Virtually all therapies of modern medicine carry the potential for harm, which may be unpredictable, and lead to long-term consequences. Most drug reactions and radiation injuries are relatively mild, seldom lead to significant morbidity or mortality, and are diagnosed and treated without the necessity of an invasive biopsy procedure. When the clinical presentation is unusual or other problematic circumstances arise, the evaluation of lung tissue becomes necessary to distinguish iatrogenic injury from other entities in the differential diagnosis such as infection, metastatic or recurrent neoplasia, or underlying disease. This chapter reviews the characteristic clinical and morphologic features of the more common manifestations of drug and radiation injury to the lungs.

Drug Toxicity

The respiratory system is a frequent target for drug-induced injury. In slightly more than half a decade, the number of drugs implicated in lung injury has grown to over 350 and continues to increase as new agents are being introduced into the clinical armamentarium.\(^1\) For the clinician, the recognition of drug-induced lung disease can be quite difficult, requires a high index of suspicion and vigilance, and is often based on a diagnosis of exclusion.\(^1\) In certain instances there is a somewhat distinctive clinical presentation, such as in the case of anaphylaxis, bronchospasm, or pulmonary edema immediately following certain medications. However, most patients typically present with varying nonspecific symptoms, physical findings, and radiographic patterns that do not point to a specific disorder. In many instances the diagnosis of drug toxicity is determined without the necessity of a lung biopsy procedure.\(^2,3\) However, in other circumstances, a lung biopsy is performed in an attempt to distinguish drug-induced lung disease from other entities that are under consideration in the differential diagnosis. For the pathologist, it is a daunting task to impugn or exonerate a specific drug based solely on the morphologic changes present in tissue biopsies. Just as there may be varying clinical presentations, the myriad of pathologic findings are rarely specific and overlap with other disorders such as infection, malignancy, or underlying disease that are considered in the differential diagnosis.\(^4\)

The relationship between a particular drug and the development of injury can be (1) causative, (2) probable, (3) possible, (4) coincidental, or (5) unrelated.\(^5\) Therefore, the diagnostic criteria for causation of drug-induced lung disease must be quite strict.\(^2\) The following guidelines have been proposed to establishing a definitive diagnosis of drug toxicity\(^1,3,5,6,8\):

1. Drug exposure: the respiratory disease follows the administration of the drug in question. A temporal association must exist between the medication and the development of adverse effects. The time course from the administration of drug to the development of symptoms should be within the realm of what has been reported in the literature. Some drug toxicities occur in a short time span, whereas other adverse reactions have a long latency and it may take months to years following discontinuation of therapy. In addition, various routes (ingested, inhaled, intravenous, direct contact) of administration of the drug may need to be explored.

   The relationship between a single agent and toxicity is easier to establish than when multiple drugs are given concurrently. Often in the case of suspected drug toxicity there are several other medications and it may become difficult to implicate a single agent.

   A complete and careful drug history should include not only prescription and over the counter medications, but also recreational drugs, nutritional supplements, dietary compounds, medicinal herbs, and alternative therapies.

2. The clinical, radiographic, and pathologic findings fit with previous reports found in the literature. On occasion
the presentation may be somewhat variable from what has been previously documented, and it may be difficult to ascribe all of the features to drug toxicity. Pulmonary as well as extrapulmonary manifestations may be evident; the latter not only may pose problems for diagnosis, but also may complicate the clinical course.

The published literature is based on individual case reports, clinical series, and review articles, as well as data derived by the pharmaceutical industry, reports of post-release adverse events to the Food and Drug Administration (in the U.S.: http://www.fda.gov), and data from other monitoring agencies. One should be particularly cautious in proving causality when the number of cases is small or if there are limited reports in the literature.

The definitions of drug-related injury, such as “pneumonitis” or “toxicity” are somewhat arbitrary and vary considerably in the literature. Likewise, there is a somewhat arbitrary distinction between the terms acute, subacute, and chronic in describing the clinical or pathologic presentations.

3. Other disorders in the differential diagnosis (infection, malignancy, progression of underlying disease, other iatrogenic injury) need to be excluded. These disorders may not be able to be excluded immediately, as it may take weeks to get the results from serologic tests for autoimmune diseases and cultures for infections.

4. Cessation of the drug should lead to clinical improvement. Discontinuation of a suspected drug is recommended in instances of drug-induced toxicity. Ideally, this should lead to diminution or disappearance of the clinical symptoms. However, in some circumstances, it may be difficult to justify the removal of the candidate drug. In addition, the use of alternative or substitute medications may make causation more difficult to evaluate. This association between a particular drug and toxicity becomes more difficult to prove in instances of long duration between exposure and development of toxicity.

5. A rechallenge of the drug leads to recrudescence of the disease process. In practice, the reintroduction of the suspect medication is not clinically indicated or may be ethically contraindicated. On occasion in highly controlled environments, a small dose of the drug may be administered to determine whether the symptoms reappear.

Obviously, it may be impossible to fulfill each of these criteria when evaluating a suspected case of drug toxicity, particularly since the last criterion of drug challenge may not be possible. In practice, the use of the term drug toxicity is referred to those cases in which the majority of these criteria have been fulfilled and all other causes have been excluded. The pathologist should describe the histologic findings and synthesize how these features integrate with the radiographic and clinical findings.

Classifications of Drug Toxicity

Pulmonary drug reactions may be classified in many ways: mechanistic, clinical, and pathological. In a historical sense, many drug reactions had been classified in the past as being either cytotoxic or noncytotoxic; the latter included those drugs that produce disease through idiosyncratic or hypersensitivity mechanisms. While this classification is certainly relevant to the pharmacogenomic and pathophysiologic processes leading to pulmonary drug toxicity, this distinction may not be clinically or diagnostically relevant.

A Classification Based on Clinical/Radiographic Patterns

In practice, a classification based on clinical and radiographic presentation is particularly attractive, as it serves to guide the treating physician into recognizing somewhat distinctive clinical syndromes associated with specific drugs. The many clinical patterns associated with drug-induced lung disease are summarized in Table 22.1. This classification is wholly derived from the Pneumotox Web site (http://www.pneumotox.com), which is distilled from the clinical and pathologic manifestations of lung toxicity that has been gleaned from over 400 articles in the published literature. Through this Web site, the user is able to search for particular drug reactions by generic drug name, and clinical/radiographic pattern; it also provides a rough estimate of the prevalence of adverse effects as reported in the literature. Since it is continuously updated with new information, the Pneumotox Web site provides an up-to-date and readily identifiable reference for use in the public domain.

Other electronic subscription services with information on drug toxicity include the DRUGDEX® system, DRUG-REAX® system, and DrugKnowledge® system (Thomson Micromedex, Greenwood Village, CO; http://www.micromedex.com). These databases offer current information on adverse effects. The Center for Drug Evaluation and Research of the United States Food and Drug Administration (http://www.fda.gov/cder/index.html) maintains the Medwatch Web site (http://www.fda.gov/medwatch/index.html), which contains useful information regarding drug safety and adverse event reporting.

A Classification Based on Pathological Patterns

A classification based on tissue site and pattern of histopathologic reaction is perhaps the most appealing to the pathologist. It should be recognized, however, that the lungs can only react to injury in a limited number of histologic patterns of response and very few drugs produce distinctive or pathognomonic findings of toxicity.