CASE REPORT

Chronic myelomonocytic leukemia presenting with polyserositis due to an immune-mediated monocyte activation

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Introduction
Chronic myelomonocytic leukemia (CMML) has been categorized as a clonal hematological malignancy with manifestations of both myelodysplastic syndrome (MDS) and myeloproliferative neoplasm (MPN) [1]. CMML had been recognized as MPN featuring a persistent increase in monocytes with a background of MDS. Monocytosis in both peripheral blood (PB) and bone marrow (BM) is a characteristic laboratory finding, and in some studies, monocytes infiltrated tissues at the onset of CMML [2–4]. Among the reported cases, some presented pleural effusion observed in overt monocytic leukemia [2], while others described reactive monocyte penetration into a pleural effusion [4]. Leukemic infiltration is not an uncommon phenomenon, especially in the management of acute monocytic leukemia, although nonmalignant components of monocytes in CMML seldom extravasate and create symptoms.

We report the case of a patient who repeatedly developed symptomatic serositis with effusions during the course of CMML and discuss the presumed mechanism of monocytic overflow in effusion. We also speculate that activated monocytes behave differently upon intrinsic or extrinsic pathogenic stimulation.

Case Report
A 63-year-old woman developed pericarditis and pleuritis of unknown etiology, followed by symptoms of infection. She was admitted to a different hospital and underwent a drainage procedure for pericardial effusion and pleural effusion. Subsequently, she received antibiotics and her clinical problems resolved.

Approximately 15 months after this initial episode of double effusion, symptoms of the patient’s third serositis became overt as peritonitis with a fever. She was admitted to our institute with a chief complaint of abdominal pain persisting 8 h after her most recent dinner, and she was diagnosed as having an abdominal emergency requiring surgical view the next morning. Her body temperature was 37.9°C, and physical examination at admission...
revealed tenderness and rebound tenderness in her upper abdomen. Laboratory findings showed elevated WBC count $24.72 \times 10^3/\mu L$ and CRP $13.09 \text{ mg/dL}$, as well as increased monocyte population 27.8% in WBC. The patient’s history of persistent monocytosis for more than 6 months, together with trilineage dysplasia in bone marrow at admission, met the criteria of CMML. Computed tomography (CT) scanning depicted higher density of the peritoneum and panniculus around the anterior of the antrum (Fig. 1A) with Douglas pouch fluid. A subemergent elective operation was decided on, but during the preparation for surgery, the patient’s abdominal pain diminished. The surgical emergency was avoided, and the patient was transferred to the department of internal medicine.

After conservative therapy was initiated, antibiotic treatment made the patient afebrile in 3 days, and her inflammatory status reached remission. Conversely, however, a bilateral pleural effusion increased on day 10 after onset (Fig. 1B), making $O_2$ inhalation necessary. The patient’s chest CT showed bilateral pleural effusion. Thoracocentesis indicated exudative effusion with 4.5 g/dL total protein and 1036 U/L LDH, but normal glucose concentration (89 mg/dL). Cytology revealed no malignant cells, resulting in a class I categorization, but a substantial component (90.5%) of the collected cells was mature monocytes expressing CD16 and CD45RO (Fig. 1C). Microbial screening culture identified no organism. A biochemical analysis for various tumor markers, enzymes, and cytokines (CEA, hyaluronidase, ADA, elastase 1, lysozyme, lipase, acid phosphatase, IL-1$\beta$, and TNF-$\alpha$) revealed that all were within normal range (Table 1).

After obtaining the cytological findings of the patient’s pleural effusion, we saw that her BM aspiration demonstrated dysplasia in three hematological lineages, and a myelogram revealed monocyte proliferation (27.8%) but no increase in blasts (1.4%). Even after remission of the acute inflammation phase, her monocyte counts in PB increased persistently to more than $1000/\mu L$, which led to a diagnosis of CMML (FAB classification) and CMML-1 (WHO). A chromosomal analysis detected trisomy (46, XX, +1, der(1;15)(q10;q10)) in 11 of 20 interphase cells.

