Case Report

Sing-Ting Wang, Chieh-Lung Chen, Shih-Hsin Liang, Shih-Peng Yeh, Wen-Chien Cheng*

Acute myeloid leukemia with leukemic pleural effusion and high levels of pleural adenosine deaminase: A case report and review of literature

https://doi.org/10.1515/med-2021-0243
received September 11, 2020; accepted January 29, 2021

Abstract: Pleural effusions are rarely observed in association with acute myeloid leukemia (AML), and their true incidence remains unknown. Given the low diagnostic yield from cytopathologic analysis of malignant pleural effusions and the fact that patients with leukemia are often thrombocytopenic and unable to tolerate invasive procedures, the incidence of leukemic effusions may be underestimated. Here, we report a rare case of pleural effusion in a patient with newly diagnosed AML. Initial analysis revealed an exudative, lymphocyte-predominant effusion. High levels of adenosine deaminase (ADA) were detected in pleural fluid, consistent with a diagnosis of tuberculosis. However, the analysis of pleural cytology revealed leukemic cells, permitting the diagnosis of leukemic effusion to be made. The patient underwent induction chemotherapy and pleural effusion resolved without recurrence. This case emphasizes the diagnostic dilemma presented by high levels of ADA in a leukemic pleural effusion, as this association has not been previously considered in the literature.

Keywords: acute myeloid leukemia, leukemic pleural effusion, adenosine deaminase, extramedullary

1 Introduction

Nearly, all hematologic malignancies can present with pleural effusions. Among the most common diseases associated with this complication are Hodgkin lymphoma and non-Hodgkin lymphoma because the mediastinum is a typical site of primary disease [1]. Leukemic pleural effusions are observed rarely only in patients with leukemia and even more infrequently among those diagnosed with acute myeloid leukemia (AML). The true incidence of leukemic effusion is not known, but it is believed to be underestimated; this complication may become more common with improved supportive care and prolonged survival for patients with AML [2].

In patients with leukemia, other causes of the pleural effusion such as infections, other disseminated solid tumors, and/or treatment-associated toxicities should be excluded [3]. The results from immunocytologic examination, as well as flow cytometry and polymerase chain reaction methodologies applied to cytology specimens, can contribute to the differential diagnosis [4].

Leukemic pleural effusion has been considered to be a reflection of the severity of the underlying hematologic malignancy; most cases have been associated with a poor prognosis [3,5,6]. The treatment of the primary disease usually results in resolution of the pleural effusion [1]; survival relies on an appropriate response to the treatment [2,3].

Adenosine deaminase (ADA) is an enzyme involved in the proliferation and differentiation of lymphocytes, especially T lymphocytes. The two principal isoenzymes are ADA1 and ADA2 [7]. While ADA1 can be detected in all cells, ADA2 is found only in macrophages and monocytes [8]. The presence of live intracellular microorganisms stimulates the release of ADA [9]. Currently, well-established evidence suggests that ADA levels >40 U/L in lymphocytic pleural effusions can be used as virtually diagnostic for tuberculous pleural effusion (TPE); this is especially true in the regions of high disease prevalence [10]. ADA levels in
nontuberculous lymphocytic effusions seldom exceed the diagnostic cutoff for TPE [11]. Conversely, similar or higher ADA levels have occasionally been reported in parapneumonic effusion [12]; furthermore, empyema or lymphoma should be considered in cases with extremely high ADA activity [13]. In one retrospective study that evaluated 156 patients with malignant pleural effusion, ADA levels >40 U/L were detected in only 16 patients (1%) and none were related to acute leukemia [14].

