CORRESPONDENCE

Obstructive Uropathy as an Initial Presentation of Primary Myelofibrosis: Case Report and Review of Literature

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Abstract Primary myelofibrosis (PMF) is a rare hematological disorder associated with progressive cytopenia and extra-medullary hematopoiesis. Acute kidney injury in this disease has been reported from diverse etiologies such as renal and peri-renal extramedullary hematopoiesis and tumor lysis syndrome. We report a patient who presented with obstructive uropathy from uric acid stones who was incidentally diagnosed with PMF during workup for persistent thrombocytosis and leukocytosis. Marrow histopathology was unique in presenting features of early PMF despite clinical picture mimicking essential thrombocythemia. Despite a common background of hyperuricemia in myeloproliferative neoplasms, AKI resulting from urate nephrolithiasis has seldom been reported in PMF. Published data on this association and clinical management is reviewed briefly.

Keywords Primary myelofibrosis · Obstructive uropathy · Renal calculi · Acute kidney injury

Dear editor,

Renal involvement has rarely been reported in myeloproliferative neoplasms (MPN) which are diverse clonal bone marrow (BM) disorders and include chronic myeloid leukemia, essential thrombocythemia (ET), polycythemia

vera (PV) and primary myelofibrosis (PMF) that typically cause myelofibrosis, extramedullary hematopoiesis leading to hepatosplenomegaly and leukemogenesis if untreated [1–5]. We present an interesting case report of acute kidney injury (AKI) in a patient who was subsequently diagnosed with PMF. Informed consent was taken from patient prior to publication. The index case was a 60 year old male farmer with no significant past medical history and normal baseline renal function who presented with anuria for 2 days. Patient noticed progressive fatigue, pruritus, intermittent episodes of gross painless hematuria and abdominal discomfort since the last 2 months. Examination revealed a cachectic patient, fully oriented with pulse 100/min, BP = 142/80 mmHg RR = 18 breaths/min and O₂ saturation 94 %. Physical examination was unremarkable except for massive hepatosplenomegaly. Hematological and biochemical tests on presentation (Table 1) suggest thrombocytosis, leuco-erythroblastosis, hyperkalemia, anion gap metabolic acidosis and acute kidney injury (AKI) associated with mild hyperphosphatemia and hyperuricemia. Sonogram and non-contrast CT abdomen confirmed hepatosplenomegaly and bilateral renal pelvis and ureteral stones with bilateral hydronephrosis. Urgent cystoscopy followed by retrograde urography with bilateral double ureteral J stent were placed following which urine output improved rapidly and AKI resolved. In view of consistent picture of uric acid nephrolithiasis urinary alkalization was attempted with oral potassium citrate salt and allopurinol was started for hyperuricemia.

Post-discharge leukocytosis (23,000/μL), thrombocytosis (683,000/μL) and peripheral smear leuco-erythroblastosis persisted so a work up for MPN was done. Philadelphia chromosome/bcr-abl translocation was negative on chromosomal analysis. Since BM aspiration was dry a trephine BM biopsy was done (Figs. 1, 2) which

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Table 1 Hematological and biochemical parameters in patient at admission and time of discharge

