

# Chronic myelomonocytic leukemia (CMML)-0 with pleural effusion as first manifestation

## A case report

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### Abstract

**Rationale:** Extramedullary invasion of chronic myelomonocytic leukemia (CMML) usually occurs in the liver, spleen, and lymph nodes, while the pleural infiltration of CMML is rare. The presence of pleural effusion is usually associated with uncontrolled leukocytosis and increased monocytes.

**Patient concerns:** Here we reported a rare case of CMML-0 with pleural effusion as the first manifestation in a 44-year-old woman. The pleural effusion was caused by blasts infiltration confirmed by the flow cytometer and the pleural biopsy.

**Diagnoses:** CMML with pleural invasion.

**Interventions:** The patient was treated with azacitidine 75 mg/m<sup>2</sup> d for 2 cycles, followed by daily oral intake of hydroxyurea (500 mg/d).

**Outcomes:** Pleural effusion was resolved and chest pain was relieved.

**Lessons:** The current case indicated that leukemic infiltration into pleura could occur despite mild leukocytes, while demethylation may be an effective therapy.

**Abbreviations:** Ara-C = cytarabine, CMML = chronic myelomonocytic leukemia, CRP = C-reactive protein, CT = computed tomography, IHC = immunohistochemistry, LDH = lactate dehydrogenase, MDS = myelodysplastic syndrome, MPN = myeloproliferative tumor, VP-16 = etoposide, WBC = white blood cell.

**Keywords:** azacitidine, chronic myelomonocytic leukemia, pleural effusion

## 1. Introduction

Chronic myelomonocytic leukemia (CMML) is characterized by myelodysplastic syndrome and myelo-proliferative tumor.<sup>[1]</sup> The incidence of CMML is low and the mean age of diagnosis is 65 to

70 years.<sup>[2]</sup> Extramedullary leukemic infiltration, which can be observed in CMML, is most commonly found in the liver and spleen, but can sometimes invade the skin, gingiva, and other areas during disease progression.<sup>[3]</sup> Serous effusion including pericardial effusion, pleural effusion, and ascites, is a rare complication of CMML.<sup>[4]</sup> Pleural effusion is usually caused by leukemic infiltration into the pleura and may also be associated with extramedullary hematopoiesis and immune responses. Pleural effusion is closely related to the transformation from CMML to acute leukemia. In the present study, we report a rare case of pleural effusion in a patient with CMML-0 and slight monocytosis as the first clinical manifestation.

## 2. Case presentation

A 44-year-old woman was admitted to our hospital in July 2019 due to cough, sputum production, and chest pain lasting for 1 week. Chest computed tomography showed pulmonary infection, bilateral pleural effusions, and left pleural hypertrophy (Fig. 1). The initial complete blood count revealed: white blood cell (WBC) count  $21.5 \times 10^9/L$  (22.7% monocytes, 65% neutrophils, 8.1% lymphocytes), hemoglobin 132 g/L, and platelet  $233 \times 10^9/L$ . C-reactive protein level was 13.1 mg/L (0–10 mg/L). The patient received antibiotics; however, her clinical symptoms did not improve, and the WBC count increased to  $22.3 \times 10^9/L$  with 26.9% monocytes, while no blasts were observed. The pleural effusion was bloody. Thoracentesis indicated exudative effusion with 47 g/dL total protein, 277 U/L lactate dehydrogenase, and 7.37 mg/dL glucose concentration.

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The patients have provided informed consent for publication of the case. Informed written consent was obtained from the patient for publication of this case report and accompanying images.

