Clinics in Oncology

Case Report
Published: 28 Jun, 2022

Q-Box Region Deletion of the ATRX Gene is Linked to Acquired α-Thalassemia Myelodysplastic Syndrome (ATMDS)

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Abstract

Acquired a-Thalassemia Myelodysplastic Syndrome (ATMDS) is a very rare form of acquired thalassemia defined by a down-regulation of α globin synthesis in a myelodysplastic context. Herein we present the case of an 87-year-old man with myelodysplastic syndrome and a progressive microcytic anemia highlighted during his biological check-ups carried out over the years. Eventually, a rare ATRX gene mutation on exon 35 leading to a premature stop codon (p.R2407*) is found confirming that carboxyl domain deletion is tightly linked to ATMDS phenotype. Moreover, this case provides further support that EPO long term treatment seems to work well with MDS presenting ATRX mutation, but larger studies need to be conducted on MDS patient cohort to evaluate the impact of these mutations on disease evolution and prognosis.

Keywords: ATMDS; ATRX; Microcytosis

Introduction

Acquired a-Thalassemia Myelodysplastic Syndrome (ATMDS) is a very rare form of acquired thalassemia defined by a down-regulation of α globin synthesis in a myelodysplastic context.

This syndrome is characterized by somatic point mutation or splicing defect in a particular gene located on the X chromosome [1], the ATRX gene involved in some mental retardation state [2].

Indeed, the ATRX gene code for a chromatin remodeling factor belonging to the SNF2 family whose constitutional mutations result in ATR-X syndrome [3] or alpha thalassemia associated with mental retardation. Somatic mutation is associated with ATMDS. There is a greater male predominance (sex ratio 5:1) in this disease and α-thalassemia is more severe in patients with ATMDS than ATR-X but the explanation still remains unclear nowadays [2,4]. Furthermore, ATMDS geographical distribution isn't overlapping with α-thalassemia inherited form location as it seems that most cases are seen in North European patient [5]. Herbaux et al. [6] also showed that ATRX gene mutation frequency is very low in MDS patient (less than 1%) but microcytosis detection seems to play a key role to detect ATRX mutation.

Currently, more than 150 mutations have been described in the literature, mostly missense mutations [3]. There is two domain located at the ATRX carboxyl terminus that have potential great value for the protein, the P domain which is highly conserved in SNF2 protein family and the Q domain, a glutamine-rich region useful for protein-protein interaction [7].

Here we describe a rare nonsense mutation resulting in Q-box abolition leading to ATMDS.

Case Presentation

An 87-year-old male was followed since 2015 for medical events that are not necessarily related to each other. Indeed, he presented very expansive shingles in 2015 and then a bilateral tendinitis of the shoulders which was treated by systemic corticosteroid therapy in 2016. From 2015 to 2018 he was very tired but there has been no weight loss.

On the biological tests carried out regularly, there was a progressive decrease in his hemoglobin level which has gone from 13.5 g/dl to 11.4 g/dl (normal values: 13 g/dl to 17 g/dl) between 2015

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Received Date: *28 May 2022*
Accepted Date: *20 Jun 2022*
Published Date: *28 Jun 2022*

Citation:
Chea M, Badens C, Brun S, Gris JC, Jourdan E. Q-Box Region Deletion of the ATRX Gene is Linked to Acquired α-Thalassemia Myelodysplastic Syndrome (ATMDS). Clin Oncol. 2022; 7: 1928.

ISSN: 2474-1663

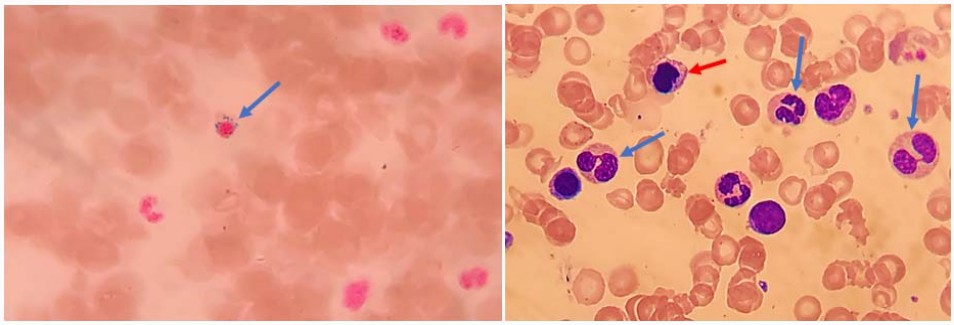

Figure 1: A) Bone aspirate with Perls coloration. Blue arrow shows a ring sideroblast. B) Bone marrow with May-Grünwald Giemsa coloration. Blue arrows show dysgranulopoiesis and red arrow dyserythropoiesis.

