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CASE REPORT

Concomitant Occurrence of Blastic Plasmacytoid Dendritic Cell Neoplasm and Acute Myeloid Leukaemia after Lenalidomide Treatment for del(5q) Myelodysplastic Syndrome

Nicola S. Fracchiolla [1], Alessanda Iurlo [1], Valeria Ferla [1, 2], Bruno Fattizzo [1, 2], Alessandra Freyrie [1], Gianluigi Reda [1], Agostino Cortelezzi [1, 2]

[1] U.O. Onco-Hematology, IRCCS Ca' Granda Foundation Policlinico Hospital, Milan, Italy
[2] University of Milano, Milano, Italy

SUMMARY

Background: **Myelodysplastic syndromes with chromosome 5 long arm deletion (5q-mds) may benefit from lenalidomide treatment. However, unresponsive patients have a high risk for clonal evolution and progression to acute myeloid leukemia.**

Case: **We describe a 5q-patient treated with lenalidomide, who concomitantly developed acute myeloid leukemia and blastic plasmacytoid dendritic cell neoplasm, a rare and highly aggressive lymphoma.**

Conclusions: **Evolution of 5q- syndrome to acute myeloid leukemia and blastic plasmacytoid dendritic cell neoplasm may have occurred through various mechanisms, including persistence of neoplastic lenalidomide-resistant stem cells and selection of a more aggressive clone via lenalidomide augmentation of the ARPC1B gene, or because of lenalidomide stimulation on dendritic cells. Further studies are needed to clarify lenalidomide oncogenic potential.**

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Correspondence:
Nicola Stefano Fracchiolla, MD
U.O. Onco-Ematologia
Padiglione Granelli
Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico
Via F. Sforza 35
20122 Milano
Italy
Phone: +39 0255033429
Fax: +39 0255034182
Email: ns.fracchiolla@gmail.com

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KEY WORDS

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INTRODUCTION

Myelodysplastic syndromes (MDSs) are a heterogeneous group of diseases characterized by ineffective hematopoiesis, hypercellular bone marrow, and peripheral blood cytopenias, with variable rate of progression (~ 40%) to acute myeloid leukemia (AML). Isolated interstitial deletion of the long arm of chromosome 5 [del (5q)] is one of the most common karyotypic abnormalities in de novo MDS (10 - 20%) and its isolated presence in a patient with less than 5% marrow blasts configures the 5q- syndrome. This condition is characterized by severe macrocytic anemia, often with transfu-

sion-dependence, normal or elevated platelet count with hypolobated micromegakaryocytes, normal or slightly decreased neutrophil count, and a 10% rate of AML transformation [1]. In a high proportion of 5q-MDS patients, transfusion independence and complete cytogenetic remission is achieved with administration of lenalidomide; however, unresponsive patients have a high risk for clonal evolution and AML progression. In refractory/relapsing patients, genetic instability and clonal evolution seem to be the driving forces of leukemic transformation [2].

Here we describe a 5q-MDS patient treated with lenalidomide, who developed concomitantly AML and blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare and highly aggressive lymphoma (about 0.7% of skin lymphomas and 0.4% of all hematological malignancies), characterized by spleen, skin, lymph node and marrow infiltration, whose leukemic form represents less than 1% of acute leukemia [3]. Moreover, we discuss the potential role of the immune-modulator drug lenalidomide in the pathogenesis of such haematological malignancies.

