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A Case of Synchronous Bone Marrow Chronic Myelomonocytic Leukemia (CMML) and Nodal Marginal Zone Lymphoma (NMZL)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Male, 67
Final Diagnosis: Nodal marginal zone lymphoma and chronic myelomonocytic
Symptoms: Cervical lymphadenopathy and leukocytosis
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Rare co-existance of disease or pathology

Background: Leukemias and lymphomas can arise from myeloid or lymphoid stem cells. Combined myeloid leukemia and non-Hodgkin's lymphoma (NHL), either synchronous or metachronous, rarely occur in the same patient. This report is of a 67-year-old man with a synchronous diagnosis of both bone marrow chronic myelomonocytic leukemia (CMML) and nodal marginal zone lymphoma (NMZL), which a peripheral low-grade B-cell NHL.

Case Report: A 67-year-old Caucasian man, who was a long-term cigarette smoker, presented with a five-year history of leukocytosis and cervical lymphadenopathy. He had no symptoms of night sweats, fever, or weight loss. Review of his medical records showed a progressively increasing leukocytosis with a peak of 58×10^9/L. Computed tomography (CT) imaging of the chest and abdomen showed lymphadenopathy, including enlarged cervical, axillary, mediastinal, and retroperitoneal lymph nodes. Bone marrow biopsy and histology showed CMML. Lymph node biopsy and histology showed NMZL. The patient was treated for NMZL with weekly intravenous rituximab infusions. Although his CMML was stable, the patient requested an evaluation for treatment with hematopoietic allogeneic stem cell transplantation (ASCT). At the time of this report, the patient remains asymptomatic.

Conclusions: The synchronous occurrence of bone marrow CMML and NMZL in a single patient is rare and may be attributed to a genetic mutation common to both. There are no current treatment guidelines for this group of patients, and treatment strategies should be individualized to provide an optimum outcome or symptomatic improvement.

MeSH Keywords: Dendritic Cells • Leukemia, Myelomonocytic, Chronic • Lymphoma, B-Cell, Marginal Zone

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Background

Hematopoietic stem cells differentiate into myeloid and lymphoid lineages. Most of the hematologic malignancies diagnosed and treated in clinical practice arise from one of these progenitor cell lines. Only rarely do patients present with both a lymphoid and myeloid neoplasm.

This report is of a 67-year-old man with synchronous diagnosis of both bone marrow chronic myelomonocytic leukemia (CMML) and nodal marginal zone lymphoma (NMZL), which is a peripheral B-cell non-Hodgkin's lymphoma (NHL).

Case Report

A 67-year-old Caucasian man, who was a long-term cigarette smoker, presented with a five-year history of leukocytosis and cervical lymphadenopathy. On examination, his vital signs were normal. Physical examination showed prominent left-sided cervical and axillary lymphadenopathy, but no palpable inguinal lymphadenopathy or splenomegaly. The review of his medical records from the previous five years showed a progressive increase in leukocytosis, including a monocytosis, which reached a peak of 58×10^9/L. A peripheral blood film showed 3% blast cells.

Laboratory investigations showed mildly elevated levels of lactate dehydrogenase (LDH) and uric acid. Serum immunoglobulin levels were mildly elevated but with normal ratios (Table 1). Computed tomography (CT) imaging of the chest and abdomen showed lymphadenopathy, including enlarged cervical, axillary, mediastinal, and retroperitoneal lymph nodes, but there was no hepatosplenomegaly. A cervical lymph node biopsy and a bone marrow biopsy were performed for histopathology.

The cervical lymph node histology showed replacement of normal lymph node architecture by a uniform population of lymphocytes, consistent with lymphoma. Immunohistochemistry was performed using a routine diagnostic antibody panel, which showed that the lymphoid cells were positive for CD19, CD20, and Bcl-2 and negative for CD5, CD10, CD23 and cyclin D1, consistent with a diagnosis of B-cell lymphoma. Also, there were prominent spindle-shaped cells that showed positive immunostaining for S100 and CD123, consistent with the presence of plasmacytoid dendritic cells, and for expression of T-cell leukemia/lymphoma protein 1A (TCL1A) (Figure 1). The lymph node histopathology diagnosis was low-grade B cell NHL consistent with nodal marginal zone lymphoma (NMZL) with plasmacytoid dendritic cell hyperplasia (Table 1).

The bone marrow histology showed chronic myelomonocytic leukemia (CMML) type 1, also with plasmacytoid dendritic cell hyperplasia. The spindle cells seen on the lymph node sections were also prominent in the bone marrow biopsy. A clonal myeloid malignancy was considered when the patient presented with persistent monocytosis, but there was negative

Table 1. Laboratory results and results from the lymph node and bone marrow aspirate, blood smear, and cytogenetics.

