13 Hematological Disorders

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Sickle Cell Disease

(Philip A. Bromberg)

General Features

The process whereby deoxygenated hemoglobin (Hb) molecules containing at least one β^S chain (β6 glu→val) ($\alpha_2{}^A\beta_2{}^S$ or $\alpha_2{}^A\beta^S\beta^X$) form large polymers within red cells, thus causing their rigid deformation into various characteristic shapes ('sickled' cells), has been studied for the past half century or more and is now relatively well understood structurally and kinetically [1–7]. Understanding how this molecular defect translates into the wide spectrum of clinical manifestations that characterize the fluctuating course of sickle cell disease has challenged physicians and scientists for many years and, despite many important advances, still offers diagnostic puzzles and therapeutic dilemmas. It is clear that intravascular red cell sickling lies at the core of all the clinical features – i.e., both the chronic hemolytic anemia and the vasoocclusive manifestations. However, with improved understanding of the biology of blood vessels and especially the interactions of endothelium with the formed as well as soluble blood elements, the process of vasoocclusion in sickle cell disease now is seen to be much more complex in its pathogenesis. These advances are well summarized in recent texts (e.g., reference [8]) and in synthetic reviews (e.g., references [9,10,11]). Space constraints preclude further discussion of these mechanisms.

The co-dominant β^S gene is widely distributed and has a high frequency not only in black populations in Africa, but also in the United States, the Caribbean and Great Britain. The gene is also found in the Mediterranean basin, eastern Arabia and western India. About 8% of Afro-Americans are $\beta^A\beta^S$ heterozygotes (HbAS) and the prevalence may be even higher in England [12]. HbS constitutes 35%–45% of total hemoglobin, although most of the S hemoglobin actually exists in the form of the mixed tetramer, $\alpha_2{}^A\beta^A\beta^S$, within the red cells. HbAS heterozygotes are essentially healthy and enjoy a normal life expectancy. They do not have hemolysis. Nevertheless, their red cells can undergo sickling and this may (rarely) cause grave consequences such as collapse or sudden death during or following severe exertion, especially in the presence of ambient hypoxia (altitude). Hyperthermia may play an important role in such episodes [13]. In addition, AS heterozygotes appear to have an increased incidence of renal disease (renal epistaxis, hyposthenuria) and of splenic infarction under hypobaric conditions. One wonders whether pulmonary microvascular sickling and vasoocclusion might occur secondarily in AS heterozygotes who develop severe pulmonary disease for other reasons (e.g., ARDS) or in patients undergoing cardiac surgery, but this remains speculative [14,15].

The most common type of sickle cell disease is due to homozygosity for the β^S allele. After birth, Hb S rapidly replaces most of the Hb F ($\alpha_2{}^A\gamma_2{}^F$) as γ chain synthesis wanes in favor of β chain synthesis and fetal red cells reach the end of their life span, and disease appears. A variable amount of Hb F continues to be produced and higher levels appear

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to be associated with a less severe clinical course. Interestingly, steady state total Hb levels are directly (rather than inversely) related to severity of clinical course [16,17].

Hemoglobin C (β6 glu→lys) is a relatively common mutation among Afro-Americans and is therefore found in conjunction with its allele, HbS. These doubly heterozygous individuals (HbSC) express approximately equal amounts of the two beta chains. They have less severe hemolysis than do other patients with sickle cell disease and generally are only mildly anemic. This allows the presence of sickle cell disease to be overlooked clinically. Nevertheless, HbSC patients can and do develop all the serious complications of sickle cell disease including the 'acute chest syndrome' and pulmonary hypertension [18–20]. Double heterozygotes in whom a β-thalassemia mutation is allied with β^S have disease that is similar to homozygous sickle cell disease, especially when no β^A chains are produced.

The severity of sickle cell disease is also influenced by genetic factors in addition to the nature of the second β chain allele. These include α or β chain mutants that involve the polymerization contact sites, the level of expression of hemoglobin F (which unfortunately is heterogeneously distributed among the reticulocytes being produced), and the presence of certain haplotypes (a series of polymorphisms in the region of the β-chain gene on chromosome 11) which have been traced to defined regions in Africa and western Asia. These interesting features are reviewed elsewhere [21–25] and are beyond the scope of this chapter.

Patients with sickle cell disease exist in a state of metastable equilibrium. They are subject at any time to the sudden onset of various types of 'crises' [8]. These include: arrest of red cell production (aplastic crisis) which is particularly associated with parvovirus B19 infection; splenic or hepatic red cell trapping (sequestration crisis); painful crisis due to vasoocclusion (dactylitis, pain in long bones, spine, abdomen, chest wall) for which risk factors include surgical procedures, general anesthesia, pregnancy, the peripartum state, exposure to cold, etc.; priapism; cerebral vascular accidents (which are due to macrovascular disease as well as microvascular occlusion); and infection with overwhelming secondary bacteremia in the absence of a spleen (previous splenic infarction). A final problem responsible for many hospital admissions and morbidity, and a major contributor to mortality, is the so-called acute chest syndrome.

Respiratory System in Sickle Cell Disease

From the standpoint of the consultant in respiratory medicine, the respiratory problems associated with sickle cell disease can be described in three categories: (a) the 'acute chest syndrome' (ACS), an episode of acute illness that results from focal or multifocal lung injury and edema generally involving pulmonary vasoocclusion; (b) chronic abnormalities of respiratory mechanics and gas exchange which contribute to the chronic exertional dyspnea perceived by many of these patients; (c) the development of chronic, progressive pulmonary hypertension (often terminating in fatal ACS or in sudden death).

Patients with sickle cell disease may of course develop independent respiratory diseases, especially as improved medical care (and other factors) have resulted in prolongation of life span. Lupus erythematosus [26] and bronchoalveolar cell carcinoma [27] have been described in sickle cell disease patients. The potential for interaction of independent lung disease processes such as asthma, chronic bronchitis, sarcoidosis or obstructive sleep apnea (further discussed in the section on lung function) with the sickling disorder must be considered. Even illnesses (e.g., infection) that do not primarily involve the lung, procedures like surgery and general anesthesia, or physiologic states like pregnancy and the peripartum period, are associated with precipitation of ACS as well as vasoocclusive crisis.

Acute Chest Syndrome (ACS): Clinical Features and Mechanisms

The acronym ACS designates an acute pulmonary illness of variable severity consisting of a constellation of symptoms and findings referable to the chest in both children and adults with sickle cell disease. About 4% of ACS episodes in adults terminate fatally. The ACS is a major cause of hospitalization and of mortality for sickle cell disease patients. According to Vichinsky et al. [28] this is usually a febrile event associated with cough in young children but may be afebrile (one-third of cases) with chest pain (unilateral or bilateral) and shortness of breath in adults. New radiologic infiltrates are required to justify a formal diagnosis of ACS [17] but their appearance is often somewhat delayed in the evolution of the clinical picture [34,36]. Indeed, Vichinsky and Styles [29] suggest that painful,

vasoocclusive crisis involving bone marrow may lead to marrow necrosis and pulmonary fat embolism which is in turn a recognized cause of ACS. Upper lobe disease is more common in children, lower lobe disease in adults. The infiltrate may progress locally and may spread to new areas over the period of a few days. Hypoxemia is often present (i.e., decreased Pa_{O_2} and increased A–a ΔP_{O_2}), and may become increasingly resistant to oxygen therapy, leading to an ARDS-like picture. Rales or dullness to percussion are common in febrile patients with multilobe disease, but a normal lung examination is not uncommon. Wheezing is uncommon. Hemoptysis is surprisingly uncommon. Cough, if present, is usually non-productive. Sputum production, if present, has been suggested to represent a possible clue to the presence of significant infection. Unilateral or bilateral neutrophilic exudative (but sterile) pleural effusions occur in up to as many as 40% of adult cases of ACS in various series. Peripheral blood neutrophilia (which is often present at baseline during periods of clinical stability) is commonly increased in ACS and a significant decrease from baseline hemoglobin levels and thrombopenia may be observed.

ACS is commonly preceded by a painful sickle cell crisis involving the bones (extremities, vertebral column, chest wall). Narcotic administration and vigorous parenteral fluid therapy in patients hospitalized for painful crisis have been cited as possible contributory factors to the in-hospital development of ACS. However, it now seems that marrow infarction followed by fat embolism [38,39] constitutes a frequent clinical pathway leading to ACS[1] except in very young children in whom an infectious etiology is more likely. Although the Johns Hopkins Hospital autopsy series of 72 sickle cell disease patients [42] reported only 13% with evidence of necrotic marrow embolism, this finding was present in a much larger fraction of those patients who died in painful crisis and/or with ACS. Gelfand et al. [43] found bone-scan evidence of thoracic bone infarction in 21 of 22 cases of ACS complicating painful crisis but in only 11 of 33 episodes of painful crisis without lung infiltrates. In addition to furnishing sources for marrow and fat embolism, rib and sternal infarcts are probably a frequent cause of chest pain leading to regional hypoventilation and hypoxemia which in turn favor *in situ* pulmonary microvascular occlusion. Bellet et al. [44] carried out a prospective randomized trial of intensive incentive spirometry in 29 sickle cell disease patients, 8–21 years of age, who were hospitalized for 38 episodes of acute thoracic pain (40% shown by scan to have thoracic bone infarcts), and who did not have new chest infiltrates on admission. As compared with post-admission development of pulmonary complications in 8 of 19 episodes managed with standard therapy, only one of 19 receiving incentive spirometry (in addition to standard therapy) developed such complications.

Although macrovascular arterial disease causes serious cerebral vascular accidents in sickle cell disease [45], *in situ* thrombosis at sites of intimal disease in major pulmonary arteries is probably unusual and pulmonary thromboembolism from venous sources is also uncommon. Anticoagulation is rarely prescribed for the treatment of ACS although there is some evidence to support the notion that sickle cell disease is associated with a degree of hypercoagulability [46].

The role of specific pulmonary infections in the pathogenesis of ACS remains difficult to define in individual cases even when the clinical picture suggests its presence. Kirkpatrick et al. [47] reported on quantitative lower airway cultures obtained prior to antibiotic treatment by protected brush sampling during fiberoptic bronchoscopy in 19 instances of ACS in adults (83% were cigarette smokers). Two samples grew out more than 10^3 c.f.u per ml *S. pneumoniae* and two (one from a patient with a seizure disorder) grew out mixed aerobic and anaerobic organisms. None of 45 blood cultures were positive (one contaminant). Organisms associated with 'atypical' pneumonia were not methodically looked for. Previous retrospective studies of ACS in adults [36,37] also came to the conclusion, on the basis largely of non-invasive microbiologic studies, that infection was uncommon. However, the retrospective studies of Barrett-Connor [48,49] pointed to a significant role for *S. pneumoniae* infection in ACS in children (though less so in adults), and a prospective study of 102 episodes of ACS in children [24] concluded that more than one-third were caused by infections (*M. pneumoniae* 16%, bacterial 12%, viral 8%). Vichinsky et al. [28] reported on 1722 ACS episodes observed in 939 patients during a prospective multi-center study of 3751 sickle cell disease patients enrolled in the NIH-supported 'Cooperative Study of Sickle Cell Disease'. They found bacteremia (mostly *S. pneumoniae* and some *H. influenzae*) in 14% of infants with ACS but only in 1.8% (a variety of bacteria) of ACS episodes in patients over 10 years of age.

Noting the differences in the patterns of ACS as seen in young children vs. adults, Vichinsky et al.

[1]Among the viruses, parvovirus B19 is noted for its ability to cause aplastic crisis in sickle cell disease but has also been associated with marrow infarction and ACS [40,41].

[28] suggested that the increased winter-time incidence, febrility, higher rate of bacteremia and upper lobe infiltrates suggested an infectious etiology in young children. In adults, ACS was associated with severe chest pain, lower lobe infiltration and autopsy evidence of pulmonary thrombosis and fat embolism. Among adult ACS cases 50% had preceding pain crisis.

The resolution of focal chest infiltrates is slow in patients with sickle cell disease. This may reflect the presence of alveolar wall necrosis and non-cardiogenic pulmonary edema [43,50]. In some cases, complete radiologic resolution does not take place. Alveolar wall necrosis may result from ischemia-reperfusion injury as the microvasculature is occluded first by blood cells adherent to activated venular endothelium, and then in retrograde manner by dense red cells with high MCHC (and low O_2 affinity) that undergo hemoglobin polymerization and rigidification in the capillaries and arterioles [9,51]. Membrane-bound iron derived from denatured hemoglobin in such red cells may provide an additional source of reactive O_2 species (ROS) [52]. ROS can induce expression of potent cytokines like TNFα and IL-1 which in turn upregulate expression of a variety of proinflammatory cytokines and mediators, including secretory phospholipase A_2 ($sPLA_2$). This enzyme has been found to be markedly elevated in serum of sickle cell disease patients with ACS, but not with simple painful (vasoocclusive) crisis, and these $sPLA_2$ levels appeared to correlate with other measures of clinical severity (e.g., A–a Po_2 gradient) [53]. Thus, modest degrees of infection, or of mucus occlusion of airways, or even of regional hypoventilation caused by bony chest wall pain, may induce microvascular stasis with an ensuing cascade of events leading to parenchymal damage by ROS. In addition to vasoocclusion and its consequences, it is suggested that impaired endothelial nitric oxide (NO) signalling [54] as well as enhanced endothelin synthesis [55] causes vasoconstriction.

ACS Associated with 'Multiorgan Failure'

As previously noted, the ACS in patients older than 10 years is frequently preceded by a painful crisis. In such patients, the ACS may develop in a setting of acute 'multi-organ failure' often triggered by an initial unusually severe vasoocclusive pain crisis [56]. Sudden onset of a constellation of findings including: fever, striking reductions in hemoglobin and platelets (splenic and hepatic sequestration and hemolysis); ACS with significant hypoxemia; marked increases in total serum bilirubin, AST, ALT and LDH; acute renal insufficiency sometimes with significant hyperkalemia; rhabdomyolysis with serum CPK elevation; confusion and lethargy unresponsive to naloxone – is seen in most of these patients. A number of these features suggest fat embolism or sepsis, which may indeed play a role. However, the striking reversibility of the syndrome within 24 hours following institution of large volume transfusion or exchange-transfusion therapy, and return of organ function to baseline within 2 months in 16 of 17 such patients in the series of Hassell et al. [56], suggests that vasoocclusion and hypoxia plays a critical role.

Diagnosis of ACS

'Formal' diagnosis currently appears to require the presence of new pulmonary infiltrate(s) on plain chest films in a compatible clinical setting. The clinical features of the latter have been discussed and include the onset of increased dyspnea, tachypnea and hypoxemia with or without chest pain and fever. Ancillary features are an acute fall in hemoglobin, rise in peripheral blood neutrophils and fall in platelets. However, as previously noted, appearance of detectable chest X-ray infiltrates may lag symptoms by one or more days. Plain chest radiographs are likely not the most sensitive technique for detecting abnormality, and high resolution chest CT with a suitable choice of slice thickness and reconstruction algorithm has been reported [57] to show evidence of small vessel disease and ground-glass opacities in apparently 'clear' regions (*see* section on imaging). Pulmonary vascular functional imaging techniques such as conventional perfusion scans do not have much use since their resolving power is limited and macrovascular occlusion is believed to be quite uncommon. The use of bone scans to define thoracic bone infarction may be helpful since only one of 22 cases of ACS occurring in the setting of a pain crisis had a negative scan whereas 22 of 33 pain crisis patients without ACS had a negative scan [43]. The presence of pleural effusion generally does not call for diagnostic or therapeutic thoracentesis although clinical judgment is needed in individual cases.

Analysis of BAL fluid or serum for $sPLA_2$ levels is not a readily available procedure at the moment and its sensitivity and specificity will require further definition although the initial report of Styles et al. [53] has generated considerable interest, and knowledge of the biology of an increasing number of newly identified PLA_2 species is advancing [58–64]. The use of bronchoalveolar lavage in an

effort to find fat-laden macrophages which might support a diagnosis of acute pulmonary injury secondary to fat embolism [65] would require development of widely accepted and validated criteria and techniques to make this an acceptably sensitive and specific procedure [66–68]. Even if such a diagnosis were established, it is not clear what specific therapy would be added.

Treatment of ACS

Because of their instability, and the substantial risk of mortality, patients with ACS require in-hospital management and monitoring. Relief of hypoxemia (pulse oximetry) with supplemental (but not excess) O_2, control of pain (increasingly done with patient-controlled morphine pumps [69,70] and preferably not with meperidine) [71] and careful hydration (to avoid overhydration and potential need for diuretics) are standard therapy. The development of oxygen-resistant hypoxemia (ARDS-like) necessitates ventilatory support [72] or ECMO [73]. The use of inhaled nitric oxide is discussed below. Although infection probably plays a role in only a distinct minority of patients older than 5 years of age, it remains appropriate to obtain blood cultures in febrile patients (although these are not a sensitive indicator of bacterial lung infection), to culture lower airway secretions (when available), and treat empirically with a broad-spectrum antibiotic such as a macrolide to cover possible *Chlamydia* [74] and *Mycoplasma* [35] infection as well as with an agent like cefuroxime or ceftriaxone to cover *S. pneumoniae* and *H. influenzae* [30]. There seems to be little sentiment for aggressive early bronchoscopy in order to obtain protected brush cultures from the lower airways. The emergence of antibiotic-resistant organisms is of course a source of increasing concern. Pulmonary infection with various viral agents have been reported to be associated with ACS (see reference [28], but no efforts at early diagnosis or use of antiviral agents are reported.

To the extent that *S. pneumoniae* is a significant pathogen in ACS, penicillin prophylaxis beginning in early infancy and continued to about 3 years of age should be effective. Polyvalent pneumococcal vaccine administration starting at age 2 years and repeated every 4–5 years should provide later protection (especially against bacteremia). Better vaccines may allow earlier immunization to be effective. Pneumococcal prophylaxis is important even without regard for ACS since sickle cell disease patients are essentially asplenic from infancy (due to vasoocclusive infarction) and vulnerable to overwhelming bacteremia. H. influenzae vaccination is also recommended. Life-styles that include cigarette smoking and consumption of alcohol should be discouraged.

Intensive application of incentive spirometry has come into vogue as a therapeutic as well as preventive measure for ACS since a prospective randomized trial of this modality in young patients hospitalized for acute thoracic pain was found by Bellet et al. [44] to significantly reduce subsequent development of ACS. Vichinsky and Styles [29] recommend a trial of inhaled beta-adrenergic agonists and claim that PEFR may improve substantially. Glucocorticoid therapy has been reported to reduce analgesic needs in management of painful crisis [75] but its use in ACS has no support.