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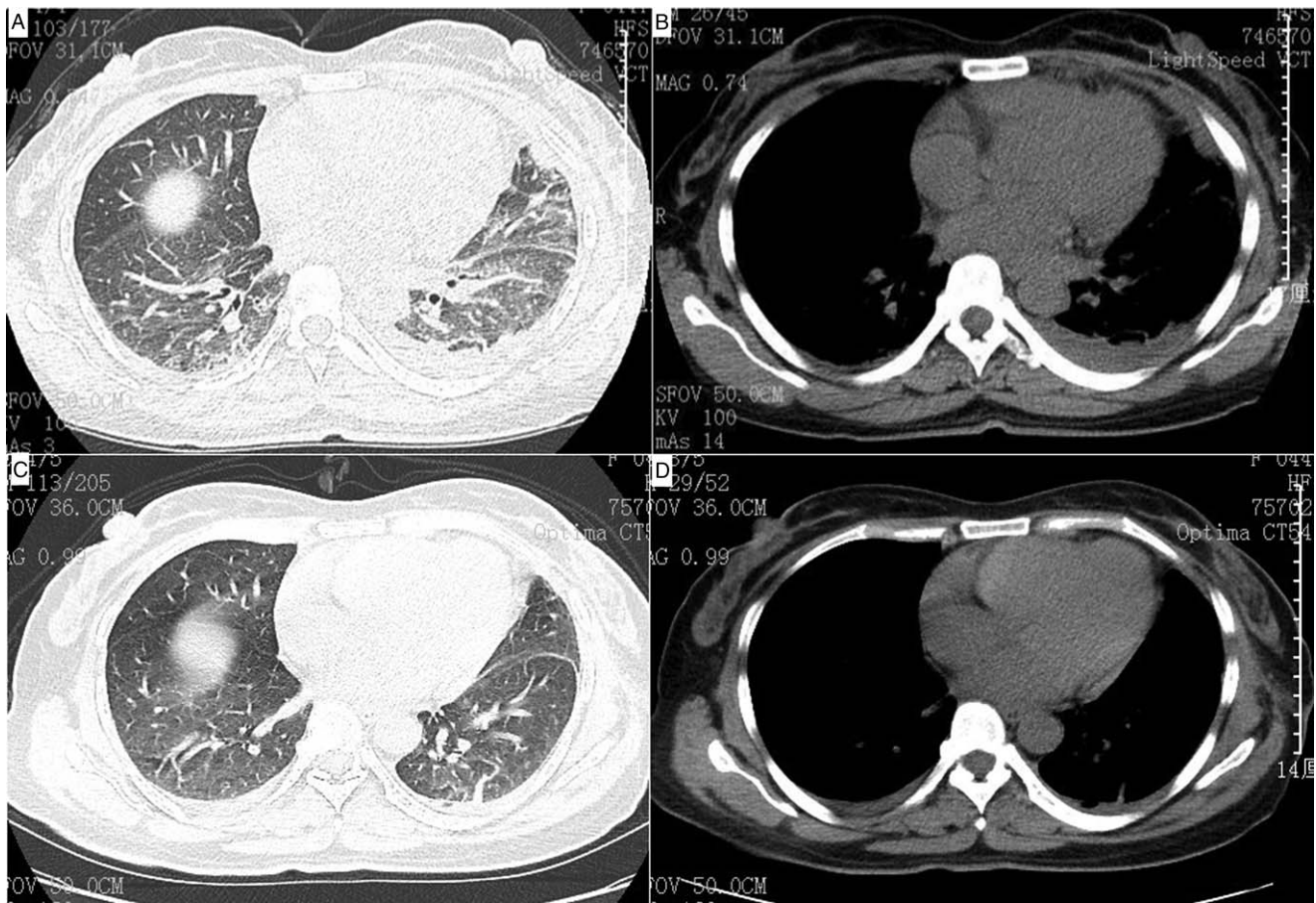
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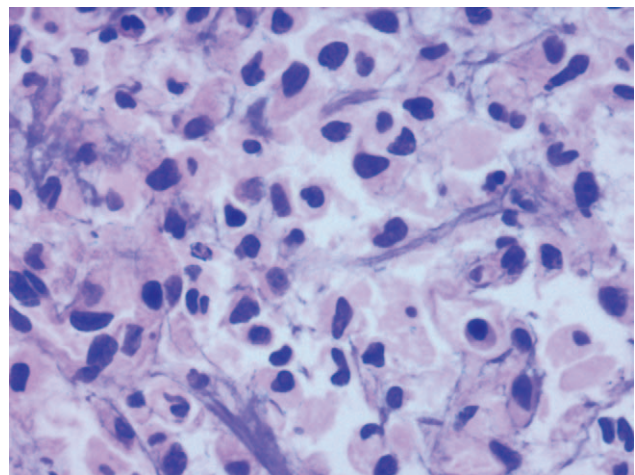
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**Figure 1.** (A and B) Chest computed tomography (CT) showed pulmonary infection, bilateral pleural effusions, and left pleural hypertrophy. (C and D) CT showed the pleural effusion was almost absorbed after 2 courses of azacitidine treatment.

