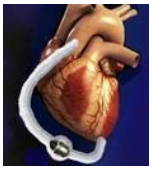

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Peer-Reviewed Case Report

Fever of Unknown Origin in Patient after Left Ventricular Assist Device Implantation

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Abstract

Mechanical circulatory support (MCS) is a lifesaving procedure in patients with refractory cardiogenic shock. Despite improvement in surgical techniques, ICU care and restored hemodynamics, some patients on MCS remain severely debilitated due to multiple medical problems, including infections, respiratory failure, de-conditioning and nutritional deficits.

Here we present a case of a patient with persistent high degree fever, devastating muscle weakness, and elevated lactatedehydrogenase (LDH) level, who dramatically responded to treatment with vitamin B 12.

Keywords: Fever of unknown origin, vitamin B12 deficiency, left ventricular assist device

Introduction

Mechanical circulatory support (MCS) is a lifesaving treatment for patients with refractory cardiogenic shock[1]. Despite improvement in surgical techniques, intensive care and restored hemodynamics, some patients on MCS remain severely debilitated due to multiple medical problems, including infections, respiratory failure, de-conditioning and nutritional deficits[2]. Here we present a case of a patient with persistent high degree fever, devastating muscle weakness, and an elevated lactate dehydrogenase (LDH) level, who dramatically responded to treatment with vitamin B 12.

Case Report

Early Experience

A 25-year-old male with history of repaired truncus arteriosus, placement of right ventricle-to-pulmonary artery homograft, bioprosthetic aortic valve replacement and severe left ventricular dysfunction, presented with cardiogenic shock, hypoxia and acute renal failure on June 1, 2015. He initially required veno-arterial extracorporeal membrane oxygenation (VA ECMO) support and continuous veno-venous hemofiltration (CVVH). Transesophageal echocardiogram showed a severely dilated left ventricle with an ejection fraction of 10%, severe prosthetic aortic valve stenosis, severe mitral valve regurgitation secondary to a flailed posterior leaflet segment, and moderate pulmonary stenosis. Trans-catheter aortic valve replacement was performed, which did not improve the patient's condition. The patient developed thrombocytopenia and anemia, and required multiple blood transfusions.

On June 24, 2015, the patient underwent Heartmate II left ventricular assist device (LVAD) implantation with mitral valve repair and replacement of the right ventricle to pulmonary artery conduit. Despite normalization of cardiac hemodynamics and recovery of renal function, the patient's condition progressively worsened during the five weeks after surgery. He required a tracheostomy after failing several weaning trials due to an inability to clear secretions and poor oxygenation. He remained ventilator dependent in the ICU for six weeks.

During this time, he developed persistent high fevers up to 40°C which did not respond to multiple broad spectrum antibiotics and were resistant to antipyretics (Figure 1A). Blood cultures and bronchoalveolar lavages were all negative for an infectious etiology. Full body scans, including computed tomography (CT), positron emission tomography (PET), and an echocardiogram did not reveal a source of infection. All markers of autoimmune disease were negative.