Once the diagnosis was confirmed, we treated the patient with a 1-mg/kg dose of prednisolone, and her

### Table 1. Biochemical findings of pleural effusion in a 63-year-old woman with CMML with heterochronological serositis.

| Test                  | Result   |
|-----------------------|----------|
| CEA                   | <0.5 ng/mL|
| Hyaluronidase         | 86,400 ng/mL |
| ADA                   | 38 IU/L |
| Elastase 1            | 190 ng/dL |
| Lysozyme              | 32.3 $\mu$g/mL |
| Lipase                | 25 U/L |
| Acid phosphatase (AcP)| 54.6 U/L |
| IL-1$\beta$           | $\leq 10$ pg/mL |
| TNF-$\alpha$          | 5.3 pg/mL |

Figure 1. (A) Abdominal CT on admission showed a high-density area of the intraceliac panniculum in front of the gastric antrum (indicated by arrows). (B) Chest X-ray on admission (day 1) identified no pleural effusion (top). Chest X-ray on day 10 showed a pronounced bilateral pleural effusion (bottom). (C) May–Giemsa staining of pleural fluid obtained from a left thoracocentesis on day 7 demonstrated infiltration of many mature monocytes, which accounted for the majority (90.5%) of the smeared cells. There was no evidence of malignant cells, including of CMML tumor cells. Cells from the pleural effusion were collected and fixed on glass slides by the cytospin centrifug technique.
pleural effusion responded well. The corticosteroid therapy was followed by daily oral hydroxyurea (500 mg/body), and within 3 weeks, the pleural effusion was eliminated completely. During treatment, the corticosteroid was tapered at 5 mg/week under close observation, but there was no recurrent finding. After 5 weeks of treatment in the hospital, she switched to the outpatient clinic with oral administration of 25-mg/day predonisolone and 500-mg/day hydroxyurea. The predonisolone was intermittently tapered at 5 mg at intervals of a couple of weeks. The patient is currently free of symptoms derived from CMML, and the monocytosis has been under complete control without predonisolone for 14 months.

Discussion
Considering the essential functions and endogenous features of monocytes, a case with infiltrating monocytes overflowing into an effusion does not appear to be a rare form onset of CMML; however, the concomitance of pericardial and pleural effusion is uncommon [3]. Fenaux et al. reported that primary overt CMML manifesting as effusion (called “primary effusion CMML”) occurred in only one case among 60, for an incidence of 1.67% [3]. Thus, effusion CMML is uncommon. This case is particularly notable due to the evidence of a benign monocytic effusion determined by cytological detection, placing it solidly in the minority.

Our patient had high PB monocyte counts whenever effusions developed. Heterochronological evidence of effusions, we believe, supports a repeated common mechanism underlying the monocyte infiltration in serous tissue (pericardium, peritoneum, and pleura) based on this patient’s clinical condition. Because, in our patient, pericarditis, peritonitis, and pleuritis were all followed by infectious symptoms, we propose the pathogenesis of the biology of chronic CMML responding to an external stimulation, such as a bacterial or viral infection, or an immunogenic reaction. The effusions resolved after the patient received corticosteroid therapy, and thus it is likely that they were triggered by some systemic immunological reaction. Since disease progression was not observed after corticosteroid therapy, active and contiguous infection seemed not to be associated with effusion episodes. It is, however, critically important to distinguish infectious events from other causes.

Reviewing past case reports, we see that infiltrating monocytes were the leukemic cells in some patients during the course of the disease, and that these patients responded to conventional chemotherapy [2, 4–6]. In those cases, the mechanism was straightforward, because extramedullary involvement of monocytic leukemia is a common manifestation based on the biology of leukemia cells [2]. In our patient, the penetrating monocytes in the pleura were not malignant. The absence of malignant cells was a second determinant to clarify the underlying condition of CMML with effusion.

Immunological “reactive” effusion is the most representative definition for our patient, as it both explains the mechanism and confirms the utility of the corticosteroid therapy [3]. From the perspective of an immunogenic activation of monocytes without infection or malignancy, an activation marker such as a monokine or cytokine might be increased in the serum or effusion. We could not detect elevation of any cytokines, however [3] (Table 1).

Our patient’s case illustrates that treating primary effusion CMML with corticosteroid therapy can be successful after eliminating the possibility of an infectious episode and malignant infiltration of CMML.

Conflict of Interest
None declared.

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