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Differential diagnoses and the mutational landscape of myelodysplastic/myeloproliferative neoplasm with neutrophilia: A case report

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Abstract. Myelodysplastic/myeloproliferative neoplasm with neutrophilia (MDS/MPN-N; previously referred to as atypical chronic myeloid leukemia) is a type of myelodysplastic syndrome/myeloproliferative neoplasm. A molecular genetic precondition for diagnosis is *BCR::ABL* negativity; further diagnostic criteria include clinicopathological assessments, such as peripheral blood leukocyte counts, the number of neutrophils and their precursors, and the presence of dysgranulopoiesis. The present case report highlights the importance of differential diagnoses with a stringent diagnostic workup according to the 5th Edition of the World Health Organization Classification of Hematolymphoid Tumors. A systematic review of the literature from 2013 to 2022 covering the mutational landscape of MDS/MPN-N was also performed to highlight recent improvements in the molecular genetic diagnostics of this disease.

Introduction

Myelodysplastic/myeloproliferative neoplasm with neutrophilia (MDS/MPN-N) exhibits a higher acute leukemia transformation rate (up to 40%) compared with other myelodysplastic/myeloproliferative neoplasms, including chronic myelomonocytic leukemia (CMML), myelodysplastic/myeloproliferative neoplasm with SF3B1 mutation and thrombocytosis and myelodysplastic/myeloproliferative neoplasm, not otherwise specified (1). Therefore, the diagnosis of MDS/MPN-N and the differentiation from other myelodysplastic/myeloproliferative neoplasms remains pivotal, although it requires a complex interplay of hematopathological and molecular genetic assessment. The increasing availability of targeted sequencing and the first applications of whole genome sequencing in routine use are expanding the diagnostic armamentarium of MDS/MPN-N. The diagnostic criteria of the World Health Organization (WHO) for MDS/MPN-N include leukocytosis (a white blood cell count >13x10^9/l), left-shifted and dysplastic granulopoiesis and a blast count <20% (1,2).

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Case report

Patient's history and hematological investigations. A patient was referred to the Hospital Wels-Grieskirchen (Wels, Austria) in March 2022 with a leukocyte count of 105 10^9/l. As reactive leukocytosis usually does not exceed 100 10^9/l leukocytes, which is even true for patients with sepsis, this result indicated the presence of a myeloid neoplasm (3). Initial laboratory assessment showed normal to slightly increased levels of C-reactive protein and procalcitonin, which excluded an infectious etiology for the notable elevation in leukocyte counts; however, lactate dehydrogenase levels were notably increased, indicative of increased cell turnover (4). In further laboratory assessments, there was no evidence of autoimmune disease. Supplementary abdominal sonography revealed a normal size proportion of the liver and a slightly enlarged spleen (14 cm), which was confirmed by computed tomography. Moreover, there was no evidence of lymphadenopathy. Therefore, secondary causes of the elevated leukocyte count were not considered (5,6).

Microscopic differential blood examination showed a picture of proliferatively dominating myelopoiesis that was pathologically left shifted with a myelocyte peak. A bone marrow puncture was performed, the results of which corresponded with that of the peripheral blood smear. The bone marrow was hypercellular, with a dominating granulopoiesis that was left shifted with a distribution in favor of myelocytes and a blast count of 15%. Basophilic granulocytes and eosinophilic granulocytes were massively underrepresented in the hematopoiesis (<2%). When considering classical chronic myeloid leukemia (CML), this microscopic appearance with low counts of basophilic granulocytes and eosinophilic

granulocytes is very atypical (7,8). Second, the erythropoietic precursor cells accounted for between 27-31% of the hematopoiesis, as assessed by three different investigators. Moreover, such a high percentage of erythropoiesis in an untreated patient with *de novo* CML in the chronic phase implied an atypical disease course (9). Ultimately, the hematopoiesis showed trilinear dysplasia. Secondary causes of hematopoietic dysplasia were evaluated and excluded (10); the patient had no history of alcohol abuse, his carbohydrate-deficient transferrin value was not increased, and vitamin B12, folic acid, and iron levels were within the reference ranges, excluding deficiencies. The patient's medical records did not contain any prescribed cytotoxic medications or prior radiation therapy, and a congenital disorder was implausible because the male patient was 69 years old. In addition, the patient's clinical status and subsequent laboratory assessment did not indicate an infectious disease.

