Pulmonary Infiltrates with Eosinophilia Associated with Tetracycline*

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Two cases of diffuse skin rash and pulmonary infiltrates with eosinophilia (PIE) associated with administration of a tetracycline drug alone and subsiding after discontinuance of the drug are presented. The clinical course and appearance of the chest roentgenograms suggest that the dermal and pulmonary changes represented hypersensitivity reactions to tetracycline.

Tetracycline continues to be one of the most frequently used antibiotics. It is often prescribed for the treatment of acute bronchitis, urinary tract infections and refractory facial acne. Longstanding familiarity with the drug has established its relative safety when administered orally, even for prolonged periods of time, as in the treatment of acne. Current reviews have summarized the adverse reactions common to the tetracycline family and its derivatives. To date, no pulmonary side effects related to use of tetracycline have been reported, except for those associated with presumed tetracycline-induced systemic lupus erythematosus. We have recently seen two patients in whom the development of pulmonary infiltrates and eosinophilia was associated with the concurrent use of tetracycline drugs. We propose that tetracycline may be another causative agent associated with the syndrome of pulmonary infiltrates with eosinophilia (PIE).

CASE REPORTS

CASE 1

A 36-year-old man who did not smoke was treated with oral tetracycline (250 mg qid) for a presumed urinary tract infection in April, 1971. A chest roentgenogram taken at that time was normal. Within 12 hours after taking his first tablet of tetracycline, he developed a generalized maculopapular rash and discontinued use of the drug. The rash subsided after 36 hours. On a follow-up visit to his personal physician one week later, he was found to have pyuria, and oral tetracycline (500 mg qid) was again prescribed. Approximately four days later he again experienced a pruritic rash involving his extremities, followed by the gradual development of progressive dyspnea. He was admitted to the Los Angeles County-University of Southern California Hospital because of persistent shortness of breath. On examination, he was noted to be afebrile. The only abnormal findings included a respiratory rate of 32/min, a discrete popular rash over the forearms, upper arms and thighs, and diffuse ronchi and a few scattered crackling inspiratory rales on auscultation of the chest.

The admission chest film revealed bilateral interstitial changes in the mid- and lower lung zones (Fig 1). Severe hypoxemia was present with the patient breathing room air (Table 1). The total white blood cell count was normal without evidence of neutrophilia or bands, but the total eosinophil count was elevated (Table 1). Spirometric tests performed shortly after admission demonstrated vital capac-

![Figure 1. Posteroanterior chest x-ray film of case 1 obtained upon admission to the hospital in May, 1971. Interstitial changes are present in the mid- and lower-lung zones, characterized by increased linear densities with resultant loss of the normally crisp definition of the pulmonary vasculature. The nature of the radiopaque density in the lateral aspect of the left lung is unknown. There are some calcified lymph nodes within the right hilum. There is no evidence of pleural effusion on either posteroanterior or lateral view. The heart is within normal limits. A chest film obtained one month earlier had shown the lungs to be normal.](http://journal.publications.chestnet.org/pdffacess.ashx?url=/data/journals/chest/21049/ on 04/05/2017)
Table 1—Blood Gas Data and Peripheral Blood Eosinophil Counts

<table>
<thead>
<tr>
<th>Hospital Day</th>
<th>Case 1</th>
<th>Case 2</th>
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<tbody>
<tr>
<td></td>
<td>FIO₂</td>
<td>PaO₂</td>
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<tr>
<td>2 days before admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.21</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>2492 (28%)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.21</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td></td>
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<tr>
<td>9</td>
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<tr>
<td>10</td>
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<tr>
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<td>17</td>
<td></td>
<td></td>
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<td>47</td>
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*Estimated from total white blood cell count and differential
**Absolute eosinophil count
↑Via nasal prongs
( )Values in parentheses represent percentage of eosinophils in peripheral blood at time of maximal peripheral eosinophilia

Tetracycline was administered during the first two days of hospitalization. Because of progression of the rash and a further increase in the peripheral eosinophilia, the possibility of a hypersensitivity reaction to tetracycline was considered and the drug was discontinued. The rash and pulmonary symptoms rapidly improved. Serial eosinophil counts and arterial blood gas determinations showed gradual improvement (Table 1). Within two weeks, the patient was symptom-free and his peripheral blood eosinophil count was normal. He was advised not to take further tetracycline and has remained asymptomatic during a four-year follow-up period.

Case 2

A 20-year-old Mexican-American woman was given oral minocycline (100 mg bid), a tetracycline derivative, in January, 1977 for control of facial acne. Approximately four weeks later, she noted a pruritic erythematous rash over her chest. She was treated with an antihistamine and continued taking minocycline. The rash persisted and three days later she developed a fever of 38.4°C, associated with a non-productive cough. She returned to the hospital where a chest film showed negative findings and arterial PO₂ was 71 mm Hg while breathing room air. A diagnosis of viral bronchitis with a viral exanthem was entertained and the patient was sent home. However, over the next two days she developed progressive dyspnea and was admitted to University of California (Los Angeles) Hospital. She denied sputum production or pleuritic chest pain and had no history of asthma or other allergic disorders.