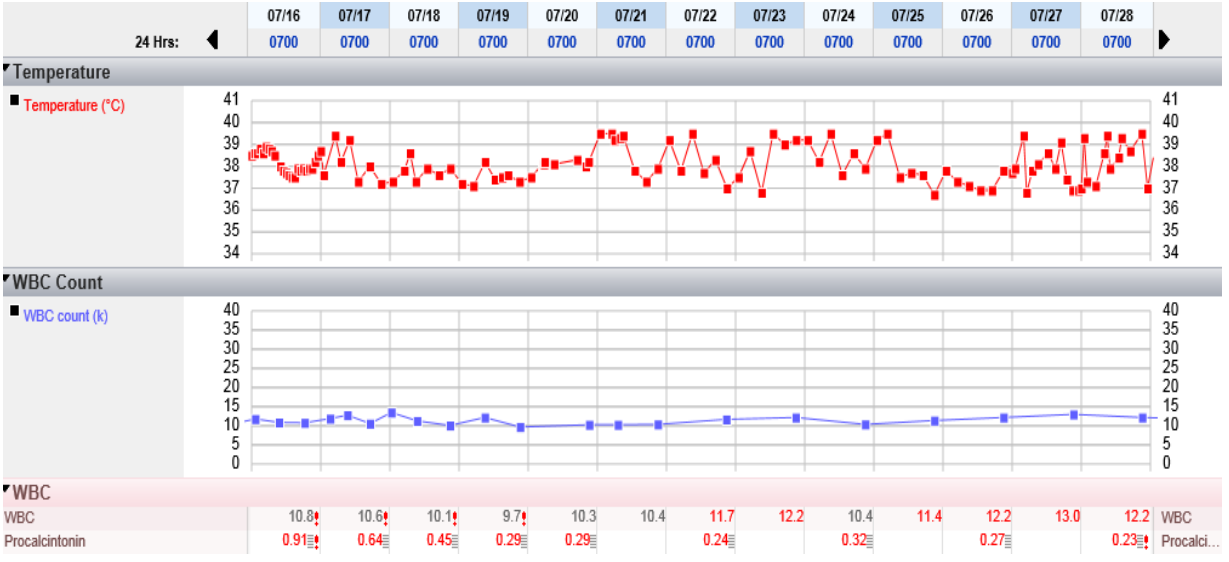

Figure 1A

In addition, the patient developed profound muscle weakness. A CT scan of the brain was unremarkable, electromyography (EMG) of lower extremities was inconclusive, and his neurological symptoms were attributed to critical illness myopathy.

The patient developed anemia with macrocytosis and required several blood transfusions. His LDH level was elevated at 630 U/L (reference range 98-182 U/L), but there were no clinical signs of LVAD thrombosis. His vitamin B12 level was within the normal reference range, and a methylmalonic acid (MMA) level was at upper limit of the normal reference range (Table 1). Based on our previous experience with vitamin B12 treatment in the setting of fever of unknown origin [3], oral vitamin B12 supplementation was initiated. There was resolution of the fever four days after vitamin B12 initiation (Figure 1B). Importantly, no changes in antibiotics or other medications were made at this time. There was also a dramatic improvement in neurological symptoms. The patient was weaned from mechanical ventilation one week later. He was transferred to the cardiac step down unit ten days after initiating vitamin B12. He continued to improve with regard to his neurological condition and was discharged home from the rehabilitation unit after one month. His fever did not recur.

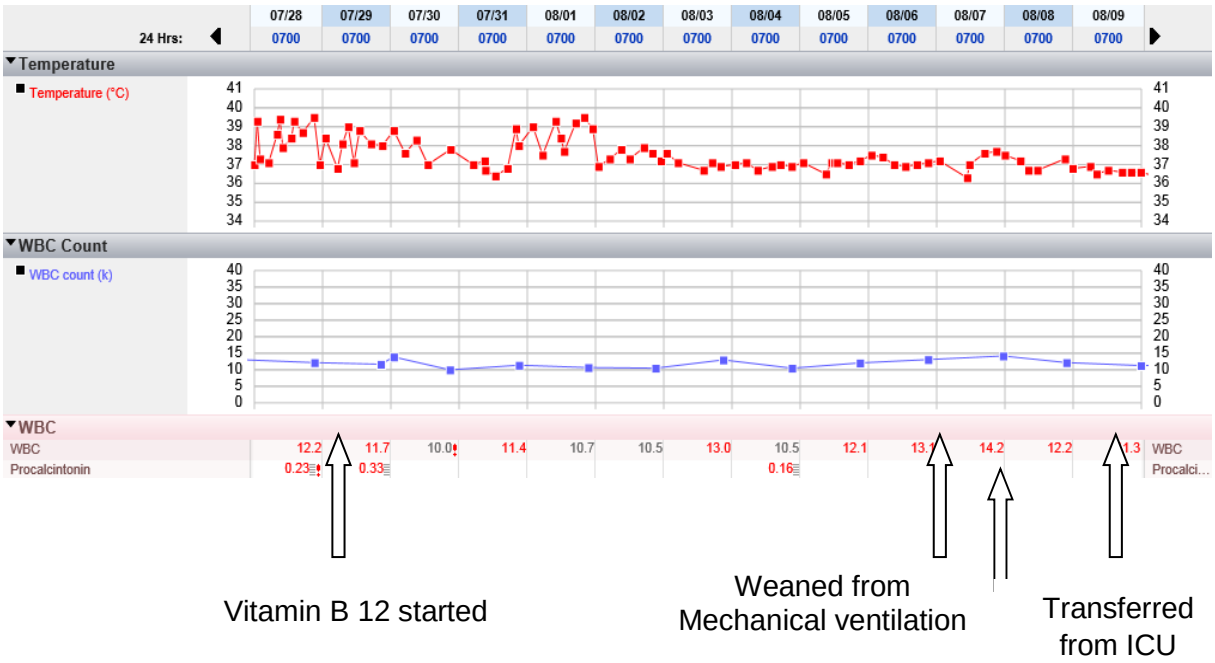

Figure 1B

Table 1 shows the hematologic data obtained prior to initiation of vitamin B12 supplementation, one and two months after initiation vitamin B12 supplementation. The level of vitamin B12 increased, the concentration of MMA decreased, and the LDH level returned to normal range.

