Two autopsy cases of pulmonary leukemic infiltration mimicking severe pneumonia in patients with acute myeloid leukemia

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ABSTRACT

Although a previous autopsy series demonstrated that pulmonary leukemic infiltration (PLI) is a major pulmonary complication in patients with acute myeloid leukemia (AML), an antemortem diagnosis of PLI is rare. Diverse pulmonary complications cause acute respiratory failure (ARF) in patients with AML undergoing chemotherapy. This article reports two elderly patients with AML who presented with ARF due to PLI mimicking severe pneumonia during induction chemotherapy. Accurate antemortem diagnosis of PLI was almost impossible without pathological examination since the clinical course was not typical of PLI. We recommend considering PLI in patients with AML who have an unknown etiology of ARF.

1. Introduction

Despite improvements in the survival rate of patients newly diagnosed with acute myeloid leukemia (AML) over the last decades, early mortality remains high with an average rate of 10% by day 28 among patients undergoing induction chemotherapy [1]. Pulmonary complications account for a significant proportion of these early deaths. Patients with AML encounter several different pulmonary complications during the first days, including leukemia-specific complications (leukostasis, pulmonary leukemic infiltration [PLI], and acute lysis pneumopathy [ALP]), infection, pulmonary edema, and hemorrhage [2]. Identifying the cause of ARF is very important for facilitating the selection of the appropriate strategy. However, histopathological diagnosis through invasive examination, including a transbronchial lung biopsy, is often difficult to perform, especially among patients with substantial bleeding tendencies [3]. This article describes two autopsy cases of PLI that mimic severe pneumonia. We believe that reports of detailed pathological findings obtained through autopsy examinations in patients with AML showing PLI could facilitate the correct recognition and accurate diagnosis of PLI.

2. Case 1

A 74-year-old man with no medical history presented to our hospital with pancytopenia. He had a history of smoking 20 cigarettes a day for 50 years. On admission, the patient was afebrile. Laboratory examination revealed pancytopenia (white blood cell count of 3600/μL, with 27.0% blasts, 24.0% neutrophils, and 32.0% lymphocytes; hemoglobin level 8.9 g/dL; and platelet count 1.6 × 10^4 /μL). Bone marrow (BM) examination revealed hypercellular marrow with 84.5% myeloblasts, which was consistent with “AML without maturation.” Cytogenetic MB analysis showed that 45,XY,del(5)(q?),−7,add(12)(p11.2),−17,−18,del(19)(p13),+mar1,+mar2. FLT3 mutation was absent. We did not perform mutation analysis for any mutations other than FLT3, which was done by next generation sequencing (NGS). An admission chest computed tomography (CT) scan yielded normal findings (Fig. 1a). The patient was administered induction chemotherapy involving daily continuous infusion of etoposide 200 mg/m2/day for 8 days and daunorubicin 30 mg/m2/day for 3 days. The patient took levofloxacin + iraconazole daily per os (po) prophylactically. On day 14 of induction chemotherapy, he developed febrile neutropenia; subsequently, the antibiotic agent was changed to intravenous (IV) meropenem and vancomycin. On day 19, he developed ARF, with chest CT scan showing ground-glass opacities and septal thickening in the bilateral lung fields.
Initially, we suspected pneumocystis pneumonia (PCP) and initiated treatment with trimethoprim/sulfamethoxazole. However, his ARF rapidly progressed and showed daily worsening. Additionally, there was a daily increase in the blast count in the peripheral blood. The patient had bilateral diffuse pulmonary edema, congestion, and pleural effusion (volume = 200 ml, respectively). Flow cytometry of the pleural effusion revealed a myeloblast population showing CD34+/HLA-DR+/CD13+ expression (Fig. 1c). Hematoxylin-eosin (HE) staining revealed moderate-to-severe infiltration of inflammatory cells in the lung tissue. Further, there was organization of a hyaline membrane-like substance, which was consistent with the findings of diffuse alveolar damage (Fig. 1d, e). Immunohistochemical (IHC) staining revealed extensive myeloperoxidase (MPO)-positive blast infiltration and PLI (Fig. 1f, g). Grocott staining was negative in the lung tissue, ruling out fungal pneumonia and aspergillosis. Finally, he was diagnosed with acute respiratory distress syndrome due to PLI, which was determined as the main mortality cause.

3. Case 2

The patient was an 81-year-old man with prostate cancer treated using a luteinizing hormone-releasing hormone agonist. He had a history of smoking 30 cigarettes a day for 10 years. He was referred to our department with thrombocytopenia 3 months prior and subsequent leukocytopenia/anemia. He was independent in his activities of daily living (ADL) and could work until a few weeks before admission, despite his advanced age. On admission, he was febrile with a temperature of 38.6 °C. His-oxygen saturation slightly dropped to 94% in room air. Initial laboratory findings revealed leukocytosis (white blood cell count: 51.300/µL with 94.0% blasts), anemia (hemoglobin level 8.2 g/dL), and thrombocytopenia (platelet count 1.2 × 10^4 /µL). BM examination revealed hypercellular marrow with 84.6% myeloblasts, showing a background of multi-lineage dysplasia, which was consistent with “AML with myelodysplasia-related changes.” The cytogenetic analysis was normal; further, there were no FLT3 mutations. No gene mutation analyses were performed other than for FLT3 mutations by NGS. An admission chest CT scan revealed patchy ground-glass infiltration in the right lower lung field (Fig. 2a). He received IV cefepime and induction chemotherapy involving the daily continuous infusion of cytarabine 20 mg/m2/day; further, we initiated acracrubicin 14 mg/m2/day. However, on day 4 of induction chemotherapy, he developed ARF; further, chest radiography revealed bilateral lung field infiltration.

