therapies, and plasma exchange have varying degrees of success. The outcome with plasma exchange is generally poor, as in many other cases of secondary TTP. Rituximab is successfully used in patients with chemotherapy-induced HUS as well as in ADAMTS13-deficient TTP.

NEUTROPENIA AND INFECTION

These remain the most common serious complications of cancer therapy. **They are covered in detail in Chap. 104.**

PULMONARY INFILTRATES

Patients with cancer may present with dyspnea associated with diffuse interstitial infiltrates on chest radiographs. Such infiltrates may be due to progression of the underlying malignancy, treatment-related toxicities, infection, and/or unrelated diseases. The cause may be multifactorial; however, most commonly they occur as a consequence of treatment. Infiltration of the lung by malignancy has been described in patients with leukemia, lymphoma, and breast and other solid cancers. Pulmonary lymphatics may be involved diffusely by neoplasm (pulmonary lymphangitic carcinomatosis), resulting in a diffuse increase in interstitial markings on chest radiographs. The patient is often mildly dyspneic at the onset, but pulmonary failure develops over a period of weeks. In some patients, dyspnea precedes changes on the chest radiographs and is accompanied by a nonproductive cough. This syndrome is characteristic of solid tumors. In patients with leukemia, diffuse microscopic neoplastic peribronchial and peribronchiolar infiltration is frequent but may be asymptomatic. However, some patients present with diffuse interstitial infiltrates, an alveolar capillary block syndrome, and respiratory distress. In these situations, glucocorticoids can provide symptomatic relief, but specific chemotherapy should always be started promptly.

Several cytotoxic agents, such as bleomycin, methotrexate, busulfan, nitrosoureas, gemcitabine, mitomycin, vinorelbine, docetaxel, paclitaxel, fludarabine, pentostatin, and ifosfamide may cause pulmonary damage. The most frequent presentations are interstitial pneumonitis, alveolitis, and pulmonary fibrosis. Some cytotoxic agents, including methotrexate and procarbazine, may cause an acute hypersensitivity reaction. Cytosine arabinoside has been associated with noncardiogenic pulmonary edema. Administration of multiple cytotoxic drugs, as well as radiotherapy and preexisting lung disease, may potentiate the pulmonary toxicity. Supplemental oxygen may potentiate the effects of drugs and radiation injury. Patients should always be managed with the lowest FIO2 that is sufficient to maintain hemoglobin saturation.

The onset of symptoms may be insidious, with symptoms including dyspnea, nonproductive cough, and tachycardia. Patients may have bibasilar crepitant rales, end-inspiratory crackles, fever, and cyanosis. The chest radiograph generally shows an interstitial and sometimes an intraalveolar pattern that is strongest at the lung bases and may be symmetric. A small effusion may occur. Hypoxemia with decreased carbon monoxide diffusing capacity is always present. Glucocorticoids may be helpful in patients in whom pulmonary toxicity is related to radiation therapy or to chemotherapy. Treatment is otherwise supportive.

Molecular targeted agents, imatinib, erlotinib, and gefitinib are potent inhibitors of tyrosine kinases. These drugs may cause interstitial lung disease (ILD). In the case of gefitinib, preexisting fibrosis, poor performance status, and prior thoracic irradiation are independent risk factors; this complication has a high fatality rate. In Japan, incidence of interstitial lung disease associated with gefitinib was about 4.5% compared to 0.5% in the United States. Temsirolimus and everolimus, both esters a derivative of rapamycin, are agents that block the effects of mammalian target of rapamycin (mTOR), an enzyme that has an important role in regulating the synthesis of proteins that control cell division. It may cause ground-glass opacities in the lung with or without diffuse interstitial disease and lung parenchymal consolidation. Patients may be asymptomatic with only radiologic findings or may be symptomatic. Symptoms include cough, dyspnea, and/or hypoxemia, and sometimes patients present with systemic symptoms such as fever and fatigue. The incidence of everolimus-induced interstitial lung disease also appears to be higher in Japanese patients. Treatment includes dose reduction or withdrawal and, in some cases, the addition of glucocorticoids.

