Fisher AJ, Lordan JL, Dark JH, Corris PA (2005) Azithromycin reverses airflow obstruction in established bronchiolitis obliterans syndrome. Am J Respir Crit Care Med 172:772–775

Yeldandi V, Laghi F, McCabe MA, Larson R, O'Keefe P, Husain A, Montoya A, Garrity ER Jr. (1995) Aspergillus and lung transplantation. J Heart Lung Transplant 14:883–890

Yousem SA, Berry GJ, Cagle PT, Chamberlain D, Husain AN, Hruban RH, Marchevsky A, Ohori NP, Ritter J, Stewart S, Tazelaar HD (1996) Revision of the 1990 working formulation for the classification of pulmonary allograft rejection: Lung Rejection Study Group. J Heart Lung Transplant 15:1–15

Zenati M, Dowling RD, Dummer JS, Paradis IL, Arena VC, Armitage JM, Kormos RL, Hardesty RL, Griffith BP (1990) Influence of the donor lung on development of early infections in lung transplant recipients. J Heart Transplant 9:502–508; discussion 508–509

Zhang L, Irion K, da Silva Porto N, Abreu e Silva F (1999) High-resolution computed tomography in pediatric patients with postinfectious bronchiolitis obliterans. J Thorac Imaging 14:85–89

Bone Marrow Transplantation

6

6.1 Hematopoietic Transplantation

Jorge Sierra

CONTENTS

J. Sierra, MD, PhD
Professor of Medicine, Director, Clinical Hematology and Hematopoietic Transplantation Program, Hospital de la Santa Creu i Sant Pau, Universitat Autónoma de Barcelona, Barcelona, Spain

6.1.1 Introduction

Hematopoietic transplantation is increasingly being used as treatment for a variety of severe diseases. Data from International Registries indicate that more than 25,000 transplants are performed every year in Europe, and a similar number in the United States (US) (Copelan 2006; Gratwohl et al. 2007). The objectives of this procedure are: (1) to replace hematopoiesis affected by a severe and irreversible disorder, (2) to rescue the patient from intense marrow toxicity induced by high-dose chemotherapy and/or radiation, and (3) to use a fraction of cells contained in the graft as anti-tumor immunotherapy. Of note, one or more of these objectives may be pursued in a particular situation; for example, in a patient with acute leukemia, transplantation aims to replace the neoplastic hematopoiesis by administering high-dose cytotoxic therapy and taking advantage of the graft-versus-leukemia effect of donor T-lymphocytes from the graft. In contrast, in aplastic anemia the only goal of the procedure is to restore an adequate hematopoiesis.

There are several transplantation modalities, depending on the type of donor and the source of hematopoietic cells. In all cases, the donor has to be identical or very similar to the recipient in the major histocompatibility system of human leukocyte antigens (HLA). If the donor is an identical twin of the recipient the transplant is named syngeneic, whereas if the donor is another type of individual the denomination is allogeneic; in the latter circumstance the donor may be related or unrelated to the patient. Frequently, the patient acts as his own hematopoietic donor and the name for such an approach is autologous transplantation. In this situation, the transplanted cells have to be collected and cryopreserved before the administration of high-dose therapy.

Regarding the source of hematopoietic stem cells, the transplant may be from bone marrow, mobilized peripheral blood or umbilical cord blood.

6.1.2 History

In 1939, Osgood administered repeated injections of a small amount of intravenous bone marrow to treat aplastic anemia without observing a response (Thomas 1999). One year later, Morrison unsuccessfully treated another aplastic anemia patient by infusing marrow cells into the sternum. During the Second World War, the Atomic Energy Commission of the US promoted investigations on the intravenous administration of bone marrow cells to irradiated dogs. The low dose of radiation, 350 rads or 3.5 Gy, was insufficient to facilitate the engraftment of infused marrow.

Between 1949 and 1954, Jacobson, Lorenz, Barnes and Loutit made important experiments in mice showing that cells from the spleen or the bone marrow protected from death caused by radiation. Of note, a different evolution was observed after syngeneic and allogeneic transplantation, since mice in the latter group usually died due to complications defined as "secondary disease". This experience anticipated the most relevant problem after this type of transplantation, graft-versus-host disease (GVHD).

In 1957, Thomas and Ferrebee published a report on six patients with end-stage hematologic cancer who received extensive radiation and intravenous marrow cells from healthy donors (Thomas et al. 1957). This pioneering experience in human hematopoietic transplantation led to engraftment in only one case. One year later, Kurnick described the first two cases of autologous transplantation of human marrow cells to treat radiation toxicity.

In 1959 Thomas published the first series of successful bone marrow transplants in humans using identical twin donors. One year before, Dausset and van Rood had discovered the HLA system, enabling the possibility of performing allogeneic transplantation with a reasonable chance of success. In 1965, Mathé et al. were the first to obtain a sustained allogeneic engraftment, although the patient subsequently died from chronic GVHD.

In 1969, the Seattle transplant team, under the leadership of Donnall Thomas, established the program of hematopoietic transplantation as a treatment for severe aplastic anemia and advanced-stage acute leukemia. These investigators demonstrated that this treatment allowed long-term survival in a small fraction of otherwise incurable patients. The results encouraged this group to investigate this approach in earlier phases of disease evolution. In 1972 and 1974 the Seattle team published two reports in aplastic anemia patients achieving 40% long-term survival. These experiences increased the interest about marrow transplantation in other Western countries during the second half of the 1970s.

The first unrelated donor marrow transplantation was performed in 1972 (Thomas 1999). In 1973, the Anthony Nolan Registry of the United Kingdom (UK) was created to increase the access to HLA-typed unrelated volunteers. However, due to the initial complexity of donor search, these transplants were infrequent until the second half of the 1980s.

In 1989, Gluckman et al. performed the first human transplantation with hematopoietic cells from the umbilical cord blood of a newborn, in a patient with Fanconi anemia. One year later, in 1990, Donnall Thomas was awarded with the Nobel Prize of Medicine for his pioneer work and achievements in hematopoietic transplantation field.

Until the late 1980s, bone marrow was the stem cell source in practically all transplants. In those days it became evident that large numbers of hematopoietic progenitors could be obtained from peripheral blood during the recovery phase following chemotherapy. The introduction of colony-stimulating factors (CSF) in clinical practice led to the same observation: these agents were able to mobilize large amounts of hematopoietic progenitor cells to peripheral blood. Of note, the combination of chemotherapy and CSF increased the harvestable cells by means of apheresis devices compared with either alone. In autologous transplants, peripheral blood rapidly replaced bone marrow as the source of hematopoietic progenitors. In contrast, in allogeneic procedures the introduction of peripheral blood was slower. The reason was the particular concern that GVHD could be very frequent and severe, since peripheral blood contains 10 times more T-lymphocytes than bone marrow. However, this drawback was not confirmed by clinical experience and since 1995 the proportion of peripheral blood transplants has progressively increased, accounting now for more than 70% of allogeneic procedures.

6.1.3 Indications

Hematopoietic transplantation is mostly indicated for hematologic malignancies that can be treated with high doses of cytotoxic agents (Copelan 2006). Figure 6.1.1 reflects the most frequent diagnoses in patients with neoplastic diseases. Current indications and practice of this treatment have been recently reviewed (Gratwohl et al. 2007). Patients with lymphoma, myeloma, acute leukemia or myelodysplasia may benefit from this procedure, among others. Hematopoietic transplantation is also useful for replacing insufficient or defective cells derived from the marrow progenitors. This is the case in patients with marrow aplasia, central cytopenias, paroxysmal nocturnal hemoglobinuria, marrow myelofibrosis or inherited disorders of metabolism. Depending on the disease and degree of marrow involvement, patients will be suitable for allogeneic, autologous transplantation, or both. Of note, progress in non-transplant therapies is limiting some classical indications for this procedure. A good example of this is chronic myelogenous leukemia, where the introduction of imatinib, a bcr-abl tyrosine kinase inhibitor, has dramatically decreased the number of transplants for this disease (Baccarani et al. 2006). On the other hand, studies showing no superiority of autologous transplantation over conventional treatment in patients with breast cancer mean that the former is almost never used now.

6.1.4 Transplantation Technique

The main phases of hematopoietic transplantation procedure are as follows (Fig. 6.1.2): (1) identification of stem cell donor and stem cell source, followed in autologous transplants by the harvest of hematopoietic cells, (2) administration of a preparative regimen (conditioning) to damage the recipient's hematopoiesis and immune system, to create marrow space, and eventually to treat the neoplastic disease, (3) collection and infusion of hematopoietic progenitors from the donor, or thawing and administration of the autologous stem cells, (4) supportive measures until hematologic and immune recoveries are achieved, (5) in allogeneic transplants, management of the immune interaction between donor cells and recipient tissues potentially leading to graft rejection and/or GVHD.

6.1.4.1 Donor Selection in Allogeneic Transplants

HLA compatibility between donor and recipient may be studied by serologic methods or DNA techniques. The required resolution of HLA-typing methods is lower when recipient and donor are siblings compared to unrelated donor transplantation. In the latter circumstance, high-resolution allele typing is necessary for an adequate HLA matching. HLA-A,

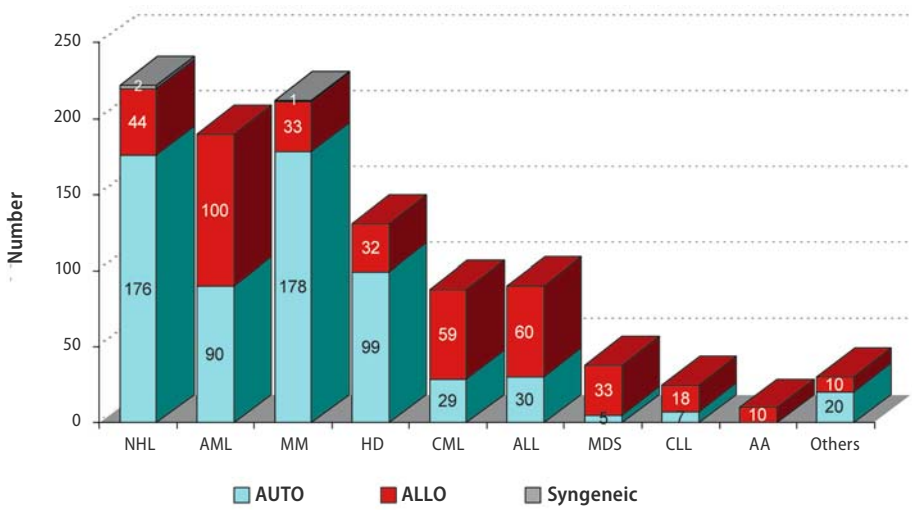


Fig. 6.1.1. Indications of autologous, allogeneic or syngeneic hematopoietic transplantation at the Hospital de la Santa Creu i Sant Pau in Barcelona. (*AA*, Aplastic anemia; *ALL*, acute lymphoblastic leukemia; *AML*, acute myeloid leukemia; *CLL*, chronic lymphocytic leukemia; *CML*, chronic myelogenous leukemia; *HD*, Hodgkin's disease; *MDS*, myelodysplastic syndrome; *MM*, multiple myeloma; *NHL*, non-Hodgkin's lymphoma)

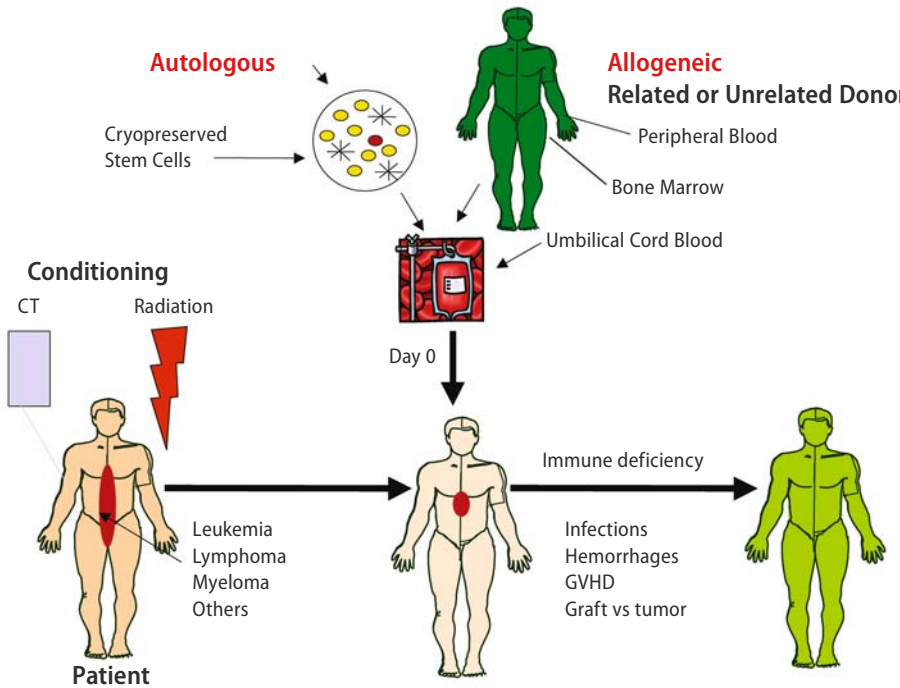


Fig. 6.1.2. Schema of hematopoietic stem cell transplantation. The patient receives conditioning regimen with chemotherapy (*CT*) and/or radiation to create marrow space and reduce the tumor. On day 0, autologous or allogeneic hematopoietic cells are administered through a right atrial catheter. The patient experiences profound aplasia and immune suppression. During this period immediate toxicity and opportunistic infections appear. After hematologic recovery, recipient tissues are recognized by immune-competent donor-derived T-cells and graft-versus-host disease (*GVHD*) develops. Graft-versus-tumor effect contributes to the eradication of residual neoplastic cells

-B, and -DR antigens are analyzed in transplants between siblings, whereas HLA-A, -B, -C, DRB1 and DQB1 alleles are studied in unrelated pairs. No more than one antigen mismatch is acceptable if the donor is a relative of the recipient, and no more than one allele mismatch in transplants from unrelated volunteers. In umbilical cord blood transplantation, units are selected by HLA-A and -B serologic or low-resolution DNA typing, whereas allele identification is required for matching at HLA-DRB1. Up to two HLA disparities are acceptable in this type of transplantation.

6.1.4.2 Hematopoietic Stem Cell Harvest

Multiple punctures in the iliac crests (more than 100–150) are necessary to aspirate enough marrow cells for transplantation. This procedure is made under general or less frequently regional anesthesia. Harvest of marrow cells from the sternum is exceptional. Marrow blood (1000–1500 ml) has to be obtained and subsequently filtered to eliminate bone fragments. This product is collected in transfusion bags with red cells being removed in case of donor–recipient major ABO incompatibility. The amount of hematopoietic progenitors of an adequate marrow product is at least 1×10^6 CD34-positive cells/kg of the recipient. Administering a high marrow cell dose is particularly relevant for improving the outcome after unrelated transplantation.

Hematopoietic stem cells may also be obtained from the peripheral blood by means of apheresis machines. These devices are sophisticated centrifuges which separate circulating blood cells and allow their selective aspiration. To mobilize hematopoietic progenitor cells from marrow to blood, CSF have to be administered to the donor. In autologous harvesting chemotherapy is frequently combined with CSF. The usual dose of granulocyte CSF (G-CSF) is 10 µg/kg daily if used alone and 5 µg/kg when combined with chemotherapy. This chemotherapy may be the patient's standard treatment or consist of a single high dose of cyclophosphamide (1–3 g IV). In chemotherapy-plus-CSF mobilization, peripheral blood stem cell collection usually begins on day 11–14 after the start of treatment, whereas in CSF priming alone harvesting is initiated on day 4 or 5 of therapy. In most instances, one to four apheresis sessions are required to obtain at least 2×10^6 CD34+ cells/kg, the adequate number of cells for transplantation. In autologous collection from heavily pretreated patients it is relatively frequent to observe a low

number of circulating CD34+ cells during the mobilization attempt. This circumstance is known as mobilization failure.

Collection of cord blood stem cells consists of canalization of the umbilical vein after delivery to obtain, by gravidity and pressure on the placenta, 100–150 ml of blood. An adequate cord blood unit for transplantation contains at least 5×10^6 total CD34+ cells. The infused cell dose has to be at least 1×10^5 CD34 cells/kg or 2×10^7 nucleated cells (NC)/kg.

All cell products for transplantation have to be bacteriologically and virologically tested. In autologous and in cord blood transplantation the cells collected are cryopreserved and stored for future use.

6.1.4.3 Conditioning Regimen

The conditioning or preparative regimen includes chemotherapy, radiation or both. There are two categories of conditioning: (1) high-dose conditioning also known as myeloablative, and (2) reduced intensity conditioning or non-myeloablative.

High-dose conditioning has a powerful antineoplastic effect but significant toxicity precluding its administration to elderly or debilitated patients. This type of regimen leads to early full engraftment of donor cells. Reduced intensity conditioning has an immunosuppressive effect with low anti-tumor activity (Martino et al. 2001). This modality of preparative approach has improved short-term toxicity in old and sick patients. Engraftment of donor cells is progressive with full replacement of recipient hematopoiesis and lymphopoiesis (chimerism) being achieved after several weeks or months (Fig. 6.1.3). In some circumstances, complete hematopoietic and immune recovery from transplanted cells requires the infusion of additional donor T-lymphocytes.

Cytotoxic drugs commonly administered in conditioning regimens are alkylating agents such as cyclophosphamide, busulphan or melphalan, topoisomerase inhibitors, antimetabolites such as cytarabine, nitrosoureas such as BCNU and purine analogs such as fludarabine. Total body irradiation is frequently added in high dose (8–12 Gy) or as part of reduced-intensity conditioning (2 Gy). Polyclonal [antithymocyte globulin (ATG)] or monoclonal (Campath 1H) antibodies may also be incorporated into the preparative regimen to facilitate engraftment and decrease GVHD after transplantation.

6.1.4.4 Stem Cell Infusion

A right atrial catheter has to be placed in the recipient of hematopoietic transplantation. The collected cells are infused freshly, or after rapid thawing in autologous or cord blood transplantation. Infusion duration is variable, from minutes to more than 1 h, depending on the volume to be administered. Vitals have to be monitored every 10–15 min. The main complications of cell infusion are chills, fluid overload and, infrequently, fat emboli in the lungs.

6.1.4.5 Graft-Versus-Host Disease Prophylaxis in Allogeneic Transplantation

Allogeneic stem cell infusion without post-transplant immunosuppression or T-cell depletion of the graft is followed by hyperacute and lethal GVHD. In T-cell replete transplantation, prophylaxis of this complication has to be administered. This consists of cyclosporine or tacrolimus together with methotrexate, prednisone, mycophenolate mofetil (MMF), rapamycin or the combination of two of these drugs. Adverse effects of cyclosporine and tacrolimus are renal and central nervous system toxicities, hyperbilirubinemia and thrombotic microangiopathy. Methotrexate prophylaxis is associated with mucositis, delayed engraftment, and liver toxicity. Prednisone facilitates the development of fungal and viral infections. Mycophenolate and rapamycin lead to gastrointestinal secondary effects.

