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Review Article

FILGRASTIM : A SAVIOUR IN A PATIENT HAVING SEPSIS WITH REFRACTORY NEUTROPENIA IN ICU

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ABSTRACT

Sepsis remains a critical problem with significant morbidity and mortality even in the modern era of critical care management. Previously, it was believed that sepsis merely represented an exaggerated, hyperinflammatory response with patients dying from inflammation induced organ injury. More recent data indicate that substantial heterogeneity exists in septic patients' inflammatory response, with some appearing immunostimulated whereas others appear immunosuppressed.The following case report evaluates the revolutionary role of filgrastim, a GM-CSF in a patient admitted in the ICU with persistent neutropenia and thrombocytopenia associated with sepsis.

A 35 year old man came to our emergency with altered sensorium, pain abdomen and fever for the past 10 days with thready pulse and an unrecordable BP. Upon investigations, free air under the diaphragm was obtained. Emergency surgery was performed, a primary repair and anastomosis was done. He was shifted to our ICU on inotropic support. On repeat investigations, anaemia, neutropenia and thrombocytopenia was seen. Multiple infusions of FFPs and platelets were of no use. It was the third day of admission that we started Inj. Filgrastim at doses of 5µg/kg/day subcutaneously for 3 days. There was a remarkable improvement in the clinical profile of the patient since the very next day. He was afebrile, conscious with good respiratory efforts and haemodynamically stable after the second dose only. Inotropic support was gradually tapered off. He was weaned off the ventilator and extubated the same day.The blood counts improved significantly and the patient was shifted back to the ward on the fifth day.

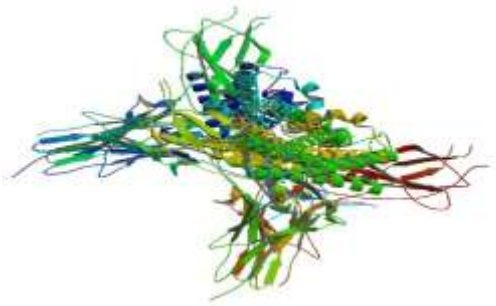
Results: We conclude that granulocyte colony-stimulating factor therapy helped symptom alleviation and accelerated the recovery.

Keyword: Filgrastim, Neutopenia, Sepsis.

INTRODUCTION

Sepsis remains a serious problem with significant morbidity and mortality even in the modern era of critical care management. Previously, it was believed that sepsis merely represented an exaggerated, hyperinflammatory response with patients dying from inflammation induced organ injury. More recent data indicate that substantial heterogeneity exists in septic patients' inflammatory response, with some appearing immunostimulated whereas others appear immunosuppressed. [1] The following case report evaluates the revolutionary role of filgrastim, a GM-CSF in a patient admitted in the ICU with persistent neutropenia and thrombocytopenia associated with sepsis.

CASE REPORT



A 35 year old man came to our emergency with pain abdomen and fever for the past 10 days with altered sensorium, pulselessness and an unrecordable BP. Rapid aggressive resuscitation was done with intravenous fluids and inotropes and a BP of around 110 mm hg systolic was achieved with titration. On reviewing the history, he did not have any other comorbid illness. Hb was found to be 9.0gm%, TLC was 2900/cumm and platelet count was 1lac/cumm. On peripheral smear, neutropenia with microcytic hypochromic picture was obtained. Upon further investigations, free air under the diaphragm was seen. Antibiotic therapy with intravenous ceftriaxone sodium, amikacin and metronidazole was started. He was immediately shifted to the operation theatre for exploration under general anaesthesia and a perforation in the ileocaecal region was obtained. Haemodynamics were maintained with titrated infusions of inj. Dopamine and inj. Noradrenaline throughout. Two units of FFPs were transfused intraoperatively. After a primary repair and anastomosis was done, an unsatisfactory recovery of both the mental status and respiration was seen. It was then that the patient was shifted to our ICU on mechanical ventilation and inotropic infusions at quite high rates. His chest X-ray revealed bilateral pulmonary infiltrates suggestive of acute respiratory distress syndrome. On repeat investigations, a haemoglobin of 8.0gm%, TLC of 2200/cumm, platelet count of 60,000lacs/cumm were obtained. When his leucocyte count dropped to less than 2000, intravenous hydrocortisone 100 mg BD was started. Despite this his leucocyte count dropped to 2000/mm^3 with differential count of polymorpholeucocytes of 46% and fever persisted. Multiple infusions of FFPs and platelet concentrates were of no use. The patient continued to have fever and haemodynamic instability despite maximal resuscitative efforts and broad spectrum antibiotic therapy.The blood counts continued to drop as shown in Fig.1. It was the third day of admission that we started Inj. Filgrastim at doses of 5µg/kg/day subcutaneously. There was a remarkable improvement in the clinical profile of the patient since the very next day as shown in Fig.1. He was afebrile, conscious with good respiratory efforts and haemodynamically stable after the second dose only. Inotropic support was gradually tapered off. He was weaned off the ventilator and extubated on the fifth day. The blood counts improved significantly and the patient was shifted back to the ward on the seventh day. He was discharged from the surgical ward after a week.