CASE PRESENTATION

In 2005, a 40-year-old man was referred to our hematologic department for asthenia, shortness of breath, and severe anemia (Figure 1). His medical history revealed nothing significant and laboratory tests showed severe anemia with normal platelets and leukocyte counts, vitamins and iron levels, and liver and kidney function. Abdomen ultrasound and chest X-ray were also negative. Bone marrow biopsy and aspirate evaluation showed a slightly hypercellular marrow, with significant erythroid dysplasia and less than 5% CD34+ precursors. Cytogenetic analysis was positive for del (5) (q15q31) and molecular tests were negative for BCR/ABL and JAK2 V617F mutations. The patient was therefore diagnosed with 5q- Syndrome and stratified as low risk according to the international prognostic scoring system (IPSS). Given inadequate erythropoietin serum levels (200 mU/mL) erythropoietin alfa administration was started and interrupted after 5 months because of loss of response. Since September 2007, the patient has been transfusion dependent (1 - 2 packed red blood cells monthly) and iron chelation with oral deferasirox (30 mg/kg/day) was initiated. Beginning in November 2007, the patient received lenalidomide 10 mg per day orally for 21 days every 4 weeks. After 4 cycles of therapy, bone marrow re-evaluation showed haematological and cytogenetic complete remission of disease (Figure 1). In June 2010 the patient lost hematologic response, developing mild anemia and displaying 5q-deletion at cytogenetic and erythroid dysplasia at bone marrow evaluation. Lenalidomide was continued until December 2010 when the patient became frankly pancytopenic (Figure 1). Bone marrow analysis showed the presence of 15% myeloid blasts infiltrate (CD13+, CD33+, CD34+, CD117+, HLA-DR+, CD45+, MPO+ at flow cytometry) and 53% NK blasts cells with cytoplasmic vacuolization and blebbing (CD34-, CD117-, CD4+, CD38+, CD33+, CD123+, HLA-DR+, CD7+/-, CD13+/-, CD56+/-, CD57+/-). Cytogenetic analysis showed del5q positivity on 22 metaphases and del3p, del5q, and der17 with t (1;17) on 2 metaphases. Induction therapy according to "3 + 7" scheme was performed with no response (December 2011) and bone marrow re-evaluation showed 90% mixed infiltrate of myeloblasts (30%) and elements with lymphoid-like appearance (70%). In March 2012, an excavated lesion appeared in the intergluteal region; skin biopsy demonstrated neoplastic cells expressing CD4, CD56, and CD68, consistent with the diagnosis of blastic plasmacytoid dendritic cell neoplasm. Total body computed tomography (CT) scan demonstrated a solitary nodule in the right lower lung lobe, multiple thoracic and abdominal lymph nodes, and enlarged spleen (20 cm diameter). Positron emission tomography (PET) showed increased uptake at the lung lesion level. Lesion biopsy was not performed because of elevated haemorrhagic risk. Chemotherapy according to the hyper-CVAD (hyperfractionated cyclophosphamyde, doxorubicine, vincristine, dexametazone) scheme was started with no response at first recovery (40% marrow blasts with unchanged immunophenotype). In May 2012, a chest CT was performed because of persistent cough and fever, showing an enlarged nodule in the right medium lung lobe, with ground-glass interstitial alterations and massive pleural effusion (fluid analysis showed a transudate, and cultural and flow cytometry tests were negative), which responded to broad-spectrum antibiotics and antifungal systemic therapy. In August 2012, an allogeneic matched related donor PBSC transplant was performed after TBV conditioning. The clinical course was complicated by septic shock and severe veno-occlusive disease leading to lung failure and death.

DISCUSSION

This case report describes a typical 5q- syndrome, transiently responsive to erythropoietin and then successfully treated with lenalidomide until response. The 5q deletion invariably affects the q31 to q33 bands, leading to RPS14, EGR1, and SPARC haplo-insufficiency which induces a P53-dependent erythroid proliferation/differentiation block. In these cases, haplo insufficiency of two microRNAs, mir145 and mir146a, may also lead to dysmegakaryopoiesis and thrombocytosis [4,5]. After losing response to lenalidomide, the patient progressed to AML and concomitantly developed BPDCN. This rare and heterogeneous disease, characterized by a CD4+CD56+ and CD3-CD20-MPO-CD33- phenotype, usually responds to polychemotherapy but relapses within a year [6]. As observed for our patient, up to 20% of BPDCN are associated with or develop after myeloid disorders [7], leading to the hypothesis of a

Table 1. Genes influenced by lenalidomide (modified from Belickova and collaborators [13]).

