Drugs and the Pleura*

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**Purpose:** To identify the drugs associated with pleural disease and to review the clinical, radiographic, and pleural fluid findings that occur, the natural history of the pleural reaction, and the response to therapy.

**Data sources:** English-language articles published from January 1966 through April 1998 were identified through searches of the MEDLINE database, selective bibliographies, and personal files.

**Data extraction:** Case reports, letters, and review articles were assessed for relevancy. Reports of drug-associated pleural effusion, pleuritis, and/or pleural thickening were analyzed. Drug effect was believed to be causal when exposure induced pleural disease, when the pleural response remitted on discontinuation of the drug, and when the pleural disease recurred with reexposure. Drug association was inferred when the pleural disease occurred following drug exposure and remitted after drug discontinuation. The incidence, clinical presentation, dose and duration of drug therapy, chest radiographic findings, pleural fluid analysis, and response to therapy were recorded.

**Conclusions:** A relatively small number of drugs were found to induce pleural disease when compared to the number of drugs implicated in causing disease of the lung parenchyma. Treatment of drug-induced pleural disease consists of drug therapy withdrawal and corticosteroids for refractory cases. Knowledge of the potential of drug-induced pleural disease will provide a clinical advantage to the physician and should lead to decreased morbidity and economic burden for the patient by avoidance of further diagnostic testing.

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Key words: drug-induced lupus pleuritis; drugs; pleural effusions; pleural fibrosis

Abbreviations: ANA = antinuclear antibodies; GCSF = granulocyte colony-stimulating factor; SLE = systemic lupus erythematosus

The medical literature is replete with case reports and review articles describing the adverse effects of various drugs on the pulmonary parenchyma. The drugs, the mechanism by which they incite this effect, and the results of therapy have been documented. However, less attention has been directed to studying drug-induced disease of the pleura. The purpose of this article is to educate the clinician about the drugs most commonly associated with pleural disease (Table 1); the clinical, radiographic, and serologic abnormalities that occur; the natural history of the pleural reaction; and the response to therapy.

**Materials and Methods**

A review of the English-language literature from January 1966 through April 1998 was performed by MEDLINE search (keywords: drug, pleura, pleural effusion, pleurisy). Case reports, letters, and review articles were assessed for relevance. Reports of drug-associated pleural effusion, pleuritis, and/or pleural thickening were analyzed. A drug effect was deemed causal when exposure to the drug induces some form of pleural disease, the insult remits following discontinuation of the agent, and the pleural reaction recurs with reexposure to the drug. Drug association was inferred when pleural reaction occurs after exposure to the drug and remits following discontinuation.
incidence, clinical presentation, dose and duration of drug therapy, chest radiographic manifestations and pleural fluid analysis, when available, are provided in tabular display.

**Cardiovascular Agents**

A select group of cardiovascular drugs is known to cause pleuropulmonary disease. Those agents that cause worsening heart failure with resultant effusions are not included.

**Amiodarone**

Amiodarone, an iodinated benzofuran derivative, is commonly used for the treatment of ventricular and supraventricular dysrhythmias. Its adverse effect profile is extensive, and toxic effects have been reported in multiple organs including the liver, bone marrow, thyroid, integument, heart, and lung. Pulmonary side effects occur in up to 6% of patients and include interstitial or alveolar infiltrates, pleural thickening, and, rarely, pulmonary nodules or pleural effusions.3-17 These adverse effects may present 2 to 30 weeks after initiation of therapy, and they usually occur at a dosage > 400 mg/d. Patients present with dyspnea, cough, low-grade fever, and pleuritis. Pleural thickening results from chronic inflammation. Although rare findings, pleural effusions usually occur in the setting of accompanying interstitial disease. A single case report18 describes an isolated exudative effusion in a patient treated with amiodarone for 6 years at a dosage of 400 mg/d. Pleural effusions from amiodarone have demonstrated the presence of foamy macrophages akin to those seen in BAL samples of patients with concurrent pneumonitis.15 The pleural fluid has been described8 as a paucicellular exudate. Therapy for the interstitial pneumonitis is drug therapy withdrawal, and systemic corticosteroids in patients with profound diffusion abnormalities and hypoxemia.

**Minoxidil**

Minoxidil is a vasodilator that is commonly used for the treatment of recalcitrant hypertension. Its use has been associated with the development of pericardial effusions.19 Webb and Whale30 reported a single patient who developed both pericardial and bilateral pleural effusions 2 months into treatment with minoxidil. Pleural fluid analysis revealed protein contents of 4.3 g/dl, in both fluids. Drug discontinuation led to resolution of both the pleural and pericardial effusions. Rechallenge with the drug resulted in recurrence of the pericardial fluid only; the pericardial effusion again resolved with cessation of therapy.

