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## **Granulocyte-macrophage colony-stimulating factor-related eosinophilia and Loeffler's endocarditis [letter]**

K Donhuijsen, C Haedicke, S Hattenberger, C Hauswaldt and M Freund

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## GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR-RELATED EOSINOPHILIA AND LOEFFLER'S ENDOCARDITIS

To the Editor:

Activated eosinophils exert toxicity to the myocardium mediated by their major basic protein.<sup>1-3</sup> We have evidence that eosinophilia induced by recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF) may not be a harmless phenomenon in some patients.

**Case Report.** A 66-year-old caucasian man presented first in 1986 with fever and an absolute neutrophil count of 400 to 800/ $\mu$ L. In the following years, the patient had recurrent bacterial infections with several episodes of pneumonia and perianal abscesses. In September 1990, he was admitted with another episode of fever. The white blood cell count (WBC) was 1,300/ $\mu$ L with 4 segmented neutrophils and 96 lymphocytes in the differential. The hemoglobin (Hb) was 11.1 g/dL and the platelets were 117,000/ $\mu$ L. Fibrotic scars in the upper lungs were visualized in the CT but no infiltrates. A normal-sized hyperkinetic ventricle, normal morphology of the valves without vegetations, and 5 mm of pericardial effusion was seen by echocardiography. No infectious pathogen was identified. Myelodysplasia classified as refractory anemia without ringed sideroblasts and without clonal abnormality in a cytogenetic analysis was found in the bone marrow aspirate.

Because empiric antibacterial and antifungal therapy was ineffective, daily subcutaneous doses of 3  $\mu$ g/kg GM-CSF (Schering-Plough, Kenilworth, NJ) were started on October 16. The WBC increased from 900 to 4,500/ $\mu$ L within 8 days, peaking at a maximum of 22,300/ $\mu$ L on November 8, with a differential of 86% eosinophils and 14 lymphocytes. The dose of GM-CSF was reduced to 1.5  $\mu$ g/kg. The patient's fever resolved 2 days later.

He developed a severe paranoid depression, subsequently requiring hospitalization at the end of December. On February 21, he was still afebrile and his general condition improved. Eosinophils were prevalent in the bone marrow, and blasts were below 5%, whereas neutrophils were completely absent. The results of another cytogenetic analysis were normal. GM-CSF was discontinued.

The fever reappeared 2 weeks later after a decrease in the WBC to 2,100/ $\mu$ L with 18% neutrophils and 82% lymphocytes. No specific infection was identified. On March 20, GM-CSF was restarted at a dose of 2  $\mu$ g/kg. The WBC increased again to 7,900/ $\mu$ L with 35% eosinophils, 1% basophils, and 64% lymphocytes. With a persistent fever and a poor general condition, the patient refused further specific treatment and the administration of GM-CSF on May 3. He died 7 days later.

At the time of the autopsy, neutrophils were completely absent in the bone marrow, and a marked eosinophilia was present with no evidence of fibrosis. The parietal endocardium of both ventricles was thickened with fibrosis and lined with large mural thrombi of different ages. Foci of microscopic scars were detected in the inner third of the myocardium. The patient had died from necrotizing pneumonia with excessive eosinophilia and clusters of Charcot-Leyden crystals.

Pleural and pericardial effusions are well known with high doses of GM-CSF, but no myocardial side-effects have yet been reported. Loeffler's endocarditis is a feature of certain systemic diseases with significant eosinophilia.<sup>3</sup> Because GM-CSF is a potent activator of eosinophils,<sup>4,5</sup> we believe that the patient's Loeffler's endocarditis was induced by GM-CSF. His psychotic depressions can possibly be attributed to a cerebral arteritis based on the same mechanism. Patients in future studies should be carefully screened for similar side-effects.

K. DONHUIJSEN  
C. HAEDICKE  
S. HATTENBERGER  
C. HAUSWALDT  
*Municipal Hospital  
Braunschweig, Germany*  
M. FREUND  
*Hannover Medical School  
Hannover, Germany*

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