Parameter and laboratory range(in SI units)	Values at admission (in SI units)	Values at last follow up (in SI units)
Hemoglobin (g/dl): 14–16 g/dl for men	14.3	9.3
TLC (10^3 cells/ μ L): $3.9\text{--}10.7 \times 10^9$ cells/L	29.4	9.8
DLC (%) and peripheral smear	P85 %L3 %Eosino2 % Baso3 % Myelo&Metamyelocyte6 % Blasts1 % Marked anisopoikilocytosis, numerous tear drop cells, giant platelets	P78 %L20 %E2 %, occasional myelocytes, no blasts Mostly normocytic normochromic RBCs, few tear drop cells, occasional giant platelets
Platelet count ($\times 10^9$ cells/ μ L) 150–350	680	230
RBC count ($\times 10^6$ / μ L) 3.9–5.5	7.8	3.2
MCV (fL) 80–100	86	102
MCHC (g/L) 330–370	350	340
Reticulocyte count (%) 0.5–1.5	10.2	5.2
LAP Score (per/100/polymorphonuclear (PMN) leukocyte neutrophils and bands) 35–100	144	104
ESR(mm in 1st h) 0–15 in men	52	56
PT(secs) 11–13	15	13
aPTT (secs) 25–35	38	38
Blood urea nitrogen (mmol/L) 2.9–7.1	128	38
S. Cr (μ mol/L) 61.9–115	839.80	123.76
S. Sodium (mEq/L) 136–145	138	141
S. Potassium (mEq/L) 3.5–5	5.6	4.5
Arterial blood pH 7.35–7.45	7.16	–
Partial pressure CO ₂ (kPa) 4.7–5.9	2.26	–
S. Bicarbonate (mmol/L) 23–28	8	22
S. Chloride (mmol/L) 98–106	108	110
S. Calcium (mmol/L) 2.2–2.6	1.85	2.23
S.Phosphorus (mmol/L) 0.97–1.45	2.10	1.23
Total bilerubin (μ mol/L) 0.1–20.5	30.79	20.52
Direct bilerubin (μ mol/L) 0–5.1	25.66	5.13
ALT or SGPT (pkat/L) 0–0.58	0.7	0.75
AST or SGOT (pkat/L) 0–0.58	0.47	0.67
S.Alkaline phosphatase (μ kat/L) 0.5–1.5	3.39	3.16
S.Albumin (g/L) 35–55	36.00	35.00
S.Uric acid (mmol/L) 0.15–0.47	904.17	327.17
LDH (μ kat/L) 1–1.67	13.16	3.89
Urine analysis	Urine pH:6, Protein: 1 + Glucose: nil WBC: 20–30/HPF RBCs; too numerous to be counted	Urine pH:7.5, Protein: traces Glucose: nil WBC: 3–5/HPF RBCs; 3–5/HPF

ALT alanine transaminase, APTT activated partial thromboplastin time, AST aspartate transaminase, DLC differential leucocyte count, ESR erythrocyte sedimentation rate, HPF high power field, LAP leucocyte alkaline phosphatase score, LDH lactate dehydrogenase, MCV mean corpuscular volume, MCHC mean corpuscular hemoglobin concentration, PT prothrombin time, RBC red blood corpuscle, SGPT serum glutamate pyruvate transaminase, SGOT serum glutamate oxaloacetate transmainase, TLC total leucocyte count

showed features suggestive of primary myelofibrosis. Hydroxyurea (HU) was started at 500 mg orally twice a day which resulted in significant improvement of constitutional symptoms and attenuation of splenomegaly. Repeat blood and urine tests (Table 1) indicated

normalization of renal function while follow up non-contrast CT abdomen showed complete dissolution of renal and ureteric calculi. Ureteric stents were removed subsequently. Despite improvement in most hematological parameters hemoglobin(Hb) dropped leading to institution

Fig. 1 Shows bone marrow biopsy (haematoxylin and eosin stain) in high power with bony trabeculae enclosing marrow spaces. Marrow spaces showing megakaryocytic hyperplasia with relative paucity of myeloid and erythroid cell lineages. Increased connective tissue is seen in marrow spaces as pink hyaline material with reduction of marrow fat spaces ($\times 400$ magnification)

Fig. 2 Shows bone marrow biopsy stained with Gondon and Sweet's silver impregnation method showing increased reticulin deposition (grade 3+) arranged in diffuse fibre network with scattered thick coarse fibres ($\times 400$ magnification)

of subcutaneous epoetin with which Hb stabilized around 10–11 g/dL at last follow up.