**Practolol**

Practolol, a β-blocking agent previously used in the European market, has induced pleuropulmonary complications.21-27 Initial symptoms occurred 12 to 36 months into therapy, including progressive dyspnea in the setting of pleural thickening and pleural effusions. Although drug therapy withdrawal and corticosteroid administration ameliorated some of the other adverse effects (oculomucocutaneous syndrome and pleural effusion), no improvement in the pleural thickening occurred. These serosal manifestations have not occurred secondary to the use of β-blocking agents administered in the United States.27

**Ergoline Drugs**

Pleuropulmonary insult is known to occur following administration of various ergoline drugs (nicergoline, dihydroergocriptine, dihydroergotamine, ergotamine tartrate, bromocriptine, and methysergide).28-30 Two of the most common offenders are described in detail below.

**Bromocriptine**

Bromocriptine, a dopamine agonist, is known to ameliorate the dyskinesias associated with Parkinson’s disease. More than 20 cases of pleuropulmonary disease attributed to bromocriptine have been reported.44-46 Radiographic changes reported in these patients include pleural effusion, pleural thickening, and interstitial infiltrates. The onset occurs 12 to 48 months after institution of therapy. While pleural fluid eosinophilia (12% and 30%) has been noted in two patients,35 the typical pleural fluid analysis reveals a lymphocytic-predominant (51 to 99%) exudate without eosinophilia. Drug therapy withdrawal leads to resolution of pleural effusions, but pleural thickening and interstitial parenchymal changes do not resolve completely in all patients. Recently, two groups reported on patients with prior asbestos exposure who developed exudative pleural effusions and/or pleural thickening while receiving bromocriptine for Parkinson’s disease; the pleural changes tended to resolve with stoppage of the drug.31,33 Whether ergolines and asbestos act in concert to inflict pleural injury awaits further study.

**Methysergide**

Methysergide is an ergot alkaloid used for the treatment of vascular headaches. Its common adverse effects include dermatitis, alopecia, cardiovascular (coronary and valvular) disease, and GI distress. This drug has been identified as a causal factor in the development of retroperitoneal and pleural fibrosis.42-50 Although limited, reports in the literature describe extensive, bilateral pleural fibrosis with associated effusions.43,47,48 The fibrosis is presumed due to increased serotonin levels with subsequent increase in fibroblast activity. Treatment consists of drug therapy withdrawal, which leads to regression of pleural fibrosis in most cases.

**Sclerotherapeutic Agents**

**Sodium Morrhuate/Absolute Alcohol**

The esophageal variceal sclerotherapeutic agents (sodium morrhuate and absolute alcohol) are common causes of pleural effusions. The reported incidence of pleural effusions with the use of sodium morrhuate is 40 to 50%, and with absolute alcohol, 19%.51 The proposed mechanism is transmediastinal spread of inflammation from the esophagus to the mediastinal pleura and pleural space. Pleural effusions associated with sclerotherapy are more commonly right sided, although they may be left sided or bilateral, depending on the site of injection. The most common symptom is persistent chest pain. The effusions are radiographically evident by 24 to 48 h after therapy and resolve spontaneously within 7 days.

**Pleural Fluid Eosinophilia**

Pleural fluid eosinophilia (> 10% of nucleated cells) is a nonspecific finding. Air or blood in the pleural space, benign asbestos-related pleural effusion, parasitic infection, and drug effect are on the list of differential diagnoses. However, only a
Nitrofurantoin

Nitrofurantoin is well known for its use in the prophylaxis and treatment of uncomplicated lower urinary tract infections. The drug exhibits an extensive adverse effect profile that includes GI upset, rash and urticaria, hepatotoxicity (chronic active hepatitis and cholestatic jaundice), arthralgias, angioedema, neuropathy, and pulmonary reactions. Adverse pulmonary effects are categorized into acute and chronic reactions. Nitrofurantoin causes acute pleuropulmonary effects in 5 to 25% of patients. The acute effects may manifest hours to days following institution of drug therapy. These effects are thought to be caused by a hypersensitivity, and therefore are not dose related. Patients present with fever, dyspnea, and cough. Radiographic abnormalities include alveolar and/or interstitial infiltrates with the bases most commonly affected. Pleural effusions may be seen in up to one third of cases and rarely occur in the absence of parenchymal infiltrates. Peripheral blood eosinophilia has been reported with values as high as 83%, and pleural fluid eosinophilia has been reported. Treatment consists of prompt drug therapy withdrawal. Adjunctive corticosteroid administration can hasten resolution of symptoms.

