Acute Eosinophilic Pulmonary Disease Associated with the Ingestion of L-Tryptophan-Containing Products*

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A series of four patients with pulmonary infiltrates, pleural effusions, hypoxemia, peripheral eosinophilia, and symptoms of dyspnea, fatigue, and weakness is reported. Lung tissue obtained in three patients revealed interstitial pneumonitis, small-to-medium-vessel mixed-cell vasculitis, and alveolar exudate of histiocytes and eosinophils. All patients reported ingestion of L-tryptophan-containing products at a time when an association between L-tryptophan and the eosinophilia-myalgia syndrome was established. This clinical pattern of pulmonary involvement may be part of the continuum of the eosinophilia-myalgia syndrome. The pathophysiology of this syndrome and the relationship with the ingestion of L-tryptophan-containing products have not yet been identified. (Chest 1991; 99:8-13)

A cluster of four patients has been identified with pulmonary infiltrates, pleural effusions, hypoxemia, peripheral eosinophilia, and histologic evidence of pneumonitis and pulmonary vasculitis. In addition, these patients report ingestion of L-tryptophan-containing products at a time when the public was made aware of an association between the ingestion of L-tryptophan-containing products and the development of an eosinophilia-myalgia syndrome.1,2

The L-tryptophan ingested by these patients was purchased as an over-the-counter medication for relaxation and to induce and promote sleep. It is probable that this clinical presentation is a variant of the eosinophilia-myalgia syndrome and is associated with the ingestion of L-tryptophan-containing products. An alternative etiology based on history, laboratory determinations, or available histologic material could not be established.

CASE REPORTS

Clinical findings for each case are summarized in Table 1.

CASE 1

A 41-year-old female smoker with no prior medical illnesses reported a one-week history of increasing dyspnea at rest and with exertion, a dry cough, and an inability to take a deep breath. There was an associated ache in the chest wall and a substernal abdominal burning sensation. There was no history of fever, hemoptysis, chills, exposure to sick animals, travel, or known exposure to inhaled toxins.

Table 1—Clinical and Laboratory Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
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<tr>
<td>Age, yr</td>
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<td>61</td>
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<td>60</td>
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<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>F</td>
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<td>Race</td>
<td>W</td>
<td>W</td>
<td>W</td>
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</tr>
<tr>
<td>Dyspnea</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Cough</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Sputum production</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Fever</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>−</td>
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<tr>
<td>Rash</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Myalgias</td>
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<td>−</td>
<td>+</td>
<td>+</td>
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<td>Arthralgias</td>
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<td>−</td>
<td>−</td>
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<td>−</td>
<td>−</td>
<td>−</td>
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<td>13.9</td>
<td>43.5</td>
<td>11.9</td>
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<tr>
<td>Percent eosinophils</td>
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<td>37</td>
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<td>Chest roentgenogram</td>
<td></td>
<td></td>
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<tr>
<td>Interstitial infiltrates</td>
<td>+</td>
<td>+</td>
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</tr>
<tr>
<td>Alveolar infiltrates</td>
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<td>Pleural effusion</td>
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<td>Arterial blood gas levels</td>
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<tr>
<td>(FIO₂, 0.21)</td>
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<td></td>
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<tr>
<td>PaO₂, mm Hg</td>
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<td>50</td>
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<td>54</td>
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<tr>
<td>PaCO₂, mm Hg</td>
<td>38</td>
<td>29</td>
<td>32</td>
<td>32</td>
</tr>
</tbody>
</table>

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The patient was treated with intravenous erythromycin and supplemental oxygen, and observed. Increasing symptoms of dyspnea and weakness led to an open lung biopsy. Of interest, during her hospitalization, the patient had requested and received L-tryptophan for sleep. Because of newspaper reports of L-tryptophan-induced eosinophilia, the patient later reported that she had a one-year history of nightly ingestion of L-tryptophan (500-mg tablets) to promote sleeping; and one month prior to the onset of her illness, she had changed brands of L-tryptophan.

Physical examination revealed an acutely ill, afibrile woman with no rash and inspiratory rales without wheezes or rhonchi. Prior to open lung biopsy, the patient’s WBC was 24,500/cu mm, with 43 percent eosinophils; and a gallium scan showed evidence of increased uptake in the lower two-thirds of both lung fields, with sparing of the apices. Before biopsy a chest x-ray film (Fig 1) revealed bibasilar infiltrates and blunting of both costophrenic angles consistent with pleural effusions.

