In patients with acute myeloid leukemia (AML), pleural effusion may be attributed to various factors, including infection, hypoalbuminemia, and renal failure. However, leukemic infiltration of the pleural fluid is rarely reported and poorly understood. Extramedullary diseases have been reported with increasing frequency as the survival rates of patients with AML have increased. However, the reported prognostic effects of leukemic pleural effusion in patients with AML range from none to a worse prognosis. Here, we report a case of acute promyelocytic leukemia (APL) in a patient exhibiting leukemic pleural effusion with fluorescence in situ hybridization (FISH) results indicating the presence of the PML-RARA fusion gene. A 52-year-old man presented with pancytopenia, dyspnea, and fever. He had a medical history of hypertension, end-stage renal disease, and hepatitis B virus-related liver cirrhosis. A peripheral blood smear revealed the presence of multiple abnormally hypergranular promyelocytes. White blood cell differential counts were not performed due to severe pancytopenia. A bone marrow examination, immunophenotyping analysis, and cytogenetic and molecular studies revealed APL. The patient was treated with all-trans retinoic acid immediately after abnormal promyelocytes were observed in the peripheral blood smear, but induction chemotherapy was delayed because of his poor condition. His persistent dyspnea and abdominal discomfort led to a thoracentesis and the observation of abnormal promyelocytes that were positive for PML-RARA fusion gene by FISH. To our knowledge, this is the first report of leukemic pleural infiltration with PML-RARA fusion gene-positivity via FISH.

Key Words: Acute promyelocytic leukemia, Leukemic pleural effusion, PML-RARA

INTRODUCTION

The recent increases in survival rates among patients with acute myeloid leukemia (AML) have been accompanied by increasingly frequent reports of extramedullary disease (EMD). EMD, with an overall incidence of 2.5–30%, has mainly been reported in AML cases involving myelomonocytic or monoblastic disease and those with recurrent genetic abnormalities such as t(8;21) and inv(16) [1-4]. The prognosis for EMD varies among reports from no effect to an unfavorable clinical outcome [2, 5, 6].

In AML, pleural effusion may be attributed to various factors, including infections, hypoalbuminemia, and renal failure. By contrast, leukemic infiltration of the pleura is rarely reported and poorly understood. Only a few reports have described leukemic pulmonary infiltration in the extramedullary relapse of M2, M3, and M5 French-American-British subtypes of AML (Table 1) [4, 7-10]. A few reports of extramedullary relapse in acute promyelocytic leukemia (APL) have revealed that the central nervous system (CNS) was the most common extramedullary site, followed by the skin [11, 12]. However, reports of leukemic pleural infiltration in the M3 subtype at initial presentation are scarce [4, 7]. Herein, we report a rare case of APL, with leukemic pleural effusion that was identified as positive for the PML-RARA fusion gene via in situ hybridization (FISH).
CASE

A 52-year-old man visited the emergency room of our institution presenting with dyspnea and fever. He had a medical history of hypertension, end-stage renal disease, and hepatitis B virus-related liver cirrhosis. He was on continuous ambulatory peritoneal dialysis. Laboratory examinations indicated pancytopenia with the following measurements: Hb, 6.4 g/dL; leukocyte count, 0.9 × 10^9/L; and platelet count, 24 × 10^9/L. A peripheral blood smear showed multiple abnormally hypergranular promyelocytes. White blood cell differential counts were not performed due to severe pancytopenia. A bone marrow aspirate smear revealed increased cellularity, comprised of 56.3% abnormal promyelocytes with Auer rod bundles (Fig. 1A). The cells were strongly positive for peroxidase and negative for periodic acid–Schiff staining. Flow cytometric analysis revealed a typical APL immunophenotype, with strong surface expression of CD13, CD33, and CD117 and cytoplasmic myeloperoxidase expression, but no CD34 or HLA-DR expression. The 47,XY,+add(5)(q11.2)x2,der(5;8)(q10;p10),del(7)(q32), t(15;17)(q22;q21) chromosome complement was observed in all 21 metaphase cells (Fig. 1B). Real-time quantitative reverse transcription PCR for PML-RARA indicated a PML-RARA/ABL ratio of 0.553. KIT and FLT3 mutation analyses were negative. Laboratory examinations revealed azotemia with the following measurements: blood urea nitrogen, 69.5 mg/dL (reference ranges 6.0–20.0); creatinine, 14.09 mg/dL (0.7–1.3); erythrocyte sedimentation rate, 112 mm/h (0–10); C-reactive protein (CRP), 2.88 mg/dL (<0.5); procalcitonin, 0.804 ng/mL (<0.1); prothrombin time, 13.5 seconds (10–14); and activated partial thromboplastin time, 31.6 seconds (20–40). The patient was treated with all-trans retinoic acid (ATRA) immediately after detection of abnormal promyelocytes in the peripheral blood smear, but induction chemotherapy was delayed because

