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Case Report Open Access

Meningeal Infiltration of Chronic Myelomonocytic Leukemia

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Abstract

Chronic Myelomonocytic Leukemia (CMML) is a hematologic malignancy considered a subtype of Myelodysplastic Syndrome (MDS)/Myeloproliferative Disease (MPD). According the World Health Organization (WHO) two subtypes of CMML, CMML-1 and CMML-2 are defined depending on the percentage of blasts in Bone Marrow (BM) and Peripheral Blood (PB).

The clinical presentation is variable, but the majority of patients present with fatigue, weight loss, fever, night sweats and splenomegaly, less often skin infiltration or serous effusions.

Meningeal leukemic involvement is rarely a presenting feature of CMML. We are reporting a case of 67-year old male with central nervous system involvement of CMML.

Introduction

Chronic Myelomonocytic Leukemia (CMML) is a rare clonal hematologic disorder, with a heterogeneous clinical and morphological manifestation. The estimated incidence of CMML is 3 per 100,000 individuals older than 60 years. The median age at diagnosis is 65 to 75 years, and there has been a higher incidence in men [1].

The 2008 WHO diagnostic criteria for CMML are persistent peripheral blood monocytosis (>1×10^9/L), without Philadelphia chromosome or BCR-ABL1 fusion gene, no arrangement of PDGFRA or PDGFRB (these rearrangements should be specifically excluded in cases with eosinophilia), less than 20% blasts in the peripheral blood and the BM (blasts includes myeloblasts, monoblasts, and promonocytes), and at least one of the following: (a) dysplasia in one or more cell lines, (b) an acquired clonal cytogenetic abnormality or molecular genetic abnormality present in hematopoietic cells, or (c) persistence of monocytosis for at least 3 months and no evidence of other causes of monocytosis (such infection, inflammation, or malignancy) [2,3].

CMML-1 is characterized with more than 1×10^9 /L monocytes and up to 5% blasts in peripheral blood, dysplasia in more than one hematopoietic cell line and less than 10% of blasts in the bone marrow. CMML-2 is characterized with more than 1×10^9/L monocytes and 5 to 19% of blasts and Auer rods in peripheral blood, dysplasia in one or more than one hematopoietic cell line and 10 to 19% blasts or Auer rods in the bone marrow [3,4].

CMML-1 patients have better expected prognosis than CMML-2 patients. It is probably due to the more frequent development of Acute Leukemia (AML) than patients with CMML-1.7 AML transformation has been observed in 14 to 20 % CMML patients.

Case Presentation

An 67-year old male was admitted to our Hematology Department in September 2011 with nonspecific clinical status presentation, and the laboratory findings were as follow: WBC 20.22×10^9/L, RBC 6.52×10^{12}/L, Hb 155 g/L, Hct 0.49 L/L, Plt 521×10^9/L, Fe 4 mmol/L, UIBC 50 mmol/L, urate 461 mmol/L, AST 95 U/L, ALT 139 U/L, GGT 85 U/L, LDH 647 U/L, CRP 22.3 mg/L, ESR 14 mm/3.6ks. The bone marrow analysis revealed accelerated phase of CMML. Karyotype done on bone marrow cells was normal male in 25 metaphases, without clonal aberrations, and there were negative results of PCR analysis for bcr-abl and JAK2. Bone marrow flow cytometry analysis detected phenotype: $CD45^{+/-}$ $CD34^+$ $CD117^+$ $CD13^+$ REFRIG/DR^+ $CD61^+$ and $CD33^-$ $CD14^-$ $CD64^-$ MPO^- $lysozyme^-$, $CD2^-$ $CD56^-$ $CD4^-$ TDT^-.

The patient was treated with hydroxiurea once daily and check-up was done during the next 12 months at the outpatient department.

In early January 2012, the patient presented with fever and intense headache. In the peripheral blood were found leukocytosis with myeloblasts and promyelocytes. Lactate dehydrogenase activity was increased, and β2-microglobulin concentration elevated. He was empirically treated with broad spectrum antibiotics and in the next 48 hours fever resolved, but the headache was persistent. The signs of multifocal leukoencephalopathy and cortical atrophy were found by the magnetic resonance imaging of the head and neck. The neurological examination of the patient was completely normal, as well as ophthalmic fundoscopy finding. Cytologic analysis of Cerebrospinal Fluid (CSF) revealed atypical cells (1692/3 per visual fields), numerous monocytes, some lymphocytes, eosinophils, basophils and neutrophils. Biochemical CSF analysis detected glucose 2.4 mmol/L, lactate 2.6 U/L, total protein concentration 0.87 g/L. Due to meningeal infiltration of CMML, the patient was treated with cytarabine 40 mg weekly intermittently with methotrexate 12mg intrathecally weekly for two months.

His headache and fever resolved, and the cell count in the CSF gradually decreased with clinical improvement.