Anticoagulation is rarely considered since frank thrombosis in the pulmonary vessels is not thought to be an important process, venous thromboembolism is thought to be rare, and patients with sickle cell disease are at increased risk for cerebral and renal bleeding. However, VanAgtmael et al. [76] in Curacao treated most of their 81 episodes of ACS with i.v. heparin (to double the control APTT) without complications. Their observations were uncontrolled, but the authors were not impressed by the value of heparin treatment. Any consideration of fibrinolytic therapy would require full documentation of thromboembolism to warrant assuming the risks of bleeding. Low intensity oral anticoagulation (acenocoumarol) has been reported to normalize increased baseline endogenous thrombin activity in seven sickle cell anemia patients during a 2-month period of steady-state disease [46] and this approach to prophylactic therapy might be worthy of prospective investigation.

Transfusion of normal red cells, with or without withdrawal of the patient's red cells, must be performed in any patient with ACS whose respiratory status is deteriorating or who has had a sharp decline in hemoglobin level. There does not appear to exist a prospective, randomized trial of transfusion therapies in ACS but many retrospective analyses support its use. Wayne, Kevy and Nathan [77] have published an authoritative review of transfusion in sickle cell disease, including a section on its use in the ACS and a review of their own experience in 35 such patients. One should avoid undue elevation of hematocrit which increases whole blood viscosity, slows the circulation time and favors vasoocclusion and intravascular hemoglobin polymerization. This is more readily achieved with red cell exchange than with simple transfusion. Reduction of blood Hb S to 20%–30% of total Hb while maintaining a hematocrit less than 30 vol % is a reasonable goal. Special phenotyping and selection of the transfused cells may diminish the rate of alloimmunization (see also reference [78]).

Prophylactic red cell exchange is often used in preparation for surgical procedures and general anesthesia [79].

The recognition of NO as an important modulator of vascular endothelial and smooth muscle function has drawn attention to its metabolism in sickle cell vasoocclusive disease [80,81] and in animal models of sickle cell disease [82–84]. Futhermore, NO can be inhaled so as to achieve selective effects on the pulmonary circulation and has been widely used as a pulmonary vasodilator in various clinical situations. Finally, NO has exceptionally high affinity for hemoglobin heme groups and has recently been shown [85] to increase the oxygen affinity of sickle cell (but not normal) blood both *in vitro* and *in vivo* when used at clinically acceptable concentrations (up to 80 ppm). It therefore would seem reasonable to consider administration of inhaled NO to patients with severe ACS (and perhaps even for less severe cases). With the availability of excellent transgenic-knockout mouse models of sickle cell disease [86,87], it should be possible to obtain information on the safety and efficacy of inhaled NO in mice with sickle cell pulmonary vasoocclusion. Prospective clinical trials of NO inhalation could also be organized as well as obtaining more experience in uncontrolled circumstances.

The discussant of a case of fatal ACS associated with bone marrow embolism in a 22-year-old Ghanaian student in Boston (clinico-pathologic conference at the Massachusetts General Hospital) strongly recommended aggressive treatment of patients who fail to respond to conventional therapy '... with high frequency ventilation and extracorporeal membrane oxygenation and with nitric oxide inhalation'. The discussant also anecdotally reported her own experience with a gravely ill child with progressive ACS who responded remarkably to NO inhalation and recovered [88].

Treatment of Recurrent ACS

Because of the recurrent morbidity and augmented risks for acute mortality as well as development of pulmonary hypertension and cor pulmonale, patients with recurrent ACS become candidates for: (1) chronic transfusion therapy [78,89]; (2) hydroxyurea administration [90]; (3) bone marrow transplantation [91–93]. A discussion of these approaches is beyond the scope of this chapter, but all have been shown to be effective. Each has its own set of risks.

Pulmonary Hypertension and Sickle Cell Chronic Lung Disease

Multiple sickle cell disease patients with evidence of pulmonary artery hypertension have been described since the initial recognition by Yater and Hansmann in 1936 [94] (e.g., references [20,95–98]. Powars et al. [99] at the Los Angeles County–University of Southern California Sickle Cell Center reviewed their patient records and identified 28 patients with chronic forms of lung disease. They developed a 4-stage scheme that describes orderly progression of lung disease in individual cases. Their scheme incorporated respiratory symptoms, lung mechanical function and gas exchange, chest roentenographic findings and electrocardiograms (LV preponderance giving way to signs of pulmonary artery hypertension), and right heart catheterization data. They described increasing (radiologic) diffuse, 'fine' pulmonary fibrosis (no CT data) with increasing restrictive impairment, reduction in D_LCO and increasing hypoxemia. This synthesis finds some support in the high resolution CT study of Aquino et al. [100] of sickle cell disease patients with various numbers of prior episodes of ACS (*see* section on imaging below). In Stage 4, the patients are disabled by dyspnea at rest, recurrent severe, prolonged chest pain, and very marked limitation of exertion. The life expectancy of such individuals is extremely limited. Death is often sudden, perhaps due to myocardial infarction, severe hypoxemia or arrhythmia. In some cases ACS is the terminal event.

Repeated episodes of ACS and especially clusters of such episodes after early childhood were noted to be a frequent, but not invariable, pattern in these patients, even prior to development of the earlier stages of chronic lung disease. This finds support in the report of Bowen et al. [101] of reduced peak expiratory flow rates in sickle cell disease children with a history of multiple ACS episodes compared to a well-matched group without any ACS history. (Bowen et al. did not report any other lung function tests). Painful crises with chest pain (but without overt pulmonary infiltrates) and aseptic necrosis of bone were also noted to be statistically associated with chronic lung disease development [99].

A more recent retrospective evaluation of echocardiographic studies in 60 consecutively referred sickle cell disease patients [102] found evidence of pulmonary hypertension in 12, of whom 6 had been referred because of clinical suspicion of this diagnosis. Five of these 12 died in 5–49 months (3 of intractable RV failure, 2 of sudden death) whereas only 4 of the 48 without pulmonary hypertension died in the same period.

The management of this problem is not well defined at present [39]. Nevertheless, accepting the scenario proposed by Powars et al. [99] implies that identification of an individual as having entered upon the process leading to chronic lung disease would provoke serious consideration of more classic therapy (chronic transfusion program) or of more recent approaches (e.g., chronic hydroxyurea administration or bone marrow transplantation). (See reference [93]).

Castro [39] reviews existing data on the prevalence of pulmonary hypertension in sickle cell disease and comments on possible etiologies other than scarring and fibrosis caused by repeated ACS episodes, as suggested by Powars et al. [99]. These include chronically high pulmonary blood flow, sleep-related hypoxemia, impairment of pulmonary vascular NO production, increased vasoconstrictor mediators, etc. Castro [39] suggests the sickle cell disease patients with established pulmonary hypertension (PH) be viewed to some extent as if they had primary pulmonary hypertension (PPH) although none of the various treatments used for PPH have been studied in sickle cell disease patients with PH. Vasodilators (chronic prostacyclin infusion or NO inhalation as well as oral drugs) might be tried, oxygen supplementation is indicated if any hypoxemia is present, anticoagulation with warfarin aiming for INR values of 2.0–3.0 was derived from a study of PPH by Fuster et al. [103] and is used clinically by Dr. Castro's group. More sickle-cell disease- 'specific' approaches are discussed by Charache [93]. It would be of great interest to learn whether successful bone marrow transplant could stabilize or reverse established PH in sickle cell disease.

Imaging

The general radiology of the chest in sickle cell disease has been reviewed in a 1965 monograph by Reynolds [104] and more recently by Smith [105]. Newer techniques of lung imaging seem to have been applied sparingly judging from published literature. Fear of provoking intravascular sickling by infusion of hypertonic contrast seems to have inhibited the use of pulmonary angiography in the past, although isosmotic contrast media have been available for some time.

Heart

The heart is enlarged from an early age, probably due to severe anemia. The configuration is often globular although a left ventricular contour may be seen, and some individuals develop pulmonary hypertension with prominence of the central pulmonary arteries. A prospective multicenter study of stable sickle cell disease patients under the auspices of the NIH-sponsored Cooperative Study of Sickle Cell Disease [106] reported echocardiographic studies of anatomy and function in 191 patients aged 13 years or more. LV, LA, RV and aortic root dimensions (normalized by body surface area) were increased. LV free wall thickness was not increased but septal thickness was. These changes (except for RV dimension) were inversely related to hemoglobin level. Contractile function parameters of both ventricles were mostly normal although LV ejection time was prolonged. Abnormalities of diastolic function appear to be uncommon (*see* chapter by Covitz in reference [8]).

Chronic congestive heart failure is an uncommon event. Large vessel coronary artery disease is rare, even in patients with evidence of acute myocardial infarction. Chronic renal disease with secondary hypertension may lead to selective LV effects. Iron overload from transfusion therapy may cause myocardiopathy. More acutely, severe worsening of the chronic anemia or iatrogenic fluid overload may acutely precipitate heart failure and its pulmonary consequences.

Lungs (Plain Films)

The acute pulmonary findings relate to the ACS. Infiltrates may be patchy or more lobar in distribution and often involve more than one region. Upper zone infiltrates are much more common in young children and are thought to be consistent with an infectious etiology. Lower zone infiltrates are more characteristic of adolescents and adults and are thought to be less likely due to infection and more likely to other causes of vasoocclusion and lung injury. Following an initially clear chest film, infiltrates may appear after 1–3 days of hospitalization and treatment for pain crisis. They may also lag clinical presentations that are otherwise suggestive of ACS. Progression of infiltrate with extensive bilateral consolidation can occur and may lead to an ARDS-like clinical-radiologic picture. Pleural effusion is common and may be bilateral. Microbial pneumonias are more extensive, more likely to be accompanied by pleural effusion, and resolve more slowly radiologically, than would be expected from experience with pneumonia due to similar organisms in non-sickle-cell-disease patients. This is presumably due to the superimposition of vasoocclusion and alveolar wall necrosis.

Chronic changes (patchy infiltrate, stranding) may first appear after incomplete radiologic resolution of an acute event. Such changes must thereafter be taken into account in interpretation of the films in clinical context since they do not represent acute changes compatible with ACS.

Lungs (High Resolution)

Ordinary chest films cannot differentiate between lung infiltrates due to infection vs. microvascular occlusion and its consequences. Nor do perfusion scans offer adequate resolving power. Bhalla et al. [57] evaluated the findings on uncontrasted chest CT in 10 children with ACS showing areas of segmental or lobar consolidation on plain film. None were considered to be infected. Three-millimeter sections were obtained at 10 mm intervals during suspended deep inspiration. This imaging algorithm was adopted in the hope of maximizing visualization of arterioles and venules at the level of the secondary lobule while retaining ability to detect areas of ground glass opacity. Similar scans in a variety of other diseases served as controls. The two interpreting radiologists were 'blinded' and the cases and controls were mixed.

The CT examinations confirmed the plain film changes, generally due to dense consolidation. In addition, multiple regions with paucity of venules and arterioles associated with areas of ground-glass opacity were noted in non-consolidated, radiologically clear areas in each of 9 ACS patients with technically adequate studies. An average sensitivity of 84% and specificity of 94% for detection of ACS was noted in this small series. The authors further claim that CT-determined extent of vasoocclusion correlated better with clinical severity and hypoxemia than did the extent of consolidation on chest radiographs. The small vessel changes showed improvement in three convalescent patients along with resolution of ground-glass opacities but more extensive changes were noted in one patient examined during a recurrence of ACS. Confirmatory studies by others do not seem to have been published.

The authors suggest that the apparent paucity or absence of visible arterioles and venules is attributable to 'microthrombi within their lumen or upstream occlusion of subsegmental arteries' which diminished their caliber, but active vasoconstriction could also be considered (as previously noted). The ground-glass opacities are explained as areas of hemorrhagic edema secondary to reversible ischemic damage to alveolar capillaries. Dense consolidation is thought to represent 'infarcts' but without major tissue necrosis. Such areas are known to resolve, albeit relatively slowly.

A second paper [100] describes the findings with thin-section chest CT in a prospective study of 29 sickle cell disease patients (5–54 years) who were not acutely ill but had a history of ACS (median number of episodes was 6). Collimation was for 1.0 or 1.5-mm sections during suspended maximum inspiration in both supine and prone positions. Almost all observed parenchymal abnormalities were confined to the bases. A variety of findings considered to represent interstitial disease and their extent were combined into a scoring system with 0 being normal and 3 being most severe. Of 17 studies graded from 0 to 1, only 2 were entirely normal. The remaining 15 had limited areas of interlobular septal thickening, parenchymal bands and triangular visceral pleural tags (usually continuous with parenchymal bands). Two studies showed mosaic perfusion, both in patients with evidence of sleep apnea, hypoxemia and pulmonary hypertension. In 12 studies, the scoring index was greater than 1. Findings included more extensive changes of the type described above, leading to architectural distortion and traction bronchiectasis. Honeycombing was never observed.

Apart from the two patients with sleep apnea, only two others (both with interstitial disease scores greater than 1) had resting arterial O_2 unsaturation. Twenty-four of 29 patients had lung function tests. Only 5 were normal. The others had various combinations of restrictive change and diffusion defect. These abnormalities failed to correlate with the CT scores but the latter did correlate with the number of prior ACS episodes. The individual diffusion test data are not provided in the paper and it is not clear whether the values were normalized for the degree of anemia. If so normalized, the D_LCO values were indeed well below predicted in a number of the patients with minimal CT changes and the authors speculate that obliterative vascular disease below the level of resolution afforded by HRCT may account for reduced D_LCO. These findings are generally consistent with the post-mortem findings in sickle cell disease patients [42,107,108], but do not entirely fit the scenario for chronic sickle cell lung disease proposed by Powars et al. [99].

Lung Function

Earlier studies of lung volumes and spirometry and of gas exchange at rest and during exercise, largely in adults with sickle cell disease, have been summarized by Bromberg and Berkowitz [109], and factors leading to exertional dyspnea discussed. Since the writing of that text, Pianosi et al. [110] have studied 37 children with sickle cell disease associated with

Hb SS and Hb SC (the latter being much less anemic than the former), and healthy children of similar age, height and racial background. As reported earlier in adult sickle cell disease patients in Jamaica [111], both FVC and FEV_1 (% predicted) were low in Hb SS patients and somewhat low in Hb SC patients. However, the FEV_1/FVC ratio was normal in all groups. Pianosi et al. [110] also found TLC to be reduced in the SS patients but the RV/TLC ratio was normal in all sickle cell disease groups as opposed to the normal RV (and therefore somewhat elevated RV/TLC) reported in adults by Miller and Serjeant [111]. Pianosi et al. [110] found no effect of a history of previous episode(s) of ACS on spirometry and lung volumes. Furthermore, after correction for hemoglobin level, and especially when normalized for V_A, single breath D_LCO was elevated in all the sickle cell disease groups (SS and SC), and actually highest in the group with previous ACS. This surprising finding might suggest that reduced lung volumes are not accompanied by a proportional reduction in alveolar wall area or numbers of capillaries, or that a larger fraction of available capillaries are perfused at rest in anemic sickle cell disease patients than in healthy individuals or even other anemic patients. Furthermore, it suggests that ACS episodes do not necessarily lead to loss of pulmonary vascular bed or restriction of lung mechanics, at least during childhood.

Hypoxemia (excluding ACS)

The combination of increased A-a ΔP_{O_2} due to low V_A/Q regions (including 'shunt' as determined by arterial blood P_{O_2} during breathing of 100% O_2), with a right-shifted blood O_2 equilibrium curve, is known to produce significant resting hypoxemia (decreased S_aO_2) in some patients with sickle cell disease [109,112].

There is now a body of evidence to indicate that a significant fraction of children with sickle cell disease have obstructive sleep apnea (OSA) and some of these have OSA-related nocturnal desaturation episodes. The literature is reviewed by Samuels et al. [113] in the context of their case control study of 53 children with sickle cell disease. One may speculate that nocturnal events like stroke and sudden death might be related to severe hypoxemia associated with sleep. It is not clear, however, what the most cost-effective approach to screening the sickle cell disease population for nocturnal hypoxemia would be, especially since movement artefacts can confuse the interpretation of unobserved overnight digital pulse oximetry recordings.

Samuels et al. [113] suggest that combinations of tonsillar-adenoidal hypertrophy with (possible) underlying narrowing of the bony architecture of the upper airway (conceivably related to infarctive autosplenectomy and chronic marrow hyperplasia, respectively) may account for the relatively high frequency of OSA in this population. Abnormal engorgement of the nasal mucosal vascular plexus secondary to vasoocclusion (nasal 'priapism') has also been suggested [114,115] to occur. There is some evidence that adenotonsillectomy is beneficial in reversing nocturnal episodes of significant desaturation related to OSA, but the risks of anesthesia and surgery must be borne in mind. Non-surgical approaches commonly used in obstructive sleep apnea patients such as CPAP or bi-PAP applied via well-fitted nasal masks might also be considered.

Hemophilia (Philip A. Bromberg)

Males with hemophilia (usually due to genetically determined sex-linked factor VIII coagulant (FVIIIc) deficiency) may of course develop unrelated lung disease of any etiology. In this event, one must have heightened concern for the possibility of hemorrhage, e.g., into a necrotic cavity [116] or into bullous lesions [117] or in a bronchiectatic area [118]. In the absence of lung disease, spontaneous bleeding into the lower airways or the lung parenchyma is extremely unusual in hemophilia (even with FVIIIc levels <1%). 'Spontaneous' hemothorax is uncommon but does occur [119–121] and has also been reported in association with a lung teratoma [122]. As is true of undrained collections of blood in other areas, a hemothorax may become encapsulated and enlarge either due to subsequent bleeds or to presumed 'osmotic' mechanisms. In the pleural space this 'pseudotumor' (to use the terminology of hemophilia specialists) can erode ribs and compress underlying lung. Nevertheless, in a 1976 paper, Putman et al. [123] reported frequent abnormalities in a review of plain chest radiographs of 44 adult hemophiliacs. No more recent radiographic surveys using more sophisticated imaging techniques appear to have been published. These included localized areas of parenchymal scarring and of pleural thickening, and of irregularity and distortion of pulmonary vessels associated with prominence of the central pulmonary arteries. The authors suggested that the focal parenchymal/pleural abnormalities might represent sequelae of intrapulmonary hemorrhage and hemothorax.

