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Diffuse alveolar hemorrhage in patients with hematological malignancies: HRCT patterns of pulmonary involvement and disease course

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ABSTRACT

Objective: To analyze high-resolution computed tomography (HRCT) patterns of lung involvement and disease course in patients with hematological malignancies experiencing diffuse alveolar hemorrhage (DAH) after chemotherapy±allogeneic stem cell transplantation (allo-SCT). **Materials and methods:** Sixteen patients experiencing DAH after chemotherapy±allo-SCT were enrolled. A total of 74 computed tomography (CT) scans obtained before, during, and after onset of DAH were evaluated retrospectively. **Results:** CT features of DAH are each, by oneself, nonspecific. However, conjoint bilateral, diffuse, and dependent ground glass opacity±crazy paving, accompanied by airspace bronchograms, should suggest this complication. The HRCT course comprises a wide range of trends that are not predictive for patient's outcome, but progression of parenchymal consolidations at follow up was more often detrimental.

1. Introduction

An abundance of noninfectious pulmonary complications is induced by chemotherapy and hematopoietic (particularly allogeneic) allogeneic stem cell transplantation (allo-SCT), commonly including diffuse alveolar damage (DAD), pulmonary edema, idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage (DAH), and manifestations related to acute pulmonary graft-versus-host disease (GVHD) [1–4].

DAH in the allo-SCT setting holds a poor prognosis with a mortality rate ranging between 64% and 100% [5]. It is characterized by multilobar pulmonary infiltrates, hypoxemia, absence of infection compatible with the diagnosis, progressively bloodier return in bronchoalveolar lavage (BAL), and the presence of blood in ≥30% of alveolar surfaces at autopsy [5,6]. The exact pathogenesis still remains elusive although capillary endothelial damage by chemotherapy followed by intravascular microthrombosis and transendothelial neutrophil engraftment following allo-SCT is known to cause leakage of red blood cells into the pulmonary alveoli [7]. Clinical symptoms and signs are those of pneumonia, that is, dyspnea, cough, fever, tachycardia, and rarely hemoptysis [8].

Accurate diagnosis and close monitoring of DAH via imaging is imperative for patient care. The radiographic appearance of DAH is described as unspecific with an interstitial or alveolar pattern of lung opacification primarily involving the central portion of the lung with predilection for the middle and lower lung zones [9]. High-resolution computed tomography (HRCT) is the most accurate imaging method displaying parenchymal lung involvement and is ideally suited to recognize and follow the extent and macroscopic morphology of DAH. However, apart from several excellent review articles and book chapters overviewing the field of DAH [10–12], we did not find a comprehensive analysis of HRCT findings in patients with hematological malignancies developing DAH.

Thus, we analyzed lung involvement and disease course by HRCT in patients with hematological malignancies who developed DAH after chemotherapy±allo-SCT. Our work addresses two principle points: to determine the leading computed tomography (CT) morphologic finding or combination of findings and their prevalence in this patient group and to trace the temporal course of lung parenchymal changes.

2. Methods

2.1. Patient demographics

This retrospective study was approved by our institutional review board that waived informed consent. Between May 2008 and

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December 2011, 16 patients with hematological malignancies (11 men, 5 women; age range: 21–70 years, mean: 46.4 years) who developed DAH after chemotherapy±allo-SCT were enrolled (Table 1). Eight patients underwent allo-SCT before the development of DAH. All patients were examined for signs of acute GVHD in the skin, the liver, or the gut after allo-SCT.

2.2. Inclusion criteria

DAH was defined (according to current guidelines of National Institutes of Health) as the sudden development of multilobar infiltrates, symptoms and signs of pneumonia with abnormal pulmonary physiology, the absence of active lower respiratory tract infection, and the presence of hemorrhage as determined by BAL or retrospectively by autopsy [5]. In our study, the following additional criteria were considered necessary for confirmation of DAH and subsequent patient enrollment: (a) BAL at ≤2 days after the beginning of symptoms showing progressively bloodier return ($n=10$); (b) autopsy revealing blood in >30% of the alveolar surfaces of lung tissue ($n=1$); or (c) the combination of thrombocytopenia (<50.000/μl), a sudden drop in hemoglobin of ≥1g/dl, multilobar infiltrates, and an acute drop in oxygen saturation accompanied by clinically evident hemoptysis ($n=3$) or generalized bleeding diathesis (i.e., massive epistaxis, cutaneous, and retinal bleeding) ($n=2$) were considered diagnostic for DAH.

2.3. Exclusion criteria

Patients with evidence of viral, bacterial or fungal infection, vasculitis, connective tissue disorders, trauma, as well as those with evident focal bleeding to the lung from bronchial or pulmonary vessels were excluded from the analysis.