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Table 1. Reported cases of pleural infiltration in AML

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex</th>
<th>WBC (×10^9/L)</th>
<th>Hb (g/dL)</th>
<th>Platelet (×10^9/L)</th>
<th>FAB</th>
<th>BM*</th>
<th>FCM</th>
<th>FISH or RT-PCR</th>
<th>EMD</th>
<th>P</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>34/M</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>M3</td>
<td>N</td>
<td>ND</td>
<td>RT-PCR PML-RARA (+)†</td>
<td>Pleura, heart, pericardium</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>39/M</td>
<td>4.52</td>
<td>14</td>
<td>212</td>
<td>M3</td>
<td>N</td>
<td>PF</td>
<td>ND</td>
<td>Pleura</td>
<td>CR</td>
<td>[4]</td>
</tr>
<tr>
<td>3</td>
<td>53/M</td>
<td>11.5</td>
<td>8</td>
<td>103</td>
<td>M2</td>
<td>Y</td>
<td>ND</td>
<td>FISH RUNX1-RUNX1T1 (+)</td>
<td>Pleura</td>
<td>CR</td>
<td>[8]</td>
</tr>
<tr>
<td>4</td>
<td>19/M</td>
<td>6.9</td>
<td>9.5</td>
<td>94</td>
<td>M5</td>
<td>Y</td>
<td>BAL</td>
<td>ND</td>
<td>BAL, CSF</td>
<td>CR</td>
<td>[9]</td>
</tr>
<tr>
<td>5</td>
<td>4/M</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>M2</td>
<td>Y</td>
<td>ND</td>
<td>FISH Lung Bx: RUNX1-RUNX1T1 (+)</td>
<td>Lung</td>
<td>CR</td>
<td>[10]</td>
</tr>
</tbody>
</table>

*BM involvement; † PML-RARA (+) in peripheral blood

Abbreviations: N, No; Y, Yes; ND, not done; NA, not available; CR, complete remission; FCM, flow cytometry; P, prognosis; R, reference; D, dead; PF, pleural fluid; BAL, bronchoalveolar lavage; EMD, extramedullary disease; FAB, French-American-British classification; Bx, biopsy.

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Fig. 1. Abnormal promyelocytes with multiple Auer rods in the bone marrow (Wright’s stain x1,000) (A) and conventional bone marrow chromosome analysis result showing a 47,XY,+add(5)(q11.2)x2,der(5;8)(q10;p10),del(7)(q32), t(15;17)(q22;q21) [21] karyotype (B).
of his poor condition. On the ninth day after admission, the patient complained of severe dyspnea and arthralgia and chest x-ray results suggested pleural effusion. Accordingly, an immediate thoracentesis was performed. The pleural fluid was serous and exudative, with the following parameters: protein, 4.0 g/dL; glucose, 216 mg/dL; and lactate dehydrogenase, 360 IU/L. A cytospin analysis revealed abnormal promyelocytes containing multiple Auer rods (Fig. 2A) and interphase FISH of the pleural fluid indicated the presence of the PML-RARA fusion gene (Fig. 2B). The patient began AIDA (ATRA+idarubicin) induction chemotherapy and the pleural effusion resolved rapidly, according to a chest x-ray. Further complaints of dyspnea and arthralgia suggested retinoic acid syndrome and the patient was switched from ATRA to dexamethasone (10 mg, three times a day for 10 days). ATRA was restarted when the patient’s condition improved after dexamethasone therapy. On the eighth day in the hospital, Aspergillus antigen was detected in his serum and amphotericin B was administered intravenously. Repeated tests for Aspergillus antigen were negative after 20 days of amphotericin B therapy. Pleural fluid and blood culture findings remained negative for other fungi, bacteria, and viruses. However, on the twenty-third day in the hospital, he developed a fever, with an increased CRP level (20.95 mg/dL; normal is <0.5) and was intravenously administered empirical antibiotics, including meropenem, vancomycin, and fluconazole. Despite the combined administration of ATRA, chemotherapy, and supportive care, his uremia and general condition became worse and he refused aggressive therapies such as renal replacement therapy, mechanical ventilation, and intensive care unit admission. He died in the hospital on day 37 of shock and multi-organ failure.