The pulmonary vascular changes described by Putman et al. [123] also suggested the possibility of therapy-related events. Infusion of crude preparations of FVIII occasionally caused acute pulmonary infiltrates and hypoxemia. At the present time, however, FVIII preparations are either highly purified or of recombinant origin, and such complications are generally not seen. Reversible decreases in D_LCO were described in a series of hemophiliacs immediately post-factor VIII infusion [124] and attributed to particulate materials in the factor concentrates [125]. Use of 40-μm filters was recommended for these products. However, a subsequent report [126] on 20 adults with hemophilia A (16 with severe FVIIIc deficiency but none with FVIII inhibitors) found a mean decrease in s.b. D_LCO of only 0.8 per min per mm. immediately following a clinically uneventful therapeutic infusion of 20 μ/kg of Hemofil (Hyland Division, Travenol Labs), administered without the precaution of using 40-μm filters. Baseline DLCO was modestly reduced among the 8 smokers in this group but generally normal in the non-smokers.

The speculation of Putman et al. [123] concerning pulmonary vascular disease seemed to find some support in a report [127] of severe 'primary' pulmonary hypertension in 5 adults (23–56 yr of age) with classic hemophilia (severe Factor VIIIc deficiency), all of whom had self-administered lyophilized Factor VIII concentrates in substantial amounts (20 000–56 000 units per year)[1] for at least 10 years. [This product was introduced in 1970–75 and was responsible for marked improvements in morbidity and longevity.] The authors ruled out other causes of pulmonary hypertension. However, all 5 patients were HIV seropositive, although without clinical evidence of AIDS (no peripheral blood CD4+ lymphocyte counts were provided). This report elicited a subsequent case report [128] of a 11-year-old HIV-positive hemophiliac boy (CD4 count 550 mm^{-3}) with 'primary' pulmonary hypertension (supported by open lung biopsy) who had received a total of only 55 000 units of Factor VIII concentrate from 3 to 10 yr. of age for treatment of bleeding. With the subsequent recognition of the association of 'primary' pulmonary hypertension with HIV infection in non-hemophiliacs [129–133], it seems likely that the patients reported by Goldsmith et al. [127] represent instances of this association rather than a complication of chronic FVIII infusions.

In the early years of the AIDS epidemic, most hemophiliacs became HIV-positive and many of these individuals have subsequently died from AIDS-related diseases (primarily infections). (Current factor replacement technology appears to have effectively protected the hemophilia population against infection by HIV or hepatitis B.) These complications are not peculiar to hemophiliacs although their diagnosis and management and proclivity for bleeding from lung lesions require special attention. The use of invasive endobronchial or transthoracic diagnostic procedures requires preliminary treatment to reverse the underlying coagulopathy and to maintain adequate coagulation parameters during the immediate post-procedure period. Even resectional thoracic surgery can be performed, providing that adequate reversal of the coagulopathy is achieved and maintained. The details of such management are best ascertained by consultation with competent specialists in this area. The presence of an circulating inhibitor of FVIIIc substantially complicates the process of achieving hemostasis, but new methods of management which induce tolerance to exogenous FVIIIc are emerging [134].

Finally, the possibility of upper airway compromise from bleeding into the fascial planes of neck tissues should be considered in any hemophiliac with 'croup' or inspiratory stridor or respiratory difficulty [135]. Effective Factor VIII replacement therapy has of course greatly reduced the likelihood for such events occurring, for example in relation to dental procedures. However, spontaneous bleeding can occur even in the absence of obvious trauma.

Pulmonary Involvement in Lymphoma and Leukemia

(M. Patricia Rivera)

Lymphoma

Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) are lymphoproliferative malignancies primarily involving lymph nodes and spleen but not infrequently involving extranodal sites. Intrathoracic involvement is common in both diseases. Radiological evidence of disease in the chest is present in 85% of patients with HD and in 66% of patients with NHL [136,137].

[1] A previous case of pulmonary hypertension in a 30-year-old hemophiliac woman (!) was attributed to i.v. drug (pentazocine) abuse with talc granulomas seen in the pulmonary vasculature at autopsy.

Hodgkin's Disease

Hodgkin's disease can be histologically classified into four subtypes, named according to their characteristic features [138]: (1) nodular sclerosing, which comprises 40% to 75% of cases; (2) lymphocyte predominant (5%–15% of cases); (3) mixed cell (20%–40% of cases); and (4) lymphocyte depleted (5%–15% of cases). Nodular lymphocyte-predominant Hodgkin's disease is considered a B-cell lymphoma and is the only subtype for which the cell of origin is known [139,140,141]. Hodgkin's disease is staged according to the Ann Arbor staging system (Table 13.1).

Non-Hodgkin's Lymphoma

The non-Hodgkin's lymphomas represent a heterogeneous group of lymphomas which arise from a lymphoreticular cell of a specific lineage: B lymphocyte, T lymphocyte, or true histiocyte. The non-Hodgkin's lymphomas are divided on morphological grounds into three grades that correspond to prognosis: low, intermediate, and high (Table 13.2), and staged according to the Ann Arbor Staging system (Table 13.1).

Table 13.1. Ann Arbor staging system for Hodgkin's and non-Hodgkin's lymphomas

Stage I A single lymph node region (I) or single extra lymphatic site (I_E)
Stage II Two or more lymph-node regions on the same side of the diaphragm (II) or localized disease in an extralymphatic site with one or more lymph node regions on the same side of the diaphragm (II_E)
Stage III Two or more lymph-node regions on both sides of the diaphragm (III) or localized involvement of an extra-lymphatic site (III_E), spleen (III_S), or both (III_{ES})
Stage IV Diffuse or disseminated involvement of one or more extra-lymphatic organs or tissues, with or without associated lymph node involvement
A or B Denotes absence (A) or presence (B) of unexplained fever, night sweats, or weight loss of >10% body weight

Low grade non-Hodgkin's lymphomas are more difficult to eradicate than the non-Hodgkin's lymphomas with more malignant morphologic features. Low-grade non-Hodgkin's lymphomas usually present with widespread lymphadenopathy, are slowly progressive, and often disseminated at the time of initial presentation [142]. Intermediate and particularly high-grade non-Hodgkin's lymphoma often shows extranodal involvement at initial presentation.

Table 13.2. Working classification of non-Hodgkin's lymphomas

Low grade Small lymphocytic Follicular, predominantly small-cleaved cell Follicular mixed, small-cleaved and large-cleaved cell
Intermediate grade Follicular, predominantly large-cell Diffuse small-cleaved cell Diffuse mixed small and large-cell epithelioid component Diffuse large-cell
High grade Large cell immunoblastic Lymphoblastic Small non-cleaved cell

Radiographic Features of Hodgkin's and non-Hodgkin's Lymphoma

Intrathoracic Lymphadenopathy. Mediastinal and hilar lymph node enlargement is the most common roentgenographic manifestation of HD and NHL. Although the appearances of intrathoracic lymphadenopathy are similar in HD and NHL, the frequency and distribution of the abnormalities differ. In a study by Filly et al. 67% of patients with untreated HD had evidence of intrathoracic lymphadenopathy on the plain chest radiograph, whereas only 43% of patients with NHL showed evidence of intrathoracic disease [143]. Superior mediastinal lymphadenopathy is a hallmark of HD. Indeed, in the study by Filly, superior mediastinal lymphadenopathy was seen alone, or in association with other sites of intrathoracic disease, in 90% of the patients with HD [143]. Involvement of a single lymph node group is more common in NHL, reported to occur in 40% of patients with intrathoracic involvement [143]. Posterior mediastinal lymphadenopathy and paracardiac lymphadenopathy as the only areas of intrathoracic tumor involvement are rare and seen only in patients with NHL [143]. The paracardiac nodes become important as sites of recurrence because they may not be included in the radiation field [144]. Hilar adenopathy in the absence of detectable mediastinal adenopathy is unusual in both HD and NHL at initial diagnosis [145].

Lymph node calcification before therapy is very rare, but following radiation therapy, tumor-

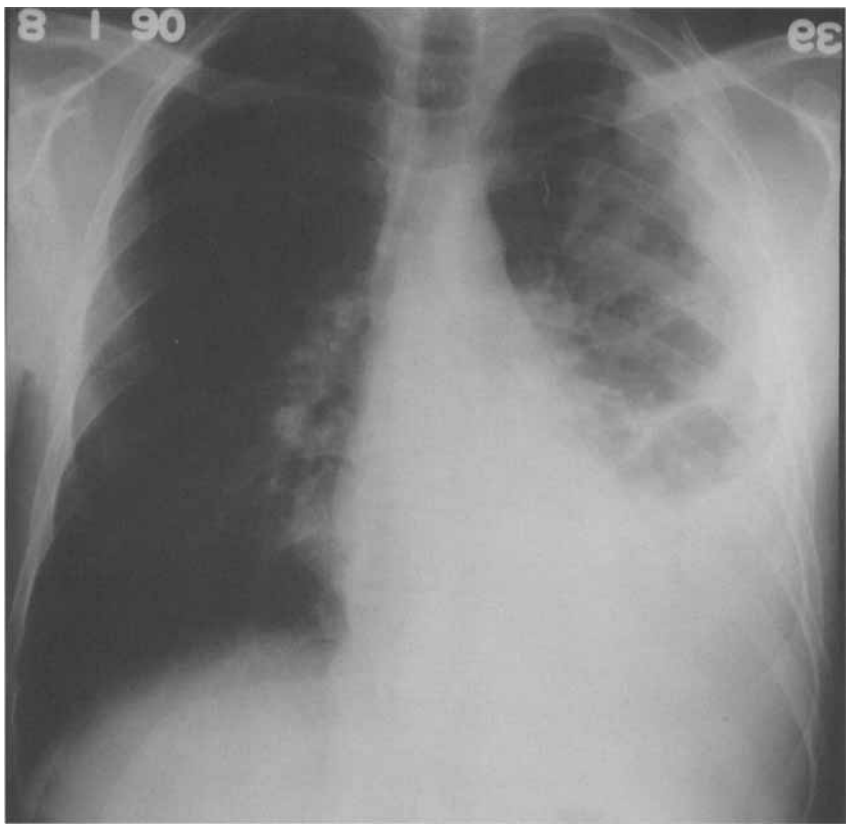
bearing nodes may reveal irregular, eggshell, or diffuse patterns of calcification [146].

Pulmonary Parenchymal Involvement. Pulmonary parenchymal involvement in malignant lymphoma is uncommon at initial presentation, reported to occur in about 12% of patients with HD and 4% of patients with NHL [143]. However, approximately 20%–25% of patients with lymphoma eventually have pulmonary parenchymal involvement [147,148]. Almost all untreated patients with HD who have pulmonary parenchymal involvement have concomitant evidence of intrathoracic adenopathy [143,149]. A parenchymal lesion without mediastinal adenopathy in the patient with HD who has not received therapy should therefore be evaluated for a second process such as infection or other neoplasm [149]. With recurrent disease, pulmonary involvement without nodal disease is more common than it is at initial presentation. In the non-Hodgkin's lymphomas, isolated pulmonary involvement is more common and reported to occur more than 50% of the time [150].

Table 13.3. Radiographic manifestations of lymphoma

Hilar and mediastinal adenopathy
Nodules with or without cavitation
Focal or patchy consolidation
Parenchymal consolidation with air bronchograms
Reticulonodular infiltrates
Peribronchovascular thickening on HRCT

The radiographic findings in pulmonary lymphoma are varied (Table 13.3; Figure 13.1 a,b,c). Discrete parenchymal nodules or masses, either solitary or multiple, are a common radiographic manifestation of pulmonary involvement by HD and NHL [145]. Nodules tend to be ill-defined and less rounded than pulmonary metastases The lesions may vary in size ranging between 1.0 and 3.5 cm in diameter. Cavitation may occur, occasionally with an air-fluid level [145] (Figure 13.2a,b,c). Subpleural plaque-like nodules or masses are commonly seen on the chest CT scan in both HD and non-Hodgkin's lymphoma [151,152]. Focal or patchy areas of consolidation that resemble pneumonia



a

Figure 13.1 a, b, c. Nodular sclerosing Hodgkin's lymphoma with pleural, pericardial and chest wall involvement. **a**. PA chest film; **b**. Chest CT scan showing extensive pleural and pericardial involvement; **c**. Chest CT scan showing pleural and chest wall involvement.

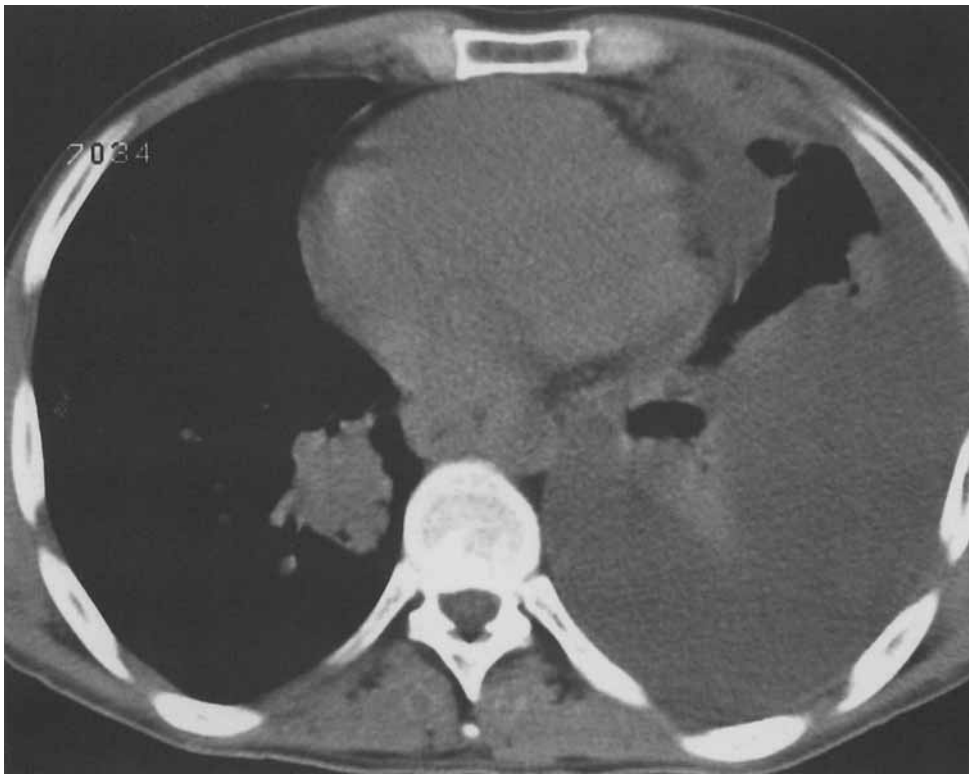


Figure 13.1b

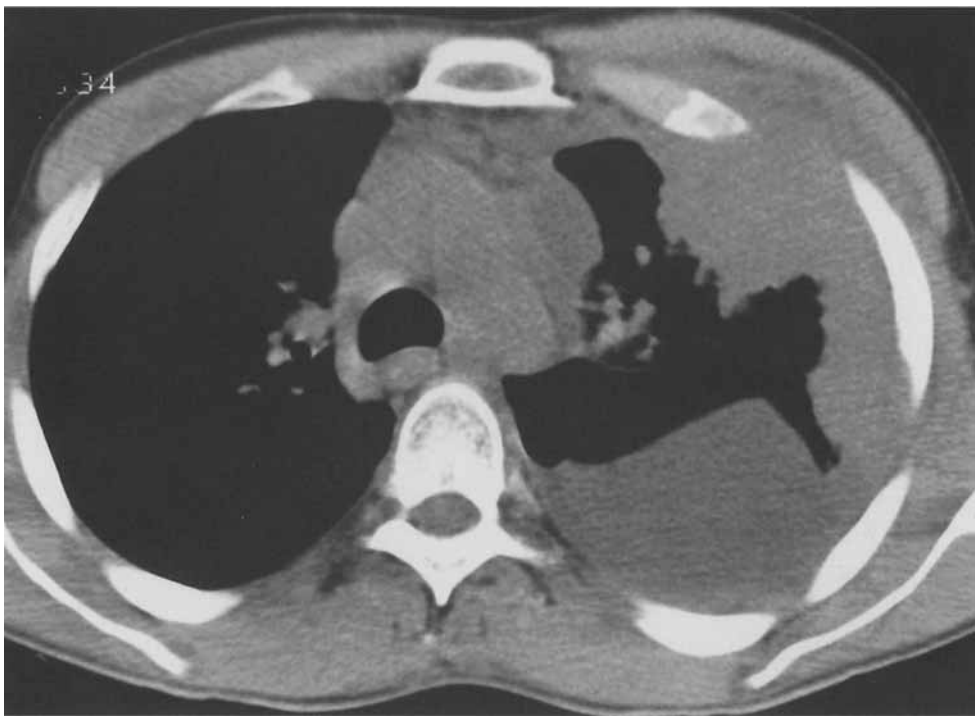
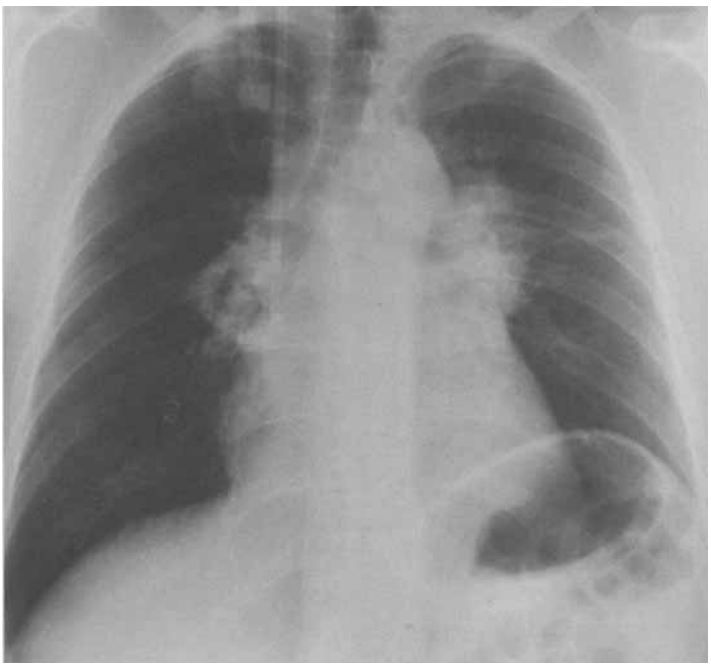


Figure 13.1c



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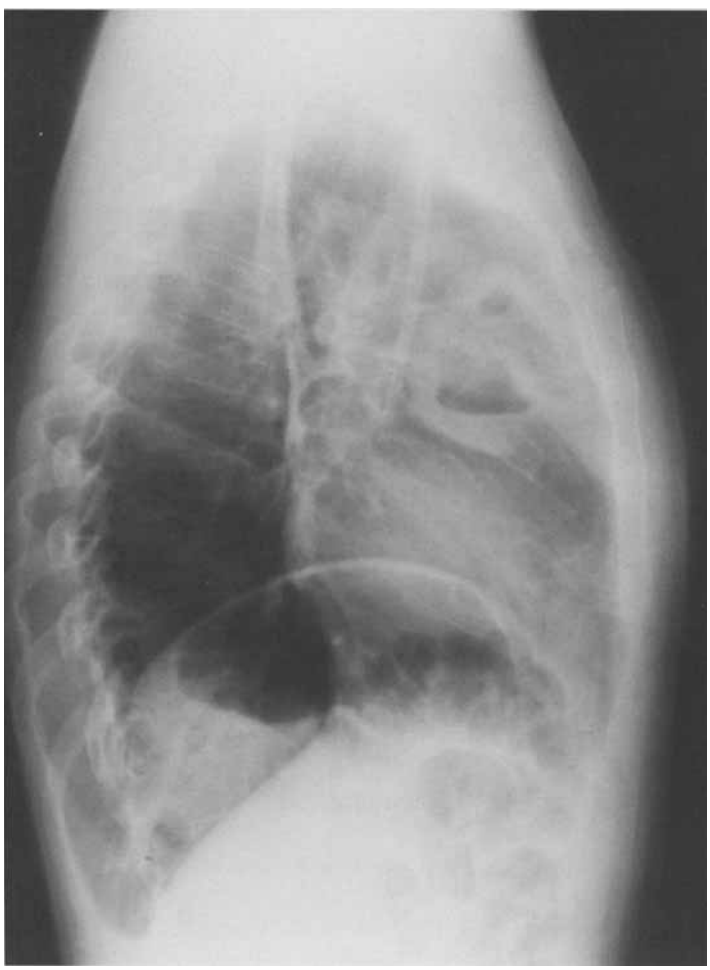


b

Figure 13.2 a, b, c. Hodgkin's disease with cavitating mass and calcified lymph nodes. **a**. PA chest film; **b**. Lateral chest film; **c**. Chest CT scan.

