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Myelodysplastic syndrome (MDS)/Myeloproliferative neoplasm (MPN) with loss of long arm of chromosome 5 (del 5q): Clinical case and treatment perspectives

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Abstract: *this clinical case report presents a patient diagnosed with a myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN), specifically myelofibrosis with a deletion of the long arm of chromosome 5 (del 5q), an exceedingly rare anomaly in chronic myeloproliferative disorders. We performed a thorough analysis of the patient's clinical, laboratory, and molecular-genetic characteristics to evaluate their impact on prognosis, treatment decisions, and therapeutic outcomes. After excluding other genetic abnormalities, the patient was treated with lenalidomide and prednisolone, resulting in improved clinical and hematological parameters. These findings are consistent with previous studies and suggest the potential efficacy of lenalidomide in treating patients with MDS/MPN characterized by del 5q, especially when no additional genetic abnormalities are present.*

Keywords: Chronic Myeloproliferative Neoplasm; Myelofibrosis; Myelodysplastic Syndromes; Del 5q; Lenalidomide.

Introduction

Myelodysplastic syndrome (MDS)/myeloproliferative neoplasm (MPN) is a heterogeneous group of clonal myeloid malignancies that exhibit features of both disease types. Myelodysplastic syndrome/myeloproliferative neoplasm not otherwise specified (MDS/MPN-NOS) is a hematologic disorder characterized by aberrant cellular proliferation and dysplasia of myelopoiesis, affecting various aspects of neoplastic hematopoiesis (Patnaik & Tefferi, 2023; Khoury et al., 2022; Moyo et al., 2022; Meggendorfer et al., 2018). According to the latest WHO classification in 2022, MDS/MPN-NOS is clinically characterized by thrombocytosis (>450 × 10^9/L) or leukocytosis (>13 × 10^9/L), the presence of cytopenias, and specific molecular features in tumor cells, including mutations in TET2, NRAS, RUNX1, CBL, SETBP1, and ASXL (Patnaik & Tefferi, 2023; Khoury et al., 2022; Moyo et al., 2022; Meggendorfer et al., 2018). Giagounidis et al. (2014) demonstrated that the loss of the long arm of chromosome 5 (del 5q) represents a complex hematologic syndrome involving various pathological processes, such as aberrant cellular proliferation, dysplasia of myelopoiesis, disruptions in cellular signaling pathways, defects in cell cycle regulation, apoptosis, and disturbances in the bone marrow microenvironment (Giagounidis et al., 2014). While the role of genetic anomalies, particularly del 5q, in the pathogenesis of MDS has been extensively

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studied, research on the underlying mechanisms driving the development of MDS/MPN-NOS is ongoing. Investigating molecular markers, genetic variants, and signaling pathways that influence cellular processes is crucial for understanding the pathogenesis and for developing new therapeutic strategies for MDS/MPN-NOS with del 5q.

Aim

To analyze the clinical, laboratory, and molecular-genetic characteristics of MDS/MPN-NOS with loss of the long arm of chromosome 5 (del 5q) to determine their impact on prognosis and treatment outcomes.

Clinical Case Description

In October 2023, a 66-year-old female patient, Mrs. A., presented with complaints of general weakness, drowsiness, intermittent shortness of breath during physical exertion, dizziness, night sweats, and itching of the skin after bathing. The patient reported experiencing general weakness and dizziness since July 2023.

Peripheral blood tests revealed the following results: hemoglobin at 67 g/L (Normal range(N)-120-140 g/L), erythrocyte count of 1.82×10^{12}/L (N-3.7-4.7x1012/L), leukocyte count of 4.6×10^{9}/L (N-4.0-9.0x109/L), platelet count of 610×10^{9}/L (N-150-450x109/L), with 5% band neutrophils (N-1-5%), 49% segmented neutrophils (N-47-70%), 5% eosinophils (N-0.5-5%), 2% basophils (N-0-1%), 35% lymphocytes (N-20-40%), and 4% monocytes (N-3-8%). The lactate dehydrogenase (LDH) level was recorded at 397 U/L (N-240-480 U/L). An investigation was subsequently conducted to assess the presence of anemia. An investigation was conducted to determine the presence of anemic conditions (Table 1).

CT scan of the neck, thoracic cavity, abdominal cavity, and pelvic organs with contrast: no pathological abnormalities were identified.

The patient underwent a bone marrow trepanobiopsy for pathological, cytomorphological, immunocytological, genetic, and molecular analyses. The results of these studies are described in Table 2.

