□ LETTERS TO THE EDITOR □

POEMS Syndrome, Congestive Heart Failure and Thalidomide—Food for Thought**Key words:** thalidomide, POEMS syndrome**(Inter Med 49: 1919, 2010)****(DOI: 10.2169/internalmedicine.49.3758)**

To the Editor I read with interest the recent article by Inoue et al (1) describing a patient with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome and severe congestive heart failure (CHF) who was successfully treated with a combination chemotherapy regimen of thalidomide and dexamethasone. The decrease in vascular endothelial growth factor (VEGF) levels was coupled with marked improvement in cardiac markers, including ejection fraction and brain natriuretic peptide. While the role of VEGF in altering the microcirculation of the heart and the potential benefit of thalidomide in reducing the serum levels of VEGF and subsequently reversing the heart failure is described proficiently in this paper, there are other considerations which should not be overlooked.

The role of high levels of VEGF in causing acute systolic dysfunction is at best controversial. Recently, researchers have demonstrated VEGF to be a key therapeutic trophic factor in mesenchymal stem cell-mediated myocardial regeneration in an animal model (2). In the same breath, experimental and clinical data accumulating over the last decade suggests a causal relationship between immunological and inflammatory processes and heart failure. Tumor necrosis factor (TNF) levels are elevated in patients with advanced heart failure and have been reported to correlate with the severity of symptoms and with mortality. In an *in vitro* study lipopolysaccharide stimulated cardiac myocytes to excrete TNF in a dose-dependent manner, a phenomenon that could be inhibited by thalidomide and thalidomide analogues (3). In another pilot study nine patients with heart failure and left ventricular ejection fraction (LVEF) of lower than 40% who were on “optimal” therapy were given thalidomide 200 mg daily for 6 weeks. TNF alpha and LVEF were measured

at baseline and after 6 weeks of treatment (4). At baseline, plasma TNF levels were elevated and the ejection fraction was $26 \pm 9\%$. After 6 weeks of treatment TNF levels decreased significantly and the ejection fraction increased to $34 \pm 10\%$ ($p < 0.05$).

It is thus plausible that an interval decrease in the inflammatory milieu of the heart, including TNF alpha, achieved by thalidomide could have resulted in the resolution of CHF. It would have been very interesting to note the TNF levels in this patient at various stages of disease management and further explore the interplay between the inflammatory and immunological processes in the pathophysiology of heart failure, and the role of thalidomide in its management.

It is not to be forgotten that in addition to being implicated in heart failure, the activation of TNF alpha along with the pro-inflammatory cytokine network has been held responsible for the diverse manifestations of POEMS syndrome (5). Description of further cases recounting the association between POEMS syndrome and heart failure should be accompanied by a serial and more comprehensive evaluation of serum cytokines and soluble factors which can further help our understanding of the pathogenesis and manifestations of this little-known disorder.

Nishant Tageja

References

1. Inoue D, Kato A, Tabata S, et al. Successful treatment of POEMS syndrome complicated by severe congestive heart failure with thalidomide. *Intern Med* **49**: 461-466, 2010 Epub 2010 Mar 1.
2. Zisa D, Shabbir A, Suzuki G, Lee T. Vascular endothelial growth factor (VEGF) as a key therapeutic trophic factor in bone marrow mesenchymal stem cell-mediated cardiac repair. *Biochem Biophys Res Commun* **390**: 834-838, 2009 Epub 2009 Oct 15.
3. Agoston I, Dibbs ZI, Wang F, et al. Preclinical and clinical assessment of the safety and potential efficacy of thalidomide in heart failure. *J Cardiac Fail* **8**: 306-314, 2002.
4. Gullestad L, Semb AG, Holt E, et al. Effect of thalidomide in patients with chronic heart failure. *Am Heart J* **144**: 847-850, 2002.
5. Gherardi RK, Bélec L, Soubrier M, et al. Overproduction of proinflammatory cytokines imbalanced by their antagonists in POEMS syndrome. *Blood* **87**: 1458-1465, 1996.