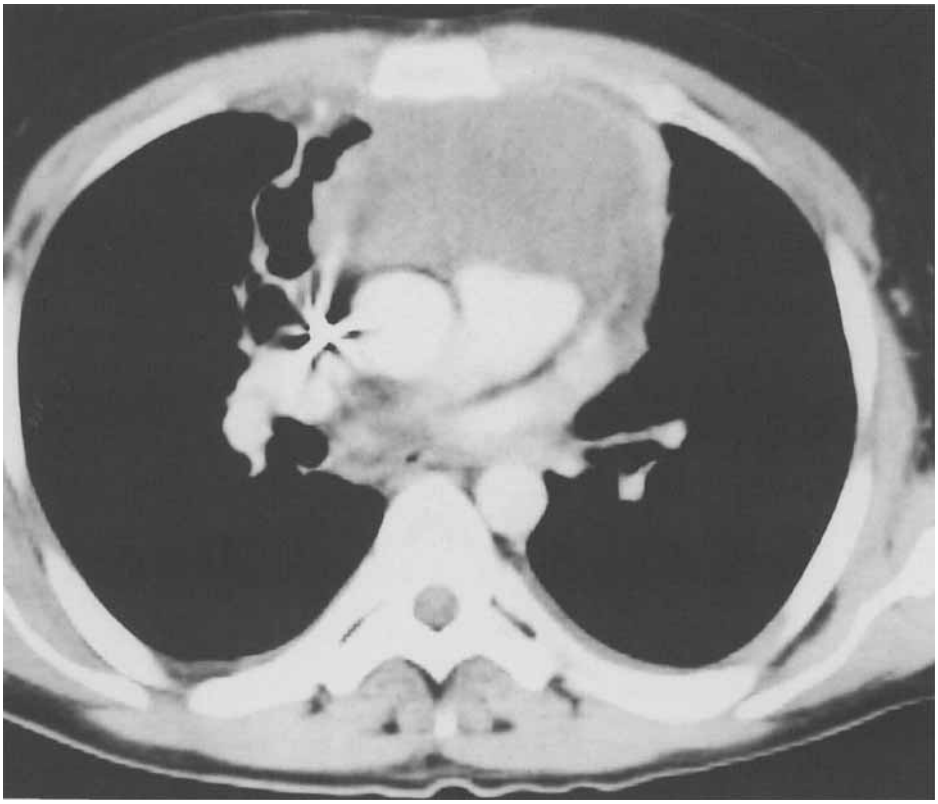


Figure 13.2c

may be seen on the plain chest radiograph or chest CT. An air bronchogram may be seen in association with parenchymal consolidation in lymphoma, due to alveolar collapse or alveolar filling by malignant cells [145,150]. Thickening of the bronchovascular bundles and septal lines has been described on high resolution CT scan [153]. The least common parenchymal manifestation of the lymphomas is an interstitial pattern representing disease along the lymphatic routes.

Pleural Disease. About 16% of patients with HD and NHL will develop radiographic evidence of pleural effusion during the course of the disease [154]. In most of these patients the pleural effusion is present at the time of initial diagnosis and usually occurs in the presence of disease elsewhere [136,145, 155]. A pleural effusion as the only intrathoracic manifestation of lymphoma is rare. Pleural effusions may be small to moderate in size, unilateral or bilateral, and are usually exudative. The effusions are presumed to result from venous or lymphatic obstruction by enlarged mediastinal nodes rather than neoplastic involvement of the pleura, and may completely resolve following radiation to the mediastinum alone [136,149]. A chylous effusion (triglycerides above 110 mg or the presence of chylomicrons) may occur because of obstruction of the thoracic duct or upper abdominal lymphatics by enlarged lymph nodes. Chylous effusions are much more common in NHL (19%) than in HD (3%) [156].

With lymphoma, cytologic evaluation of the pleural fluid is only positive in 10%–25% of cases [155,157].

Lymphomatous plaques may occur anywhere along the pleural surface and are commonly accompanied by small pleural effusions [151]. The subpleural disease may appear as plaques and/or discrete nodules [151].

Primary Lymphoid Lung Lesions

Primary Pulmonary Lymphoma

Malignant lymphomas arising in the lung are rare tumors that comprise an estimated 0.4% of all lym-

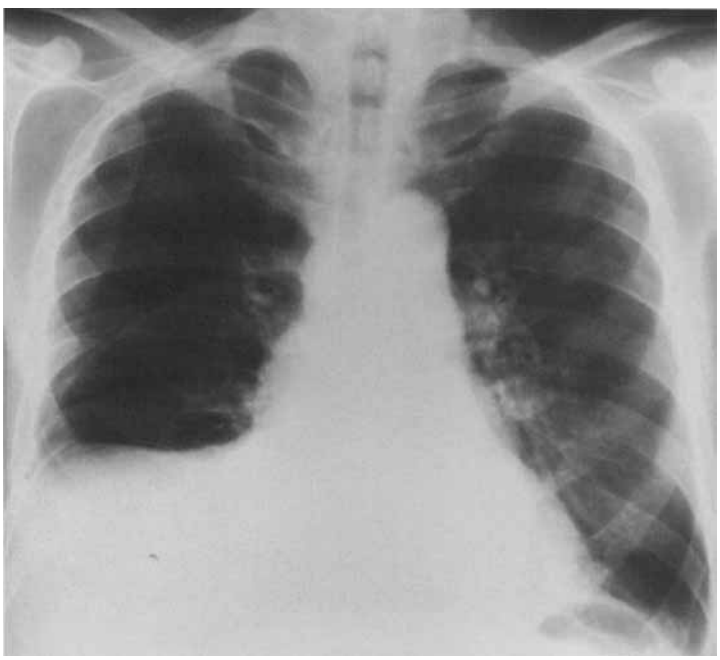
phomas [158]. Lymphoma is considered a primary pulmonary lymphoma if it affects the lung, unilaterally or bilaterally, with or without intrathoracic lymph node involvement, and shows no evidence of extrathoracic dissemination for at least 3 months after initial diagnosis [159]. Small, well-differentiated lymphocytic lymphoma is the most frequently encountered primary lymphoma of the lung [160]. The patient may be asymptomatic, the lung lesion being an incidental finding on a routine chest film, or develop non-specific symptoms such as cough and dyspnea [16] (Figure 13.3 a,b,c). The radiographic manifestations of primary pulmonary lymphoma include solitary or multiple well-circumscribed nodules, or diffuse infiltrates in all or part of a lobe. Air bronchograms are commonly present, and occasionally the lesion(s) may cavitate [161]. The histologic features include a cellular infiltrate composed primarily of mature small lymphocytes and plasma cells which are closely spaced and with little visible fibrosis [162]. Germinal centers and granulomas may be present and should not be taken as evidence of a benign process [160,161]. The infiltrate is distributed along the bronchovascular tree and the interlobular septa often with extension into the pleura [162]. Evidence of monoclonality is usually evident on immunohistochemical staining [162].

Most patients with primary pulmonary lymphoma require only surgical resection, and the role for additional radiotherapy or chemotherapy after surgery is not well defined [158,161]. The 5-year survival rate for patients with small, well-differentiated lymphocytic lymphoma is reported to be 75%–88% [158,161].

Post-Transplantation Lymphoproliferative Disorder

Post-transplantation lymphoproliferative disorders (PTLD) ranging from benign polyclonal B cell hyperplasia to monoclonal NHL are a well-recognized complication of organ transplantation, which usually become manifest within 1 year of transplantation [163,164]. Immunosuppression following solid-organ transplantation may cause an Epstein– Barr virus (EBV) infection-related polyclonal lymphoproliferative disease that can develop into a typical NHL [165]. The risk of PTLD is increased in patients who are EBV-seronegative before transplantation and then acquire a primary EBV infection after the organ transplant [166,167]. Indeed, the incidence rate of PTLD in transplant recipients who seroconvert is 42% compared to an incidence rate of less than 2% in patients who are EBV-seropositive prior to transplantation [166]. Pediatric and adolescent transplant recipients have a higher risk of developing PTLD since they are more likely to be EBV-seronegative pre-transplant [167]. The use of cyclosporine appears to increase the risk of the development of PTLD [168].

The time from transplantation to the diagnosis of PTLD can vary from months to years, but most patients are diagnosed within the first year follow-



a

Figure 13.3 a, b, c. Lymphoma: bilateral pleural effusions (primarily subpulmonic effusions). **a.** PA chest film; **b.** Lateral chest film; **c.** Chest CT scan showing bilateral pleural effusions; note the anteriorly displaced aortic calcification due to lymphadenopathy.

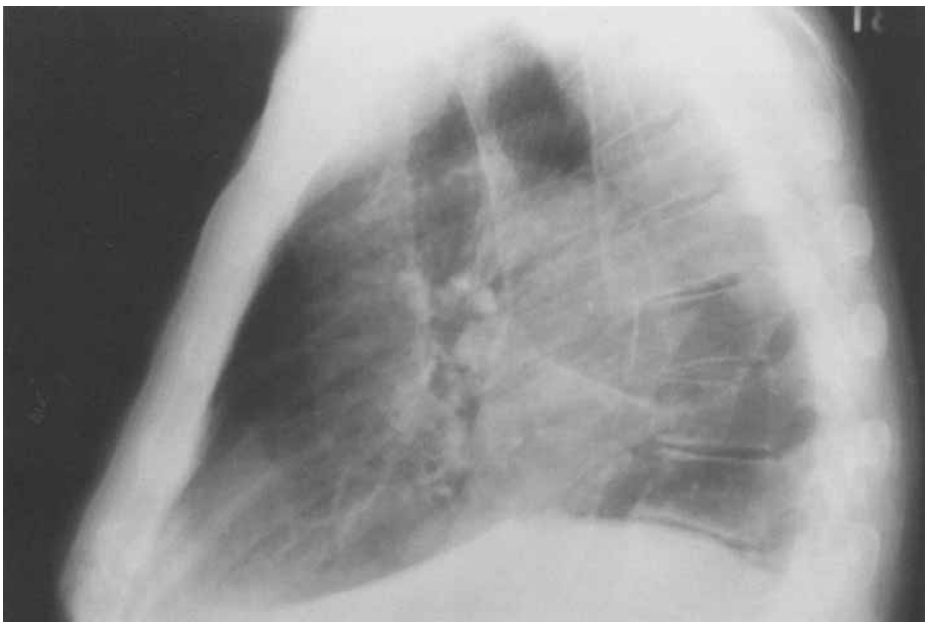


Figure 13.3b

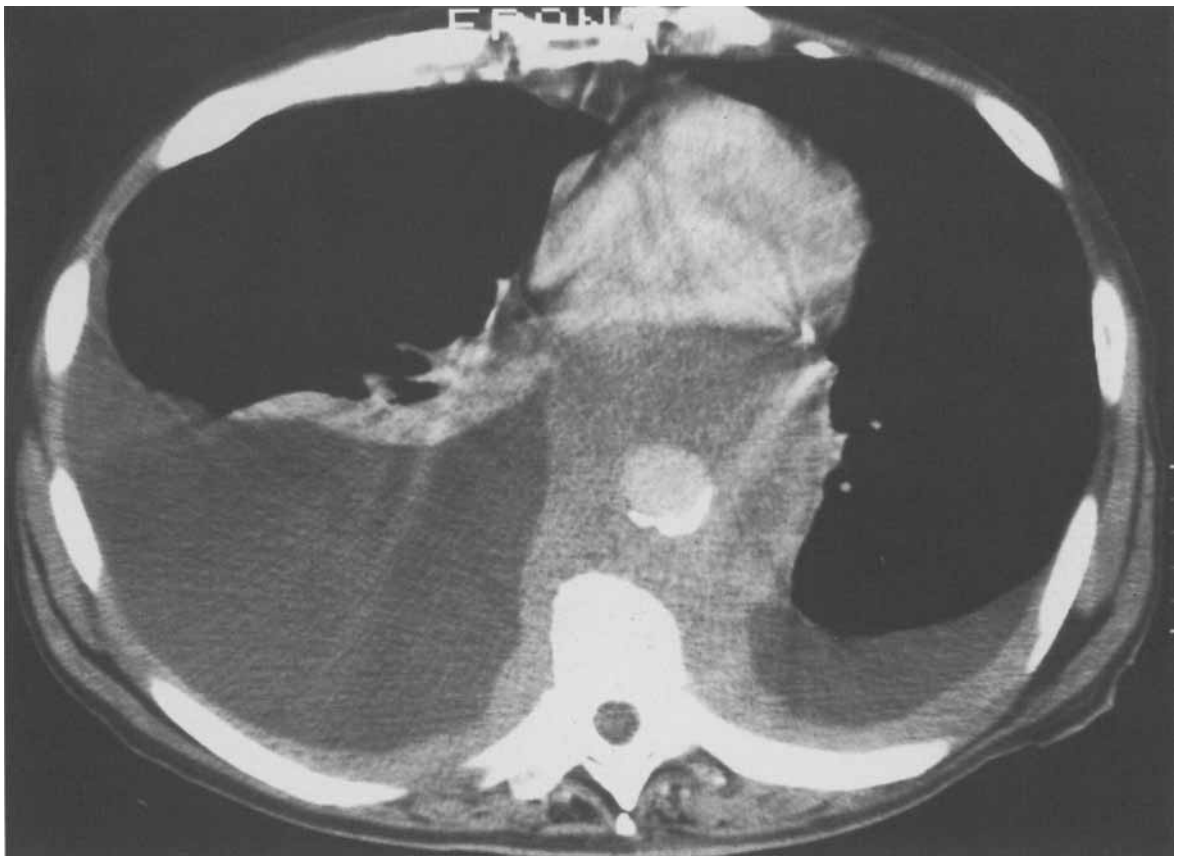


Figure 13.3c

ing transplantation [169,170]. The radiographic features include single, or more commonly, multiple well-defined pulmonary nodules that range from 1 to 5 cm in size [169,171,172], and less commonly, areas of patchy air-space consolidation mimicking pneumonia [169]. The chest CT may reveal hilar or mediastinal lymphadenopathy, and occasionally solitary nodal masses in the superior mediastinum or paravertebral regions may be seen [169]. Thymic enlargement and pericardial effusions are rare manifestations of PTLD [169].

Regression of PTLD has been reported after reduction of maintenance immunosuppression, but the risk of obliterative bronchiolitis has been high [168]. Treatment options also include surgical resection, combination chemotherapy, and radiation therapy [173,174]. The mortality rate has been reported to be 40% for patients diagnosed with PTLD during the first year following transplant [166,168].

Lymphoid Interstitial Pneumonia

Lymphoid interstitial pneumonia (LIP) is a rare pulmonary disorder characterized by an interstitial infiltrate of mature lymphocytes, plasma cells, and histiocytes that widen the alveolar septa and surround the small airways and vessels. A variable amount of fibrosis accompanies the cellular infiltrate [162]. Various dysproteinemias such as diffuse polyclonal gammopathy, monoclonal gammopathy, or hypogammaglobulinemia are commonly present in LIP [175,176,177]. Most cases of LIP are associated with other conditions, the most common being Sjögren's syndrome [176]. Cases of LIP have also been reported in association with chronic active hepatitis, primary biliary cirrhosis, the acquired immunodeficiency syndrome (AIDS), renal tubular acidosis, myasthenia gravis, and allogeneic bone marrow transplantation [178–181].

Most patients with LIP present with progressive dyspnea or cough. The chest radiograph may be normal or show a spectrum of changes that range from streaky bilateral lower lobe infiltrates to coarse, reticulonodular infiltrates with a predominantly basilar distribution [182,183]. On CT scan of the chest, nodules ranging from 2 to 4 mm in diameter with a peribronchovascular distribution of a diffuse pattern of ground-glass opacities are typical [184,185]. Hilar lymph node enlargement does not occur in LIP and pleural effusions are rarely seen [182].

The clinical course of LIP is variable. In some cases the pulmonary lesions remain stable, but in others there is progression to end-stage pulmonary fibrosis and honeycomb lung [176,177,180]. Steroid therapy may be helpful in some eases [176,177]. The development of malignant lymphoma has been reported as a complication of LIP [177,180,186,187].

Angioimmunoblastic Lymphadenopathy

Angioimmunoblastic lymphadenopathy is a rare, idiopathic disease which typically presents as an acute systemic illness characterized by fever, weight loss, and diffuse lymphadenopathy [188,189]. The disease may be associated with polyclonal hypergammaglobulinemia, a maculopapular rash, or a Coomb's positive hemolytic anemia [188,189]. The most common radiographic manifestations are paratracheal, anterior mediastinal, or hilar lymphadenopathy [190,191]. Pulmonary nodules may be seen, but diffuse parenchymal infiltrates and pleural effusions are rare [190,191].

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis (LYG) is a rare disorder which typically presents in older patients (median age 50 years) with men affected 3 times more commonly than women [192,193]. LYG was first described by Liebow et al. as a disease that clinically and radiologically resembled Wegener's granulomatosis, but the histologic findings were most suggestive of lymphoma [192].