2 Case report

A 55-year-old man with no medical history presented with a chief complaint of dyspnea on exertion for a period of 1 month. His body temperature was 37.4°C, pulse rate was 105 beats per minute, blood pressure was 111/63 mm Hg, respiratory rate was 18 breaths per minute, and oxygen saturation was 98% with ambient air. Physical examination revealed a chief complaint of dyspnea on exertion for a period of 1 month. His body temperature was 37.4°C, pulse rate was 105 beats per minute, blood pressure was 111/63 mm Hg, respiratory rate was 18 breaths per minute, and oxygen saturation was 98% with ambient air. Physical examination was normal except for pallor. Chest radiograph (Figure 1a) and electrocardiogram were normal at presentation. A complete blood count revealed leukocytosis (white blood cell [WBC] count, 97,600/μL) with 26% blasts and an elevated fraction of circulating monocytic cells (45%), anemia (hemoglobin 6.6 g/dL), and thrombocytopenia (platelet count, 23,000/μL). Other laboratory test results are presented in Table 1. Bone marrow examination was notable for hypercellularity with increased myeloblasts (Figure 2a). Immunophenotyping of bone marrow cells by flow cytometry revealed that cells were positive for CD13, CD123, CD7, CD34, CD117, and HLA-DR, but not for CD56 or terminal deoxynucleotidyl transferase (Tdt). A cytogenetic study revealed an abnormal karyotype of 47, XY, +21; e8e2(e11e3); a histone-lysine N-methyltransferase 2A (KMT2A)-partial tandem duplication (PTD) fusion was detected by a real-time reverse transcriptase-polymerase chain reaction (RT-PCR). A diagnosis of AML with e11e3(e8e2) MLL-PTD was made. However, the patient developed direct type hyperbilirubinemia (Table 1) and progressive shortness of breath during hospitalization; chest radiograph revealed rapid growth of left side pleural effusion (Figure 1b). Abdominal sonography showed no evidence of mechanical obstruction. Subsequently, 650 mL of a bloody effusion was withdrawn through ultrasound-guided thoracentesis. Laboratory analysis of the pleural fluid indicated an exudative, lymphocyte-predominant effusion (red blood cells, 21,692/L; WBCs, 2,025/L with a leukocyte differential including 46% lymphocytes, 38% monocytes, and 16% neutrophils; protein <3 mg/dL, glucose 84 mg/dL, and lactate dehydrogenase [LDH] 922 U/L). A high level of ADA (42 U/L) was also detected in pleural fluid. Given these findings, a diagnosis of tuberculous pleural effusion was considered. Nevertheless, rapid growth of tuberculous pleural effusion is relatively uncommon. Antituberculosis agents were not prescribed because of the diagnostic uncertainty and hyperbilirubinemia. MTB quantitative PCR (Cepheid Xpert MTB/RIF TEST with real-time PCR) of the pleural fluid yielded negative results. Chest computed tomography showed no evidence of pulmonary tuberculosis, mass lesion, or pulmonary embolism. However, cytologic examination of the pleural fluid revealed some abnormally large cells with fine chromatin and scant cytoplasm; the morphological features of these cells resembled those of the myeloblasts in the bone marrow (Figure 2b). Therefore, the diagnosis of AML with leukemic pleural effusion and suspected liver involvement was considered. The patient was treated with induction chemotherapy that included Idarubicin (12 mg/m² from days 1 to 3) and Cytarabine (100 mg/m² from days 1 to 7).

Figure 1: (a) Initial chest radiograph revealed no abnormal findings. (b) Chest radiograph taken revealed rapid accumulation of a left side pleural effusion within 1 week of admission. (c) Pleural effusion largely resolved after induction chemotherapy.
Follow-up chest radiograph on day 7 of induction chemotherapy revealed significant resolution of the pleural effusion, and laboratory test results showed alleviation of hyperbilirubinemia (Table 1). The patient developed neutropenic fever after chemotherapy and underwent several courses of broad-spectrum antibiotic treatment. Bacterial cultures were negative in all sterile sites. Bone marrow examination on day 14 revealed significant cytoreduction with a low percentage of residual blasts. There was no recurrence of the pleural effusion (Figure 1c); culture of the pleural fluid was negative for Mycobacterium tuberculosis. Subsequently, the patient experienced a relapse and developed refractory disease in the clinical course and eventually died of septic shock ∼4 months after the diagnosis. Nevertheless, there was no recurrence of left side pleural effusion throughout the clinical course.

