Fatal Myocardial Necrosis Caused by *Staphylococcus lugdunensis* and Cytomegalovirus in a Patient with Scleroderma

Laura Pirilä,¹ Karl-Ove Söderström,² Marja Hietarinta,¹ Jari Jalava,^{3,6} Ville Kytö,^{4,5*} and Auli Toivanen¹

Departments of Medicine,¹ Pathology,² Medical Microbiology,³ Virology,⁴ and Anatomy,⁵ University of Turku, Turku, Finland, and Department of Bacterial and Inflammatory Diseases, National Public Health Institute, Turku, Finland⁶

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A 42-year-old woman developed a rapidly progressing fatal heart failure. At the autopsy extensive necrosis of the myocardium was seen, with an almost complete absence of inflammatory cells and the presence of bacterial structures identified as *Staphylococcus lugdunensis* by PCR. In addition, the cytomegalovirus genome was found to be located inside the cardiomyocytes.

CASE REPORT

A 42-year-old nonsmoking woman was diagnosed with CREST-type scleroderma in December 1996. She was placed on penicillamine treatment after a poor therapeutic response to prednisone. Her heart seemed slightly enlarged on chest X-ray but appeared normal on echocardiography. Both of her parents had rheumatoid arthritis. For almost the whole summer and fall of 1997 she had had a severe cough, a slight fever, and fatigue. One week before she arrived at the emergency room her company physician diagnosed a pneumonia and started her on a 6-day treatment with azithromycin. On 3 November, at 3 a.m., she walked to the emergency room with cough and dyspnea as the main symptoms. Just after she arrived, she collapsed and underwent cardiorespiratory arrest. After successful resuscitation she was transferred to the intensive care unit and was connected to a respirator. A chest X ray showed pulmonary edema and inflammation. The electrocardiogram showed no abnormalities at this point. Blood cultures, as well as several bacterial cultures of bronchoalveolar lavage, tracheal aspiration, and pleural fluid samples, were negative. The medication included methylprednisolone, which was continued in the intensive care unit at a dose of 500 mg daily for 3 days; thereafter, the dose was lowered. Ceftriaxone was started, but after a week it was replaced by ceftazidime and fluconazole was added. Myocarditis, pulmonary embolism, and myocardial infarction were considered as possible etiologies for the heart failure. The patient's blood had leukocytosis of $20.3 \times 10^9/\text{liter}$. The lymphocyte counts were slightly decreased ($0.44 \times 10^9/\text{liter}$) on arrival, but on the day of death the count was low normal ($0.81 \times 10^9/\text{liter}$). After a week, signs of myocardial damage appeared in the electrocardiogram. Echocardiography showed severe diastolic dysfunction. Two weeks after admission, the patient's condition deteriorated; she had an attack of cough, bradycardia, and

then asystole. There was no response to the resuscitation efforts.

At the autopsy hemorrhagic edema of the lungs was found. The pulmonary arteries were open. The coronary arteries were open and thin walled. Extensive fresh necrosis of the myocardium, comprising over half of the heart muscle, was found. In the other organs lesions compatible with cardiac failure were the main findings. By microscopic examination, necrosis of the myocardium was a dominant feature, with severe destruction of the cardiomyocytes (Fig. 1). The most surprising finding was the almost absolute absence of inflammatory cells and the presence of grape-like accumulations of round structures. On electron microscopy they seemed to be microbes (Fig. 1).

All efforts to isolate bacteria or viruses from the myocardial samples were unsuccessful. PCR with primers recognizing 16S rRNA-coding genes was performed with DNA extracted from the myocardium (8, 9). The PCR product was cloned by using a TOPO TA cloning kit (Invitrogen, Carlsbad, CA), according to the manufacturer's instructions. The 16S rRNA gene inserts of eight different plasmids were sequenced, and the sequences were compared to those in the European Bioinformatics Institute sequence database (8). As a surprise, the results indicated the presence of *Staphylococcus lugdunensis*, which also fit well with the microscopic structures seen abundantly in the myocardium. Myocardial samples from our patient were later included in a systematic study on the viral etiology of myocarditis (5). Cytomegalovirus was found by PCR, and in situ hybridization demonstrated the viral genome inside the cardiomyocytes (5).