The histologic features of LYG include a cellular infiltrate composed of plasma cells, small lymphocytes, atypical lymphoid cells, and histiocytes associated with parenchymal necrosis and prominent vascular infiltration [192,194,195]. Focal areas of lymphoma can be found in almost all cases of LYG when the tissue is carefully examined [162]. Indeed, given the similarity of the cellular infiltrates to lymphoma, and the high incidence of progression to malignant lymphoma (up to 50%), several reports suggest that LYG should be regarded as a pulmonary malignant lymphoma [161,175,183,192,194,196].

Patients with LYG usually present with dyspnea, cough, chest pain and, rarely, hemoptysis [192,193]. Systemic complaints such as fever, malaise, and weight loss are common [192,194,195]. The disease commonly involves the skin and the central and peripheral nervous systems [192,193,197]. Focal nodular lesions may be found in the kidneys at autopsy, but glomerulonephritis does not occur [192,193]. The most common radiographic finding is that of multiple, bilateral nodules or masses with ill-defined margins, that often suggest metastatic lesions [183,192,193,198,199]. The lesions have a propensity for the middle and lower lung zones, may have air bronchograms, and may cavitate in up

to 25% of cases [192,198,199]. Hilar lymph node enlargement and pleural effusions are not common features of LYG [192,198,199].

The prognosis of LYG is poor [194,195]. Treatment strategies have included cyclophosphamide and prednisone, combination chemotherapy, and radiation therapy for localized lesions [195,200–202].

Castleman's Disease

Castleman's disease, also known as angiofollicular lymph node hyperplasia, is an uncommon lymphoproliferative disorder first described by Castleman in 1956 [203]. The disease is heterogeneous, divided into a localized form (hyaline vascular and plasma cell varieties) and a systemic form due to the profound clinical differences seen between the two variants. The localized form of Castleman's disease is often an asymptomatic condition diagnosed incidentally in young patients (typically in the fourth decade of life), as enlarged mediastinal lymph nodes on a chest radiograph. Occasionally there is associated fever and weight loss, and rarely, symptoms of cough or dyspnea may be present due to compression of the tracheobronchial tree [204]. Histologically one sees redundancy of lymphoid follicles with germinal-center involution and marked capillary proliferation with endothelial hyperplasia [203]. The radiographic appearance of localized Castleman's disease often resembles thymoma, with the exception that the lesions of Castleman's disease may lie on either side of the mediastinum [205]. The mediastinal mass is usually large, lobulated, and well defined, and may contain calcium which is a helpful finding in the differential diagnosis of anterior mediastinal masses [206,207]. The striking feature of Castleman's disease on chest CT is the presence of a soft tissue mass with uniform contrast enhancement [208–210]. This feature helps differentiate Castleman's disease from lymphoma. The anterior mediastinum is the most common location but about 15% of the lesions in Castleman's disease are located in the posterior mediastinum, mimicking neurogenic tumors [204,211]. Rarely, hilar lymphadenopathy and solitary pulmonary nodules may be seen [204,211]. The treatment of choice in localized Castleman's disease is complete surgical resection which is curative in almost all cases [203,204].

The systemic or multicentric form of the disease tends to occur in older patients (typically in the sixth decade of life), with men affected 2.5 times more frequently than women [211,212]. The disease usually presents with malaise, fever, anorexia, fatigue, and extrathoracic lymphadenopathy [211–213]. Hepatosplenomegaly, pleural effusions, pericardial effusions, pulmonary infiltrates, rashes hypergammaglobulinemia, and CNS symptoms may occur [211,213]. Many of the clinical manifestations of the systemic form of the disease may be related to elevated levels of IL-6 [214,215]. Histologically, the systemic form is similar to the localized form of the disease, except for the presence of dense fields of mature plasma cells in the latter [216]. The clinical course of systemic form of Castleman's disease is usually progressive with a median survival of about 29 months [212,213].

Leukemia

Autopsy studies show that thoracic involvement is a common finding in leukemia of all types [217]. However, the incidence of clinical and radiographic abnormalities that can be attributed to leukemic infiltration is low [218], most abnormalities being caused by pneumonia, drug-induced toxicity, hemorrhage, and congestive heart failure.

Radiographic Features of Leukemia

Several chest roentgenographic abnormalities may be seen in leukemic patients. These can be divided into intrathoracic lymph node enlargement, leukemic infiltration of the lung parenchyma and the pleura, and non-neoplastic complications including infection, hemorrhage, edema, and drug reactions. The radiographic features of lung disease in leukemia are often non-specific, however, and multiple pulmonary abnormalities occurring simultaneously are reported in about 24% of patients [219].

Intrathoracic Lymphadenopathy. The most common radiographic manifestation of leukemia is hilar and mediastinal lymph node enlargement which occurs in up to 25% of patients [218,220]. Leukemic infiltration of the lymph nodes is detected in up to 50% of patients at autopsy [218]. Leukemic lymphadenopathy is more common in the lymphocytic leukemias, particularly CLL, than in the myelogenous leukemias [219].

Pleural Disease

Pleural effusion, usually unilateral, is second only to mediastinal lymph node enlargement in frequency, identified in 25%–43% of patients at autopsy [218,219]. Because pulmonary infection, infarction, hemorrhage, and edema so frequently coexist with these pleural effusions, autopsy

information is often insufficient to determine their cause [219].

Granulocytic sarcoma (GS) is an extra-medullary tumor composed of granulocytic cells which usually develops in the course of leukemia and myeloproliferative disorders, in sites such as skin, bone, cervix, heart, kidney, and CNS [220]. GS of the pleura has also been described [220,221]. The roentgenographic features include pleural thickening with or without pleural effusion, and on CT scan marked pleural thickening coupled with mediastinal adenopathy has been noted [221].

Pulmonary Parenchymal Involvement

Leukemic lung infiltration is described as extravascular collection of leukemic cells in regions of lung parenchyma not demonstrating some other apparent cause for their presence [222]. Although rarely a cause of pulmonary symptoms or radiographic abnormalities, leukemic infiltration of the lungs is found at autopsy in 20%–66% of patients who die of leukemia [218,220]. It occurs most commonly in patients with chronic myelogenous leukemia (CML) [218], and in patients with high peripheral blast counts [219]. The most frequent radiographic presentation of leukemic lung infiltration is diffuse bilateral interstitial infiltrates [218]. Less commonly, it can present as focal consolidation or discrete parenchymal lung nodules [219].

Pulmonary leukostasis, or hyperleukocytic syndrome, is characterized by diffuse accumulations of leukemic cells in minor vessels of the lung [223]. It is found in about 40% of patients with leukemia at autopsy, and in most of these cases, leukostasis is considered the cause of death [223,224]. The hyperleukocytic syndrome is almost always associated with the myelogenous leukemias in patients with peripheral leukocyte counts greater than 100 000 per microliter [223,225]. The radiograph may be normal or show diffuse alveolar infiltrates [224]. The latter is due to pulmonary edema that develops in some patients with leukostasis [224]. The most common symptom is dyspnea, but neurologic manifestations, such as confusion, personality changes, and somnolence are found in some patients and have been attributed to CNS leukostasis, which commonly coexists with pulmonary leukostasis [223].

Infectious Complications of Lymphoma and Leukemia

The infectious complications in the immunocompromised host are covered in more detail elsewhere in this book. The following is a brief summary of the infectious complications common in patients with leukemia and lymphoma.

Patients with lymphoma and leukemia are immunosuppressed by virtue of their underlying disease and by the chemotherapy that they receive for their disease. They represent a heterogeneous group of patients in terms of their susceptibility to infections. Recognition of the underlying immunologic defect can help narrow down the differential diagnosis of the infectious pathogen [226,227]. For example, patients with Hodgkin's disease have impaired T-cell function therefore are at increased risk of developing pneumonia due to *Pneumocystis carinii* or viruses. Patients with impaired granulocyte function, such as occurs in acute leukemia, are more at risk to develop infection due to gram-negative bacteria and fungi (Table 13.4). It is important to remember, however, that not only intrinsic immunologic defects, but other factors such as travel history, iatrogenic procedures, and recent chemotherapy, must be considered when trying to identify the likely causative pathogen [227]. The radiographic pattern also helps to narrow down the differential diagnosis. For example, a segmental or lobar infiltrate favors the diagnosis of a bacterial infection, whereas a diffuse infiltrate suggests an opportunistic infection such as *Pneumocystis carinii* (PCP) pneumonia [228] (Table 13.5).

Bacteria

Patients with leukemia are commonly immunocompromised by virtue of granulocyte defects. As such, they are at risk to develop bacterial pneumonias commonly caused by gram-negative organisms including *Pseudomonas aeruginosa*, *Escherichia coli*, *Serratia marcescens*, *Klebsiella* and *Enterobacter* species, and less commonly by gram-positive organisms including *Staphylococcus aureus* [229]. Patients with globulin defects, such as those with CLL, have a high incidence of pneumonia due to *Streptococcus pneumoniae* and *Haemophilus influenzae*.

The clinical signs and symptoms of pneumonia are usually atypical in the immunocompromised host, especially in the setting of granulocytopenia [230]. Cough is common but sputum production is very rare especially when the neutrophil count is less than 100 per mm^3 [230]. Fever, although non-specific, is the most sensitive sign and is seen in almost all cases [231]. The chest radiograph typically shows localized infiltrates [228,230]. Because bacterial pneumonia in the patient with lymphoma or leukemia can progress rapidly, empiric broad spectrum antibiotic coverage should be initiated as soon as the diagnosis is suspected [232].

Table 13.4. Immune defects and associated pulmonary infections*

Immune defect	Underlying disease	Organism
B-cell defect (decreased globulins or impaired antibody function)	Lymphoproliferative disorders: ALL, CLL, multiple myeloma, NHL,	*S. pneumoniae* *H. influenzae* *P. aeruginosa* Other Gram (–) bacteria *P. carinii*, CMV
T-cell defect (impaired cell mediated immunity)	Lymphoproliferative disorders: ALL, Hodgkin's, NHL, hairy cell leukemia Drugs: steroids, alkalating agents	*P. carinii* *C. neoformans* and other fungi *M. tuberculosis* *Nocardia* *Strongyloides* Herpes viruses
Granulocyte defect (decrease in number or impaired function)	Myeloproliferative disorders: AML, CML, Myelodysplastic syndromes Drugs: most chemotherapeutic agents	*S. aureus* *Pseudomonas* species Enteric bacilli Opportunistic fungi (especially *Aspergillus*)

* Adapted from Stover DE (1989) Diagnosis of pulmonary disease in the immunocompromised host. Sem Respir Med 10:89.

Table 13.5. Radiographic appearance associated with pulmonary infection in the immunocompromised host

Segmental or lobar infiltrates	Diffuse infiltrates
Bacteria	*P. carinii* pneumonia
Mycobacteria	Viral pneumonia
Fungi	
Cavitation	Pleural effusion
Anaerobes	Bacteria
Fungal pneumonia	Fungi (occasionally)
M. tuberculosis	*M. tuberculosis*
Nocardia	
Adenopathy	Nodules
Septic emboli	*Nocardia*
Tuberculosis	*Aspergillus*
Atypical mycobacteria	Atypical mycobacteria
Endemic fungi	
Cryptococcosis	

Uncommon Bacteria

Atypical bacterial pneumonia caused by *Legionella pneumophilia* and *Mycoplasma pneumoniae* can occur in immunocompromised patients, particularly when these patients are being treated with immunosuppressive drugs, including corticosteroids [233,234]. Among patients with leukemia, those with hairy cell leukemia appear to be at increased risk for infection with atypical bacteria [235,236]. The radiologic appearance of *L. pneumophilia* in the immunocompromised patient is commonly that of a unilateral patchy infiltrate which can progress to consolidation involving contiguous and non-contiguous areas of the lung, and to bilateral infiltrates [237]. Cavitation is relatively frequent [238]. The most common radiographic manifestation of *Mycoplasma* is lower lobe patchy or reticular interstitial infiltrates.

Impaired T-cell mediated immunity, as is the case in patients with lymphoma, acute lymphocytic leukemia (ALL), and hairy cell leukemia, are at increased risk for infection with *Nocardia* species. The radiographic features of *Nocardia* pneumonia include segmental or lobar infiltrates, thick-walled cavitary lesions, single or multiple nodules, and lobar pneumonia with bulging fissures [239].

Mycobacteria

The prevalence of tuberculosis in the cancer patient is higher than that in the general population, and thus tuberculosis should always be considered in the differential diagnosis of pulmonary disease in this patient population. In a recent study, Libshitz et al. provided an update on tuberculosis in the cancer patient [240]. They reported an increased incidence of tuberculosis in foreign-born and non-white cancer patients. In addition, in contrast to an earlier study [241], *M. tuberculosis* is now less frequently seen in lung cancer, head and neck cancer and lymphoma patients but has increased in patients with leukemia [240]. The radiographic features of pulmonary tuberculosis in the patient with

leukemia or lymphoma are not unusual and consist of upper lobe infiltrates (predominantly in the apical and posterior segments), with or without the development of cavitation [242,243]. Mortality from pulmonary tuberculosis among patients with cancer has been reported to be as high as 48% [241].

Patients with lymphoma and leukemia, particularly those with hairy cell leukemia, are also at increased risk for developing pulmonary infection with non-tuberculous *Mycobacteria* [244]. Defects in cell-mediated immunity related to the underlying malignancy or iatrogenically induced with cytotoxic therapy predisposes these patients to disseminated infection with non-tuberculous *Mycobacteria* [245,246]. Patients with hairy cell leukemia are particularly at risk for developing disseminated infection [247]. The mortality rate of disseminated non-tuberculous mycobacterial infection in the immunocompromised host is reported to be as high as 90% [246].

Fungi

Approximately one-third of patients with leukemia and lymphoma who are neutropenic and remain persistently febrile on broad-spectrum antibacterial therapy, develop invasive fungal infections due to *Aspergillus*, *Candida*, and *Mucorales* species [248,249,250]. The most common fungal infection in this group of patients is invasive pulmonary aspergillosis, which is a necrotizing pneumonia characterized pathologically by vascular invasion and thrombosis. The classic description of invasive pulmonary aspergillosis is a syndrome mimicking pulmonary embolism with sudden onset of pleuritic pain, fever, tachycardia, and pleural friction rub. Unfortunately, this classic syndrome occurs in less than 30% of patients [251]. Most patients with *Aspergillus* infection have prolonged fever with nonspecific pulmonary infiltrates that fail to respond to antibacterial therapy [232]. Hemoptysis is a rare complication and tends to occur during the stage of bone marrow recovery and cavity formation [252]. The earliest radiographic findings are single or multiple nodules. As the disease progresses, the chest radiograph may show one of three patterns: cavitation of nodules; progression of nodules to form single or multiple areas of consolidation; or the rapid development of large, wedge-shaped, pleural based lesions [232]. The chest CT may allow early recognition of invasive pulmonary aspergillosis by the characteristic appearance of nodules with a surrounding halo of ground-glass opacification or the so called 'CT halo sign' [253,254]. The diagnosis of fungal infection is particularly difficult in immunocompromised patients. The success rate of fiberoptic bronchoscopy in establishing the diagnosis of invasive pulmonary aspergillosis is about 50% [255]. Most patients are treated presumptively. Early treatment with antifungal therapy is associated with a better outcome, and withholding treatment until a definitive diagnosis is established results in dissemination and increased mortality [248]. Amphotericin B lipid complex (ABLC) is an effective alternative therapy to amphotericin-B, with improved response rate (overall 66%), and less nephrotoxicity [256].

Pneumocystis Carinii

Patients with lymphoma and certain leukemias (ALL, hairy cell leukemia, CLL) are at increased risk for developing *Pneumocystis cariini* pneumonia (PCP) because of impaired cell-mediated immunity. Immunosuppressive therapy, especially cyclosporine or corticosteroids also predisposes these patients to PCP [232]. Typically these patients present with fever, non-productive cough, and dyspnea. It is important to remember that unlike the clinical presentation of PCP in the patient with AIDS, respiratory symptoms progress relatively rapidly in the non-AIDS patient with PCP [257]. The chest radiograph commonly reveals bilateral reticulonodular infiltrates, but can be normal in about 5% of patients [258]. The most serious complication of PCP is the development of respiratory failure, reported to occur in 5%–30% of patients [259]. A high mortality rate is observed among patients who progress to respiratory failure [260]. The non-AIDS patient with PCP tends to be significantly more hypoxemic on room air than the AIDS patient with PCP [260]. This disparity in the arterial oxygen tension may be due to an increased host inflammatory response in the non-AIDS patient [260,261]. Bronchoalveolar lavage studies (BAL) have shown an increased number of neutrophils in BAL in non-AIDS patients with PCP compared with that of AIDS patients with the infection [260,261]. BAL neutrophilia appears to be a reliable predictor for the development of respiratory failure [261,262]. Early recognition, diagnosis via bronchoscopy, and initiation of appropriate treatment is paramount.

Viruses

Patients receiving therapy for acute leukemia and for lymphoma are susceptible to a variety of viral pathogens, particularly those belonging to the herpesvirus family. Herpes simplex virus (HSV), cytomegalovirus (CMV), and varicella zoster virus

(VZV) commonly cause active infection in these patients [263]. Infection by herpes simplex virus (HSV) in leukemia patients results from reactivation of latent endogenous virus [263]. It is reported that 60%–80% of seropositive patients with leukemia receiving intensive chemotherapy reactivate the virus [264]. Reactivation is commonly associated with mucocutaneous disease characterized by painful oral, lip, or facial ulcerations which are slow to heal and are much more likely to become superinfected [263]. Pulmonary HSV is uncommon and varies from tracheobronchitis to pneumonia [232]. Infection by CMV can occur either by reactivation of latent endogenous virus or by acquisition of exogenous virus through transfusions of blood products [263]. Patients with leukemia and Hodgkin's disease, particularly those receiving induction therapy and corticosteroids, are at increased risk for developing serious CMV infection [265,266]. Commonly these patients present with gastrointestinal symptoms and pneumonitis is rare [266]. Patients with leukemia and lymphoma who are VZV-seropositive can reactivate latent virus infection during immunosuppressive therapy [263]. In the adult patient, reactivation is associated with a vesicular rash (shingles). The most serious complication of reactivated varicella in this patient population is visceral dissemination, especially pneumonia, which is reported to occur in as many as 20% of patients [232,263].