Conversely, the interstitial pneumonitis and fibrosis seen with chronic nitrofurantoin administration is thought to occur from damage elicited by oxygen free radicals. Symptons present over months to years in the setting of continued drug use. Pleural effusions are rarely associated with chronic nitrofurantoin-induced pulmonary toxicity.

Dantrolene

Dantrolene, a hydantoin derivative, is structurally similar to nitrofurantoin and is a commonly used skeletal muscle relaxant. The most common adverse effects include drowsiness, nausea, hepatitis (dose-dependent), and GI atony. Dantrolene-induced pleural disease has been reported in six patients. Pleural effusion and fibrosis are late sequelae, with an onset 2 months to 12 years after initiation of the drug. Pleural fluid analysis has shown an eosinophilic inflammatory exudate. Peripheral blood eosinophilia was present, suggesting an allergic pathogenesis. No pulmonary parenchymal abnormalities have been reported with the use of dantrolene. Treatment is drug therapy withdrawal.

Valproic Acid

Valproic acid is most often used for the treatment of absence and photosensitive seizure disorders. Side effects, which usually occur early and are transient, include GI upset, alopecia, and hepatic enzyme elevation. Valproic acid has been described as a cause of an eosinophilic pleural effusion in a single case report of a 42-year-old man who received therapy for 9 months. The effusion occurred 1 week after completion of treatment (with...

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**Table 1—Drugs Associated With Pleural Disease**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Incidence</th>
<th>Pleural Fluid Analysis</th>
<th>Onset of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>Case report</td>
<td>NR</td>
<td>3 d</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Unknown</td>
<td>NC, 490 to 1050 µL; protein, 2.8 to 3.7 g/dL; LDH, 125 to 392 µL</td>
<td>1 to 36 mo</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>31 patients</td>
<td>NC, 300 to 2700 µL (51 to 99% lymphocytes; 12 to 30% eosinophils); protein, 3.5 to 5.5 g/dL</td>
<td>12 mo to 4 y</td>
</tr>
<tr>
<td>Clozapine</td>
<td>2 patients</td>
<td>PMNs predominant; protein, 3.0 g/dL; LDH, 614 IU</td>
<td>16 d</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>&lt; 20 patients</td>
<td>NC, 0; protein, 2.68 g/dL; LDH, 32 IU/L</td>
<td>Acute, 1 to 6 mo; late, 1.5 to 13 yr</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>6 patients</td>
<td>NC, 1,500 to 5,500 µL (33 to 66% eosinophils); protein, 4.8 g/dL; LDH, 3,437 IU/L</td>
<td>Months to years</td>
</tr>
<tr>
<td>D-Penicillamine</td>
<td>Case report</td>
<td>“Exudate”</td>
<td>12.5 yr</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>2 patients</td>
<td>Eosinophilia &gt; 20%</td>
<td>5 mo</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Case report</td>
<td>Protein, 4.3 g/dL</td>
<td>8 wk</td>
</tr>
<tr>
<td>L-Tryptophan</td>
<td>Case report</td>
<td>NR</td>
<td>Weeks</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1 to 8.5%</td>
<td>NR</td>
<td>4 wk</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Rare</td>
<td>NC, 880 µL; protein, 2 to 4.4 g/dL</td>
<td>Weeks to years</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Case reports</td>
<td>NR</td>
<td>2 wk to 7 mo</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>Case report</td>
<td>NR</td>
<td>2 mo</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>Case reports</td>
<td>NR</td>
<td>Months</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>8% acute, 7% chronic</td>
<td>NC, 419 µL (17% eosinophils)</td>
<td>Acute, hours to days; chronic, months</td>
</tr>
<tr>
<td>Prilocain</td>
<td>Case reports</td>
<td>Protein, 3.5 g/dL</td>
<td>12 mo to 3 yr post–drug cessation</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Case report</td>
<td>NC, 1,500 to 2,167 µL (16 to 45% eosinophils); LDH, 2,249 IU/L</td>
<td>3 wk</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Case reports</td>
<td>NR</td>
<td>Hours to days</td>
</tr>
<tr>
<td>Sclerotherapy agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute alcohol</td>
<td>19%</td>
<td>“Exudate”</td>
<td>48 h</td>
</tr>
<tr>
<td>Sodium morrhuate</td>
<td>40 to 50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastin</td>
<td>Case report</td>
<td>NR</td>
<td>6 wk</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Case report</td>
<td>NC, 5,120 to 9,688 µL (62 to 81% eosinophils); protein, 4.5 g/dL; LDH, 1,150 IU/L</td>
<td>9 mo</td>
</tr>
</tbody>
</table>