Our case has some very unusual features. The extensive necrosis but the almost complete absence of inflammatory cells in the postmortem examination was unexpected, and the classical histopathological Dallas criteria of myocarditis (2) were barely fulfilled. We are aware of only one similar case published earlier, by Gordon and Madhok in 1999 (3). Their 36-year-old patient also had a rheumatological disease characterized by Raynaud's phenomenon that was considered to be

* Corresponding author. Mailing address: Department of Anatomy, Institute of Biomedicine, University of Turku, Kiinamyllynkatu 10, 20520 Turku, Finland. Phone: 358 2 333 7589. Fax: 358 2 333 7352. E-mail: ville.kyto@utu.fi.

FIG. 1. Histological (A) and electron microscopic (B and C) pictures of the heart muscle. The muscle cells are better preserved to the left (A), but small microorganisms can be seen in the cytoplasm of the muscle cells. They are more numerous in the muscle cells to the right, which also show extensive hydropic degeneration. Note the almost complete lack of inflammatory cells. Small round microorganisms can be seen in the cytoplasm of the degenerative muscle cell (B). A central, less dense region can be seen in the microorganisms (C). Magnifications, $\times 100$ (A), $\times 3,000$ (B), and $\times 10,000$ (C).

polymyositis. In that case a myocardial biopsy sample was taken, and it showed gross myocardial necrosis with no evidence of inflammatory infiltration. Extensive necrosis was confirmed in the postmortem microscopic examination of the myocardium, with no evidence of coronary artery disease, vasculitis, or inflammation. The authors supposed that the etiology was widespread coronary vasospasm. This can hardly be attributed to our case, in which infection was obvious. During the postmortem examination, more than half of the myocardium of our patient was found to be necrotic. A recent study has demonstrated that not only necrotic cell death but also apoptotic cell death is a common mechanism of cardiomyocyte destruction in myocarditis and may play a role in the development of fatal heart failure (4). Our patient was included in that study, and 4% of her cardiomyocytes were found to be apoptotic (4). The role of scleroderma in the pathogenesis of myocarditis remains uncertain. Penicillamine is not known to cause severe immunosuppression, and no severe cytopenias were seen. It is possible that autoimmune diseases such as polymyositis or scleroderma could predispose an individual to this type of fulminant myocardial damage.

The second surprise was the microbe-like structures that were seen in abundance among the necrotic cardiomyocytes and which turned out to be *Staphylococcus lugdunensis* by 16S rRNA analyses. Five of the eight cloned 16S rRNA sequences gave the 16S rRNA of *Staphylococcus lugdunensis* as the most similar sequence. The highest degree of similarity to published *Staphylococcus lugdunensis* 16S rRNA sequences was 99.7% (575-nucleotide overlap), and the lowest degree of similarity was 96.0% (300-nucleotide overlap). Three other cloned 16S rRNA gene sequences showed low or moderate similarities to *Abiorthopia adiacens* (93.0%), *Propionibacterium acnes* (98.3%), and *Fusobacterium prausnitzii* (86.7%).

Staphylococcus lugdunensis is known to cause endocarditis (1, 7), but it has never been described in myocarditis. Then, in a later study, a systematic search for different viruses by PCR and in situ hybridization in fatal myocarditis was carried out. It turned out that cytomegalovirus was most often found (5). Cytomegalovirus is known to cause a wide spectrum of diseases, including, among others, pneumonitis (6). Thus, the long-lasting cough can also be explained.

We conclude that in this patient with scleroderma, a double infection with *Staphylococcus lugdunensis* and cytomegalovirus led to the extensive necrosis of the myocardium, but the almost complete absence of inflammatory cells remains without explanation. According to our knowledge, this is the first report of a case of myocarditis caused by *Staphylococcus lugdunensis*.

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