Fig. 1. Chest computed tomography (a) on admission and (b) at the time of acute respiratory failure onset in Case 1. Fig. 1c shows flow cytometry of pleural effusion at autopsy in Case 1. Fig. 1d-g shows histopathologic examination of lung tissue at autopsy in Case 1 (d; HE, × 40; e; HE, × 400; f; MPO, × 40; g; MPO, × 400). HE, hematoxylin-eosin; MPO, myeloperoxidase.
predominantly in the right lung (Fig. 2b). The brain natriuretic peptide levels increased to 164.9 pg/mL, which was suggestive of pulmonary edema due to acute heart failure and pneumonia. He was placed on noninvasive positive-pressure ventilation with daily administration of diuretics. Although oxygenation was temporarily improved and chest X-ray findings were slightly improved, the blast count in the peripheral blood remained at approximately 90%; further, the patient’s clinical condition gradually declined. He presented with a rapid fatal course and died on day 22 of induction chemotherapy. Postmortem examination was performed with the consent of the patient’s family. An autopsy examination revealed that the BM was hypercellular with numerous blast cells. The patient had diffuse pulmonary congestion, pneumonia, hepatomegaly (weight = 1380 g), and splenomegaly (weight = 220 g). In the lung tissue, HE staining revealed blast infiltration; additionally, IHC staining revealed extensive MPO-positive blast infiltration and PLI (Fig. 2c-f). Additionally, Gram staining revealed gram-positive cocci infiltration. Furthermore, there was leukemic infiltration in the liver and spleen (Fig. 2g-j). Finally, he was diagnosed with multiorgan leukemic infiltration and bacterial pneumonia.

4. Discussion

We described the autopsy findings of two patients with AML who developed ARF during induction chemotherapy. PLI typically occurs before chemotherapy initiation, with or without hyperleukocytosis. The mechanism underlying PLI is not clearly understood. However, it is suggested that PLI is caused by lung injury and blast affinity for the pulmonary endothelium [4]. We considered that the occurrence of PLI is not only due to hyperleukocytosis, but also damaged alveolar epithelial cells that trigger infiltration into the alveolar space. In our cases, autopsy studies showed blast cells along the alveolar septum and partial blast aggregates within the alveolar space. Leukemia-specific lung involvement was more likely to occur in patients with factors such as hyperleukocytosis, higher circulating blast count, and extramedullary/extrapulmonary involvement, older age, preexisting respiratory diseases, or a history of smoking [5]. In practice, our cases had all the above risks except hyperleukocytosis. Therefore, we suggest that PLI should be suspected in patients with these risks.

It may be difficult to differentiate among infection, pulmonary edema, and PLI. CT studies on PLI have described different radiological patterns, including the thickening of the bronchovascular bundles and/or interlobular septa, ground-glass opacities, and air-space consolidation [6]. The CT findings of Case 1 were diffuse ground-glass opacities with intralobular reticulation that did not affect the peripheral cortex of the lung. This was a rather characteristic finding of PCP; moreover, we suspected PCP given the patient’s immunodeficiency. In this case, an
acurate PLI diagnosis could not be made without pathological examination. There could have been other patients with AML and PLI who could not receive an accurate antemortem diagnosis. A previous study reviewed autopsy findings in 59 patients with AML with comorbid ARF and reported that >50% of patients had missed major clinical diagnoses [7]. Further, PLI was frequently observed and accounted for most deaths among patients without complete remission at the time of death.

Although transbronchial lung biopsy and bronchoalveolar lavage are usually recommended for the diagnosis of the causes of pulmonary complications, there is an expected high risk of complications such as hemoptysis in patients with AML [8]; however, early intervention with chemotherapy in case of early PLI diagnosis can result in a rapid clinical response. Various noninvasive or invasive diagnostic tests should be used as much as possible to confirm the PLI. Notably, a recent case report demonstrated the utility of Giemsa-stained sputum for PLI diagnosis [9], which revealed myeloblast cells. Moreover, fluorescence in-situ hybridization indicated that the patient had monosomy 7, which was further detected in the BM. There is a crucial need to develop such non-invasive examinations for PLI diagnosis. In other reports, it has been demonstrated that NGS, which enables the detection of both mutations and translocations with prognostic relevance, is possible from formalin-fixed-paraffin-embedded (FFPE) specimens, even if the material is limited [10]. We believe that it would be valuable for these techniques to become widespread and standardized.

There is no standard therapy for PLI. In cases of high hyperleukocytosis, cytoreduction with hydroxyurea and leukapheresis is the most likely treatment [2]. However, in patients without hyperleukocytosis, as in our cases, it is difficult to apply these treatments. Moreover, it is essential to modify antileukemic therapy because AML patients with PLI are usually in a poor general condition. Recently, several new molecular targeted therapies for refractory AML have been investigated and developed. New insights into the efficacy of these therapies for AML patients with PLI are expected to develop.

Taken together, we reported two autopsy cases to create awareness regarding the possibility of PLI being an important cause of ARF, even without hyperleukocytosis. Autopsy remains valuable in patients with AML and ARF of unknown etiology. Further, we hope that this report could be useful for selecting the appropriate therapy in similar cases.

**Author contributions**

All authors collected and summarized the data. H.I., Y.M., Y.F., N.I., and M.K. drafted the article or revised it critically for important intellectual content. H.I. and M.N. approved the submitted version.

**Declaration of Competing Interest**

None

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