Table 1. The hematologic data before and after vitamin B12 supplementation

	Reference range	7/15/201*	8/15/2015†	9/15/2015‡
MCV, fL/red cell	80-96	101	98	95
Vitamin B12, pg/mL	180-914	473		975
MMA, µmol/L	0.00-0.40	0.4		0.2
LDH, U/L	98-192	650	367	284

*** 2 weeks prior to initiation of vitamin B12 supplementation,**
† 2 weeks after initiation of vitamin B12 supplementation,
‡ 6 weeks after initiation of vitamin B12 supplementation

Discussion

The important role of vitamin B12 and it deficiency in the hematological and neurological processes in human body has been well documented. However, vitamin B12 deficiency in patients on mechanical circulatory support has not been described.

Fever was reported in patients with pernicious anemia more than 100 years ago [4]. It usually persists after blood transfusion, despite correction of anemia, and resolves only after B12 administration. The mechanism of the antipyretic effect of vitamin B12 remains unclear [5,6]. In this case of prolonged fever of unknown origin, the levels of vitamin B12 was near the lower limit of the normal reference range and the MMA level was at the upper limit of the normal reference range. Hence, the vitamin B12 treatment was not considered at an earlier point in time. Our patient had only transient macrocytosis. However, the typical hematological picture of vitamin B12 deficiency may be masked by multiple blood transfusions. The rational for the decision to start vitamin B12 treatment was based on anecdotal evidence regarding treatment of persistent fever of unknown origin in a debilitated patient with a mechanical mitral valve[3]. We observed complete resolution of the fever four days after vitamin B12 initiation in our patient.

The patient developed severe muscular weakness, failed weaning from the ventilator, and required a prolonged ICU stay. After initiation of vitamin B12 treatment we observed a sustained and dramatic improvement with regard to muscle weakness and paresthesia. Demyelization of the dorsal columns and the corticospinal tract resulting in peripheral neuropathy is a known complication of vitamin B12 deficiency. It causes irreversible neurological damage if untreated [7,8]. A growing body of evidence demonstrates the role for vitamin B12 in the development, progression, and treatment of different neuropsychiatric disorders [9-11]. To date, its role in critically ill and malnourished patients on mechanical circulatory support has not been evaluated.

Hemolysis with LDH ≥ 600 IU/liter (2.5-times the upper limit of laboratory normal) has been identified as an important marker of thrombosis and adverse outcomes after left ventricular assist device implantation[12,13]. Furthermore, LDH elevation in patients with vitamin B12 deficiency is a well-recognized phenomenon and is often associated with both intravascular and intramedullary hemolysis and thrombosis at unusual sites[14]. While its mechanisms are not entirely understood, it has been attributed to the marked hyperhomocysteinemia [15,16]. Remarkably, the increased LDH levels rapidly returned to a normal level after initiation of vitamin B12 treatment as in our case.

Our case poses several issues regarding the diagnosis and appropriate treatment of vitamin B12 deficiency in severely debilitated and critically ill patients on mechanical circulatory support. First, the best diagnostic approach for vitamin B12 deficiency in patients on mechanical circulatory support is unclear[17]. Second, the mechanism of the antipyretic effect of vitamin B12 remained inexplicit. Vitamin B12 utilizes multiple binding proteins that facilitate its absorption and transport [18]. Deficiency of these proteins in critically ill patients may cause functional vitamin B12 deficiency and result in additional difficulty in the diagnosis. It has been suggested that vitamin B12 has important immunomodulatory effects and its supplementation could correct defects caused by other biologically active substances under the stress of prolonged severe illness, even if the vitamin B12 serum level is within the normal range[19]. This phenomenon is called the ‘‘Master Key’’ effect[20]. Furthermore, LDH elevation in patients with vitamin B12 deficiency is a well-recognized phenomenon and is often associated with both intravascular and intramedullary hemolysis and thrombosis. The role of vitamin B12 in ventricular assist device thrombosis has not yet been assessed.

