy, and poor R-wave progression across the precordium with no acute ST- or T-wave changes.
- Echocardiography
  - Echocardiograms may show a moderate pericardial effusion, an enlarged right ventricle with decreased function, or a thickened mitral valve.
  - Echocardiograms may show cor pulmonale with tricuspid regurgitation in patients with pulmonary hypertension.

Histologic Findings

Biopsy samples of the skin and the underlying fascia reveal the following characteristic findings: thickening of the fascia with homogenization of collagen accompanied by an inflammatory cell infiltrate in the fascia, subcutaneous adipose tissue, interlobular septa, and deep reticular dermis. This infiltrate is primarily composed of lymphocytes, but eosinophils and plasma cells are also found.

Biopsy samples of the muscle reveals prominent findings in the endomysium, the perimysium, and the fascia that consist of a perivascular and interstitial inflammatory infiltrate composed of lymphocytes, histiocytes, plasma cells, and rare eosinophils.

Histopathologic features in the nervous tissue may include perivascular, perineural, epineural, or endoneural inflammation with mononuclear cells with or without eosinophils, in addition to axonal degeneration.

Histologic findings in the lung may show perivascular inflammation, interstitial inflammation with or without fibrosis, and alveolar exudate.

Treatment

Medical Care

- The most important component of treatment is to discontinue the use of any product containing L-tryptophan.
- The mainstay of pharmacologic treatment is glucocorticoid therapy, which benefits many patients but is not effective for all symptoms of EMS.
- Other care depends on the manifestations of the disease. In many cases, it is mostly supportive.

Consultations

Because of the high morbidity associated with EMS, referral to mental health experts should be obtained.

- Psychotherapy may be helpful in dealing with alterations in mood and behavior secondary to the acquired disabilities.
- Furthermore, psychological evaluation may provide techniques to use in dealing with compromised function for patients who are affected.

Medication

Glucocorticoids appear to benefit most patients with EMS, but many symptoms do not respond to this treatment. Usually, eosinophilia markedly decreases, and edema and pulmonary infiltrates resolve in response to glucocorticoids. Nonsteroidal anti-inflammatory agents and narcotic analgesics may be useful for the relief of severe muscle pain.

Glucocorticoids

These agents have anti-inflammatory properties and cause profound and varied metabolic effects. Corticosteroids modify the body's immune response to diverse stimuli.

Prednisone (Deltasone, Orasone, Meticorten)

May decrease inflammation by reversing increased capillary permeability and suppressing PMN activity. Stabilizes lysosomal membranes and also suppresses lymphocyte and antibody production.

Dosing

Adult

5-60 mg PO qd or divided bid/qid; taper over 2 wk as symptoms resolve

Pediatric

4-5 mg/m^2/d PO; alternatively, 0.05-2 mg/kg PO divided bid/qid; taper over 2 wk as symptoms resolve

Interactions

Coadministration with estrogens may decrease clearance; concurrent use with digoxin may cause digitalis toxicity secondary to hypokalemia; phenobarbital, phenytoin, and rifampin may increase metabolism of glucocorticoids (consider increasing maintenance dose); monitor for hypokalemia with coadministration of diuretics

Contraindications

Documented hypersensitivity; fungal, viral, connective tissue, and tubercular skin infections; peptic ulcer disease; GI disease

Precautions

Pregnancy

B - Fetal risk not confirmed in studies in humans but has been shown in some studies in animals

Precautions

Abrupt discontinuation of glucocorticoids may cause adrenal crisis; hyperglycemia, edema, osteonecrosis, myopathy, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, myasthenia gravis, growth suppression, and infections may occur with glucocorticoid use

Follow-up

Further Outpatient Care

- Physical rehabilitation
    - For most patients, a physician-directed rehabilitation program is recommended.
    - The rehabilitation program should be tailored for each individual.
- Psychological support
    - Many patients experience anxiety and/or depression as a result of EMS.
    - Psychological distress should be treated with the appropriate psychotherapy and/or medication.

Deterrence/Prevention

- The principal preventative measure is to avoid the use of products containing L-tryptophan.
- The use of a multivitamin or a B-complex vitamin may also provide protection against some of the subacute symptoms in EMS.

Complications

- EMS is a multiorgan disease that affects the lungs, the skin, the gastrointestinal tract, the nervous system, and the blood system. Complications affecting these organs can arise from the disease or from adverse effects of therapy.
- In one patient, juxta-articular adiposis dolorosa developed secondary to long-term treatment with high doses of corticosteroids. The condition involved multiple, painful, symmetrically distributed, fatty deposits that were localized to the lower extremities. The condition resolved when the corticosteroid dose was reduced.

Prognosis

- In a few patients, eosinophilia and other clinical manifestations rapidly resolved after they discontinued their use of products containing L-tryptophan. However, improvement is generally slower. In many individuals, the disease appears to progress after they cease using products containing L-tryptophan.
- In certain patients, progressive and potentially fatal ascending polyneuropathy can develop. This ascending neuropathy can lead to respiratory arrest, which is the leading cause of death in patients with EMS.
- Myocardial infarction, cardiac arrhythmias, pulmonary hypertension, pneumonitis, thromboembolic phenomena, and cerebral vasculitis are other causes of morbidity and mortality.

Patient Education

- For excellent patient education resources, visit eMedicine's Muscle Disorders Center. Also, see eMedicine's patient education article Chronic Pain.

Miscellaneous

Medicolegal Pitfalls

- EMS is a rare syndrome outside of the epidemic. In considering this diagnosis in a patient today, other disorders that may mimic it need to be recognized.

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