The bcr-abl translocation negative MPNs are rare hematological disorders diagnosed by the WHO 2008 revised criteria based on clinical features, marrow histopathology and demonstration of clonality through testing for Janus Kinase-2 gene exon 14 (JAK2V617F) or myeloproliferative leukemia oncogene exon 10 (MPL) mutations [1]. Despite the lack of JAK/MPL gene mutation analysis in our patient, diagnostic criteria for PMF was met and all potential causes of secondary myelofibrosis were ruled out [1]. Notably the persistently high platelet counts

at presentation mimicked ET although this was overruled by typical BM findings of early PMF [6]. It would be reasonable to assume that our patient had prefibrotic PMF since he lacked severe cytopenias characteristic of late (fibrotic) PMF [6]. BM histology resembled prefibrotic PMF due to hypercellularity with granulocytic and megakaryocytic proliferation, decreased erythropoiesis and presence of atypical and pleomorphic megakaryocytes with hypolobulated nuclei although dense reticulin fibrosis strongly suggested a transition to advanced myelofibrosis [1, 6]. Of note, BM features of ET such as hypocellularity, intact erythro-granulopoiesis and increased megakaryopoiesis with atypical hyperlobulated (staghorn-like) megakaryocytes were not seen [6].

Treatment of PMF primarily addresses reducing symptom burden while attempting to reduce clonal proliferation which leads to progressive myelofibrosis and leukemogenesis [3]. Our patient had a DIPSS-PLUS prognostic score of 3 indicating high risk disease and substantial symptomatology making allogeneic stem cell therapy (allo-SCT) the treatment of choice given survival benefit in observational but not randomized studies [2, 3]. Unfortunately this was not available to us. Cyto-reductive therapy with HU is the next best option while newer agents like ruxolitinib, a JAK-2 kinase inhibitor, has shown promising results in symptom reduction and survival in PMF [2, 3].

PMF is rarely implicated as a cause of acute kidney injury (AKI) with most reported cases being extra-medullary hematopoiesis (EMH) in renal and peri-renal tissues in long standing PMF [4]. Hyperuricemic renal disease is next commonly reported with one case report of advanced PMF presenting with spontaneous tumor lysis syndrome (TLS) that resolved with dialytic support and long term allopurinol therapy [5]. Obstructive uropathy in PMF is rare and reported in a patient from EMH enveloping the renal pelvis, ureter and bladder [7]. Urolithiasis, as a cause of obstructive AKI in MPN has not been reported despite uric acid (UA) stones being commoner in hematological cancers than in general population where the most common renal stones are composed of calcium oxalate [8]. Three factors are commonly implicated in the genesis of UA stones- hyperuricosuria, low urinary volume, and persistently low urinary pH that converts urate to less soluble uric acid [9]. Treatment of UA stones is unique in that, other than emergent situations of obstructive AKI, infected stones or unremitting colic requiring urgent surgical intervention, medical stone dissolution is the first line treatment since it is highly successful [9]. Stone chemolysis in our patient with urinary alkalinization using oral potassium citrate to maintain urinary pH in the 6.5–7.0 range while increasing fluid intake and reducing hyperuricosuria was successful [9]. Differential diagnosis for AKI in our patient was limited given classic presentation and

appropriate response to therapy. Although our patient had metabolic derangements qualifying for a clinical and biochemical diagnosis of TLS, it seems that, apart from hyperuricemia, these were likely from obstructive nephropathy given rapid resolution after urinary drainage. Simultaneous occurrence of UA stones and TLS is rare despite both sharing a common pathophysiology. However, the distinction between the two is therapeutically relevant in that while volume expansion and serum urate lowering is emphasized in both, urinary alkalinization is no longer recommended in TLS given the possibility of renal injury from intratubular and interstitial CaP deposition and fall in ionized serum calcium levels [10].

In summary, we report a rare presentation of MPN with obstructive uropathy from uric acid stones which was successfully treated surgically and despite the non-availability of allo-SCT, patient was clinically optimized with HU over a short observation period of 6 months.

Sincerely,
The authors.

Compliance with Ethical Standards

Conflict of interest Anirban Ganguli, Ramandeep Singh Chalokia and Brahm Jyot Kaur declare that they have no conflict of interest related in any way to the design, conduct or publication of this manuscript.

Research Involving Human Participants and/or Animals This article is a retrospective case review and does not involve any experimentation on animals or human participants.

Informed Consent Informed consent was obtained from patient for publishing this case report (also mentioned in manuscript).

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