Case Report

Refractory Anemia with Ring Sideroblasts Associated with Marked Thrombocytosis Complicated by a Parasternal Granulocytic Sarcoma

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Abstract

Refractory anemia with ring sideroblasts associated with marked thrombocytosis (RARS-T) and granulocytic sarcoma are two rare myeloid neoplasms. RARS-T is a Myelodysplastic/Myeloproliferative Neoplasm (MDS/MPN) characterized by overlapping myeloproliferative (platelets count higher than 450x10⁹/L associated with proliferation of large atypical megakaryocytes similar than those observed in essential thrombocythemia) and myelodysplastic features (dysplastic erythroid proliferation with ring sideroblasts >15%). RARS-T molecular pattern also exhibited myelodysplastic and myeloproliferative overlap with frequent SF3B1 and JAK2 mutations, justifying its classification in MDS/MPN disorders. Granulocytic Sarcoma also referred as myeloid sarcoma or chloroma are rare extramedullary tumors of immature myeloid cells that partially or totally efface the tissue architecture. Extramedullary involvements include a large variety of clinical significant phenomena that often pose diagnosis problems. Granulocytic sarcoma may develop de novo or concurrently with acute myeloid leukemia or myeloproliferative neoplasms. However, no previous case of granulocytic sarcoma associated to myelodysplastic/myeloproliferative neoplasms has been reported. Herein, we report a case of RARS-T revealed by an asymptomatic thrombocytosis complicated by a granulocytic sarcoma ten months after initial diagnosis. This extramedullary megakaryoblastic mass invaded the sternum and the parietal soft tissues without associated myeloid leukemia.

ABBREVIATIONS

MDN: Myelodysplastic Neoplasm; MPN: Myeloproliferative Neoplasms; AML: Acute Myeloblastic Leukemia; RARS-T: Refractory Anemia with Ring Sideroblasts and Marked Thrombocytosis; GS: Granulocytic Sarcoma; ET: Essential Thrombocytosis; SF3B1: Splicing Factor 3B Subunit1

INTRODUCTION

Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) are rare clonal myeloid proliferations that show overlapping myeloproliferative and myelodysplastic features at initial presentation [1]. Refractory Anemia with Ring Sideroblasts associated with Thrombocytosis (RARS-T) is included in MDS/MPN and retained as a provisional entity of the World Health Organization classification of myeloid neoplasms (WHO 2008) [2,3]. Diagnostic criteria for RARS-T are ineffective erythropoiesis with more than 15% of ring sideroblasts and prominent myeloproliferative features with a marked thrombocytosis (higher than 450x10⁹/L) associated with the proliferation of large atypical megakaryocytes in the bone marrow. Moreover, a careful exclusion of well-defined Myelodysplastic (MDN) and Myeloproliferative Neoplasms (MPN) is essential before establishing the diagnosis of RARS-T. In particular, an exhaustive molecular and cytogenetic work-up should exclude the presence of t (9;22) or BCR-ABL transcript identifying a chronic myeloid leukemia, Acute Myeloid Leukemia (AML) defining translocations...
Here, we report a case of factors in RARS-T and are associated with a better survival [6]. A case of GS associated with RARS-T has been reported. However, no previous affected [9]. Those extra-medullary involvements often pose a diagnostic dilemma [10]. GS may develop de novo, concurrently with AML or more rarely with MPN [11].

### CASE PRESENTATION

A 57-year-old woman was referred for the exploration of an asymptomatic thrombocytosis. In January, her complete blood count showed a generative macrocytic anemia and confirmed thrombocytosis (Hemoglobin 10g/dL, mean corpuscular volume 100fL, reticulocytes 75x10^9/L, Platelets 1,500x10^9/L, leucocytes 6.5x10^9/L). The bone marrow aspirate smears showed a markedly increased number of large megakaryocytes, frequently occurring in cluster, associated with large platelet clumps. They exhibited deeply lobulated nuclei and abundant mature cytoplasm.

Emperipolesis of marrow elements in the cytoplasm of megakaryocyte was observed on the smears (Figure 1A). Otherwise, these myeloproliferative features were concomitant with a marked dysplasia in the erythroid lineage. Erythroblasts exhibited a defective hemoglobinization with laminated cytoplasm, and nuclear abnormalities (hypercondensation, nuclear lobulation). In addition, 68% of ringsideroblasts were visualized with Perls stain (Figure 1A). Finally, blasts represented fewer than 5% of nucleated cells and did not exhibit morphologic abnormalities. Moreover, the bone marrow trephine biopsy was hypercellular and revealed a proliferation of large to giant megakaryocytes occurring in loose cluster without blast excess. The network of reticulin fibers was increased, revealing a diffuse grade 2-3 myelofibrosis (Figure 1B). BCR-ABL transcript, JAK2-V617F and CALR (Calreticulin) mutations were negative.

The karyotype was normal. We identified a SF3B1 (Splicing factor 3b, subunit 1) mutation that is more supportive of a diagnosis of MDS [4]. RARS-T cases frequently harbor SF3B1 (Splicing factor 3b, subunit 1) mutations that are implicated in ring sideroblasts formation [5]. Indeed, SF3B1 mutations are found in about 20% of total MDS whereas they are strongly associated with the presence of ring sideroblasts with a frequency of 64-82% in RARS and 66-72% in RARS-T. SF3B1 and JAK2 mutations are the main prognostic factors in RARS-T and are associated with a better survival [6].