	DAY1	DAY2	DAY3	DAY4	DAY5	DAY6	DAY7
Hb(gm%)	9.0	8.0	8.4	9.0	9.8	9.2	9.0
TLC(/cumm)	2900	2200	2000	2600	3200	3500	3400
Neutrophil count (%)	56	48	46	46	49	52	58
Platelets(lacs/cumm)	1.2	0.6	0.8	0.9	1.0	1.4	1.2
Fever	Present	Present	Present	Absent	Absent	Absent	Absent
Treatment	Broad spectrum antibiotics+ inotropes+ supportive + IPPV+ 4 U FFP	Broad spectrum antibiotics + inotropes+ supportive+ IPPV+ Hydrocortisone+ 4 U FFP + 2 U PC	Broad spectrum antibiotics + inotropes + supportive + IPPV + Hydrocortisone + 2 U FFP+ Inj. Filgrastim DAY 1	Broad pectrum antibiotics + IPPV + supportive + Hydrocortisone + Inj.Filgrastim DAY 2	Broad spectrum antibiotics+ spont+ supportive+ Hydrocortisone + Inj Filgrastim DAY	Broad spectrum antibiotics+ supportive + Hydrocortisone + RT feed	Broad spectrum antibiotics + supportive + accepting orally

RESULTS AND DISCUSSION

- Our patient had persistent deterioration in clinical status and did not respond to routine management including antibiotics and mechanical ventilation support. He required continous inotropic support and had features suggestive of sepsis. The causes of sepsis are multifactorial but can include virtually any infectious organism. Microbial contamination of the peritoneal cavity is termed peritonitis or intra-abdominal infection and is classified according to etiology.

- Primary microbial peritonitis occurs when microbes invade the normally sterile confines of the peritoneal cavity via haematogenous dissemination from a distant source of infection or direct inoculation. Intra-abdominal sepsis, as suspected in our patient is more commonly the sequelae of secondary peritonitis which occurs subsequent to contamination of the peritoneal cavity due to perforation or severe inflammation and infection of an intra abdominal organ. Unfortunately, even with effective antimicrobial agent therapy, this disease process is associated with mortality rates in excess of 50%.[2] So despite the advent of newer broad spectrum antibiotics and modern surgical interventions the mortality rate of intra-abdominal sepsis is still very high and there has always been a search for some alternate or supportive treatment.

- It has been observed experimentally that GM-CSF has several effects in peritonitis, such as enhancement of hematopoiesis and immune reaction, and it may also play a role in the down-regulation of inflammatory mediators that are produced by bone marrow cells during abdominal sepsis. It is well known that GM-CSF enhances many of the granulocyte and monocyte-macrophage functions, such as the generation of superoxide anion in response to bacterial peptides, among many others.[3]

- Filgrastim has been mentioned as a rescue drug in certain high risk patients with established febrile neutropenia seen in pneumonia, hypotension, sepsis syndrome, multiorgan dysfunction, fungal infection, uncontrolled primary disease, or profound neutropenia (absolute neutrophil count (ANC) <100/mcL). [4] It is a hematopoietic hormone that promotes the growth and maturation of myeloid cells, and particularly, the proliferation and differentiation of neutrophils. The usual dose of filgrastim in cancer chemotherapy is 5 μg/kg/day and the duration depend on indication.

- Treatment with GM-CSF enhances cellular functions that are critical in wound healing such as neutrophil, monocyte, and macrophage activation; endothelial cell migration; keratinocyte proliferation; and fibroblast phenotype modulation. As a result, healing time is significantly reduced, even when contamination or radiation is present. In addition, GM-CSF has been shown to be useful in the treatment of chronic venous leg ulcers.[5]

- In our case filgrastim use resulted in resolution of patient's fever and improvement of his clinical condition probably by reversing bone marrow depression and increasing leucocyte and lymphocyte count, thus enabling him to mount an immune response and leading thereby to resolution of fever. There is an ongoing debate over use of filgrastim as an adjunct to antibiotic therapy because of its high cost and considering its unconvincing outcomes. Safety profile and low-dose use of filgrastim for shorter duration resulted in improved outcome of our case. Further randomized controlled trials are needed in similar scenarios to study adjunctive role of low-dose filgrastim as rescue therapy with antibiotics.

REFERENCES

1. Baron RM, Baron MI, Perella MA. Pathobiology of sepsis: are we still asking the same questions ? Am J Respir Cell Mol Biol 2006;34:129-34.
2. Lamme V, Mahler CW, VanRuler O. Clinical predictors of ongoing infection in secondary periotonitis : systemic review. World J Surg 2006;30:2170-2.
3. Pistoia V. Granulocyte-Macrophage colony-stimulating factor (GM-CSF); sources, targets and mechanism of action. Leukemia 1991;5(1):114-8.
4. T. J. Smith, J. Khatcheressian, G. H. Lyman et al. Update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. Journal of Clinical Oncology, vol. 24, no. 19, pp. 3187–3205, 2006.
5. Bodry GP, Anaissie E, Guttermann J, Vadhan-Raj S. Role of granulocyte macrophage colony-stimulating factor as adjuvant treatment in neurotpenic patients with bacteria and fungal infection. Eur J Clin Microbiol Infect Dis 1994;13(2):818-22.