

Diagnosis, complications and management of chronic neutrophilic leukaemia: A case report

PATRÍCIA ROCHA SILVA¹, CRISTINA FERREIRA¹, SUSANA BIZARRO², NUNO CERVEIRA²,
LURDES TORRES², ILÍDIA MOREIRA¹ and JOSÉ MÁRIO MARIZ¹

Departments of ¹Oncohaematology and ²Genetics, The Francisco Gentil Portuguese Institute of Oncology,
Porto 4200-072, Portugal

Received July 2, 2014; Accepted March 9, 2015

DOI: 10.3892/ol.2015.3148

Abstract. Chronic neutrophilic leukemia (CNL) is a rare myeloproliferative neoplasm characterized by sustained neutrophilia and the absence of the Philadelphia chromosome or the *BCR-ABL1* fusion gene. The present study reports the case of a 59-year-old Caucasian female that was referred to The Francisco Gentil Portuguese Institute of Oncology (Porto, Portugal) with constitutional symptoms (mainly asthenia), marked leukocytosis ($51.33 \times 10^9/l$ with 90% neutrophils), macrocytic anemia and splenomegaly. Bone marrow aspiration and biopsy revealed hypercellular marrow with clear predominance of segmented neutrophils. The karyotype was normal and the *BCR-ABL1* fusion gene was not detected. After excluding a leukemoid reaction, a diagnosis of CNL was established. The clinical follow-up was complicated by hemorrhagic brain lesions and relapsing episodes of erythematous, well-demarcated and painful subcutaneous nodular lesions, consistent with Sweet's syndrome (SS). Multiple treatment strategies were administered, including use of hydroxyurea, imatinib and intensive chemotherapy. Nevertheless, progression was documented and the patient succumbed at 28 months post-diagnosis. The clinical course of CNL varies, and can be complicated by cerebral hemorrhage, blastic transformation or infection. Dermatological manifestations such as SS have seldom been reported in association. No evidence-based treatment currently exists and the majority of our knowledge is based on results from case reports and small series.

Introduction

Chronic neutrophilic leukemia (CNL) is a rare myeloproliferative neoplasm characterized by sustained mature neutrophilic leukocytosis with few or no circulating immature granulocytes, hepatosplenomegaly and hypercellular bone marrow with a predominance of myeloid mature cells. In addition, no Philadelphia chromosome or *BCR-ABL1* fusion gene are detected. Generally affects older adults and both genders (1,2). The cause of CNL is not known (1). The majority of patients have a poor prognosis, with a median survival of <3 years (3). Treatment has consisted largely of cytoreductive agents such as hydroxyurea, with an allogenic bone marrow transplant being the only curative treatment (4).

The present study reports the case of a patient with CNL complicated with Sweet's syndrome (SS) and hemorrhagic brain lesions. The study also describes the multiple therapeutic strategies and the difficulties in managing this disease.

Case report

Presentation and diagnosis. A 59-year-old Caucasian female, with a past history of hypertension, was referred to The Francisco Gentil Portuguese Institute of Oncology (Porto, Portugal) in October 2010, presenting with asthenia, shortness of breath, abdominal pain, pallor, splenomegaly (6 cm below the costal margin) and profuse lower limb oedema. Laboratory analysis showed macrocytic anemia and leukocytosis [haemoglobin level, 8.4 g/dl (normal range, 11.5-16.5 g/dl); mean cell volume, 117.3 fl (normal range, 76.0-96.0 fl); white blood cell count, $51.33 \times 10^9/l$ (normal range, $4.0-11.0 \times 10^9/l$); with 90% neutrophils; and platelet count, $173 \times 10^9/l$ (normal range, $150-400 \times 10^9/l$); a raised lactate dehydrogenase level, 392 U/l (normal range, 67-248 U/l); and a raised vitamin B12 level, >2000 pg/ml (normal range, 191-663 pg/ml)] and mild hepatic dysfunction. Bone marrow aspiration revealed hypercellular marrow with a clear predominance of segmented neutrophils, few immature granulocytes and no myeloblasts (Fig. 1). The biopsy confirmed these findings plus the presence of diffuse reticulin fibrosis. The karyotype was normal and the *BCR-ABL1* and *BCR-PDGFR*A fusion genes were not detected. Mutation analysis of the *JAK2*, *MPL* and *CALR* genes was negative. Causes of leukemoid reaction, including other

Correspondence to: Dr Patrícia Rocha Silva, Department of Oncohaematology, The Francisco Gentil Portuguese Institute of Oncology, Rua Doutor António Bernardino de Almeida, Porto 4200-072, Portugal
E-mail: patricia.rocha.silva81@gmail.com

Key words: chronic neutrophilic leukaemia, myeloproliferative disorders, atypical chronic myeloid leukaemia, Sweet's syndrome

malignancies, severe infections or inflammatory conditions, drugs, severe hemorrhage or acute hemolysis were excluded based on obtaining a detailed clinical history, physical examination, imaging and laboratory studies, and the diagnosis of CNL was determined.