6.1.4.6 Post-Transplant Supportive Measures

Transplanted patients develop profound aplasia and immunosuppression as a consequence of the conditioning regimen. During the neutropenic period it is recommended to keep the patients in isolated rooms equipped with high-efficiency particulate air (HEPA) filters. Diet has to be free of germ contamination, and oral antibacterial, antifungal, and

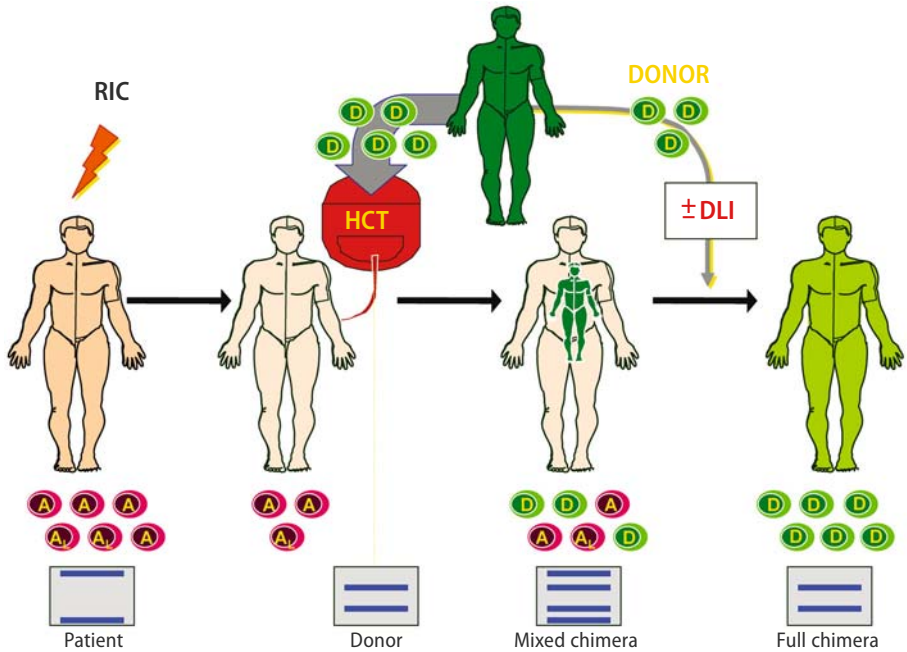


Fig. 6.1.3. Allogeneic hematopoietic cell transplantation (HCT) after reduced intensity conditioning (*RIC*). In the first weeks after transplant there is coexistence of donor and recipient hematopoietic cells (mixed chimerism). Spontaneously or after donor lymphocyte infusions (*DLI*) full donor chimerism is established

antiviral prophylaxis is administered. Red cell and platelet transfusions are given until these cells are produced by the graft. In some circumstances, CSF are administered to accelerate hematological recovery. In patients with severe hypogammaglobulinemia the substitutive intravenous supply of immunoglobulins is recommended.

6.1.4.7 Hematopoietic and Immune Reconstitution from Transplanted Cells

More than 0.5×10^9/l neutrophils are achieved at a median of 10–14 days after transplantation of peripheral blood progenitor cells, 21–28 days after marrow infusion, and 25–35 days when umbilical cord blood is the hematopoietic source. A self-sustained platelet count above 20×10^9/l is usually reached 5 days to 3 weeks after neutrophil recovery. Full immune reconstitution is slow and takes several months. CD4+ cell counts are low after transplantation. B-cell production and function are also impaired after the procedure. New ontogeny of the immune system after allogeneic transplantation requires vaccination against the most common pathogens, once the ability to effectively produce antibodies is restored.

As soon as hematopoietic cells appear in marrow and in blood, their origin from the donor may be demonstrated by several techniques. These include, among others, studies of red cell antigens, sex disparities, and molecular methods such as analysis of the variable number of tandem repeats (VNTR). The circumstance of donor hematopoiesis in the recipient is known as chimerism. This chimerism may be full donor or mixed with the persistence of a variable proportion of host cells. Chimerism is early and complete when high-dose conditioning is administered. In contrast, mixed chimerism for weeks or months may be observed after reduced-intensity conditioning transplantation. Persistent mixed chimerism is frequently associated with disease recurrence or graft rejection. On the other hand, full donor chimerism is usually a requisite for developing GVHD.

6.1.5 Transplant Complications

6.1.5.1 Graft Failure

Lack of engraftment (or primary graft failure) is exceptional in transplantation after full-dose conditioning for neoplastic diseases, provided that the patients receive an adequate hematopoietic cell dose of autologous origin or from an HLA-identical sibling. Transplantation from unrelated donors, par-

ticularly if there is some degree of HLA disparity, and from umbilical cord blood increases the risk of graft failure, as well as the administration of reduced-intensity conditioning. Graft failure is also more frequent if the patient has preserved immune integrity before the procedure, such as in aplastic anemia or chronic myeloid leukemia without prior intensive treatment. In the high-risk circumstances mentioned, the frequency of this complication ranges between 5% and 20%.

Secondary graft failure, also known as poor graft function, develops in patients with severe systemic infections early post-transplant and in those with CMV replication after the procedure. Parvovirus B19 is another pathogen that has to be investigated in cases of secondary graft failure. Certain drugs used after transplantation such as methotrexate, cotrimoxazole, ganciclovir, amphotericin B, and mycophenolate mofetil are myelotoxic and may cause or contribute to poor graft function.

6.1.5.2 Opportunistic Infections

A wide variety of infectious complications may develop after transplantation (Fig. 6.1.4). During the neutropenic period, fever appears in practically all patients. The causative pathogens are usually Gram positive cocci entering the body through the intravenous catheter or as a consequence of severe oral mucositis. Gram-negative sepsis may also occur with the more frequent entry route being the gastrointestinal tract.

Bacterial, viral or fungal pneumonia is also relatively common after transplantation. Computed tomography of the thorax is useful for early detection of this complication and the radiologic findings will be extensively reviewed in this book. In patients with pulmonary infection, bacteria, fungi, community viruses, CMV, and *Pneumocystis carinii* have to be investigated by antigenemia or polymerase chain reaction (PCR) in blood, nasopharyngeal cultures and direct staining and cultures of bronchoalveolar brushing and lavage. Transbronchial or transparietal lung biopsy may be necessary for an etiologic diagnosis. If the pulmonary complication is not under adequate control severe respiratory failure may develop requiring mechanical ventilation.

Viral infections that occur after transplantation are not limited to the lung. Herpes simplex infections are frequent early after the procedure, manifesting as oral vesicles or ulcerations. Less frequent is genital involvement by herpes simple virus, hepatitis or encephalitis. Herpes zoster and varicella reactivate in most patients, particularly if aciclovir prophylaxis is discontinued. Occasionally, severe cerebral arteritis or pneumonia caused by this virus may occur. CMV infection is frequent after transplantation and has to be regularly monitored by antigenemia and/or PCR for early treatment avoiding CMV disease. Epstein Barr virus (EBV) infection and EBV-associated lymphoproliferative disorders have also to be tested on a regular basis, especially in transplants with "in

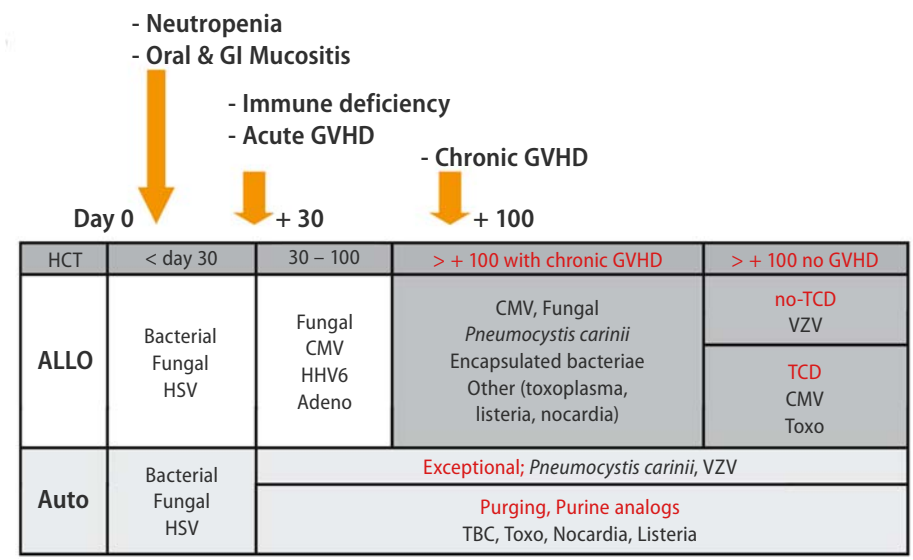


Fig. 6.1.4. Pattern of infections after hematopoietic cell transplantation (*HCT*). (*Adeno*, adenovirus; *CMV*, cytomegalovirus; *GVHD*, graft-versus-host disease; *HHV6*, human herpes virus 6; *HSV*, herpes simple virus; *TCD*, T-cell depletion; *TOXO*, toxoplasma; *VZV*, varicella zoster virus)

vivo" or "ex vivo" T-cell depletion. Rituximab™, a monoclonal antibody against cells expressing CD20 antigen, is an effective treatment of post-transplant EBV-related disorders.

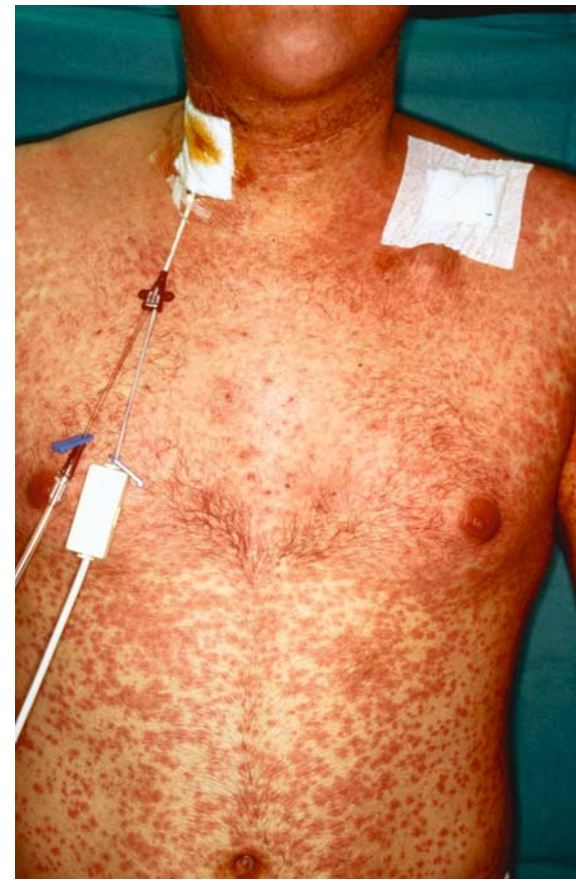
Aspergillus infection is frequent after transplantation, despite galactomannan antigen monitoring and antifungal prophylaxis. Prolonged neutropenia, GVHD, and immunosuppressive treatment predispose to this complication. Angioinvasive pulmonary involvement is the most frequent clinical picture. Bronchial aspergillosis and solitary lung lesions are less common. If the disease does not respond to treatment, widespread aspergillosis may occur with cerebral disease. In the latter situation, mortality is practically constant.

Other filamentous fungi and *Candida* sp. infection are much less frequent than aspergillosis, although they have also to be taken into account in the differential diagnosis of patients with suspected fungal infection.

Occasional post-transplant infections include toxoplasma or tuberculosis of the lungs and/or central nervous system disease, and *Pneumocystis carinii* pneumonia. These diseases respond well to treatment and because of that early and precise diagnosis is mandatory.

6.1.5.3 Graft-Versus-Host Disease

The recognition of several tissues of the recipient by the immune-competent T-cells from the donor causes GVHD. This phenomenon occurs in 50%–90% of allogeneic transplants, being more frequent in cases of HLA disparity, transplantation from unrelated donors, and in male recipients transplanted from female donors. There are two forms of GVHD with a different clinical picture. The acute form develops before day 100 after transplant and involves skin, liver, and gastrointestinal tract. Patients have erythema, papulae (Fig. 6.1.5a) or epidermolysis (Fig. 6.1.5b), hepatitis and/or cholestasis, vomiting and diarrhea. Chronic GVHD is diagnosed when present after day 100. This complication manifests as lichenoid, sclerodermiform or hypopigmented skin lesions, mucosal and ocular involvement (Sicca syndrome), restrictive or obstructive (obliterans bronchiolitis) lung disease, chronic hepatitis and/or cholestasis, and less frequently muscular or fasciae inflammation. The treatment of GVHD consists of immunosuppressive and immunomodulatory drugs such as steroids, cyclosporine or tacrolimus, mycophenolate mofetil, thalidomide, rapamycin, and polyclonal or monoclonal anti T-cell antibodies. The overall complete response rate to treatment for GVHD is higher than 50%. In contrast, patients who do not respond or have a relapse have poor outcome in terms of long-term survival. In patients transplanted for malignancies, the best scenario is to develop moderate and sustained GVHD which


a

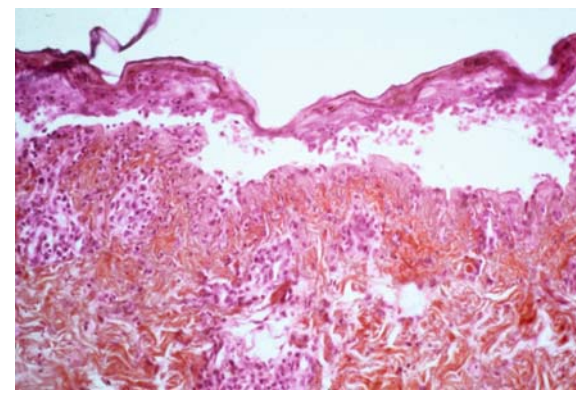

b

Fig. 6.1.5a,b. Acute graft-versus-host disease of the skin with **a** papulae and **b** epidermolysis

responds to treatment. This circumstance is associated with decreased recurrence of the neoplastic disease due to the powerful graft-versus-tumor effect (Martino et al. 2002).

6.1.5.4 Other Complications

Liver veno occlusive disease, recently defined as sinusoid obstruction syndrome (SOS), may develop in the first 40 days after transplantation as a consequence of a high-dose conditioning regimen. Prior liver disease predisposes to this complication which manifests as cholestasis and fluid retention secondary to portal hypertension and renal dysfunction. Current treatment of SOS consists of fluid restriction, diuretics, and defibrotide. Although transiently severe, the evolution is favorable in most cases.

Renal insufficiency, usually reversible, is common after the procedure and commonly related to the use of nephrotoxic drugs such as ciclosporin, tacrolimus, vancomycin or amphotericin B. In a minority of instances dialysis may be required. Microangiopathic hemolysis and thrombocytopenia secondary to ciclosporin or tacrolimus may further impair renal function. Hemorrhagic cystitis is also a possible complication of the transplant and is related to the use of high-dose cyclophosphamide, bacterial or viral infection (adenovirus) or mucosal GVHD. Infertility is almost inevitable after transplantation, unless a reduced-intensity conditioning regimen is administered.

With the improvement of long-term results of hematopoietic transplantation, late complications of the procedure are becoming evident. Cataracts, hypothyroidism, growth retardation, impaired hair growth, sexual dysfunction, and depression among other disorders have to be carefully evaluated and treated. However, more than 80% of transplant survivors are asymptomatic and able to carry on with a normal life.

6.1.6 Results

The results of hematopoietic transplantation depend mainly on age, disease stage, and type of procedure (Copelan 2006). The results are best in young pa-

Table 6.1.1. Results according to type of hematopoietic transplantation and disease-stage (modified from reference Copelan 2006). (CP, Chronic phase; NHL, non-Hodgkin's lymphoma)

	100-Day mortality	5-Year relapse	5-Year event-free survival
Autologous			
Diffuse large-cell NHL			
1st CT-sensitive relapse	3–5	45–52	45–50
2nd CT-sensitive relapse	5–8	47–65	30–35
Refractory	10–20	70–85	5–10
Allogeneic			
Acute myeloid leukemia			
1st complete remission	7–10	25–38	55–65
2nd complete remission	10–20	40–60	30–40
Refractory	30–40	40–55	15–20
Chronic myeloid leukemia			
CP<1 year after diagnosis	5–10	10–25	70–80
CP>1 year after diagnosis	10–15	25–40	50–60
Accelerated	15–20	45–55	30–35
Blastic	35–45	40–60	5–15

tients with early disease transplanted from HLA-identical siblings. The use of adult unrelated donors has an approximately 15% higher procedure-related mortality and decreased survival as compared to HLA-identical sibling transplants. An additional 10% mortality should be generally predicted if the stem cell source is umbilical cord blood. Autografting has a lower procedure-related mortality but a higher relapse rate than allogeneic transplantation. The same phenomenon is observed after reduced-intensity conditioning compared to conventional allogeneic transplant, a lower mortality but more recurrences. The main results obtained in the different disease categories are summarized in Table 6.1.1.

6.1.7 Future Developments

Hematopoietic transplantation is a field of active research. New methods are being developed to refine the transplantation technique to make it safer and more effective. Conditioning regimens targeted to neoplastic and/or immune cells and to preserve extrahematological tissues are under investigation. Antigen or molecularly targeted treatment may also be useful for eradicating minimal residual disease after the procedure (Ravandi et al. 2004). Improved knowledge of the mechanism of GVHD and the graft-versus-tumor effect may allow them to be separated, to achieve control over the neoplasia without undesirable toxicity. Progress in the field of immune tolerance may allow the surpassing of HLA barriers in some donor–recipient pairs, and the safe performance of HLA-haploidentical transplants. Finally, the selective use of hematopoietic and mesenchymal cell subsets may improve engraftment and allow further exploitation of these cells for tissue repair or as a form of immune modulation and therapy (Xia et al. 2004; Lazarus et al. 2005).