Discussion

The natural course of chronic myelomonocytic leukemia is highly variable, with reported life expectancy ranging from months to several years.

In a meta-analysis of reported series of chronic myelomonocytic leukemia median survival was 20 months, ranging from seven to 60 months, but 12 to 24 months with transformation to AML.

Peripheral blood analysis usually shows cytopenia(s). The monocytes may be normal appearing or have dysplastic features of increased basophilic cytoplasm, abnormal granulation, hyperlobulated nuclei. Other lineage cells may have dysplastic changes. Bone marrow reveals hypercellularity with mildly increased monocytes (but not diagnostic by itself) and increased granulocytes, may have increased reticulin fibers, variable dysplastic changes in erythroid cells and megakaryocytes. Flow cytometry is additional method which describes two or more aberrant phenotypes such as decreased CD14, CD13, HLA-DR, CD64 or CD36, overexpression of CD56 or more than 20% of marrow monocytes showing CD14+ expression, which is specific for CMML versus reactive monocytosis [2-5].

Spanish MDS registry studied 414 CMML patients who had a conventional cytogenetic analysis at diagnosis and identified three cytogenetic risk categories: (1) low-risk (normal karyotype or loss of Y chromosome as a single anomaly), (2) high-risk (presence of trisomy 8 or abnormalities of chromosome 7 or complex karyotype), and (3) intermediate risk (all other abnormalities) with median survival of patients within these 3 cytogenetic subgroups 37, 18, and 11 months [6].

Clonal chromosome abnormalities are found in 20 to 40% of CMML cases with the most frequent recurring chromosome abnormalities include trisomy 8, monosomy 7, deletions of part of the long arm of chromosome 7, structural abnormalities of the short arm of chromosome 12 and complex karyotypes. Patients with a clonal chromosome abnormality usually have a shorter survival time compared to cytogenetically normal CMML patient [7,8].

Onida and colleagues retrospectively investigated the prognostic assessment of clinical outcome, the associations of patient and disease characteristics with survival times of 213 patients with CMML. The factors associated with shorter survival were low hemoglobin level (under 120 g/L), lower platelet count (under 100×10^9/L)-, high white blood cell, monocyte, and lymphocyte counts in peripheral blood, presence of circulating immature myeloid cells, high percentage of marrow blasts, low percentage of marrow erythroid cells, abnormal cytogenetics, and high level of serum lactate dehydrogenase activity (LDH above 700 U/L) and increased β2-microglobulin concentration (above 4). Hemoglobin level below 120 g/L, presence of circulating immature myeloid cells, absolute lymphocyte count above 2.5×10^9/L, and marrow blasts 10% or more were independently associated with shorter survival [9].

A retrospective cohort study with the investigation of clinical and laboratory characteristics of 41 CMML patient showed that age, neutrophil count, lymphopenia, monocytosis and severe anemia are associated with poor prognosis of CMML. Authors concluded that adversely independent prognostic factors are lymphocyte count less than 1.0×10^9/L and neutrophil count less than 2.0×10^9/ L [10].

The hematologic presentation of CMML is heterogeneous, ranging from isolated monocytosis without cytopenia to a frank myeloproliferative disorder with leukocytosis and splenomegaly, similar to Chronic Myeloid Leukemia (CML). Polyclonal hypergammaglobulinemia can appear. CMML is characterized by chronic and consistent monocyte elevation, while higher number of blasts plus promonocytes (more than 5%) can detect patients with transformation to acute leukemia [11,12].

An expert panel of hematologists proposed recommendations for CMML therapy to be started when the disease is symptomatic or progressive, and, in particular, when one of these events occurs: a) severe anemia (Hb less than 10g/dL; b) percentage of blasts in peripheral blood >5% (including myeloblasts, monoblasts and promonocytes); c) platelet count ≤ 50×10^9/L; d) WBC count ≥ 30×10^9/L; e) immature granulocytes ≥ 10% in peripheral blood; f) extramedullary manifestations of the disease; g) symptomatic splenomegaly. Response to treatment should be assessed according to the MD- and MP-disease classification at the time of treatment.

There have been several published reports about extramedullary presentation of CMML with renal involvement [13] thyroid mass [14] skin involvement, [15] pericardial effusion, [16] colonic infiltration, [17] pleural involvement [18].

There are few case presentations of CMML involvement in the central nervous system19.

Factors at diagnosis associated with the subsequent development of central nervous system leukemia are patient's age, elevated WBC count (greater than 10×10^9/L), increasing number of blasts plus promonocytes, elevated serum lysozyme, lactate dehydrogenase and β2-microglobulin, extramedullary infiltration including splenomegaly [19-21].

The diagnosis of central nervous system leukemic infiltration has to be confirmed by lumbar puncture and cytological examination of the cerebrospinal fluid. Treatment consists of weekly intrathecal chemotherapy with methotrexate alternating with cytarabine [19].