Treatment and evolution. Cyto reduction with hydroxyurea (1,500 mg/day) was started, resulting in initial hematological improvement. One month later, fever and erythematous, well-demarcated and painful subcutaneous nodular lesions developed in the right breast, right upper limb and suprapubic region. These symptoms were reversed following administration of ceftriaxone (1 g/day; duration, 3 days) followed by 14 days of levofloxacin (500 mg/day) and suspension of hydroxyurea. Meanwhile, disease progression was documented with increasing splenomegaly (10 cm below the costal margin), peripheral blood neutrophilia ($12.08 \times 10^9/l$; normal range, $2.0\text{--}7.5 \times 10^9/l$), anaemia (haemoglobin 7.7 g/dl; normal range, 11.5–16.6 g/dl) and the development of deep vein thrombosis of the left lower limb. Intensive treatment with acute leukemia induction-like chemotherapy was proposed, but was postponed due to fever and profuse new skin lesions. The largest lesion (15x10 cm), located in the right thigh, was ulcerated with extensive loss of skin tissue. A skin biopsy revealed predominantly lobular neutrophilic panniculitis compatible with SS. Improvement was achieved with prednisolone (1 mg/kg) and amoxicillin and clavulanic acid (875/125 mg/twice per day) for a duration of 2 weeks. Upon steroid administration, a reduction in spleen size (3 cm below the costal margin) and recovery of the hematological values were observed, and a partial hematological response was achieved with low doses of corticosteroids (40 mg/day) and hydroxyurea (500 mg/day). Six months later, while the skin lesions were recovering, worsening of the anemia, thrombocytopenia and splenomegaly (20 cm below costal margin) led to the administration of 400 mg/day imatinib for one month. No hematological improvement was observed and the patient required blood transfusions. When intensive chemotherapy was finally proposed at 15 months post-diagnosis, the patient presented with a mild headache and gait imbalance. Brain computed tomography and magnetic resonance imaging were performed, showing multiple hemorrhagic lesions, and the hypothesis of cerebral nervous system invasion by CNL was consequently considered. The lumbar puncture, even without trauma, showed a persistently hematic and neutrophilic cerebrospinal fluid, with negative cultures. Intensive chemotherapy with high-dose cytarabine, daunorubicin and cyclosporine (protocol SWOG 9126) (5) was administered for two cycles. During treatment, several infectious complications and another set of erythematous skin lesions were observed (Fig. 2). The skin lesions were resolved using corticosteroids (1 mg/kg/day; duration, 2 weeks); and large spectrum antibiotic treatment (meropenem, amikacin, vancomycin and voriconazol) was concomitant. The final histology was inconclusive. Following the chemotherapy, the spleen was reduced in size, the cytopenia was improved and the neurological symptoms were resolved, along with the brain imaging changes.

No siblings were available for allogeneic hematopoietic progenitor transplant, so this treatment could not be considered, and the disease was therefore only controlled for four

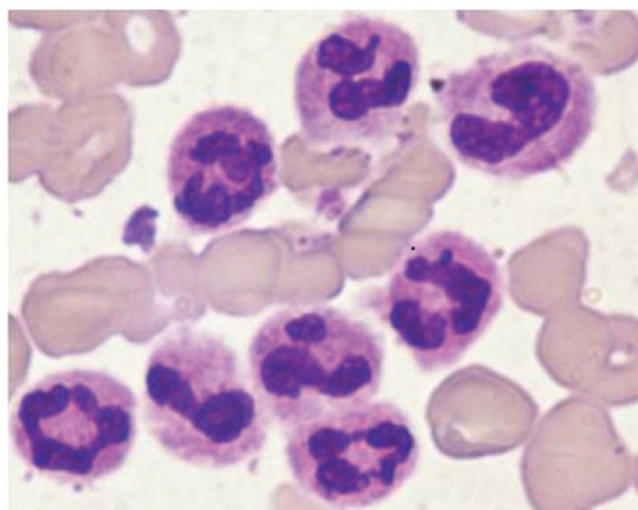


Figure 1. Bone marrow aspirate smear demonstrating neutrophilic proliferation (Wright-Giemsa staining; original magnification, x1,000).



Figure 2. Erythematous, well-demarcated nodular lesions in the right leg consistent with Sweet's syndrome.

months. When progression was documented, best supportive and palliative care was instituted with oral cyto reduction and transfusion support. The patient succumbed at 28 months post-diagnosis.