Molecular biological assessment. Conventional cytogenetic assessment was performed, and karyotype analyses on unstimulated and stimulated (24 and 48 h) cultures showed no aberrations (karyotype: 46, XY). PCR analysis of *BCR::ABL1* major and minor breakpoints produced negative results, as did fluorescence *in situ* hybridization.

In summary, the hypercellular bone marrow in combination with significant dysplasia of hematopoiesis and *BCR::ABL1* negativity led to the diagnosis of MDS/MPN-N (1). Finally, next-generation sequencing (NGS) was performed with a myeloid solution panel, including 30 gene sections of *ABL1*, *ASXL1*, *BRAF*, *CALR*, *CBL*, *CEBPA*, *CSF3R*, *DNMT3A*, *ETV6*, *EZH2*, *FLT3*, *HRAS*, *IDH1*, *IDH2*, *JAK2*, *KIT*, *KRAS*, *MPL*, *NPM1*, *NRAS*, *PTPN11*, *RUNX1*, *SETBP1*, *SF3B1*, *SRSF2*, *TET2*, *TP53*, *U2AF1*, *WT1*, and *ZRSR2*. The detected mutations that matched with the final diagnosis of MDS/MPN-N (11,12) are presented in Table I.

TET2, SRSF2 and *ASXL1* mutations are the most frequent reported mutations in MDS/MPN-N. Thus, the mutational profile of our patient confirmed the diagnosis of MDS/MPN-N (13-21). In our patient the dysplastic features, in particular the granulopoiesis accounted for MDS/MPN-N, albeit the most specific mutations of MDS/MPN-N in *ETNK1* and *SETBP1* genes were not analyzed or detected (13,15). After one year of follow up, a progression of MDS/MPN-N (e.g. transformation to acute leukemia) was not observed in our patient, even though *ASXL1* mutations and ≥3 mutations are associated with an adverse clinical outcome (20,21).

Haemato-oncological differential diagnoses. As MDS/MPN-N was diagnosed, it was differentiated from other MPN/MDS neoplasms in adults (1,2).

CMML. This possibility was excluded due to the absence of monocytosis in peripheral blood: A persistent absolute (≥0.5x10^9/l) and relative (≥10% of white blood cells) monocytosis is required according to the 5th Edition of the WHO classification of hematolymphoid tumors (1).

MDS/MPN neoplasm with SF3B1 mutation and thrombocytosis. This possibility was excluded as SF3B1 mutations were not detected by NGS analysis. In addition, persistent thrombocytosis with a platelet count ≥450x10^9/l was not detected (1).

MDS/MPN neoplasm not otherwise specified (NOS). This entity remains a diagnosis of exclusion in MPN/MDS overlap syndromes. In the present case report, the drastic myelodysplasia determined MDS/MPN-N (1).

In addition to MDS/MPN overlap syndromes, a CML as a relevant differential diagnosis was considered; however, as the molecular-biological analyses yielded negative *BCR::ABL1* results, a classical CML could not be confirmed (22). One of the most important differential diagnoses is chronic neutrophilic leukemia (CNL). However, diagnosing CNL requires >80% banded and segmented neutrophils (1,23). Further differential diagnoses included acute myeloid leukemia (AML) as the blast count was 15% in the bone marrow. In the 5th Edition of the WHO classification of hematolymphoid tumors, the 20% blast requirement for most AML types with recurrent genetic abnormalities was eliminated. However, in the present case report, molecular-biological assessment did not yield those specific rearrangements, nor the corresponding translocations (1,24). Primary myelofibrosis was also considered, as leukocytosis is a possible presentation of myelofibrotic disease, and the patient exhibited leucoerythroblastosis on the peripheral blood smear. Primary myelofibrosis (or even pre-fibrotic or post-essential thrombocythemia or post-polycythemia vera myelofibrosis) was excluded, as the patient's bone marrow did not exhibit substantial fibrosis, which is essential for the diagnosis of myelofibrotic diseases (1,25). A flowchart for diagnosing MDS/MPN-N is shown in Fig. 1.

