Research letter

Hematology

Synchronous myelodysplastic syndrome and multiple myeloma: a DDX41-associated double-hit across two lineages

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Myelodysplastic syndromes (MDS) comprise a heterogeneous group of clonal myeloid disorders arising from hematopoietic stem cells. In contrast, multiple myeloma (MM) is a malignant plasma cell neoplasm characterized by clonal proliferation of monoclonal plasma cells within the bone marrow. Although both diseases predominantly affect older adults, the synchronous occurrence of MDS and MM as double primary hematologic neoplasms is exceedingly rare [1]. Previous studies have demonstrated that patients with MM are at increased risk of developing therapy-related MDS/AML following prolonged exposure to alkylating agents and immunomodulatory drugs, with a cumulative incidence estimated at 2–10% [2, 3]. However, simultaneous de novo presentation of MDS and MM remains uncommon, and the underlying pathogenic mechanisms are poorly understood.

In recent years, mutations in DEAD-box helicase 41 (DDX41) have emerged as one of the most common germline predisposition mutations in adult myeloid neoplasms [4]. DDX41 encodes a multifunctional RNA helicase involved in RNA splicing, ribosome biogenesis, and innate immune signaling [5]. The pathogenic mechanism of DDX41-associated neoplasms generally follows a classical "two-hit" model, in which an inherited germline mutation, such as a frameshift mutation, is followed by acquisition of a second somatic mutation, commonly a missense mutation such as R525H, in hematopoietic stem or progenitor cells. This process results in functional impairment of DDX41 and subsequent development of myeloid lineage clonal malignancies [6, 7]. Clinically, germline DDX41 mutations are frequently associated with male predominance, older age at disease onset, normal cytogenetics, hypocellular bone marrow, and relatively favorable initial responses to lenalidomide and hypomethylating agents, such as azacitidine [8, 9]. Notably, DDX41 mutations have only exceptionally been implicated beyond the myeloid compartment: isolated DDX41-mutated hematolymphoid neoplasms, including rare cases with plasma cell differentiation, have been described [10]. The phenotypic spectrum of DDX41-associated disease may extend to plasma cell disorders, underscoring just how exceptional synchronous myeloid and plasma cell malignancies are in this setting.

Here, we report a case of synchronous diagnosis of MDS-EB2 and IgA λ-type MM in a patient who presented with severe pancytopenia and IgA λ-type monoclonal gammopathy. Next-generation sequencing

(NGS) revealed a double-hit genetic profile in DDX41, consisting of a rare germline frameshift mutation (c.232_233insAA) together with a somatic missense mutation. This case is notable for two reasons. First, the concurrent germline and somatic DDX41 mutations appeared to drive malignant transformation across both myeloid and plasma cell lineages, providing clinical evidence that the two-hit model may extend to double primary cancers. Second, although the patient initially responded to combination therapy with azacitidine and lenalidomide, the remission was brief, followed by rapid disease progression and an extremely poor prognosis, ultimately resulting in death within 15 months of diagnosis. Given the rarity of concurrent MDS and MM associated with DDX41 double mutations, this report expands the known phenotypic spectrum of DDX41-associated hematologic malignancies and provides important insights into diagnostic evaluation, including comprehensive multiparameter bone marrow assessment and NGS analysis of DDX41, as well as therapeutic management, including combination therapy and early consideration of allogeneic hematopoietic stem cell transplantation.

Patient information. A 68-year-old man was admitted on January 10, 2023, with progressive limb weakness for 4 months, which had worsened over the preceding 2 weeks. He had previously been in good health. Physical examination revealed marked pallor without petechiae or mucosal bleeding.

Laboratory examination. Initial complete blood count revealed severe pancytopenia, with a white blood cell count of 0.89 × 10^9/l, hemoglobin level of 36 g/l, and platelet count of 51 × 10^9/l. Serum biochemical analysis showed a total protein level of 54 g/l, albumin of 29.1 g/l, and globulin of 24.9 g/l. Immunoglobulin quantification demonstrated IgG 11.9 g/l, IgA 10.22 g/l, and IgM 0.55 g/l. β2-microglobulin was elevated at 4.37 mg/l, while lactate dehydrogenase remained within the normal range. Serum immunofixation electrophoresis identified an IgA λ-type monoclonal protein measuring 5.47 g/l.