According to the NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) criteria, the diagnosis of MPN/MDS-NOS (Myeloproliferative Neoplasm/Myelodysplastic Syndrome – Not Otherwise Specified) can be applied to cases exhibiting features of both MPN and MDS but not fully meeting the criteria for either category. This includes situations where clinical, histological, cytomorphological, immunocytological, cytogenetic, and molecular characteristics do not align with the clearly defined criteria for specific MPN or MDS diagnoses (Gerds et al., 2022; Vannucchi et al., 2015). In this case, the diagnosis of MPN/MDS-NOS was established based on the presence of isolated deletion 5q, which is characteristic of myelodysplastic syndromes (MDS), as well as features of myelofibrosis observed during the pathological examination of the bone marrow, which are typical of myeloproliferative neoplasms (MPN). Additionally, anemia, common to both categories, and elevated platelet levels, more frequently observed in MPN, were present.

The absence of additional mutations in this patient was a significant factor in determining the prognosis and selecting the appropriate treatment strategy. This information guided the choice of lenalidomide as the primary therapeutic agent, as

Table 1. Blood analysis in cases of anemic conditions

Parameters	Values	Values Reference
Iron	14.9 µmol/L	6.6-26 µmol/L
Transferrin	2.13 g/L	2-3.6 g/L
Transferrin Saturation	27.3%	20-55%
Ferritin	71.10 ng/mL	6-159 ng/mL
Cyanocobalamin	308 pg/mL	180-800 pg/mL
Folic Acid	6.77 ng/mL	3-17 ng/mL
Erythropoietin	87.9 mIU/mL	3.5-17.6 mIU/mL

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Table 2. Results of bone marrow analysis

Research	Results
Pathohistological	The bone marrow is hypercellular with evidence of reticulin fibrosis (MF-2), and morphological changes are consistent with myeloproliferative disorders.
Cytomorphological	Granulopoiesis cells predominate, Blast cells – 2.5%
Cytochemical	[1]MPO-positive, [2]NSE-normal, Ring sideroblasts-absent.
Immunocytological	Myeloid precursor cells-0.2%, hypogranular granulocytes-48%, monocytes-2%, erythropoietic cells-0.3%, demonstrate reduced CD71 expression. Granulocytes exhibit regular expression of CD55, CD59, CD24. Monocytes demonstrate regular expression of CD55, CD59, CD14. Erythrocytes demonstrate regular expression of CD55, CD59.
Cytogenetic iFISH method	Karyotype: 46,XX,del(5)(q14q34)[17]/46,XX[3]
	Detected: del 5q31 The following were not detected: del(7q31), monosomy 7, trisomy 8, del(13q14), TP53/del(17p), del(20q12).
Molecular-genetic	The following mutations were not detected: ASXL1, BCOR, BCORL1, BRAF, BCR:ABL, CALR, CBL, CEBPA, DNMT3A, ETNK1, ETV6, EZH2, FLT3, FLT3-ITD, GATA2, GNB1, IDH1, IDH2, JAK2, KRAS, MPL, NF1, NPM1, NRAS, PHF6, PPM1D, PRPF8, PTEN, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, TET2, TP53, U2AF1, WT1, ZRSR2

1. MPO- myeloperoxidase, 2. NSE – neuron-specific enolase

it is particularly effective in patients with isolated del 5q without complicating genetic abnormalities.

Given the identified genetic abnormality, a treatment plan was formulated involving lenalidomide and prednisone. Lenalidomide, which is effective for conditions with deletion 5q, was administered at a dose of 10 mg from days 1 to 21 of each cycle with a 7-day break, as it effectively targets cells with this genetic alteration. Prednisone was prescribed at doses of 30 mg daily during the first cycle, 15 mg daily in the second cycle, and 15 mg every other day in the third cycle. Following this, the patient received three additional cycles of monotherapy with lenalidomide at a dose of 10 mg from days 1 to 21 of each cycle with a 7-day break, in accordance with the recommendations for treating isolated deletion 5q.

Treatment monitoring was conducted according to the IWG-MRT and ELN criteria from 2013. This included evaluating symptom improvement or resolution, normalization of laboratory parameters, and analysis of functional criteria, as well as morphological and immunocytological characteristics of the bone marrow (Gerds et al., 2022; Vannucchi et al., 2015). The results are presented in Table 3.

Results of treatment monitoring control The patient's condition has markedly improved, with full restoration of her functional capacity; however, she continues to experience night sweats. In accordance with the NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology) guidelines, and based on the IWG-MRT and ELN criteria from 2013, a partial response has been observed following the completion of the treatment course (Gerds et al., 2022; Vannucchi et al., 2015). As a result of this partial response, maintenance therapy with lenalidomide

Table 3.

Research	Results
Blood parameters	Hemoglobin: 134 g/L Erythrocytes: 4.44 x 10^{12}/L Leukocytes: 6.1 x 10^{9}/L Platelets: 180 x 10^{9}/L Granulocytes: 44.5% Lymphocytes: 44.6% Monocytes: 10.9%
Cytomorphological	Blast cells: 1.6%. Bone marrow: hypocellular. Erythron: constricted, without rejuvenation. Granulocytic series: Narrowed, with predominance of mature forms. Lymphocytes: 40.8%

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at a dose of 10 mg daily for 21 days, followed by a 7-day break, has been initiated (Tefferi, 2021).