After surgery the patient was treated with prednisone (60 mg daily). Within five days, her oxygenation had dramatically improved. Within three weeks, her chest x-ray film had returned to normal. After several weeks of treatment, the patient’s diffusing capacity for carbon monoxide was mildly reduced (78 percent of predicted), while spirometry and lung volumes were normal. Despite documented improvement, the patient continued to complain of fatigue, abdominal discomfort, chest wall aching, and a nondescript rash not seen by a physician.

Case 2

A 61-year-old female nonsmoker with treated hypothyroidism and diet-controlled diabetes mellitus was hospitalized because of a one-week history of increasing dyspnea, pleuritic chest pain, nonproductive cough, and diffuse myalgias. She had been placed on erythromycin three days prior to admission for fever to 38.4°C (101.1°F) and bibasilar interstitial infiltrates on the chest roentgenogram.

Medications taken prior to admission were levothyroxine (0.125 mg daily) and L-tryptophan (1,000 mg at bedtime). Physical examination revealed an afibrile woman in mild respiratory distress with bibasilar pulmonary rales, diminution of breath sounds, and dullness to percussion. The findings from cardiac examination were normal.

The patient was initially treated with intravenous cefuroxime and erythromycin. These medications were discontinued by the fifth day of hospitalization. The chest x-ray film, confirmed with computed tomography, demonstrated large bilateral pleural effusions and bilateral lower lobe infiltrates.

Bilateral thoracocenteses revealed sterile exudative pleural effusions. A right-sided pleural biopsy demonstrated nondiagnostic focal inflammatory changes.

After a right open lung biopsy, the patient was treated with 1 g of intravenous methylprednisolone daily for three days and then converted to oral prednisone (60 mg daily). Her condition rapidly improved over the next four weeks, with resolution of the pleural effusions and improved oxygenation at rest, but persistent exercise-induced hypoxemia. She developed an erythematous macular nonvesicular rash on the extensor surface of both forearms, which resolved spontaneously. Pulmonary function tests performed after several weeks of therapy demonstrated a mildly reduced FEF25-75%, normal lung volumes, and a reduced diffusing capacity for carbon monoxide (38 percent of predicted).

Case 3

A 55-year-old cabinetmaker with a history of exposure to acrylics was in good health until two weeks prior to admission, when he experienced fever to 38.9°C (102°F), anorexia, nausea, vomiting, weakness, dyspnea, and a patchy macular rash. Physical examination demonstrated bibasilar rales, hepatomegaly about 5 cm below the right costal margin, and a rash consistent with erythema multiforme. The patient’s generalized strength was reduced.

A chest x-ray film (Fig 2) showed bilateral patchy infiltrates and blunted costophrenic angles. Fiberoptic bronchoscopy and transbronchial lung biopsy were performed, and the airways were found to be normal. A liver biopsy showed normal tissue and architecture. A bone marrow biopsy revealed eosinophilic myeloid hyperplasia with increased numbers of eosinophilic precursors but was otherwise normal.

The patient was empirically treated with prednisone (100 mg daily for one week and then 60 mg every other day). Within days the peripheral eosinophilia and chest roentgenographic abnormalities resolved. The patient felt better, and his strength improved.

During his hospitalization, the patient’s only reported medications were acetaminophen, ibuprofen, and sulindac for degenerative joint disease. Multiple inquiries about other medications were negative until the patient’s wife recalled that she had given the patient one...
or two doses of her L-tryptophan. They were unable, in retrospect, to report the dosage or brand of L-tryptophan tablet administered. The wife reported no ill effects from the L-tryptophan nor any illness similar to her husband's.

**Case 4**

A 60 year-old woman with prior chronic thyroiditis was admitted with a one-week history of cough productive of greenish-yellow mucus, sore throat, sneezing, chills, and night sweats, but fever was not documented. The new onset of dyspnea with exertion, weakness, fatigue, and tiredness prompted medical evaluation. The patient had been camping but had no known insect bites or exposure to sick animals.

Five months previously, the patient had received prednisone for back pain, but she had not taken any corticosteroids for at least one month prior to admission. On physical examination, there were sparse end-inspiratory rales in the right side of the chest. A chest x-ray film revealed a small, right lower lobe infiltrate and blunting of both costophrenic angles consistent with bilateral pleural effusions.

The patient was empirically treated with erythromycin, first intravenously and then orally. She remained afebrile and improved clinically, allowing discharge to complete outpatient therapy with oral erythromycin. Within ten days, the chest x-ray film was normal.