Bone marrow aspirate cytology indicated myelodysplastic syndrome, with 12% myeloid blasts and increased plasma cells accounting for 6.5% of nucleated cells. Flow cytometric immunophenotyping revealed approximately 10% blasts expressing HLA-DR, CD33, CD34, CD117, and CD123. In addition, approximately 4% of cells showed strong CD38 expression, CD56 positivity, and CD19 negativity, with co-expression of CD138 and cytoplasmic λ light chain, consistent with an abnormal plasma cell population.

Conventional cytogenetic analysis demonstrated a normal karyotype, and fluorescence in situ hybridization for common MDS- and MM-associated abnormalities was negative. Bone marrow biopsy revealed marked plasma cell proliferation, accounting for approximately 20% of bone marrow cellularity with λ light-chain restriction, along with a significant increase in CD34-positive cells (Figures 1 A–C). Immunohistochemistry further supported these findings, demonstrating positivity for CD138, CD38, CD56, and λ light chain, with absence of κ light-chain expression. CD34-positive cells accounted for approximately 15% of marrow cells, whereas staining for CD3, CD5, CD20, PAX5, MPO, and CD235a was negative.

NGS identified a germline DDX41 frameshift mutation, c.232_233insAA (p.Pro78GlnfsTer3), with a variant allele frequency (VAF) of 47.6%, along with a somatic DDX41 missense mutation, c.1032G>T (p.Asp344Glu), with a VAF of 5.3% (Supplementary Figure S1).

Diagnostic assessment. Based on these findings, the patient was diagnosed with two concurrent hematologic malignancies: myelodysplastic syndrome with excess blasts-2 (MDS-EB2), classified as intermediate-2 risk according to the International Prognostic Scoring System (IPSS), high risk according to the WHO Classification-Based Prognostic Scoring System (WPSS), and high risk according to the Revised International Prognostic Scoring System (IPSS-R); and multiple myeloma, IgA λ subtype.

Treatment. From February to May 2023, the patient received four cycles of azacitidine combined with an RD regimen, consisting of azacitidine 75 mg/m² on days 1–7, lenalidomide 10 mg on days 1–21, and dexamethasone 40 mg weekly. Following treatment, the hemoglobin level increased to 95 g/l and the platelet count improved to 152 × 10^9/l, indicating an initial hematologic response.

However, on May 29, 2023, the patient developed worsening anemia and marked leukopenia. Repeat bone marrow examination showed plasma cells accounting for 11.5% of nucleated cells and blasts accounting for 7.5%. Treatment was subsequently switched to a VPD regimen consisting of bortezomib 1.3 mg/m² on days 1, 4, 8, and 11; pomalidomide 4 mg on days 1–14; and dexamethasone 40 mg on days 1, 4, 8, and 11, for two cycles.

Due to treatment-related peripheral neuropathy, therapy was modified to an IPD regimen consisting of ixazomib 4 mg on days 1, 8, and 15; pomalidomide 4 mg on days 1–14; and dexamethasone 40 mg once weekly, for four cycles. During this period, the white blood cell count and hemoglobin level transiently normalized.

In January 2024, pancytopenia recurred. Repeat bone marrow biopsy demonstrated active hematopoietic hyperplasia, with an increased myeloid blast proportion of 10% and residual malig-