Discussion

A PubMed/Medline search was performed by three different investigators with the MeSH terms 'atypical CML' AND 'BCR/ABL negative CML' AND 'MDS/MPN-neoplasm with neutrophilia'. More than 400 articles were found; however, all reviews and case reports, clinical letters with <10 reported patients with MDS/MPN-N, and clinical trials that lacked reproducible molecular genetic data of the mutations were all excluded. The literature search on articles published was limited to January 2013 and December 2022 to gain more detailed information of the molecular genetic profile of the disease after the advent of NGS, with the first exome sequencing trial of MDS/MPN-N by Piazza *et al* (16) in 2013. An overview of the identified studies and mutation prevalence is presented in Table II.

In 2013, Piazza *et al* (16) performed the first whole-genome sequencing of 8 MDS/MPN-N cases and identified *SETBP1* as a common mutation. Accordingly, targeted sequencing of SETBP1 in 70 MDS/MPN-N samples was performed. During those analyses, *SETBP1* mutations were detected in 17 of 70 patients, which resulted in a frequency of 24%. Most of the SETBP1 mutations occurred between codons 858 and 871 and were reported as being similar to mutations in Schinzel-Giedion syndrome. *SETBP1* was assumed to be a mutation that was predominately enriched in MDS/MPN-N and related disorders as the researchers were unable to detect this mutation in 458 individuals with other hematological neoplasms, nor in 344 cell lines representative of lymphomas and the most common solid tumors. Distinctively, patients with *SETBP1* mutations showed higher leukocyte counts at diagnosis compared with patients with wildtype *SETBP1*

Table I. Mutations in our patient detected via next-generation sequencing.

Gene	DNA sequence change	Amino acid change	Exon	Type of mutation	VAF (%)
ASXL1	c.1892_1938del	p. (His631Profs*11)	13	Frameshift	43.90
RUNX1	c.1256_1262dup	p. (Glu422Glyfs*180)	9	Frameshift	48.60
SRSF2	c.284C>T	p. (Pro95Leu)	1	Missense	50.40
TET2	c.5618T>C	p. (IIe1873Thr)	11	Missense	49.50
TET2	c.3782G>A	p. (Arg1261His)	6	Missense	49.10

VAF, variant allele frequency.