Discussion

The evaluation of the treatment response in the patient with MDS/MPN-NOS was conducted according to the IWG-MRT and ELN criteria from 2013 and encompassed several key aspects. Hematological response was assessed based on the levels of hemoglobin and platelets. Following treatment, the patient's hemoglobin level increased to 134 g/L, meeting the criteria for partial remission. Additionally, the platelet count normalized to 180 × 10^9/L, reflecting positive changes in hematological parameters. Morphological response was evaluated by the reduction in the percentage of blast cells in the bone marrow. The patient's blast cell count decreased to 1.6%, which aligns with the criteria for partial remission in MDS/MPN-NOS. Clinical response was evidenced by a significant overall improvement in the patient's condition, with notable reductions in symptoms such as weakness and fatigue. Although night sweats did not fully resolve, the restoration of functional capacity and enhanced well-being underscore the positive clinical impact of the treatment.

In selecting the optimal therapy for our patient, we relied on recommendations from organizations such as the NCCN (National Comprehensive Cancer Network) and ESMO (European Society for Medical Oncology), as well as the results of previous studies in patients with MPN with del 5q, both as a standalone anomaly and in combination with other anomalies (Gerds et al., 2022; Vannucchi et al., 2015). For instance, Takahashi et al. studied 939 patients, of whom 8 had del 5q; seven had complex cytogenetic anomalies, and one had a simple karyotype. All had pancytopenia, and lenalidomide treatment was effective in achieving long-lasting hematologic remission in one patient (Takahashi et al., 2013). Furthermore, Tefferi investigated three cases of myelofibrosis with del 5q and JAK2 V617F mutation, demonstrating a response to lenalidomide. One patient achieved complete hematologic and bone marrow remission, including cytogenetic remission and JAK2 V617F clone elimination. Two additional patients experienced hematologic response and partial bone marrow response, though cytogenetic remission was not achieved (Tefferi, 2021). In 2006, Quintás-Cardama et al. treated 40 patients with myelofibrosis and del 5q using combined therapy with lenalidomide and prednisolone. Lenalidomide was administered at 10 mg daily for 21 days with a 7-day break for 6 months, and prednisolone was given at varying doses across three courses. This regimen resulted in partial response in three patients and clinical improvement in nine patients, lasting on average for 18 months (Cervantes, 2014).

Considering the results of previous studies and the specific characteristics of our patient's condition, the selected therapy aimed to achieve the most favorable outcome, particularly in the presence of myelofibrosis and del 5q. The observed partial response justifies the continuation of treatment with lenalidomide, aiming for more sustained remission.

Conclusions

Based on the findings from our clinical case and a detailed review of the literature on the management of MDS/MPN-NOS with del 5q, it is evident that lenalidomide exhibits a significant therapeutic benefit for patients with this condition, especially when del 5q is the exclusive genetic abnormality. The clinical and hematological improvements observed in our patient align with those reported in previous studies, reinforcing the efficacy of lenalidomide as an effective treatment modality. Thus, lenalidomide emerges as a promising therapeutic strategy for patients with MDS/MPN-NOS characterized by del 5q, aiming to achieve more durable and favorable clinical outcomes.

Financing

The investigation of this clinical case did not receive any specific grants from financial institutions in the public, commercial, or non-profit sectors.

Conflicts of Interest

There were no conflicts of interest during the conduct of the study.

Consent to publication

The patient provided consent for the publication prior to the writing of this case report.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F -Final approval of article

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Мієлодиспластичний синдром (МДС)/Мієлопроліферативна неоплазія (МПН) з втратою фрагменту довгого плеча хромосоми 5 (del 5q): Клінічний випадок та перспективи лікування

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Анотація: *цей клінічний випадок представляє пацієнта, діагностованого з мієлодиспластичним синдромом (MDS)/мієлопроліферативною неоплазією (MPN), зокрема*

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мієлофіброзом з делецією довгого рукава хромосоми 5 (del 5q), надзвичайно рідкісною аномалією у хронічних мієлопроліферативних розладах. Ми провели детальний аналіз клінічних, лабораторних та молекулярно-генетичних характеристик пацієнта для оцінки їх впливу на прогноз, рішення щодо лікування та терапевтичні результати. Після виключення інших генетичних аномалій пацієнт отримав лікування леналідомідом і преднізолоном, що призвело до покращення клінічних і гематологічних параметрів. Ці результати відповідають попереднім дослідженням і вказують на потенційну ефективність леналідоміду при лікуванні пацієнтів з MDS/MPN, характерних для del 5q, особливо коли відсутні додаткові генетичні аномалії.

Ключові слова: хронічна мієлопроліферативна неоплазія, мієлофіброз, мієлодиспластичний синдром, del 5q, леналідомід.