References

Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F et al (2006) Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 108:1809–1820

Copelan EA (2006) Hematopoietic stem-cell transplantation. N Engl J Med 354:1813–1826

Gratwohl A, Baldomero H, Frauendorfer K, Urbano-Ispizua A, Niederwieser D for the Joint Accreditation Committee of the International Society for Cellular Therapy ISCT and the European Group for Blood and Marrow Transplantation EBMT (JACIE) (2007). Results of the EBMT activity survey 2005 on haematopoietic stem cell transplantation: focus on increasing use of unrelated donors. Bone Marrow Transplant 39:71–87

Lazarus HM, Koc ON, Devine SM, Curtin P, Maziarz RT, Holland HK et al (2005) Cotransplantation of HLA-identical sibling culture-expanded mesenchymal stem cells and hematopoietic stem cells in hematologic malignancy patients. Biol Blood Marrow Transplant 11:389–398

Martino R, Caballero MD, Canals C, Simon JA, Solano C, Urbano-Ispizua A et al (2001) Allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning: results of a prospective multicentre study. Br J Haematol 115:653–659

Martino R, Caballero MD, Simon JA, Canals C, Solano C, Urbano-Ispizua A et al (2002) Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. Blood 100:2243–2245

Ravandi F, Kantarjian H, Giles F, Cortés J (2004) New agents in acute myeloid leukemia and other myeloid disorders. Cancer 100:441–454

Thomas ED (1999) A history of haemopoietic cell transplantation. Br J Haematol 105:330–339

Thomas ED, Lochte HL, Ching-Lu W, Ferrebee J (1957) Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med 257:491–496

Xia G, Kovochich M, Truitt RL, Johnson BD (2004) Tracking ex vivo-expanded CD4+CD25+ and CD8+CD25+ regulatory T cells after infusion to prevent donor lymphocyte infusion-induced lethal acute graft-versus-host disease. Biol Blood Marrow Transplant 10:748–760

6.2 Imaging in Bone Marrow Transplantation

Tomas Franquet

CONTENTS

6.2.1 Introduction

The term "hematopoietic stem cell transplantation" has supplanted the previously employed term "bone marrow transplantation" to reflect the broader range of donor stem cell sources that are now available: bone marrow, fetal cord blood, and growth-factor-stimulated peripheral blood (Kotloff et al. 2004). Hematopoietic stem cell (HSC) transplantation is being used with increasing frequency for the treatment of leukemia, aplastic anemia, myeloma, and some forms of lymphoma and solid tumors. It is estimated that more than 50,000 marrow and HSC transplantations are performed annually worldwide (Tabbara et al. 2002).

Although HSC transplantation is a well-established procedure, thoracic complications are common (Winer-Muram et al. 1996; Yen et al. 2004) and occur in a significant number of patients after marrow transplantation (Krowka et al. 1985; Chan et al. 1990; Soubani et al. 1996; Worthy et al. 1997; Kotloff et al. 2004).

Pulmonary complications are a common cause of morbidity and mortality after HSC transplantation occurring in 40%–60% of recipients and accounting for more than 90% of mortality (Yen et al. 2004). The spectrum of pulmonary complications has been influenced by changes in transplantation technique, prophylactic treatment for infections, and the use of new chemotherapeutic drugs that contribute to lung injury. Allogeneic recipients develop pulmonary complications at a much higher frequency than those receiving autologous HSC transplant (Tabbara et al. 2002).

Marrow grafting is preceded by intense immunosuppressive treatment to prevent rejection of the

T. Franquett, MD
Professor, Hospital de Saint Pau, Department of Radiology, Avenida S. Antonio Maria Claret 167, Barcelona 08021, Spain

transplanted marrow. Preparative regimens cause a spectrum of pulmonary acute toxicities and complications that may be either infectious and related to the degree of ongoing immunosuppression, or non-infectious and related to previous chemotherapy, degree of immunosuppression, and, in allogeneic transplants, the presence of graft-versus-host disease (GVHD) (Chan et al. 1990).

Pneumonia remains a common life-threatening complication in HSC recipients occurring as a direct result of transplantation-induced immune suppression (Aronchick 2000). Non-infectious complications include pulmonary edema, engraftment syndrome, alveolar hemorrhage, drug-induced lung injury, idiopathic pneumonia, obliterative bronchiolitis, cryptogenic organizing pneumonia, pulmonary veno-occlusive disease, and post-transplant lymphoproliferative disorder (Alam and Chan 1996; Soubani et al. 1996; Worthy et al. 1997). As the number of survivors increases, several late effects of treatment are becoming evident. Sarcoidosis has been sporadically reported as a rare complication following either autologous or allogeneic HSC transplantation (Bhagat et al. 2004). In these patients the prevalence of sarcoidosis may be tenfold higher than that of the normal population (Bhagat et al. 2004).

In this chapter, imaging features of various infectious and non-infectious pulmonary complications following HSC transplantation are discussed and illustrated.

6.2.2 Clinical Considerations

Specific pulmonary complications tend to occur during identifiable phases that correspond with the state of immune reconstitution after the marrow transplant. It is useful to divide the post-transplant period into three phases: (1) neutropenic phase (the first 30 days); (2) early phase (days 31–100); and (3) late phase (more than 100 days after the transplant). Although this division is clinically useful, overlap occurs in the timing of specific complications (Chan et al. 1990; Soubani et al. 1996; Worthy et al. 1997).

Signs and symptoms of pulmonary disorders related to HSC transplantation are often non-specific and rapid and accurate diagnosis is essential in these life-threatening disorders.

6.2.3 Integrating Clinical Factors, Imaging Findings, and Other Diagnostic Procedures

Although imaging has a limited role before HSC transplantation, it is important after transplantation when it may support the clinical diagnosis of a variety of complications. It may also be used to monitor the effect of therapy and to detect recurrence of the underlying disease if the transplant is unsuccessful (Evans et al. 2003). The most useful imaging modalities available for the evaluation of the patient with known or suspected post-transplant pulmonary complications are chest radiography and computed tomography (Wah et al. 2003).

Combining clinical factors, including the type of transplant and the point of time during the post-transplantation course, with characteristic imaging features yields the most specific and accurate differential diagnosis for radiologic findings in these patients (Nusair et al. 2004; Coy et al. 2005; Franquet et al. 2005a). In the absence of clinical information, radiologists cannot reliably distinguish between pneumonia and other non-infectious pulmonary processes.

Diffuse parenchymal infiltrates are common radiographic findings in HSC transplant recipients. In the neutropenic phase, < 30 days after transplantation, infectious causes of pulmonary infiltrates have been documented in fewer than 20% of recipients who underwent open lung biopsy (Crawford et al. 1988). In this phase, pulmonary edema secondary to cardiac decompensation, intravascular volume excess, acute respiratory distress syndrome, or pulmonary capillary leak is the major reason for diffuse parenchymal infiltrates. However, between 30 and 180 days after transplantation, infections are the commonest cause of diffuse parenchymal abnormalities (Crawford et al. 1988; Cunningham 1992). Pulmonary edema and the idiopathic pulmonary syndrome (IPS) are the most common conditions to be distinguished from bronchopneumonia when a generalized pulmonary abnormality is radiographically demonstrated (Cardozo and Hagenbeek 1985; Crawford 1999).

Focal parenchymal infiltrates are frequently due to infection regardless of the time of presentation after transplant; however, distinction of localized pneumonia from other pulmonary processes cannot be made with certainty on radiologic grounds (Janzen et al. 1993). Unfortunately, the clinical data

and imaging findings often fail to lead to a definitive diagnosis of pneumonia because an extensive number of non-infectious processes associated with febrile pneumonitis – i.e., drug-induced pulmonary disease, IPS, and organizing pneumonia – mimic pulmonary infection (Janzen et al. 1993). Localized pulmonary disease of a lobar or segmental distribution can also be produced by pulmonary edema and hemorrhage.

6.2.3.1 Conventional Chest Radiography

A posteroanterior (PA) (and lateral when possible) chest radiograph is the primary imaging modality used in the initial evaluation and follow-up of HSC transplant recipients with fever. Other roles for chest radiography are an enhanced ability to assess the extent of disease, to detect complications (i.e., cavitation, abscess formation, pneumothorax, pleural effusion), and to detect additional or alternative diagnoses and sometimes to guide invasive diagnostic procedures. The non-specificity of radiographic findings as well as the wide range of potential causes often lead to frustration when evaluating the imaging findings of a patient with a suspected thoracic complication.

6.2.3.2 Computed Tomography

Although CT is not recommended for the initial evaluation of patients with pneumonia, it is useful in the detection, differential diagnosis, and management of the HSC transplanted recipient with acute pulmonary disease when chest radiographs show non-specific abnormal findings or when the radiographic findings are normal with clinical findings of pulmonary disease (Worthy et al. 1997; Tanaka et al. 2002; Franquet et al. 2005a).

There is a large literature indicating that CT is a sensitive method capable of imaging the lung with excellent spatial resolution providing anatomical detail similar to that seen by gross pathological examination. Differences in tissue attenuation and parenchymal changes caused by an acute inflammatory process can be seen readily by CT. Unlike chest radiography, CT provides cross-sectional images and the pattern and distribution of pulmonary processes are therefore much more readily appreciated than on conventional examinations. The findings of air-space disease, air-space (acinar) nodules, ground-glass opacities, consolidation, air bronchograms, and centrilobular or perilobular distribution are seen better by CT than by conventional radiography. Air-space nodules represent the size of the acinus (6–10 mm) and are centrilobular in distribution. They are best appreciated in early disease and best seen at the edge of the pathologic process where consolidation is incomplete.

6.2.3.3 Non-Invasive and Bronchoscopic Diagnostic Procedures

The clinical and radiographic presentation of pulmonary disease in HSC transplant recipients often fails to allow the specific identification of a causative pathogen or to permit the distinction between infectious and non-infectious processes (Ettinger 1993; Starobin et al. 2003).

Non-invasive and bronchoscopic procedures have been shown to be safe and useful techniques for evaluating pulmonary infiltrates in immunocompromised patients. Fiber-optic bronchial aspirates (FBAS) and broncho-alveolar lavage (BAL) are the procedures of choice for evaluating pulmonary infiltrates in HSC transplant recipients and they have the highest diagnostic yield and impact on therapeutic decisions (Young et al. 1984; Springmeyer et al. 1986; Heurlin et al. 1991; Soubani et al. 2001). BAL has proved valuable even in patients who have severe thrombocytopenia (Stover et al. 1984; Huaringa et al. 2000). Negative results do not exclude angioinvasive fungal infections, such as aspergillosis.

6.2.3.4 Invasive Diagnostic Procedures

Diagnostic information may also be obtained by transbronchial or percutaneous needle aspiration. Transbronchial biopsy may be unsafe to perform in severely thrombocytopenic patients.

Despite its reported results in the diagnosis of pulmonary infection being variable (11.7%–73%), percutaneous fine needle aspiration is an alternative method used to identify causative pathogens in selected patients with pneumonia (Jantunen et al. 2002). Transthoracic needle aspiration should be considered for patients who have not responded to

initial therapy, who may have nosocomial superinfection, who are immunocompromised, or in whom TB is suspected but has not been confirmed by examination of the sputum or gastric lavage. It is not clear whether use of transthoracic needle aspiration results in a reduction in mortality and morbidity in a cost-effective fashion, compared to a less invasive approach.

6.2.3.5 Open Lung Biopsy

Surgical lung biopsy (SLB), by way of either thoracotomy or video-assisted thoracoscopy, may be diagnostic (Crawford et al. 1988; Snyder et al. 1990). SLB provides a specific diagnosis in the majority of patients with hematologic malignancy or HSC transplant recipients and unexplained pulmonary infiltrates (Wong et al. 2002; Zihlif et al. 2005). Even in severely immunosuppressed patients, the morbidity and mortality that are associated with this technique seem to be acceptable, especially when the biopsy is performed thoracoscopically (Roviaro et al. 2002).

6.2.4 Infectious Complications

Although the incidence of pulmonary infection after HSC transplantation has declined, pneumonia remains a common life-threatening complication in these patients and occurs as a direct result of transplantation-induced immune suppression (Crawford et al. 1988; Choi and Leung 1999). During the initial post-transplant period, patients are profoundly neutropenic (absolute neutrophil count < 500 cells/μl) and the majority of microbiologically documented pneumonias are caused by fungi or bacteria (Cunningham 1992). If neutropenia is prolonged beyond 2 weeks, *Aspergillus* spp. as well as other opportunistic moulds may cause life-threatening infections (Kaiser et al. 1998; Fukuda et al. 2004). While fungi are the most common cause of pulmonary infection in the early pre-engraftment phase, viruses most commonly occur in the post-engraftment phase (Kapoor et al. 1989; Giacchino et al. 1993). Conversely, in the late post-engraftment phase, from day 100 until the patient regains normal immunity usually 1–2 years later, there is no predominant pathogen and the majority of infections are usually bacterial (Paulin et al. 1987; Kotloff et al. 2004).

6.2.4.1 Bacterial Infection

Bacterial infections are responsible for approximately 90% of infections during the early phase of neutropenia and are not lethal as often as are viral and fungal infections (Maschmeyer 2001). The list of pathogens that can cause bacterial pneumonia in HSC transplant recipients is extensive, but a narrow spectrum accounts for most cases. During the first few days after transplantation, the organisms involved are aerobic bacteria found in the bowels (*Escherichia coli*, *Klebsiella*, *Pseudomonas*) and those found on the skin or intravenous catheters (*Staphylococcus aureus*, coagulase-negative staphylococci); other causative organisms are *Legionella*, *Haemophilus influenza*, Viridans streptococci, *Enterobacter,* and *Nocardia* (Villablanca et al. 1990; Kumar and Jimenez 2001; Lin et al. 2004). Viridans streptococcal shock syndrome may occur early in the transplantation course (6 or 7 days post-transplantation) in patients with severe neutropenia and viridans streptococcal bacteremia (Martino et al. 1995).

Clinical symptoms of bacterial infection include fever, cough, and progressive dyspnea that is present in more than 90% of patients. Although the pulmonary examination may reveal rhonchi and crackles, the examination may be normal in 50% of patients.

The radiographic findings in bacterial infections are non-specific. Plain radiographs most commonly show focal alveolar infiltrates, but may be normal in 30% of patients, most likely because of the routine use of broad-spectrum antibiotics for febrile patients (Maschmeyer 2001). On high-resolution CT, a focal air-space consolidation, which typically presents in either a segmental or lobar distribution, is frequently identified. Differentiation from atypical patterns of opportunistic infections is often impossible on the basis of radiographic findings. Conversely, atypical patterns, including bilateral diffuse opacities, are not uncommon manifestations of bacterial pneumonia.

Pyogenic airways disease, including infectious bronchitis and bronchiolitis, are increasingly seen in HSC transplant recipients. Histologically, they are characterized by an active cellular bronchiolitis

with mononuclear cell inflammation of the respiratory bronchioles and the presence of an inflammatory exudate and mucus in the bronchiolar lumen (Aquino et al. 1996). Bronchogenic dissemination of pyogenic bacteria can result in dilatation and thickening of bronchiolar walls. Chest radiography may have normal or non-specific findings consisting of heterogeneous ill-defined opacities, especially visible in the lower lung regions. Other common radiographic findings are peribronchial thickening occasionally observed as "tram tracking".

Associated airway abnormalities can also be depicted by CT. Characteristic CT findings include: (1) small ill-defined centrilobular densities representing bronchioles impacted with inflammatory material and peribronchiolar inflammation ("tree-in-bud"), (2) branching linear opacities corresponding to inflammatory cells in the walls of the airways, and (3) focal areas of consolidation due to bronchopneumonia (Fig. 6.2.1) (Aquino et al. 1996). Although these findings are reversible in the majority of cases, recurrent and persistent infections may lead to bronchiolectasis.

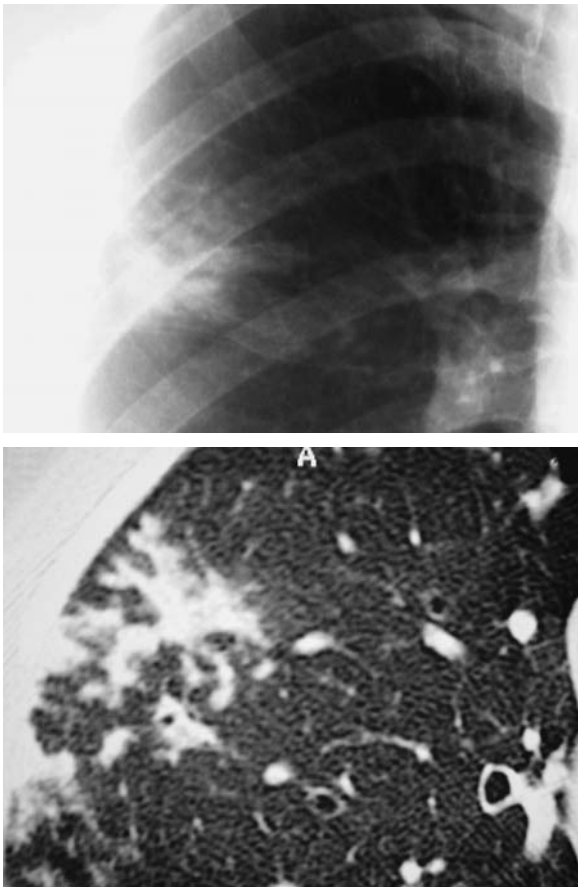


Fig. 6.2.1a,b. A 48-year-old man with *Pseudomonas aeruginosa* pneumonia after allogeneic hematopoietic stem cell transplantation. **a** Close-up view of an anteroposterior chest radiograph shows an ill-defined opacity in the right upper lobe. **b** Corresponding HRCT scan at the same level shows multiple branching linear opacities and some areas of lobular consolidation

6.2.4.1.1 Mycobacterial Infection

Infection with *Mycobacterium tuberculosis* and a variety of non-tuberculous mycobacteria has been observed in HSC transplant recipients (Navari et al. 1983; Mohite et al. 2001). *Mycobacterium tuberculosis* infection can occur after HSC transplantation, but the incidence in the reported series is lower than that of other infections (Roy and Weisdorf 1997; Aljurf et al. 1999; Mohite et al. 2001). Overall, the incidence of tuberculosis has bee reported to be between 0.19% and 5.5% of cases (Martino et al. 1996; Roy and Weisdorf 1997). Reports of non-tuberculous mycobacterial disease in both HSC and solid organ transplant recipients have also increased (Ozkaynak et al. 1990; Busch et al. 1991; Doucette and Fishman 2004).

6.2.4.2 Fungal Infections

A major infectious cause of death in HSC transplant recipients is invasive fungal infection (Allan et al. 1988; Bodey and Vartivarian 1989; Bag 2003). Beyond the first week after transplantation, fungal infections become increasingly common, being identified as a cause of pneumonia in 12%–50% of patients (Connolly et al. 1999). With increased use of prophylactic fluconazole, infections with resistant fungi have become more common. Other less common pulmonary mycoses (e.g., *Penicillium purpurogenum*, *Acremonium strictum* and *Scedosporium apiospermum*) have been also observed.

6.2.4.2.1 Pneumocystis Jiroveci (Formerly Pneumocystis Carinii)

The disease known as *Pneumocystis* pneumonia (PCP) is a major cause of illness and death in persons with impaired immune systems. Pneumocystis organisms from different host species have very dif-

ferent DNA sequences, indicating multiple species. In recognition of its genetic and functional distinctness, the organism that causes human *Pneumocystis carinii* pneumonia is now named *Pneumocystis jiroveci* (Stringer et al. 2002).

Pneumocystis jiroveci has been reported to be a rare cause of pulmonary infection in HSC transplant recipients (Saito et al. 2001; Chen et al. 2003; Resnick et al. 2005). The manifestations of disease depend on the severity of infection. Clinical symptoms of PCP include non-productive cough, shortness of breath, and hypoxia on room air.

Abnormal chest radiographs have been reported in up to 90% of patients with suspected PCP showing the typical findings of diffuse bilateral interstitial infiltrates most marked in a perihilar distribution (Soubani et al. 1996; Worthy et al. 1997; Resnick et al. 2005). As the disease progresses, alveolar infiltrates may also develop. The widespread use of *Pneumocystis* prophylaxis has led to a larger proportion of patients that present with normal radiographs. However, normal radiographs do not exclude the diagnosis (Boiselle et al. 1997).