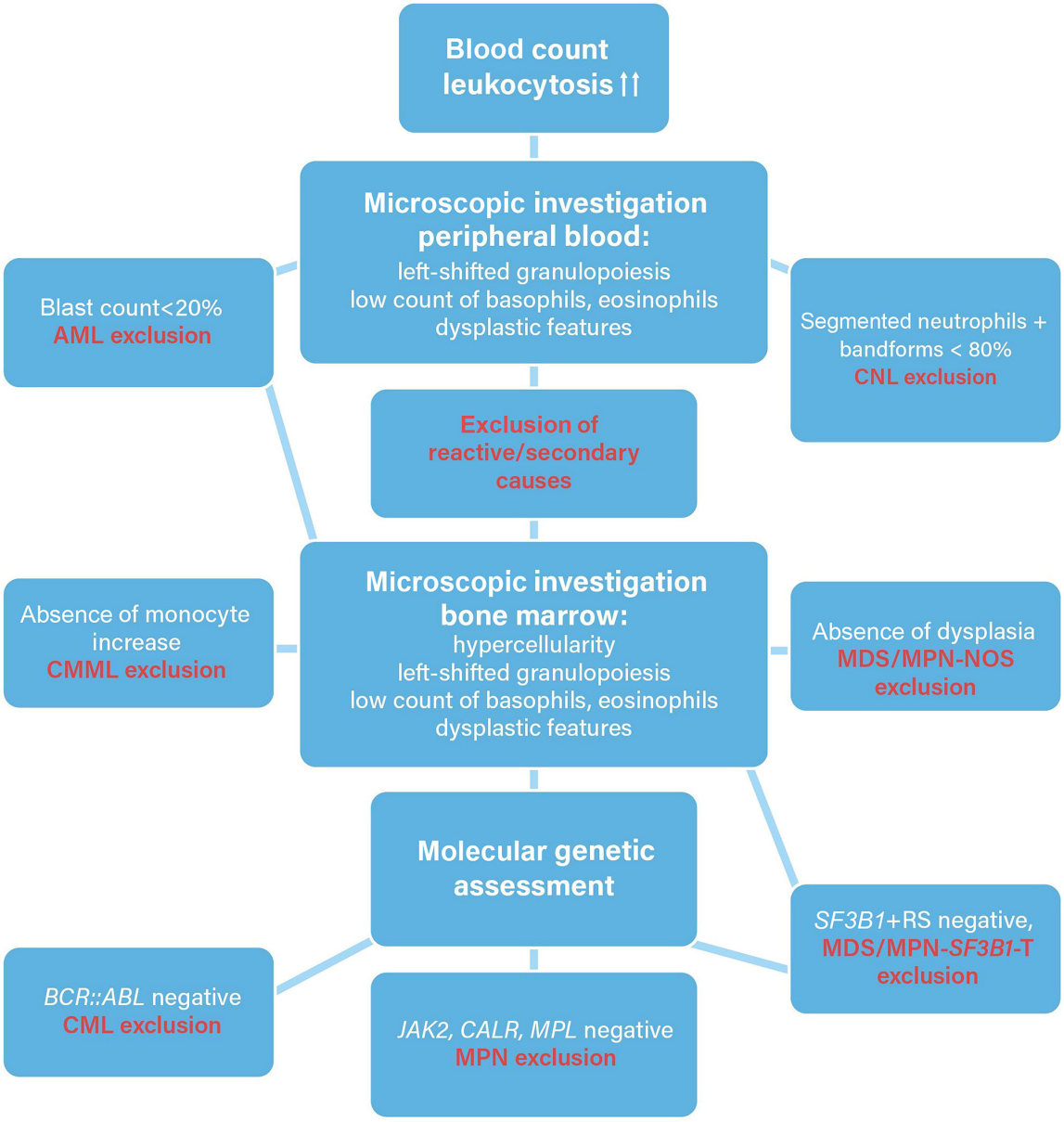

Figure 1. A diagnostic algorithm for MDS/MPN-N. MDS/MPN-N, myelodysplastic/myeloproliferative neoplasm; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CNL, chronic neutrophilic leukemia.

status and MDS/MPN-N (median of 81.0 vs. 38.5x10^9 cells/l, P=0.008). In addition, *SETBP1* mutations were associated with an adverse clinical course in MDS/MPN-N patients, as the overall survival was significantly worse compared with patients who lacked the mutation (median survival=22 vs. 77 months, P=0.01, hazard ratio=2.27). This study also

Table II. Mutation frequencies of MDS/MPN-N.

First name, year	Mutations	MDS/MPN-N[a]	(Refs.)
Maxson *et al*, 2013	42.1% CSF3R	19	(17)
Montalban-Bravo *et al*, 2021	86% ASXL; 63% SRSF2; 56% SETBP1; 34% TET2; 20-30% GATA, NRAS and CBL; 10-20% RUNX1, NF1 and JAK2; <10% Miscellaneous	65	(20)
Piazza *et al*, 2013	25% TET2; 23% ASXL1; 23-24% SETBP1; 15% EZH2; 10% N/KRAS	18/61/70[a]	(16)
Wang *et al*, 2014	35% N/KRAS; 7.3% JAK2	65	(18)
Meggendorfer *et al*, 2013	31.7% SETBP1	60	(13)
Patnaik *et al*, 2017	28% ASXL1; 16% TET2 and NRAS; 12% SETBP1 and RUNX1	25	(21)
Meggendorfer *et al*, 2014	66% ASXL1; 41% TET2; 40% SRSF2; 33% SETBP1; 10% CBL; 3% CSF3R; ≤3% JAK2, CALR and MPL	58	(14)
Gambacorti-Passerini *et al*, 2015	27% NRAS and SETBP1; 20% EZH and ASXL1; 13 and 9% ETNK1; 13% U2AF1	15/68[b]	(15)
Zhang *et al*, 2019	81% ASXL1; 37% SRSF2 and TET2; 20-30% EZH2, CSF3R and NRAS	27	(19)

MDS/MPN-N, myelodysplastic/myeloproliferative neoplasm. [a]Number of MDS/MPN-N cases. [a]A multicenter study: Different cohorts were analyzed; 8 samples for exome sequencing, 70 for targeted sequencing of SETBP1, and 61 for targeted sequencing of 15 genes. [b]15 samples for whole-genome sequencing and 68 for targeted sequencing of ETNK1.

provided NGS data covering 15 gene sections of 61 MDS/MPN-N individuals. The most frequent mutation was in the *TET2* gene at 25%, followed by *SETBP1* and *ASXL1*, both at 23%. This study decisively discovered *SETBP1* mutations as a possible recurrent mutation in MDS/MPN-N that also played a causative role in the entity's pathophysiology and provided a comprehensive overview of the mutational profile of MDS/MPN-N patients (16).

