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Infiltrative lung disease due to noncytotoxic agents

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Some drugs that are used in the treatment of benign disorders can cause parenchymal pulmonary disease (Table 1). Pulmonary reactions to amiodarone, are the most-studied, but other drugs, particularly those that are used in the treatment of rheumatoid arthritis (RA), also have been associated with pulmonary disease. Since a review in 1986 [1], there has been significant new information on the pulmonary reactions that are associated with these drugs. This article reviews mechanisms of adverse pulmonary reactions to disease modifying antirheumatic drugs and describes pulmonary reactions to certain other noncytotoxic drugs. The subjects of lung involvement with systemic reactions to drugs, such as drug-induced lupus or classic allergic reactions, are not addressed in this article. Instead, the reader is referred to two reviews of these subjects [2,3].

Pulmonary parenchymal reactions to noncytotoxic drugs are associated with limited histopathologic manifestations (Box 1). These drug reactions can be difficult to recognize because of the rarity of the reactions and the similarity of the reactions to pulmonary disease that is due to underlying disorders, particularly RA. Some characteristics that are associated with drug reactions can help to differentiate them from the underlying disorder; these are discussed in this article.

Specific drugs

Methotrexate

This drug is used often as a first line disease-modifying antirheumatic drug, especially in patients who have RA who are at increased risk for joint destruction [4]. The mechanism of action of methotrexate (MTX) is inhibition of dihydrofolate reductase which reduces tetrahydrofolates before their use as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, MTX interferes with DNA synthesis, repair, and cellular replication. Unlike the other major side effects of MTX, pulmonary complications do not correlate with underlying folate deficiency [5]. Pulmonary toxicity from MTX can be seen at all dosages used for RA, even the conventional 7.5 mg/week beginning dosage. The overall likelihood that patients who have RA will develop pulmonary complications while receiving MTX ranges from 0.3% to 11.6% [5]. Pulmonary complications have been reported as early as 1 month after initiation of MTX therapy; complications usually occur within 2 years of initiating therapy [6].

A recent multi-center case control study was undertaken to determine which risk factors predispose patients who have RA to MTX-induced lung injury [6]. Twenty-seven definite and two probable cases were identified and matched with 82 controls. Data analysis revealed five conditions that were most likely to confer increased risk for the development of MTX-induced lung injury (Table 2).

The clinical presentation of pulmonary toxicity to MTX, when used for benign conditions, is varied and is similar to manifestations of pulmonary toxicity that is associated with its use in malignancy [7]. Usual

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Table 1
Noncytotoxic drugs that cause parenchymal pulmonary reactions

Drug class	Specific drugs
Antirheumatic drugs	Methotrexate
	Penicillamine
	Gold salts
	Aspirin (overdose only)
Opiates	Heroin
	Methadone
	Codeine
	Morphine
Thiazides	Buprenorphine
	Hydrochlorothiazide

symptoms that are most consistent with the syndrome of hypersensitivity pneumonitis, including dyspnea, fever, and cough, occur in a subacute manner over weeks, but onset also can be rapid and suggestive of acute pneumonitis. Physical examination often reveals bilateral inspiratory crackles. Laboratory findings may include mild leukocytosis or eosinophilia. More than 50% of chest radiographs show bilateral interstitial infiltrates, but a mixed alveolar filling and interstitial pattern also is seen. Less commonly, unilateral changes, hilar lymphadenopathy, and a restrictive pattern on pulmonary function testing are identified. High-resolution CT scanning shows “ground glass” appearance, and, occasionally, fibrotic changes are noted in lung parenchyma [5]. If the diagnosis remains questionable, bronchoalveolar lavage (BAL) in patients who have MTX pneumonitis typically shows a lymphocytosis with a low CD4:CD8 ratio. This contrasts with the BAL of patients who have pulmonary complications of RA, where a predominance of neutrophils may be noted [8]. Transbronchial or open lung biopsy generally is needed for definitive diagnosis or exclusion of infection in patients who are

Box 1. Histopathologic manifestations of pulmonary reactions to noncytotoxic drugs

Chronic pneumonitis/fibrosis
 Acute pneumonitis
 Noncardiogenic pulmonary edema
 (diffuse alveolar damage)
 Hypersensitivity pneumonitis
 Eosinophilic pneumonia
 Bronchiolitis obliterans/organizing
 pneumonia

Table 2
Risk factors for developing methotrexate-induced pulmonary reactions in patients who have RA

Risk factor	Odds ratio
Diabetes mellitus	35.6
Hypoalbuminemia	19.5
Rheumatoid pleuropulmonary involvement	7.1
Previous use of disease-modifying agents, (gold, sulfasalazine, or penicillamine)	5.6
Older age	5.1

suspected of having MTX-induced pulmonary adverse effects.