Computed tomography is the imaging modality of choice to evaluate those symptomatic patients with a clinical suspicion of PCP but with an otherwise normal or equivocal chest radiograph. Characteristic CT features are perihilar ground-glass opacity, often in a patchy or geographical distribution, with areas of affected lung interspersed by normal lung parenchyma (Fig. 6.2.2). In addition to the ground-glass pattern, there is often associated thickening of the interlobular septa giving a "crazy paving" appearance. Other less common radiographic patterns of PCP are parenchymal consolidation, mass lesions, multiple pulmonary nodules, pleural effusion, and lymph node enlargement (Boiselle et al. 1999).

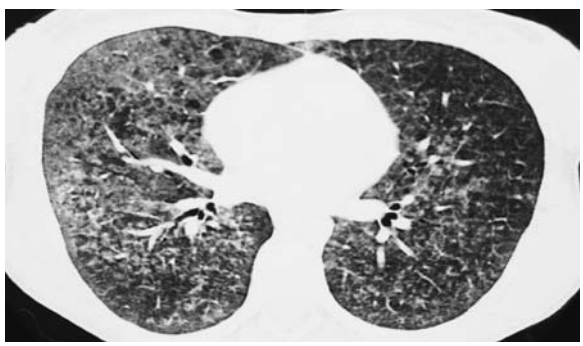


Fig. 6.2.2. A 36-year-old female patient with *Pneumocystis* pneumonia (*PCP*) after allogeneic hematopoietic stem cell transplantation. HRCT scan at the level of the lower lobes demonstrates diffuse bilateral patchy areas of ground-glass attenuation

6.2.4.2.2 Aspergillosis

Aspergillus are ubiquitous organisms that are part of the normal environmental flora and abound in the soil around us (Denning 2000, 2001). Aspergillosis is a mycotic disease caused by *Aspergillus* species, usually *A. fumigatus*. Other pathogenic species include *A. flavus*, *A. niger*, and *A. terreus*. *Aspergillus* infections can result in a variety of clinical, radiologic, and histologic manifestations (Aquino et al. 1994; Gotway et al. 2002). Although all humans beings are commonly exposed to these organisms, the type and severity of pulmonary involvement are influenced by the patient's immunologic status and the presence of pre-existing lung disease. Disseminated and invasive forms most often occur in immunologically compromised hosts representing a common cause of life-threatening opportunistic infection in neutropenic patients (Allan et al. 1988; Alangaden et al. 2002; Bag 2003).

The definitive diagnosis of invasive pulmonary aspergillosis is traditionally based on the histologic evidence of tissue invasion by branched septate hyphae. In recent years it has been shown that *Aspergillus* infection can result in a broad range of airway complications (Gotway et al. 2002; Franquet et al. 2004).

6.2.4.2.2.1 Angioinvasive Aspergillosis

Angioinvasive aspergillosis is commonly seen in immunocompromised patients with severe neutropenia (Denning 2000; Fukuda et al. 2004). There has been a substantial increase in the number of patients at risk of developing invasive aspergillosis for many reasons, including the development of new intensive chemotherapy regimens for solid tumors, difficult-to-treat lymphoma, myeloma, and resistant leukemia as well as an increase in the number of solid organ transplantations and increased use of immunosuppressive regimens for other autoimmune diseases. Angioinvasive aspergillosis is the most common fungal pulmonary infection in severe neutropenic patients. It is much more common in allogeneic than in autologous HCT recipients and in patients with acute leukemia (Denning 2000; Fukuda et al. 2004).

The diagnosis of angioinvasive aspergillosis is based on clinical, radiological, and mycological data. Although a febrile neutropenic patient with pulmonary infiltrates should be evaluated for aspergillosis, a conclusive diagnosis of angioinvasive aspergillosis is seldom straightforward and remains a significant clinical problem. Disseminated aspergillosis occurs in up to 60% of patients with invasive pulmonary aspergillosis; sites of involvement include the brain, kidney, liver, thyroid, heart, and spleen.

The consensus criteria for angioinvasive aspergillosis developed by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) were intended to provide uniform criteria for inclusion and evaluation of oncohematologic patients with suspected angioinvasive aspergillosis enrolled in clinical trials (Ascioglu et al. 2002).

Newer techniques, such as polymerase chain reaction and the galactomannan test, may change the current diagnostic approach. Galactomannan and nucleic acid detection in serum or in bronchoalveolar lavage (BAL) fluid are useful for the early identification of invasive aspergillosis in the immunocompromised host; however, a definite diagnosis of invasive aspergillosis still requires the demonstration of the fungus in tissue specimens (Maertens et al. 2001). The value of early diagnostic criteria such as the galactomannan test needs to be proven in prospective trials.

Angioinvasive aspergillosis is characterized histologically by invasion and the occlusion of small to medium pulmonary arteries by fungal hyphae. This leads to the formation of necrotic hemorrhagic nodules or pleural-based wedge-shaped hemorrhagic infarcts. The clinical diagnosis is difficult, and the mortality rate is approximately 85%. The characteristic CT findings consist of nodules surrounded by a halo of ground-glass attenuation (halo sign) or pleural-based wedge-shaped areas of consolidation (Fig. 6.2.3) (Kuhlman et al. 1985). These findings correspond to hemorrhagic infarcts. In severely neutropenic patients the halo sign is highly suggestive of angioinvasive aspergillosis (Kuhlman et al. 1985, 1987, 1988).

However, a similar appearance has been described in a number of other conditions including infection by *Mucorales*, *Candida*, Herpes simplex and cytomegalovirus, Wegener's granulomatosis, Kaposi's sarcoma and hemorrhagic metastases (Primack et al. 1994). Separation of fragments of necrotic lung (pulmonary sequestra) from adjacent parenchyma results in air-crescents similar to those seen in mycetomas. The air-crescent sign in angioinvasive aspergillosis is usually seen during convalescence, i.e., 2–3 weeks after onset of treatment and concomitant with resolution of the neutropenia (Franquet et al. 2001; Gotway et al. 2002).

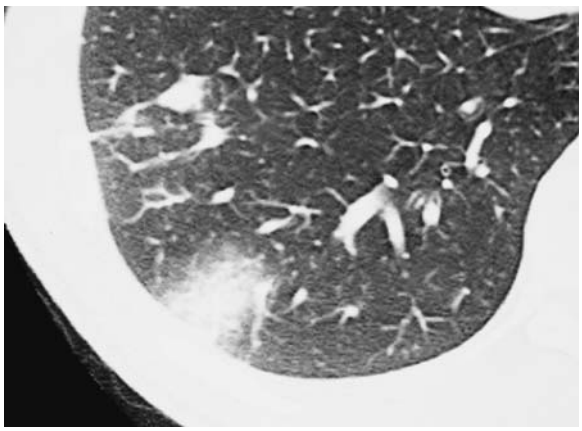


Fig. 6.2.3. Halo sign due to angioinvasive aspergillosis in a 47-year-old woman after allogeneic hematopoietic stem cell transplantation. Close-up view of a HRCT scan at the right lower lobe shows a peripheral nodular opacity with a surrounding halo of ground-glass attenuation. These findings correspond to a nodular area of infarction surrounded by hemorrhage

6.2.4.2.2.2 Airway Invasive Aspergillosis

Aspergillus bronchopneumonia, also known as airway invasive aspergillosis, occurs in up of 10% of cases of invasive pulmonary aspergillosis. It is characterized histologically by the presence of *Aspergillus* organisms deep to the airway basement membrane (Franquet et al. 2004). Airway invasive aspergillosis occurs most commonly in immunocompromised neutropenic patients and in patients with acquired immunodeficiency syndrome (AIDS) (Franquet et al. 2002). Clinical manifestations include acute tracheobronchitis, bronchiolitis, and bronchopneumonia. Patients with acute tracheobronchitis usually have normal radiologic findings. Occasionally tracheal or bronchial wall thickening may be seen. Bronchiolitis is characterized on high-resolution CT by the presence of centrilobular nodules and branching linear or nodular opacities giving an appearance resembling a "tree-in-bud". The centrilobular nodules have a patchy distribution in the lung. *Aspergillus* bronchopneumonia

results in predominantly peribronchial areas of consolidation. Rarely, the consolidation may have a lobar distribution.

Centrilobular nodular opacities similar to those seen in *Aspergillus* bronchiolitis have been described in a number of conditions, including endobronchial spread of pulmonary tuberculosis, *M. avium-intracellulare*, viral and mycoplasma pneumonia (Aquino et al. 1996). The radiologic manifestations of *Aspergillus* bronchopneumonia are indistinguishable from those of bronchopneumonias caused by other microorganisms (Aquino et al. 1996; Franquet et al. 2004).

A similar appearance has been described in bronchocentric mycosis. Although this process is histologically somewhat similar to bronchocentric granulomatosis, a high index of suspicion of infection needs to be maintained when this pathologic process is identified in a transplant host (Tazelaar et al. 1989).

6.2.4.2.3 Mucormycosis

The *Mucor* species are ubiquitous , saprophytic molds, usually found in soil and in decaying food. Infection occurs by either inhalation of airborne fungal spores or through hematogenous spread from a distant focus. The spectrum of disease includes rhinocerebral and pulmonary, gastrointestinal, cutaneous, and disseminated manifestations (Connolly et al. 1999; Maertens et al. 1999).

The most common associated conditions include diabetes mellitus, solid organ transplantation, renal failure, chemotherapy, and hematologic malignant neoplasms (Gaziev et al. 1996). Lung involvement occurs in more than 30% of cases. Radiographic manifestations are non-specific and include consolidation, cavitation or abscess formation, nodules and masses. Lesions are most often unifocal affecting more frequently the upper lobes. As occur in other angioinvasive fungal infections such as aspergillosis and candidiasis, the "air-crescent" sign and the "halo" sign may also be seen in patients with mucormycosis (McAdams et al. 1997; Connolly et al. 1999).

6.2.4.2.4 Cryptococcal Pneumonia

Cryptococcus neoformans is an encapsulated non-mycelial, budding yeast found worldwide, particularly in soil contaminated by bird droppings (Cameron et al. 1991). *Cryptococcus* is a common pulmonary fungal pathogen in the AIDS population usually when the CD4 count is below 100 cells/mm^3 (Sider and Westcott 1994). Although the central nervous system is the most commonly affected organ, the lungs are also involved (Vilchez et al. 2001). In a series of 31 HIV-infected patients with cryptococcal infection, 12 (39%) had cryptococcal pneumonia (Sider and Westcott 1994). Presenting symptoms are non-specific and include fever, cough, dyspnea, sputum production, and pleuritic chest pain. The most common radiographic findings consist of a reticular or reticulonodular interstitial pattern. Less common manifestations include ground-glass attenuation, air-space consolidation, "tree-in-bud" opacities, and miliary nodules (Fig. 6.2.4) (Khoury et al. 1984). The CT pattern in immunocompromised non-AIDS patients seems to differ from that in AIDS

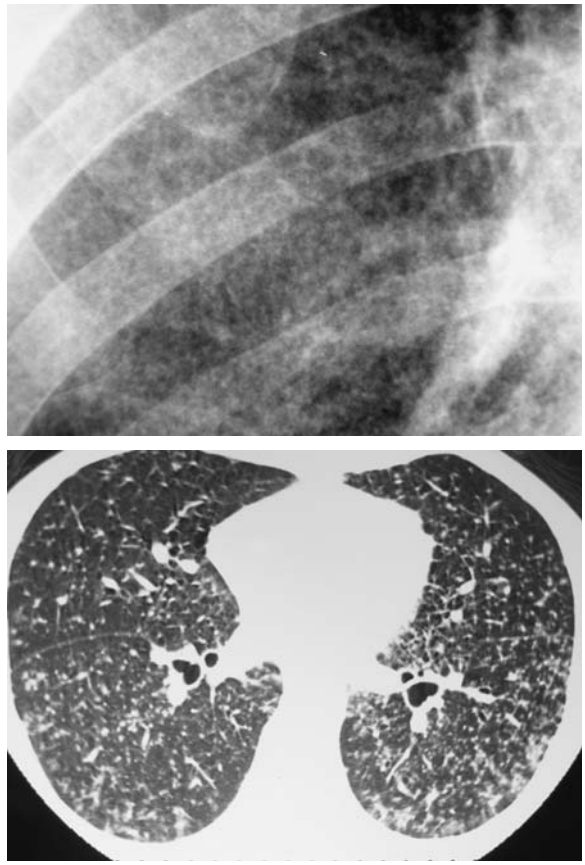


Fig. 6.2.4a,b. A 39-year-old woman with acute myelocytic leukemia and miliary cryptoccocosis. **a** Close-up view of an anteroposterior radiograph shows a diffuse miliary pattern. **b** Corresponding HRCT scan confirms numerous small miliary nodules in a random distribution

patients by the presence of nodules and the absence of reticular or reticulonodular interstitial infiltrates (Zinck et al. 2002).

6.2.4.2.5 Histoplasmosis

Histoplasma capsulatum is a pathogenic dimorphic yeast found in temperate regions throughout the world. Histoplasmosis is rare in Europe and occurs in endemic areas in North America such as the Ohio-Mississippi and St Lawrence River valleys (Conces et al. 1993; McAdams et al. 1995). Histoplasmosis is rare, but often a life-threatening infection in patients with AIDS and hematologic malignancies. Most cases of disseminated histoplasmosis occur either as a result of new infection after an environmental exposure or as a result of reactivation of a remote infection (Conces et al. 1993; Kauffman 2002). The radiographic findings of disseminated histoplasmosis are varied and non-specific; approximately 40% of patients with pulmonary disseminated histoplasmosis have a normal chest radiograph (Conces et al. 1993). CT can be helpful in the assessment of patients who have symptoms of pulmonary disease and normal or non-specific radiographic findings. The most common radiographic findings are diffuse nodular opacities 3 mm or less in diameter, nodules greater than 3 mm in diameter, small linear opacities, and focal or patchy areas of consolidation (McAdams et al. 1995).

6.2.4.2.6 Candidiasis

Pulmonary candidiasis is a relatively uncommon complication seen in immunocompromised patients and is rarely reported in patients without predisposing conditions. *Candida* sp. have been increasingly recognized as an important source of fungal pneumonia in patients with hematologic malignancies (acute leukemia and lymphoma) and allogeneic bone marrow transplant recipients (Buff et al. 1982; Allan et al. 1988; Connolly et al. 1999; Franquet et al. 2005b, 2005c). Factors that predispose bone marrow transplant recipients to *Candida* infections include allogeneic bone marrow transplantation, increased age, and a prolonged neutropenia (Verfaillie et al. 1991). A definitive diagnosis of pulmonary candidiasis requires demonstration of the organism in tissue. Pathologically, areas of consolidation represent areas of bronchopneumonia, intra-alveolar hemorrhage, exudates, and hyaline membranes. Chest radiographic and CT abnormalities consist of multifocal patchy areas of consolidation, focal cavitation, and multiple pulmonary nodules (Franquet et al. 2005b).

6.2.4.3 Viral Infection

Viruses have been increasingly recognized as important causes of serious respiratory illnesses in HSC transplant recipients. Most respiratory viral infections produce acute symptoms such as fever, non-productive cough, dyspnea, and hypoxemia. These infections may result from reactivation of a latent process or reflect newly acquired infection.

6.2.4.3.1 Community Respiratory Viruses

Community respiratory viruses particularly respiratory syncytial virus (RSV), influenza, parainfluenza, and adenovirus have been recognized as potential causes of severe pneumonia, accounting for the majority of non-CMV pulmonary infections in both autologous and allogeneic HCT recipients (Krinzman et al. 1998; Markovic et al. 1998; Ghosh et al. 1999; Nichols et al. 2001; Chakrabarti et al. 2002; Ison et al. 2003; Nichols et al. 2004). In these patients, respiratory viral infections can be mild and self-limited, but also can lead to severe, life-threatening disease more frequently than in normal immune hosts. The prevalence of respiratory viral infections in HSC transplanted patients is variable. In a prospective study conducted by the European Group for Blood and Marrow Transplantation, 40 respiratory virus infections (2%) were diagnosed in 1863 patients (Ljungman 2001). In another study, Leung et al. (1999) found respiratory viral infections in only three (5%) of the 59 infectious episodes (two RSV and one influenza B).

Human metapneumovirus (HMPV) is a recently identified new RNA respiratory virus that belongs to the *Paramyxoviridae* family and to the larger *Pneumovirinae* subfamily (Boivin et al. 2002; Williams et al. 2004). Their clinical manifestations are virtually indistinguishable from those associated with other respiratory viruses. Clinical symptoms typically consist of fever exceeding > 38°C, non-productive cough, progressive dyspnea, and hypoxemia (Boivin et al. 2002). Despite the fact that HMPV may

cause serious pneumonia in high-risk patients, it is often unsuspected in an immunocompromised host because their clinical features are indistinguishable from those associated with other respiratory viruses.

The descriptions of the thin-section CT appearances in respiratory viral infections have been limited to very few studies. Oikonomou et al. (2003) reviewed the thin-section CT findings in four patients with hematologic malignancies and influenza A pneumonitis and found that the predominant CT findings were ground-glass opacities and centrilobular nodules lesser than 10 mm in diameter (Fig. 6.2.5). Gasparetto et al. (2004) reviewed the thin-section CT findings in 20 patients with RSV pneumonitis after HSC transplantation and found that the most common thin-section CT findings consisted of small centrilobular nodules and multifocal areas of consolidation and ground-glass opacities in a bilateral asymmetric distribution. The CT appearances of HMPV infection were patchy areas of ground-glass attenuation, small nodules, and multifocal areas of consolidation in a bilateral asymmetric distribution (Fig. 6.2.6) (Franquet et al. 2005c). Similar findings have been described in patients with CMV, Herpes simplex virus, and Herpes varicella-zoster virus pulmonary infections (Foot et al. 1993; Kang et al. 1996; Franquet et al. 2003a; Gasparetto et al. 2005).