Conclusion

Vitamin B 12 supplementation in our patient was delayed due to the normal levels of vitamin B12 and MMA. However, the vitamin B12 deficiency was established by responses to therapy. The recognition and treatment of the condition was critical in the presented case. Since vitamin B12 has no known significant toxic effects and has a low cost effectiveness ratio, it should be supplemented in this patient population without delay.

References

1. Starling RC, Naka Y, Boyle AJ, et al. Results of the post-U.S. food and drug administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: A prospective study using the INTERMACS (interagency registry for mechanically assisted circulatory support). *J Am Coll Cardiol*. 2011;57(19):1890-1898.

2. Holdy K, Dembitsky W, Eaton LL, et al. Nutrition assessment and management of left ventricular assist device patients. *J Heart Lung Transplant*. 2005;24(10):1690-1696.

3. Mouallem M, Matetzky S, Raichlin E, Farfel Z. A man with a prosthetic valve, anaemia, fever, and splenomegaly. *Lancet*. 1996;348(9036):1216.

4. Cabot RC. In: Osler and McCrae's a system of medicine. *London: Henry Frowde and Hodder & Stoughton*. 1908;4(612).

5. Davidson S. Clinical picture of pernicious anaemia prior to introduction of liver therapy in 1926 and in edinburgh subsequent to 1944. *Br Med J*. 1957;1(5013):241-243.

6. McKee LC,Jr. Fever in megaloblastic anemia. *South Med J*. 1979;72(11):1423-4, 1428.

7. Allen RH, Stabler SP, Lindenbaum J. Relevance of vitamins, homocysteine and other metabolites in neuropsychiatric disorders. *Eur J Pediatr*. 1998;157 Suppl 2:S122-6.

8. Scalabrino G. Subacute combined degeneration one century later. the neurotrophic action of cobalamin (vitamin B12) revisited. *J Neuropathol Exp Neurol*. 2001;60(2):109-120.

9. Fava M, Borus JS, Alpert JE, Nierenberg AA, Rosenbaum JF, Bottiglieri T. Folate, vitamin B12, and homocysteine in major depressive disorder. *Am J Psychiatry*. 1997;154(3):426-428.

10. Bottiglieri T. Folate, vitamin B(1)(2), and S-adenosylmethionine. *Psychiatr Clin North Am*. 2013;36(1):1-13.

11. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. 1988. *Nutrition*. 1995;11(2):181; discussion 180, 182

12. Cowger JA, Romano MA, Shah P, et al. Hemolysis: A harbinger of adverse outcome after left ventricular assist device implant. *J Heart Lung Transplant*. 2014;33(1):35-43.

13. Dalsania CJ, Khemka V, Shum M, Devereux L, Lachant NA. A sheep in wolf's clothing. *Am J Med*. 2008;121(2):107-109.

14. Mishra VA, Harbada R, Sharma A. Vitamin B12 and vitamin d deficiencies: An unusual cause of fever, severe hemolytic anemia and thrombocytopenia. *J Family Med Prim Care*. 2015;4(1):145-148.

15. Limal N, Scheuermaier K, Tazi Z, Sene D, Piette JC, Cacoub P. Hyperhomocysteinaemia, thrombosis and pernicious anaemia. *Thromb Haemost*. 2006;96(2):233-235.

16. Remacha AF, Souto JC, Pinana JL, et al. Vitamin B12 deficiency, hyperhomocysteinemia and thrombosis: A case and control study. *Int J Hematol*. 2011;93(4):458-464.

17. Stabler SP. Vitamin B12 deficiency. *N Engl J Med*. 2013;368(21):2041-2042.

18. Klee GG. Cobalamin and folate evaluation: Measurement of methylmalonic acid and homocysteine vs vitamin B(12) and folate. *Clin Chem*. 2000;46(8 Pt 2):1277-1283.

19. Naimer S, Volkov I. Periodic fever responds to vitamin B12 treatment. *Rheumatol Int*. 2010;30(12):1661-1663.

20. Volkov I, Press Y, Rudoy I. Vitamin B12 could be a "master key" in the regulation of multiple pathological processes. *J Nippon Med Sch*. 2006;73(2):65-69.