SOHO Supplement 2015

Distinguishing the Causes of Pulmonary Infiltrates in Patients With Acute Leukemia

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Abstract

Pulmonary infiltrates are frequent in patients with acute leukemia, and may have infectious and non-infectious causes. The timing of the appearance in relation to the treatment of leukemia and the radiologic pattern may help to select appropriate diagnostic tools. Early intervention is critical and is based on the most likely diagnosis with modification when the etiology is confirmed.

Pulmonary infiltrates are commonly observed in patients with acute leukemia (AL), particularly acute myeloid leukemia, who undergo remission induction therapy. The mortality rate is unacceptably high and depends on 3 factors: the host (performance status, comorbidities, and frailty), the etiology of the infiltrates and the type of response to antileukemic therapy. The approach to the diagnosis of pulmonary infiltrates in patients with AL includes a medical history, thorough physical examination, radiologic pattern of the infiltrates (focal vs. diffuse), and timing of their appearance in relation to the start of antileukemic therapy (early, ie, within the first 2 weeks or late). Localized infiltrates are most commonly caused by bacterial (early) and fungal infections (late). Diffuse early infiltrates might be caused by leukemic infiltration of the lungs, pulmonary hemorrhage and/or edema, diffuse alveolar damage, viral pneumonia, and rarely transfusion-related acute lung injury (TRALI) or the differentiation syndrome. Similar to the early phase, pulmonary edema, viral pneumonia, and rarely TRALI might cause diffuse infiltrates during the late phase, in addition to immune reconstitution and pneumocystosis, particularly among patients with acute lymphoblastic leukemia. Diagnostic tests, invasive and noninvasive, can be particularly useful to establish the diagnosis. Early intervention is critical and is based on the most likely diagnosis with modification when the etiology is confirmed.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. S1, S98-103
Keywords: Acute leukemia, Diagnosis, Infection, Lung infiltrates, Pneumonia

Introduction

Patients with acute leukemia frequently present with pulmonary complications during the course of the disease and treatment. The frequency of pulmonary infiltrates (PI) during induction remission has varied from 29% in a study of 141 patients with acute leukemia[1] to 62% among 139 adults with leukemia (acute leukemia in 85) (Table 1).[1-13] In addition to the high frequency, the occurrence of PI during induction remission is associated with prolonged hospitalization and increased cost,[12,14] and depending on the etiology, host factors (performance status, comorbidities), and response to induction chemotherapy, the mortality rate might exceed 50%.[1,3-10,12,13]

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Submitted: Mar 18, 2015; Accepted: Mar 18, 2015; Epub: Mar 22, 2015

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The etiology of PI in patients with acute leukemia includes infiltration of the lungs by leukemia, hemorrhage, infection, and others (Table 2).[15,16] The radiologic pattern (localized, diffuse) and the time of occurrence during the course of treatment (before chemotherapy, first 1-2 weeks, and after 2 weeks) might help to establish an etiology and define the appropriate workup and treatment.

Defining the Etiology of PI in Patients With Acute Leukemia

Defining the etiology of PI in patients with acute leukemia is not an easy task. In a study that evaluated PI in 53 patients who underwent induction remission chemotherapy, an infectious etiology could be established in 21 patients (40% of cases).[4] In another study, 13 (34%) of 38 PI were of infectious origin, 13 (34%) were noninfectious, and in 9 (24%) the cause could not be established.[9] The timing of the occurrence and the radiologic pattern (localized or diffuse) might help to establish the diagnosis.

Pulmonary infiltrates might occur at any time during the course of treatment of acute leukemia. However, most PI occur in the first

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.03.007

Table 1 Studies Evaluating PI in Patients With AL, ALL, or AML Including MDS

First Author	Patients With AL, n	Patients With PI, n	Radiologic Assessment of PI	Mortality Rate
Tenholder[2]	139 Adults (85 had AL)	87 (62%)	CXR	50%
Wardman[1]	141 Adults (AL)	41 (29%)	CXR. Localized infiltrates in 80%, diffuse in 20%	40%
Wilhelm[3]	278 With AML or MDS	67 (24%)	Not stated	39%
Ewig[4]	123 (AL)	57 (46%)	CXR and/or CT scan	43%
Kirchner[5]	95 (AML)	52 (55%)	CXR and/or CT	NR
Yoshida[6]	577 (AML)	113 (20%)	Not stated	26%
Rossini[7]	458 (343 With AML)	109 (24%)	CXR	38%
Specchia[8]	288 (218 With AML)	80 (28%)	CXR and/or CT	45%
Chaoui[9]	67 (39 With AML)	30 (45%)	CXR and/or CT	54%
Erdur[10]	163 Children With AL	66 (40%)	CXR and/or CT	11%
Yoshida[11]	2585 AML	433 (16.8%)	Not stated	25.1%
Garcia[12]	801 (645 With AML)	233 (29%)	CXR and/or CT	17%
Muslimani[13]	363 AML	120 (33%)	CXR and/or CT	38%

Abbreviations: AL = acute leukemia; ALL = acute lymphoblastic leukemia; AML = acute amyloid leukemia; CT = computed tomography; CXR = chest x-ray; MDS = myelodysplastic syndrome; PI = pulmonary infiltrates.