Informed consent: Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

3 Discussion

Leukemic effusion, similar to other extramedullary manifestations, can develop simultaneously with or precede...
| Year | Author (Ref.) | Age (years)/sex | How the diagnosis was achieved | Pleural ADA | Leukemia status at leukemic effusion diagnosis | Treatment | Outcome |
|------|---------------|-----------------|-------------------------------|------------|---------------------------------------------|-----------|---------|
| 1955 | Raynolds et al. [34] | 26/M | Cytologic examination, necropsy | Not reported | AML, newly diagnosed | Supportive care | Death 5 months after diagnosis |
| 1974 | Wu and Burns [15] | 67/F | Cytologic examination | Not reported | AML, in BM remission | COAP therapy, intrapleural araC, radiation therapy | Effusion resolved |
| 1989 | Green et al. [35] | 59/M | Cytologic examination | Not reported | AML, M1, newly diagnosed | Chemotherapy with mitoxantrone and araC | CR with the resolution of effusion after the first course of chemotherapy |
| 1994 | Ohe et al. [36] | 51/M | Not reported | Not reported | CD7 + AML, newly diagnosed | Induction araC + Daunorubicin, then autologous HSCT | CR for minimum 8 months |
| 1996 | Schmetzer et al. [37] | 49/F | Cytologic examination | Not reported | AML, M5b, relapse | Induction chemotherapy, then daunomycin and araC containing consolidation | Second CR; died 6 years after diagnosis during fourth relapse of AML |
| 2002 | Park et al. [38] | 41/M | Cytologic examination with cyogenetic confirmation | Not reported | AML, M2, s/p HSCT, with isolated pleural relapse 31 months after HSCT, in BM remission | Chemotherapy | Died of septicemia while undergoing chemotherapy |
| 2003 | Azoulay et al. [39] | 19/F | By clinical history | Not reported | AML, M5, newly diagnosed | Chemotherapy | Died, respiratory status deteriorated and cardiac arrest developed after chemotherapy |
| 2003 | Azoulay et al. [39] | 45/F | By clinical history | Not reported | AML, M5, newly diagnosed | Chemotherapy | Died, respiratory status deteriorated after chemotherapy |
| 2003 | Azoulay et al. [39] | 50/M | By clinical history | Not reported | AML, M5, newly diagnosed | Chemotherapy | Alive, respiratory failure developed after chemotherapy |
| 2003 | Disel et al. [40] | 39/M | Pleural biopsy | Not reported | APL, with pleural relapse | Chemotherapy with FLAG-IDA regimen | CR with resolution of pulmonary signs and symptoms |
| 2004 | Khan et al. [17] | 71/F | Cytologic examination | Not reported | MDS with transformation to AML M5 | Induction araC + Daunorubicin | Died of overwhelming sepsis 22 days after the initiation of induction chemotherapy |
| 2005 | Farray et al. [41] | 45/F | Cytologic examination, flow cytometry | Not reported | Acute megakaryoblastic leukemia, M7, newly diagnosed | Not reported | Not reported |
| 2005 | Leong et al. [42] | 25/M | Cytologic examination | Not reported | AML, M4Eo, newly diagnosed | Induction araC + Daunorubicin, re-induction with high dose araC due to refractory disease | Refractory disease, death 8 weeks after diagnosis |
| 2007 | Fatih et al. [43] | 50/M | Cytologic examination, flow cytometry | Not reported | AML, M1, newly diagnosed | 3 + 7 induction with Idarubicin + araC, then FLAG-IDA regimen due to refractory and old age | Effusion resolved without recurrence, but leukemia was refractory; death 3 months after discharge |
| 2008 | Huang et al. [18] | 56/F | Cytologic examination | Not reported | CMMoL with transformation to AML | 3 + 7 induction with Idarubicin + araC | Respiratory failure; died on day 64 during hospitalization |
| Year | Author (Ref.)     | Age (years)/sex | How the diagnosis was achieved | Pleural ADA | Leukemia status at leukemic effusion diagnosis | Treatment | Outcome                                                                 |
|------|------------------|----------------|-------------------------------|-------------|-----------------------------------------------|-----------|------------------------------------------------------------------------|
| 2008 | Raina et al. [44] | 22/M           | Cytologic examination         | Not reported | AML, M4, newly diagnosed                      | Chemotherapy | Died on day 3 of initiating treatment                                    |
| 2009 | Rigamonti et al. [45] | 52/M | Cytologic examination, cytogenetic study | Not reported | AML, newly diagnosed | Induction chemotherapy with EMA protocol | Died of septic emboli with ICH 4 weeks after initiation of induction chemotherapy |
