Chapter 10
Immunocompromised Patients

Scenario

A 56 years old male with underlying B-cell lymphoma was admitted to the hospital with febrile neutropenia (absolute neutrophil count of 100/mm^3) after CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone). The patient was previously treated with a monoclonal antibody against lymphocytes to which he developed allergy and subsequently received high-dose steroids for several weeks before admission. The patient was asymptomatic except for fever on admission, with no dyspnea, the physical examination was unremarkable and there was no hypoxia. The chest x-ray was normal (Fig. 10.1, panel A), while CT revealed diffuse, bilateral ground-glass infiltrates (Fig. 10.2). The patient was admitted to hospital and treated with piperacillin-tazobactam. A few days later the neutrophil count increased to >500/mm^3, the patient remained asymptomatic but pyrexial with no apparent source of infection. The antibiotic was discontinued. One day later the patient developed severe dyspnea and hypoxia requiring transfer to the ICU. Chest X-ray demonstrated diffuse bilateral infiltrates (Fig. 10.1, panel B).

1. *What is the appropriate evaluation?*
2. *What treatment should be initiated empirically?*
3. *Should steroids be discontinued?*
4. *What is the likely diagnosis?*

Admission and General Management Aspects of Cancer Patients

Admission and ICU Trial

The ominous prognosis of cancer patients with or without neutropenia in need of intensive care has led to reservations with regard to admission of cancer patients to the ICU. However, significant improvements in ICU and in-hospital survival of cancer patients in ICU have been demonstrated in studies in recent years [1–4]. Risk
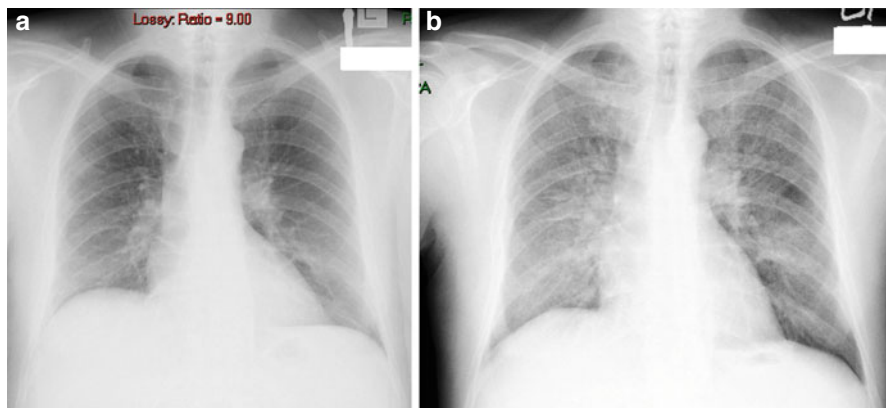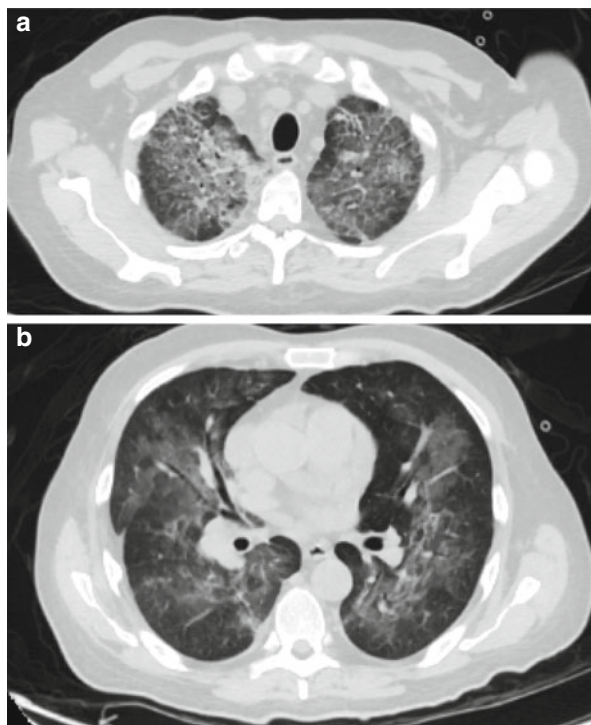
Fig. 10.1 *Panel A*: chest X-ray of case described in scenario at presentation. *Panel B*: chest X-ray 5 days after onset of respiratory symptoms