Patients who have suspected MTX-induced lung toxicity should be withdrawn from MTX therapy immediately and carefully monitored. Most patients improve without further intervention. Uncontrolled studies in patients who had residual symptoms or pulmonary function defects suggested that therapy with oral prednisolone at 50 mg/day accelerated recovery [5]. Although not recommended, some patients have been rechallenged with MTX without recurrence of pulmonary pathology; this suggests that this is not a true hypersensitivity reaction to the drug. Fatalities have been reported during rechallenge of the patients with MTX [9]. Although methotrexate generally is safe when used in patients who have RA, with the growing armamentarium of disease-modifying agents, withdrawal of this agent in patients who are suspected of having a pulmonary reaction to it is less difficult than in the past.

Aspirin

Therapeutic doses of aspirin can result in bronchospasm in asthmatics as a result of aspirin sensitivity. Ingestion of toxic doses of aspirin may lead to severe alterations in mental status, noncardiogenic pulmonary edema, metabolic acidosis, renal failure, and death.

Acute salicylate poisoning presents with a well-described clinical syndrome [10], that changes in character depending on the amount of drug absorbed. Salicylate, the metabolic product of acetylsalicylic acid, is a mitochondrial poison that uncouples oxidative phosphorylation and leaves cells increasingly dependent on anaerobic metabolism. Because the brain is exquisitely sensitive to changes in glucose metabolism, it is not surprising that initial signs of mild to moderate salicylate intoxication are referable to the central nervous system. They include tinnitus,

vertigo, nausea, and vomiting. There also is a direct stimulant effect on the medullary respiratory center which leads to hyperventilation and respiratory alkalosis. More severe poisoning can result in coma, profound metabolic acidosis secondary to the failure of aerobic metabolism, and noncardiogenic pulmonary edema. Subacute aspirin-induced pulmonary edema may simulate infiltrative lung disease.

The pulmonary edema that is seen in salicylate poisoning can complicate more than 30% of cases of severe poisoning. Older patient age and chronic salicylate intoxication constitute major risk factors [9]. Pulmonary edema in these patients may be compounded by initial volume resuscitation and myocardial dysfunction from severe metabolic acidosis. Management consists of preventing further salicylate absorption, promoting drug excretion by way of alkalinization with intravenous sodium bicarbonate, and close monitoring in an intensive care setting (see the article by Lee-Chiong and Matthay elsewhere in this issue).

Nonsteroidal anti-inflammatory drugs

As a drug class, nonsteroidal anti-inflammatory drugs and their prototype, aspirin, have been associated with the development of pulmonary infiltrates with eosinophilia (PIE) syndrome (see the article by Allen elsewhere in this issue). Although the incidence of this hypersensitivity reaction is low, a 1992 review by Goodwin et al [11] suggested adding this drug class to the list of medications that cause PIE syndrome. Management usually consists of withdrawal of the offending agent. More than 90% of patients have prompt resolution of their symptoms, although improvement of radiographic infiltrates and peripheral eosinophilia seem to lag behind clinical improvement. Occasionally, patients may have persistent infiltrates and diffusion impairment; they often are managed with oral corticosteroid therapy, although no consensus about dose or duration of steroid administration exists [10].

D-penicillamine

This drug is a product of the hydrolysis of penicillin. Although it is a heavy metal chelating agent, its anti-inflammatory effect in patients who have RA seems to stem from its ability to downregulate T-lymphocyte function, decrease rheumatoid factor and immune complex levels, and impair fibroblast proliferation. Three described clinical syndromes of pulmonary toxicity are associated with D-penicillamine administration.

Pulmonary-renal syndrome

The most severe, but rare, complication of penicillamine therapy is a pulmonary-renal syndrome that is similar in presentation and course to Goodpasture's syndrome. It is a rare complication in patients who have RA who are treated with this agent but has not been described in patients who were treated with the agent for other diseases (eg, Wilson's disease). The dosage or duration of exposure that is required for induction of the syndrome is not clear; dosages that ranged from 300 mg/day to 3.5 g/day and exposures of 10 months to 20 years have been described in association with the syndrome [12].