The Rivalta test was positive, with a nucleated cell count of 12,800/ $\mu\text{L}$ , red blood cell count of 4800/ $\mu\text{L}$  (the ratio of red blood cells to nucleated cells was obviously lower than that of the peripheral blood), and 86% of macrophages. The cytology revealed no malignant cells, but 0.7% of blasts were detected by the flow cytometer. Microbial screening culture identified no organisms. The chest pain obviously improved after thoracocentesis; nevertheless, the severe chest pain recurred after 5 days of thoracocentesis. Subsequently, the pleural biopsy was performed under thoracoscopy. Extensive pleural adhesions were found in the patient. Postoperative histopathology confirmed heterotypic mononuclear cell infiltration (Fig. 2) in fibrous adipose tissue, with a few lymphocytes, plasma cells and neutrophils. Immunohistochemistry (IHC) were: CD68+, CD20 B cells+, CD79a B cells+, CD3 T cells+, CD43 T cells+, CD10–, S-100–, CR mesothelial cells+, D2–40–, Ki67 hotspot area about 20%+. Bone marrow aspiration revealed the increase in blasts (3%), and 2.9% blasts that had the same immunophenotype as the pleural effusion with abnormally expressed CD56 on granulocytes by flow cytometer. The bone marrow biopsy specimen showed extremely active hyperplasia, megalokaryocyte with a single round nucleus, and no reticulin fibrosis. The G-banding analysis revealed normal karyotype (46, XX); BCR/ABL fusion gene and other genes were not detected by the PCR assay, while ASXL1, SETBP1, BRAF, SETD2 mutations were observed.

Based on these results, the patient was diagnosed with CMML-0 according to WHO 2016. She was treated with azacitidine 75 mg/ $\text{m}^2$  d for 2 cycles, followed by daily oral intake of hydroxyurea (500 mg/d). Within 2 weeks, the chest pain was



**Figure 2.** Pleural biopsy showed heterotypic mononuclear cell infiltration in fibrous adipose tissue, with a few lymphocytes, plasma cells and neutrophils, H&E stain 400 $\times$ . H&E=hematoxylin and eosin.