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select group of pharmacologic agents have been determined to cause pleural fluid eosinophilia (Table 2). These drugs are discussed in detail below.
amoxicillin) for a left lower-lobe pneumonia. Pleural fluid analysis revealed a paucicellular (400 nucleated cells) exudate. The cell differential was notable for 62% eosinophils, which increased to 84% of 9,688 nucleated cells/L on a second thoracentesis. The percentage of blood eosinophils were likewise elevated at 26%. The effusion completely resolved 6 months after the drug was discontinued.

**Propylthiouracil**

Propylthiouracil, a thionamide used for the treatment of thyrotoxicosis, is believed to be a cause of eosinophilic pleuritis. In an isolated report, an exudative, inflammatory, eosinophilic effusion (16% and 45% on sequential pleural fluid analyses) developed 3 days after initiation of propylthiouracil for treatment of Graves disease in a 49-year-old man.62 No associated infiltrate was present. Pleural biopsy revealed chronic inflammation with pronounced eosinophilia. However, there was no concomitant serum eosinophilia. Resolution of the effusion occurred within 3 months of discontinuation of the drug.

**Isotretinoin**

Isotretinoin, a retinoid compound, is well known for its treatment of cystic acne by inhibition of keratinization and sebaceous gland function. This drug has also been shown to act as a chemopreventive agent that alters the development and outcome of various malignancies (skin and other carcinomas). A 41-year-old man being treated with isotretinoin for cystic acne developed cough, fever, and a pleural effusion 1 month into therapy.63 Pleural fluid analysis revealed 20% eosinophils. Isotretinoin therapy was discontinued, and there was radiographic resolution of the effusion at 1 month.

Isotretinoin has also been studied in the treatment of systemic sclerosis. A pleural effusion was reported in a 49-year-old woman receiving isotretinoin for systemic sclerosis.64 After 6 months of therapy at a dosage of 1 mg/kg/d, the patient developed dyspnea on exertion and a left-sided pleural effusion in the absence of accompanying infiltrates. Pleural fluid analysis was remarkable for “striking” eosinophilia (the absolute numbers were not reported). Tissue examination of the pleura revealed chronic inflam-

### Table 1—(continued)

<table>
<thead>
<tr>
<th>Time to Resolution</th>
<th>Chest Radiograph</th>
<th>Pleural Biopsy</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 d</td>
<td>Effusion and infiltrates</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>Weeks to 18 mo</td>
<td>ILD, pleural effusion/thickening, nodules</td>
<td>Fibrinous exudate</td>
<td>Drug therapy withdrawal, steroids</td>
</tr>
<tr>
<td>Months (persistent radiographic abnormalities)</td>
<td>Effusion, pleural thickening</td>
<td>Chronic inflammation</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>9 d</td>
<td>Effusions</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>Months unknown</td>
<td>Pleural thickening, ILD, effusion</td>
<td>ND</td>
<td>Drug therapy withdrawal, steroids not beneficial</td>
</tr>
<tr>
<td>Months</td>
<td>Effusions, no parenchymal disease</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>NR</td>
<td>Effusion</td>
<td>Normal</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>4 wk to 3 mo</td>
<td>Effusion</td>
<td>Chronic inflammation</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>Thoracic drainage</td>
<td>Effusion, parenchymal infiltrate</td>
<td>Nondiagnostic</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>ILD +/- effusion</td>
<td>ND</td>
<td>Drug therapy withdrawal, steroids</td>
<td></td>
</tr>
<tr>
<td>3 to 5 d</td>
<td>Pleural thickening, effusion</td>
<td>ND</td>
<td>Drug therapy withdrawal, decortication</td>
</tr>
<tr>
<td>Months (minimal residual fibrosis)</td>
<td>Effusions; pleural fibrosis</td>
<td>Chronic fibrosis</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>Weeks</td>
<td>Effusion</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>NR</td>
<td>Effusion (pleural/pericardial)</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>Weeks to months</td>
<td>Effusion, pleural thickening, ILD</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>Weeks</td>
<td>ILD +/- effusion</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>NR</td>
<td>Effusion, pleural thickening</td>
<td>Chronic fibrosis</td>
<td>Drug therapy withdrawal, +/- steroids, ? pleurectomy</td>
</tr>
<tr>
<td>3 mo</td>
<td>Effusion</td>
<td>Chronic inflammation with eosinophilia</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>Days to weeks</td>
<td>Effusion with ILD</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
<tr>
<td>7 d</td>
<td>Effusion</td>
<td>ND</td>
<td>Observation</td>
</tr>
<tr>
<td>Unknown</td>
<td>Effusion, ILD, pleural thickening</td>
<td>ND</td>
<td>Drug therapy withdrawal, +/- steroids</td>
</tr>
<tr>
<td>Days</td>
<td>Effusion, no parenchymal infiltrates</td>
<td>ND</td>
<td>Drug therapy withdrawal</td>
</tr>
</tbody>
</table>

