Leukemia Research Reports 14 (2020) 100228

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

Use of Tocilizumab in Management of Post-Operative Myelomonocytic Leukemoid Reaction

Megan Melody [a], Emily Butts [a], David Menke [b], Kevin Landolfo [c], Keith Oken [d], Taimur Sher [e], Sharad Khurana [f,*]

[a] Department of Internal Medicine, Mayo Clinic, Jacksonville, FL, United States
[b] Department of Laboratory Medicine and Pathology, Mayo Clinic, Jacksonville, FL, United States
[c] Department of Cardiovascular and Thoracic Surgery, Mayo Clinic, Jacksonville, FL, United States
[d] Department of Cardiology, Mayo Clinic, Jacksonville, FL, United States
[e] Division of Hematology-Oncology, Mayo Clinic, Jacksonville, FL, United States
[f] Division of Hematology-Oncology, University of Arizona Cancer Center, Tucson, AZ, United States

ARTICLE INFO

Keywords:
Chronic myelomonocytic leukemia
Tocilizumab
Leukemoid reaction
Systemic inflammatory response

ABSTRACT

Interleukin 6 receptor (IL6R) inhibitor, tocilizumab, has been effectively used in the treatment of cytokine release syndrome in patients receiving chimeric antigen receptor T-cell therapy. Here we present a patient with chronic myelomonocytic leukemia (CMML) who developed a steroid refractory, post-operative myelomonocytic leukemoid reaction (PO-MMLR), effectively treated with tocilizumab. Although, further studies are needed to validate the effectiveness of tocilizumab in management of PO-MMLR, this case serves to provide a new management approach in treatment of this rare but lethal syndrome with no standardized treatment options.

1. Introduction

Chronic myelomonocytic leukemia (CMML) is a myeloproliferative neoplasm (MPN) that is characterized by the presence of absolute monocytosis (>1 × 10(9)/L) of >10% of total peripheral white blood cell count (WBC). In addition, it is also associated with cytopenias, hepatosplenomegaly, and bone marrow dysplasia [1, 2]. CMML occurs twice as often in men as in women, most commonly in older adults, with a median age at diagnosis of 65 to 75 years [3, 4]. Due to the late onset of disease, patients with CMML often have additional comorbidities, requiring medical therapy and occasionally surgical or procedural intervention. Interestingly, CMML patients are at a higher risk of developing post-operative severe systemic inflammatory response syndrome, known as post-operative myelomonocytic leukemoid reaction (PO-MMLR), presenting with marked leukocytosis, vasodilation, and elevation in non-specific inflammatory markers [1, 2, 5]. The proposed mechanism for an increased rate of PO-MMLR in CMML patients is attributed to the increased baseline concentration of pro-inflammatory cytokines such as IL-6 and/or IL-2 [3, 6]. Review of the literature reveals two case reports and one case series of PO-MMLR [1, 3, 5]. Four of the five cases reported occurred after a cardiac procedure [aortic valve replacement, cardiac catheterization, with two following coronary artery bypass graft (CABG)], and the other reported case occurred after hip arthroplasty. Although these case reports cite the use of steroids or hypomethylating agents in the management of PO-MMLR, no clear guidelines exist for the treatment of this systemic inflammatory reaction. Here we present a life threating case of PO-MMLR after CABG managed with tocilizumab, a targeted interleukin-6 (IL-6) receptor antagonist.

2. Case report

A 66-year-old male with treatment naïve, low risk CMML-0 and additional past medical history of hypertension, gastroesophageal reflux disease, secondary hyperparathyroidism, impaired fasting glucose, and obesity presented to the local emergency department with a 12-hour history of intermittent chest pain radiating to the mid back. EKG showed ST segment depression with elevated and up-trending troponins. He was diagnosed with a non-ST elevated myocardial infarction (NSTEMI) and started on aspirin, heparin, metoprolol, lisinopril, and simvastatin. Echocardiogram revealed mild anteroseptal hypokinesis and ejection fraction of 55- 60%. Coronary angiography was performed and revealed multi-vessel disease for which CABG was recommended,

* Corresponding author.
E-mail addresses: skhurana@arizona.edu, khurana.sharad@mayo.edu (S. Khurana).

https://doi.org/10.1016/j.lrr.2020.100228
Received 9 April 2020; Received in revised form 25 October 2020; Accepted 27 October 2020
Available online 4 November 2020

and patient was transferred to our institution for surgical intervention.