**Table 1.**  
Literature reports on CMML presenting with pleural effusion.

Studies	Count in PB					Prior Treatment	Treatment	Response	Cause
	Age	Sex	WBC (10 <sup>9</sup> /L)	Monocytes (%)	Pleural effusion				
Manohara (1991) <sup>[6]</sup>	52	F	87.0	27.0%	Right-sided	None	Thoracentesis Ara-C, VP16 and TG	Disappearance and recurrence after 4 months. Died of septicemia after several days.	Leukaemic infiltration
Hicsonmez (1998) <sup>[7]</sup>	7	M	84.4	24.0%	Left-sided and pericardial	MIT,6-TG and Ara-c	HDMP, MIT, Ara-c and 6-TG	Disappearance and without recurrence. Died of AML-M5 after 12 months.	Leukaemic infiltration
Hicsonmez (1998) <sup>[7]</sup>	16	F	16.3	8.0%	Left-sided	None	HDMP, MIT, Ara-c and 6-TG	Disappearance and without recurrence.	Leukaemic infiltration
Bourantas et al (1998) <sup>[8]</sup>	54	F	14.0	30.0%	Bilateral	None	Prednisone	Disappearance and without recurrence.	Immune response
Bourantas et al (1998) <sup>[8]</sup>	67	M	130.0	40.0%	Bilateral	None	Ara-c, Prednisone	Disease progression. Died of septicemia after 15 days.	Leukaemic infiltration
Bourantas et al (1998) <sup>[8]</sup>	70	F	18.0	25.0%	Right-sided	None	Prednisone	Disappearance and without recurrence.	Immune response
Bourantas et al (1998) <sup>[8]</sup>	70	M	26.0	25.0%	Right-sided	None	Prednisone	Disappearance and without recurrence.	Immune response
Watanabe et al (2004) <sup>[10]</sup>	68	M	60.2	47.0%	Bilateral	HU	Ara-C, VP16	Disappearance and without recurrence. Died of bowel perforation after 3 months.	Leukaemic infiltration
Yamazaki et al (2005) <sup>[9]</sup>	61	M	26.5	31.0%	Bilateral	None	HU	Disappearance and without recurrence.	Leukaemic infiltration
Jun-Ichi et al (2008) <sup>[11]</sup>	66	M	15.8	22.0%	Right-sided	None	None	Disappearance within one year and without recurrence.	Leukaemic infiltration
Huang et al (2008) <sup>[12]</sup>	56	F	97.0	12.0%	Bilateral	HU	Thoracentesis Idarubicin, Ara-c	Disappearance and recurrence after one month. Died of respiratory failure after 2 days.	Leukaemic infiltration
Imataki et al (2014) <sup>[13]</sup>	63	F	24.7	27.8%	Bilateral	None	Prednisone,HU	Disappearance within 3 weeks and without recurrence.	Immune response
Sunami et al (2016) <sup>[14]</sup>	68	M	8.7	21.2%	Left-sided	Azacitidine, HU	Thoracentesis HU	Decreased to a small amount. Died of disease progression after 5 months.	Leukaemic infiltration or hematopoiesis
Our case	44	F	21.3	22.7%	Bilateral	None	Azacitidine, HU	Disappearance	Leukaemic infiltration

AML-M5 = acute monocytic leukaemia, Ara-C = cytarabine, F = female, HDMP = high-dose methylprednisolone, HU = hydroxyurea, M = male, MIT = mitoxantrone, TG = thioguanine, 6-TG = 6-thioguanine, VP-16 = etoposide.

relieved. After 2 courses of azacitidine treatment, pleural effusion was almost absorbed (Fig. 1). The patient is currently free of symptoms (chest pain and pleural effusion), and the monocytosis has been under control for 6 months.

### 3. Discussion

Here we report a rare case of CMML with pleural effusion as the initial manifestation. This case was diagnosed as CMML-M0 according to the WHO diagnostic criteria from 2016.<sup>[11]</sup> Our patient had pleural effusion as the first symptom that led to the diagnosis of CMML-0 stage. It has been reported that 1 out of 60 CMML patients (1.7%) has serosal effusion at the time of diagnosis.<sup>[5]</sup> So far, more than 10 cases of CMML with pleural effusion have been found since the 1990s (Table 1). Pleural effusion occurs during the whole clinical process of CMML and is usually accompanied by a high or rapid increase in leukocyte and monocyte count. Yet, 1 patient with CMML developed pleural effusion during the decline of WBC and monocytes.<sup>[13]</sup> It is important to emphasize that it is rare for patients with CMML to have mild leukocytosis accompanied by pleural effusion as the first clinical sign.