Non-infectious Pulmonary Complications of Lymphoma and Leukemia

Recognizing drug-induced pulmonary toxicity in the lymphoma and leukemia patient is often difficult because the clinical, radiographic, and pathologic features are often non-specific [267]. In the differential diagnosis of pulmonary disease in this patient population, one must always consider recurrence of the underlying disease, opportunistic infection, and iatrogenic lung disease resulting from radiation therapy and or cytotoxic drugs. It is important to recognize radiation and drug-induced pulmonary disease because continuing the offending agent may cause death and withholding it can result in resolution of pulmonary toxicity [268].

I do not intend to fully review radiation and cytotoxic drug-induced pulmonary toxicity, for such a task is beyond the scope of this chapter. The following is a brief overview for the reader and references are provided for a more in-depth review.

Radiation-induced Pulmonary Toxicity

Radiation therapy plays an important role in the management of patients with HD and NHL. Radiation pneumonitis develops in 5%–15% of all patients who are treated with radiotherapy. Several factors such as concomitant chemotherapy, previous irradiation, and withdrawal of corticosteroids can add to the development of radiation pneumonitis [268]. Typically the onset of radiation pneumonitis is 2 to 6 months following completion of radiation therapy, but cases have been reported as early as 2 weeks following treatment [269]. Patients may present with insidious onset of dyspnea with exertion which can progress to severe dyspnea at rest, non-productive cough, and low grade fever [270]. The initial radiographic finding is a diffuse haze in the region of radiation which progresses to patchy alveolar infiltrates with air bronchograms [271,272]. The infiltrates coalesce so as to define the treatment portals in a 'straight-edge effect' [273]. Indeed the single most striking feature of radiation pneumonitis is the geometric shape of the resulting infiltrate, which does not correspond to anatomic lung boundaries. Small, asymptomatic pleural effusions are rare. Pleural effusions caused by radiation therapy usually occur within 6 months of the completion of treatment, are associated with radiation pneumonitis, and spontaneously resolve [274].

Radiation fibrosis develops in the area of radiographic abnormality in nearly all patients with clinical radiation pneumonitis [275]. In most cases, radiographic evidence of fibrosis is present by about 1 year after completion of radiotherapy [275]. In most patients symptoms are mild; however, severe respiratory failure has been described particularly in patients with impaired pulmonary function prior to receiving radiotherapy [275].

Chemotherapy-Induced Pulmonary Toxicity

Numerous cytotoxic drugs have been shown to cause pulmonary disease (Table 13.6), the most common ones being bleomycin, carmustine (BCNU), busulfan, and methotrexate [276]. Bleomycin, an antitumor antibiotic used in the treatment of Hodgkin's and non-Hodgkin's lymphomas, is the chemotherapy agent most commonly associated with drug-induced pulmonary toxicity [277]. There is a spectrum of pulmonary manifestations associated with chemotherapy-induced pulmonary toxicity but interstitial pneumonitis which can progress to pulmonary fibrosis is by far the most common (Table 13.7). The cardinal symptom of drug-induced pul-

Table 13.6. Chemotherapeutic agents associated with pulmonary toxicity

Alkylating agents	Nitrosoureas
Cyclophosphamide	Carmustine (BCNU)
Busulfan	Lomustine (CCNU)
Uracil mustard	Semustine (Methyl-CCNU)
Chlorambucil	
Melphalan	Vinca alkaloids
	Vinblastine
Antimetabolites	Vindesine
Methotrexate	
Cytosine arabinoside (Ara-C)	Other agents
Azathioprine	Paclitaxel
	Gemcitabine
Cytotoxic antibiotics	All *trans*-retinoic acid
Bleomycin	Procarbazine
Mitomycin	

Table 13.7. Pulmonary manifestations of cytotoxic drug toxicity

Interstitial pneumonitis/ fibrosis	Non-cardiogenic pulmonary edema
Bleomycin	Methotrexate
Mitomycin	Cytosine arabinoside (Ara-C)
Cyclophosphamide	? Mitomycin/vinca alkaloids
Chlorambucil	
Busulfan	Capillary leak syndrome
Carmustine (BCNU)	? All-*trans* retinoic acid
Melphalan	? Mitomycin/vinca alkaloids
Methotrexate	
	Hypersensitivity pneumonitis
Bronchiolitis obliterans with organizing pneumonia (BOOP)	Methotrexate
Bleomycin	Bleomycin
	Paclitaxel
Bronchospasm	Procarbazine
Vinca alkaloids	
Paclitaxel	

monary toxicity is dyspnea [268]. Patients can also present with non-productive cough, fatigue, and fever. Symptoms develop insidiously, that is over a period of several weeks to months, however, hypersensitivity drug-induced lung disease, which can occur with methotrexate and paclitaxel, can develop over hours [278,279]. Hemoptysis is an uncommon feature of drug-induced pulmonary toxicity, and when present other diagnoses should be considered [268].

The most common radiographic abnormality associated with drug-induced pulmonary toxicity is bibasilar reticular opacities that may progress to diffuse infiltrates [153]. Pleural effusions are rare, but occasionally are present with mitomycin, busulfan, and methotrexate toxicity [267,280,281]. A normal chest radiograph has been reported with methotrexate and carmustine toxicity [281,282], and hilar adenopathy has been reported only with methotrexate toxicity [281]. The chest CT has been shown to be more sensitive than the chest radiograph in detecting the presence of chemotherapy-induced lung disease [153]. In one study, bleomycin-induced lung disease was detected in 38% by chest CT but only in 15% by chest radiograph [283]. The CT findings consisted of small pleural-based linear and subpleural ill-defined nodular densities in the posterior region of the lung bases [283].

Several new pulmonary drug reactions have been reported in cancer patients. Apropos to this chapter is the retinoic acid syndrome described in patients with leukemia following therapy with all-*trans* retinoic acid (ATRA). ATRA is an effective agent for inducing complete remission in patients with acute promyelocytic leukemia [284,285]. It acts by promoting differentiation of leukemic cells into phenotypically mature myeloid cells [284,285]. The retinoic acid syndrome has been described in up to 25% of patients treated with ATRA [286,287]. Patients develop fever, dyspnea, weight gain, and transient hypotension usually in the first 3 weeks of treatment [286]. Lower extremity edema, pericardial effusions, renal insufficiency, and hyperbilirubinemia may be seen [286]. The chest radiograph typically shows bilateral interstitial infiltrates and bilateral pleural effusions. The initial clinical picture suggests pulmonary edema or pneumonia; however, there is no response to antibiotic or diuretic therapy. High dose corticosteroid therapy (dexamethasone 10 mg administered intravenously every 12 hours for 3 or more days) is effective in reversing the syndrome in a high percentage of patients [287]. The etiology of the retinoic acid syndrome is not known, but it does not appear to be related to leukocyte plugging of the pulmonary vessels, nor to hyperleukocytosis [286]. Clinically, the syndrome most closely resembles the capillary leak syndrome associated with the administration of various cytokines, particularly interleukin-2 [288]. It has also been postulated that all-*trans* retinoic acid may increase the expression of leukocyte adhesion receptors on the leukemic cell surface, which would enhance the cell's adherence to capillary endothelium and promote focal endothelial damage [286]. The syndrome is fatal in 50% of untreated cases, thus prompt recognition and aggressive treatment with corticosteroids is necessary [286,287].

Pulmonary Hemorrhage

Pulmonary hemorrhage, varying in severity from microscopic intraalveolar bleeding to massive pulmonary hemorrhage, has been observed at autopsy

in about 74% of patients with leukemia [218]. Pulmonary hemorrhage, however, as the sole cause of pulmonary infiltrates is rare, reported in only 12%–38% of leukemic patients [218,289,290]. Hemorrhage usually is associated with a clotting disorder and or a low platelet count (less than 15 000 mm^{-3}) [228,289,290], and at autopsy, it is usually found in areas of pulmonary infection [218]. The patient may be febrile, and complain of cough and dyspnea, but hemoptysis is very rare [228]. Typically, the radiographic manifestation of pulmonary hemorrhage is that of diffuse infiltrates, but focal infiltrates can occur [228,290].

References

1. Mirchev R, Ferrone FA (1997) The structural link between polymerization and sickle cell disease. J Mol Biol 265:475–9.
2. Noguchi CT, Rodgers GP, Serjeant G et al. (1988) Current concepts: levels of fetal hemoglobin necessary for treatment of sickle cell disease. N Engl J Med 318:96–9.
3. Noguchi CT, Schecter AN (1985) Sickle hemoglobin polymerization in solution and in cells. Annu Rev Biophys and Biophys Chem 14:239–63.
4. Cao Z, Ferrone FA (1996) A 50th order reaction predicted and observed for sickle hemoglobin nucleation. J Mol Biol 256:219–22.
5. Briehl R (1995) Nucleation, fiber growth and melting, and domain formation and structure in sickle cell hemoglobin gels. J Mol Biol 245:710–23.
6. Ho C, Willis BF, Shen T-J et al. (1996) Roles of alpha 114 and beta 87 amino acid residues in the polymerization of hemoglobin S: implications for gene therapy. J Mol Biol 263:475–85.
7. Eaton WA, Hofrichter J (1990) Sickle cell hemoglobin polymerization. Advan Protein Chem 40:63–279.
8. Embury SH, Hebbel RP, Mohandas N et al. (eds) (1994) Sickle Cell Disease: Basic Principles and Clinical Practice. Raven Press, New York.
9. Kaul DK, Fabry ME, Nagel RL (1996) The pathophysiology of vascular obstruction in the sickle syndromes. Blood Revs 10:29–44.
10. Weil JV, Castro O, Malik AB et al. (1993) Pathogenesis of lung disease in sickle hemoglobinopathies. Amer Rev Respir Dis 148:249–56.
11. Ballas SK, Mohandas N (1996) Pathophysiology of vaso-occlusion. Hematol/Oncol Clin N Amer 10:1221–39.
12. Murtaza LN, Stroud CE, Davis LR et al. (1981) Admissions to hospital of children with sickle cell anaemia: a study in South London. Br Med J 282:1048–51.
13. Kark JA, Ward FT (1994) Exercise and hemoglobin S. Sem Hematol 31:181–225.
14. Hasleton PS, Orr K, Wester A et al. (1989) Evolution of acute chest syndrome in sickle cell trait: an ultrastructural and light microscopic study. Thorax 44:1057–8.
15. Knasel A (1982) Is sickle cell trait a health hazard? Medical problems: a brief review. Amer J Pediatr Haematol Oncol 4:179–81.
16. Baum KF, Dunn DT, Maude GH et al. (1987) The painful crisis of homozygous sickle cell disease. Arch Intern Med 147:1231–4.
17. Platt OS, Thorington BD, Brambilla DJ et al. (1991) Pain in sickle cell disease. N Engl J Med 325:11–16.
18. Williams S, Maude GH, Serjeant GR (1986) Clinical presentation of sickle cell-hemoglobin C disease. J Pediatr 109:586–9.
19. Shao SH, Orringer EP (1996) Case report: splenic sequestration and multiorgan failure as the presenting manifestation of hemoglobin SC disease. Amer J Med Sci 311:139–41.
20. Collins FS, Orringer EP (1982) Pulmonary hypertension and cor pulmonale in the sickle hemoglobinopathies. Amer J Med 73:814–21.
21. Powars DR, Chan L, Schroeder WA (1990) β^S-Genecluster haplotypes in sickle cell anemia: clinical implications. Amer J Pediatr Hematol/Oncol 12:367–74.
22. Charache S (1990) Fetal hemoglobin, sickling, and sickle cell disease. Adv in Pediatr 37:1–31.
23. Chang YC, Smith KD, Moore RD et al. (1995) An analysis of fetal hemoglobin variation in sickle cell disease: the relative contributions of the X-linked factor, β-globin haplotypes, α-globin gene number, gender, and age. Blood 85:1111–17.
24. Steinberg MH, Hsu H, Nagel RL et al. (1995) Gender and haplotype effects upon hematological manifestations of adult sickle cell anemia. Amer J Hematol 48:175–81.
25. Lu Z-H, Steinberg MH (1996) Fetal hemoglobin in sickle cell anemia: relation to regulatory sequences cis to the β-globin gene. Blood 87:1604–11.
26. Eissa MM, Lawrence JM, McKenzie L et al. (1995) Systemic lupus erythematosus in a child with sickle cell disease. Southern Med J 88:1176–8.
27. Labi M, Haponik EF, Welsh RA et al. (1989) Alveolar cell carcinoma complicating sickle cell anemia: a chance occurrence? Amer J Hematol 32:222–5.
28. Vichinsky EP, Styles LA, Colangelo LH et al. (1997) Acute chest syndrome in sickle cell disease: clinical presentation and course. Blood 89:1787–92.
29. Vichinsky E, Styles L (1996) Pulmonary complications (of sickle cell disease). Hematol/Oncol Clin North Amer 10:1275–87.
30. Dreyer ZE (1996) Chest infections and syndromes in sickle cell disease of childhood. Sem in Respir Infections 11:163–72.
31. Castro O, Brambilla DJ, Thorington B et al. (1994) The acute chest syndrome in sickle cell disease: incidence and risk factors. Blood 84:643–9.
32. Kirkpatrick MB, Haynes J (1994) Sickle cell disease and the pulmonary circulation. Seminars in Respir

and Crit Care Med 15:473–81.
33. Haynes J, Kirkpatrick MB (1993) The acute chest syndrome of sickle cell disease. Amer J Med 305:326–30.
34. Sprinkle RH, Cole T, Smith S et al. (1986) Acute chest syndrome in children with sickle cell disease: a retrospective analysis of 100 hospitalized cases. Amer J Pediatr Hematol Oncol 8:105–10.
35. Poncz M, Kane E, Gill FM (1985) Acute chest syndrome in sickle cell disease: etiology and clinical correlates. J Pediatr 107:861–6.
36. Davies SC, Win AA, Luce PJ et al. (1984) Acute chest syndrome in sickle-cell disease. Lancet 1:36–8.
37. Charache S, Scott JC, Charache P (1979) Acute chest syndrome in adults with sickle cell anemia: microbiology, treatment, and prevention. Arch Intern Med 139:67–9.
38. Vichinsky E, Williams R, Das M et al. (1994) Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. Blood 83:3107–12.
39. Castro O (1996) Systemic fat embolism and pulmonary hypertension in sickle cell disease. Hematol/Oncol Clin North Amer 10:1289–303.
40. Kolquist KA, Vnencak-Jones CL, Swift L et al. (1996) Fatal fat embolism syndrome in a child with undiagnosed hemoglobin S/β^+ thalassemia: a complication of acute parvovirus B19 infection. Pediatr Pathol Laboratory Med 16:71–82.
41. Rao SP, Desai N, Miller ST (1996) B19 parvovirus infection and transient aplastic crisis in a child with sickle cell anemia. J Pediatr Hematol/Oncol 18:175–7.
42. Haupt HM, Moore GW, Bauer TW et al. (1982) The lung in sickle cell disease. Chest 81:332–7.
43. Gelfand, MJ, Daya SA, Rucknagel DL et al. (1993) Simultaneous occurrence of rib infarction and pulmonary infiltrates in sickle cell disease patients with acute chest syndrome. J Nuclear Med 34:614–18.
44. Bellet PS, Kalinyak KA, Shukla R et al. (1995) Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. N Engl J Med 333:699–703.
45. Francis RB (1991) Large-vessel occlusion in sickle cell disease: pathogenesis, clinical consequences, and therapeutic implications. Medical Hypotheses 35:88–95.
46. Wolters HJ, Cate HT, Thomas LL et al. (1995) Low-intensity oral anticoagulation in sickle-cell disease reverses the prethrombotic state: promises for treatment? Brit J Haematol 90:715–17.
47. Kirkpatrick MB, Haynes J, Bass JB (1991) Results of bronchoscopically obtained lower airway cultures from adult sickle cell disease patients with the acute chest syndrome. Am J Med 90:206–10.
48. Barrett-Connor E (1971) Bacterial infection and sickle cell anemia. Medicine 50:97–112.
49. Barrett-Connor E (1973) Pneumonia and pulmonary infarction in sickle cell anemia. JAMA 224:997–1000.
50. Athanasou NA, Hatton C, McGee JO et al. (1985) Vascular occlusion and infarction in sickle cell crisis and the sickle chest syndrome. J Clin Pathol 38:659–64.
51. Kaul DK, Fabry ME, Nagel RL (1989) Microvascular sites and characteristics of sickle cell adhesion ot vascular endothelium in shear flow conditions: pathophsiological implications. Proc Natl Acad Sci 86:3356–60.
52. Shalev O, Hebbel RP (1996) Catalysis of soluble hemoglobin oxidation by free iron on sickle red cell membranes. Blood 87:3948–52.
53. Styles LA, Schalkwijk CG, Aarsman AJ et al. (1996) Phospholipase A_2 levels in acute chest syndrome of sickle cell disease. Blood 87:2573–8.
54. Mosseri M, Bartlett-Pandite AN, Wenc K et al. (1993) Inhibition of endothelium-dependent vasorelaxation by sickle erythrocytes. Amer Heart J 126:338–46.
55. Phelan M, Perrine SP, Brauer M et al. (1995) Sickle erythrocytes, after sickling, regulate the expression of the endothelin-1 gene and protein in human endothelial cells in culture. J Clin Invest 96:1145–51.
56. Hassell KL, Eckman JR, Lane PA (1994) Acute multiorgan failure syndrome: a potentially catastrophic complication of severe sickle cell pain episodes. Amer J of Med 96:155–62.
57. Bhalla M, Abboud MR, McLoud TC et al. (1993) Acute chest syndrome in sickle cell disease: CT evidence of microvascular occlusion. Radiology 187:45–9.
58. Jacques C, Berenbaum F (1996) Role of type II secreted phospholipase A2 in inflammatory processes. Comptes Rendus Seances Soc Biol 190:437–43.
59. Lambeau G, Ancian P, Nicolas JP et al. (1996) A family of receptors for secretory phospholipases A2. Comptes Rendus Seances Soc Biol 190:425–35.
60. Samet JM, Madden MC, Fonteh AN (1996) Characterization of a secretory phospholipase A2 in human bronchoalveolar lavage fluid. Experimental Lung Res 22:299–315.
61. Roberts MF (1996) Phospholipases: structural and functional motifs for working at an interface. FASEB J 10:1159–72.
62. Grass DS, Felkner RH, Chiang MY et al. (1996) Expression of human group II PLA2 in transgenic mice results in epidermal hyperplasia in the absence of inflammatory infiltrate. J Clin Invest 97:2233–41.
63. Chilton F (1996) Would the real role(s) for secretory PLA2s please stand up? J Clin Invest 97:2161–2.
64. Murakami M, Kudo I, Inoue K (1995) Secretory phospholipases A2. J Lipid Mediators & Cell Signalling 12:119–30.
65. Godeau B, Schaeffer A, Bachir D et al. (1996) Bronchoalveolar lavage in adult sickle cell patients with acute chest syndrome: value for diagnostic assessment of fat embolism. Amer J Respir Crit Care Med 153:1691–6.
66. Mimoz O, Edouard A, Beydon L et al. (1995) Contribution of bronchoalveolar lavage to the diagnosis of posttraumatic pulmonary fat embolism. Intensive Care Med 21:973–80.
67. Roger N, Xaubet A, Agusti C et al. (1995) Role of