A clinical trial in 2013 with the goal of additional molecular genetic characterization of MDS/MPN-N was conducted by Meggendorfer *et al* (13), as the previous discovery of *SETBP1* as a novel molecular marker for MDS/MPN-N increased interest in this scientific field. This study group analyzed the *SETBP1* mutational status of 1,130 patients with MPN and MPN/MDS overlap neoplasms. Meggendorfer *et al* (13) demonstrated a dominance in the MDS/MPN cohort (9.4% vs. 3.8% in MPN), with the highest frequencies in MDS/MPN-N (31.7%; 19/60) and MDS/MPN-NOS (9.3%; 20/240). Furthermore, *SETBP1* mutations were associated with significantly higher leukocyte counts, lower thrombocyte counts, and hemoglobin levels, and a more dysplastic phenotype (dysplasia of granulopoiesis and megakaryopoiesis) on cytomorphological assessment. The effect of *SETBP1* mutations in leukemogenesis of different diseases has been well described in prior publications; overexpression of *SETBP1* leads to the protection of the molecule SET from proteolytic cleavage and, in terms of quantitative increase of the SET protein, a complex is formed comprising of *SETBP1*, SET, and protein phosphatase 2, which is responsible for the proliferation of leukemic cells. Unexpectedly, in that context, it must be mentioned that mutation of *SETBP1* did not significantly alter the overall survival. However, the authors addressed a relevant limitation of the study; the relatively short median follow-up time of 17.1 months in MDS/MPN-N and 12 months in CMML patients. Moreover, a pattern of concomitant occurrence of *SETBP1* and *ASXL1* mutation was described. Of note, this study was the first to discover *ASXL1* mutations in MDS/MPN-N, which has been reported in recent publications as one of the most frequent molecular abnormalities in MDS/MPN-N (13).

In the same year, Maxson *et al* (17) simultaneously conducted a trial to discover more regarding the clonal nature of MDS/MPN-N. They investigated MDS/MPN-N and CNL as, at the time of the study, little was known regarding the mutations in those diseases and both entities lacked knowledge of specific cytogenetic aberrations. They identified *CSF3R* as a potential driver mutation of those diseases as *CSF3R* is a receptor of colony-stimulating factor 3, which is hypothesized to play a pivotal role in the growth and differentiation of granulocytes. Previous reports have described *CSF3R* mutations, amongst others, as a contributor to severe congenital neutropenia, which frequently evolves into AML. While the study population was small, with 9 CNL patients and 18 patients with MDS/MPN-N, this trial revealed an association between *CSF3R* mutations and those entities. The high frequency of *CSF3R* mutations in leukemia with neutrophilic expansion was consistent with its function as a receptor that promotes neutrophilic differentiation and proliferation. However, it must be noted that *CSF3R* mutations occurred in ~89% of CNL cases and only 44% of MDS/MPN-N cases. Therefore, this study identified *CSF3R* mutations in MDS/MPN-N and CNL; however, this mutation was determined to be more specific to CNL than MDS/MPN-N. This was an important finding, as the discrimination of these entities had previously relied more or less on hematological parameters, such as leukocyte counts (>25x10^9/l for CNL and >13x10^9/l for MDS/MPN-N), the percentage of immature precursor leukocytes in the total

white cell population (<10% for CNL and >10% for MDS/MPN-N), and the presence of dysgranulopoiesis in MDS/MPN-N. Consequently, consecutive studies could not confirm the distinctive frequency of *CSF3R* mutations in MDS/MPN-N but promoted it as a typical marker of CNL. This study group also investigated different types of *CSF3R* mutations with different susceptibilities to tyrosine kinase inhibitors. *CSF3R* truncation mutations are preferentially activators of SRC family-TNK2 kinase signaling, with a sensitivity to dasatinib, whereas *CSF3R* membrane proximal mutations resulted in activation of the JAK signaling pathway and should be treated with *JAK1/2* inhibitors (such as ruxolitinib). Notably, the *T618I* variant was the most detected commonly *CSF3R* mutation of the proximal membrane mutations (17).