White blood cell count prior to the procedure was 4.8 × 10(9)/L with an absolute monocyte count (AMC) of 1.92 × 10(9)/L (39.8%), absolute neutrophil count (ANC) of 1.48 × 10(9)/L, platelets at 107 × 10(9)/L and a hemoglobin (HgB) of 12 g/dl. Renal and hepatic functions were within normal limits. Review of prior hematology work up showed a history of mild thrombocytopenia, neutropenia, and absolute monocytosis with a bone marrow aspirate/biopsy confirming CMML-0 with 4% myeloblasts. Cytogenetics and molecular studies showed a normal 46 XY [20] male karyotype, however next generation sequencing reported *TET2*: c.538C>*T*;p.Gln180* (6%), c.774dup; p.Glu259* (14%), c.2524dup; p.Ser842Phefs*4 (6%), c.4546C>*T*;p.Arg1516* (7%), and *ZRSR2*: c.122–1G>*A*; p.? (89%) mutations. CABG was performed successfully and the patient was transferred to intensive care for post-operative monitoring. Twelve hours after the procedure he was extubated and weaned off pressor support. Shortly following extubation, the patient became hypotensive and developed severe lactic acidosis with a pH of 7.198, PaCO2 36.4, PaO2 112.1, HCO3 13.8, and lactate of 15.1 mmol/L, requiring vasopressor support and reintubation. He was started on steroids, broad spectrum antibiotics, continuous renal replacement therapy (CRRT), and an intra-aortic balloon pump was placed. A cardiac origin of low cardiac output was excluded by placement of a Swan-Ganz catheter for hemodynamic monitoring and an echocardiogram was performed which showed normal right and left ventricular systolic function. Blood and urine cultures were negative for infectious etiology. Computed tomography (CT) of the abdomen, and pelvis did not demonstrate any acute abdominal or pelvic process and were without evidence of bowel ischemia or fluid collection. CT angiography of the chest was negative for pulmonary embolism (PE) or infectious/inflammatory process. These findings excluded sepsis or splanchnic ischemia as causes of SIRS and multi-organ dysfunction.

Laboratory work showed anemia of critical illness with HgB of 7.6 g/dL and thrombocytopenia with a platelet count of 33 × 10(9)/L, requiring multiple transfusions. Peripheral blood smear showed a leukemoid reaction with a WBC of 51.5 × 10(9)/L, AMC of 6.9 × 10(9)/L (17%), and ANC of 30.44 × 10(9)/L (71%) without peripheral blasts (Image1). Serum ferritin and C-reactive protein (CRP) were markedly elevated at >120,000 mcg/L and 79.2 mg/L, respectively. In addition, plasma levels of both IL-6 and tumor necrosis factor (TNF) were elevated at >400 pg/ml (normal< 1.8 pg/ml) and 5.2 pg/ml (normal <2.8 pg/ml) respectively.

Given these laboratory abnormalities and a negative infectious work up, patient was thought to have developed a systemic inflammatory response syndrome (SIRS) in setting of PO-MMLR which had not been responsive to high doses of steroids. At this time, patient was given a trial of tocilizumab 800 mg every 8 hrs for 3 doses. Within the next 24 hrs, patient had decreased pressor requirements and his lactate started to trend down. At 48 hrs following tocilizumab dosing, intra-aortic balloon pump was removed, patient was extubated, and steroids were tapered. WBC, AMC, and ANC all trended down within 48 hrs following tocilizumab. Ferritin, CRP, and lactate notably improved (Table 1). Patient was weaned off all pressor support and steroids at 5 days following tocilizumab administration.

Despite initial clinical and laboratory improvement, nine days following the last dose of tocilizumab patient again became hypotensive requiring vasopressors with worsening leukocytosis and lactic acidosis. He was re-intubated and initiated on mechanical ventilation, CRRT, and pressor support. However, his CRP and ferritin remained stable, which was felt to be reassuring that this was not a systemic inflammatory response syndrome, and no additional doses of tocilizumab were given. In addition, CT chest revealed bilateral pneumonia as the likely source of septic shock. Hydroxyurea was started for cytoreduction with good control of the WBC at this time. Patient had a prolonged hospital course and, unfortunately, passed away 46 days post CABG due to persistent multi-organ failure.

3. Discussion

The exact mechanism of PO-MMLR has not been fully elucidated. Studies have shown that patients with CMML have increased concentrations of pro-inflammatory cytokines including IL-8, IL-10, IL-1 receptor antagonist, tumor necrosis factor α, and IL-6 compared with healthy controls [6-9]. We hypothesize that in our patient the increased risk of PO-MMLR was perhaps due to the presence of *TET-2* mutation. *TET-2* is a tumor suppressor gene located on chromosome 4q24 and it is mutated in approximately 60% of CMML cases [10].*TET-2*-deficient mice demonstrate increased expression of CXCL1, CXCL2, CXCL3, platelet factor 4, IL-1B, and IL-6 [11, 12]. Both *TET-2* mutation and high IL-6 was noted in our patient.

The presence of *TET-2* mutations has also been linked to increased risk of atherosclerotic disease in *TET-2* deficient mice [12]. This increased risk of atherosclerotic disease in combination with elevation in inflammatory markers, may help to explain why PO-MMLR has been most commonly noted following cardiac procedures in 4 of the 5 reported cases [1, 3, 5, 13, 14]. Molecular analysis was only published for two of these cases, both of which were found to have *TET-2* mutations [1, 3, 5]. Based on these observations and our own experience, we recommend that CMML patients requiring cardiac intervention could benefit from genetic sequencing to evaluate for *TET-2* mutations prior to procedure. Identification of *TET-2* mutation should warrant a more intense monitoring for post procedural complications and elevation in leukocyte count. Additional, helpful monitoring tests may include pre and post procedure serum IL-6 and TNF-alpha levels.

