

Case Report

Ectopic G-Csf Production by Malignant Plasma Cells in Patients with Diagnostic Criteria of Chronic Neutrophilic Leukemia

Rodríguez-Medina C, Sevillano-Zamarreño B, Gómez-Casares M T*, Lemes Castellano A, López-Jorge CE, Quiroz Cervantes K, Campo C, Jiménez S, Luzardo H, de la Iglesia S and Molero T

Servicio de Hematología, Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain

Abstract

Chronic Neutrophilic Leukemia (CNL) is a relatively uncommon myeloproliferative neoplasia. Its diagnosis is based on the exclusion of the possible causes of neutrophilia altogether by the laboratory findings. The ectopic production of G-CSF by pathological plasma cells is well known in the medical literature.

We present the case of a 77 year old woman fulfilling the diagnostic criteria of CNL. We verified G-CSF production by her pathological plasma cells using cellular separation techniques and PCR.

The purpose of this paper is to communicate another case of the uncommon association between myeloma and neutrophilia, and reinforce the necessity of ruling out the existence of an underlying monoclonal gammopathy when a patient presents with CNL-like symptoms.

Keywords: Multiple myeloma; G-CSF; Leukocytosis; Chronic neutrophilic leukemia

Introduction

The diagnosis of CNL requires the presence of chronic leukocytosis, with more than 80% mature forms, and also the exclusion of reactive neutrophilia and other myeloproliferative neoplasms. The WHO classification of hematopoietic tumors [1], in its 2008 edition, stresses that it is essential to rule out all inflammatory, infectious or tumoral processes, and if possible, to prove the clonality of the myeloid lineage.

Nevertheless, in the medical literature ectopic production of G-CSF by different types of tumoral cells in solid tumors is well described. More recently, GCS production by plasma cells in a monoclonal gammopathy context, as well as the association between this rare MPN and plasma cell dyscrasias has been reported [2].

We describe a case in which the clinical and laboratory abnormalities supported the diagnosis of CNL, but the investigations revealed that the myeloid component was secondary to the ectopic production of G-CSF by malignant plasma cells.

Case Report

We report the case of a 77 year old woman with a good functional performance status who was referred to our institution with constitutional symptoms for a duration of one month. The patient did not present any symptoms of an infectious process, with no documented fever throughout her whole hospitalization. Her medical history included hypertension and allergy to penicillin.

On physical examination, the patient appeared pale; there were no palpable adenopathies in accessible lymph territories although she presented with splenomegaly about 5 cm below the left costal margin.

The CBC showed leukocytosis (WBC, 45×10^9 /L), neutrophilia (90% PMN) and anemia (Hb, 10.8 g/dL). Biochemistry tests revealed renal impairment (creatinine, 4.87 mg/dL; uric acid, 10.77 mg/dL; LDH, 455 U/L).

Exhaustive investigations of the renal failure and leukocytosis revealed no inflammatory or infectious cause.

The imaging techniques only showed a 17 cm wide splenomegaly without other significant findings.

Bone marrow aspiration showed hypercellularity with myeloid proliferation without maturation arrest or significant dysplasia. Unexpectedly, 15% plasma cells with aberrant immunophenotype (CD38⁺, CD138⁺/CD19^{-/}CD56⁺/CD117⁺/CD28⁻, monoclonal kappa) were also found. The bone marrow biopsy showed similar findings with intense myeloid and plasma proliferation, and stage 2 reticulin fibrosis.

The cytogenetic study revealed a normal karyotype 46 XX in 15 metaphases; *BCR-ABL* rearrangement was negative as were *JAK2 V617F* and *MPLW515L* mutations.

The proteinogram confirmed the existence of a monoclonal component in the gamma globulin fraction: IgA-kappa 7.2 g/L with the following immunoglobulin values: IgG 377 mg/dL (700-1600); IgA 549 mg/dL (70-400); IgM 4.83 mg/dL (40-240); free light kappa chain 1100 mg/L (3.3-19.4); free light lambda chain 7.12 mg/L (5.71-26.3); rFLC 1558.99 (0.26-1.65). The presence of a similar monoclonal component in the 24 hour urine, IgG kappa of 3 g/L, was also confirmed.