2.4. CT evaluation

All CT examinations were performed on either a 64- or a 128-row multidetector CT (Sensation 64/Definition+; Siemens, Erlangen, Germany) using a 250–330-mm field of view, a 512×512 reconstruction matrix, 120 kV, 100–120 effective mAs, and a tube rotation time of 0.5/0.3 ms. No intravenous contrast material was applied. A single spiral acquisition was obtained from the apex to the base during one breath-hold at suspended end-inspiratory volume. Examinations were performed with patients in the supine position. Reconstruction of the data was done at 1-mm slices with a sharp reconstruction algorithm (filter, B70, equivalent to HRCT) and 1-mm reconstruction increment for visual assessment. Systems were calibrated on air daily [13].

Table 1
Treatment regimens

Patient	Disease	Treatment regimen
1	Multiple myeloma	Total body irradiation, busulfan, cyclophosphamide
2	AML	Clofabrine, thiotepa, melphalan
3	Mycosis fungoides	Fludarabine, melphalan, MabCampath
4	AML	Total body irradiation, fludarabine
5	ALL	Clofabrine, thiotepa, melphalan
6	AML	Cyclophosphamide, anti-thymocyte globulin
7	Mantle cell lymphoma	Fludarabine, melphalan
8	AML	Cytarabin, idarubicin
9	AML	Clofabrine, thiotepa, melphalan
10	AML	Total body irradiation, cyclophosphamide
11	T-NHL	Total body irradiation, etoposide
12	AML	Fludarabine, cytarabine, amsacrine
13	AML	Cytarabine
14	AML	Clofabrine, THIOTEPA, MELPHALAN
15	ALL	Treosulfane, etoposide, cyclophosphamide
16	AML	Total body irradiation, cyclophosphamide

2.5. Clinical and laboratory findings

The time interval from radio-/chemotherapy as well as allo-SCT to the development of DAH was recorded. At onset of DAH, peripheral blood platelet count, C-reactive protein (CRP), clinical presentation, and the presence/absence of signs of acute GVHD were assessed in all patients.

2.6. Chest CT evaluation of lung parenchymal abnormalities

Images were viewed at lung (window width 1200 HU, window level 600 HU) and mediastinal (window width 350 HU, window level 50 HU) window settings. CT images were reevaluated retrospectively by two radiologists with 17 and 4 years (MH, DS) experience in reading chest CT via consensus reading. Both investigators were blinded to the original interpretations and mortality data. Criteria for HRCT findings were those defined by the Fleischner Society's glossary of terms for chest CT [14]. Ground glass opacity (GGO) was defined as a hazy increase in lung attenuation with preservation of bronchial and vascular margins being distributed either diffuse or patchy (Fig. 1A). Airspace consolidation was defined as an area of dense increase in attenuation with obscuration of the underlying vessels and airway walls, showing different morphology either in form of segmental or subsegmental or patchy opacifications (Fig. 1B). Reticulation was defined as an interlacing line shadow suggesting a mesh or net (Fig. 1C). Crazy paving was defined as a superimposition of GGO and reticulation (Fig. 1D). GGO, airspace consolidation, reticulation, or crazy paving, distributed throughout the parenchyma without zonal predominance, was called diffuse, while focal parenchymal infiltrates with lobular, segmental, or lobar distribution involving one or both lungs were named focal. If more or less sharply demarcated regions of different density (to the point of unattained secondary lobules) were noted within infiltrated lung parenchyma, the term *mosaic pattern* is used. A dependent distribution was defined as an increase in attenuation of more dorsally located lung parenchymal abnormalities (i.e., GGO, crazy paving, reticulation, consolidation) or a clear predominance of such abnormalities in dependent lung areas with preservation of nondependent regions. Airspace bronchograms were defined as air-filled bronchi surrounded by GGO, crazy paving, or consolidation. Tree-in-bud sign was defined as nodular dilatation of centrilobular branching structures resembling a budding tree. The presence or the absence of associated centrilobular nodules, lymphadenopathy, or pleural effusion was likewise recorded. Furthermore, we analyzed all residual changes in lung texture such as traction bronchiectasis, persistent septal thickening, coarse reticulation, linear opacities, focal residual consolidation, micro- or macrocystic honeycombing, or distortion of lung parenchyma compatible with fibrosis.

2.7. Treatment of DAH

Treatment of DAH included high-dose steroids in 9/16 patients (56%), tumor necrosis factor alpha blockage via etanercept in 5/16 patients (31%), and platelet transfusion in all patients with clinically evident hemoptysis or profound thrombocytopenia (10/16 patients; 63%). No specific treatment of DAH was applied in 3/16 patients (19%) with an inconspicuous clinical presentation.

2.8. Disease course, follow up, and outcome

All 16 patients underwent routine nonenhanced chest CT before initiation of consolidation chemotherapy to exclude lower respiratory tract infection and preexisting fibrosis, plus as symptoms