*ILD = interstitial lung disease; LDH = lactate dehydrogenase; NC = nucleated cells; ND = not done; NR = not reported; PMN = polymorphonuclear leukocyte.

### Table 2—Drug-Induced Pleural Fluid Eosinophilia*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pleural Fluid Eosinophilia (%)</th>
<th>Peripheral Eosinophilia (%)</th>
<th>Parenchymal Infiltrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin</td>
<td>Yes (17)</td>
<td>Yes (9 to 83)</td>
<td>Interstitial</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Yes (33 to 66)</td>
<td>Yes (7 to 18)</td>
<td>No</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Yes (16 to 45)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Yes (62 to 84)</td>
<td>Yes (26)</td>
<td>No</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Yes (&gt; 20)</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Yes (12 to 30)</td>
<td>NR</td>
<td>No</td>
</tr>
</tbody>
</table>

*NR = not reported.
mation with eosinophils. Peripheral eosinophilia was absent. Isotretinoin therapy was discontinued, and the patient’s dyspnea and effusion resolved at 3 months. The patient was not rechallenged.

Chemotherapeutic Agents

Chemotherapeutic agents have been implicated in the development of adverse pleuropulmonary effects. These effects may occur from hypersensitivity reactions or direct cytotoxicity.

Bleomycin

Bleomycin, a chemotherapeutic agent first derived from the bacteria Streptomyces, is used for the treatment of a variety of malignancies, including lymphoma and testicular cancer. Its association with progressive interstitial pneumonitis and ARDS (exacerbated by the adjunctive use of supplemental oxygen therapy; radiation therapy; and other chemotherapeutic agents) has been well established. This effect is a dose-related phenomenon and usually presents after a cumulative dose $\geq 450$ IU has been administered. Associated pleural effusions have been reported in a small number of patients with bleomycin lung toxicity.65–67 Steroids, in combination with drug therapy withdrawal, have been used for treatment, although efficacy has not been clearly defined.

Mitomycin

Mitomycin, a second antibiotic-derived chemotherapeutic agent, has been used in the treatment of malignancies of the breast, lung, and GI tract. The most common adverse effects include GI upset, dermatitis, and renal insufficiency. Like bleomycin, mitomycin also induces interstitial pneumonitis. Pleural disease, including effusion and thickening, has been noted.68–70 Pleural fluid analysis has not been reported, and biopsies of the pleura have demonstrated nonspecific fibrosis. Treatment consists of drug therapy withdrawal. Administration of systemic corticosteroids has eradicated symptoms and led to partial clearing of radiographic abnormalities.

Procarbazine

Procarbazine is a methylhydrazine agent used in the treatment of lymphomas. Its mechanism of action has not been completely defined. The most serious adverse effects include GI upset, neurologic changes (lethargy, ataxia, etc.), and bone marrow depression. Pleuropulmonary reactions due to procarbazine are rare. Allergic pneumonitis is the presumed insult because of the presence of peripheral blood and tissue eosinophilia.71,72 Rechallenge with the drug produced the same clinical syndrome, including an effusion.71 Although pleural effusion has been reported, pleural fluid analysis has not been documented.71 Radiographic abnormalities resolved in all cases after cessation of therapy.

Methotrexate

Methotrexate is used for the treatment of malignancies, dermatologic disorders, collagen vascular disease, and asthma. The common adverse effects include hepatitis, mucositis, interstitial lung fibrosis, and bone marrow suppression.73–76 Pleural disease was reported in 18 of 210 patients being treated for osteogenic sarcoma with high-dose methotrexate.77 Those patients presented with pleuritic chest pain (usually right-sided) within 4 weeks of treatment. The pain persisted for 3 to 5 days and often recurred with reinstitution of the drug. The radiographic abnormality observed was a thickening of the intralobar pleura. Interstitial pneumonitis has also been seen with a lower dose of methotrexate therapy and has been presumed to be caused by a hypersensitivity reaction. Corticosteroids have improved symptoms but have not effected the resolution of radiographic abnormalities.