| 2011 | Stoll et al. [46]  | 54/M           | Cytologic examination, flow cytometry | Not reported | AML–MDS with erythroid differentiation, refractory to chemotherapy | None, ineligible due to renal function | Home hospice; death 6 months after diagnosis                                |
| 2011 | Ou et al. [16]    | 53/M           | Cytologic examination, flow cytometry | Not reported | AML, newly diagnosed | 3 + 7 induction with Idarubicin + araC, re-induction with high-dose araC due to refractory pleural effusion | CR with first induction, but effusions did not resolve. After re-induction with high-dose Cytarabine, effusions resolved. Later underwent HSCT, remained disease free for minimum 1 year |
| 2012 | Nieves-Nieves et al. [47] | 66/M | Cytologic examination | Not reported | AML, newly diagnosed | 3 + 7 induction with Idarubicin + araC, re-induction with EMA protocol due to refractory disease | Effusion resolved without recurrence, but leukemia was refractory; death through complications of leukemia |
| 2013 | Chang [2]         | 74/F           | Cytologic examination         | Not reported | AML, M4, newly diagnosed                      | Induction araC and four cycles of postremission chemotherapy with araC and etoposide | Effusions resolved; CR for minimum 11 months                              |
| 2013 | Chang [2]         | 75/M           | Cytologic examination         | Not reported | AML M4                                         | CMMoL with transformation to AML M4 | Death 1 month after diagnosis                                           |
| 2013 | Chang [2]         | 74/M           | Cytologic examination         | Not reported | AML, M4, refractory                           | AML, M4, refractory and subsequently four different regimens due to refractory disease | Death 1 month after diagnosis                                           |
| 2013 | Agrawa [48]       | 45/M           | Cytologic examination         | Not reported | AML, M2, newly diagnosed                      | Chemotherapy | Death 1 week after diagnosis                                            |
| 2013 | Oka et al. [49]   | 63/F           | Cytologic examination, flow cytometry | Not reported | AML without maturation, with CD56 expression, newly diagnosed | Not reported | Death 11 month after diagnosis                                           |
| 2014 | Duhan et al. [50] | 26/F           | Cytologic examination         | Not reported | AML, M4, newly diagnosed                      | Induction chemotherapy with Daunorubicin, araC, and cladribine | Died of refractory disease                                               |
| 2014 | Morell-García et al. [51] | 76/M | Cytologic examination | Not reported | AML, during the treatment | 5-Azacytidine | Death 15 days after diagnosis                                           |
| Year | Author (Ref.) | Age (years) / sex | How the diagnosis was achieved | Pleural ADA | Leukemia status at leukemic effusion diagnosis | Treatment | Outcome |
|------|---------------|-------------------|-------------------------------|------------|---------------------------------------------|-----------|---------|
| 2014 | Pemmaraju et al. [33] | 55/M | Cytologic examination, flow cytometry | Not reported | Progression of PV to AML | Decitabine for 5 days then BIDFA for 4 days | Relapsed prior to stem cell transplant; died 11 months after transformation to AML |
| 2014 | Hanenberg and Marionneaux [52] | 64/F | Cytologic examination | Not reported | Progression of PV to AML | Induction araC + Daunorubicin, replaced with decitabine and ruxolitinib | Not reported |
| 2014 | Agarwal et al. [53] | 22/M | Cytologic examination | 20 U/L | AML, M2, diagnosed 2 months after leukemic effusion | Induction araC + Daunorubicin, second induction with HAM, consolidation with HiDAC | Bone marrow remission on day 47 of HAM; died during the neutropenic phase |
| 2015 | Lokireddy et al. [54] | 74/M | Cytologic examination, flow cytometry | Not reported | AML, newly diagnosed | Induction araC + Daunorubicin | Clearance of blast cells in pleural fluid |
| 2015 | Suharti et al. [55] | 46/F | Cytologic examination | Not reported | AML, M0, newly diagnosed | Induction araC + Daunorubicin | Refused further chemotherapy and home hospice |
| 2020 | Present study | 55/M | Cytologic examination | 42 U/L | AML, M4, newly diagnosed | 3 + 7 induction with Idarubicin + araC | Effusion resolved without recurrence, patient died of septic shock about 4 months after diagnosis |