When evaluated two months later, the patient reported knowledge of an association between L-tryptophan ingestion and eosinophilia. She then reported that she had ingested L-tryptophan (500 mg nightly) for ten years. Just prior to her illness, she had been taking L-tryptophan tablets (500 mg) three to four times per day and, in addition, had recently changed brands. She had stopped consuming L-tryptophan upon hospitalization and had resumed 2½ months after discharge, but for only two doses. She stopped again when she became aware of the L-tryptophan product recall, and she then brought her history of L-tryptophan ingestion to the attention of her physicians. She also reported a nondescript painful rash which was not seen by a physician.

**Pathologic Evaluation**

Gross examination of the lung biopsies showed essentially normal, spongy pink tissue, with no areas of firmness or masses identified; however, histologic sections in all cases showed pronounced pathologic abnormalities which varied in severity from case to case (Table 2).

![Figure 3. Open lung biopsy (case 2). A (left): Transmural inflammation, most prominent subendothelially, with many eosinophils (thin arrows) and deposition of hyaluronic collagen in vessel wall (thick arrows). B (right): Vessel almost completely destroyed by vasculitis, with marked intimal thickening (hematoxylin-eosin, original magnification ×400).](image-url)
Pulmonary vasculitis was generally prominent, with infiltration of many (but not all) small to medium arteries and veins by lymphocytes, histiocytes, eosinophils, and rare neutrophils. Not all vessels showed the same degree of inflammation, with some containing only patchy subendothelial collections of inflammatory cells and associated endothelial hyperplasia (Fig 3A). Other vessels had a marked transmural inflammatory cell infiltrate, often with prominent fibrointimal proliferation and luminal narrowing (Fig 3B). A few vessels demonstrated collagen deposition (Fig 3A).

Chronic interstitial pneumonitis was widespread, with widening of alveolar septae by an infiltrate of lymphocytes and eosinophils (Fig 4). Intra-alveolar aggregates of macrophages and eosinophils (with fibrinous material in case 3) were also seen (Fig 5), in a pattern suggestive of early eosinophilic pneumonia. The pleurae in cases 1 and 2 were focally thickened, with a patchy infiltrate of lymphocytes and eosinophils. No granulomas, areas of necrosis, atypical mononuclear cells, or leukocytoclastic changes were found.

**Discussion**

The four cases reported are characterized by strikingly similar clinical abnormalities, including abnormal chest x-ray films with bilateral alveolar and interstitial infiltrates, bilateral pleural effusions, profound hypoxemia, and peripheral eosinophilia. The patients were acutely ill with weakness, fatigue, myalgia, dyspnea, dry cough, and occasionally fever. On physical examination, lung sounds were normal, or bibasilar rales were present; reduced breath sounds consistent with a pleural effusion occasionally obscured the rales.

One patient had an erythema multiforme-like rash, one patient was observed to have a macular rash, and the others reported nondescript rashes not seen by physicians. Muscle weakness was present in two of the four patients, but all described various degrees of muscular discomfort at one time or another.

Histologic examination of lung tissue in three of the four cases exhibited overlapping and often strikingly similar pathologic features, including the following: (1) small-to-medium-vessel vasculitis, with a mixed inflammatory cell infiltrate (primarily lymphocytes and eosinophils) involving both arteries and veins; variability in the number of involved vessels and in the severity of inflammation in the affected vessels was noted; (2) interstitial pneumonitis, with thickening of alveolar septae by an inflammatory cell infiltrate containing mostly eosinophils and lymphocytes; and (3) alveolar exudate of histiocytes and eosinophils. Similar pathologic findings have been reported by others in association with the ingestion of L-tryptophan-containing products.6,7

These pathologic features varied quantitatively from case to case, but all biopsies were qualitatively very similar. It is highly conceivable that the changes seen represent the same disease process being biopsied at different phases of its evolution, possibly starting as a vasculitis, with subsequent migration of inflammatory cells into alveolar septae and then into alveolar spaces. Case 2 showed primarily a vasculitis, with only a very mild degree of interstitial inflammation and alveolar inflammatory exudate, and could possibly be the earliest biopsied phase of this disease process. Case 1 showed a striking vasculitis, but with more interstitial and alveolar inflammation, suggestive of a more advanced stage than case 2. Case 3 was a very limited
biopsy sample, but the predominant pathologic finding was that of pneumonitis, possibly representing the most evolved stage of the disease process.

