Pleural effusion in hematological pathology

Neeraja Yerrapotu, MD1, Abid Rahman, MD1, Ali Gabali, MD, PhD1, Vinod B. Shidham, MD, FIAC, FRCPath1

1Department of Pathology, Detroit Medical Center, Karmanos Cancer Center and Wayne State University School of Medicine, Detroit, Michigan, United States.

A 51-year-old male with a history of chronic myelomonocytic leukemia-2 (CMML-2) presented with fatigue, night sweats, dyspnea, and right-sided chest pain exacerbated by deep breath. Computed tomography scan demonstrated right-sided pleural effusion with atelectasis. Pleural fluid cytology showed reactive mesothelial cells mixed with atypical cells [Figure 1]. The immunostains are performed using the SCIP approach.[1] The atypical cells were immunoreactive for vimentin, CD68, and CD163, while non-immunoreactive for cytokeratin, calretinin, BerEP4, and MOC31.

Figure 1: (a and b) Diff-Quik stain ×10 and ×40, respectively. Pleural fluid consisting of a mildly cellular specimen with reactive mesothelial cells and atypical cells. B. The atypical cells showed high N/C ratio, irregular nuclear membranes with apoptotic bodies. (c and d) H&E ×10 and ×40, cell block was cellular specimen with an increased number of atypical cells, high N/C ratio, irregular nuclear membrane in a background of extensive apoptotic bodies.

Q1. What is the cytopathology interpretation here?

a. Mesothelioma
b. Metastatic melanoma
c. Metastatic adenocarcinoma
d. Small cell carcinoma of the lung
e. Myeloproliferative process.
Answer to Q1: (e) The correct cytopathologic interpretation is myeloproliferative process.

Choice #(e): Myeloproliferative process involving pleural cavity is presented as this quiz case. The patient had a history of CMML-2. The cytology of pleural fluid shows atypical non-cohesive cells with various cells of myeloid series, including myeloblasts, monoblasts, promyelocytes, promonocytes, myelocytes, and metamyelocytes. Atypical cells were immunoreactive for vimentin, CD68, and CD163 and non-reactive for calretinin, BerEP4, and MOC31, consistent with monocytic lineage. The clinical history of CMML with cytomorphological and immunohistochemical features are consistent with CMML involving pleural cavity.

Option (a): On cytology, neoplastic cells of mesothelioma are cohesive groups seen as flat sheets, three-dimensional groups, and papillary or tubular acinar pattern. The mesothelioma cells are immunoreactive for calretinin (nuclear) and cytokeratin (CK) 7. The diagnosis of mesothelioma requires correlation with radiological findings, including pleural-based lesions/diffuse pleural thickening with a history of exposure to environmental factors such as asbestos.

Option (b): Metastatic melanoma may show singly scattered atypical cells with bizarre, hyperchromatic irregular nuclei with prominent nucleoli. Although most of the melanomas are amelanotic, some tumor cells may show melanin pigment.

Option (c): Metastatic adenocarcinoma shows loosely cohesive small nests/clusters of neoplastic cells with proliferation spheres. The cells may have intracytoplasmic targetoid vacuoles with secretion/foamy cytoplasm with peripherally pushed nuclei. Other features that can be identified are touching of the nucleus to the cell membrane, round to oval nuclei with fine to coarse chromatin, and sometimes prominent nucleoli. Some cases may show singly scattered cells. Adenocarcinoma cells usually are non-immunoreactive for vimentin with immunoreactivity for BerEP4 with characteristic immunoprofile of a particular primary site.

Option (d): Small cell carcinoma cells show atypical cells with high nuclear to cytoplasmic ratio, scant delicate basophilic cytoplasm, nuclear molding, diathesis, or necrosis, and granular (salt and pepper) chromatin. Although generally small cell carcinoma cells usually do not show easily detectable nucleoli, the metastatic small carcinoma cells in the serous effusion fluids may show an indistinct nucleolus.

ADDITIONAL QUIZ QUESTIONS

Q2. Which of the following is a feature of a myeloproliferative process?
   a. Nuclear molding
   b. Chromogranin immunoreactivity
   c. TTF-1 positivity
   d. MPO cytoplasmic staining
   e. Synaptophysin immunoreactivity.

Q3. Which of the following features favor an epithelial neoplasm over a hematological malignancy?
   a. Proliferation spheres
   b. CD45/LCA immunoreactivity
   c. Lymphoglandular bodies
   d. CD20 immunoreactivity
   e. t(9:22) BCR/ABL.