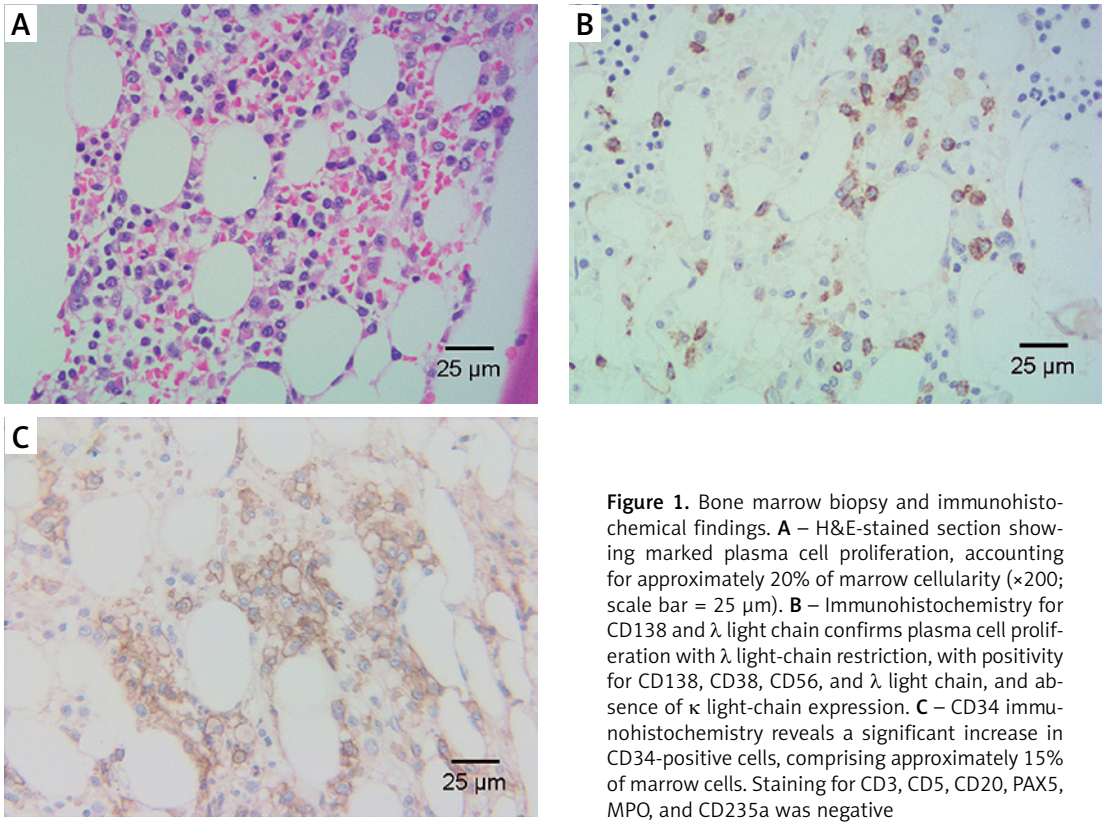

Figure 1. Bone marrow biopsy and immunohistochemical findings. **A** – H&E-stained section showing marked plasma cell proliferation, accounting for approximately 20% of marrow cellularity (×200; scale bar = 25 μm). **B** – Immunohistochemistry for CD138 and λ light chain confirms plasma cell proliferation with λ light-chain restriction, with positivity for CD138, CD38, CD56, and λ light chain, and absence of κ light-chain expression. **C** – CD34 immunohistochemistry reveals a significant increase in CD34-positive cells, comprising approximately 15% of marrow cells. Staining for CD3, CD5, CD20, PAX5, MPO, and CD235a was negative

nant plasma cells. The patient was subsequently switched to one cycle of the VA regimen, consisting of venetoclax 100 mg on days 1–14 plus azacitidine 75 mg/m² on days 1–7.

Follow-up and outcomes. During treatment with venetoclax and azacitidine, the patient developed severe pneumonia and died on April 13, 2024. The overall survival from diagnosis was 15 months.

This case suggests that patients with concurrent germline and somatic DDX41 mutations may initially respond to azacitidine- and lenalidomide-based therapy; however, the coexistence of synchronous myeloid and plasma cell neoplasms may indicate aggressive disease biology characterized by rapid relapse, short remission duration, and poor overall prognosis. Early consideration of allogeneic hematopoietic stem cell transplantation may therefore represent a more favorable treatment option for such patients.

Discussion. Germline DDX41 mutations represent one of the most common hereditary predisposition factors for adult myeloid neoplasms, which typically follow a classical two-hit pathogenic mechanism in which a germline mutation is followed by acquisition of a second somatic DDX41 mutation in hematopoietic stem cells, thereby driving malignant transformation [4, 11]. It has been well documented that patients with DDX41 double-mutated myeloid neoplasms, particularly MDS or AML, commonly present at an older age and show male predominance, normal karyotypes, favorable treatment responses, and relatively prolonged survival [12, 13]. The present case is noteworthy because the patient simultaneously developed MDS-EB2 and IgA λ-type MM in the setting of concurrent germline and somatic DDX41 mutations (c.232_233insAA, p.Pro78GlnfsTer3, and c.1032G>T, p.Asp344Glu). Although previous studies have suggested that the spectrum of DDX41-associated disorders may extend beyond myeloid neoplasms to include plasma cell dyscrasias [10], synchronous MDS and MM as double primary cancers remain exceptionally rare among DDX41 mutation carriers. In addition, most previously reported synchronous MDS–MM cases involved IgG-subtype myeloma, whereas our patient had IgA λ disease. To our knowledge, no specific biological association between IgA-subtype MM and myeloid dysplasia has been established; the predominance of IgG in published cases may simply reflect the higher background prevalence of IgG myeloma. Whether IgA-subtype disease preferentially co-occurs with myeloid dysplasia in DDX41 mutation carriers remains an open question that deserves attention in future case series.