Clinical manifestations of pulmonary-renal syndrome that are due to penicillamine include a rapid development of cough, dyspnea, hemoptysis, and hematuria. Respiratory and renal failure may occur. Chest radiographs show diffuse alveolar infiltrates that may coalesce into large, nodular "cannonball-like infiltrates." Urinary sediment may be active. Although the clinical presentation of pulmonary-renal failure is similar to Goodpasture's syndrome, circulating antiglomerular basement membrane antibodies are not found. High titers of antinuclear antibodies often are seen [13]. Lung biopsy specimens show alveolar hemorrhage with hemosiderin-laden macrophages. Renal biopsy usually displays crescentic glomerulonephritis, but without the typical linear basement membrane immunofluorescence pattern [14] (see article by Schwarz and Fontenot elsewhere in this issue).

Overall, the prognosis for pulmonary-renal syndrome that is due to penicillamine therapy is poor. The syndrome has a 50% mortality and some patients require long-term hemodialysis [15]. Treatment is supportive; immediate drug discontinuation is required. In some cases, administration of 1 mg/kg/day of prednisone alone, or in combination with cyclophosphamide or azathioprine, was successful at inducing remission. Plasmapheresis has been used in some patients but its role and efficacy are unclear; however, aggressive immunosuppression with corticosteroids and cyclophosphamide or azathioprine generally are believed to be useful [16].

Interstitial lung disease

Interstitial lung disease develops in approximately 3% of patients who have RA and are treated with D-penicillamine. Hypersensitivity pneumonitis and chronic alveolitis with fibrosis also have been described [17]. Dosages varied widely in affected patients. Those who develop the syndrome usually present with dyspnea, cough, and fever. Inspiratory crackles often are heard on physical examination.

Chest radiograph shows diffuse interstitial infiltrates, and, occasionally, alveolar filling. Pulmonary function testing demonstrates a restrictive pattern with decreased diffusing capacity; however, pulmonary function abnormalities can be seen in asymptomatic patients who receive penicillamine [16]. Prognosis is excellent after the process is recognized and the drug is discontinued. Occasionally, corticosteroids are used in patients who have persistent symptoms.

Gold salts

Targeted immunomodulatory therapies have joined MTX and hydroxychloroquine at the heart of current antirheumatic regimens. Parenteral gold remains a therapeutic option for patients who are refractory to other single or combination modalities. Oral or parenteral gold also is used in the management of selected cases of juvenile RA, ankylosing spondylitis, polyarthritis, psoriatic arthritis, and pemphigus [18,19].

Gold's mechanism of action is through its immunomodulatory properties which have been associated with decreased neutrophil chemotaxis, decreased monocyte responsiveness, and decreased elaboration of proteolytic enzymes in synovial fluid [20]. In addition, gold may be used to manage acute rheumatoid flares in Felty's syndrome complicated by anemia or thrombocytopenia, where further bone marrow suppression from increased doses of MTX are harmful.

Chrysotherapy-induced acute lung injury was reported in 1976 by Winterbauer et al [20]. Since then, a series of cases has accumulated in the literature that were reviewed and analyzed in detail by Tomioka and King in 1997 [19]. A cohort of 140 patients, from 1966 to 1994, who had pulmonary toxicity that was believed to be related to chrysotherapy, was analyzed. A database of demographic and laboratory information was analyzed and used to clarify differences between patients who had true gold-induced pulmonary toxicity (GIPT) and patients who had RA interstitial lung disease. Among patients who had GIPT, women outnumbered men four to one, with a mean age of onset of 53.1 years \pm 12.3 years. The cumulative dose of gold did not correlate with the onset of pulmonary symptoms or their eventual severity. There seemed to be an inverse correlation between acute rheumatoid inflammation and the development of GIPT; less than 4% of patients had both simultaneously.

Most patients who have GIPT complain of dyspnea or cough on presentation—92% and 67%, respectively. On examination, nearly 50% of patients have fever and more than 35% have an erythematous skin rash. Physical examination is most notable for in-

spiratory crackles, which are present in more than 75% of patients [19]. When a complete blood count is obtained, the most common abnormality is the presence of peripheral eosinophilia [18]. Other serologic work-ups reveal increased lactate dehydrogenase levels in almost 40% of patients [19].

