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Post-operative hyperleukocytosis and leukostasis as the initial presentation of chronic myelomonocytic leukemia: A case report and review of literature.

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ABSTRACT

Leukemoid reactions following surgery are commonly caused by infections or tissue injury. Management is directed towards underlying condition and cytoreduction is not indicated.

Chronic myelo-monocytic leukemia (CMML) is a clonal hematological malignancy characterized by persistent monocytosis and overlapping features of myelodysplastic and myeloproliferative neoplasms.In this case report we describe a 51-year-old Hispanic female without any significant prior medical history, who underwent a cholecystectomy for calculous cholecystitis. Post-operative course was complicated by hyperleukocytosis leading to splenic infarction and intracranial hemorrhage. Further investigations led to a diagnosis of CMML-2. A literature review of patients with CMML who developed post-operative leukocytosis and leukostasis (POLL) is presented.Case high lights two critical points:

Post-operative hyperleukocytosis with leukostasis can be the first presentation of CMML

Rapid diagnosis and institution of cytoreductive therapy with hydroxyurea is critical to avoid high morbidity and mortality.

1. Introduction

CMML is a MDS/MPN overlap neoplasm with features of morphological dysplasia, in-effective hematopoiesis combined with sustained proliferation of monocytes [1]. It is a heterogenous disease with survival ranging from a few months to more than 10 years. It is broadly classified into a proliferative and a dysplastic variant based on WBC count of more than or less than 13 × 10(9)/L, with the proliferative variant having a worse prognosis. Pathologically, based on the blast count, it is divided into CMML-0, CMML-1 or CMML-2, with higher blast counts associated with a worse prognosis.

Multiple somatic mutations have been identified in CMML. Mutations in epigenetic regulators (TET-2, ASXL1, EZH), spliceosome machinery (SRSF2, SF3B1), cell signaling (NRAS, KRAS, CBL, PTPN11,CBL) and transcription factors (RUNX1, SETBP1) account for the vast majority of reported cases. Amongst these, TET2(40–60%), ASXL1 (30–50%) and SRSF2(40–50%) are the most common while mutations in NRAS, RUNX1, SETBP1 and ASXL1 have been shown to be associated with a worse prognosis [2,3].

However, multivariate analysis suggests that gene mutations only partially account for the variability in outcomes seen in CMML [4].

The monocytes in CMML are highly inflammatory. RNA sequencing from CMML monocytes show enrichment of multiple pro-inflammatory pathways including TNF, HMGB1, IL-6, IL 17 [5]. Consistent with this, CMML is clinically associated with multiple systemic inflammatory and autoimmune diseases [6]. GM-CSF (granulocyte monocyte colony stimulating factor) levels are elevated in inflammatory states and GM-CSF hypersensitivity is characteristic of CMML cells [7,8]. As such autocrine loops can be set up between inflammatory states supporting CMML progression and CMML cells supporting systemic inflammation.

We present a patient without a prior history of any myeloid malignancy who underwent cholecystectomy for calculous cholecystitis. Clinical course was complicated by a post-surgical profound hyperleukocytosis and clinical leukostasis with splenic infarction and intracranial bleeding. She was eventually diagnosed with CMML-2 with a pathogenic RAS mutation. Prompt institution of cytoreductive therapy with hydroxyurea led to a favorable outcome.

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2. Case report

A 51-year-old Hispanic female was transferred to our institute after clinically deteriorating at a community hospital. She had undergone an un-complicated laparoscopic cholecystectomy for acute calculous cholecystitis. She had no other prior medical comorbidities. Her pre-operative laboratory data had shown a WBC count of 17,540 × 10(9)/L with 48% neutrophils, 32% lymphocytes, 15% monocytes, 2% eosinophils and 3% blasts. Hemoglobin was 11.3 gm/dl, MCV (mean corpuscular volume) 83fl (femtolitres); reticulocytes 1.1% (45.377 × 10(9)/L) and platelets were 119 × 10(9)/L.

Few hours after surgery patient developed hypotension, decrease in consciousness and right sided hemiparesis. Labs now showed WBC count had increased to 75,420 × 10(9)/L with 35%neutrophils, 45% monocytes, 10% lymphocytes, 5% blasts. Hemoglobin had decreased to 4 gm/dl and platelets had decreased to 18 × 10(9)/L. Prothrombin time was mildly prolonged at 15.6 s while partial thromboplastin time was normal. CT (computed tomography) scan of the abdomen showed a 6.8 cm x 5.1 cm fluid collection in the right upper quadrant, splenomegaly (15cms) with area of evolving infarct. CT of the head showed large left sided subdural hematoma.