Fig. 10.2 CT scan of case described in scenario at presentation

factors for mortality have shifted from those related to the underlying condition to those related to the severity of acute illness similar to other critically-ill patients. Neutropenia per se and the underlying malignancy (solid and hematological) do not have an impact on the outcome of patients in ICU. Recent chemotherapy is

associated rather with improved survival [3, 5–7], while organ dysfunction, severity of disease scores, need for vasopressor treatment, need for mechanical ventilation immediately or after noninvasive ventilation, no definite diagnosis and a non-infectious diagnosis are associated with mortality [1–3, 8]. Invasive aspergillosis is also associated with very high mortality rates in ICU (see below). In several studies, admission to ICU in the early stages of sepsis or other acute event was associated with better survival than admission later, after development of organ dysfunction. Performance status is perhaps the most important and only variable relating to the underlying condition that is correlated with ICU death. The prognosis remains guarded for certain cancer patients, including patients after allogeneic hematopoietic stem cell transplantation (HSCT) with active uncontrolled graft versus host disease, those with relapse of the primary disease after allogeneic HSCT and special cases of solid cancer including pulmonary carcinomatous lymphangitis and carcinomatous meningitis with coma [9].

An "ICU trial" consisting of patient admission and re-assessment after 3–5 days has been suggested for cancer patients [9]. Outcomes were better associated with the hemodynamic and respiratory status after the first stabilization phase than at the time of admission. Another study supporting this concept showed that organ failure scores predicted survival more accurate on day six than at admission [7]. All patients who required initiation of mechanical ventilation, vasopressors, or dialysis after 3 days in the ICU died.

General Management

An early invasive diagnostic strategy should be pursued in immune compromised patients, since the differential diagnosis is broad including infectious and non-infectious etiologies and the spectrum of infectious agents is large. This includes bronchoalveolar lavage (BAL) with or without lung biopsy for pulmonary disease, functional endoscopic sinus surgery (FESS) for sinusitis/ rhinocerebral disease, endoscopy for colitis, biopsies from liver nodules, etc. Some infectious conditions by organ system to be considered in immune compromised patients are provided in Table 10.1. In additions, patients presenting with respiratory insufficiency should be evaluated for community-acquired respiratory viruses using PCR, direct antigen tests and cultures of respiratory samples. These include influenza, parainfluenza, adenovirus, respiratory syncytial virus (RSV), and human metapneumovirus.

Empirical antibiotic treatment is recommended for neutropenic cancer patients (neutrophil count <500/mm^3 or <1,000/mm^3 and expected to decline to <500/mm^3) with fever, diarrhoea or suspected infection [10]. Intravenous empirical treatment for high- risk patients should provide broad coverage against Gram-negative (including *Pseudomonas aeruginosa*) and Gram-positive bacteria. Vancomycin should not be administered routinely, but is reserved for patients with hypotension or other hemodynamic compromise, those with a source of infection likely to be caused by Staphylococci (skin/ soft tissue, catheter-related and pneumonia).

Table 10.1 Infectious agents to consider in immune compromised patients by organ system

Organ system	Infection	Specimen	Evaluation; specimen
Central nervous system	*Listeria* spp.	Blood and CSF	Culture
	Cryptococcus neoformans	Blood and CSF	Cryptococcal antigen culture
	Herpes viruses HSV-1 and HSV-2 CMV HHV-6	CSF	PCR Culture
	West nile virus	Blood and CSF	PCR Antibodies
Lungs – diffuse and interstitial infiltrates	*Pneumocystis jirovecii* (PCP)	BAL and lung biopsy	Giemsa or immunofluorescent stain; PCR
	CMV	Blood, BAL, lung biopsy	PCR
			Antigenemia
		BAL, lung biopsy	Culture
		Tissue	Histology
Lung – nodular, cavitary or other local infiltrates	*Aspergillus* sp.	BAL and biopsy	Calcofluor stain PCR
		Sputum, BAL and lung biopsy	Culture
		Lung tissue	Histology
	Other mould infections	BAL and biopsy	Calcofluor stain PCR
		Sputum, BAL and lung biopsy	Culture
		Lung tissue	Histology
	Cryptococcus neoformans	Blood	Cryptococcal antigen
		Lung tissue	Histology
	Nocardia spp.	Blood, BAL and lung biopsy	Culture PCR
	Mycobacterium spp.	Sputum, BAL and lung biopsy	Ziel-Nielsen stain Culture PCR
Sinuses and cerebral extension	*Aspergillus* spp.	Tissue biopsy	Calcofluor stain Culture PCR Histology
	Other mould infections	Tissue biopsy	Calcofluor stain Culture PCR Histology

BAL bronchoalveolar lavage

Antibiotic treatment should not be automatically discontinued with neutrophil recovery, even if infection has not been confirmed during neutropenia. Rather repeated patient examination, imaging and microbiological evaluation for suspected sources of infection should be performed after neutrophil recovery to exclude new or exacerbations of pre-existing infections.