Compared with previously reported DDX41-mutated myeloid neoplasms, the disease course in this patient was notably complex and aggressive. Previous studies have shown that patients with

DDX41 double-mutated MDS or AML often exhibit relatively indolent disease progression, favorable responses to hypomethylating agents, such as azacitidine, and lenalidomide-based therapy, as well as comparatively prolonged survival [12, 14]. Although the present patient initially responded to azacitidine plus lenalidomide, the remission was brief, followed by rapid disease progression and death within 15 months of diagnosis. This outcome contrasts sharply with the generally favorable prognosis reported in DDX41-mutated MDS/AML [13]. The coexistence of myeloid and plasma cell neoplasms in this patient raises the possibility of distinct or partially related clonal processes in the setting of germline DDX41 predisposition. However, the cellular distribution of the somatic variant could not be established, and the mechanisms underlying the simultaneous development of the two malignancies remain uncertain.

Additionally, patients with DDX41 mutations have been reported to lack other accompanying mutations, and the adverse prognostic impact of TP53 mutations may be mitigated in the context of DDX41 mutations [11]. In the present case, no TP53 mutation was detected; however, the rapid disease progression suggests that DDX41 double mutations may confer a high-risk disease phenotype under certain conditions, such as synchronous involvement of both myeloid and plasma cell lineages. This finding expands our understanding of the genotype–phenotype correlations associated with DDX41 mutations.

The diagnostic process in this case also highlights the clinical challenges posed by the concurrent presence of MDS and MM. In patients presenting with pancytopenia and monoclonal gammopathy, distinguishing cytopenia caused by ineffective myelopoiesis from that resulting from plasma cell infiltration of the bone marrow can be difficult. In this patient, bone marrow aspirate showed increased blasts at 12% and plasma cells accounting for 6.5% of nucleated cells, whereas bone marrow biopsy confirmed marked increases in both CD34-positive blasts (~15%) and λ-restricted plasma cells (~20%). These findings suggest concurrent occupation of the bone marrow niche by two malignant clones, jointly contributing to hematopoietic failure [15]. This case underscores the importance of comprehensive multiparameter evaluation, including morphology, flow cytometry, immunohistochemistry, cytogenetics, and immunophenotyping, particularly for distinguishing CD34-positive myeloid blasts from CD138-positive aberrant plasma cells, to avoid incomplete or missed diagnoses.

From a mechanistic perspective, this case provides additional evidence supporting expansion of the DDX41 two-hit model beyond myeloid malignancies. DDX41 plays essential roles in RNA splicing and DNA damage repair, and its dysfunction may promote genomic instability and subsequent malignant transformation [16]. In this case, the germline DDX41 mutation, with a VAF of 47.6%, likely established an inherited predisposition, whereas the somatic DDX41 mutation, with a VAF of 5.3%, may have served as the second hit driving clonal evolution in a subset of hematopoietic stem/progenitor cells. However, the precise mechanism by which this two-hit process might promote simultaneous malignant transformation in both myeloid and plasma cell lineages, rather than a single lineage, remains unclear. One possibility is that altered RNA splicing could disrupt hematopoietic lineage differentiation, while impaired DNA repair could promote the accumulation of mutations across multiple lineages, thereby facilitating oncogenesis in multiple hematopoietic compartments [17]. The VAF data warrant particular attention. The somatic mutation was detected at a VAF of only 6.2%, whereas malignant plasma cells accounted for approximately 20% of marrow cellularity and myeloid blasts for 10–15%. Given that malignant plasma cells accounted for approximately 20% of marrow cellularity, a heterozygous variant present in all plasma cells would be expected to produce a VAF of approximately 10%, assuming the variant was absent from other cell populations. The observed VAF was lower, which may be compatible with the variant being present in only a subset of cells. However, bulk marrow sequencing cannot determine its lineage distribution. Lineage-sorted sequencing of CD138-positive plasma cells versus CD34-positive blasts, or single-cell genotyping, would be required to resolve this critical question. Regarding the cell of origin, because the germline DDX41 lesion is present in hematopoietic cells, it is biologically plausible that the first hit occurred in an early hematopoietic stem or progenitor cell with multilineage potential, so that progeny committed to either the myeloid or the B-cell/plasma lineage inherited the same predisposition. A subsequent second hit, together with additional cooperating events, could then have driven transformation in both compartments. Alternatively, DDX41 haploinsufficiency may create a permissive milieu of genomic instability and aberrant RNA splicing in which two lineages undergo parallel, independent transformation. Either model would explain how a single germline "hit" may contribute to synchronous cancers of two lineages.