**DISCUSSION**

PML-RARA-positive APL has the most favorable prognosis among all AML subtypes because the differentiating agent, ATRA, when used in combination with anthracycline, can induce complete remission in most patients [13]. Pulmonary involvement is a rare complication of AML, and only a few reports have described this phenomenon [4, 7-10]. Azoulay and colleagues reported 20 cases of acute monocytic leukemia involving acute respiratory failure related to leukemic pulmonary involvement from leukostasis or leukemic infiltration [14]. In their case series, all patients developed respiratory problems after initiation of chemotherapy, with 50% of the patients dying during chemotherapy. Therefore, the authors suggested that early invasive diagnostic and therapeutic management along with intensive care unit admission before chemotherapy initiation is recommended for all patients with any degree of respiratory impairment [14]. This strategy will be helpful for patients.
because radiographic features of leukemic pulmonary infiltration are known to be heterogeneous and can be difficult to differentiate from other non-infectious causes such as hemoptysis and acute respiratory distress syndrome [15]. Others reported a case of granulocytic sarcoma that was initially mistaken for pneumonia in a patient with t(8;21)(q22;q22). This chromosomal translocation formed the RUNX1-RUNX1T1 fusion gene, causing AML. In this patient, the bronchoalveolar lavage (BAL) fluid contained 71% myeloblasts, and the abnormal chest radiograph findings did not change despite the administration of empirical broad-spectrum antibiotics. However, the x-ray findings resolved after systemic chemotherapy [10].

Currently, the skin and central nervous system (CNS) are the most common sites of EMD in patients with APL, followed by the mediastinum, gingiva, and auditory canal. By contrast, pulmonary involvement in APL is very rare. Botton and colleagues analyzed 740 APL cases in which only ten (1.35%) patients relapsed with EMD, most with CNS relapses and none with pulmonary EMD [16]. Only two previous reports described APL with pulmonary EMD [10].

In the present case, multiple comorbidities such as end-stage renal disease, liver cirrhosis, the lack of early disease management, and the refusal of therapy contributed to the rapid demise of the patient. Although there have been a few reports of leukemic pleural infiltration in relapsed APL, this is the first report to document a pleural fluid infiltration of APL at the initial presentation that tested positive for the PML-RARA fusion gene by FISH.

요 악

급성골수성백혈병 환자에서 가슴막삼출의 원인은 감염, 저혈관 증증, 신부전 등으로 다양하다. 햇빛병 세포가 가슴막액에 침범한 사례는 드물게 보고되고 있다. 급성골수성백혈병에서 생존율이 증가하면서 공수외백혈병의 사례가 증가하고 있으나 이에 대한 영향은 예후와 관계없다는 보고부터 더 좋지 않은 예후까지 다양하게 보고되고 있다. 자들은 급성전골수구백혈병 화자의 가슴막액에서 전골수구가 관찰되었고 PML-RARA 유전자형의 진단에 도움을 주고 있다. 또한 난 자가 병원감소증, 호흡곤란, 발열을 주소로 응급실에 내원하였고 이 환자는 기저질환으로 호흡향방, 말기질환, B형 간염 바이러스로 인한 간경화가 있는 환자였다. 말초혈액모혈구검사상 다수의 비정상적인 과표정성의 전골수구가 관찰되었고 백혈구 감별계산은 심한 변형구가소증 때문에 실시하지 않았다. 공수흡인검사, 면역표현검사, 세포유전학, 분자유전학검사에서 급성전골수구백혈병이 확인되었다. 환자는 말초혈액모혈구검사에서 비정상적인 전 골수구가 확인된 직후 ATRA 치료를 바로 시작하였으나 유도항암요법은 환자의 전신상태가 힘들어 시행되었다. 환자는 지속적인 호흡곤란과 복부팽만감을 호소하여 가습침대술이 시행되었고 가습막액에서 Auer rod를 가지고 항원양성의 전골수구가 관찰되었고 현상체가리부합법으로 PML-RARA 유전자 형이 확인되었다. 본 사례는 급성전골수구백혈병 환자의 가슴막액에서 PML-RARA 유전자 양성인
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

No potential conflicts of interest relevant to this article were reported.

REFERENCES