Discussion

The first case of CNL was described in 1920 by Tuohy (6), and since then, not much has been elucidated with regard to its pathogenesis and treatment due to the rarity of this myeloproliferative neoplasm. CNL equally affects the two genders and is more common in the elderly population (>60 years) (1,4). In total, ~150 cases have been described (1), however, a review performed in 2006 indicated that only 40 cases met the rigid criteria of the World Health Organisation classification (7). In the present study, CNL was considered following the proper exclusion of secondary causes of neutrophilia, such as occult malignancy, ongoing infections and other inflammatory conditions (8). The diagnosis was based on peripheral blood leukocytosis with neutrophilia, the presence of hepatosplenomegaly, hypercellular bone marrow with a predominance of myeloid lineage (mature forms), and the absence of the *BCR-ABL1* fusion gene and the Philadelphia chromosome. It was essential to exclude

BCR-ABL1-positive chronic myelogenous leukemia (CML), the main variant that encodes the p230 protein, since similar to CNL, the condition exhibits peripheral blood neutrophilia. Although *BCR-ABL1*-positive CML was previously considered to be a form of CNL (9,10), it is now considered a form of CML (2). The *BCR-PDGFR*A rearrangement and the *JAK2* and *CALR* mutations were also tested for in the present study. These mutations have been identified in myeloproliferative disorders, but only *JAK2* has been reported in CNL (11-13). Recently, Maxson *et al* reported the association between receptor for colony-stimulating factor 3 (*CSF3R*) mutations and CNL and atypical CML (14), which could be a promising marker of the disease (15). In the present case, the karyotype was normal, but nearly 10% of CNL cases are associated with cytogenetic abnormalities, including trisomy 8, 9, 21 and deletion of 11(q), 12(p), 17(p) and 20(q), the latter possibly being associated with a more favorable prognosis (16-18).

SS, a neutrophilic dermatosis characterized by the development of erythematous, tender plaques or nodules frequently with fever and leukocytosis, has been associated with hematological malignancies (19,20). The differential diagnosis is wide and includes infectious disorders, as well as neoplastic conditions such as leukemia cutis (19). To the best of our knowledge, only two cases of SS have previously been reported in association with CNL (21,22). In the present patient, SS was histologically confirmed following a second febrile episode of cutaneous lesions, and was successfully treated with prednisolone. Corticosteroids are the standard treatment for this condition, but antibiotics may assist, particularly when lesions became secondarily infected. Spontaneous remissions can occur (19); this may explain the apparent response to antibiotics in the first episode (although this was not histological-proven SS) and justified their use on the other relapses.

During disease progression, the patient presented with neurological symptoms caused by brain hemorrhagic lesions. In CNL, two possible causes may be responsible for this: Invasion of the central nervous system and/or thrombocytopenia. While thrombocytopenia and abnormal platelet function have been reported as causes of the bleeding tendency in CNL (23,24) by certain studies, others have demonstrated either invasion and mass formation of neutrophils in the brain parenchyma upon autopsy (25), or extensive infiltration of mature and immature neutrophils, resulting in the destruction of vascular walls (26). Based on the absence of other systemic hemorrhagic manifestations in the present study, these last explanation appear more likely.

There is no standard therapy for CNL. Hydroxyurea has been shown to control the disease temporarily, while intensive chemotherapy confers an increased risk of mortality by infection or hemorrhage (27). The only curative treatment is allogeneic bone marrow transplant, however, the age of the majority of CNL patients excludes this therapeutic approach (28). In the present case, hydroxyurea was efficient for less than one year, and imatinib treatment was attempted one month with no response. This selective tyrosine kinase inhibitor has proven valid against atypical myeloproliferative neoplasms harboring mutations in the *ABL1*, *KIT* and platelet-derived growth factor receptor (*PDGFRB* or *PDGFRA*) genes (29,30). In the absence of an identified molecular marker, the success of this therapeutic approach in anecdotal reports is believed to be due

to unknown molecular mechanisms. The study by Choi *et al* reported the case of a CNL patient carrying t(15;19)(q13;p13.3) in which cytogenetic remission was achieved following daily treatment with 400 mg imatinib (31). In the present case, the two cycles of intensive chemotherapy resulted in a short partial response of four months.

The overall prognosis of patients with CNL is poor, with a median survival time of 30 months (3,7). Death is usually due to cerebral hemorrhage, blastic transformation or fulminant infection (32,33). In spite of therapeutic intervention, the present patient followed the natural history of the disease. The rarity of CNL makes clinical trials unlikely to be conducted, and the majority of our knowledge is based on case reports and small series. Novel genetic markers, such as *CSF3R*, will provide a better understanding of this disorder, and provide novel diagnostic tools and therapeutic targets.

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