The transient therapeutic response observed in this patient also raises important clinical considerations. DDX41 mutations and associated RNA splicing dysfunction may contribute to sensitivi-

ty to lenalidomide and hypomethylating agents. However, the rapid relapse observed in this case suggests that myeloid and plasma cell clones may exhibit distinct patterns of drug sensitivity in the setting of double primary cancers [18]. Clonal heterogeneity and microenvironment-mediated resistance may further contribute to therapeutic resistance and treatment failure. Therefore, early assessment of eligibility for allogeneic hematopoietic stem cell transplantation may be appropriate in selected patients with high-risk myeloid disease, although the potential role and timing of transplantation in patients with synchronous MDS and MM require individualized assessment. Several factors may have contributed to the limited durability of treatment response in this patient. The agents used are largely lineage-selective: hypomethylating agents and venetoclax preferentially target the myeloid clone, whereas proteasome inhibitors and immunomodulatory drugs preferentially target the plasma cell clone. In biclonal disease, suppression of one lineage may permit compensatory expansion of the other, so sequential regimens produced only transient control. Moreover, whether DDX41-associated genomic alterations contributed to treatment resistance in this patient remains uncertain. Although allogeneic transplantation is potentially curative for selected patients with appropriate indications, our patient was 68 years old with profound pancytopenia and recurrent infections and may have had limited transplant eligibility at diagnosis, with further deterioration as the disease progressed. his case therefore highlights the potential importance of early transplant assessment when clinically appropriate, rather than establishing a specific "transplant window" for patients with synchronous MDS and MM.

Several limitations should be acknowledged. First, this report describes a single patient and lacks a control group. Second, the therapeutic approach was empirical and not guided by prospective clinical evidence. Third, germline screening for DDX41 mutations was not performed in family members, precluding assessment of familial predisposition. Fourth, DDX41 variant analysis was performed on bulk bone marrow cells without lineage-specific cell sorting or single-cell sequencing; therefore, whether the somatic mutation resided in the myeloid clone, the plasma cell clone, or both could not be definitively determined. Fifth, serial molecular monitoring during treatment was unavailable, limiting our ability to correlate clonal dynamics with therapeutic response. Finally, as a single-case observation, the mechanistic interpretations proposed here remain hypothesis-generating and require validation in larger series.

In conclusion, this case provides important clinical insights into the diagnosis and treatment of synchronous MDS-EB2 and MM in the presence of concurrent germline and somatic DDX41 mutations. It highlights the need for systematic multiparameter bone marrow evaluation and DDX41 genetic testing in patients with unexplained cytopenia accompanied by M-proteinemia. The presence of concurrent germline and somatic DDX41 mutations may warrant further investigation in patients with synchronous MDS and MM, although their prognostic and predictive significance remains uncertain. The patient showed an initial response to treatment followed by rapid disease progression, but this single case cannot establish an association between DDX41 status and treatment resistance or support early consideration of allogeneic hematopoietic stem cell transplantation on this basis alone. Overall, this case raises the possibility that biallelic DDX41 alterations may contribute to the development of both myeloid and plasma cell malignancies, potentially through pathways involving RNA splicing and DNA repair. However, because sequencing was performed on bulk bone marrow without lineage-specific or single-cell analysis, a shared clonal origin cannot be established. Finally, this case illustrates the potential value of next-generation sequencing in selected patients with synchronous or otherwise unusual hematologic malignancies, particularly when a shared genetic predisposition is suspected.

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Ethical approval

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Conflict of interest

The authors declare no conflict of interest.

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