

Is There a Connection Between Mannan-binding Lectin Deficiency and Chronic Leg Ulcers?

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Accepted August 28, 2008.

Sir,

Mannan-binding lectin (MBL) is an important member of the innate immune system. Deficiency of MBL has been associated with increased propensity to infections, particularly in childhood (1). MBL deficiency is the most frequent immunodeficiency and 10–15% of the Caucasian normal population has significantly reduced MBL levels due to polymorphisms in the promoter region and first exon of the MBL gene (2). Recently, a plasma-derived MBL has been produced, MBL SSI (Statens Serum Institut, making intravenous substitution therapy possible (3, 4).

CASE REPORT

We describe here the case of a 58-year-old MBL-deficient (serum MBL concentration <10 µg/l and genotype XA/B) man with a 15-year history of chronic leg ulcer

following extraction of the saphenous vein for coronary bypass surgery (Fig. 1). A small ulcer in contact with bone in the sternal cicatrix also remained. Peripheral perfusion was normal (ankle/arm blood pressure index >0.8). Two biopsies showed no signs of malignancy. Over the years the patient was treated with compression due to venous insufficiency, three split skin transplantations were performed and the patient was treated with antibiotics for several months because of colonization of the chronic wound with *Staphylococcus aureus* and *Pseudomonas* spp.

When it was discovered that the patient was MBL-deficient we tried to improve the healing of his wounds by substitution therapy with MBL SSI. Using a dose of 12–18 mg/ml MBL in isotonic saline twice a week for 4 weeks, we achieved complete healing of the sternal ulcer and a significant reduction in both depth and area of the leg ulcer (Fig. 1). The serum concentration of MBL rose from <10 µg/l to >4000 µg/l 30 min after infusion and did not fall below 500 µg/l between infusions. The MBL treatment was performed according to guidelines from the manufacturer. Following the first treatment series the patient was discharged to home healthcare. After 3 months the leg ulcer had relapsed to its original size, but the sternal lesion remained healed. Two years later the patient was referred back to Copenhagen Wound Healing Center where a second MBL treatment was undertaken. Again, MBL treatment resulted in almost complete healing of the leg ulcer. *S. aureus* and *Pseudomonas* spp. are very frequent in chronic ulcers and the same was seen in this case, but no infection was recognized. Antibiotic treatment was not introduced. Following discharge the ulcer recurred within 3 months.

During the MBL treatment periods chronic obstructive lung disease (COLD) and paradontitis also improved significantly, as judged from positive end experience pressure and cessation of the paradontitic process.

DISCUSSION

This is to our knowledge the first attempt to treat chronic ulcers in MBL-deficient patients with MBL substitution therapy and the results are very encouraging. The patient acted as his own control in the period between the two treatments and we must conclude that only during MBL treatment was an improved healing seen. The improvement could be a parallel phenomenon



Fig. 1. The chronic ulcer (A) before and (B) after 4 weeks of mannann-binding lectin substitution therapy. (A) Initially the ulcer was split in two areas, 5 × 15 cm and 5 × 5 cm, surrounded by toxic eczema due to tissue liquefaction. The ulcer showed sparse granulation. (B) After treatment the ulcer was markedly reduced in depth and size and granulation was extensive.

and not due to the MBL, but neither the type of dressing nor the type of compression bandage was changed during of between MBL-substitution periods. Different mechanisms may explain the effect of MBL on wound healing: a general improvement of opsonic function and modulation of the cytokine response to tissue damage and a combination of both these mechanisms (1, 5). The quality of treatment of chronic ulcers in clinical practice is of great importance for the quality of life of the individual patient and, due to the large number of such patients, for the cost of the total healthcare system. We propose that MBL substitution therapy to MBL-deficient patients with recurrent or treatment-resistant leg ulcers is examined within the framework of clinical trials. With a 10–15% prevalence of MBL deficiency the number of patients that might benefit from such therapy is considerable.

REFERENCES

1. Kilpatrick DC. Mannan-binding lectin: clinical significance and applications. *Biochim Biophys Acta* 2002; 1572: 401–413.
2. Madsen HO, Garred P, Thiel S, Kurtzhals JA, Lamm LU, Ryder LP, Svejgaard A. Interplay between promoter and structural gene variants control basal serum level of mannan-binding protein. *J Immunol* 1995; 155: 3013–3020.
3. Laursen I. Mannan-binding lectin (MBL) production from human plasma. *Biochem Soc Trans* 2003; 31: 758–762.
4. Valdimarsson H, Vikingsdottir T, Bang P, Saevarsdottir S, Gudjonsson JE, Oskarsson O, et al. Human plasma-derived mannose-binding lectin: a phase I safety and pharmacokinetic study. *Scand J Immunol* 2004; 59: 97–102.
5. Jack DL, Read RC, Tenner AJ, Frosch M, Turner MW, Klein NJ, et al. Mannose-binding lectin regulates the inflammatory response of human professional phagocytes to *Neisseria meningitidis* serogroup B. *J Infect Dis* 2001; 184: 1152–1162.