In the following year, Meggendorfer *et al* (14) performed a trial including 14 patients with CNL, 68 with MDS/MPN-N, and 146 with CMML to enable improved differentiation within this group of common MDS/MPN overlapping malignancies based on molecular genetic markers. Importantly, this was the first trial to describe *ASXL1* mutations as the most frequent mutation in an MDS/MPN-N cohort. Nevertheless, its value as a differentiation marker of other MPN/MDS neoplasms could not be determined, as *ASXL1* mutations were also detected with comparable prevalence in CNL (57%) and CMML (66%). A novel observation was made, as they discovered *SRSF2* mutations with 40% prevalence in MDS/MPN-N. Interestingly, MDS/MPN-N patients with *SETBP1* mutations presented with higher hemoglobin levels than wild-type patients. Importantly, *CSF3R* was often mutated in CNL (43%), but rarely in MDS/MPN-N or CMML (1-3%) which supported previous data suggesting that *CSF3R* was a molecular genetic marker of CNL (14).

Wang *et al* (18) compared the clinical outcomes of MDS/MPN-N patients with patients diagnosed with MDS/MPN-NOS. In addition, they provided data on the detected mutations, thereby contributing to an improved understanding of the molecular nature of those diseases. This previous study clearly highlighted adverse features, inferior overall survival, and inferior AML-free survival of patients with MDS/MPN-N compared with MDS/MPN-NOS. There was controversy surrounding studies on *CSF3R*, as certain publications reported a strong association with MDS/MPN-N while others reported no association. In 27 patients with MDS/MPN-N, *CSF3R* mutations were not detected. Therefore, they proposed that an initial diagnosis of MDS/MPN-N should be reconsidered when *CSF3R* analysis was positive; instead, a diagnosis of CNL should be considered (18).

In 2015, Gambacorti-Passerini *et al* (15) performed whole-exome sequencing on 15 MDS/MPN-N cases. They detected a groundbreaking somatic *ETNK1* mutation for the first time in cancer in two patients. *ETNK1* encodes an ethanolamine kinase that catalyzes the biosynthesis of phosphatidylethanolamine, a molecule that is involved in the regulation of the transmembrane domains of membrane proteins, the progression of cytokinesis during cell division, and the activation of the respiratory complex in mitochondria. The discovery of *ETNK1* mutations in MDS/MPN-N prompted the study group to sequence 515 cases of several hematologic diseases. *ETNK1* mutations were detected exclusively in MDS/MPN-N (9%, 6/68) and CMML (2.6%, 2/77) (15).

In 2017, Patnaik *et al* (21) performed an MDS/MPN-N trial with an extended panel of 29 genes and analyzed bone marrow specimens. Based on prior publications, they were also interested in clinical outcomes. The most mutated gene was *ASXL1*. Notably, *ASXL1* mutations did not adversely impact overall survival in contrast to *NRAS* (P=0.04), TET2 (P=0.03), *PTPN11* (P=0.02), and ≥3 myeloid mutations. However, in two patients, leukemic transformation was documented. One of these patients harbored an *ASXL1* separate from *JAK2*, and the second was positive for *TET2* and *PTPN11* mutations (21).

Zhang *et al* (19) analyzed specimens from 158 patients with MDS/MPN neoplasms (27 MDS/MPN-N) and CNL by whole exome and RNA sequencing. In these rare leukemic diseases, an increased variant allele frequency of mutations in signal-transduction genes was observed; this may indicate a preferential pharmaceutical target. In >50% of the patients with either MDS/MPN neoplasms or CNL, ≥3 or more co-occurring pathway mutations involving genes of chromatin modification, epigenetic regulator genes, signaling pathway genes, or genes of the splicing complex were observed. In contrast, in MPN, only mutations of signal-transduction genes were predominant, whereas in MDS, mutations of the splicing complex typically predominated. In conclusion, this trial contributed to an improved understanding of the differentiation of MDS/MPN neoplasms, including MDS/MPN-N, from other myeloid malignancies; the authors also stated that malignancies classified as MDS/MPN neoplasms more often represent a group of related diseases than discrete diagnostic entities (19).

In 2021, the most recent clinical trial investigating the mutational architecture of MDS/MPN-N was conducted. The study included 68 MDS/MPN-N patients from 2005-2020, and NGS data were available for 35 patients. One major strength of this study was the long follow-up time (median 35.6 months). Transformation to AML was observed in 28% of patients. The genes that contributed to AML transformation were *ASXL1*, *PTPN11*, *N/KRAS*, *NF1*, *CEBPA*, *ETV6*, and *FLT3-ITD*. The median leukemia-free survival was 19.8 months, and the median post-transformation survival was 8.9 months. One of the most important key messages of this study was that MDS/MPN-N is a disease prone to transformation to AML (20).

