



Bladder Myeloid Sarcoma with *TP53* mutated Myelodysplastic Syndrome/Myeloproliferative Neoplasm Overlap syndrome: Response to Decitabine-Venetoclax regimen

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ARTICLE INFO

Keywords:

Myeloid sarcoma
MDS/MPN overlap
TP53 mutation
Decitabine-venetoclax
Hematopoietic stem cell transplantation

ABSTRACT

Myeloid sarcoma (MS) is a rare extramedullary blast proliferation of immature cells of myeloid origin. It is commonly associated with acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or myeloproliferative neoplasm (MPN), and may precede, coincide with, or follow the diagnosis of a myeloid disorder. MS treatment is controversial, but AML induction like regimens is usually recommended. We present an unusual case of *de novo* *TP53* mutated MDS/MPN overlap with bladder MS. Due to the high-risk nature of the disease, the patient was induced with decitabine and venetoclax combination therapy, resulting in complete remission. The response was further consolidated by an allogeneic hematopoietic stem cell transplantation.

1. Introduction

Myeloid sarcoma (MS), also referred as granulocytic sarcoma or chloroma, is a rare extramedullary blast proliferation of one or more myeloid lineages [1]. It mostly presents as an extramedullary manifestation of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or myeloproliferative neoplasm (MPN). MS is described in approximately 9% of patients with AML as an early manifestation of the disease, or in the relapsed setting; observed frequently after allogeneic hematopoietic stem cell transplantation (allo-HCT). Rarely, MS develops as an isolated lesion, with a wide variation of size and location, accounting for 2 cases per million adults [2]. The most common sites of MS involvement are the skin/breast (11–46%) and connective tissues (31–35%). Other sites that are less frequently involved include bone, head and neck, and organs of the gastrointestinal, cardiopulmonary, reproductive, urinary, and central nervous systems [3]. MS is a pathological diagnosis which is supported by clinical presentation and radiologic findings when applicable. Molecular abnormalities are prevalent in 54–70% of MS cells [4], including *NPM1*, *NRAS*, *t(8;21)*, *TET2* and *FLT3-TKD* mutations, however, no definitive association was found between the occurrence of MS and detection of AML cytogenetic abnormalities [5].

Due to the lack of randomized trials (RCTs), MS treatment is

controversial and dictated by the patient's age, symptoms, and performance status, as well as the tumor site and size. Systemic therapy classically includes anthracycline and cytarabine-containing regimens, as almost all patients are likely to develop systemic disease and progress to acute leukemia if left untreated [4]. While isolated lesions benefit from intensive AML-like chemotherapy followed by consolidation with radiation therapy, relapsing lesions and those with concurrent bone marrow involvement mostly necessitate the consideration of an allo-HCT [6]. In this report, we present an unusual case of a patient who developed bladder MS with a concurrent diagnosis of *de novo* *TP53* mutated MDS/MPN overlap; successfully treated with decitabine and venetoclax combination.

2. Case

A 63-year-old man, with unremarkable past medical history, except for generalized anxiety disorder, presented to his primary care physician with complaints of worsening shortness of breath on exertion and lightheadedness. Work up at that time revealed macrocytic anemia (Hb = 10 g/dL; MCV = 113.4), with normal folate and vitamin B12 levels. Thyroid function tests were consistent with hypothyroidism (TSH = 14.96; free T4 = 0.79) which prompted the initiation of levothyroxine treatment. Other test results included normal white cell count (5.2 ×

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<https://doi.org/10.1016/j.lrr.2021.100286>

Received 7 October 2021; Received in revised form 4 December 2021; Accepted 13 December 2021

Available online 14 December 2021

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$10^9/L$), platelets ($179 \times 10^9/L$), and a slightly elevated LDH (236 U/L). One month later, new symptoms of bilateral leg pain developed, and lab studies revealed a hemoglobin of 6.7 g/dL with neutropenia (Neutrophils = 26%; ANC = 1.5) and eosinophilia (Eosinophils = 28%; AEC = 1.3). A subsequent bone marrow biopsy revealed a hypercellular marrow with 15% excess blast and marked interstitial eosinophilia (15.2%), consistent with MDS/MPN overlap. Erythropoiesis was qualitatively megaloblastoid and hemoglobinization was impaired. Granulopoiesis was increased with left-shift and abnormal maturation. Megakaryocytes were increased, atypical, varying in size, and multinucleated in appearance. Myelofibrosis was also present. Karyotyping showed complex cytogenetics including monosomies 18, 19, 21 and structural abnormalities of 5q/7q. A *TP53* mutation with a variant allele frequency of 34% was detected by next generation sequencing of myeloid mutation panel.