Cyclophosphamide

Cyclophosphamide-induced pleuropulmonary disease has been reported in 18 cases. Symptoms at presentation include dyspnea, fever, and cough.78–80 Radiographs reveal infiltrates and pleural thickening (late), which were variable in onset.

Cyclophosphamide-induced lung toxicity can be divided into two categories.78 Early-onset pneumonitis may be seen 1 to 6 months after drug exposure. Symptoms and radiographic abnormalities usually remit with drug therapy withdrawal and institution of corticosteroids. Late-onset pneumonitis occurs months to years after institution of the drug, and the toxicity may not be apparent until years after the cessation of therapy. Patients with late-onset pneumonitis may present with pleural thickening associated with reticular or reticulonodular infiltrates. Pleural effusion associated with cyclophosphamide has been documented only once. Schaap et al81 reported a 37-year-old man with chronic myelogenous leukemia who developed massive pleural effusions 2 days after receiving conditioning chemotherapy (two consecutive-day infusions of 4,200 mg of cyclophosphamide) prior to bone marrow transplantation. The patient complained of nonpleuritic chest pain and progressive dyspnea. An echocardiogram revealed preserved right and left ventricular function without evidence of pericardial effusion. The effusions progressed bilaterally, and the patient subsequently suffered a pulseless-electrical-activity arrest. After successful resuscitation, thoracostomy drainage revealed a transudative fluid (protein, 2.68 g/dL; lactate dehydrogenase, 32 IU/L). Sixteen hours after arrest, a chest radiograph revealed only a small left effusion, and the pleural drains were removed. The residual left-sided fluid completely resolved on day 3. The patient continued to transplantation and had no further pulmonary sequelae.

Other Agents

Many of the drugs associated with pleuropulmonary disease cannot be succinctly categorized. A synopsis of these agents is provided alphabetically below.

Acyclovir

Acyclovir, a nucleoside analog that inhibits viral replication, is used in the treatment of herpes virus disease. The reported adverse effect profile includes GI distress, elevation of serum creatinine, injection site irritation/eruption, and fever. Acyclovir as a cause of pleural effusion has been reported only once.82 A 71-year-old man who was being treated with acyclovir for herpes zoster ophthalmicus developed fever and bilateral infiltrates 3 days into treatment. A left-sided pleural effusion in the setting of hemoptysis occurred on the fourth day of therapy. A ventilation-perfusion lung scan was “not suggestive” of pulmonary embolism, and BAL revealed no pathogens. Acyclovir therapy was discontinued on day 6, with the prompt abatement of fever. The left-sided effusion and pulmonary infiltrates resolved within 10 days of drug therapy withdrawal.
Clozapine

Clozapine, a commonly used neuroleptic agent, has been proposed as a cause of polyserositis. Daly and associates reported a schizophrenic patient who developed fever and bilateral pleural effusions 16 days after clozapine therapy was initiated. Pleural fluid analysis revealed a neutrophil-predominant exudate. Fever and radiographic changes resolved 9 days after discontinuation of the drug. The patient underwent rechallenge with clozapine and again developed fever and recurrent pleural effusion. An echocardiogram showed a moderate pericardial effusion. The drug was discontinued, and both the pleural and the pericardial effusions resolved after 14 days, respectively.

Chatterjee and Safferman reported the case of a schizoaffective man who developed fore arm cellulitis and contralateral pleural effusion while his clozapine dose was being escalated. At a dosage of 200 mg qd, the patient developed fever, leukocytosis with eosinophilia, right fore arm cellulitis, and a left pleural effusion with associated chest pain. No pleural fluid analysis was performed. Antibiotic treatment for the cellulitis was instituted. When clozapine was discontinued, the effusion resolved. After a 12-day period, clozapine was reinstalled. At a dosage of 100 mg qd, the cellulitis and left effusion recurred. Discontinuation of clozapine resulted in resolution of both signs without further antimicrobial intervention.