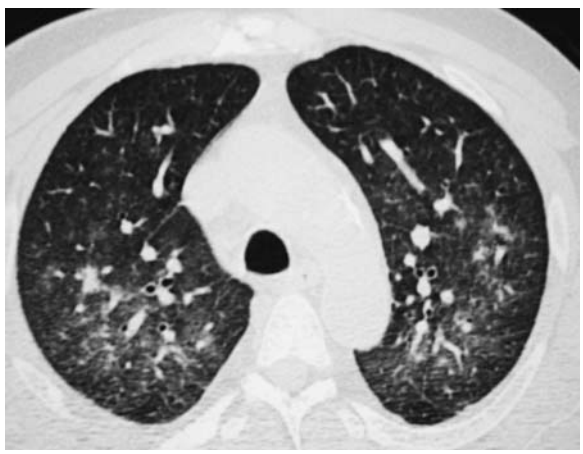


Fig. 6.2.5. *Parainfluenza 3* infection in a 60-year-old man who had severe neutropenia secondary to chemotherapy and HSC transplant for myelodysplastic syndrome. Transverse thin-section (1-mm collimation, lung window) CT scan at the level of the aortic arch shows bilateral areas of ground-glass opacity in the upper lobes

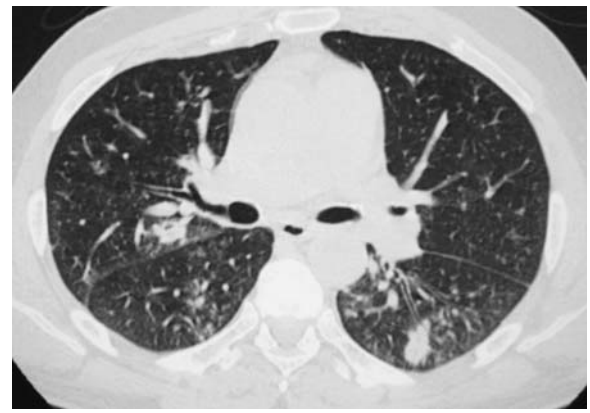


Fig. 6.2.6. *Human metapneumovirus* pneumonia in a 58-year-old man with neutropenia following HSC transplantation. Transverse thin-section (1-mm collimation) CT scan obtained at level of the carina shows bilateral areas of ground-glass attenuation and multiple ill-defined nodules affecting the posterior segment of the right upper lobe and both superior segments of the lower lobes

6.2.4.3.2 Cytomegalovirus (CMV)

The incidence of CMV pneumonia has been significantly reduced with the use of ganciclovir prophylaxis. Nevertheless, CMV remains one of the major complications in the post-engraftment phase, mostly within the first 4 months, being responsible for up to 50% of cases of pneumonia occurring in 50%–70% of allogeneic bone marrow transplant recipients (Cordonnier 1990; Kotloff et al. 2004). CMV disease rarely develops earlier than 14 days after transplantation and may become evident as late as 4 months after the procedure. CMV infection may be related to primary acquisition or to reactivation of latent infection or reinfection with a different strain in a previously seropositive patient.

CT findings of CMV pneumonia are diverse and consist of unilateral or bilateral interstitial infiltrates, alveolar consolidation, ground-glass opacities, and multiple small nodules with associated areas of ground-glass attenuation ("halo") (Fig. 6.2.7) (Kang et al. 1996; Franquet et al. 2003a). It has recently been reported that nodule size is helpful in the differential diagnosis of infectious causes of nodules in immunocompromised patients (Franquet et al. 2003b).

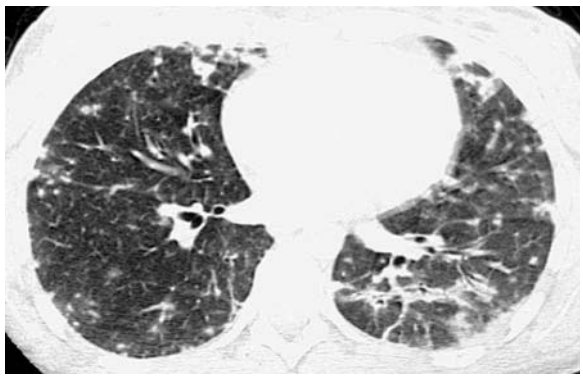


Fig. 6.2.7. Cytomegalovirus (*CMV*) infection in a 23-year-old man with acute myeloid leukemia and allogeneic HSC transplantation. CT scan obtained at the level of the inferior pulmonary veins shows diffuse ground-glass attenuation and multiple small ill-defined nodules in both lungs

6.2.5 Non-Infectious Complications

Non-infectious causes of lung injury after HSC transplantation include a spectrum of syndromes: pulmonary edema, engraftment syndrome, alveolar hemorrhage, drug-induced lung injury, idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans (BO), cryptogenic organizing pneumonia (COP), pulmonary veno-occlusive disease (VOD), and post-transplantation lymphoproliferative disorder (PTLD) (Worthy et al. 1997; Khurshid and Anderson 2002).

Most of these causes are attributed to treatment-related toxicities and are influenced by the myeloablative conditioning regimens used before transplantation, the degree of immunosuppression, and the interaction of the graft with the host. Therefore, these causes tend also to occur within specific time periods after transplantation. "Early" complications occur within the first 100 days after transplantation and "late" complications occur beyond day 100 (Worthy et al. 1997).

6.2.5.1 Early Complications

Early complications can be further subdivided into those that appear in the neutropenic phase (first 30 days of transplantation) or in the early phase (within 30–100 days of transplantation).

During the period of neutropenia, patients have a significant risk of developing non-infectious pulmonary complications such as pulmonary edema, engraftment syndrome, alveolar hemorrhage, and drug-induced lung injury.

6.2.5.1.1 Neutropenic Phase

6.2.5.1.1.1 Pulmonary Edema

Pulmonary edema is one of the earliest complications following HSC transplantation and may occur even in those patients with normal cardiac function. It is usually secondary to the large volumes of fluids infused to minimize the toxicity of conditioning regimens, and to transfusion of blood products (Worthy et al. 1997). Characteristic chest radiographic findings include diffuse interstitial lines such as Kerley A and Kerley B. The HRCT findings include enlarged pulmonary vessels, septal lines, peribronchial cuffing, ground-glass opacities, and small pleural effusions (Evans et al. 2003; Wah et al. 2003) (Fig. 6.2.8). The ground-glass opacities tend to involve mainly the dependent lung regions.

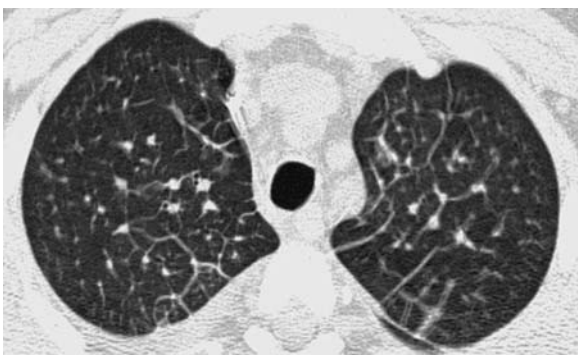


Fig. 6.2.8. Pulmonary edema due to fluid overload in a 28-year-old woman after allogeneic HSC transplantation. HRCT scan through upper lobes shows smooth septal thickening in a gravity-dependent distribution. The left interlobar fissure is also prominent due to subpleural edema. (With permission from Franquet et al. 2005a)

6.2.5.1.1.2 Engraftment Syndrome

Engraftment syndrome is a non-infectious pulmonary complication that represents a form of diffuse capillary leak associated with lung injury and pul-

monary edema. It has been described, during recovery from neutropenia, in autologous HSC transplantation. The median time of onset is 7 days after HSC transplantation (Khurshid and Anderson 2002). Clinically, as occurs with other non-infectious pulmonary complications, patients are febrile and may also present with skin rash similar to that in acute GVHD, and hypoxia. Chest radiograph findings are non-specific and range from normality to bilateral air-space opacification, diffuse vascular redistribution, and pleural effusions (Fig. 6.2.9). On CT, engraftment syndrome usually manifests as bilateral ground-glass opacification, air-space consolidation distributed at the hilar or peribronchial regions, and smooth thickening of interlobular septa (Evans et al. 2003; Wah et al. 2003).

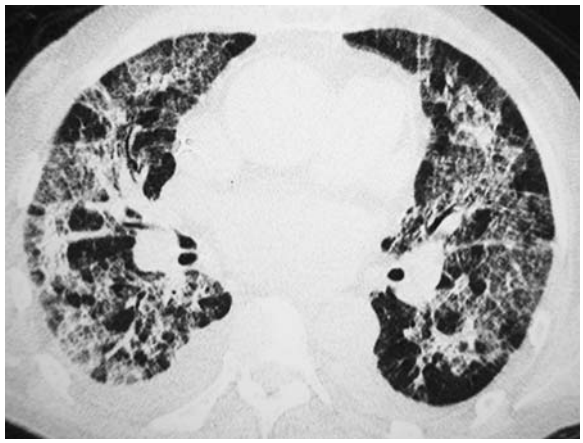


Fig. 6.2.9. Engraftment syndrome in a 46-year-old woman with non-Hodgkin lymphoma 3 weeks following allogeneic HSC transplantation. HRCT scan shows bilateral areas of consolidation having a peribronchovascular and subpleural distribution. Note a right pleural effusion. (With permission from Franquet et al. 2005a)

6.2.5.1.1.3 Diffuse Alveolar Hemorrhage (DAH)

Diffuse pulmonary alveolar hemorrhage (DAH) is a life-threatening complication following bone marrow transplantation with a reported mortality of approximately 70%–100% (Afessa et al. 2002; Ben-Abraham et al. 2003). The overall incidence of DAH is higher following autologous (20%) than allogeneic (10%) HSC transplantation. It typically occurs as a diffuse process in the first month after transplant, often at the time of granulocyte recovery (Schmidt-Wolf et al. 1993; Alam and Chan 1996; Afessa et al. 2002). Although its pathogenesis is not entirely understood, predisposing risk factors include intensive pre-transplantation chemotherapy and total body and thoracic irradiation (Worthy et al. 1997). The HRCT findings consist of extensive bilateral ground-glass opacities with or without superimposed intralobular linear opacities ("crazy-paving" pattern) (Fig. 6.2.10) (Evans et al. 2003; Wah et al. 2003).

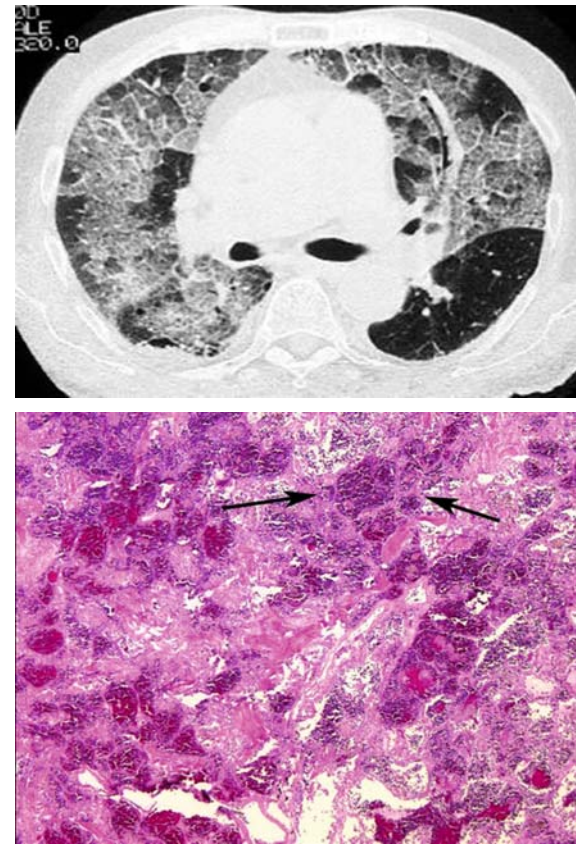


Fig. 6.2.10a,b. Diffuse alveolar hemorrhage in a 46-year-old woman with non-Hodgkin lymphoma 3 weeks after allogeneic HSC transplantation. **a** HRCT scan at the level of carina shows diffuse ground-glass opacity in addition to septal thickening ("crazy-paving"). **b** Histologically, macrophages containing hemosiderin are present within the alveolar spaces (*arrows*). (H and E, ×100; with permission from Franquet et al. 2005a)

6.2.5.1.1.4 Drug-Induced Lung Injury

Drug-induced lung disease occurs in up to 10% of patients following autologous or allogeneic HSC transplantation and must always be considered in the differential diagnosis of pulmonary infiltrates in transplant recipients. A wide range of histologic re-

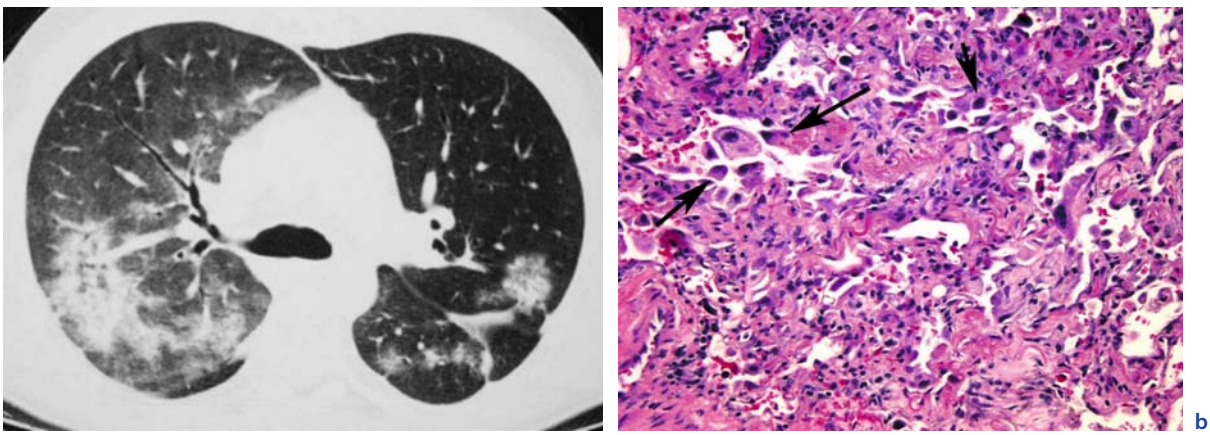
action patterns can be seen, the most common being diffuse alveolar damage, hypersensitivity reaction, non-specific interstitial pneumonia, and organizing pneumonia (Ellis et al. 2000).

Plain chest radiography is likely to underestimate subclinical forms of drug-induced lung disease, compared with HRCT. The CT manifestations are non-specific and reflect the histologic findings. CT features have been divided into four categories according to their dominant pattern and distribution of disease: fibrosis (irregular linear opacities with architectural distortion) with or without consolidation, ground-glass opacities, widespread bilateral consolidation, and bronchial wall thickening with areas of decreased attenuation (Fig. 6.2.11) (Evans et al. 2003; Wah et al. 2003).

6.2.5.2 Early Phase

6.2.5.2.1 Idiopathic Pneumonia Syndrome (IPS)

Idiopathic pneumonia syndrome (IPS) is defined as diffuse lung injury occurring after HSC transplantation in the absence of active lower respiratory tract infection even in the presence of non-lobar radiographic infiltrates and physiologic changes consistent with pneumonia (Kantrow et al. 1997). Thus, the diagnosis of IPS is one of exclusion, which requires the elimination of potential infectious agents as a cause of the patient's respiratory status. Idiopathic pneumonia is the most common cause of diffuse radiographic abnormalities between 30 days and 180 days after HSC transplantation. Clinical symptoms include dyspnea, cough, and fever. The mortality rate of IPS remains greater than 70%, and two-thirds of all deaths are associated with progressive respiratory failure (Kantrow et al. 1997). The histologic features of IPS range from a primarily interstitial reaction with diffuse or focal widening of the alveolar septa and interstitial spaces by mononuclear inflammatory cells and edema to diffuse alveolar damage with intra-alveolar hyaline membranes, edema, and hemorrhage. Other associated patterns such as organizing pneumonia and vascular damage have also been described. The pathologic findings of IPS are similar to those found in acute interstitial pneumonia and acute respiratory distress syndrome (ARDS) and can be separated into acute exudative, subacute proliferative, and chronic fibrotic phases. Characteristic CT findings include focal or diffuse ground-glass opacity and air-space consolidation with a basilar predominance (Fig. 6.2.12), a pattern consistent with non-cardiogenic pulmonary edema (Kantrow et al. 1997). Pleural effusions may be present. Architectural distortion, traction bronchiectasis, and the presence of honeycombing are indicative of the fibrotic phase of IPS.



a b

Fig. 6.2.11a,b. Vincristine-induced interstitial pneumonitis in a 63-year-old man with myeloma. **a** HRCT scan at the level of the carina shows diffuse ground-glass attenuation in the right lung and bilateral patchy areas of consolidation. **b** Photomicrograph of histopathologic section shows patchy expansion of the interstitium by lymphocytic infiltrate, mild interstitial fibrosis, and reactive hyperplastic type II pneumocytes (*arrows*) (H and E, ×250) (with permission from Franquet et al. 2005a)

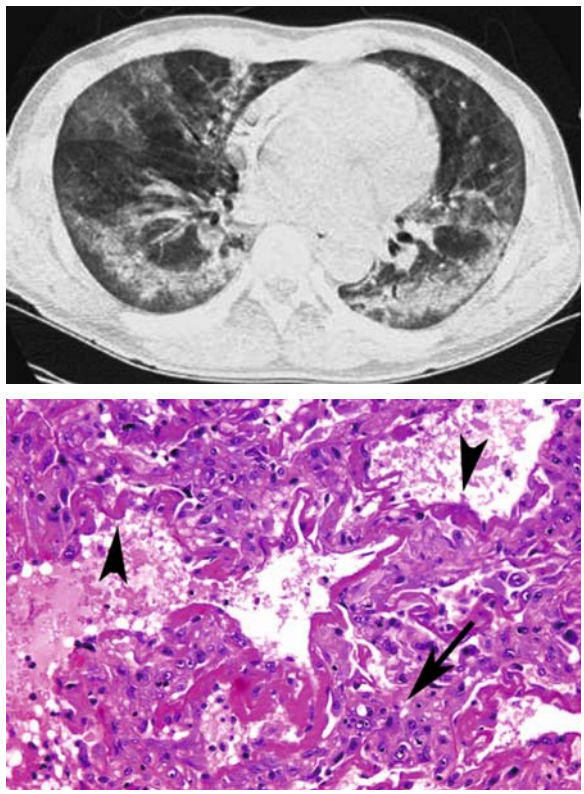


Fig. 6.2.12a,b. Idiopathic pneumonia syndrome in a 40-year-old man with AML 4 weeks following allogeneic HSC transplantation. **a** HRCT scan at the level of lower lung zones shows bilateral patchy areas of consolidation and ground-glass attenuation. **b** Histologically, the alveolar septa are thickened by edema and round cell infiltration (*arrow*). Hyperplasia and desquamation of the alveolar lining cells, fibrinous exudation, and hyaline membranes (*arrowheads*) are seen within the alveolar spaces. (H and E, ×250) (with permission from Franquet et al. 2005a)

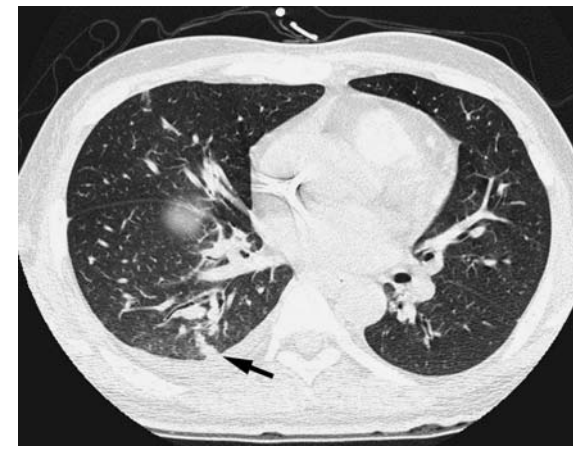


Fig. 6.2.13. Acute graft-versus-host disease in a 34-year-old man with CML 5 weeks following allogeneic HSC transplantation. HRCT at the level of the inferior pulmonary veins shows small areas of consolidation (*arrow*) in association with discrete right pleural effusion. (With permission from Franquet et al. 2005a)

6.2.5.2.2 Acute GVHD

GVHD is an immune reaction mediated by donor T-lymphocytes that recognize the recipient's tissue as a foreign body. It may present as acute or chronic pulmonary complication after HSC transplantation (Cooke and Yanik 2004). Acute GVHD develops in 20%–75% of patients (Tabbara et al. 2002; Freudenberger et al. 2003). The most commonly affected tissue systems are the skin, liver, and gastrointestinal system. Pulmonary involvement is rare. The median time of onset of respiratory symptoms is 5 months (range 1–13 months). The reported radiologic manifestations include mild perihilar or diffuse interstitial fibrosis, cysts, and lung nodules (Fig. 6.2.13).