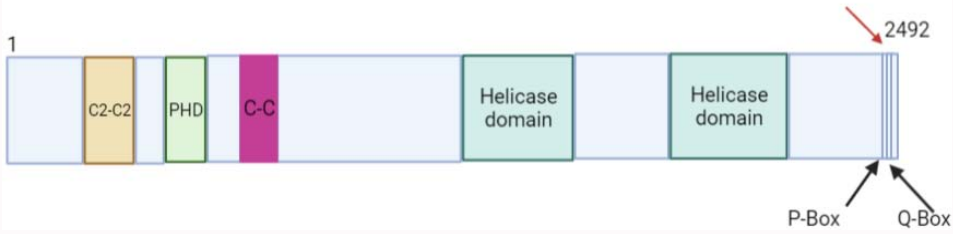

Figure 2: ATRX protein schematic representation (not at scale) adapted from Picketts et al. [7].
C2-C2 is a zinc finger domain; PHD a cysteine-rich PHD-like finger; CC a coiled-coil structure; P-box a highly conserved region in other SNF2 family and Q a glutamine-rich region. Red arrow shows our patient mutation on exon 35 and its protein location p.R2407*.

and 2018, with a progressive decrease in his MCV up to 78 fL (normal values: 82 fL to 98 fL) and therefore an anemia with a microcytic tendency with no iron deficiency. In parallel with the decrease in hemoglobin, a very slow reduction in platelet count is also observed up to 112 G/L (normal values: 150 G/L to 400 G/L).

A bone marrow aspirate was performed in order to identify an underlying hemopathy and it revealed a multi-lineage dysplasia with the presence of ring sideroblast (Figure 1). Karyotype was also normal without any clonal rearrangements.

Since then, the patient was under EPO treatment and regular follow-up. However, despite bone marrow exploration, no explanation was given for the persistent microcytic anemia associated with dysplasia.

In 2021, to explore more deeply this anemia, a hemoglobin electrophoresis was performed and showed a decrease in hemoglobin A2 to 1.6% (normal values: 2, 2-3, 2%). Unfortunately, no supravital staining was performed with electrophoresis.

As a result, the most likely assumption in front of this combination of microcytic anemia, myelodysplasia and decrease in hemoglobin A2 is a very rare form of acquired thalassemia named α-thalassemia-myelodysplastic syndrome or ATMDS. To support this hypothesis, a genetic analysis was performed at Timone Hospital, Marseille, France to seek for specific mutations (Ion torrent®, ThermoFischer) found in the ATRX gene which code for the chromatin remodeling factor ATRX.

Finally, bone marrow genetic analysis highlights a nonsense mutation p.R2407* taking place in ATRX gene present in 65% of cells and already describe twice by Costa et al. [8] and Herbaux et al. [6]. This mutation leads to a premature stop codon between the P and the Q-box suggesting a deficient ATRX protein.

Eventually, patient's case was presented in a multidisciplinary meeting during which a long-term EPO treatment was decided in view of its effectiveness on patient's anemia.

Discussion

In this case we provide further support to highlight the essential role of carboxyl region in ATRX gene. Indeed, many mutations are common in ATMDS and ATR-X but there is some that are mostly found in ATMDS like carboxyl region missense or nonsense mutations. In Figure 2 we represent the main region of interest and our mutation location.

This specific mutation leads to a premature stop codon between the P-box and a glutamine-rich domain known as a protein-protein interacting region and which is highly conserved between species. Since the first description of this mutation by Costa et al. in 2006, only Herbaux et al. [6] cited this nonsense mutation in a CMML patient who died from AML at the end. Here we confirm that Q-box abolition leads to ATMDS as it suppresses an important region for the ATRX protein. Currently, the regulating role of ATRX and its involvement in ATMDS has been extensively studied. Indeed ATRX loss of function results in an inappropriate silencing of α-globin expression during erythropoiesis [9].

Nevertheless, there remains the mutation prognostic question on the clinical evolution of the patient. Indeed, they are generally associated with poor prognosis in acute myeloid leukemia according to Serrano et al. [10]. Herbaux et al. [6] highlight that in MDS patient, patients with ATRX mutations seems to have a more sustainable response to EPO than MDS patients with no mutation. In our case, MDS diagnosis was done in 2019 (but anemia started in 2015) and the patient still respond to EPO in 2022 with stable clinical state. These findings seem to correlate with the fact that MDS patient with ATRX mutation respond better to EPO treatment, but it is clearly obvious that larger studies need to be conducted to evaluate the prognostic

value of these mutations.

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