D-Penicillamine

D-Penicillamine is a chelating agent that additionally exhibits immunosuppressive effects. Its chelating properties (for copper) determine its efficacy for the treatment of Wilson's disease. This agent, which also forms a water-soluble compound when bound to cystine, aids in the treatment and prevention of urolithiasis due to cystine stones. D-penicillamine administration is associated with a number of adverse effects, including blood dyscrasias; dermatologic changes (Stevens-Johnson syndrome, pemphigus); renal effects (nephrotic syndrome, hematuria); and autoimmune-like syndromes of drug-induced systemic lupus erythematosus (SLE), rheumatoid arthritis, myasthenia, and Goodpasture's syndrome. An isolated report suggested that pleural effusion due to D-penicillamine occurred in the absence of the above conditions. A 35-year-old woman presented with a large left-sided effusion after receiving D-penicillamine therapy, 250 mg/d, for 12 years and 6 months for treatment of Wilson's disease. Three liters of pleural fluid was removed, and analysis revealed a straw-colored exudate with negative findings on cytology. Serologic evaluation for connective tissue disease was negative. Thoracoscopic talc poudrage was unsuccessful. The patient underwent decortication, and pathologic evaluation of the pleura revealed chronic, nonspecific inflammation without evidence of malignancy or infection. After decortication, there was complete re-expansion of the left lung. Drug therapy with D-penicillamine was continued at the dosage of 1.5 g/d without further sequelae.

Granulocyte Colony-Stimulating Factor

Granulocyte colony-stimulating factor (GCSF), a hematopoietic growth factor, is now commonly used to hasten the recovery from neutropenia following myelosuppressive chemotherapy. Pleural effusion related to this agent has been reported only once. A 43-year-old woman with breast carcinoma developed a highly cellular (16,800/μL), exudative (protein, 2.2 g/dL) pleural effusion after 10 days of GCSF therapy. No parenchymal infiltrates were present. Infection and malignancy were excluded. Cytologic preparation of the pleural effusion revealed an increase of immature and mature myeloid cells. GCSF was discontinued, and the effusion subsequently resolved slowly.

Interleukin-2

Recombinant interleukin-2 may be used to treat malignancy, particularly renal cell carcinoma and melanoma. Acute reversible adverse effects include chills, fever, contusion, and skin rash. Pleural effusions were found on chest radiograph in half of the 108 patients receiving interleukin-2 in two separate studies. Pulmonary edema was noted in virtually all patients with pleural effusion. Effusions generally improve following cessation of therapy, but about 20% persist for at least a month. Effusions appear to result from capillary leak pulmonary edema, as would be seen with any cause of ARDS.

Itraconazole

Itraconazole, a triazole, is used frequently for the treatment of systemic mycoses. This drug has been shown to cause pleural reaction/effusion in a single patient. The exudative effusion (protein, 4.3 g/dL) occurred 8 weeks after itraconazole therapy at a dosage of 200 mg bid. A tube thoracostomy was performed, and results of a pleural biopsy were negative for infection and malignancy. One week later, the patient developed a pericardial effusion requiring pericardiocentesis. The patient developed cardiomegaly (without pericardial effusion) and parenchymal infiltrates after re-exposure to the drug 6 weeks later. No etiologic mechanism was identified.

L-Tryptophan

L-Tryptophan, a sleep-promoting agent available over the counter, has been associated with the development adverse pulmonary reactions. This drug has been implicated as a causal factor in the development of vasculitis, which induced the clinical entity known as the eosinophilia-nyalgal syndrome. Patients present with myalgias and fatigue in the setting of peripheral eosinophilia. Pulmonary reactions include bilateral alveolar/interstitial infiltrates and pleural effusions, with a clinical presentation of progressive dyspnea and nonproductive cough. Although pleural effusions have been demonstrated on chest radiographs, pleural fluid analysis has not been performed. Because of the severity of clinical symptoms, no rechallenge was attempted. Steroid therapy and drug therapy withdrawal were the therapeutic interventions. Radiographic resolution occurred in days to weeks; however, mild hypoxemia with exercise as well as mild diffusion abnormalities persisted.

Simvastin

Simvastin, an HMG Co-A reductase inhibitor used for the treatment of dyslipidemia, has a limited adverse effect profile, with drug-induced hepatitis as its most serious effect. This agent has recently been reported to cause a hypersensitivity pneumonitis in a 61-year-old man with BAL eosinophilia (34%) and new-onset interstitial lung disease. The patient also had a right-sided pleural effusion and left-sided pleural thickening. Thoracoscopic biopsy results of the parietal and visceral pleura were negative for infection. Pleural fluid analysis was not performed. Therapeutic intervention included drug therapy withdrawal and corticosteroids. With the addition of prednisone, 40 mg/d, the patient had marked symptomatic and physiologic improvement within days. Long-term follow-up was not available.