Here, we report a case of JAK2-negative RARS-T complicated with a Granulocytic Sarcoma (GS) of megakaryoblasts involving the sternum and the parietal soft tissues. GS are rare extra-medullary tumors of immature myeloid cells that partially or totally efface the tissue architecture [7,8]. Although bone, skin, or lymph nodes are the most frequent localizations, any part of the body may be affected [9]. Those extra-medullary involvements often pose a diagnostic dilemma [10]. GS may develop de novo, concurrently with AML or more rarely with MPN [11].

In November, the patient presented with sternal pain associated with rapid loss of weight and anemia (Hb 8g/dL; platelets 150x10^9/L and leucocytes 20x10^9/L without circulating blast). Computed tomography identified an osteolytic bone lesion of the inferior third of the sternum and a mass invading pectoral muscle and local soft tissues. A surgical biopsy of this mass revealed a severe fibrotic process that massively invaded the striated muscle and a proliferation of atypical cells (Figure 2). These cells were of medium to large size, with a unique large round nucleus, rarely bi-nucleated with nucleoli and a clear chromatin. Some cells were larger and exhibited megakaryoblastic differentiation. This tumoral infiltrate occurred in large clusters separated by fibrotic patches. An exhaustive immunohistochemistry study showed a high CD34 positivity and reacted with antibodies to megakaryocyte-restricted antigens CD41, CD31 and Factor VIII. All the cells strongly expressed CD41 and CD31, whereas factor VIII expression was restricted to the large atypical megakaryocytes (Figure 2). The pan-leukocyte marker CD45, myeloid (MO, CD15, CD117) and lymphoid (CD20, CD79a, CD3, CD5) antigens were absent. These features matched with a megakaryoblastic granulocytic sarcoma. The concomitant bone marrow aspirate did not show evidence of blast excess.

Induction chemotherapy with idarubicin and ara-cytarabine resulted in a rapid decrease of the sternal mass on CT scan. However, nine months later, the patient presented with a mandibular osteolytic bone lesion and femoral neck fracture treated by surgical osteosynthesis with hip screw. Histological analysis of the surgical reaming products revealed an infiltration by megakaryoblasts, exhibiting the same phenotype as previous sternal tumor. This relapse of granulocytic sarcoma was treated...
Since 2008, RARS-T is morphologically defined by a combination of objective signs of erythroid dysplasia (ring sideroblasts) and megakaryocytes with proliferative pattern. On the molecular level, recent sequencing studies have identified the role of RNA-splicing machinery in the pathogenesis of MDS [17,18]. Thus, mutations in the SF3B1 gene are involved in the formation of ring sideroblasts and are found in about 80% of cases of RARS-T [5,19,20]. Furthermore, the JAK2-V617F mutation is found in over 60% of RARS-T, regardless of SF3B1 mutations [19,21]. The frequency of CALR mutations in RARS-T seems to be lower than in ET or primary myelofibrosis [17]. TET2, ASXL1 and EZH2 mutations show similar frequencies as those observed in MDS and a higher occurrence of DNMT3A has been reported in RARS-T [17,22]. JAK2-V617F and SF3B1 are independent factors associated with better prognosis and a higher median survival whereas ASXL1, DNMT3A and EZH2 mutations are associated with poorer outcomes [6,22]. Concordantly, our case of JAK2-negative RARS-T presented an unfavorable outcome with an early transformation in GS and therapeutic failure.

Finally, the prognosis of patients with RARS-T is more pejorative than ET, justifying a systematic Perls staining in the assessment of thrombocytosis, particularly if it is associated with erythroid dysplasia. Indeed, AML rarely complicates ET, particularly in patients younger than 60 years old [23]. In this report, the proliferation of dysplastic megakaryocytes on bone marrow biopsy, severe thrombocytosis (>450x10^9/L) fulfilled the diagnostic criteria of ET. However, the identification of >15% of ring sideroblasts, together with the SF3B1 mutation provide evidence in the diagnosis of RARS-T.

RARS-T transformation in a granulocytic sarcoma is an exceptional condition. Megakaryoblastic GS can rarely complicate ET with frightening outcome [24]. However, to our knowledge, the association of RARS-T with GS has never been described. The diagnosis of GS is often difficult and requires an histological study with comprehensive immunochemistry [10]. In this case, CD34 and CD41 positivity enabled the diagnosis of megakaryoblastic GS without bone marrow involvement. CD34 and CD41 are found positive in 74% and 90% of megakaryoblastic leukemia respectively, but the lack of other myeloid markers is unusual [25]. CD31 and Factor VIII, also known as endothelial markers, can be used to detect normal and atypical megakaryocytes [26]. Megakaryoblastic GS is generally localized in bones and adjacent soft tissues [24,27]. Thus, GS has to be suspected when facing an isolated lytic bone lesion in the context of known MDS/MPN, even without biological signs of leukemic transformation. The diagnosis of GS requires intensive treatment whatever the bone marrow status because of their constant transformation in AML [28].

CONCLUSION

RARS-T is a very rare myelodysplastic/myeloproliferative disorder. Perls staining may be systematic for the assessment of thrombocytosis, especially in association with dyserythropoiesis, in order to exclude the diagnosis of RARS-T. Today, the prognosis of RARS-T depends on the presence of the JAK2, SF3B1 and ASXL1 mutations.
REFERENCES