Among patients with documented infections during neutropenia, neutrophil recovery may be associated with "deterioration" in the status of the patient. Local signs and symptoms of infection are frequently exacerbated. Thus, pulmonary infiltrates may increase with new onset respiratory compromise (see Figs. 10.1 and 10.2), an abscess may appear or enlarge or local signs of catheter-related infection may become manifest. In this case, treatment should not necessarily be changed or expanded. This is the normal response to neutrophil recovery.

An immune reconstitution inflammatory response (IRIS), originally described among patients with HIV following treatment initiation (see below), has also been described among cancer patients following neutrophil recovery [11]. This syndrome represents an overly robust and dysregulated inflammatory response resulting in re-appearance or deterioration in clinical signs and symptoms of infection. It occurs usually later than the initial worsening following neutrophil recovery, days to weeks after immune reconstitution. Diagnosis is difficult and is based mostly on negative cultures and biomarkers for the initial infection and treatment is with corticosteroids. A specific syndrome of adult respiratory distress syndrome (ARDS) has been described following neutrophil recovery in hematological cancer patients [12]. The only independent risk factor for ARDS is pneumonia during neutropenia.

The importance of administering chemotherapy, if needed, cannot be over-emphasized, even during an acute infection. While inducing immune suppression during an acute infection is counter intuitive, it is the underlying malignancy that is most commonly responsible for infection among cancer patients. Without control of the underlying malignancy the long term outcomes of most or all infections remain ominous. Close liaison with hematologists/ oncologists is recommended for oncological patients admitted to the ICU [9].

Role of Platelet and Neutrophil Transfusions and Immunoglobulins

Cancer patients, especially hematological cancer patients are frequently thrombocytopenic as part of their underlying illness or as a result of chemotherapy. While randomized controlled trials have not shown an advantage to a threshold higher than 10×10^9/l for thrombocyte transfusions, these studies did not include critically ill patients [13]. A higher threshold should probably be used ($20–30 \times 10^9$/l) in critically ill hematological cancer patients, especially with sepsis or with pulmonary involvement. Pulmonary and intracerebral hemorrhage are frequent terminal events in these patients and prophylactic transfusions may prevent mortality.

Neutrophil transfusions have not been shown to improve survival for patients with severe neutropenia as part of the management of acute infections. However, when sub-grouped according to the dose of neutrophils transfused, survival was improved with average neutrophil doses of 1×10^{10}. This dose can be obtained by pre-treating donors with granulocyte growth stimulating factors (G-CSF) [14]. Neutrophil transfusions should be reserved for severely neutropenic patients (<100/ml^3) for whom the neutrophil count is expected to increase in a few days, as a bridge until bone marrow reconstitution. Neutrophil transfusion is probably futile when there is no expectation that the natural neutrophil count will increase.

Hematological cancer patients may be hypoglobulinemic as part of the underlying hematological malignancy or following chemotherapy. There is no evidence from high-quality studies that intravenous immuneglobulins (IVIG) reduces mortality in sepsis in general and in cancer patients specifically [15]. In one randomized controlled trial specifically assessing patients with hematological malignancies, there was no survival advantage with IVIG [16]. IVIG is used in some centers for infection prevention among patients with multiple myeloma or chronic lymphocytic leukemia, known hypogammaglobulinemia and recurrent respiratory infections [17].

The HIV Positive Patient

Patients with HIV may be seen in the ICU as the first presentation of their disease or following an infectious complication after diagnosis. Highly active antiretroviral therapy (HAART) has changed the epidemiology of HIV such that the latter group of patients is rare nowadays in locations where treatment is available (and depending on patient's compliance). Clearly, the change in prognosis of HIV with HAART has led to a shift in management such that HIV patients are offered maximal treatment, including full ICU support, organ transplantation in the appropriate circumstances, or chemotherapy if needed. The impact of HAART availability on mortality has been shown also in ICU, where predictors of mortality in the HAART era are no longer HIV-related [18]. A thorough discussion of the management of HIV patients is beyond the scope of this book. However, we will address a few critical decisions in the management of infections with suspected or known HIV.