Q4. Which of the following features would favor a reactive lymphoproliferative process over lymphoma in pleural fluid?
   a. Elevated Ki-67 proliferation index
   b. A polymorphous population of lymphocytes
   c. BerEP4 immunoreactivity
   d. Cytoplasmic vacuoles with mucin (PAS-D and mucicarmine positive).

Answers to additional quiz questions
Q2. d, Q3. a, and Q4. b

BRIEF REVIEW OF CMML

Cytomorphological features
- Cellular specimen with non-cohesive cells
- Variable cell morphology is seen, including rare myeloblasts, monoblasts, promyelocytes, promonocytes, myelocytes, metamyelocytes, bands, and segmented neutrophils. Eosinophils may show a full spectrum of maturation.
- Usually, a necrotic background is not present
- Some of the cells may show granular cytoplasm.[2]

Clinical presentation
- Blood count shows marked leukocytosis, monocytosis, and organomegaly. The cells may show dysplastic changes
- Around 80% of cases are de novo; 20% have a prior myelodysplastic syndrome, occasionally with monocytosis
- Splenomegaly is present in 30–50% of cases, rarely causing a splenic rupture
- May have a reactive aggregate of CD123+ benign plasmacytoid dendritic cells
- More closely related to myelodysplastic syndrome than myeloproliferative neoplasms (the loss of heterozygosity evaluation).

WHO diagnostic criteria (2016 WHO classification)
- Persistent peripheral blood monocytosis $>1 \times 10^9$/L or monocyes accounting for $>10\%$ of WBC
- WHO criteria for BCR-ABL1-positive chronic myeloid leukemia, primary myelofibrosis, polycythemia vera,
and essential thrombocythemia are not met

- No rearrangement of PDGFRα, PDGFRβ, or FGFR1 and no PCM1-JAK2 present
- <20% blasts (includes myeloblasts, monoblasts, and promonocytes) in blood and bone marrow.

Type 0: About <2% blasts in the blood and <5% in the bone marrow, no Auer rods.

Type 1: About 2–4% blasts in blood or 5–9% blasts in the bone marrow and no Auer rods.

Type 2: About 5–19% blasts in blood, 10–19% blasts in bone marrow, or Auer rods present with any number of blasts.

If blasts and/or promonocytes (blast equivalents) are 20% more in bone marrow differential count or blood, it is classified as acute myeloid leukemia (AML).

- Peripheral blood may have dysplastic changes typical of myelodysplasia in one or more myeloid lineages
- In case of minimal or absent myelodysplasia, the diagnosis can be established in the presence of acquired or clonal genetic abnormality or if persistent monocytosis of >3 months and after excluding reactive causes for monocytosis.

Microscopy

**Peripheral blood**

Most of the cases have increased WBC count because of monocytosis and neutrophilia. However, sometimes, the number is slightly decreased. In general, the monocytes appear normal but may have abnormal granulation, more nuclear convolutions, and denser chromatin than promonocytes (termed as abnormal monocytes).

**Bone marrow**

Hypercellular marrow with mildly increased monocytes (this is not diagnostic by itself) and increased granulocytes; may have increased reticulin fibers; variable dysplastic changes in erythroid cells, myeloid cells, and megakaryocytes. Cases with eosinophilia need screening for PDGFRα, PDGFRβ, and FGFR1 gene abnormalities.[3]

**Immunohistochemistry**

Variable immunoreactivity for CD68, CD163, CD64, and CD14 is observed [Figures 2 and 3]. CD64, CD68, and CD163 are markers of monocytic differentiation. CD163 is also the marker of histiocytic differentiation. The cells are immunoreactive for myelomonocytic markers such as CD13 and CD33. When an increased number of CD34 immunoreactive cells are present, evolving acute leukemia should be considered.

**Genetics**

**Molecular description**

- Mutational analysis is beneficial when benign cases of monocytosis cannot be ruled out
- In most cases, a clonal abnormality can be identified in one of the following nine genes: SRSF2, ASXL1, CBL, EZH2, JAK2, KRAS, NRAS, RUNX1, and TET2.[4]

**Cytogenetics description**

- Abnormalities in 20–40% of cases, including trisomy 8, monosomy 7, monosomy 5, deletion 12p, and deletion 20q.
The absence of the Philadelphia chromosome, BCR-ABL-1 fusion gene, PDGFRα, PDGFRβ, or FGFR1 rearrangements.