Consequently, decitabine chemotherapy (20 mg/m² of decitabine for 5 days) was started for the treatment of high risk MDS. Three days into the first cycle, the patient presented with severe lower abdominal pain, hematuria, and difficulty urinating. Pelvic MRI showed an asymmetric circumferential bladder wall thickening and a bladder mass along the left wall resulting in mild bilateral hydronephrosis. Cystoscopy revealed a mass of tan/yellow to brown tissue occupying two-thirds of the bladder space. The patient underwent a partial resection of the bladder mass and the biopsy showed a patchy myeloid infiltrate composed of histiocytes, eosinophils, neutrophils, and occasional atypical mononuclear cells, as well as dilated vessels (Fig. 1a). The diagnosis was consistent with extramedullary myeloid leukemia, or MS expressing CD68 in areas of prominent histiocytic infiltrate (Fig. 1b) and strongly positive for myeloperoxidase (MPO) in patchy areas of histiocytes and granulocytes (Fig. 1c). Additional histochemical staining revealed CD33 staining in a similar pattern to MPO, in addition to CD34 highlighting vascular structures and rare blast-like cells. CD117 highlighting occasional scattered mast cells were also observed. Upon this new diagnosis of MS, an AML-defining illness, a repeat bone marrow biopsy was performed for baseline disease evaluation within 2 weeks of the first cycle of decitabine therapy. Bone marrow biopsy showed a trilineage hematopoiesis, hypercellular marrow with atypical megakaryocytes and a residual myeloid clone, but no evidence of increased blasts. Accordingly, the patient was re-admitted for induction with a combination of decitabine and venetoclax, a moderately aggressive approach warranted by the extramedullary leukemia to increase the depth of response. This combination regimen consisted of 20 mg/m² of decitabine for 5 days and a ramp up of venetoclax (100 mg → 200mg → 400 mg)– 400 mg once

daily for 28 days. The regimen was well tolerated without complications and the patient reported a major improvement in urinary symptoms. The response was further supported by MRI findings that showed a milder thickening of the bladder wall measuring up to 1 cm in its greatest width, after only one cycle of combined treatment. Cycle 3 was delayed by 2 weeks due to cytopenia. The patient continued to receive the decitabine and venetoclax combination. Considering the high-risk cytogenetics and *TP53* mutation, an allo-HCT was planned. The patient received total of 5 cycles while waiting for a suitable donor. Repeat bone marrow biopsy confirmed complete remission with complete cytogenetic response. A repeat MRI of the abdomen and pelvis showed complete resolution of the bladder wall thickening and hydronephrosis. In the absence of suitable match related and match unrelated donors, the patient subsequently received a haploidentical HCT with reduced intensity conditioning, utilizing his nephew as a donor. The post-transplant course was notable for grade 1 cytokine release syndrome requiring 2 doses of tocilizumab, a mild acute pulmonary edema secondary to aggressive hydration which was managed by diuresis, and a concern for an infectious/inflammatory process which resolved after a 7-day course of azithromycin. Disease evaluation on day+30 showed a normocellular bone marrow biopsy with trilineage hematopoiesis and no definite morphologic evidence of myeloid neoplasm. Chimerism analysis of the peripheral blood showed a CD3-positive fraction containing approximately 95% donor DNA, and a CD33-positive fraction with 100% donor DNA. Meanwhile, the bone marrow chimerism was 100% donor DNA. Subsequent evaluation on day +60 yielded the same chimerism analysis. The patient is planned to receive low dose decitabine at 15 mg/m² for 3 days every 4 weeks with venetoclax as post-transplant maintenance therapy after day +100.

3. Discussion

Only 2–7% of the reported MS cases involve the kidney or urinary system [7]. Those cases vary in clinical presentation between hematuria, dysuria, lower abdominal pain, flank pain, fatigue, incontinence, and urinary retention. Bladder MS tumor was described in the bladder trigone, base, or left anterolateral wall, and is usually preceded by an initial diagnosis of a hematological disorder [8]. Commonly expressed markers detected on immunophenotyping of paraffin sections include the monocytic marker CD68, marker for immature blast CD34, as well as markers for myeloid (CD13, CD33, CD117, and MPO) and monoblastic (CD14, CD163, and CD11c) differentiation. Notably, 66–69% of MS masses express MPO, a marker of granulocytic activity, which helps differentiate them from lymphoma [3].