Abbreviations: BM = Bone marrow; COAP = Cyclophosphamide, Vincristine, Cytarabine, and Prednisone; araC = Cytarabine; CR = Complete remission; HSCT = Hematopoietic stem cell transplant; APL = Acute promyelocytic leukemia; ATRA = All trans retinoic acid; FLAG-IDA regimen = Fludarabine, Cytarabine, Idarubicin and G-CSF; MDS = Myelodysplastic syndrome; CMMoL = Chronic myelomonocytic leukemia; EMA protocol = Etoposide, Mitoxantrone, and Cytarabine; ICH = Intracerebral hemorrhage; PV = Polycythemia vera; BIDFA = twice-daily Fudarabine and Cytarabine; HAM = High-dose Cytarabine and Mitoxantrone.

*a Only studies with full-text or abstract in English available from PubMed were included.*  
*b Negative finding from cytologic examination and flow cytometry.*
bone marrow involvement. Pleural effusions have been reported to be associated with different phases of AML, including at the time of initial diagnosis, during advanced refractory disease, upon relapse, or after stem cell transplantation; it may even be an isolated finding after bone marrow remission [15,16] (Table 2). Some studies report that the development of pleural effusion may serve as an indicator of the development of AML in patients with myelodysplastic syndrome [17,18].

Predisposing risk factors associated with extramedullary involvement include monocytic or myelomonocytic differentiation (French-American-British [FAB] subtypes M4/M5), chromosomal abnormalities such as t(8;21) and inv(16), and expression of T cell markers including CD2, CD4, and CD7 [6,19,20]. Adhesion molecules, including CD15 and CD56, are believed to play a crucial role in the adhesion of leukemic cells to interstitial tissues [21]. In this case, high pleural ADA levels might be attributed to excessive extramedullary proliferation of monocytic leukemic cells.

The incidence of tuberculosis is twofold higher in patients with hematological malignancies when compared to that in the general population [22]. Both Gupta et al. [23] and Chen et al. [22] reported significantly higher incidences of tuberculosis disease among patients with AML than among those with other subtypes of hematological malignancies, at 6.3% (n = 95) and 2.87% (n = 1,011), respectively. The main risk factors associated with the development of tuberculosis included reduced immunity due to the primary hematological disease, age ≥50 years, and treatment with cytotoxic chemotherapy or steroids. Definitive diagnosis of *M. tuberculosis* infection is based on the clinical signs and symptoms as well as positive sputum and/or tissue culture(s); these methods can be very time consuming. As such, ADA in the pleural fluid has been used since 1983 [24] to facilitate early diagnosis of tuberculous pleural effusion; currently, this test is in wide use and has notably high sensitivity and specificity [25]. The ADA cut-off level typically considered in regions with high disease prevalence is 40 IU/L. Reportedly, high-ADA level in the pleural fluid is associated with a higher probability of TPE; furthermore, the diagnostic accuracy of ADA in TPE was influenced by age [26]. ADA level in the pleural fluid of 40 IU/L in a 55-year-old patient indicated the possibility of TPE with 60% certainty [26]. The ADA level in our 55-year-old patient was 42 IU/L. Therefore, it is possible that the evidence is not strong enough to consider TPE as a differential diagnosis in our patient. However, immunosuppressed patients may reportedly have significantly lower ADA activity [27]. Indeed, this case suggests that ADA levels detected in pleural effusions in patients with AML may introduce diagnostic complexities and lead to inappropriate therapy. Of note, this patient was unable to undergo more invasive procedures, including pleuroscopy or thoracoscopy with surgical biopsy, due to severe thrombocytopenia. Interferon-gamma release assays (IGRA) are in vitro blood tests to assess cell-mediated immune response by measuring the release of interferon-γ by T cells following the stimulation by antigens specific to the *M. tuberculosis* complex; these assays are now widely used to identify latent tuberculosis infections [28]. Because of the simplicity and noninvasive nature of IGRA, these offer an attractive alternative to promptly diagnose TPE. However, two meta-analyses have suggested that commercial IGRA that use either whole blood or pleural fluid have poor diagnostic accuracy in patients with suspected TPE [29,30].