Flow cytometry

Flow cytometry is generally considered non-specific. The neoplastic monocytes in CMML have the same immunophenotypic expression as mature monocytes with bright expression of CD45, CD11b, CD11c, CD13, CD14, CD64, and CD15. Aberrant phenotypes including dim/variable CD14, CD13, HLA-DR, CD64, and overexpression of CD56 are also observed in majority of cases

Abnormal antigen expression of two or more antigens plus 20% of marrow monocytes showing moderate CD14 expression is found to be 100% specific for CMML versus reactive monocytosis[5]

Monocytes show no expression of stem cell markers, including CD34 and CD117.

Prognosis

Median survival is 20–40 months. Progression into acute leukemia occurs in 15–30% cases, which is the most crucial factor conferring a poor prognosis. Various clinical factors, including but not limited to, lactate dehydrogenase, splenomegaly, and blast count, are included in the CMML-specific prognostic scoring system.[6]

Differential diagnosis in this case

**Melanoma**

- Tumor cells with occasional cytoplasmic brown pigment, with bizarre; hyperchromatic, irregular nuclei with prominent nucleoli
- Necrosis and occasional mitotic figures can also be seen
- Immunoreactive for S100 protein, HMB45, and MelanA/MART1.

**Mesothelioma**

- The effusion fluid is usually highly cellular
- Cohesive flat sheets with papillary or tubular/acinar patterns are common
- The nuclei are centrally or near centrally located
- Binucleation or multinucleation is common
- The nuclei show a varying degree of pleomorphism, but nuclear to cytoplasmic ratio remains relatively consistent
- Immunoreactive for calretinin (nuclear immunostaining), D2-40 (membranous/microvillous immunostaining), and CK 5/6.

**Small cell carcinoma**

- High nuclear to cytoplasmic ratio
- Scant delicate basophilic cytoplasm
- Nuclear molding
- Crush artifact
- Diathesis or necrosis
- Granular (“salt and pepper”) chromatin
- Cells are approximately 1.5 times the size of mature lymphocytes
- Immunoreactive for pan-keratin (dot-like pattern), TTF-1, chromogranin, and synaptophysin.

**Adenocarcinoma of lung**

- Tightly cohesive small nests/clusters of neoplastic cells arranged in the form of glandular architecture
- Proliferation spheres may be present
- Intracytoplasmic vacuoles/foamy cytoplasm, displacing nuclei at the periphery (rhabdoid appearance)
- Neoplastic cells have large round to oval nuclei with smooth to coarse chromatin and occasional prominent nucleoli
- Extracellular mucin
- Immunoreactive for MOC31, Napsin, TTF-1, Ber-EP4, and CK7.

**Reactive/inflammatory process**

- Increased cellularity
- Reactive mesothelial cells with wide cytomorphological spectrum
- Background of mixed inflammatory cells
- Granulomas (+fibrosis)
- Microorganisms may be seen.

**SUMMARY**

CMML is a rare aggressive entity. The incidence is fewer than 1100 newly diagnosed cases each year in the United States and is characterized by cytopenia, dysplasia, and monocytosis within the bone marrow and peripheral blood. It comes under a category called myelodysplastic syndrome/myeloproliferative neoplasm. This disease is typically found in older men with a mean age of 70 years and is notoriously difficult to treat. Although there are multiple prognostic models discussed, there has not yet been a definite CMML-specific prognostic system involving molecular alterations. Despite the advent of new drug treatments such as hypomethylating agents, currently, the allogeneic hematopoietic stem cell transplantation (allo-HSCT) still is the only curative treatment available. Even with allo-HSCT, the overall 5-year survival rates after therapy are 18–47%,[7] The transformation rate to AML is 17–19%.
There are only 10 reported cases of pleural effusions associated with CMML reflecting the incidence of this poorly understood phenomenon. These cases are summarized in Table 1. Five of these cases resulted from leukemic infiltration; two of these patients expired soon after transformation into AML and further systemic complications, but three of them resolved with steroids and chemotherapeutic drugs.

The case, we presented, is 1.6 years into post-unrelated donor peripheral blood stem cell transplant and is doing well without relapse or leukemic infiltration.

**COMPETING INTEREST STATEMENT BY ALL AUTHORS**

Vinod B. Shidham is the editor of this journal. He does not have any competing interest.