With all these findings, we came to the conclusion that we were dealing with an IgA-kappa stage III-B multiple myeloma (MM) with leukocytosis and a leukemoid reaction, rather than a CNL MPN.

Given the association in our patient of suspected MM with leukocytosis, and the existence in the literature of previous cases where this association had to do with G-CSF production by plasma cells, we

*Corresponding author: Gómez-Casares MT, Servicio de Hematología. Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain, E-mail: mgomcasf@gobiernodecanarias.org

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Sample	Normalized RATIO (G-CSF/control gene)
BM patient	1
BM patient CD138-negative cells	0
BM patient CD138-positive cells	239.7
BM control	0.4586

 Table 1: Relative quantification by qRT-PCR and normalized expression of G-CSF mRNA in patient and control bone marrow (BM) samples.

decided to analyze the expression of this gene in the bone marrow. To do this, we selected plasma cells by CD138-positive cell separation. The analysis by real-time quantitative PCR demonstrated intense expression of G-CSF mRNA by the pathological plasma cells of the patient (Table 1). The diagnosis was IgA-MM producing G-CSF.

The patient was treated with bortezomib and dexamethasone, showing a reduction in the number of leukocytes, which coincided with decreased in filtration of bone marrow by plasma cells; however, our patient's disease progressed, and she died 7 months after being diagnosed.

Discussion

The coexistence of MM and other monoclonal gammopathies with MPN is well described in the medical literature [3]. In 1994, Cerehli et al. [4] published a series of 10 cases in which MM and CNL were found simultaneously. These cases would be reviewed afterwards in 2007 by Gnerre et al. [5], in a revision of 28 cases showing an association between monoclonal gammopathies and leukocytosis.

However, we should point out that the WHO classification of hematopoietic tumors [1] requires demonstration of clonality of the granulocytic component for CNL diagnosis because there are described cases of MM associated with leukocytosis where the myeloid component was polyclonal [6]. Moreover, it is necessary to determine the underlying neoplastic disease, given the evidence that G-CSF production can be a paraneoplastic event. These findings have allowed different authors to confirm that the myeloid component in these associations were due to the production of ectopic cytokines such as G-CSF [2,6].

In the last few years, the coexistence of high G-CSF levels in patients with MM and leukocytosis has been further documented. Initially, using serological methods, it was observed that the serum G-CSF levels were significantly higher than in a non pathological status, and they returned to a normal value after anti-myeloma therapy [7]. Subsequently other authors demonstrated the production of G-CSF by pathological plasma cells using immunohistochemical methods in a patient with MM [8]. This has been subsequently confirmed by other authors who have described a MM case with morphological findings of a CNL [9].

More recently, Kohmura et al. [2] demonstrated the production of G-CSF by the plasma cells in the context of MM and neutrophilia. They determined serum G-CSF levels, characterized plasma cells with an anti-G-CSF antibody using immunohistochemistry protocols, and they amplified the G-CSF mRNA of CD138-positive plasma cells obtained by magnetic sorting using PCR techniques. In our case, we used a diagnostic method similar to that described by Komura.

The role played by the cytokines in MM pathogenesis has been well characterized; especially as regards survival of the tumor cell in the bone marrow microenvironment [10]. Nevertheless, it has never been demonstrated that the non pathological plasma cell is able to produce G-CSF [11].

Page 2 of 2

Currently, the WHO classification of hematopoietic tumors [1] requires exclusion of other neoplasms for the diagnosis of CNL. It is considered an extremely rare myelo proliferative disorder, requiring that there are no other findings indicating a secondary cause for the neutrophilia: infectious, inflammatory or neoplastic.

In view of our experience and the existing data in the literature, we believe that even though the association between MM and CNL has been well established [4,5] when the diagnosis of CNL is considered, a concerted effort should be made to rule out a monoclonal gammopathy as the underlying tumor.

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