There are several possible mechanisms for the development of pleural effusion in CMML patients, the first one being a non-malignant cause, such as infection. This mechanism was excluded in our patient by the identification of microorganisms. The second mechanism is the infiltration of leukemia into the pleura, which usually occurs at the time of transition to the acute leukemia stage or before.<sup>[6-8,12]</sup> Pleural effusion analysis of these cases revealed different stages of monocytes and leukemic cells. Cases of pleural invasion of leukemia without leukemia transformation are relatively rare.<sup>[11,14]</sup> The patient's bone marrow blasts had the same immunophenotype as the pleural effusion, but there were no blasts in peripheral blood. Pleural biopsy pathology also suggested atypical mononuclear cell invasion. Although there was no crisis of leukemia transformation, it was still considered that the patient's pleural effusion was caused by leukemia cells invading the pleura. The third mechanism includes a variety of causes leading to bleeding into the pleural cavity. At this point, the proportion of red blood cells and nucleated cells in the blood should be similar to the effusion. However, the ratio of red blood cells to nucleated cells in the pleural effusion was obviously lower than that of the peripheral blood. The presence of 86% macrophages in the pleural effusion

also suggested that the patient's pleural effusion was non-bleeding. The fourth possible mechanism is pleural extramedullary hematopoiesis. Myelofibrosis is often associated with extramedullary hematopoiesis. CMML is also a proliferative tumor of bone marrow. Extramedullary hematopoietic sites generally include the liver, spleen, and lymph node. The pleura can also be the site of extramedullary hematopoiesis, while pleural effusion may also be caused by extramedullary hematopoiesis. Extramedullary hematopoiesis implies hematopoiesis of erythroid, myeloid, and megakaryocytes, and a dominant lineage, which may appear.<sup>[14]</sup> The patient's bone marrow biopsy confirmed no myelofibrosis, and pleural effusion and pleural biopsy showed no other hematopoietic cells. There is the fifth mechanism that needs to take into account the immune response. The cause of pleural effusion in CMML is an immune response to bacteria or viruses.<sup>[5]</sup> Bourantas *et al* reported that in 4 cases of CMML with pleural effusion, only 1 occurred due to CMML cell infiltration and the remaining 3 were immune responses.<sup>[8]</sup> Monocytes are hyperproliferated in the immune response, which needs to be determined by flow cytometry. An immune response did not cause pleural effusion in our patient according to the immunophenotypes.

For the treatment of CMML with pleural effusion, there is no uniform standard due to the rare incidence of the condition. Patients with pleural effusion are reported (Table 1) for treatment with hydroxyurea, etoposide (VP16), idabil, and cytarabine (Ara-c). At present, allogeneic hematopoietic stem cell transplantation is the only possible method to cure CMML. However, the patient did not have a suitable bone marrow match. Over recent years, demethylated drugs have been used to treat CMML. Methylation can lead to mutations in related genes, including TET2, UTX, EZH2, and DNMT3A. The use of demethylated drugs can prolong the median overall survival time in patients.<sup>[15]</sup> Our patient chose azacitidine for treatment. After 2 courses of azacitidine treatment, pleural effusion was almost absorbed, and chest pain relieved. The patient refused further use of azacitidine, although it was well tolerated. She was transferred to hydroxyurea for maintenance therapy. After half a year of outpatient follow-up, the patient's peripheral blood leucocytes were stable with  $15 \times 10^9/L$ , and the proportion of monocytes was about 30%. The patient's pleural effusion did not recur. Little information is available on the treatment of CMML with extramedullary invasion. Our patient was treated with azacitidine and the pleural effusion was relieved. Azacitidine may relieve extramedullary pleural invasion in CMML. Jun-Ichi *et al* proposed that pleural effusion without respiratory failure might not necessarily require an active treatment in CMML without the transformation of acute leukemia.<sup>[10]</sup> Future studies should investigate CMML with pleural effusion so as to provide more data for appropriate treatment strategies.

#### 4. Conclusion

The invasion of the pleura has been rarely documented in CMML, especially not at the stage of blast proliferation or

transformation to leukemia. In this case of CMML with pleural metastases, demethylation, and maintenance hydroxyurea treatments showed to be effective. More cases are required to confirm whether azacitidine is beneficial for CMML with extramedullary invasion, especially pleura.

#### Author contributions

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**Formal analysis:** Meiwei Hu.

**Project administration:** Meiwei Hu.

**Writing – original draft:** Lianbo Hu.

**Writing – review & editing:** Bingrong Zheng.

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