Genes up-regulated by lenalidomide	Genes down-regulated by lenalidomide
ARPC1B Actin related protein 2/3 complex, subunit 1B Activator and substrate of aurora A kinase functioning in centrosomal homeostasis	*TNF* Tumor necrosis factor Cytokine involved in regulation of a wide spectrum of biological processes
RN28S1 RNA, 28S ribosomal 1 Portion of 1 rDNA repeat that encodes a 28S rRNA	*CCL3L1* Chemokine (C-C motif) ligand 3-like 1 Cytokine involved in immunoregulatory and inflammatory processes
ERP29 Endoplasmic reticulum protein 29 Processing of secretory proteins within endoplasmic reticulum	*CCL3* *Chemokine (C-C motif) ligand 3* Plays a role in inflammatory response through binding to the receptors CCR1, CCR4, and CCR5
NCF1 Neutrophil cytosolic factor 1 Cytosolic subunit of neutrophil NADPH oxidase	*IL-1β* Interleukin-1, beta Cytokine involved in inflammatory response, proliferation, differentiation, and apoptosis
VNN2 Vanin 2 It may play a role in oxidative-stress response	*IER3* Immediate early response 3 The protection of cells from Fas-induced or tumor necrosis factor type alpha–induced apoptosis
CRTAP Cartilage associated protein It may influence the activity of the cytohesin/ARNO family in response to specific cellular stimuli	*CD83* CD83 molecule May play significant role in antigen presentation or cellular interactions
HIST1H2AC Histone cluster 1, H2ac Member of the histone H2A family. Histones play a central role in transcription regulation, DNA repair, DNA replication and chromosomal stability	*TNFAIP3* Tumor necrosis factor, alpha-induced protein 3 Gene induced by TNF
ALDOA Aldolase A Glycolytic enzyme	*JUN* Jun protooncogene Interacts directly with specific target DNA sequences to regulate gene expression
CXCR4 Chemokine (C-X-C motif) receptor 4 Specific receptor for stromal cell-derived factor-1	*CXCL2* Chemokine (C-X-C motif) ligand 2 Chemotactic cytokine involved in angiogenesis and attraction of immune cells
EEF1G Eukaryotic translation elongation factor 1 gamma Responsible for enzymatic delivery of aminoacyl tRNAs to the ribosome	*DUSP2* Dual specificity phosphatase 2 Negative regulator of members of MAPK family associated with cellular proliferation and differentiation

very early common progenitor. A link between previous lenalidomide treated myeloid neoplasm and BPDCN development may be therefore hypothesised. Lenalidomide is an immunomodulatory drug with several mechanisms of action, including angiogenesis inhibition, cytokine modulation, apoptosis induction, inhibition of growth and cell adhesion, increase of T cells and NK cells via stimulation of dendritic cells [8]. The exact mechanisms of action in MDS 5q- have not been completely understood; it has been proposed that lenalidomide primarily targets actively cycling cells in the del(5q) clone by inhibiting haplodeficient phosphatases encoded within the proximal common deleted region (5q31), resulting in cell-cycle arrest and apoptosis [9]. A second proposed mechanism involves protein p53, which is overexpressed in erythroid precursors of primary del(5q) MDS patients. In del(5q) MDS, disruption of ribosome integrity liberates free ribosomal proteins to bind to and trigger degradation of mouse double minute 2 protein (MDM2), with consequent p53 transactivation. Lenalidomide is able to stabilize MDM2, thereby accelerating p53 degradation [10]. Since lena-