6.2.5.2.3 Pleuro-pericardial Effusion/Hepatic Veno-occlusive Disease

Pleuro-pericardial effusion has been reported in approximately 16% of patients in the first few weeks after receiving HSC transplantation (Freudenberger et al. 2003). The most common non-infectious cause of pleural effusion is aggressive treatment with fluids, blood, and blood product transfusion. The effusion is usually bilateral or right sided and rarely related to an identifiable infectious source. Hepatic veno-occlusive disease, an occasional complication in allogeneic HSC transplantation recipients, is characterized by jaundice, hepatic enlargement, right upper quadrant pain, and ascites (Barker et al. 2003; Freudenberger et al. 2003). Pleural effusion has been reported in up to 50% of HSC transplantation recipients with hepatic veno-occlusive disease. Patients with veno-occlusive disease and pleural effusions have either no or minimal respiratory symptoms. Hepatic veno-occlusive disease usually precedes the development of pleural effusion (Fig. 6.2.14). Although pleural and pericardial effusions may be detected on conventional chest radiographs, they are better evaluated with CT and MR.

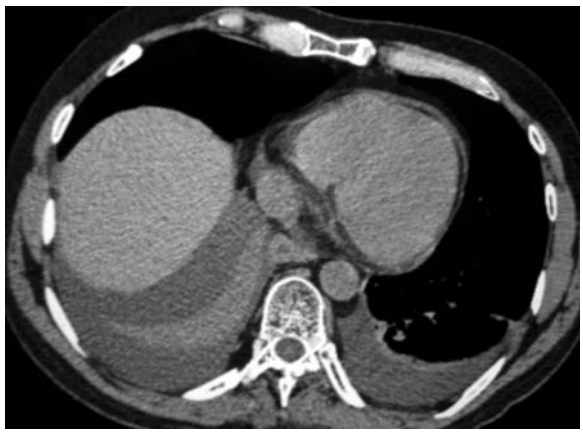


Fig. 6.2.14. Pleuro-pericardial effusion in a 28-year-old woman after allogeneic HSC transplantation. HRCT scan photographed using mediastinal window shows the presence of bilateral pleural and small pericardial effusions. (With permission from Franquet et al. 2005a)

6.2.5.2.4 Pulmonary Cytolytic Thrombi (PCT)

A rare early pulmonary vascular complication consisting of endothelial swelling with arteriolar, venular, and capillary thrombi has been described after allogeneic HSC transplantation with acute GVHD (Gulbahce et al. 2000, 2004). Active GVHD shortly before or at the time of PCT in all patients is indicative of the presence of alloreactive donor cells and supports an etiologic association. Pathologically it is characterized by intravascular formation of basophilic thrombi frequently accompanied by pulmonary infarcts (Gulbahce et al. 2000, 2004). The median time of onset of PCT is 2 months after transplantation although cases have been reported as early as 2 weeks. Although its pathogenesis is unknown, PCT may be a manifestation of acute GVHD. CT findings consist of multiple pulmonary nodules (Fig. 6.2.15).

6.2.5.2.5 Post-Radiation Thoracic Injuries

Radiation-induced thoracic injures can usually be diagnosed from characteristic imaging appearances and knowledge of the radiation port, radiation dose, and time interval since therapy. Commonest thoracic complications are acute radiation pneumonitis and fibrosis. Rare complications include spontaneous pneumothorax, thymic cysts, calcified lymph

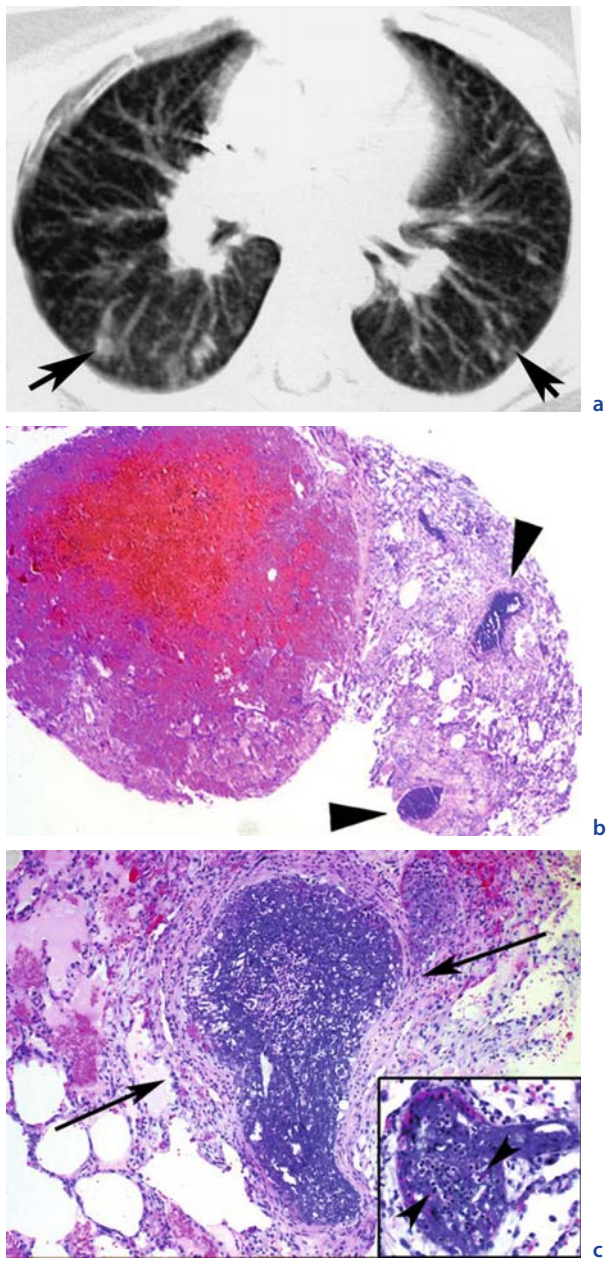


Fig. 6.2.15a–c. Pulmonary cytolytic thrombi in an 11-year-old patient after allogeneic HSC transplantation for an ALL. **a** CT scan with discrete peripheral pulmonary nodules suggestive of opportunistic infection (*arrows*). **b** Histologically, the nodules consisted primarily of hemorrhagic infarcts (*asterisk*). Occlusive vascular lesions were present within, adjacent to, and away from the hemorrhagic infarct (*arrowheads*). (H and E, ×40). **c** Intensely basophilic, tenacious, amorphous material occludes the lumen of the vessels (*arrows*). Few intact cells recognized as leukocytes (*arrowheads*) are also seen (*inset*) (H and E, ×400). (Courtesy of Gulbahce HE, Minneapolis, Mn., USA). (With permission from Franquet et al. 2005a)

nodes, vascular calcifications, and osseous sarcomas (Bluemke et al. 1991).

6.2.5.2.5.1 Radiation Pneumonitis

Radiation to the chest can result in acute pneumonitis or chronic fibrosis. Risk factors for radiation injury include total dose delivered, preexisting lung disease, and concurrent treatment with agents that sensitize the lung to radiation damage. Radiation pneumonitis presents 6 weeks to 6 months after completion of radiation therapy (Evans et al. 2003; Wah et al. 2003). In patients who progress to a clinically evident radiation pneumonitis, the radiographic findings range from normal to mild perivascular haziness. Over time, these initial lesions may develop into alveolar infiltrates. Radiologic changes may be observed in completely asymptomatic patients.

Clinical symptoms of radiation pneumonitis can be separated into early and late phases. During the early phase, 1–3 months after treatment, patients present with fever and leukocytosis making radiation injury a clinical syndrome difficult to distinguish from infection. Computed tomography is helpful in distinguishing radiation pneumonitis from pulmonary infiltrates of other causes. Given that radiation changes rarely occur outside the treated field, a characteristic CT finding consists of sharply marginated ground-glass opacities that do not follow an anatomic border (Fig. 6.2.16) (Evans et al. 2003; Wah et al. 2003).

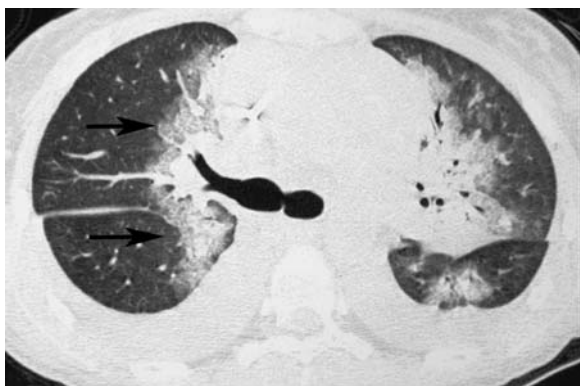


Fig. 6.2.16. Acute radiation pneumonitis in a 28-year-old woman after allogeneic HSC transplantation. HRCT shows paramediastinal ground-glass attenuation with associated broncho-vascular distortion. Notice the sharp border between the radiated area and the normal lung parenchyma (*arrowheads*). (With permission from Franquet et al. 2005a)

6.2.5.3 Late Complications

6.2.5.3.1 Chronic GVHD

Chronic GVHD is the most common non-relapse problem, occurring in approximately 60%–80% of long-term survivors of allogeneic HSC transplant and is a major cause of late morbidity and mortality. Onset is usually between 100 days and 6 months after transplantation, although earlier and later development are possible (Patriarca et al. 2004). The disease is more common in older patients, in recipients of mismatched or unrelated stem cells, and in those with a preceding episode of acute GVHD. Pulmonary complications include bronchiolitis obliterans (BO) and cryptogenic organizing pneumonia (COP). Moreover, patients with chronic GVHD have a particularly high risk of infections due to hypogammaglobulinemia and immune dysfunction. These patients must be re-immunized at 1 and 2 years for tetanus, diphtheria, polio, pneumococcus, meningococcus, and *Haemophilus influenzae* type B. In most patients, chronic GVHD resolves but it may require 1–3 years of immunosuppressive treatment.

6.2.5.3.1.1 Bronchiolitis Obliterans (BO)

Bronchiolitis obliterans, an obstructive pulmonary disorder that affects the small airways, has been reported in between 2% and 14% of allogeneic HSC transplantation recipients who survive more than 3 months (Freudenberger et al. 2003). Bronchiolitis obliterans is associated with high mortality (up to 60%) at 3 years post HSC transplantation (Freudenberger et al. 2003). Presenting symptoms include gradual dyspnea accompanied by persistent cough and expiratory wheeze. Pulmonary function testing shows new obstructive lung defects defined by a forced expiratory volume in 1 s (FEV1) $<80\%$ of predicted or a decrease of FEV1/forced vital capacity by $\geq 10\%$ within a period of less than 1 year.

Histologically, there is a predominantly constrictive bronchiolitis with destruction and narrowing of the bronchiolar lumen by fibrous tissue. This association suggests an immunologic mechanism that includes bronchial epithelial injury. High-resolution CT findings include areas of decreased attenuation and vascularity (mosaic perfusion), air

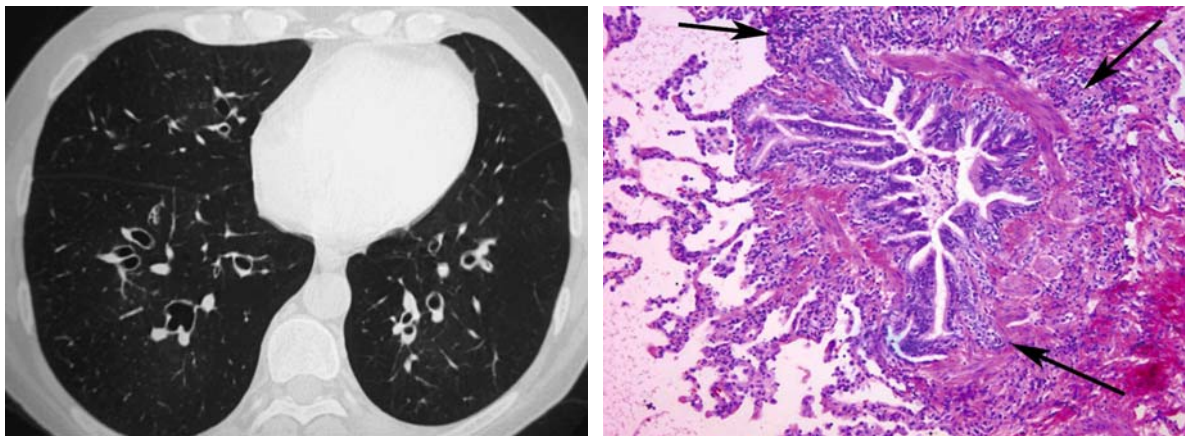


Fig. 6.2.17a,b. Chronic (obliterative) bronchiolitis in a 48-year-old woman 5 months following allogeneic HSC transplantation. **a** HRCT scan at the level of lower lobes shows a striking dilatation of subsegmental airways in the right lower lobe. A general reduction in lung parenchymal density is also noted. **b** Histologic section of lung parenchyma shows a moderately severe mononuclear inflammatory cell infiltrate in the peribronchiolar interstitial tissue (*arrows*). (With permission from Franquet et al. 2005a)

(Winer-Muram et al. 1996) trapping, and bronchial dilatation (Fig. 6.2.17) (Urbanski et al. 1987; Ooi et al. 1998).

6.2.5.3.1.2 Organizing Pneumonia (OP)

Organizing pneumonia (OP), also known as bronchiolitis obliterans organizing pneumonia (BOOP), is defined as granulated tissue plugs within lumens of small airways that extend into alveolar ducts and alveoli (Epler 1995). Organizing pneumonia is increasingly recognized as an important cause of diffuse infiltrative lung disease and is a well-known late manifestation of chronic GVHD occurring in up to 10% of stem cell transplantation (Freudenberger et al. 2003). Risk factors for OP include allogeneic HSC transplantation and GVHD (Winer-Muram et al. 1996; Khurshid and Anderson 2002). CT findings consist of patchy consolidation frequently in a subpleural or peribronchial location, ground-glass opacities, and, occasionally, centrilobular nodules (Franquet et al. 2005a) (Fig. 6.2.18).

6.2.5.3.1.3 Air-Leak Syndromes

Although air-leak syndromes have not been recognized as a fatal complication in HSC transplant recipients, pneumothorax, pneumomediastinum and subcutaneous emphysema are potential complications of patients with chronic GVHD and BO.

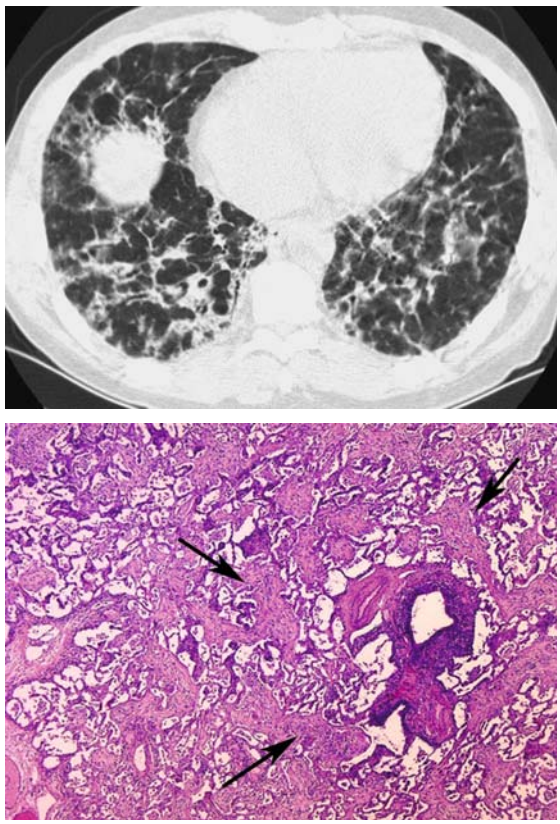


Fig. 6.2.18a,b. Organizing pneumonia after allogeneic HSC transplantation. **a** HRCT scan at the level of lower lung zones shows bilateral patchy areas of consolidation in a predominantly peribronchial distribution. **b** Photomicrograph shows the presence of fibroblastic tissue in the lumens of peribronchial alveoli (*arrows*). (H and E, ×100) (with permission from Franquet et al. 2005a)

In these patients, air in the peribronchial sheets (pulmonary interstitial emphysema) can be associated with impairment of respiratory function and/or chest pain, possibly resulting from compression of small vessels by the interstitial air. In most patients, pulmonary interstitial emphysema is transient and it is well known that this process is difficult, if not impossible, to detect by chest radiograph. Chest CT should be performed in any HSC transplant recipient with known or suspected cGVHD who present with acute clinical symptoms, especially chest pain, to rule out associated air-leak syndromes. Therefore, suspicion of BO should be high and prompt therapy should be initiated in long-term HSC transplant recipients presenting with spontaneous pneumomediastinum, pneumothorax or subcutaneous emphysema (Franquet et al. 2007).

6.2.5.3.2 Post-Transplant Malignancies

Post-transplant malignancies in HSC transplantation patients are seven times more common than primary cancer in the general population. Post-transplant malignancies include solid tumors, hematologic neoplasms, and post-transplantation lymphoproliferative disorder (PTLD) (Libshitz et al. 1978; Worthy et al. 1997).

Solid tumors have been attributed to radiation therapy with most of them occurring within or adjacent to the directly irradiated tissues or radiation ports (Bluemke et al. 1991; Bhatia et al. 2001). The risk of radiation-associated solid tumor development after HSC transplantation appears to rise with increasing levels of irradiation and is likely to increase with longer follow-up. This underscores the importance of close monitoring of patients who undergo bone marrow transplantation (Bhatia et al. 2001).

Bone and soft-tissue sarcomas and breast carcinoma are the most common radiation-induced tumors. Radiation-induced sarcoma of bone should be considered when bone destruction and an associated soft-tissue mass are shown on CT, or when changes occur in the appearance of previously stable irradiated bone (Lorigan et al. 1989). Radiation-induced mesothelioma, lung carcinoma, and esophageal carcinoma have also been described.