Laboratory findings	Lymph node biopsy	Bone marrow aspirate, blood smear, and cytogenetics
Hb: 11.6 g/dL (NR, 14–18 g/dL) WBC: 58×10^9/L (NR, 3.4–9.4×10^9/L) Platelets: 30×10^9/L (NR, 150–450×10^9/L) Segmented Neutrophils: 37% (NR, 40–70%) Lymphocytes: 13% (NR, 25–45%) Monocytes: 14% (NR, 1–9%) Eosinophils: 1% (NR, 0–6%) Basophils: 0% (NR, 0–2%) ALP: 332 IU/L (NR, 30–130 IU/L) AST: 18 IU/L (NR, 0–41 IU/L) ALT: 14 IU/L (NR, 30–130 IU/L) LDH: 220 IU/L (NR, 100–200 U/L) Uric Acid: 7.4 mg/dl (NR, 3.4–7.2 mg/dl) SPEP: marginally raised immunoglobulins	**Positive immunohistochemistry:** CD19, CD20, Bcl-2, S100, CD123, and TCL1A **Negative immunohistochemistry:** CD5, CD10, CD23, and cyclin D1 **Diagnosis:** Low-grade, B-cell Non-Hodgkin's lymphoma (NHL) consistent with nodal marginal zone lymphoma (NMZL) and plasmacytoid dendritic cell hyperplasia	**BM aspirate:** Blasts: 1% Monocytes: 3% **Peripheral blood smear:** Blasts: 3% **Cytogenetics:** 46XY Negative for: *JAK2* mutation, *BCR ABL* mutation, 8cen (*D8Z2*), 7ceb (*D721*), 7q31 (*D7S486*), 20q12-q13, 12 (*D20S108/MYNL2*) **Diagnosis:** Chronic myelomonocytic leukemia (CMML) type 1 with plasmacytoid dendritic cell hyperplasia

NR – normal range; Hb – hemoglobin; WBC – white blood cell count; ALP – alkaline phosphatase; AST – aspartate transaminase; ALT – alanine transaminase; LDH – lactate dehydrogenase; TCL1A – T-cell leukemia/lymphoma protein 1A; SPEP – serum protein electrophoresis; CD – cluster of differentiation.

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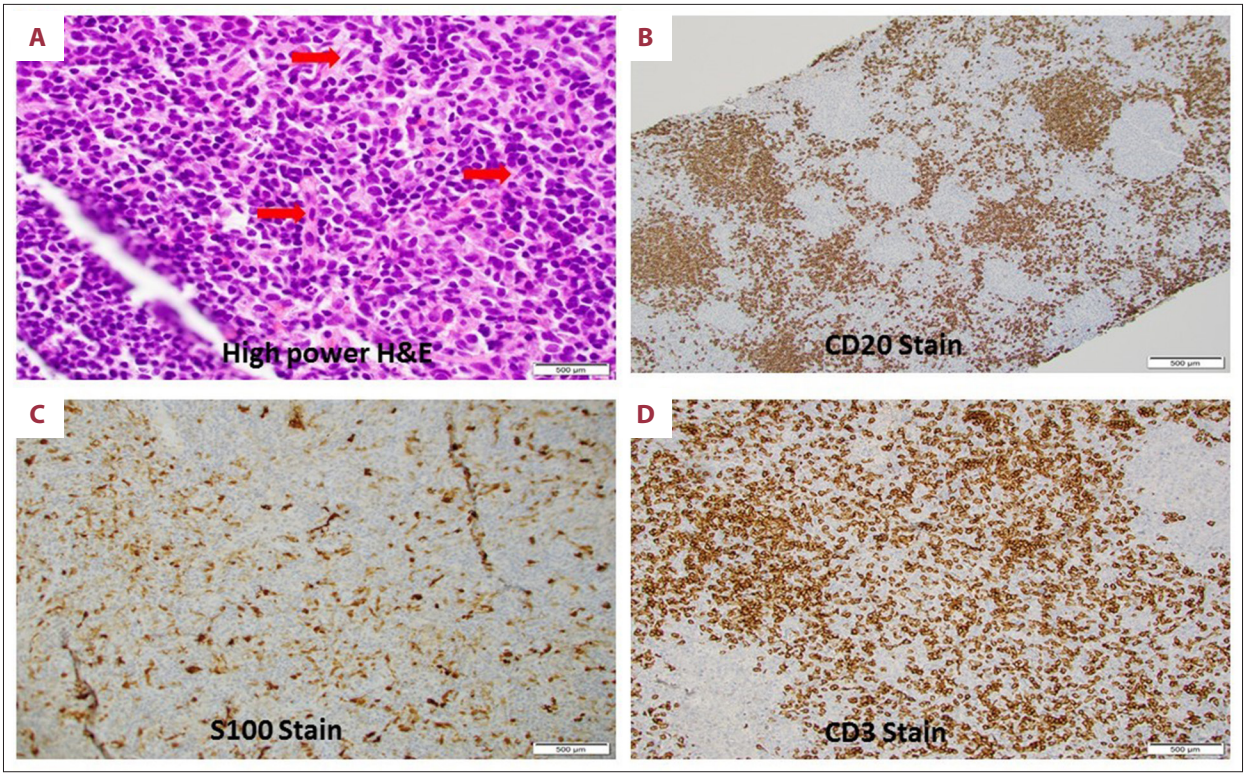