Administering HAART During Critical Illness

Administering antiretroviral therapy in the ICU is difficult [19]. All antiretrovirals except zidovudine are available only as oral preparations, most only as tablets. Beyond the poor bioavailability of orally administered drugs in the critically-ill patient, absorption and side effects of specific antiretrovirals frequently depend on the provision of concurrent oral feeding. Drug interactions are common; for

example proton-pump inhibitors and histamine-2 blockers are contraindicated with protease inhibitors (PIs). All nucleoside reverse-transcriptase inhibitors (NRTIs), except for abacavir, require dose adjustment for renal failure. Several PIs require dose adjustment for hepatic impairment [19]. Thus, fixed drug combination usually cannot be used in patients with renal and hepatic impairment; individual drugs must be dose-adjusted and administered separately. Drug-related adverse effects are common, although few may be relevant in the critical care setting. NRTIs (mainly stavudine, didanosine, and zidovudine) may induce lactic acidosis. Abacavir-related hypersensitivity is a serious adverse event and this drug should be administered only after genetic testing for HLA-B*5701.

The most common infectious scenario encountered in the ICU will be the recently diagnosed patient presenting with an opportunistic infection. The question in this scenario is whether to initiate antiretroviral therapy early while treating the acute infection or after its successful management. Aside from the practical difficulties in the administration of HAART in ICU, there is the fear of IRIS with worsening of the underlying infectious process during immune reconstitution. IRIS can occur between days to weeks after initiation of HAART [19]. Although logically predicted by rising CD4 counts, it can occur before significant CD4 cell count increase or viral load suppression [20].

There are few randomized trials to guide the strategic decision of early vs. deferred HAART initiation during infection (Table 10.2). Three trials have shown a clinical benefit for early, but not immediate antiretroviral drug initiation (e.g. within 2 weeks of starting anti-infective treatment), for patients mostly with pulmonary tuberculosis and PCP [21–23]. One study showed no difference in outcomes for patients with pulmonary and extrapulmonary tuberculoisis [24]. In contrast two trials assessing HIV patients with meningitis showed no benefit or increased harm with early initiation of HAART initiation [25, 26] (Table 10.2) . There is no direct evidence on timing of HAART initiation in the critical care setting. Summarizing the evidence from existing trials, it seems that the initiation HAART about 2 weeks after anti-infective therapy directed at the opportunistic infection is reasonable for patients with pulmonary infections, including tuberculosis. This allows the time for patient stabilization, HIV drug resistance testing and involving an HIV specialist in the management and all treatment decisions. With tuberculosis or cryptococcal meningitis, the start of HAART should probably be deferred for longer.

In previously treated HIV patients, the question is whether to continue or stop HAART in ICU. Discontinuation could result in the selection of anti-viral resistance because of the different half-lives of the drugs included in the combination and functional monotherapy with the long-acting antiretrovirals. An expert recommendation is to try and continue HAART for patients with virological suppression (plasma HIV RNA below the limit of detection) [19]. In other patients, HAART can probably be discontinued after consultation with an HIV expert. HIV/ hepatitis B co-infected patients require special consideration. Antiretroviral treatment active against hepatitis B (lamivudine, emtricitabine, and tenofovir) should not be discontinued for fear of exacerabations of hepatitis B after discontinuation.

Table 10.2 Studies assessing the time for initiation of HAART during acute infection in treatment naïve HIV-positive patients

Study	Types of infection	Treatment timing	Outcomes of early HAART initiation
[21]	Opportunistic infections, mainly PCP	Early: median of 12 days after the start of anti-infective therapy	AIDS progression or death significantly reduced with early treatment (odds ratio 0.51, 95 % CI 0.27–0.94)
[22]	Tuberculosis (mostly pulmonary)	Early: within 2 weeks Late: initiated between 8 and 12 weeks after initiation of anti-TB treatment	New AIDS-defining illness or death by 48 weeks occurred less frequently among patients with baseline CD4
[23]	Tuberculosis (mostly pulmonary)	Early: initiated during anti-tuberculous treatment, mean 70 ± 72 days after start of treatment	Mortality significantly lower with early treatment (hazard ratio 0.44, 95 % confidence interval 0.25–0.79)
[24]	Tuberculosis (pulmonary)	Early 4 weeks after start of anti-TB treatment Late: 12 weeks after start of anti-TB treatment	No differences in mortality in all CD count strata
[25]	Tuberculous meningitis	Early: initiated during the first week of anti-tuberculosis treatment	No benefit and higher rate of serious adverse events with early treatment
[26]	Cryptococcal meningitis	Early: initiated within 72 h of antifungal treatment (fluconazole) Delayed: initiated after 10 weeks of antifungal treatment	Significantly higher mortality with early treatment (adjusted hazard ratio 2.85, 95 % CI 1.1–7.23). Three-year mortality among the 54 trial participants was 88 % with early HAART and 54 % with delayed HAART (study terminated early)

Adrenal insufficiency is common among HIV patients and should be evaluated in all patients admitted to the ICU. Testing of stress cortisol concentration and low-dose adrenocorticotropic hormone (ACTH) corticotropin stimulation test (1-microg of ACTH) is recommended [27].