**AUTHORSHIP STATEMENT BY ALL AUTHORS**

Each author has participated sufficiently in the work and take public responsibility for appropriate portions of the content of this article. All authors read and approved the final
ETHICS STATEMENT BY ALL AUTHORS

As this is case without identifiers, our institution does not require approval from institutional review board (IRB) (or its equivalent).

LIST OF ABBREVIATIONS (In alphabetic order)

AML - Acute myeloid leukemia
CMML - Chronic myelomonocytic leukemia
DC - During course of disease
FNA - Fine needle aspiration
IP - Initial presentation
NS - Not specified
SCIP - Subtractive coordinate immunoreactivity pattern.

EDITORIAL/PEER-REVIEW STATEMENT

To ensure the integrity and highest quality of CytoJournal publications, the review process of this manuscript was conducted under a double-blind model (the authors are blinded for reviewers and vice versa) through automatic online system.

REFERENCES

1. Shidham VB, Atkinson AF, editors. Immunocytochemistry of effusion fluids: Introduction to the SCIP approach. In: Cytopathologic Diagnosis of Serous Fluids. 1st ed. Amsterdam: Elsevier, W. B. Saunders; 2007. p. 55-78.
2. Sanchez S, Chang C. Hematolymphoid disorders. In: Shidham V, Atkinson B, editors. Cytopathological Diagnosis of Serous Fluids. Amsterdam: Elsevier Inc.; 2007. p. 171-93.
3. Orazi A, Chiu R, O’Malley DP, Czader M, Allen SL, Caroline A, et al. Chronic myelomonocytic leukemia: The role of bone marrow biopsy immunohistology. Mod Pathol 2006;19:1536-45.
4. Meggendorfer M, Roller A, Haferlach T, Eder C, Dickmer F, Grossmann V, et al. SRSF2 mutations in 275 Cases with chronic myelomonocytic leukemia (CMML). Blood 2012;120:3080-8.
5. Xu Y, McKenna RW, Karandikar NJ, Pildain AJ, Kroft SH. Flow cytometric analysis of monocytes as a tool for distinguishing chronic myelomonocytic leukemia from reactive monocytosis. Am J Clin Pathol 2005;124:799-806.
6. Such E, Germing U, Malcovati L, Cervera J, Kuendgen A, Porta MG, et al. Development and validation of a prognostic scoring system for patients with chronic myelomonocytic leukemia. Blood 2013;121:3005-15.
7. Motohashi K, Fujisawa S, Doki N, Kobayashi T, Mori T, Usuki K, et al. Cyrogenetic risk stratification may predict allogeneic hematopoietic stem cell transplantation outcomes for chronic myelomonocytic leukemia. Leuk Lymphoma 2018;59:1332-7.
8. Bourantas KL, Tsiara S, Panteli A, Milionis C, Christou L. Pleural effusion in chronic myelomonocytic leukemia. Acta Haematol 1998;99:34-7.
9. Hıçsönmez G, Çletin M, Tunç B, Tuncer AM, Gümrük F, Yenicesu I. Dramatic resolution of pleural effusion in children with chronic myelomonocytic leukemia following short-course high-dose methylprednisolone. Leuk Lymphoma 1998;29:617-23.
10. Watanabe N, Takahashi T, Sakamoto Y, Tanaka Y, Kurata M, Matsushita A, et al. Pleural involvement in the course of chronic myelomonocytic leukemia and the development of multiple colonic perforation due to leukemic infiltration in the acute leukemia phase. Rinsho Ketsueki 2004;45:546-50.
11. Yamazaki E, Kanai M, Sakai R, Sakamoto H, Ishigatsubo Y. Chronic myelomonocytic leukemia with pleural effusion as the first clinical sign. Rinsho Ketsueki 2005;46:217-9.
12. Imataki O, Watanabe N, Matsumoto K, Uemura M. Chronic myelomonocytic leukemia presenting with polyserositis due to an immune-mediated monocyte activation. Clin Case Rep 2014;2:42-4.
13. Sunami Y, Gotoh A, Watanabe N, Edahiro Y, Hamano Y, Harada H, et al. Chronic myelomonocytic leukemia with myelofibrosis resulting in sudden massive pleural effusion during cytoreductive therapy with hydroxycarbamide. Gan To Kagaku Ryoho 2016;43:1223-6.

How to cite this article: Yerrapotu N, Rahman A, Gabali A, Shidham VB. Unusual presentation of chronic myelomonocytic leukemia as pleural effusion. CytoJournal 2021;18:3.

HTML of this article is available FREE at: https://dx.doi.org/10.25259/Cytojournal_12_2020