Figure 1. Photomicrographs of the lymph node histology and immunohistochemistry support the diagnosis of nodal marginal zone lymphoma (NMZL), a low-grade B-cell non-Hodgkin's lymphoma (NHL). (**A**) Hematoxylin and eosin (H&E) staining shows a uniform population of small lymphocytes replacing the normal lymph node architecture. (**B**) Immunohistochemistry shows positive immunostaining (brown) of the lymphocytes with the B-cell antibody, CD20. (**C**) Immunohistochemistry shows positive immunostaining (brown) of dendritic cells for S100. (**D**) Immunohistochemistry shows positive immunostaining (brown) of T-cells for CD4.

expression of the *BCR-ABL* fusion gene (expressed in myelogenous leukemia). Otherwise, the patient fulfilled the criteria for CMML (Figure 2).

The patient was treated for NMZL with weekly intravenous rituximab infusions, followed by normalization of his leukocyte counts. Although his CMML was stable, the patient requested an evaluation for treatment with a hematopoietic allogeneic stem cell transplantation (ASCT). At the time of this report, the patient remains asymptomatic.

Discussion

On presentation, the patient described in this report was suspected to have a diagnosis of a lymphoid disorder, as prominent lymphadenopathy is not typical of the presentation of chronic myelomonocytic leukemia (CMML). The combination of lymphoma with CMML is rare [1]. The annual incidence rates for both CMML and NMZL are similar at between 0.83–1 case per 100,000 adults [1,2]. Given the rarity of these conditions, descriptions of clinical features, as well as treatment

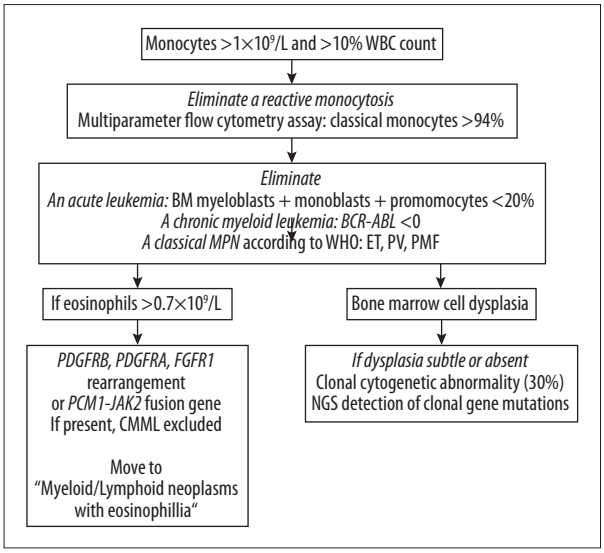

Figure 2. A proposed clinical diagnostic patient workup for chronic myelomonocytic leukemia (CMML). ET – essential thrombocytosis; NGS – next-generation sequencing; PV – polycythemia vera; PMF – primary myelofibrosis. *Modified, with permission, from Solary et al., 2017 [1].*

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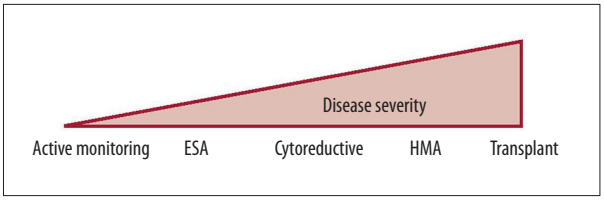

Figure 3. A proposed therapeutic strategy for patients with chronic myelomonocytic leukemia (CMML). ESA – erythropoietin stimulating agents; HMA – hypomethylating agents. *Modified, with permission, from Solary et al., 2017 [1].*

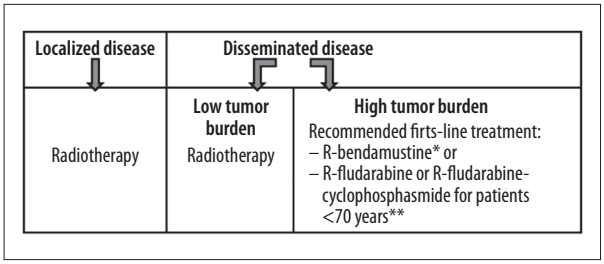

Figure 4. Therapeutic strategies for patients with nodal marginal zone lymphoma (NMZL). R – rituximab; NMZL – nodal marginal zone lymphoma. *Modified, with permission, from Thieblemont et al., 2016 [11].*

strategies, are based on very few reports with relatively small numbers of patients [1].