Solid Organ Transplant Recipients

Solid organ transplant (SOT) recipients require life long immune suppression to prevent rejection. This immune suppression affects mainly the T-cell lymphocyte function. Consequently, opportunist infections seen most frequently among SOT recipients include herpesvirus infections, mainly CMV, pneumocystis pneumonia and more rarely fungal infections. EBV-associated post-transplantation lymphoproliferative disease (PTLD) is a special entity.

In the first month after transplantation, most infections will be healthcare-associated, related to the surgical site, catheter or post-operative mechanical ventilation. Lung transplant recipients are frequently colonized before transplantation by bacteria and pneumonia is very common in the first year after transplantation (mostly in the first month) and is associated with a high relative risk of death [28]. Donors may also be colonized with antibiotic resistant bacteria [29]. Prophylaxis for a more prolonged period (i.e. days) compared with non-transplant surgery (i.e. 1–2 doses of antibiotics) should be guided by the presence of pre-existing antibiotic-resistant bacteria in the recipient or the donor. All antibiotics continued after transplantation should be reviewed early with a view to discontinuation if the recipient is clinically well and there is no other evidence to suggest infection. Antibiotics can be discontinued 48–72 h after transplantation if culture of donor and recipient samples is negative and the patient is stable.

Antibiotic prophylaxis in liver transplantation should provide a therapeutic concentration in the wound and within the biliary tract. In a European survey, all liver transplant centres administered antibiotic prophylaxis for liver transplantation, using a variety of different antibiotic regimens for a median of 3 days after transplantation [30].

Given the shortage of organs, transplant centers are increasingly using marginal donors, sometimes with documented infections at the time of death, which might have been previously treated or not. Studies describe non-inferior outcomes for recipients receiving organs from donors with clinical infections, including bloodstream infection and meningitis [31–34]. Treatment directed against the donor's isolate/s was given to recipients. Procurement of organs from previously untreated patients with meningitis has not been described.

Examples of Opportunist Infections

Severe PCP

Pneumocystis pneumonia (PCP) caused by *Pneumocystis jirovecii* most commonly affects patients with cellular immune deficiency, including lymphopenia or qualitative defects in lymphocyte activity, rather than patients with neutropenia or neutrophil dysfunction. Susceptible patients therefore include patients with:

- multiple myeloma
- chronic lymphocytic leukemia
- following HSCT with graft versus host disease (GVHD hematological cancer patients receiving anti-lymphocyte antibodies such as rituximab and alemtuzumab (mainly lymphoma)
- SOT recipients mainly during periods of high-corticosteroid therapy or anti-lymphocyte antibody treatment for rejection
- non-immune-reconstituted HIV patients.

HAART has changed the epidemiology of PCP such that most patients are now not HIV-positive. PCP is more severe and is associated with higher mortality in non-HIV patients. Prophylaxis with trimethoprim-suphamethoxazole (TMP-SMX) given daily or thrice weekly is highly effective in PCP prevention and patients who are receiving TMP-SMX prophylaxis presenting with a clinical picture suspected of PCP probably do not have PCP. Compliance with prophylaxis in the period before admission should be ensured by history taking, since discontinuation of PCP prophylaxis for adverse events is common and protection from PCP is reliable only while this drug is taken. Less is known about the efficacy of other prophylaxis agents, including dapsone or pentamidine, and their administration should not rule out the possibility of PCP in the appropriate clinical setting.

PCP presents with dyspnea, tachypnea and hypoxia. Lung imaging shows bilateral interstitial or ground glass infiltrates. Initially the chest X ray may appear near normal but a high-resolution CT scan will show these opacities better. With more severe disease bilateral diffuse infiltrates can be seen also on the chest X-ray. The radiological picture is similar to than seen with CMV pneumonitis and actually co-infection of PCP and CMV is not uncommon. A diagnosis of one does not rule out the existence of the other and a search for CMV infection should be performed when PCP is diagnosed, especially in hematological cancer and SOT patients.

The interval from symptom onset to diagnosis of PCP was 3–14 days in one study [35]. Diagnosis is established most commonly by examination of BAL fluid, but it is possible also with induced sputum (Table 10.1). Giemza stain or immunofluorescence stain with human monoclonal anti-Pneumocystis cyst antibodies will demonstrate *P. jirovecii* trophozoites or cysts. PCR is more sensitive but less specific; *P. jirovecii* was identified by nested PCR in 68 % of people dying suddenly of non-infectious reasons, representing low-level colonization [36]. In the appropriate clinical scenario a positive PCR probably mandates treatment, but in other cases PCR results may represent colonization.