On pulmonary function testing, patients usually have reduced vital capacities without evidence of obstructive ventilatory defect, as well as a significant impairment of diffusing capacity [17–19]. In the Tomioka and King study [19], 92% of patients had abnormal diffusing capacities. In two thirds of patients, pulmonary function parameters returned to baseline following discontinuation of the drug. A longitudinal study by Chakravarty and Webley [17] in 1992 suggested that gold-induced reductions in diffusing capacity take up to 12 months to resolve; however, further decline is halted by discontinuation of the drug.

There is substantial evidence that a cell-mediated hypersensitivity reaction is the basis for gold-induced lung damage. A detailed review of the data is beyond the scope of this article. A common thread is the presence of a marked lymphocytosis in the BAL fluid and a predominance of cytotoxic CD8+ lymphocytes [21,22]. Also, peripheral blood lymphocytes seem to become activated in the presence of gold salts [23]. Tomioka and King [19] made the presence of a CD8+ lymphocytic alveolitis and positive lymphocyte stimulation testing parts of their diagnostic scheme for GIPT. These observations also are the basis for recommending therapy with oral prednisone at doses of 30 to 60 mg/day for cases of GIPT that progress, despite discontinuation of the drug [19]. Rechallenge with the drug led to relapse of the syndrome.

Hydrochlorothiazide

Treatment with this drug can cause paradoxically noncardiogenic pulmonary edema. Overall, there have been fewer than 50 cases reported since the first description by Steinberg in 1968 [24]; however, this may underrepresent the true incidence of this disorder because of the nonspecific presentation of affected patients. One report described a patient who developed noncardiogenic pulmonary edema after starting hydrochlorothiazide four separate times which suggested that there was a definite association between the pulmonary disease and the drug exposure. Two other reports suggested that IgE levels [25] or IgM and complement levels [26] are increased in patients who have this disorder; however, the small number of cases has made it difficult to ascertain a definite mechanism for the pulmonary reaction to hydrochlorothiazide.

Treatment for the disorder is similar to that for other causes of noncardiogenic pulmonary edema in addition to discontinuation of the drug and avoidance of further exposure.

Opiates

Overdose of heroin [27], methadone [28], codeine [29], morphine [30], and buprenorphine [31] have been associated with acute respiratory failure. This syndrome was first described in 1880 by Osler [30]. Several recent studies characterized the risk factors [32] and clinical presentation [33] of patients who have this syndrome. One retrospective study [32] of 125 patients who had heroin overdose found that 10% developed noncardiogenic pulmonary edema; all were men. The average duration of heroin use for patients who developed noncardiogenic pulmonary edema was 2.9 years, whereas patients who had overdosed and did not develop edema admitted to an average of 13.2 years of heroin use. Patients who developed noncardiogenic pulmonary edema also were significantly more likely to have received naloxone because of more severe obtundation.

Another retrospective study [33] reviewed the charts of 1278 patients who were admitted with heroin overdose and found that 27 (2.1%) had evidence of noncardiogenic pulmonary edema. Pulmonary edema was evident on presentation or within 4 hours of presentation. Overall, the prognosis was good; only 39% of the patients who had pulmonary edema that was due to heroin required intubation and mechanical ventilation. In addition, symptoms resolved in most of the affected patients within 24 hours. Because death is rare and histology is not available in most patients who have this syndrome, one recent study of 23 patients who died of heroin overdose demonstrated acute and partly hemorrhagic pulmonary edema and hemosiderin-laden macrophages [34]. In this study, the histologic changes could not be differentiated from a control group of patients who died from sudden cardiovascular death. Therapy for the syndrome is supportive with opiate avoidance and oxygen/mechanical ventilation as needed. Overall, the prognosis is good.

Summary

Pulmonary complications of therapy for RA or other benign conditions are often difficult to diagnose and treat. Clinical presentation of lung disease that is due to noncytotoxic drugs may vary from a mild, nonspecific cough to fulminant respiratory failure.

The differential diagnosis of pulmonary disease should include drug toxicity, progression of the primary illness, and opportunistic infection. An objective assessment of the patient's baseline pulmonary status, as well as his treatment history, is crucial to differentiate drug-induced pathology from the primary process. Diagnostic work-up should include chest radiograph, repeat pulmonary function testing, and high-resolution CT of the chest. Bronchoscopy for tissue pathology or specific BAL cytokine markers also may yield useful information; occasionally, open-lung biopsy is required. If pulmonary disease that results from noncytotoxic drug therapy is suspected, the drug should be discontinued until the disease process is understood clearly.

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