Her temperature was 38.5°C and respiratory rate 33/min. She exhibited a diffuse erythematous, urticarial rash and patchy areas of coalescence and moderate periorbital and facial edema. On auscultation, breath sounds were decreased and bibasilar rales and scattered expiratory wheezes were heard over both lung bases. There was no abnormal heart sound, hepatosplenomegaly or lymphadenopathy.

Severe hypoxemia was noted along with striking eosinophilia (Table 1). The admission chest film showed a bilateral interstitial-alveolar pattern which was most marked in the mid- and lower lung zones and somewhat more pronounced peripherally (Fig 2). Heart size was within normal limits. Cultures of several specimens of blood and urine, including a transtracheal aspirate, were negative for aerobic and anaerobic bacteria, mycobacteria and fungi. Viral cultures from throat swabs, urine and stool were also negative. No ova or parasites were found on stool examination. A mono spot test and complement fixation tests for Mycoplasma pneumoniae, adenoviruses, rubella, CMV, Coxsackie virus, Coccidiodes immitis and Toxoplasma were negative. Antinuclear antibody was absent, serum complement was normal and the Coombs test was negative. Blood urea nitrogen, serum creatinine and urinalysis were normal. Serum bilirubin was normal, but SGOT, SGPT, LDH and alkaline phosphatase levels were

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a pulmonary response to underlying helminthic infection. More recently, however, exposure to a number of chemical agents and drugs has been reported to be a more common cause for development of pulmonary infiltrates with eosinophilia. Included among these agents are the antimicrobials penicillin, para-aminosalicylic acid, nitrofurantoin and several sulfonamides.6,8 Our two cases suggest that tetracycline should be added to this list.

In case 1, the patient developed pulmonary symptoms following re-exposure to tetracycline, having recently demonstrated probable dermal hypersensitivity to the drug. The radiographic changes that were seen in this patient (Fig 1) are suggestive of noncardiogenic pulmonary edema and are similar to abnormalities described in the acute pulmonary reaction to nitrofurantoin.8,9 Our second patient also developed a pruritic skin rash as the first manifestation of her illness, but the use of minocycline was continued and progressive dyspnea subsequently developed. The peripheral distribution of the radiographic changes observed in this patient (Fig 2) is very similar to the appearance of the chest roentgenogram in patients with Loeffler’s syndrome following therapy with a sulfonamide,8 para-aminosalicylic acid,11 or penicillin.12 However, the relatively diffuse and confluent involvement in our patient in the mid- and lower-lung zones also resembles the pulmonary edema-like pattern that may accompany the acute reaction to nitrofurantoin.8,9

Our two cases suggest that persistent systemic exposure to an antigenic determinant (presumably

Discussion

The PIE syndrome consists of several different clinical entities of varying etiology. Liebow and Carrington6,7 have classified the eosinophilic pneumonias into five different categories. According to their classification, the two cases reported herein fit best into the entity of Loeffler’s syndrome or “simple pulmonary eosinophilia,” since their pulmonary involvement, albeit relatively severe, was self-limited and appeared to resolve spontaneously after discontinuation of tetracycline therapy.

Classic Loeffler’s syndrome probably represented
derived from tetracycline) in a sensitized host may result in the development of peripheral eosinophilia and pulmonary infiltration. This is consistent with previous findings that it is those helminthic infections in which a sustained blood invasive phase occurs (eg, ascariasis, microfilaria and strongyloides) that are associated with the classic Loeffler's syndrome. Eosinophils are recognized to be chemoattractant for antigen-antibody complexes and play a role in their inactivation. Persistent systemic exposure to an antigen may result in the formation of large concentrations of antigen-antibody complexes which may deposit in the vast pulmonary capillary bed, leading to pulmonary infiltration and eosinophilia.

The temporal relationship in our two patients between intake of tetracycline and the development of skin rash and eosinophilia with pulmonary infiltrates strongly suggests that the dermal and pulmonary abnormalities represented a hypersensitivity reaction to tetracycline. Re-challenging these patients with tetracycline might have confirmed a cause-and-effect relationship but was felt to be contraindicated in view of the severity of the pulmonary involvement and the lack of any clinical necessity for continued use of a tetracycline drug.

The development of a definite skin rash in any patient receiving tetracycline therapy should suggest the possibility of a hypersensitivity reaction and warrant withdrawal of tetracycline. Inadvertent continuation of the drug, as in these two cases, may result in the development of the PIE syndrome.

REFERENCES


100th Anniversary "Jubilee" Seminars

The American Medical Society of Vienna (Austria) will present a series of seminars during the summer and fall at the University of Vienna Clinics, Vienna, Austria, in celebration of the 100th anniversary of the founding of the society. For full information, contact Dr. M. Arthur Kline, American Medical Society of Vienna, Lazarettgasse 13, Vienna IX, Austria.

First Pan American Congress of Critical Care Medicine

The Mexican Society of Critical Care Medicine, with the cooperation of critical care medical societies in Argentina, Brazil, Portugal, Spain, USA and Venezuela, will present the First Pan American Congress of Critical Care Medicine in Mexico City, September 23-27, at the Maria-Isabel-Sheraton Hotel. Official languages are Spanish and English with simultaneous interpretation. In addition to the scientific program, there will be technical and scientific exhibits and a social program. For information, please write to the Congress at Avenida Veracruz 93-203, Mexico II, D.F., Mexico.