Patient was felt to have developed disseminated intravascular coagulation (DIC) with leukemoid reaction, post-operative intra-abdominal hemorrhage and subdural intracranial bleed. She received transfusions of fresh, frozen plasma, platelets, packed red blood cells and was emergently transferred to our center for a higher level of care.

At the time of exam, her blood pressure was 106/62 mmHg, pulse rate 123/min, respiratory rate 16/min and temperature of 36.3 °Celsius. Glasgow coma scale was [14]. She had right sided facial droop and right pronator drift. Strength was 4/5 in right upper and lower extremities and normal on the left side. Skin exam showed petechial lesions over the lower extremities and ecchymoses over venipuncture sites and recent cholecystectomy site. She had diffuse tenderness over the abdomen. She was started on broad-spectrum antimicrobials, dexamethasone and after receiving more platelet and FFP underwent an emergent craniotomy with evacuation of the subdural hematoma and percutaneous drainage of the abdominal hematoma. Following craniotomy, she required vasopressor support for hypotension. Twelve hours later laboratory results showed increase of WBC to 179,330 × 10(9)/L with absolute monocyte count of 91,690 × 10(9)/L. Serum LDH was 482 IU/L (120–246). Patient Peripheral smear showed immature monocytes and promonocyte (Fig 1). Flow cytometry showed increased proportion of CD 14 $^{+}$CD 16 ^{dim} monocytes. Leukapheresis was not done due to hypotension and she was started on hydroxyurea. A bone marrow biopsy was performed. This showed a hypercellular marrow (100%) with significant dysplasia in the myeloid series. On average, promonocytes and blasts comprised 14% of the total marrow, however in areas there was more than 20% promonocytes. Erythropoiesis and megakaryoposis was decreased. Cytogenetics showed a normal female karyotype (46; XX). Next generation sequencing was performed on peripheral blood using a panel of 47 genes commonly mutated in myeloid malignancies. This showed a KRAS c.35G>*A* mutation with a variant frequency of 42.4%.

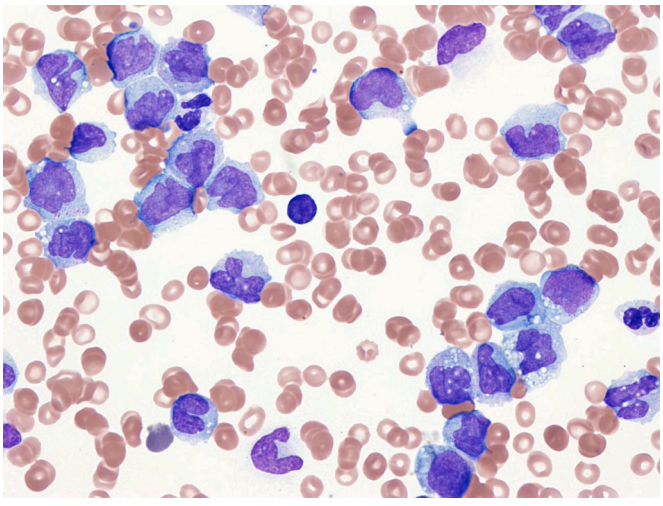

Fig. 1. (Peripheral smear showing increased monocyes and monocytic precursors).

Patient was diagnosed with CMML-2 progressing to secondary AML. Her clinical condition steadily improved and 9 day after being transferred to our institute she was discharged home on hydroxyurea 500 mg twice day. WBC count at the time of discharge were 40 × 10(9)/L and absolute monocyte count was 18 × 10(9)/L.

3. Discussion

Our patients clinical condition deteriorated rapidly after an otherwise routine procedure and was dominated by hyperleukocytosis with clinical features of leukostasis. Although she did not have a prior history of CMML., her initial labs had shown elevated WBC count with mild anemia, thrombocytopenia and monocytosis. These were attributed to reflect inflammation from underlying acute cholecystitis, however, in retrospect are also consistent with undiagnosed proliferative CMML.

CMML is more common in males (median age: 70–73 years) and most present with a leukocyte count between 1 and 50 × 10(9)/L. A WBC count above 100 × 10(9)/L is rare [9, 10].

A PubMed search was performed using the MESH terms " leukemia, myelomonocytic, chronic" and "postoperative complications". All pertinent article, associated references and citing articles were reviewed. A total of 6 similar previously published cases were identified.