Conclusion

Our patient had clinical presentation and laboratory findings which were suggestive for CNS leukemic infiltration. It is important to exclude other possible causes of neurological symptoms like medullary compression, infection, hyperviscosity and to prove leukemic infiltration of CNS. Only with this evidence it is possible to choose the right treatment and to achieve success in the treatment of the patients with meningeal involvement. The adequate treatment results in complete disappearance of neurologic manifestations of CMML.

References

1. Orazi A, Germing U (2008) The myelodysplastic/myeloproliferative neoplasms: myeloproliferative diseases with dysplastic features. Leukemia 22: 1308-1319.
2. Vardiman J, Hyjek E (2011) World health organization classification, evaluation, and genetics of the myeloproliferative neoplasm variants. Hematology Am Soc Hematol Educ Program 2011: 250-256.
3. Swerdlow SH, Campo E, Harris NL (2008) World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, IARC Press, Lyon
4. Vardiman JW, Bennett JM, Bain BJ, Baumann I, Thiele J, et al. (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue, Myelodysplastic/myeloproliferative neoplasms.

5. Voglová J, Chrobák L, Neuwirtová R, Malasková V, Straka L (2001) Myelodysplastic and myeloproliferative type of chronic myelomonocytic leukemia--distinct subgroups or two stages of the same disease? S Leuk Res 25: 493-499.
6. Such E, Cervera J, Costa D, Solé F, Vallespí T, et al. (2011) Cytogenetic risk stratification in chronic myelomonocytic leukemia. Haematologica 96: 375-383.
7. Germing U, Kündgen A, Gattermann N (2004) Risk assessment in chronic myelomonocytic leukemia (CMML). Leuk Lymphoma 45: 1311-1318.
8. Bennett JM, Catovsky D, Daniel MT (1994) The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American-British Cooperative Leukaemia Group. Br J Haematol 87: 746–754.
9. Onida F, Kantarjian HM, Smith TL, Ball G, Keating MJ, et al. (2002) Prognostic factors and scoring systems in chronic myelomonocytic leukemia: a retrospective analysis of 213 patients. Blood 99: 840-849.
10. Chen B, Ma Y, Xu X, Wang X, Qin W, et al. (2010) Analyses on clinical characteristic and prognoses of 41 patients with chronic myelomonocytic leukemia in China. Leuk Res 34: 458-462.
11. Tefferi A, Hoagland HC, Therneau TM, Pierre RV (1989) Chronic myelomonocytic leukemia: natural history and prognostic determinants. Mayo Clin Proc 64: 1246-1254.
12. Muramatsu H, Makishima H, Maciejewski JP (2012) Chronic myelomonocytic leukemia and atypical chronic myeloid leukemia: novel pathogenetic lesions. Semin Oncol 39: 67-73.
13. Hyams ES, Gupta R, Melamed J, Taneja SS, Shah O (2009) Renal involvement by chronic myelomonocytic leukemia requiring nephroureterectomy. Rev Urol 11: 33-37.
14. Adair A, Parker J, Coombes DS (2003) Chronic myelomonocytic leukaemia (CMML) presenting as a thyroid mass. below Br J Haematol 120: 548.
15. McCollum A, Bigelow CL, Elkins SL, Hardy CL, Files JC (2003) Unusual skin lesions in chronic myelomonocytic leukemia. South Med J 96: 681-684.
16. Ibrahim MI, Maslak PG, Heaney ML, George MS, Downey RJ, et al. (2009) Chronic myelomonocytic leukemia (CMML) associated with symptomatic pericardial effusion. J Clin Oncol 29.
17. LoSavio AD, Bunnag AP, Rubin DT (2007) Colonic infiltration with chronic myelomonocytic leukemia. Nat Clin Pract Gastroenterol Hepatol 4: 229-233.
18. Watanabe N, Takahashi T, Sakamoto Y, Tanaka Y, Kurata M, et al (2004) 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 45: 546-50.
19. Aoyama K, Ishikura H, Tsumura H, Watanabe T, Suyama N, et al. (2003) Meningeal involvement of chronic myelomonocytic leukemia. J Neurol 250: 993-994.
20. Nowacki P, Zdziarska B (1994) [Patient's age as a risk factor for central nervous system involvement in chronic myeloid leukemia]. Neurol Neurochir Pol 28: 7-12.
21. Kantarjian HM, Smith T, Estey E, Polyzos A, O'Brien S, et al. (1992) Prognostic significance of elevated serum beta 2-microglobulin levels in adult acute lymphocytic leukemia. Am J Med 93: 599-604.
22. Onida F, Barosi G, Leone G, Malcovati L, Morra E, et al. (2013) Management recommendations for chronic myelomonocytic leukemia: consensus statements from the SIE, SIES, GITMO groups. Haematologica 98: 1344-1352.