In the present case report, the mutational profile with *ASXL1*, 2x *TET2*, *SRSF2*, and *RUNX1* mutations in combination with the significant dysgranulopoiesis accounted for MDS/MPN-N.

MDS/MPN-N is a hematological neoplasm with a relatively low incidence. However, a systematic review of studies showed that in 251 patients, a comprehensive molecular genetic analysis by whole-genome sequencing or targeted sequencing, including a broad spectrum of myeloid genes was performed. Our analysis identified *ASXL1*, *TET2*, and *SRSF2* mutations as the most frequent molecular genetic alterations in MDS/MPN-N. Mutations in transcriptional and epigenetic regulator genes and genes encoding the spliceosome are typical in MDS/MPN overlapping neoplasms and are responsible for the phenotype of these entities including cell proliferation and myelodysplasia. Therefore, cytomorphological investigation remains a pivotal diagnostic procedure in the differentiation of MDS/MPN-neoplasms. In addition, the analysis revealed a heterogeneous picture of several myeloid gene mutations

with lower prevalence in MDS/MPN-N. However, the sample size of all included studies was low and the reproducibility was limited due to the different molecular genetic approaches (such as different gene panels) applied in the reviewed trials. Thus, the evidence of low frequent mutations in MDS/MPN-N remains insufficient, and isolated quantitative analysis of those infrequent mutations is indistinct except for *ETNK1* and *SETBP1* mutations. In those genes, the mutational mechanism of leukemogenesis was assessed. The analyzed data indicated that *ETNK1* and *SETBP1* mutations were highly specific for MDS/MPN neoplasms, particularly for MDS/MPN-N. In the absence of dysgranulopoiesis *ETNK1* and *SETBP1* mutations were associated with MDS/MPN-NOS. Moreover, MDS/MPN-N remains a diagnosis of exclusion to a certain degree: *BCR::ABL1* fusions are the indispensable diagnostic hallmark of CML, *CSF3R* mutations are known driver mutations of CNL, and *SF3B1* mutations are highly indicative of MDS or MDS/MPN-SF3B1-T.

In conclusion, MDS/MPN-N (formerly known as atypical CML) is a rare disease accounting for 5% of all CML cases (26). The information surrounding distinctive mutations in MDS/MPN-N was scarce 10-15 years ago and was predominantly based on data from small case-controlled studies. However, in the last decade, major improvements in understanding the nature of the disease and the underlying mutations have been achieved. Initial deep-sequencing trials identified *CSF3R* as one of the most common recurrent mutations of these diseases; however, following additional study of MDS/MPN-N, it was determined that the initial *CSF3R* prevalence was overestimated. To comply with several recommendations, the prevalence of *CSF3R* should justify the revision of MDS/MPN-N diagnosis, instead of considering a diagnosis of CNL. As NGS-based techniques have improved and their applications have expanded with larger gene panels, the discovery of more mutations in more genes has accelerated. Although the epidemiology of MDS/MPN-N allows for relatively small study cohorts, the tendency for recurrent mutations (such as *ASXL1*, *SETBP*, *TET2*, *SRSF2*, and *ETNK1*) has been shown. The latest data support the notion that MDS/MPN-N is an entity with more adverse clinical outcomes than other MDS/MPN neoplasms. In addition, high AML-transformation susceptibility has been observed. Completing whole-genome sequencing studies of MDS/MPN-N will be beneficial, allowing further steps to be made in this field of research.

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Availability of data and materials

The molecular genetic data of NGS analysis that were generated during the current study are available in the ClinVar repository https://www.ncbi.nlm.nih.gov/clinvar under accession numbers SCV003929446-SCV003929450. The non-NGS data are available from the corresponding author upon reasonable request.

Authors' contributions

All authors contributed to the conception and design of the study. BS wrote the manuscript. BS, MG and AH carried out microscopic investigations. BS, RS and SH carried out molecular-genetic assessment. BS, RS and MG participated in the literature analysis for the review section. SH, JT and AH contributed to revising the manuscript. BS and AH confirm the authenticity of all the raw data. All authors agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of anonymized data.

Competing interests

The authors declare that they have no competing interest.

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