Although the diagnosis of leukemic pleural effusion resulted from direct cytophologic examination in our patient and in most of the previous case reports (Table 2), cytopathology typically plays a limited role in most cases of hematologic malignancy due to its low diagnostic potential, reported at 2.7% by Cakir et al. [31] and at 1.58% by Johnston [32]. To prevent misdiagnosis, clinicians need to be aware of this atypical and rare presentation of AML. To improve the diagnostic yield, cytogenetic studies might be considered as a routine component of the pleural fluid analysis in patients diagnosed with AML and presenting with a pleural effusion [33].

Reportedly, leukemic effusion typically resolved after chemotherapy (Table 2). A case report described a patient with newly diagnosed AML in whom complete remission was achieved with first induction chemotherapy; however, the effusions did not resolve. The effusions resolved after re-induction with high-dose Cytarabine [16]. In addition, Huang et al. reported a good relationship between peripheral blast counts and the magnitude of pleural effusion [18].

This is possibly the first case report of a patient diagnosed with AML with leukemic pleural effusion associated with a high pleural ADA level. Additional studies are needed to determine more precise relationships between AML-associated pleural effusions and pleural ADA levels.

**Authors contribution:** Sing-Ting Wang, Chieh-Lung Chen, Shih-Hsin Liang, Shih-Peng Yeh, and Wen-Chien Cheng designed the report; Chieh-Lung Chen and Shih-Hsin Liang collected the patients’ clinical date; Sing-Ting Wang and Wen-Chien Cheng wrote the paper.

**Conflict of interest:** There are no conflicts of interest.
Data availability statement: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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## Appendix

**Table A1: Vital signs before, during and after the induction chemotherapy**

|                        | Body temperature (°C) | Heart rate (per minute) | Respiratory rate (per minute) | Blood pressure (mm Hg) | SpO₂ (%) | Oxygen use |
|------------------------|-----------------------|-------------------------|-------------------------------|------------------------|----------|------------|
| One day before         | 36.9                  | 110                     | 18                            | 95/68                  | 97       | Ambient air |
| chemotherapy           |                       |                         |                               |                        |          |            |
| Day 1 of chemotherapy  | 36.5                  | 113                     | 20                            | 113/80                 | 94       | Ambient air |
| Day 2 of chemotherapy  | 35.9                  | 108                     | 20                            | 120/80                 | 96       | Ambient air |
| Day 3 of chemotherapy  | 36.1                  | 102                     | 20                            | 92/53                  | 95       | Ambient air |
| Day 4 of chemotherapy  | 36                    | 88                      | 18                            | 92/61                  | 97       | Ambient air |
| Day 5 of chemotherapy  | 36.1                  | 93                      | 18                            | 97/64                  | 96       | Ambient air |
| Day 6 of chemotherapy  | 35.8                  | 98                      | 18                            | 93/58                  | 96       | Ambient air |
| Day 7 of chemotherapy  | 36                    | 88                      | 18                            | 90/62                  | 99       | Ambient air |
| One day after          | 36.2                  | 97                      | 18                            | 93/56                  | 98       | Ambient air |
| chemotherapy           |                       |                         |                               |                        |          |            |