Precise categorization of these pathologic findings is somewhat more difficult than simple description, and it is easiest to say what these biopsies are not. Allergic granulomatosis and angitis (Churg-Strauss vasculitis) is associated with a history of asthma and shows striking eosinophilic vasculitis and pneumonitis; there are often large areas of parenchymal necrosis and granulomatosis inflammation, none of which was found in our patients. Wegener's granulomatosis does not usually have eosinophilic inflammation, and the diagnostically required necrotizing granulomatosis was not seen in our cases. The atypical lymphoedematous vascular infiltrate, necrosis, and luminal thrombosis which are diagnostic of lymphomatoid granulomatosis (angiocentric T-cell lymphoma) were also not present. Absence of bronchocentric inflammation and granuloma rules against a diagnosis of bronchocentric granulomatosis. While the vasculitis seen in our cases was consistent with a diagnosis of polyarteritis nodosa, the interstitial and alveolar pneumonia rules against this diagnosis, as does the absence of appropriate systemic manifestations.

Chronic eosinophilic pneumonia is characterized by a pathologic picture of interstitial inflammation (eosinophils; lymphocytes; plasma cells) and marked filling of alveolar spaces by collections of histiocytes and eosinophils, often with a proteinaceous exudate. Eosinophilic abscesses with necrosis and a mild noncaseating vasculitis are reported. 

Infectious causes of eosinophilic pneumonia include fungal and parasitic. None of the cases presented had demonstrable bacteriologic, fungal, parasitic, or mycobacterial causes.

Eosinophilic pneumonia has been associated with a variety of drugs, for example, nitrofurantoin, chlorpropamide, and sulfonamides. Additionally, radiographic patterns associated with drug reactions are described which are similar to the present cases.

Although a relationship between the present reported cases and the ingestion of L-tryptophan is speculative, these cases occurred in patients who reported consumption of L-tryptophan-containing products at a time when an association between L-tryptophan and the eosinophilia-myalgia syndrome was established. In fact, the patients themselves, aware of media reports, brought this association to the attention of their physicians.

The eosinophilia-myalgia syndrome associated with consumption of L-tryptophan-containing products is described as a subacute illness presenting with severe myalgia and fatigue. There may be a skin rash, hepatomegaly, edema, and hypoxemia. Perivascular inflammatory infiltrates and vasculitis in biopsied muscles are reported.

Although the eosinophilia-myalgia syndrome is primarily a neuromuscular disease, a respiratory component has been noted. The present cases reported may be on the end of a continuum and demonstrate primarily pulmonary manifestations. Consistent with the histology found in these cases are similar published reports by other observers.

The association of the consumption of L-tryptophan and pulmonary disease appears to represent cause and effect; the pathogenic mechanisms underlying the development of the pulmonary manifestations as yet have not been identified. This is also true for the eosinophilia-myalgia syndrome. Contamination of L-tryptophan products has not been proven as a factor, but is considered to be quite probable. This is supported by the absence of a correlation between the dose or duration of drug use, as consumption varied from a maximum of ten years of daily use to a minimum consumption of a total of one to two pills. To establish a cause and effect from L-tryptophan, rechallenge of the affected patients would be appropriate and was considered; however, the severity of the pulmonary manifestations prompted all of these patients to decline taking any L-tryptophan-containing products again.

However strange it must seem to attribute this illness to a naturally occurring amino acid nutrient, this association is not without precedent, and a component cannot be excluded. Nutrition may affect chemical-induced lung injury. An example is acute bovine pulmonary edema and interstitial emphysema, a naturally occurring disease of cattle which can be reproduced by intratracheal doses of L-tryptophan. In the proper setting, L-tryptophan may influence the metabolic fate of other products, resulting in a toxic effect on the lungs; however, this effect in humans has been reputed.

Future data will contribute to a better understanding of pathophysiology linking the ingestion of L-tryptophan-containing products, eosinophilia-myalgia syndrome, and any association with the pulmonary manifestations described in these four cases. For the present, our patients have been advised to avoid products marketed as containing L-tryptophan supplements.

ACKNOWLEDGMENT: We thank Dr. Michael Koss, Department of Pathology, LAC-USC Medical Center, for help with the interpretation of these biopsy specimens. We also thank Ms. Sue Ann Berkefeld and Ms. Bert Lasky for preparing this manuscript.

REFERENCES