2 weeks of treatment. In a retrospective study, 72 of 109 (66%) cases of pneumonia in patients with acute leukemia occurred in the first 2 weeks of treatment, including 26 in which the diagnosis was made before the start of induction chemotherapy.[7] In another retrospective study, 139 patients with leukemia (acute or chronic) were evaluated, and 87 (62%) developed PI. In 17 patients the infiltrates occurred before or within 3 days of treatment initiation. In these early PI, localized infiltrates were of bacterial origin in most cases, whereas diffuse infiltrates were caused by pulmonary edema, leukemic infiltration, or hemorrhage.[2]

Leukemic infiltration in the lungs is frequently found in autopsy but most patients are asymptomatic.[15] However, patients with hyperleukocytosis might develop respiratory failure due to pulmonary leukostasis, and present with fever, dyspnea, hypoxemia, diffuse lung infiltrates, pleural effusions, and a rapidly fatal clinical course.[17] A study evaluated risk factors for early mortality during induction therapy in 85 patients with acute myeloid leukemia (AML) who presented with hyperleukocytosis. Pulmonary leukostasis was associated with failure to achieve complete remission and an increased risk of early mortality. Death was due to pulmonary hemorrhage and respiratory failure.[18] Occasionally a clinical picture of respiratory failure with bilateral PI might occur without hyperleukocytosis.[19]

The occurrence of PI within the first week of treatment of AML might also be due to diffuse alveolar damage caused by the lysis of leukemic cells in patients with hyperleukocytosis. Patients develop patchy multilobar PI after a few days of chemotherapy. Lung biopsy reveals diffuse alveolar damage with necrotic blast cells in the interstitium.[20,21]

Noncardiogenic pulmonary edema might occur after the use of high or intermediate doses of cytarabine.[5,22,23] Patients present with fever, dyspnea and hypoxemia. This picture must be differentiated from PI that occur in patients who have received high-dose cytarabine and develop oral mucositis and bacteremia due to viridans streptococci.[24,25] In this case respiratory symptoms begin during neutropenia that follows the administration of cytarabine; the PI might be localized or diffuse, the latter evolving to respiratory failure.

During the first 2 weeks of induction remission of acute leukemia, PI of infectious origin are usually caused by bacteria. The patients develop fever in the context of neutropenia, and chest computed tomography (CT) scan usually reveals focal infiltrates.[13] However, an etiologic agent is documented in < 50% of cases. The most frequent pathogens are viridans streptococci among Gram-positive, and enterobacteria and *Pseudomonas aeruginosa* among Gram-negative bacteria.[6,13,26]

Localized PI that occur after 2 weeks of therapy are usually caused by bacteria or fungi.[2] Although invasive aspergillosis (IA) is by far the most frequent invasive fungal disease (IFD) in this context, infection caused by other molds such as *Fusarium* and the agents of mucormycosis might also occur, and the clinical picture is usually indistinguishable from aspergillosis.[27]

Diffuse PI might also occur after treatment for acute leukemia. Viral disease (respiratory viruses),[28] transfusion-related acute lung injury,[29] cardiac dysfunction with pulmonary edema, capillary leak syndrome, diffuse alveolar hemorrhage, cryptogenic organizing pneumonia, and immune reconstitution syndrome are possible etiologies.[2,9,12,16]

Table 2 Causes of Pulmonary Infiltrates in Patients With Acute Myeloid Leukemia According to Time of Onset

Early (Within 2 Weeks of Therapy)	
Localized	**Diffuse**
Bacterial pneumonia	Leukemic infiltration
	Hemorrhage
	Diffuse alveolar damage caused by lysis of leukemic cells
	Pulmonary edema
	Differentiation syndrome
	TRALI
	Viral pneumonia
Late (After 2 Weeks of Therapy)	
Localized	**Diffuse**
Bacterial pneumonia	Viral pneumonia
Fungal pneumonia (including *Pneumocystis jiroveci*)	Pneumonia due to *Pneumocystis jiroveci*
	TRALI
	Immune reconstitution syndrome
	Pulmonary edema

Abbreviation: TRALI = transfusion-related acute lung injury.