Drug-Induced Lupus Pleuritis

More than 50 years ago, the first case of drug-induced lupus was described in a patient receiving sulfadiazine. Since that
time, about 75 drugs have been implicated as a cause of a lupus-like syndrome or exacerbating preexisting SLE. The spectrum of drugs subsequently linked to lupus-like syndrome include antihypertensives, antimicrobials, anti-inflammatory agents, immunosuppressives, recombinant cytokines, psychotropic, and antithyroidal and hormonal drugs. However, only 2 of the >70 drugs (procainamide and hydralazine) have been studied both retrospectively and prospectively. Other drugs that have a strong association with drug-induced lupus include chlorpromazine, isoniazid, methylxypa, penicillamine, and quinidine.

**Procainamide**

The drug most commonly associated with drug-induced lupus is procainamide, with approximately one third of patients developing a lupus-like syndrome after 1 year of drug therapy. Drug-induced lupus can occur as early as 1 month or as late as 12 years from the start of treatment, with an average onset of 1 year. The acetylator phenotype is an important determinant of symptom onset, with slow acetylators developing positive antinuclear antibodies (ANA) and the drug-induced lupus syndrome at a lower dose of drug and after a shorter duration of therapy. Pulmonary infiltrates have been noted in about 40% of these patients, and pleural fibrosis resulting in restriction has been reported. Arthralgias, myalgias, and fever are common clinical features, while renal disease is rare. The erythrocyte sedimentation rate is elevated and antihistone antibodies are uniformly positive, while complement levels remain normal. The specificity of antihistone antibodies varies among drugs associated with drug-induced lupus. Antihistone antibodies associated with procainamide-induced lupus are predominantly IgG and are directed against (H2A-H2B)-DNA complex and chromatin.

**Hydralazine**

The prevalence of hydralazine-induced lupus has been reported to be between 2% and 21%, with the wide range reflecting differences in duration of treatment, dose, and acetylator phenotype. A daily dosage of >200 mg or a cumulative dose of >100 g is associated with a high likelihood of disease. Hydralazine-induced lupus appears to be more common in women than in men. As in procainamide-induced lupus, arthralgias are the most common symptom, occurring in approximately 85% of patients with arthritis, and myalgias also occur in a majority of patients; fever is present in 40% of patients. Pleurisy has been reported in approximately 30% of patients, with parenchymal disease alone representing <5%. The ANA are positive in half of the patients receiving 200 mg/d, and the clinical syndrome develops in approximately 10% of patients. As with procainamide-induced lupus, the erythrocyte sedimentation rate is uniformly elevated, >95% have antihistone antibodies, complement levels are normal, and anti-double-stranded DNA study results are negative. Renal disease has been reported more commonly (an incidence of about 13%) in patients with hydralazine-induced lupus than in patients with procainamide-induced lupus.

**Other Drugs**

Quinidine reportedly induced a lupus-like syndrome in approximately 30 patients with serositis that occurred with arthralgias and fever. Although isoniazid (25%) and chlorpromazine (16 to 52%) tend to induce a positive ANA, <1% of patients taking these drugs will develop a clinical syndrome that can include serositis. Mesalamine, which is used to treat inflammatory bowel disease, has been reported to cause pleuritis and lupus-like syndrome.

Drug-induced lupus pleural effusions, as in native SLE, are exudative, with nucleated cell counts of 200 to 15,000/μL, and may demonstrate a pleural fluid ANA ratio ≥ 1.0. However, the presence of lupus erythematosus cells in the pleural fluid is the only diagnostic finding. The pleural fluid pH and glucose are low in 15 to 20% of cases.

Drug-induced lupus pleuritis typically improves rapidly after discontinuation of the drug and usually does not require specific therapy. However, nonsteroidal anti-inflammatory drugs or a short course of low-dose to moderate-dose prednisone is beneficial in prolonged cases or in patients who are markedly symptomatic.

**CONCLUSION**

Drug-induced pleural disease is relatively uncommon compared to drug-induced parenchymal lung disease, and it may occur in the absence of parenchymal infiltrates. However, clinicians should consider drugs as a potential cause for an undiagnosed pleural effusion before they embark on an extensive diagnostic evaluation that may entail unnecessary economic burden and discomfort for the patient. Especially in patients receiving procainamide or hydralazine, drug-induced lupus pleuritis should be considered in the differential diagnosis and an appropriate evaluation should be pursued.

We suspect that the number of drugs that result in pleuritis, pleural fibrosis, and pleural effusions will increase as new drugs are marketed. If the cause of an exudative pleural effusion is not clinically obvious after pleural fluid analysis, drug therapy withdrawal should be a consideration if clinically appropriate.

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