Table 1 summarizes all previously published cases, including the current one. There were 4 males and 3 females with a median age of 67 years (range 51–86). Five of the seven patients had a pre-existing diagnosis of CMML, while in two, diagnosis was made following post-operative leukocytosis and leukostatic complications. Molecular data was available in 4 patients, 3 had TET2 mutation and 2 had a KRAS mutation. RAS mutations in CMML are associated with the proliferative variant of the disease, show hypersensitivity to GM-CSF with increased STAT signaling and contribute to disease progression via the NLRP3 inflammasome activation [8, 11]. These patietns may be particularly susceptible to POLL.

Among the patients who were previously diagnosed ($n = 5$), 2 had received treatment with a hypo-methylating agent, while the remaining were on observation. 71.4% of the patients had undergone a cardiovascular intervention prior to the development of leukocytosis.

Leukapheresis along with cytotoxic chemotherapy is commonly recommended to emergently manage complications of leukostasis in patients with leukemia. Stemmler et al. had suggested using elevated LDH levels, a presumptive signs of tissue ischemia, as a guide to initiating leukapheresis in CMML patients with hyperleukocytosis [12]. However, none of the patients were hemodynamically stable to commence leukapheresis, and its role in post-operative leukocytosis/leukostasis in CMML remains to be defined.

Among the seven patients, those who had prompt initiation of hydroxyurea ($n = 2$) survived, while those who did not receive hydroxyurea or in whom it was delayed died. Treatment with steroids or hypomethylating agent did not affect survival. One patient was initially treated with tocilizumab and authors report transient improvement in clinical condition, followed again by deterioration. Treatment with hydroxyurea was then initiated, however, patient did not survive [14]. Pathophysiology of leukostasis is complex and there is poor correlation between leukocyte count and clinical outcomes. CMML is characterized by the expansion of the CD14+/CD16- classical monocytes at the expense of intermediate (CD14+CD16+) and non-classical (CD14-CD16+) subtypes [17]. In patients with sickle cell anemia, hydroxyurea has been shown to modulate the inflammatory phenotype of

Table 1
Clinical features and outcomes of patients with post-operative leukocytosis and leukostasis.

	Reference	Age	Sex	Previous diagnosis of CMML	Prior treatment of CMML	Mutation profile	Nature of surgery	Postoperative wbc count(/ mcl)	Steroid use	Postoperative Leukemia directed therapy	Patient outcome
1	current	51	F	No	No	KRAS	cholecystectomy	144,000	yes	hydroxyurea	survival
2	[13]	75	F	Yes, CMML-1	Azacytidine, decitabine	TET2, SRSF2, ASXL1, SETBP1, CBL, FLT3TKD	Hip arthroplasty	346,900	yes	none	death
3	[13]	67	M	Yes, CMML-0	no	TET2, SRSF2, KRAS	Aortic valve replacement	119,000	yes	none	death
4	[13]	86	F	Yes, CMML-1	decitabine	n/a	Cardiac catheterization	104,000	no	Hydroxyurea, decitabine	survival
5	[14]	66	M	Yes, CMML-0	none	TET2, ZRSR2	Coronary artery bypass grafting	51,500	yes	Tocilizumab*	death
6	[15]	58	M	Yes, type unknown.	none	n/a	Coronary artery bypass grafting	135,980	NR	none	death
7	[16]	70	M	No	No	n/a	Coronary artery bypass grafting	91,700	NR	none	death

CMML: chronic myelomonocytic leukemia, Patient was initially treated with tocilizumab. Hydroxyurea was administered after clinical deterioration.

monocytes enriching the non-classical CD14dim CD16+ subset over the classical CD14+ CD16- subtype, decrease the production of multiple inflammatory cytokines and decrease the expression of adhesion molecules on monocytes [18, 19]. In addition to cytoreduction, a similar immune-modulatory effect on CMML monocytes may contribute to the beneficial effects of hydroxyurea in the hyperinflammatory state associated with post-operative leukocytosis and leukostasis.

4. Conclusion

Life threatening post-operative leukocytosis with leukostasis can be the initial presentation of patients with CMML. Increased awareness amongst clinicians is needed to allow for timely diagnosis. This case report and available literature suggests rapid initiation of hydroxyurea can be beneficial while hypomethylating agents, steroids and anti-IL6 therapy may have a minor role if any. This condition should not be termed “leukemoid reaction” with CMML, as it reflects a rapid proliferation of the malignant CMML clone and, unlike true leukemoid reactions, warrants rapid institution of cytoreduction.

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Declarations of Competing Interest

none

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