TMP-SMX is considered the most effective therapy for PCP [37]. It is administered using high doses of 15–20 mg/kg/day of the trimethoprim component and 75–100 mg/kg/day of the sulphamethoxazole component, divided in four daily doses. Clinical response may be delayed until day 7 or later and treatment should be continued for 21 days. Adverse effects are common and include mainly rash and TMP-SMX-induced leucopenia. Hematologists or oncologists may be reluctant to use TMP-SMX in patients with neutropenia for fear of delaying neutrophil recovery. Leucovorin (folinic acid) can attenuate the hematologic adverse effects of TMP-SMX, but should probably not be used during active PCP infection since it has been shown to increase death and failure rates in HIV patients [38]. Alternative agents include the combination of primaquine 30 mg/ day and clindamycin 600 mg thrice daily, a combination of dapsone with trimethoprim, atovaquone alone or intravenous pentamidine alone. Each medication has its own adverse effect profile which should be considered on a patient-by-patient basis before treatment and monitored for during treatment.

Adjunctive corticosteroid treatment for patients with hypoxemia (room air PaO_2 <70 mmHg) is based on evidence of improved survival in HIV patients, but it is recommended in other immune compromised patients with severe PCP [37].

The dose recommended is 40 mg prednisone twice daily for 5 days, 40 mg/day for the next 5 days and 20 mg/day until day 21.

Invasive Aspergillosis

The classical risk factors for invasive aspergillosis include severe prolonged neutropenia, the immune deficiency state following allogeneic hematopoietic stem cell transplantation, particularly in the first year after transplantation and with GVHD and more rarely following SOT, mainly lung transplantation. However, currently, invasive aspergillosis is also reported among other patient populations in the ICU not "classically" considered as immune compromised. These include patients with chronic lung disease, cirrhosis, burns and others [39]. Post-mortem studies show that invasive aspergillosis is under-diagnosed in the ICU. Therefore, in this setting, positive respiratory cultures for *Aspergillus sp*. should not be automatically disregarded.

Aspergillus sp. may cause infectious, saprophytic and allergic syndromes. Herein, we will address three of the more important infectious syndromes seen in ICU: invasive aspergillosis, aspergillus tracheobronchitis and chronic necrotizing aspergillosis.

Invasive aspergillosis, the classical condition described in immunocompromised patients, involves the lungs, sinuses with or without cerebral extension and skin mostly. Both contiguous extension disregarding normal anatomical barriers (as in the extension from the respiratory sinuses to the brain) and hematogenous dissemination (causing lung infarction) may occur. Chest and sinus x-rays are notoriously insensitive for the diagnosis of invasive aspergillosis and CT is the imaging of choice. During neutropenia findings are usually lacking or minimal, but after neutrophil recovery lesions frequently increase in size even with adequate treatment and control of systemic infection (Fig. 10.3). Respiratory deterioration should also be expected at the time of neutrophil recovery. The classical signs of cavitation and crescent formation are usually observed at later stages of the disease (Fig. 10.4). Lung hemorrhage is a feared complication, especially after biopsy, and thus attention should be given to correcting thrombocytopenia during invasive aspergillosis (see above).

Criteria for the diagnosis of invasive Aspergillosis have been suggested [40]. These consist of at least one host risk factor and one clinical finding (Table 10.3). To diagnose probable invasive aspergillosis laboratory confirmation is needed in addition to host and clinical criteria (Table 10.4) and for proven disease histological confirmation is necessary. *Aspergillus spp*. appear as narrow, non-septate, acute-branching hyphae.