Radiation pneumonitis and/or fibrosis is a relatively frequent side effect of thoracic radiation therapy. It may be acute or chronic. Radiation-induced lung toxicity is a function of the irradiated lung volume, dose per fraction, and radiation dose. The larger the irradiated lung field, the higher is the risk for radiation pneumonitis. The use of concurrent chemoradiation, particularly regimens including paclitaxel, increases pulmonary toxicity. Radiation pneumonitis usually develops 2–6 months after completion of radiotherapy. The clinical syndrome, which varies in severity, consists of dyspnea, cough with scanty sputum, low-grade fever, and an initial hazy infiltrate on chest radiographs. The infiltrate and tissue damage usually are confined to the radiation field. The patients subsequently may develop a patchy alveolar infiltrate and air bronchograms, which may progress to acute respiratory failure that is sometimes fatal. A lung biopsy may be necessary to make the diagnosis. Asymptomatic infiltrates found incidentally after radiation therapy need not be treated. However, prednisone should be administered to patients with fever or other symptoms. The dosage should be tapered slowly after the resolution of radiation pneumonitis, because abrupt withdrawal of glucocorticoids may cause an exacerbation of pneumonia. Delayed radiation fibrosis may occur years after radiation therapy and is signaled by dyspnea on exertion. Often it is mild, but it can progress to chronic respiratory failure. Therapy is supportive.

Classical radiation pneumonitis that leads to pulmonary fibrosis is due to radiation-induced production of local cytokines such as platelet-derived growth factor β, tumor necrosis factor, interleukins, and transforming growth factor β in the radiation field. An immunologically mediated sporadic radiation pneumonitis occurs in about 10% of patients; bilateral alveolitis mediated by T cells results in infiltrates outside the radiation field. This form of radiation pneumonitis usually resolves without sequelae.

Pneumonia is a common problem in patients undergoing treatment for cancer. Bacterial pneumonia typically causes a localized infiltrate on chest radiographs. Therapy is tailored to the causative organism. When diffuse interstitial infiltrates appear in a febrile patient, the differential diagnosis is extensive and includes pneumonia due to infection with *Pneumocystis carinii*; viral infections including cytomegalovirus, adenovirus, herpes simplex virus, herpes zoster, respiratory syncytial virus, or intracellular pathogens such as *Mycoplasma* and *Legionella*; effects of drugs or radiation; tumor progression; nonspecific pneumonitis; and fungal disease. Detection of opportunistic pathogens in pulmonary infections is still a challenge. Diagnostic tools include chest radiographs, CT scans, bronchoscopy with bronchoalveolar lavage, brush cytology, transbronchial biopsy, fine-needle aspiration, and open lung biopsy. In addition to the culture, evaluation of bronchoalveolar lavage fluid for *P. carinii* by polymerase chain reaction (PCR) and serum galactomannan test improve the diagnostic yield. Patients with cancer who are neutropenic and have fever and local infiltrates on chest radiograph should be treated initially with broad-spectrum antibiotics. A new or persistent focal infiltrate not responding to broad-spectrum antibiotics argues for initiation of empiric antifungal therapy. When diffuse bilateral infiltrates develop in patients with febrile neutropenia, broad-spectrum antibiotics plus trimethoprim-sulfamethoxazole, with or without erythromycin, should be initiated. Addition of an antiviral agent is necessary in some settings, such as patients undergoing allogeneic hematopoietic stem cell transplantation. If the patient does not improve in 4 days, open lung biopsy is the procedure of choice. Bronchoscopy with bronchoalveolar lavage may be used in patients who are poor candidates for surgery.

In patients with pulmonary infiltrates who are afebrile, heart failure and multiple pulmonary emboli are in the differential diagnosis.

NEUTROPENIC ENTEROCOLITIS

Neutropenic enterocolitis (typhlitis) is the inflammation and necrosis of the cecum and surrounding tissues that may complicate the treatment