Treatment of PO-MMLR has been focused on supportive care with vasopressors, mechanical intubation, and dialysis [1-3, 5]. Hydroxyurea, allopurinol and intravenous fluids have all been suggested as a possible early intervention at the onset of leukocytosis due to risk of leukostasis in this patient population, and because of the effectiveness of these modalities in treating tumor lysis syndrome [1]. Although experience is limited, the use of stress dose steroids has been reported either alone or with hydroxyurea and decitabine to manage leukostasis [1].

The underlying pathobiology of systemic inflammatory response noted in patients with PO-MMLR is linked to increased production of the pro-inflammatory cytokine IL-6 [15, 16]. Excess IL-6 is also noted to induce hepatocytes to produce a wide range of acute phase proteins and inhibits the activity of transferrin. This typically results in increased serum CRP and ferritin levels [15]. In the case presented here, our patient continued to have clinical decline despite supportive care and high dose glucocorticoid therapy. We hypothesized that blocking the pro-inflammatory effect of IL-6 can be effectively achieved with Tocilizumab which targets the IL-6 receptor. Indeed, treatment with Tocilizumab resulted in decline in patients CRP and ferritin levels (surrogate response markers of anti-IL-6 therapy), and this translated in clinical improvement of our patient [16]. This approach to manage PO-MMLR has not been reported to the best of our knowledge and is an innovative strategy to manage this clinical complication.

4. Conclusion

PO-MMLR is a severe systemic inflammatory response seen in patients with CMML following surgical interventions; most commonly reported after cardiac procedures whose biological underpinning seems to be the aberrant pro-inflammatory cytokine milieu. Here we report a case of PO-MMLR resistant to glucocorticoid therapy effectively treated with tocilizumab, an anti-IL- 6R directed therapy. Due to the rarity of this syndrome, further prospective studies to evaluate additional treatment may be difficult to develop; however, this case serves to identify a potential new management approach for this rare syndrome.

No funding was received to support this research

This study has not been presented or published in any other capacity

No disclosures

References

[1] A.B. Patel, et al., Leukemoid reaction in chronic myelomonocytic leukemia patients undergoing surgery: perioperative management recommendations, Blood Adv. 3 (7) (2019) 952–955.

[2] V. Sakka, et al., An update on the etiology and diagnostic evaluation of a leukemoid reaction, Eur. J. Intern. Med. 17 (6) (2006) 394–398.

[3] N.E. Drury, et al., Acute leukaemoid reaction following cardiac surgery, J. Cardiothorac. Surg. 2 (2007) 3.

[4] D.E. Rollison, et al., Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs, Blood 112 (1) (2008) 45–52.

[5] S.A. Galea, J. Galea, Urgent Coronary Artery Bypass Surgery in a Patient with postinfarction angina and active myelomonocytic Leukaemia, Case Rep. Oncol. 9 (3) (2016) 781–785.

[6] S. Niyongere, et al., Heterogeneous expression of cytokines accounts for clinical diversity and refines prognostication in CMML, Leukemia 33 (1) (2019) 205–216.

[7] U. Germing, A. Kundgen, N. Gattermann, Risk assessment in chronic myelomonocytic leukemia (CMML), Leuk Lymphoma 45 (7) (2004) 1311–1318.

[8] Y. Moon, et al., The 2016 WHO versus 2008 WHO criteria for the diagnosis of chronic myelomonocytic Leukemia, Ann. Lab. Med. 38 (5) (2018) 481–483.

[9] M.M. Patnaik, A. Tefferi, Cytogenetic and molecular abnormalities in chronic myelomonocytic leukemia, Blood Cancer J. 6 (2016) e393.

[10] M.M. Patnaik, et al., Number and type of TET2 mutations in chronic myelomonocytic leukemia and their clinical relevance, Blood Cancer J. 6 (9) (2016) e472.

[11] J. Yamazaki, et al., Effects of TET2 mutations on DNA methylation in chronic myelomonocytic leukemia, Epigenetics 7 (2) (2012) 201–207.

[12] S. Jaiswal, et al., Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease, N. Engl. J. Med. 377 (2) (2017) 111–121.

[13] J.G. Augoustides, The inflammatory response to cardiac surgery with cardiopulmonary bypass: should steroid prophylaxis be routine? J. Cardiothorac. Vasc. Anesth. 26 (5) (2012) 952–958.

[14] E.V. Potapov, et al., Impact of cardiac surgery using cardiopulmonary bypass on course of chronic lymphatic leukemia: a case-control study, Ann. Thorac. Surg. 74 (2) (2002) 384–389.

[15] S. Kang, T. Tanaka, T. Kishimoto, Therapeutic uses of anti-interleukin-6 receptor antibody, Int. Immunol. 27 (1) (2015) 21–29.

[16] C.R. Stroud, et al., Tocilizumab for the management of immune mediated adverse events secondary to PD-1 blockade, J. Oncol. Pharm. Pract. 25 (3) (2019) 551–557.