Given the difficulties in obtaining histological specimens in cancer patients that are severely thrombocytopenic, diagnosis usually relies on culture, direct stains, PCR and galactommanan (GM, a cell wall component of *Aspergillus spp*. and *Penicillium spp*). PCR and GM can be tested in serum or in BAL fluid. As can be
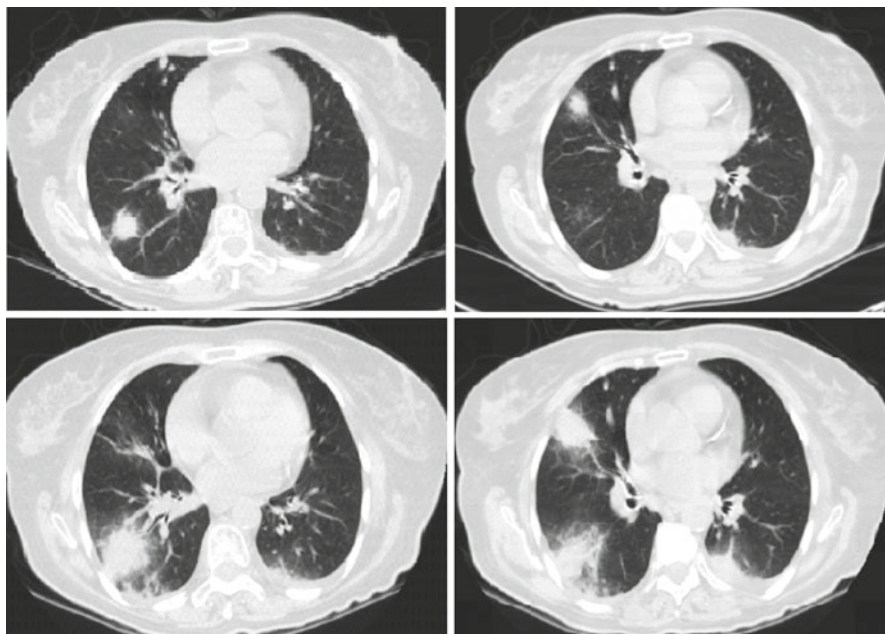
Fig. 10.3 The time course of invasive aspergillosis. *Upper panel*: initial lung CT findings during neutropenia (neutrophil count $0/ml^3$) in a patient during induction for AML, showing discrete pulmonary nodules. *Lower panel*: lung CT findings 2 weeks later after neutropenia resolution showing enlarged nodular infiltrates surrounded by "halo", a classic sign of pulmonary aspergillosis
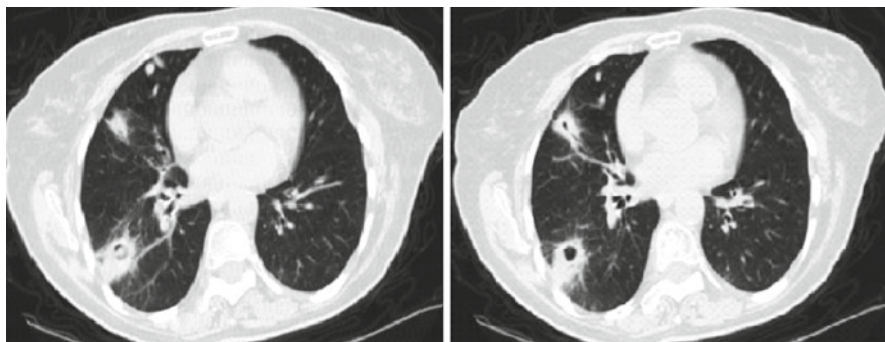

Fig. 10.4 The above patient 6 weeks after the initial CT showing resolution of pulmonary nodules with cavitation and the "crescent sign"

seen in Table 10.5, the sensitivity and specificity are slightly higher in BAL, favoring the performance of BAL for patients with suspected invasive aspergillosis.

Aspergillus tracheobronchitis represents infection of the major airways, with erythema, ulceration, nodules and pseudomembrane formation [39]. It has been described mostly among lung transplant recipients, but also among patients with COPD and

Table 10.3 Major host and clinical criteria to diagnose invasive aspergillosis

Host factors

  Neutropenia >10 days prior to onset of suspected IA

  Allogeneic stem cell transplant

  Corticosteroids ≥0.3 mg/kg/day of prednisone equivalent for >3 weeks, other T cell immunosuppressants (cyclosporine, TNF-a blockers),specific monoclonal antibodies (e.g. alemtuzumab), or nucleoside analogues

  Inherited immunodeficiency (e.g. chronic granulomatous disease or severe combined immunodeficiency)

Clinical criteria

  Findings on lung CT compatible with IA, including at least 1 of the following: dense, well-circumscribed lesions(s) with or without a halo sign; air-crescent sign; or cavity

  Evidence for tracheobronchitis on bronchoscopy

  Imaging showing sinusitis plus at least 1 of the following: acute localized pain, nasal ulcer with black eschar, extension from the paranasal sinus across bony barriers, including into the orbit

  Radiological evidence for CNS infections, including focal lesions in brain or meningeal enhancement on MRI or CT

Revised from De Pauw et al. [40]

Table 10.4 Criteria for the laboratory diagnosis of invasive aspergillosis [40]