Very rarely, isolated MS develops without a preceding or concurrent diagnosis of AML or MDS/MPN; however, most of the documented cases of primary MS report the development of acute leukemia shortly after, within a median time of 7 months [6]. Therefore, it is recommended to treat MS with AML-like induction chemotherapy [6]. An optimal treatment for MS has not been established yet, partly because patients with MS are usually excluded from RCTs investigating new AML treatment regimens. Moreover, the rarity of MS precludes conducting large RCTs. Much of the available knowledge is extrapolated from retrospective studies and registry analyses. Common practice dictates the use of remission-induction chemotherapy regimens commonly used for AML treatment, including idarubicin and cytarabine (IA), FLAG (fludarabine, cytarabine, idarubicin and granulocyte colony-stimulating factor (G-CSF)), CAT-G (cyclophosphamide, cytarabine, topotecan and G-CSF), and daunorubicin plus cytarabine (3 + 7) [6]. A considerable interest in hypomethylating agents has emerged, such as decitabine and 5-azacitidine, for the treatment of elderly patients with AML or patients with high-risk chemo-resistance phenotype. Decitabine, a deoxynucleoside analogue of cytidine, is an S-phase specific agent that works by selectively inhibiting DNA methyltransferases, which leads to DNA hypomethylation and subsequently re-expression of the silenced cellular differentiation genes at low doses, and cytotoxicity at high doses. Only a

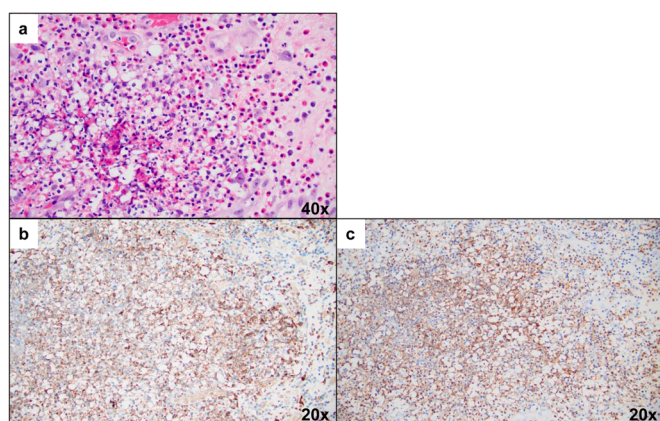


Fig. 1. Pathological findings of the urinary bladder mass biopsy: (a) Fragments of bladder mucosa and submucosa with multifocal cellular infiltrate composed of histiocytes, eosinophils, and neutrophils (hematoxylin-eosin staining; magnification 40x); Immunohistochemistry showing positive staining for (b) CD68 marking abundant histiocytes (magnification 20x) and (c) myeloperoxidase highlighting myeloid differentiation in neoplastic cells (magnification 20x).

few case reports demonstrate the efficacy of decitabine in the treatment of MS [9], mainly in patients ineligible for standard induction chemotherapy. Interestingly, after 2–4 cycles, decitabine induced long-term durable remissions in the reported cases. Conversely, in a study by Byrd et al., early chemotherapy given to nine patients with MDS-associated MS was not shown to prolong survival, with a median survival of 36 weeks [10], which further accentuates the controversy in MS treatment. Moreover, specific post-remission protocols and the role of allo-HCT in the setting of isolated primary MS, are yet to be deciphered. The choice of a regimen should be personalized based on the timing of MS presentation (isolated, with AML, or at relapse), as well as patient's age, fitness, prognosis, and comorbidities. Radiation therapy is another possible consolidation treatment, but this approach largely depends on the radiation site and associated toxicities.

Decitabine or azacitidine and venetoclax combination therapy has been a paradigm shift in the management of patients with AML who are not eligible for intensive therapy. This regimen is also being explored in patients with high-risk disease, after yielding promising results from Phase I study. The case presented here illustrates a rare presentation of MS as a bladder mass concurrent with a diagnosis of *de novo* MDS/MPN overlap (*TP53* mutated). The excess blast on bone marrow biopsy and the high-risk cytogenetics were suggestive of an evolving AML. Decitabine and venetoclax induction regimen was efficient in inducing a complete remission, warranting consolidation with an allo-HCT to potentially improve the long-term outcome.

In conclusion, MS should be considered in the differential diagnosis of suspicious masses or atypical cellular infiltrates with or without bone marrow involvement, warranting immunohistochemical studies for confirmation. AML induction chemotherapy regimens remain the standard of care for MS remission; however, the best modality for post-remission therapy is yet to be investigated. The choice between chemo- and radiotherapy as well as the role of allo-HCT for consolidation should be individualized based on the patient's risk, performance, and the extent of disease involvement. Future prospective RCTs inclusive of patients with MS are needed to clarify the best approach to this

disease and study the efficacy of novel targeted therapies in MS management.

Conflict of interest and financial disclosure statement

Talha Badar reports receiving honoraria from Pfizer-hematology and Oncology. Received Mayo Clinic Cancer Center Support Grant (CCSG) (P30 CA015083)

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