Post-transplantation lymphoproliferative disorder (PTLD) represents a heterogeneous group of Epstein–Barr-virus-related lymphoid tumors that occur in the setting of ineffective T-cell function because of pharmacologic immunosuppression after solid-organ transplant and HSC transplantation recipients (Worthy et al. 1997). Post-transplantation lymphoproliferative disorder occurs in approximately 2% of HSC transplantation patients, especially after heart-lung and renal transplantation. On chest radiograph or CT, PTLD usually consists of multiple pulmonary nodules and/or hilar or mediastinal lymph node enlargement (Fig. 6.2.19) (Bragg et al. 1994; Rappaport et al. 1998; Pickhardt et al. 2000).

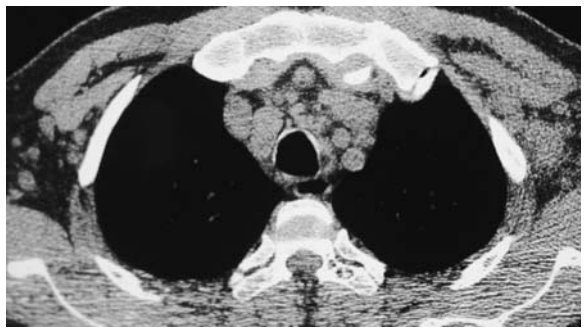


Fig. 6.2.19. Post-transplantation lymphoproliferative disorder (*PTLD*) in a 54-year-old man with multiple myeloma, 2 months after allogeneic HSC transplantation. CT scans shows multiple axilar and mediastinal adenopathies. (With permission from Franquet et al. 2005a)

6.2.5.3.3 Radiation Fibrosis

Radiation fibrosis typically occurs 6 months or more after radiation therapy. Fibrotic changes are variably present between 30 and 40 Gy, and are always seen after 40 Gy. Permanent scarring resulting in respiratory compromise may develop if the dose and volume of lung irradiated are excessive. The HRCT findings consist of a reticular pattern with associated traction bronchiectasis limited to the radiation portal (Worthy et al. 1997; Wah et al. 2003) (Fig. 6.2.20).

6.2.5.3.4 Calcification of Mediastinal Lymph Nodes and Thymic Cysts

Calcification of lymph nodes and pre-sternal soft tissue disease may be seen after radiotherapy for Hodgkin's disease (Worthy et al. 1997). Calcification of non-enlarged nodes in HD signifies a favorable response to therapy (Fig. 6.2.21). Thymic

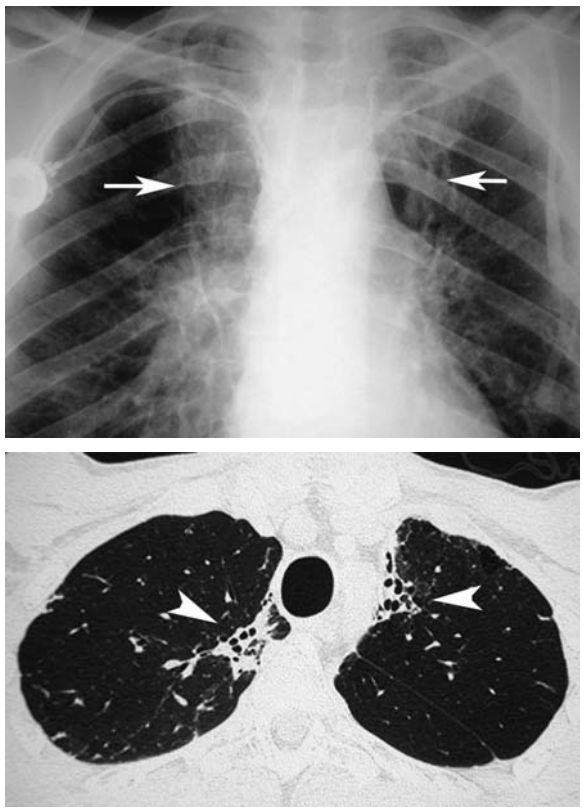


Fig. 6.2.20a,b. Radiation fibrosis in a 48-year-old man after radiation therapy for lymphoma. **a** Chest radiograph obtained 1 year after radiation therapy shows bilateral fibrotic changes in the paramediastinal lung zone (*arrows*). **b** CT scan confirms bilateral paramediastinal fibrosis in the field of irradiation (*arrowheads*). (With permission from Franquet et al. 2005a)

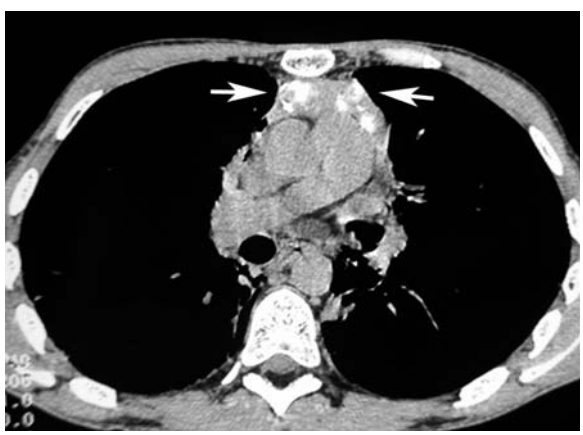


Fig. 6.2.21. Mediastinal lymph node calcification in a 38-year-old man after radiation therapy for lymphoma. Close-up view of CT shows multiple calcified retrosternal lymphadenopathy (*arrows*). The patient had undergone radiotherapy for Hodgkin's disease 3 years previously. (With permission from Franquet et al. 2005a)

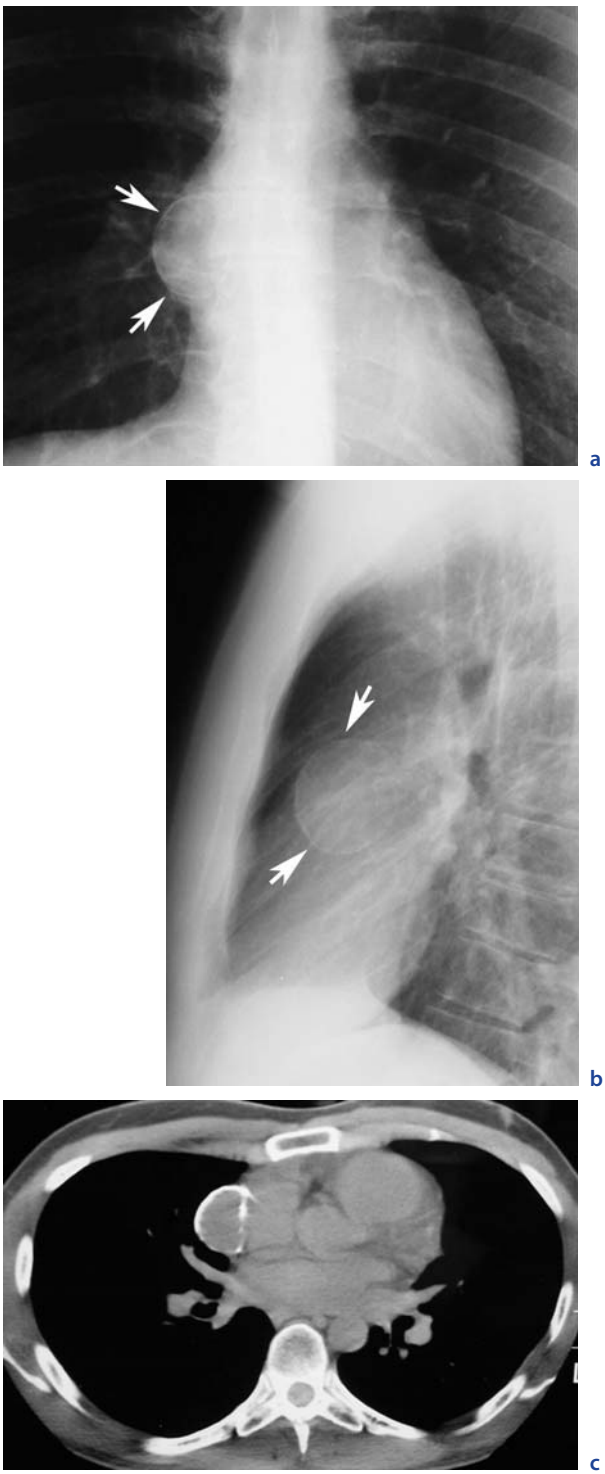


Fig. 6.2.22a–c. Calcified thymic cyst in a 30-year-old man after radiotherapy for Hodgkin's disease. **a** Posteroanterior and lateral **b** chest radiograph show a well-defined anterior mediastinal mass with a thin rim of calcification (*arrows*). **c** CT scan clearly shows a well-defined anterior mediastinal mass with a thin rim of calcification. (With permission from Franquet et al. 2005a)

cysts, sometimes with a thin rim of calcification, may develop as an inflammatory response after radiotherapy for Hodgkin's disease (Fig. 6.2.22); occasionally they enlarge and simulate recurrent tumor (Worthy et al. 1997).

6.2.6 Conclusion

The radiologist plays an important role in the diagnosis and management of HSC transplant recipients with suspected pulmonary complications. Conventional chest radiography remains the first imaging procedure in the imaging work-up of patients. Although CT is not recommended for the initial evaluation, it is frequently appropriate in those cases with normal, equivocal, or non-specific radiographic findings. High-resolution CT is helpful in the differential diagnosis of infectious from non-infectious acute parenchymal lung disease. A combination of the clinical information and HRCT findings, which are sometimes characteristic of several entities, may help the radiologist in forming a meaningful differential diagnosis of these disorders. Familiarity with the appearance of more typical pulmonary complications should improve diagnosis and patient care.

References

Afessa B, Tefferi A, Litzow MR, Peters SG (2002) Outcome of diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. Am J Respir Crit Care Med 166:1364–1368

Alam S, Chan KM (1996) Noninfectious pulmonary complications after organ transplantation. Curr Opin Pulm Med 2:412–418

Alangaden GJ, Wahiduzzaman M, Chandrasekar PH (2002) Aspergillosis: the most common community-acquired pneumonia with Gram-negative Bacilli as copathogens in stem cell transplant recipients with graft-versus-host disease. Clin Infect Dis 35:659–664

Aljurf M, Gyger M, Alrajhi A, Sahovic E, Chaudhri N, Musa M, Ayoub O, Seth P, Aslam M, Al-Fiar F (1999) *Mycobacterium tuberculosis* infection in allogeneic bone marrow transplantation patients. Bone Marrow Transplant 24:551–554

Allan BT, Patton D, Ramsey NK, Day DL (1988) Pulmonary fungal infections after bone marrow transplantation. Pediatr Radiol 18:118–122

Aquino SL, Kee ST, Warnock ML, Gamsu G (1994) Pulmonary aspergillosis: imaging findings with pathologic correlation. AJR Am J Roentgenol 163:811–815

Aquino SL, Gamsu G, Webb WR, Kee ST (1996) Tree-in-bud pattern: frequency and significance on thin section CT. J Comput Assist Tomogr 20:594–599

Aronchick JM (2000) Pulmonary infections in cancer and bone marrow transplant patients. Semin Roentgenol 35:140–151

Ascioglu S, Rex JH, de Pauw B, Bennett JE, Bille J, Crokaert F, Denning DW, Donnelly JP, Edwards JE, Erjavec Z, Fiere D, Lortholary O, Maertens J, Meis JF, Patterson TF, Ritter J, Selleslag D, Shah PM, Stevens DA, Walsh TJ (2002) Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. Clin Infect Dis 34:7–14

Bag R (2003) Fungal pneumonias in transplant recipients. Curr Opin Pulm Med 9:193–198

Barker CC, Butzner JD, Anderson RA, Brant R, Sauve RS (2003) Incidence, survival and risk factors for the development of veno-occlusive disease in pediatric hematopoietic stem cell transplant recipients. Bone Marrow Transplant 32:79–87

Ben-Abraham R, Paret G, Cohen R, Szold O, Cividalli G, Toren A, Nagler A (2003) Diffuse alveolar hemorrhage following allogeneic bone marrow transplantation in children. Chest 124:660–664

Bhagat R, Rizzieri DA, Vredenburgh JJ, Chao NJ, Folz RJ (2004) Pulmonary sarcoidosis following stem cell transplantation: is it more than a chance occurrence? Chest 126:642–644

Bhatia S, Louie AD, Bhatia R, O'Donnell MR, Fung H, Kashyap A, Krishnan A, Molina A, Nademanee A, Niland JC, Parker PA, Snyder DS, Spielberger R, Stein A, Forman SJ (2001) Solid cancers after bone marrow transplantation. J Clin Oncol 19:464–471

Bluemke DA, Fishman EK, Kuhlman JE, Zinreich ES (1991) Complications of radiation therapy: CT evaluation. Radiographics 11:581–600

Bodey GP, Vartivarian S (1989) Aspergillosis. Eur J Clin Microbiol Infect Dis 8:413–437

Boiselle PM, Tocino I, Hooley RJ, Pumerantz AS, Selwyn PA, Neklesa VP, Lange RC (1997) Chest radiograph interpretation of *Pneumocystis carinii* pneumonia, bacterial pneumonia, and pulmonary tuberculosis in HIV-positive patients: accuracy, distinguishing features, and mimics. J Thorac Imaging 12:47–53

Boiselle PM, Crans CA Jr, Kaplan MA (1999) The changing face of *Pneumocystis carinii* pneumonia in AIDS patients. AJR Am J Roentgenol 172:1301–1309

Boivin G, Abed Y, Pelletier G, Ruel L, Moisan D, Cote S, Peret TC, Erdman DD, Anderson LJ (2002) Virological features and clinical manifestations associated with human metapneumovirus: a new paramyxovirus responsible for acute respiratory-tract infections in all age groups. J Infect Dis 186:1330–1334

Bragg DG, Chor PJ, Murray KA, Kjeldsberg CR (1994) Lymphoproliferative disorders of the lung: histopathology, clinical manifestations, and imaging features. AJR Am J Roentgenol 163:273–281

Buff SJ, McLelland R, Gallis HA, Matthay R, Putman CE (1982) *Candida albicans* pneumonia: radiographic appearance. AJR Am J Roentgenol 138:645–648

Busch FW, Bautz W, Dierkesmann R, Toomes H, Schalk KP, Rusch-Gerdes S, Ehninger G (1991) [Lung changes caused by *Mycobacterium xenopi* infection in a patient with bone marrow transplantation: problems in differential diagnosis]. Pneumologie 45:340–342

Cameron ML, Bartlett JA, Gallis HA, Waskin HA (1991) Manifestations of pulmonary cryptococcosis in patients with acquired immunodeficiency syndrome. Rev Infect Dis 13:64–67

Cardozo BL, Hagenbeek A (1985) Interstitial pneumonitis following bone marrow transplantation: pathogenesis and therapeutic considerations. Eur J Cancer Clin Oncol 21:43–51

Chakrabarti S, Avivi I, Mackinnon S, Ward K, Kottaridis PD, Osman H, Waldmann H, Hale G, Fegan CD, Yong K, Goldstone AH, Linch DC, Milligan DW (2002) Respiratory virus infections in transplant recipients after reduced-intensity conditioning with Campath-1H: high incidence but low mortality. Br J Haematol 119:1125–1132

Chan CK, Hyland RH, Hutcheon MA (1990) Pulmonary complications following bone marrow transplantation. Clin Chest Med 11:323–332

Chen CS, Boeckh M, Seidel K, Clark JG, Kansu E, Madtes DK, Wagner JL, Witherspoon RP, Anasetti C, Appelbaum FR, Bensinger WI, Deeg HJ, Martin PJ, Sanders JE, Storb R, Storek J, Wade J, Siadak M, Flowers ME, Sullivan KM (2003) Incidence, risk factors, and mortality from pneumonia developing late after hematopoietic stem cell transplantation. Bone Marrow Transplant 32:515–522

Choi YH, Leung AN (1999) Radiologic findings: pulmonary infections after bone marrow transplantation. J Thorac Imaging 14:201–206

Conces DJ Jr, Stockberger SM, Tarver RD, Wheat LJ (1993) Disseminated histoplasmosis in AIDS: findings on chest radiographs. AJR Am J Roentgenol 160:15–19

Connolly JE Jr, McAdams HP, Erasmus JJ, Rosado-de-Christenson ML (1999) Opportunistic fungal pneumonia. J Thorac Imaging 14:51–62

Cooke KR, Yanik G (2004) Acute lung injury after allogeneic stem cell transplantation: is the lung a target of acute graft-versus-host disease? Bone Marrow Transplant 34:753–765

Cordonnier C (1990) [Clinical, diagnostic and physiopathological aspects of cytomegalovirus pneumonia after bone marrow transplantation]. Rev Pneumol Clin 46:244–250

Coy DL, Ormazabal A, Godwin JD, Lalani T (2005) Imaging evaluation of pulmonary and abdominal complications following hematopoietic stem cell transplantation. Radiographics 25:305–317; discussion 318

Crawford SW (1999) Noninfectious lung disease in the immunocompromised host. Respiration 66:385–395

Crawford SW, Hackman RC, Clark JG (1988) Open lung biopsy diagnosis of diffuse pulmonary infiltrates after marrow transplantation. Chest 94:949–953

Cunningham I (1992) Pulmonary infections after bone marrow transplant. Semin Respir Infect 7:132–138

Denning DW (2000) Early diagnosis of invasive aspergillosis. Lancet 355:423–424

Denning DW (2001) Chronic forms of pulmonary aspergillosis. Clin Microbiol Infect 7 [Suppl 2]:25–31

Doucette K, Fishman JA (2004) Nontuberculous mycobacterial infection in hematopoietic stem cell and solid organ transplant recipients. Clin Infect Dis 38:1428–1439

Ellis SJ, Cleverley JR, Muller NL (2000) Drug-induced lung disease: high-resolution CT findings. AJR Am J Roentgenol 175:1019–1024

Epler GR (1995) Bronchiolitis obliterans organizing pneumonia. Semin Respir Infect 10:65–77

Ettinger NA (1993) Invasive diagnostic approaches to pulmonary infiltrates. Semin Respir Infect 8:168–176

Evans A, Steward CG, Lyburn ID, Grier DJ (2003) Imaging in haematopoietic stem cell transplantation. Clin Radiol 58:201–214

Foot AB, Caul EO, Roome AP, Darville JM, Oakhill A (1993) Cytomegalovirus pneumonitis and bone marrow transplantation: identification of a specific high risk group. J Clin Pathol 46:415–419

Franquet T, Muller NL, Gimenez A, Guembe P, de La Torre J, Bague S (2001) Spectrum of pulmonary aspergillosis: histologic, clinical, and radiologic findings. Radiographics 21:825–837

Franquet T, Serrano F, Gimenez A, Rodriguez-Arias JM, Puzo C (2002) Necrotizing Aspergillosis of large airways: CT findings in eight patients. J Comput Assist Tomogr 26:342–345

Franquet T, Lee KS, Muller NL (2003a) Thin-section CT findings in 32 immunocompromised patients with cytomegalovirus pneumonia who do not have AIDS. AJR Am J Roentgenol 181:1059–1063

Franquet T, Muller NL, Gimenez A, Martinez S, Madrid M, Domingo P (2003b) Infectious pulmonary nodules in immunocompromised patients: usefulness of computed tomography in predicting their etiology. J Comput Assist Tomogr 27:461–468