	Histology	Culture	Antigen
Proven	Histopathological or cytological evidence of mold forms compatible with *Aspergillus sp.* from a tissue biopsy accompanied by tissue damage	Growth of *Aspergillus sp.* from a tissue specimen (not including BAL or sinus biopsy)	None
Probable (mandates host+clinical criteria)[a]	Cytological evidence of mold forms compatible with *Aspergillus sp.* from sputum, BAL or sinus aspirate	Growth or positive direct microscopy in sputum, BAL or sinus aspirate	GM in serum, BAL or CSF Beta-d-glucan in serum
Possible (mandates host+clinical criteria)[a]	None	None	None

BAL bronchoalveolar lavage, *GM* galactomannan
[a]See table 10.3 for host and clinical criteria

even in non-immune compromised severely ill patients in ICU. Extensive inflammation of the tracheobronchial tree, pseudomembranes or mucus plugs with Aspergillus may cause airway obstruction. Diagnosis is performed by visualization of the mucosa during bronchoscopy and histology showing hyphal invasion of the bronchial mucosa or cartilage. Cultures are usually positive because of the high fungal load.

Table 10.5 Diagnostic accuracy of tests to diagnose IA

	Sensitivity	Specificity
PCR in blood [41]	0.88 (95 % CI 0.75–0.94)	0.75 (95 % CI 0.63–0.84)
PCR in BAL [42]	0.91 (95 % CI 0.79–0.96)	0.92 (95 % CI 0.87–0.96)
GM in blood[a] [43]	0.78 (95 % CI 0.61–0.89)	0.81 (95 % CI 0.72–0.88)
GM in BAL[a] [44]	0.90 (95 % CI 0.79–0.96)	0.94 (95 % CI 0.90–0.96)

Sensitivity and specificity values refer to the diagnosis of probable or proven IA
GM galactomannan, *CI* confidence interval
[a]Values refer to a GM cut-off of 0.5 optical density index

Chronic necrotizing aspergillosis (or "semi-invasive aspergillosis") consists of a more chronic and diffuse form of lung infection, resembling pulmonary coccidioidomycosis or histoplasmosis [37]. It has been described among patients with chronic lung disease, diabetes mellitus, AIDS and with chronic corticosteroid therapy. The existence of the syndrome is important to recognize for patients presenting severe respiratory diseases and positive respiratory culture of *Aspergillus sp.*, without the classical features of invasive aspergillosis.

The primary recommended therapy for the infectious syndromes described herein is voriconazole [37, 45]. Voriconazole is available both in oral and intravenous formulations. Blood level concentrations should be monitored, since currently recommended dosing frequently results in subtherapeutic concentrations [46]. Many other antifungals are active and recommended for the treatment of invasive aspergillus infections; [37, 45] fluconazole is the only azole inactive against *Aspergillus sp.* (see Chap. 4 on antifungals). Treatment failure and mortality rates are very high, especially with ongoing immune suppression. Because of the ominous prognosis combinations of antifungals have been suggested as primary or salvage therapy. In one small randomized controlled trial, the combination of liposomal amphotericin B with caspofungin resulted in a higher rate of favorable response than liposomal amphotericin B, with no deaths in the combination arm (0/15 vs. 3/15 with monotherapy [47]. The most common combination reported in observational studies was voriconazole and caspofungin, but at this time no conclusions can be drawn on the effects of this combination over monotherapy [48].

Answers to Scenario Questions

1. The patient in the case vignette underwent bronchoalveolar lavage (BAL) with lung biopsy. CMV was isolated in cultures of the BAL fluid. CMV antigenemia was tested after neutropil recovery (the pp65 antigen is present in neutrophils which are required for CMV antigenemia assessment) and was negative. Direct immunofluorescence and PCR for *P. jirovecii* in BAL fluid were negative. Lung biopsy demonstrated diffuse alveolar damage with eosinophlic alveolar foam compatible with PCP. A methamine-silver and immunohistochemical stains for PCP were negative, as was the immunohistochemical stain for CMV. The patient was diagnosed with PCP based on the clinical presentation and histological

findings. CMV co-infection could not be ruled out. The positive CMV culture in BAL fluid could reflect CMV reactivation and infection in the presence of immune suppression, without disease.

2. The patient was empirically treated with high-dose trimethoprim-sulfamethoxazole and intravenous gancyclovir with no adverse events and these were continued after the results of the tests discussed above.
3. The dose of prednisone was increased and tapered down following the recommendations for severe PCP.
4. Respiratory insufficiency improved gradually until the patient was discharged with normal saturation on room air. Notable was the appearance of pulmonary infiltrates and respiratory distress only after neutrophil recovery, although fever started during neutropenia and probably reflected the same infection. This exacerbation after neutrophil recovery is similar to the immune reconstitution syndrome seen with HIV patients after start of HAART.

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