Data on population-based studies report that CMML patients have an average survival of between 1–3 years, with leukemic transformation rates of up to 30% [1,3–5]. According to the World Health Organization (WHO), the two most important prognostic parameters for patients with CMML are the white blood cell (WBC) count and the percentage of blast cells. WBC counts $\geq 13\times10^9$ g/L classifies patients as having myeloproliferative CMML (MPN-CMML), but WBC counts $\leq 13\times10^9$ g/L classifies patients as having myelodysplastic CMML (MDS-CMML) who have a better clinical outcome [1]. The presence of 3% blasts in the peripheral blood smear was found in this patient, which may be taken into account when considering prognosis and treatment, as for patients diagnosed with CMML it is important to identify patients who are at an increased risk for transformation into acute myeloid leukemia (AML) [1]. Determining the optimal treatment for CMML remains challenging due to lack of evidence from clinical trials.

Allogeneic stem cell transplantation (ASCT) can be curative in CMML, but the main treatment options are directed to provide symptomatic improvement (Figure 3) [1]. A personalized treatment strategy for CMML can include erythropoietin-stimulating agents (ESAs) for patients with anemia, hydroxyurea and etoposide for cytoreduction in patients with leukocyte counts >50,000/mm^3, and the use of the hypomethylating agents (HMAs), azacytidine and decitabine, which have shown response rates of between 30–60% and a median overall survival of between 12–37 months [6–9]. In patients with CMML, thrombocytopenia commonly occurs and is due to dysplasia of megakaryocytes [1]. However, although eltrombopag can be used to treat low blood platelet counts, it has only been used in clinical trials, due to safety concerns, as some patients with MPN-CMML on eltrombopag who transformed to AML [10]. For patients who are clinically stable and at low risk, clinical observation with supportive treatment is recommended, as a small percentage of patients with CMML demonstrate no disease progression for several years [1].

NMZL is classified as a low-grade, B-cell, non-Hodgkin's lymphoma (NHL). Although the Follicular Lymphoma International Prognostic Index (FLIPI) was not specifically developed to include NMZL, FLIPI has been reported to have some prognostic value in patients with NMZL [11]. The clinical outcome for patients with NMZL is similar to that of other types of low-grade B-cell NHL. The key approach to the treatment of NHL is to determine tumor behavior, in terms of grade (low-grade or high-grade), and cell of origin (T-cell or B-cell) [3]. NMZL is a low-grade, B-cell, NHL lymphoma and patient survival is more likely to be years when compared to weeks as is found in high-grade NHL [12–14]. While aggressive treatment may cure high-grade NHL, low-grade and indolent NHL can be unresponsive to therapy and characterized by a continuous pattern of relapses [14].

There are currently no standard treatment guidelines for patients with NMZL, possibly due to the limited patient numbers and heterogeneity of treatments used in retrospective clinical studies [11]. A treatment approach for NMZL is shown in Figure 4. Localized radiation is recommended for patients with strictly localized disease; in patients with disseminated NMZL with low tumor burden, a watchful clinical strategy is advocated; immunotherapy combined with chemotherapy is considered appropriate in patients with a high tumor burden. Bendamustine and rituximab (BR) is a good choice for first-line immunochemotherapy for NMZL when compared with the rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) regimen, and has been shown to have similar response rates but with a superior progression-free survival (PFS) (median PFS 69.5 *vs.* 31.2 months; hazard ratio 0.58; 95% CI, 0.44–0.74; P<0.0001), fewer serious adverse effects (19% *vs.* 29%) and fewer fatal outcomes [15]. Other treatment options for NMZL include fludarabine and rituximab (FR), and fludarabine with cyclophosphamide and rituximab (FCR), which is more frequently used for younger patients due to its increased toxicity [11].

Although not tested in this particular case, mutations of the ten-eleven translocation-2 (*TET2*) gene has been demonstrated

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in patients with synchronous lymphoid and myeloid malignancy [1,16]. Previously published studies shown that a common genetic abnormality can generate both types of hematologic malignancy [1,17,18]. Future genetic studies on this somatic mutation may identify a potential diagnostic marker or therapeutic target.

Conclusions

This case report has described the rare synchronous occurrence of bone marrow chronic myelomonocytic leukemia (CMML) and a low-grade, B-cell nodal marginal zone lymphoma (NMZL), which may be attributed to a genetic mutation common to both. This case report has reviewed the prognosis and treatment strategies of two rare myeloid and lymphoid malignancies. There are no current treatment guidelines for this group of patients, and treatment strategies should be individualized to provide the optimum outcome or symptomatic improvement.

Acknowledgments

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