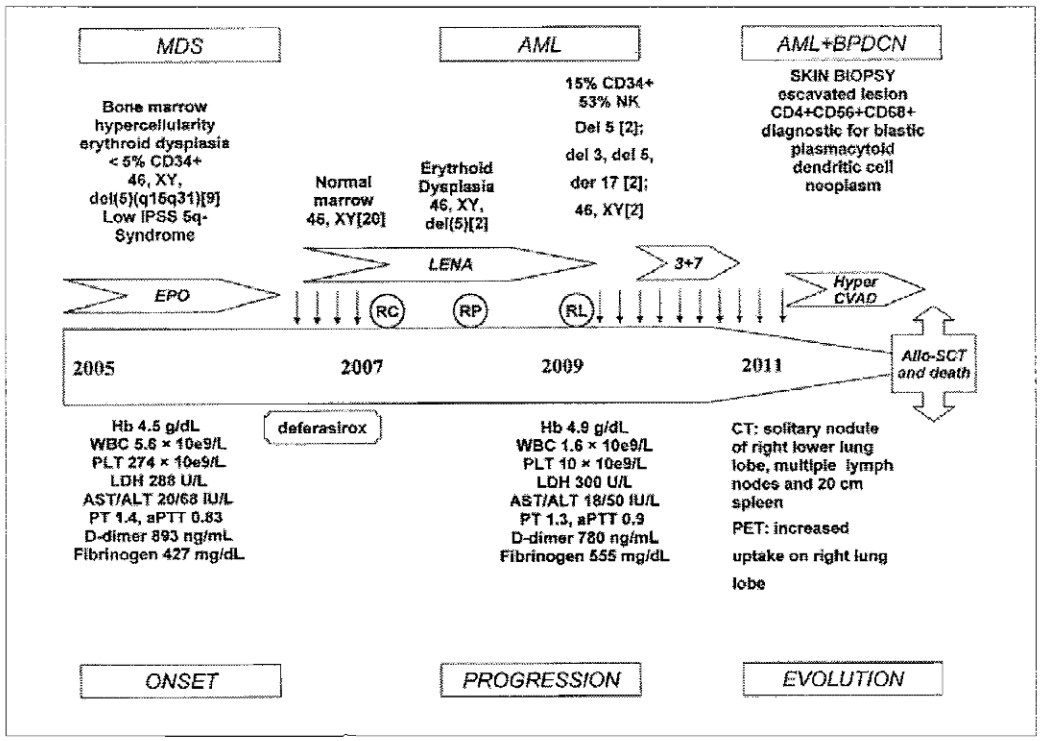

Figure 1. Patient's laboratory and clinical evaluation over time.

MDS - myelodysplastic syndrome, AML - acute myeloid leukemia, BPDCN - blastic plasmocytoid dendritic cell neoplasm, IPSS - international prognostic scoring system, EPO - erythropoietin, LENA - lenalidomide, 3 + 7 - daunorubicine for three days plus cytarabine for seven days, Hyper-CVAD - hyper fractionated cyclophosphamyde plus vincristine, doxorubicine, dexametazone. RC - complete response; RP - partial response; RL - response loss.

lidomide has been associated with occurrence of secondary malignancies [11,12], the involvement of the drug in our patient's oncogenesis cannot be excluded, and some mechanisms, potentially responsible for this effect, can be hypothesized. First, lenalidomide increases the expression of the *ARPC1B* gene, an activator and a substrate of aurora A whose overexpression leads to polyploidy and chromosomal instability. Moreover, *ARPC1B* regulates the centrosome integrity and has been described as a regulator of cell cycle [13]. Second, AML evolution in MDS is thought to be due to clonal selection through acquired chromosomal aberrations and lenalidomide, while suppressing the indolent 5q-clone, may allow for a more aggressive leukemic clone to expand.

It has been shown that there is persistence of rare, but distinct malignant stem cells harbouring the 5q- in patients even in complete remission after lenalidomide treatment. These cells may lead to relapse and clinical and cytogenetic progression. Cell-cycle quiescence and presence of multidrug-resistance efflux pumps are key mechanisms of tumor escaping. In this context, it has been hypothesized that lenalidomide may accelerate clonal evolution and transformation of persistent MDS stem cells [9].

Another observation is that a proportion of patients with low-risk MDS and an isolated del(5q) have *TP53* mutated BM progenitors that render them at higher risk for disease progression. The acquisition of *TP53* mutations confers a poor prognosis in several hematologic malignancies, including acute myeloid leukemia and myelodysplastic syndromes and is frequently observed also in blastic plasmacytoid dendritic cells neoplasm [14,15]. Lenalidomide, stabilizing MDM2, accelerates p53 degradation, reduces its tumor suppressor activity, and represents a potential facilitating factor for tumor progression/induction.

Furthermore, immunocompromised hosts are considered to be at increased risk for development of several lymphomas and other neoplasms, so the occurrence of

the double haematological malignancy in our patient may be associated to the severe immunodeficiency state induced by both MDS and lenalidomide therapy. Finally, it has been shown that lenalidomide up-regulates and down-regulates several genes (Table 1) [13]; we might speculate that there are other genes, not yet identified, stimulated or inhibited by lenalidomide, that may play a role in clonal evolution/progression.

In the patient described, AML evolution and BPDCN may have originated through various mechanisms, including the persistence of myeloid neoplastic stem cells resistant to lenalidomide and the selection of a more aggressive clone via lenalidomide augmentation of the ARPC1B gene. Moreover, the known stimulatory effect of lenalidomide on dendritic cells may have triggered the expansion of malignant plasmacytoid dendritic cells from a shared common myeloid clone, contributing to BPDCN evolution. Further studies are needed to clarify the oncogenic potential of lenalidomide in myeloid neoplasms and its effect on the development of rare malignancies like BPDCN.

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Declaration of Interest:

Authors have no personal relationships between themselves and others that might bias their work to disclose. 1) There are no relevant conflicts to the contents of the article for any authors. 2) There was no involvement of a pharmaceutical/other company.

Authorship:

All authors have made substantial contributions to the conception and design of the study, to the acquisition and interpretation of data, and to the article drafting. Finally, all authors revised the paper for important intellectual content and approved the final version to be submitted.

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