bronchoalveolar lavage in the diagnosis of fat embolism syndrome. European Respir J 8:1275–80.
68. Stanley JD, Hanson RR, Hicklin GA et al. (1994) Specificity of bronchoalveolar lavage for the diagnosis of fat embolism syndrome. Amer Surgeon 60:537–41.
69. Shapiro, BS, Cohen DE, Howe CJ (1993) Patient-controlled analgesia for sickle-cell-related pain. J Pain & Symptom Management 8:22–8.
70. Gonzalez ER, Bahal N, Hansen LA et al. (1991) Intermittent injection vs patient-controlled analgesia for sickle cell crisis pain. Arch Intern Med 151:1373–8.
71. Ward SJ, Simini B, Meltzer BA et al. (1996) Sickle cell pain crisis. In: Letters to the editor. Lancet 347:261–2.
72. Baird S, Johnson JL, Escudero, CRTT et al. (1994) Combined pressure control/high frequency ventilation in adult respiratory distress syndrome and sickle cell anemia. Chest 106:1913–16.
73. Trant CA, Casey JR, Hansell D et al. (1996) Successful use of extracorporeal membrane oxygenation in the treatment of acute chest syndrome in a child with severe sickle cell anemia. ASAIO J 42:236–9.
74. Miller ST, Hammerschlag MR, Chirgwin K et al. (1991) Role of *Chlamydia pneumoniae* in acute chest syndrome of sickle cell disease. J Pediatr 118:30–1.
75. Griffin TC, McIntire D, Buchanan GR (1994) High-dose intravenous methyprednisolone therapy for pain in children and adolescents with sickle cell disease. N Engl J Med 330:733–7.
76. Van Agtmael MA, Cheng JD, Nossent HC (1994) Acute chest syndrome in adult Afrocaribbean patients with sickle cell disease: analysis of 81 episodes among 53 patients. Arch Intern Med 154:557–60.
77. Wayne AS, Kevy SV, Nathan DG (1993) Transfusion management of sickle cell disease. Blood 81:1109–23.
78. King KE, Ness PM (1996) Treating anemia. Hematol Oncol Clinics of North Amer 10:1305–20.
79. Ware RE, Filston HC (1992) Surgical management of children with hemoglobinopathies. Surg Clinics of North Amer 72:1223–36.
80. Rees DC, Cervi P, Grimwade D et al. (1995) The metabolites of nitric oxide in sickle-cell disease. Brit J Haematol 91:834–7.
81. Lopez BL, Barnett J, Ballas SK et al. (1996) Nitric oxide metabolite levels in acute vaso-occlusive sickle-cell crisis. Academic Emergency Med 3:1098–103.
82. French JA, Kenny D, Scott JP et al. (1997) Mechanisms of stroke in sickle cell disease: sickle erythrocytes decrease cerebral blood flow in rats after nitric oxide synthase inhibition. Blood 89:4591–9.
83. Osei SY, Ahima RS, Fabry ME et al. (1996) Immunohistochemical localization of hepatic nitric oxide synthase in normal and transgenic sickle cell mice: the effect of hypoxia. Blood 88:3583–8.
84. Bank N, Aynedjian HS, Qiu JH et al. (1996) Renal nitric oxide synthases in transgenic sickle cell mice. Kidney International 50:184–9.
85. Head CA, Brugnara C, Martinez-Ruiz R et al. (1997) Low concentrations of nitro oxide increase oxygen affinity of sickle erythrocytes in vitro and in vivo. J Clin Invest 100:1193–8.
86. Ryan TM, Ciavatta DJ, Townes TM (1997) Knockout-transgenic mouse model of sickle cell disease. Science 278:873–5.
87. Paszty C, Brion CM, Manci E et al. (1997) Transgenic knockout mice with exclusively human sickle hemoglobin and sickle cell disease. Science 278:876–8.
88. Scully RE, Mark EJ, McNeely WF (eds) (1997) Case Records of the Massachusetts General Hospital. N Engl J Med 337:1293–301.
89. Styles LA, Vichinsky E (1994) Effects of a long-term transfusion regimen on sickle cell-related illnesses. J Pediatr 125:909.
90. Charache S, Terrin ML, Moore RD et al. (1995) Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. N Engl J Med 332:1317–22.
91. Walters MC, Patience M, Leisenring W et al. (1996) Bone marrow transplantation for sickle cell disease. N Engl J Med 335:369–76.
92. Platt OS, Guinan EC (1996) Bone marrow transplantation in sickle cell anemia – the dilemma of choice. N Engl J Med 335:426–8.
93. Charache S (1996) Experimental therapy: experimental versus conventional therapy. Hematol Oncol Clinics North Amer 10:1373–82.
94. Yater WM, Hansmann GH (1936) Sickle call anemia: a new cause of cor pulmonale and right heart failure. Am J Med Sci 191:474.
95. Margolies MP (1951) Sickle cell anemia: a composite study and survey. Medicine 30:357–443.
96. Petch CP (1951) Cor pulmonale from recurrent pulmonary embolism. Lancet 1:1346.
97. Moser KM, Shea JG (1957) The relationship between pulmonary infarction, cor pulmonale, and the sickle states. Am J Med 22:561–79.
98. Sproule BJ, Halden ER, Miller WF (1958) A study of cardio-pulmonary alterations in patients with sickle cell disease and its variants. J Clin Invest 37:486–95.
99. Powars D, Weidman JA, Odom-Maryon T et al. (1988) Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. Medicine 67:66–76.
100. Aquino SL, Gamsu G, Fahy JV et al. (1994) Chronic pulmonary disorders in sickle cell disease: findings at thin-section CT. Radiology 193:807–11.
101. Bowen, EF, Crowston JG, De Ceulaer K et al. (1990) Peak expiratory flow rate and the acute chest syndrome in homozygous sickle cell disease. Arch Dis Childhood 65:330–2.
102. Sutton LL, Castro O, Cross DJ et al. (1994) Pulmonary hypertension in sickle disease. Am J Cardiol 74:626–8.
103. Fuster V, Steele PM, Edwards WD et al. (1984) Primary pulmonary hypertension: natural history and the importance of thrombosis. Circulation 70:580.

104. Reynolds J (1965) The roentgenological features of sickle cell disease and related hemoglobinopathies. Charles C Thomas, Springfield, pp. 185–218.
105. Smith JA (1987) Cardiopulmonary manifestations of sickle cell disease in childhood. Sem in Roentgenology 22:160–7.
106. Covitz W, Espeland M, Gallagher D et al. (1995) The heart in sickle cell anemia: the cooperative study of sickle cell disease. Chest 108:1214–19.
107. Oppenheimer EH, Esterly JR (1971) Pulmonary changes in sickle cell disease. Amer Rev Respir Dis 103:858–9.
108. Song J (1971) Pulmonary lesions in sickle cell disease. In: Pathology of sickle cell disease. Charles C Thomas, Springfield, IL, pp. 176–91.
109. Bromberg PA, Berkowitz LR (1994) The lungs and hematologic disease. In Textbook of Respiratory Medicine, 2nd edn, Murray JF, Nadel JA (eds.), WB Saunders Co., Philadelphia, PA, pp. 2435–62.
110. Pianosi P, D'Souza SJ, Charge TD et al. (1993) Pulmonary function abnormalities in childhood sickle cell disease. J Pediatr 122:366–71.
111. Miller GJ, Serjeant GR (1971) An assessment of lung volumes and gas transfer in sickle cell anaemia. Thorax 26:309–15.
112. Bookchin RM, Lew VL (1996) Pathophysiology of sickle cell anemia. Hematol/Oncol Clinics North Amer 10:1241–53.
113. Samuels MP, Stebbens VA, Davies SC et al. (1992) Sleep related upper airway obstruction and hypoxaemia and sickle cell disease. Arch Dis Childhood 67:925–9.
114. D'Aloya N (1993) Sleep related upper airway obstruction and hypoxaemia in sickle cell disease. In: Letters to the editor. Arch Dis Childhood 68:715.
115. Ajulo SO (1991) Priapism of the turbinates: a cause of nasal obstruction in sickle cell anaemia. J Laryngol Otol 105:851–2.
116. Takeda R, Mabuchi H (1974) A massive pulmonary hemorrhage resulting in cavitation occurring in a case of hemophilia A associated with diabetes mellitus. Southern Med J 67:869–73.
117. Pursel SE, Kay SA (1972) Pulmonary resection in hemophilia. Chest 62:342–3.
118. Connolly JP (1993) Hemoptysis as a presentation of mild hemophilia A in an adult. Chest 103:1281–2.
119. Kay WR, Kupfer HG (1957) Spontaneous hemothorax in hemophilia: case report and discussion of the hemophilia syndromes, with remarks on the management of hemothorax. Case Reports. Ann Intern Med 47:152–61.
120. Barrett KE, Israels CG (1965) Haemothorax in haemophilia. Thorax 20:416–21.
121. Rasaretnam R, Chanmugam D, Sivathasan C (1976) Spontaneous haemothorax in a mild haemophiliac. Thorax 31:601–4.
122. Berghout A, Mallens WMC, te Velde J et al. (1983) Teratoma of the lung in a hemophilic patient. Acta Haemat 70:330–4.
123. Putman CE, Gamsu G, Zinn D et al. (1976) Radiographic chest abnormalities in adult hemophilia. Radiology 118:41–3.
124. Boese EC, Tantum KR, Eyster ME (1979) Pulmonary function abnormalities after infusion of antihemophilic factor (AHF) concentrates. Amer J Med 67:474–6.
125. Eyster ME, Nav ME (1978) Particulate material in antihemophilic factor (AHF) concentrates. Transfusion 18:578–81.
126. Chediak J, Chausow A, Solarski A et al. (1984) Pulmonary function in hemophiliac patients treated with commercial factor VIII concentrates. Amer J Med 77:293–6.
127. Goldsmith GH, Baily RG, Brettler DB et al. (1988) Primary pulmonary hypertension in patients with classic hemophilia. Ann Intern Med 108:797–9.
128. Bray GL, Martin GR, Chandra R (1989) Idiopathic pulmonary hypertension, hemophilia A, and infection with human immunodeficiency virus (HIV). Ann Intern Med 111:689–90.
129. Speich R, Jenni R, Opravil M et al. (1991) Primary pulmonary hypertension in HIV infection. Chest 100:1268–71.
130. Polos PG, Wolfe D, Harley RA et al. (1992) Pulmonary hypertension and human immodeficiency virus infection. Chest 101:474–8.
131. Mette SA, Palevsky HI, Pietra GG et al. (1992) Primary pulmonary hypertension in association with human immunodeficiency virus infection. A possible viral etiology for some forms of hypertensive pulmonary arteriopathy. Amer Rev Respir Dis 145:1196–2000.
132. Petitpretz P, Brenot F, Azarian R et al. (1994) Pulmonary hypertension in patients with human immunodeficiency virus infection. Circulation 89:2722–7.
133. Morse JH, Barst RJ, Itescu S et al. (1996) Primary pulmonary hypertension in HIV infection: an outcome determined by particular HLA class II alleles. Am J Respir Crit Care Med 153:1299–301.
134. Aledort LM (1996) Hemophilia: yesterday, today and tomorrow. Mt. Sinai J Med 63:225–35.
135. Pochedly C, Rosales A (1968) Respiratory obstruction in a child with classical hemophilia. Amer J Dis Child 116:103–5.
136. Castellino RA, Blank N, Hoppe RT et al. (1986) Hodgkin's disease: contributions of chest CT in the initial staging evaluation. Radiology 160:603.
137. Khoury MB, Godwin JD, Halvorsen R et al. (1986) Role of chest CT in non-Hodgkin's lymphoma. Radiology 158:659.
138. Rappaport H, Berard CW, Butler JJ (1971) Report of the committee on histopathological criteria contributing to staging of Hodgkin's disease. Cancer Res 31:1864.
139. Hellman S, Jaffe ES, DeVita VT Jr (1991) Hodgkin's Disease. In DeVita VT Jr, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology Marcel Dekker, New York, p. 249.
140. Stein H, Hansmann ML, Lennert K et al. (1986) Reed-Sternberg and Hodgkin cells in lymphocyte predominant on nodular subtype. Am J Clin Pathol 86:292.

141. Marafioti T, Hummel M, Anagnostopoulos I et al. (1997) Origin of nodular-lymphocyte predominant Hodgkin's disease from a clonal expansion of highly mutated germinal-center B cells. N Engl J Med 337:453.
142. Horning SJ, Rosenberg SA (1984) The natural history of initially untreated low grade non-Hodgkin's lymphoma. N Engl J Med 311:147.
143. Filly R, Blank N, Castellino R (1976) Radiographic distribution of intrathoracic disease in previously untreated patients with Hodgkin's disease and non-Hodgkin's lymphoma. Radiology 120:277–81.
144. Jackelson MS, Balikian JP, Mauch P et al. (1983) Peri- and paracardiac involvement in lymphoma. AJR 140:483.
145. Blank N, Castellino RA (1980) The intrathoracic manifestations of the malignant lymphomas and leukemias. Semin Roentgenol 15:225.
146. Bragg DG (1987) Radiology of the lymphomas. Curr Probl Diagn Radiol 16:183.
147. Catterrall JR, McCabe RE, Brooks RG et al. (1989) Open lung biopsy in patients with Hodgkin's disease and pulmonary infiltrates. Am Rev Respir Dis 139:1274.
148. McCabe RE, Brooks RG, Catterall JR et al. (1989) Open lung biopsy in patients with non-Hodgkin's lymphoma and pulmonary infiltrates. Chest 96:319.
149. North LB, Libshitz HI, Lorigan JG (1990) Thoracic lymphomas. Radiol Clin North Am 28:745.
150. Jenkins PF, Ward MJ, Davies P et al. (1981) Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and the lung. Br J Dis Chest 75:22.
151. Shuman LS, Libshitz HI (1984) Solid pleural manifestations of lymphoma. AJR 142:269.
152. Ellert J, Kreel L (1980) The role of computed tomography in the initial staging and subsequent management of the lymphomas. J Comput Assis Tomogr 4:368.
153. Primack SL, Muller NL (1994) High-resolution computed tomography in acute diffuse lung disease in the immunocompromised patient. Radiol Clin North Am 32:731.
154. Berkman N, Breuer R (1993) Pulmonary involvement in lymphoma. Respiratory Medicine 87:85.
155. Celikoglu F, Tierstein AS, Krellenstein DJ et al. (1992) Pleural effusions in non-Hodgkin's lymphoma. Chest 101:1357.
156. Xaubet A, Diumenjo MC, Marin A et al. (1985) Characteristics and prognostic value of pleural effusions in non-Hodgkin's lymphomas. Eur J Respir Dis 66:135.
157. Melamed MR (1963) The cytologic presentation of malignant lymphomas and related diseases in effusions. Cancer 16:413.
158. L'Hoste RJ, Filippa DA, Lieberman PH et al. (1984) Primary pulmonary lymphomas: A clinicopathologic analysis of 36 cases. Cancer 54:1397.
159. Saltzstein SL (1963) Pulmonary malignant lymphomas and pseudolymphomas: Classification, therapy, and prognosis. Cancer 16:928.
160. Turner RR, Colby TV, Doggett RS (1984) Well-differentiated lymphoma. A study of 47 patients with primary manifestation in the lung. Cancer 54:2088.
161. Kennedy JL, Nathwani BN, Burke JS et al. (1985) Pulmonary lymphomas and other pulmonary lymphoid lesions: A clinicopathologic and immunologic study of 64 patients. Cancer 56:539.
162. Katzenstein ALA, Askin FB (1990) Primary Lymphoid Lung Lesions. In: Katzenstein ALA, Askin FB eds Surgical pathology of non-neoplastic lung disease. WB. Saunders, Philadelphia, p. 290.
163. Stephanian E, Gruber SA, Dunn D et al. (1991) Post-transplantation lymphoproliferative disorders. Transplant Rev 5:120.
164. Purtillo DT, Strobach S, Okano M et al. (1992) Epstein Barr virus associated lymphoproliferative disorders. Lab Invest 67:5.
165. List AF, Greco FA, Volger LB (1987) Lymphoproliferative diseases in immunocompromised hosts: The role of Epstein-Barr virus. J Clin Oncol 5:1673.
166. Aris RM, Maia DM, Neuringer IP et al. (1996) Post-transplantation lymphoproliferative disorder in the Epstein-Barr virus naive lung transplant recipient. Am J Respir Crit Care Med 154:1712.
167. Walker RC, Paya CV, Marshall WF et al. (1995) Pre-transplantation seronegative Epstein-Barr virus status is the primary risk factor for post-transplantation lymphoproliferative disorder in adult heart, lung, and other solid organ transplantations. J Heart Lung Transplant 14:214.
168. Armitage JM, Kormos RL, Stuart RS et al. (1991) Post-transplant lymphoproliferative disease in thoracic organ transplant patients: Ten years of cyclosporine-based immunosuppression. J Heart Lung Transplant 10:877.
169. Dodd GD, Ledesma-Medina J, Baron RL et al. (1992) Posttransplant lymphoproliferative disorder: Intrathoracic manifestations. Radiology 184:65.
170. Trulock EP (1997) State of the Art: Lung transplantation. Am J Respir Crit Care Med 155:789.
171. Harris KM, Schwartz ML, Slasky BS et al. (1987) Post transplantation cyclosporine-induced lymphoproliferative disorders: clinical and radiographic manifestations. Radiology 162:697.
172. Honda H, Barloon TJ, Franken EA et al. (1990) Clinical and radiologic features of malignant neoplasms in organ transplant recipients: Cyclosporine-treated vs untreated patients. AJR 154:271.
173. Garrett TJ, Chadburn A, Barr ML et al. (1993) Posttransplantation lymphoproliferative disorders treated with cyclophosphamide-doxorubicin-vincristine-prednisone chemotherapy. Cancer 72: 2782.
174. Leblond V, Sutton L, Dorent R et al. (1995) Lymphoproliferative disorders after organ transplantation: a report of 24 cases observed in a single center. J Clin Oncol 13:961.
175. Kradin RL, Mark EJ (1983) Benign lymphoid disorders of the lung with a theory regarding their development. Hum Pathol 14:857.