Franquet T, Muller NL, Oikonomou A, Flint JD (2004) Aspergillus infection of the airways: computed tomography and pathologic findings. J Comput Assist Tomogr 28:10–16

Franquet T, Muller NL, Lee KS, Gimenez A, Flint JD (2005a) High-resolution CT and pathologic findings of noninfectious pulmonary complications after hematopoietic stem cell transplantation. AJR Am J Roentgenol 184:629–637

Franquet T, Muller NL, Lee KS, Oikonomou A, Flint JD (2005b) Pulmonary candidiasis after hematopoietic stem cell transplantation: thin-section CT findings. Radiology 236: 332–337

Franquet T, Rodriguez S, Martino R, Salinas T, Gimenez A, Hidalgo A (2005c) Human metapneumovirus infection in hematopoietic stem cell transplant recipients: high-resolution computed tomography findings. J Comput Assist Tomogr 29:223–227

Franquet T, Rodríguez S, Hernández JM, Martino R, Giménez A, Hidalgo A, Domingo P (2007) Air-leak syndromes in hematopoietic stem cell transplant recipients with chronic GVHD. High-resolution CT findings. J Thorac Imaging (in press)

Freudenberger TD, Madtes DK, Curtis JR, Cummings P, Storer BE, Hackman RC (2003) Association between acute and chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia in recipients of hematopoietic stem cell transplants. Blood 102:3822–3828

Fukuda T, Boeckh M, Guthrie KA, Mattson DK, Owens S, Wald A, Sandmaier BM, Corey L, Storb RF, Marr KA (2004) Invasive aspergillosis before allogeneic hematopoietic stem cell transplantation: 10-year experience at a single transplant center. Biol Blood Marrow Transplant 10:494–503

Gasparetto EL, Escuissato DL, Marchiori E, Ono S, Frare e Silva RL, Muller NL (2004) High-resolution CT findings of respiratory syncytial virus pneumonia after bone marrow transplantation. AJR Am J Roentgenol 182:1133–1137

Gasparetto EL, Escuissato DL, Inoue C, Marchiori E, Muller NL (2005) Herpes simplex virus type 2 pneumonia after bone marrow transplantation: high-resolution CT findings in 3 patients. J Thorac Imaging 20:71–73

Gaziev D, Baronciani D, Galimberti M, Polchi P, Angelucci E, Giardini C, Muretto P, Perugini S, Riggio S, Ghirlanda S, Erer B, Maiello A, Lucarelli G (1996) Mucormycosis after bone marrow transplantation: report of four cases in thalassemia and review of the literature. Bone Marrow Transplant 17:409–414

Ghosh S, Champlin R, Couch R, Englund J, Raad I, Malik S, Luna M, Whimbey E (1999) Rhinovirus infections in myelosuppressed adult blood and marrow transplant recipients. Clin Infect Dis 29:528–532

Giacchino M, Busca A, Miniero R, Defilippi C, Massara FM, Vassallo E, Madon E (1993) [Pulmonary complications after bone marrow transplantation]. Minerva Pediatr 45:141–150

Gotway MB, Dawn SK, Caoili EM, Reddy GP, Araoz PA, Webb WR (2002) The radiologic spectrum of pulmonary Aspergillus infections. J Comput Assist Tomogr 26:159–173

Gulbahce HE, Manivel JC, Jessurun J (2000) Pulmonary cytolytic thrombi: a previously unrecognized complication of bone marrow transplantation. Am J Surg Pathol 24:1147–1152

Gulbahce HE, Pambuccian SE, Jessurun J, Woodard P, Steiner ME, Manivel JC, Hite S, Ramsay NK, Baker KS (2004) Pulmonary nodular lesions in bone marrow transplant recipients: impact of histologic diagnosis on patient management and prognosis. Am J Clin Pathol 121:205–210

Heurlin N, Brattstrom C, Lonnqvist B, Westman L, Lidman C, Andersson J (1991) Aetiology of pulmonary diseases in immunocompromised patients. Eur Respir J 4:10–18

Huaringa AJ, Leyva FJ, Signes-Costa J, Morice RC, Raad I, Darwish AA, Champlin RE (2000) Bronchoalveolar lavage in the diagnosis of pulmonary complications of bone marrow transplant patients. Bone Marrow Transplant 25:975–979

Ison MG, Hayden FG, Kaiser L, Corey L, Boeckh M (2003) Rhinovirus infections in hematopoietic stem cell transplant recipients with pneumonia. Clin Infect Dis 36:1139–1143

Jantunen E, Piilonen A, Volin L, Ruutu P, Parkkali T, Koukila-Kahkola P, Ruutu T (2002) Radiologically guided fine needle lung biopsies in the evaluation of focal pulmonary lesions in allogeneic stem cell transplant recipients. Bone Marrow Transplant 29:353–356

Janzen DL, Padley SP, Adler BD, Muller NL (1993) Acute pulmonary complications in immunocompromised non-AIDS patients: comparison of diagnostic accuracy of CT and chest radiography. Clin Radiol 47:159–165

Kaiser L, Huguenin T, Lew PD, Chapuis B, Pittet D (1998) Invasive aspergillosis. Clinical features of 35 proven cases at a single institution. Medicine (Baltimore) 77:188–194

Kang EY, Patz EF Jr, Muller NL (1996) Cytomegalovirus pneumonia in transplant patients: CT findings. J Comput Assist Tomogr 20:295–299

Kantrow SP, Hackman RC, Boeckh M, Myerson D, Crawford SW (1997) Idiopathic pneumonia syndrome: changing spectrum of lung injury after marrow transplantation. Transplantation 63:1079–1086

Kapoor N, Copelan EA, Tutschka PJ (1989) Cytomegalovirus infection in bone marrow transplant recipients: use of intravenous gamma globulin as a prophylactic and therapeutic agent. Transplant Proc 21:3095–3096

Kauffman CA (2002) Endemic mycoses in patients with hematologic malignancies. Semin Respir Infect 17:106–112

Khoury MB, Godwin JD, Ravin CE, Gallis HA, Halvorsen RA, Putman CE (1984) Thoracic cryptococcosis: immunologic competence and radiologic appearance. AJR Am J Roentgenol 142:893–896

Khurshid I, Anderson LC (2002) Non-infectious pulmonary complications after bone marrow transplantation. Postgrad Med J 78:257–262

Kotloff RM, Ahya VN, Crawford SW (2004) Pulmonary complications of solid organ and hematopoietic stem cell transplantation. Am J Respir Crit Care Med 170:22–48

Krinzman S, Basgoz N, Kradin R, Shepard JA, Flieder DB, Wright CD, Wain JC, Ginns LC (1998) Respiratory syncytial virus-associated infections in adult recipients of solid organ transplants. J Heart Lung Transplant 17:202–210

Krowka MJ, Rosenow EC 3rd, Hoagland HC (1985) Pulmonary complications of bone marrow transplantation. Chest 87:237–246

Kuhlman JE, Fishman EK, Siegelman SS (1985) Invasive pulmonary aspergillosis in acute leukemia: characteristic findings on CT, the CT halo sign, and the role of CT in early diagnosis. Radiology 157:611–614

Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS (1987) Invasive pulmonary aspergillosis in acute leukemia. The contribution of CT to early diagnosis and aggressive management. Chest 92:95–99

Kuhlman JE, Fishman EK, Burch PA, Karp JE, Zerhouni EA, Siegelman SS (1988) CT of invasive pulmonary aspergillosis. AJR Am J Roentgenol 150:1015–1020

Kumar K, Jimenez V (2001) Pulmonary nocardiosis after bone marrow transplantation successfully treated with doxycycline. Int J Infect Dis 5:222–224

Leung AN, Gosselin MV, Napper CH, Braun SG, Hu WW, Wong RM, Gasman J (1999) Pulmonary infections after bone marrow transplantation: clinical and radiographic findings. Radiology 210:699–710

Libshitz HI, Zornoza J, McLarty JW (1978) Lung cancer in chronic leukemia and lymphoma. Radiology 127:297–300

Lin JT, Lee MY, Hsiao LT, Yang MH, Chao TC, Chen PM, Chiou TJ (2004) Pulmonary nocardiosis in a patient with CML relapse undergoing imatinib therapy after bone marrow transplantation. Ann Hematol 83:444–446

Ljungman P (2001) Respiratory virus infections in stem cell transplant patients: the European experience. Biol Blood Marrow Transplant Suppl 7:5S–7S

Lorigan JG, Libshitz HI, Peuchot M (1989) Radiation-induced sarcoma of bone: CT findings in 19 cases. AJR Am J Roentgenol 153:791–794

Maertens J, Demuynck H, Verbeken EK, Zachee P, Verhoef GE, Vandenberghe P, Boogaerts MA (1999) Mucormycosis in allogeneic bone marrow transplant recipients: report of five cases and review of the role of iron overload in the pathogenesis. Bone Marrow Transplant 24:307–312

Maertens J, Verhaegen J, Lagrou K, Van Eldere J, Boogaerts M (2001) Screening for circulating galactomannan as a

noninvasive diagnostic tool for invasive aspergillosis in prolonged neutropenic patients and stem cell transplantation recipients: a prospective validation. Blood 97:1604–1610

Markovic SN, Adlakha A, Smith TF, Walker RC (1998) Respiratory syncytial virus pneumonitis-induced diffuse alveolar damage in an autologous bone marrow transplant recipient. Mayo Clin Proc 73:153–156

Martino R, Manteiga R, Sanchez I, Brunet S, Sureda A, Badell I, Argiles B, Subira M, Bordes R, Domingo-Albos A (1995) Viridans streptococcal shock syndrome during bone marrow transplantation. Acta Haematol 94:69–73

Martino R, Martinez C, Brunet S, Sureda A, Lopez R, Domingo-Albos A (1996) Tuberculosis in bone marrow transplant recipients: report of two cases and review of the literature. Bone Marrow Transplant 18:809–812

Maschmeyer G (2001) Pneumonia in febrile neutropenic patients: radiologic diagnosis. Curr Opin Oncol 13:229–235

McAdams HP, Rosado-de-Christenson ML, Lesar M, Templeton PA, Moran CA (1995) Thoracic mycoses from endemic fungi: radiologic-pathologic correlation. Radiographics 15:255–270

McAdams HP, Rosado de Christenson M, Strollo DC, Patz EF Jr (1997) Pulmonary mucormycosis: radiologic findings in 32 cases. AJR Am J Roentgenol 168:1541–1548

Mohite U, Das M, Saikia T, Parikh P, Gopal R, Kelkar R, Advani S (2001) Mycobacterial pulmonary infection post allogeneic bone marrow transplantation. Leuk Lymphoma 40:675–678

Navari RM, Sullivan KM, Springmeyer SC, Siegel MS, Meyers JD, Buckner CD, Sanders JE, Stewart PS, Clift RA, Fefer A et al (1983) Mycobacterial infections in marrow transplant patients. Transplantation 36:509–513

Nichols WG, Corey L, Gooley T, Davis C, Boeckh M (2001) Parainfluenza virus infections after hematopoietic stem cell transplantation: risk factors, response to antiviral therapy, and effect on transplant outcome. Blood 98:573–578

Nichols WG, Guthrie KA, Corey L, Boeckh M (2004) Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. Clin Infect Dis 39:1300–1306

Nusair S, Breuer R, Shapira MY, Berkman N, Or R (2004) Low incidence of pulmonary complications following nonmyeloablative stem cell transplantation. Eur Respir J 23:440–445

Oikonomou A, Muller NL, Nantel S (2003) Radiographic and high-resolution CT findings of influenza virus pneumonia in patients with hematologic malignancies. AJR Am J Roentgenol 181:507–511

Ooi GC, Peh WC, Ip M (1998) High-resolution computed tomography of bronchiolitis obliterans syndrome after bone marrow transplantation. Respiration 65:187–191

Ozkaynak MF, Lenarsky C, Kohn D, Weinberg K, Parkman R (1990) *Mycobacterium avium-intracellulare* infections after allogeneic bone marrow transplantation in children. Am J Pediatr Hematol Oncol 12:220–224

Patriarca F, Skert C, Sperotto A, Damiani D, Cerno M, Geromin A, Zaja F, Stocchi R, Prosdocimo S, Fili C, Fanin R (2004) Incidence, outcome, and risk factors of late-onset noninfectious pulmonary complications after unrelated donor stem cell transplantation. Bone Marrow Transplant 33:751–758

Paulin T, Ringden O, Nilsson B, Lonnqvist B, Gahrton G (1987) Variables predicting bacterial and fungal infections after allogeneic marrow engraftment. Transplantation 43:393–398

Pickhardt PJ, Siegel MJ, Hayashi RJ, Kelly M (2000) Post-transplantation lymphoproliferative disorder in children: clinical, histopathologic, and imaging features. Radiology 217:16–25

Primack SL, Hartman TE, Lee KS, Muller NL (1994) Pulmonary nodules and the CT halo sign. Radiology 190:513–515

Rappaport DC, Chamberlain DW, Shepherd FA, Hutcheon MA (1998) Lymphoproliferative disorders after lung transplantation: imaging features. Radiology 206:519–524

Resnick IB, Averbuch D, Aker M, Engelhard D (2005) Is *Pneumocystis carinii* pneumonia after stem cell transplantations a contagious disease? Clin Transplant 19:427–431

Roviaro G, Varoli F, Francese M, Caminiti R, Vergani C, Maciocco M (2002) Thoracoscopy and transplantation: a new attractive tool. Transplantation 73:1013–1018

Roy V, Weisdorf D (1997) Mycobacterial infections following bone marrow transplantation: a 20 year retrospective review. Bone Marrow Transplant 19:467–470

Saito T, Seo S, Kanda Y, Shoji N, Ogasawara T, Murakami J, Tanosaki R, Tobinai K, Takaue Y, Mineishi S (2001) Early onset *Pneumocystis carinii* pneumonia after allogeneic peripheral blood stem cell transplantation. Am J Hematol 67:206–209

Schmidt-Wolf I, Schwerdtfeger R, Schwella N, Gallardo J, Schmid HJ, Huhn D, Siegert W (1993) Diffuse pulmonary alveolar hemorrhage after allogeneic bone marrow transplantation. Ann Hematol 67:139–141

Sider L, Westcott MA (1994) Pulmonary manifestations of cryptococcosis in patients with AIDS: CT features. J Thorac Imaging 9:78–84

Snyder CL, Ramsay NK, McGlave PB, Ferrell KL, Leonard AS (1990) Diagnostic open-lung biopsy after bone marrow transplantation. J Pediatr Surg 25:871–876; discussion 876–877

Soubani AO, Miller KB, Hassoun PM (1996) Pulmonary complications of bone marrow transplantation. Chest 109:1066–1077

Soubani AO, Qureshi MA, Baynes RD (2001) Flexible bronchoscopy in the diagnosis of pulmonary infiltrates following autologous peripheral stem cell transplantation for advanced breast cancer. Bone Marrow Transplant 28:981–985

Springmeyer SC, Hackman RC, Holle R, Greenberg GM, Weems CE, Myerson D, Meyers JD, Thomas ED (1986) Use of bronchoalveolar lavage to diagnose acute diffuse pneumonia in the immunocompromised host. J Infect Dis 154:604–610

Starobin D, Fink G, Shitrit D, Izbicki G, Bendayan D, Bakal I, Kramer MR (2003) The role of fiberoptic bronchoscopy evaluating transplant recipients with suspected pulmonary infections: analysis of 168 cases in a multi-organ transplantation center. Transplant Proc 35:659–660

Stover DE, Zaman MB, Hajdu SI, Lange M, Gold J, Armstrong D (1984) Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. Ann Intern Med 101:1–7

Stringer JR, Beard CB, Miller RF, Wakefield AE (2002) A new

name (*Pneumocystis jiroveci*) for Pneumocystis from humans. Emerg Infect Dis 8:891–896
Tabbara IA, Zimmerman K, Morgan C, Nahleh Z (2002) Allogeneic hematopoietic stem cell transplantation: complications and results. Arch Intern Med 162:1558–1566
Tanaka N, Matsumoto T, Miura G, Emoto T, Matsunaga N (2002) HRCT findings of chest complications in patients with leukemia. Eur Radiol 12:1512–1522
Tazelaar HD, Baird AM, Mill M, Grimes MM, Schulman LL, Smith CR (1989) Bronchocentric mycosis occurring in transplant recipients. Chest 96:92–95
Urbanski SJ, Kossakowska AE, Curtis J, Chan CK, Hutcheon MA, Hyland RH, Messner H, Minden M, Sculier JP (1987) Idiopathic small airways pathology in patients with graft-versus-host disease following allogeneic bone marrow transplantation. Am J Surg Pathol 11:965–971
Verfaillie C, Weisdorf D, Haake R, Hostetter M, Ramsay NK, McGlave P (1991) Candida infections in bone marrow transplant recipients. Bone Marrow Transplant 8:177–184
Vilchez RA, Linden P, Lacomis J, Costello P, Fung J, Kusne S (2001) Acute respiratory failure associated with pulmonary cryptococcosis in non-aids patients. Chest 119:1865–1869
Villablanca JG, Steiner M, Kersey J, Ramsay NK, Ferrieri P, Haake R, Weisdorf D (1990) The clinical spectrum of infections with viridans streptococci in bone marrow transplant patients. Bone Marrow Transplant 5:387–393
Wah TM, Moss HA, Robertson RJ, Barnard DL (2003) Pulmonary complications following bone marrow transplantation. Br J Radiol 76:373–379
Williams JV, Harris PA, Tollefson SJ, Halburnt-Rush LL, Pingsterhaus JM, Edwards KM, Wright PF, Crowe JE Jr (2004) Human metapneumovirus and lower respiratory tract disease in otherwise healthy infants and children. N Engl J Med 350:443–450
Winer-Muram HT, Gurney JW, Bozeman PM, Krance RA (1996) Pulmonary complications after bone marrow transplantation. Radiol Clin North Am 34:97–117
Wong PW, Stefanec T, Brown K, White DA (2002) Role of fine-needle aspirates of focal lung lesions in patients with hematologic malignancies. Chest 121:527–532
Worthy SA, Flint JD, Muller NL (1997) Pulmonary complications after bone marrow transplantation: high-resolution CT and pathologic findings. Radiographics 17:1359–1371
Yen KT, Lee AS, Krowka MJ, Burger CD (2004) Pulmonary complications in bone marrow transplantation: a practical approach to diagnosis and treatment. Clin Chest Med 25:189–201
Young JA, Hopkin JM, Cuthbertson WP (1984) Pulmonary infiltrates in immunocompromised patients: diagnosis by cytological examination of bronchoalveolar lavage fluid. J Clin Pathol 37:390–397
Zihlif M, Khanchandani G, Ahmed HP, Soubani AO (2005) Surgical lung biopsy in patients with hematological malignancy or hematopoietic stem cell transplantation and unexplained pulmonary infiltrates: improved outcome with specific diagnosis. Am J Hematol 78:94–99
Zinck SE, Leung AN, Frost M, Berry GJ, Muller NL (2002) Pulmonary cryptococcosis: CT and pathologic findings. J Comput Assist Tomogr 26:330–334