176. Strimland CV, Rosenow EC., III, Weiland LH et al. (1978) Lymphocytic interstitial pneumonitis. Review of 13 cases. Ann Intern Med 88:616.
177. Liebow AA, Carrington CB (1973) Diffuse pulmonary lymphoreticular infiltrations associated with dysproteinemia. Med Clin North Am 57:809.
178. Helman CA, Keeton GR, Benatar SR (1977) Lymphoid interstitial pneumonia with associated chronic active hepatitis and renal tubular acidosis. Am Rev Respir Dis 115:161.
179. Grieco H, Chinoy-Acharya P (1985) Lymphocytic interstitial pneumonia associated with the acquired immune deficiency syndrome. Am Rev Respir Dis 131:952.
180. Koss MN, Hochholzer L, Langloss JM et al. (1987) Lymphoid interstitial pneumonia: Clinicopathological and immunopathological findings in 18 cases. Pathology 19:178.
181. Perreault C, Cousineau S, D'Angelo G et al. (1985) Lymphoid interstitial pneumonia after allogeneic bone marrow transplantation. Cancer 55:1.
182. Feigin DS, Siegelman SS, Theros EG et al. (1977) Nonmalignant lymphoid disorders of the chest. AJR 129:901.
183. Glickstein M, Kornstein MJ, Pietra GG et al. (1986) Nonlymphomatous lymphoid disorders of the lung. AJR 147:227.
184. Carignan S, Staples CA, Muller NL (1995) Intrathoracic lymphoproliferative disorders in the immunocompromised patient: CT findings. Radiology 197:53.
185. McGuinness G, Scholes JV, Jagirdar JS et al. (1995) Unusual lymphoproliferative disorders in nine adults with HIV or AIDS: CT and pathologic findings. Radiology 197:59.
186. Banerjee D, Ahmad D (1982) Malignant lymphoma complicating lymphocytic interstitial pneumonia: A monoclonal B-cell neoplasm arising in a polyclonal lymphoproliferative disorder. Hum Pathol 13:780.
187. Schuurman HJ, Gooszen H, Tan I et al. (1987) Low-grade lymphoma of immature T-cell phenotype in a case of lymphocytic pneumonia and Sjögrens's syndrome. Histopathology 11:1193.
188. Steinberg AD, Seldin MF, Jaffe ES et al. (1988) Angioimmunoblastic lymphadenopathy with dysproteinemia. Ann Intern Med 108:575.
189. Pruzanski W (1980) Lymphadenopathy associated with dysgammaglobulinemia. Semin Hematol 17:44.
190. Libshitz HI, Clouser M, Zornoza J et al. (1977) Radiographic findings of immunoblastic lymphadenopathy and related immunoblastic proliferations. AJR 129:875.
191. Limpert J, MacMahon H, Variakajis D (1984) Angioimmunoblastic lymphadenopathy: Clinical and radiologic features. Radiology 152:27.
192. Liebow AA, Carrington CB, Friedman RJ (1972) Lymphomatoid granulomatosis. Hum Pathol 3:457.
193. Pisani RJ, De Remee RA (1990) Clinical implications of the histologic diagnosis of pulmonary lymphomatoid granulomatosis. Mayo Clin Proc 25:25.
194. Katzenstein A, Carrington C, Liebow A (1979) Lymphomatoid granulomatosis. A clinicopathologic study of 152 cases. Cancer 43:360.
195. Koss M, Hochholzer L, Langloss J et al. (1986) Lymphomatoid granulomatosis. A clinicopathologic study of 42 patients. Pathol 18:283.
196. Myers JC (1990) Lymphomatoid granulomatosis: Past, present, future? (editorial) Mayo Clin Proc 65:274.
197. James W, Odom R, Katzenstein A (1981) Cutaneous manifestations of lymphomatoid granulomatosis: report of forty-four patients and review of the literature. Arch Dermatol 1167:196.
198. Dee P, Arora N, Innes D Jr (1982) The pulmonary manifestations of lymphomatoid granulomatosis. Radiology 143:613.
199. Wechsler R, Steiner R, Israel H (1984) Chest radiograph in lymphomatoid granulomatosis: Comparison with Wegener's granulomatosis. AJR 142:79.
200. Lipford E., Jr, Margolick J, Longo D et al. (1988) Angiocentric immunoproliferative lesions: A clinicopathologic spectrum of post-thymic T-cell proliferations. Blood 72:1674.
201. Fauci A, Haynes B, Costa J et al. (1982) Lymphomatoid granulomatosis: Prospective clinical and therapeutic experience over 10 years. N Engl J Med 306:68.
202. Shank B, Kelley C, Nisce L et al. (1978) Radiation therapy for lymphomatoid granulomatosis. Cancer.
203. Castleman B, Iverson L, Menendez VP (1956) Localized mediastinal lymphnode hyperplasia resembling thymoma. Cancer 9:822.
204. Keller AR, Hochholzer L, Castleman B (1972) Hyaline-vascular and plasma-cell types of giant lymph node hyperplasia of the mediastinum and other locations. Cancer 29:670.
205. Charig MJ (1990) Mediastinal Castleman's disease: a missed pre-operative diagnosis? Clin Radiol 42:440.
206. Olscamp G, Weisbrod G, Sanders D et al. (1980) Castleman's disease: Unusual manifestations of an unusual disorder. Radiology 135:43.
207. Phelan MS (1982) Castleman's giant lymph node hyperplasia. Br J Radiol 55:158.
208. Fiore D, Biondetti PR, Calabro F et al. (1983) CT demonstration of bilateral Castleman tumours in the mediastinum. J Comput Assist Tomogr 7:719.
209. Onik G, Goodman PC (1983) CT of Castleman's disease. AJR 140:691.
210. Samuels TH, Hamilton PA, Ngan B (1990) Castleman's disease: Demonstration with computed tomography and angiography. J Can Assoc Radiol 154:380.
211. Frizzera G (1988) Castleman's disease and related disorders Semin Diagn Pathol 5:525.
212. Weisenberger DD, Nathwani BN, Winberg CD et al. (1985) Multicentric angiofollicular lymph node hyperplasia: a clinicopathologic study of 16 cases. Hum Pathol 16:162.
213. Frizzera G, Peterson BA, Bayrd ED et al. (1985) A systemic lymphoproliferative disorder with morphologic features of Castleman's disease: Clinical findings and clinicopathologic correlation in 15 patients. J Clin Oncol 3:1202.
214. Yoshizaki K, Matsuda T, Nishimoto H et al. (1989) Pathogenic significance of interleukin-6 (IL-6/BSF-2) in Castleman's disease. Blood 74:1360.

215. Leger-Ravet MB, Peuchmaur M, Devergne O et al. (1991) Interleukin-6 gene expression in Castleman's disease. Blood 78:2923.
216. Flendrig JA, Schillings PHM (1969) Benign giant lymphoma: The clinical signs and symptoms. Folia Med Neerl 12:119.
217. Marsh WL, Byland DJ, Heath VC et al. (1986) Osteoarticular and pulmonary manifestations of acute leukemia. Cancer 57:385.
218. Maile CW, Moore AV, Ulreich S et al. (1983) Chest radiographic-pathologic correlation in adult leukemia patients. Invest Radiol 81:495.
219. Kovalski R, Hansen-Flaschen J, Lodato RF, et al. (1990) Localized leukemic pulmonary infiltrates: Diagnosis by bronchoscopy and resolution with therapy. Chest 97:674.
220. Klatte EC, Yardley J, Smith EB et al. (1963) The pulmonary manifestations and complications of leukemia. AJR 89:598.
221. Lee MJ, Grogan L, Meehan S et al. (1991) Case report: Granulocytic sarcoma: CT characteristics. Clinical Radiol 43:57.
222. Green RA, Nichols NJ (1959) Pulmonary involvement in leukemia. Am Rev Respir Dis 80:833.
223. McKee LC, Collins RD (1974) Intravascular leukocyte thrombi and aggregates as a cause of morbidity and mortality in leukemia. Medicine 53:463.
224. van Buchem MA, Wondergen JH, Schultze Kool LJ et al. (1987) Pulmonary leukostasis: Radiologic-pathologic study. Radiology 165:739.
225. Lichtman, MA, Weed RI (1972) Peripheral cytoplasmic characteristics of leukocytes in monocytic leukemia: Relationship to clinical manifestations. Blood 40:52.
226. Singer C, Armstrong D, Rosen PP et al. (1979) Diffuse pulmonary infiltrates in immunocompromised patients: Prospective study of 80 cases. Am J Med 66:110.
227. Stover DE (1989) Diagnosis of pulmonary disease in the immunocompromised host. Sem Respir Med 10:89.
228. Tenholder MF, Hooper RG (1980) Pulmonary infiltrates in leukemia. Chest 78:468.
229. Polsky B, Armstrong D (1985) Infectious complications of neoplastic disease. Am J Infect Control 13:199.
230. Sickles EA, Greene WH, Wiernik PH (1975) Clinical presentation of infection in granulocytopenic patients. Arch Intern Med 135:715.
231. Sickles EA, Young VM, Green WH (1973) Pneumonia in acute leukemia. Ann Intern Med 1973;79:528.
232. Rivera MP, Jules-Elysee K, Stover DE (1994) Nontransplant chemotherapy immunosuppression. In: Niederman MS, Sarosi GA, Glassroth J, eds. Respiratory infections: a scientific basis for management. WB Saunders, Philadelphia, p. 163.
233. Kirby BD, Snyder KM, Meyer RD et al. (1980) Legionnaires' disease: Report of sixty-five nosocomial acquired cases and review of the literature. Medicine (Baltimore) 59:188.
234. Perez CR, Leigh MW (1991) *Mycoplasma pneumoniae* as the causative agent for pneumonia in the immunocompromised host. Chest 100:860.
235. Golomb HM, Hanauer SB (1981) Infectious complications associated with hairy cell leukemia. J Infec Dis 143:639.
236. Stewart DJ, Bodey GP (1981) Infections in hairy cell leukemia. Cancer 47:801.
237. Saravolatz LD, Burch KH, Fisher E et al. (1979) The compromised host and legionnaire's disease. Ann Intern Med 90:533.
238. Meyer RD, Edelstein PH, Kirby BD et al. (1980) Legionnaires disease. Unusual clinical and laboratory features. Ann Intern Med 93:240.
239. Feigin DS (1986) Nocardiosis of the lung: Chest radiographic findings in 21 cases. Radiology 159:9.
240. Libshitz HI, Pannu HK, Elting LS et al (1997) Tuberculosis in cancer patients: An update. J Thorac Imag 1997;12:41.
241. Kaplan MH, Armstrong D, Rosen P (1974) Tuberculosis complicating neoplastic disease. Cancer 33:850.
242. McLoud TC (1989) Pulmonary infections in the immunocompromised host. Radiol Clin North Am 27:1059.
243. McLoud TC (1991) Radiographic techniques. In: Shelhamer J, Pizzo PA, Parillo JE et al. eds. Respiratory disease in the immunocompromised host. JB Lippincott, Philadelphia, p.39.
244. Rolston KVI, Jones PG, Fainstein V et al. (1985) Pulmonary disease caused by rapidly growing mycobacteria in patients with cancer. Chest 87:503.
245. Horsburg CR Jr, Mason UG III, Farhi DC et al. (1985) Disseminated infection with Mycobacterium-avium intracellulare. A report of 13 cases and a review of the literature. Medicine (Baltimore) 64:36.
246. Ingram CW, Tanner DC, Durack DT et al. (1993) Disseminated infection with rapidly growing mycobacteria. Clin Infec Dis 16:463.
247. Bennet C, Vardiman J, Golomb HM (1986) Disseminated atypical mycobacterial infection in patients with hairy cell leukemia. Am J Med 80:891.
248. Pizzo PA (1993) Management of fever in patients with cancer and treatment-induced neutropenia. N Engl J Med 328:1323.
249. Degregorio MW, Lee WMF, Linker CA et al. (1982) Fungal infections in patients with Acute leukemia. Ann J Med 73:543.
250. Meyer RD, Young LS, Armstrong D et al. (1973) Aspergillosis complicating neoplastic disease. Am J Med 54:6.
251. Gerson SL, Talbot GH, Lusk E et al. (1985) Invasive pulmonary aspergillosis in adult acute leukemia: clinical clues to its diagnosis. J Clin Oncol 3:1109.
252. Albelda SM, Talbot GH, Gerson SL et al. (1985) Pulmonary consolidation and massive hemoptysis in invasive pulmonary aspergillosis. Influence of bone marrow recovery in patients with acute leukemia. Am Rev Respir Dis 131:115.
253. Kuhlman JE, Fishman EK, Burch PA et al. (1988) CT of invasive pulmonary aspergillosis. AJR 150:1015.
254. Kuhlman JE, Fishman EK, Burch PA et al. (1987) Invasive pulmonary aspergillosis in acute leukemia: the contribution of CT to early diagnosis and aggressive management. Chest 92:95.

255. Freeberg G, Stover DE, Levine S et al. (1990) Spectrum of pulmonary aspergillosis in immunocompromised hosts. Chest 31(Supp).
256. Mehta J, Kelsey S, Chu P et al. (1997) Ampho-B lipid complex (ABLC) for the treatment of confirmed or presumed fungal infections in immunocompromised patients with hematologic malignancies. BMT 20:39.
257. Kovacs JA, Hiemenz JW, Macher Am et al. (1984) *Pneumocystis carinii* pneumonia: A comparison between patients with the acquired immunodeficiency syndrome and patients with other immunodeficiencies. Ann Intern Med 100:663.
258. DeLorenzo LJ, Huang CT, Maguire GP et al. (1987) Roentgenographic patterns of *Pneumocystis carinii* pneumonia. Chest 91:323.
259. Masur H, Meier P, McCutchan JA et al. (1990) Consensus statement on the use of corticosteroids as adjunctive therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. N Engl J Med 323:1500.
260. Limper AH, Offord KP, Smith TF et al. *Pneumocystis carinii* pneumonia: Differences in lung parasite number and inflammation in patients with and without AIDS. Am Rev Respir Dis 140:1204.
261. Smith RL, El Sadr WM, Lewis ML (1988) Correlation of bronchoalveolar lavage cell populations with clinical severity of *Pneumocystis carinii* pneumonia. Chest 92:60.
262. Mason GR, Hashimoto CH, Dickman PS et al. (1989) Prognostic implications of bronchoalveolar lavage neutrophilia in patients with *Pneumocystis carinii* pneumonia and AIDS. Am Rev Respir Dis 139:1336.
263. Wingard JR (1993) Viral infections in leukemia and bone marrow transplant patients. Leuk and Lymph 11:115.
264. Saral R, Ambinder RF, Burns WH et al. (1983) Acyclovir prophylaxis against recrudescent herpes simplex virus infections in leukemic patients: a randomized, double-blind placebo controlled study. Ann Intern Med 99:773.
265. Wade JC, Bustamante CI, Newman KA et al. (1988) Cytomegalovirus: an important pathogen for adults receiving induction therapy for acute leukemia. 28th Annual Intersci. Conf. on Antimicrobial Agents and Chemotherapy Abstract No. 1394.
266. Rosen P, Hadju S (1968) Cytomegalovirus inclusion disease in adults. J Clin Pathol 21:311.
267. Cooper JA Jr, White DA, Matthay R (1986) Drug-induced pulmonary disease. Part 1: Cytotoxic drugs. Am Rev Respir Dis 133:321.
268. Stover DE (1991) Adverse effects of treatment In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. Marcel-Dekker, New York, pp.
269. Gibson PG, Bryant DH, Morgan GW (1988) Radiation-induced lung injury: A hypersensitivity pneumonitis? Ann Intern Med 109:288.
270. Gross N (1977) Pulmonary effects of radiation therapy. Ann Intern Med 86:81–
271. Lichtenstein H (1960) X-ray diagnosis of radiation injury of the lung. Dis Chest 38:294.
272. Libshitz HI (1984) Radiation-induced pulmonary change: CT findings. J Comput Assist Tomogr 8:15.
273. Roswit B, White DC (1977) Severe radiation injuries of the lung. AJR 129:127.
274. Bachman A, Macken K (1959) Pleural effusions following supervoltage radiation for breast carcinoma. Radiology 72:699.
275. Libshitz HI, Brosof A, Southard ME (1973) The radiographic appearance of the chest following extended field radiation therapy for Hodgkin's disease. Cancer 32:206.
276. Rosenow EC III, Myers JL, Swensen SJ et al. (1992) Drug-induced pulmonary disease: An update. Chest 102:239.
277. Jules-Elysee K, White DA (1990) Bleomycin-induced pulmonary toxicity. Clin Chest Med 11:1.
278. Weiss RB, Donehower RC, Wiernick PH et al. (1990) Hypersensitivity reactions to taxol. J Clin Oncol 8:1263.
279. White DA, Rankin JA, Stover DE et al. (1989) Methotrexate pneumonitis: bronchoalveolar lavage findings suggest an immunologic disorder. Am Rev Respir Dis 139:18.
280. Orwoll ES, Kiessling P, Patterson R (1978) Interstitial pneumonia from mitomycin. Ann Intern Med 89:352.
281. Sostman HD, Matthay RA, Putman CE (1976) Methotrexate-induced pneumonitis. Medicine 55:331.
282. Weiss RB, Poster DS, Penta JS (1981) The nitrosoureas and pulmonary toxicity. Cancer Treat Rev 8:111.
283. Bellamy EA, Husband JE, Blaquiere RM et al. (1985) Bleomycin-related lung damage: CT evidence. Radiology 156:155.
284. Huang ME, Ye YC, Chen SR et al. (1988) Use of all-*trans* retinoic acid in the treatment of acute promyelocytic leukemia. Blood 72:567.
285. Castaigne S, Chomienne C, Daniel MT et al. (1990) All-*trans* retinoic acid as a differentiation therapy for acute promyelocytic leukemia. Clinical results. Blood 76:1704.
286. Frankle SR, Eardley A, Lauwers G et al. (1992) 'Retinoic acid syndrome' in acute promyelocytic leukemia. Ann Intern Med 117:292.
287. Wiley JS, Firkin FC (1995) Reduction of pulmonary toxicity by prednisone prophylaxis during all-*trans* retinoic acid treatment of acute promyelocytic leukemia. Leukemia 9:774.
288. Margolin KA, Raynor AA, Hawkins MJ et al. (1989) Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. J Clin Oncol 7:486.
289. Cockerill FR III, Wilso WR, Carpenter HA et al. (1985) Open lung biopsy in immunocompromised patients. Arch Intern Med 145:1398.
290. Tenholder MF, Hooper RG (1980) Pulmonary hemorrhage in the immunocompromised host: an elusive reality (abstract). Am Rev Respir Dis 121 (suppl):198.