

with a lower risk of infection in such cases.⁶ Subpectoral placement is preferred not only for cosmetic reasons but also because of the greater protection provided by the pectoral muscle in young patients.

In conclusion, although patients require close lifetime follow-up due to the risk of venous thrombosis and the possible need for lead extraction, we consider that endocardial pacing in pediatric patients weighing less than 10 kg is a reasonably safe and effective option in hospitals with experience.

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A Rare Life-threatening *Kodamaea ohmeri* Endocarditis Associated With Hemophagocytic Lymphohistiocytosis



Inusual endocarditis grave por *Kodamaea ohmeri* asociada a linfohistiocitosis hemofagocítica

To the Editor,

We report the case of a 57-year-old man with a 3-month history of intermittent pyrexia. He received irregular antibacterial therapy and thrombolysis in a local hospital due to occlusion of the right distal popliteal artery. His medical history included multiple fractures, allergic purpura, and hypertension. His medications included prednisone (30 mg orally per day), metoprolol, and amlodipine.

On physical examination, breath sounds were clear and a 3/6 pansystolic murmur was auscultated at the right sternal border. Swelling of the right leg and gangrene at the fifth toe were found. Abdominal palpation revealed mild splenomegaly. The following abnormal laboratory results were identified: white cell count, $3.20 \times 10^9/L$; platelet count, $30 \times 10^9/L$; hemoglobin, 8.80 g/dL; albumin, 2.99 g/dL; erythrocyte sedimentation rate, 42 mm/h; C-reactive protein, 13.30 mg/L; and ferritin, 674 $\mu\text{g/L}$.

Three blood cultures were positive and a gram stain showed budding yeast cells. The isolate, after being subcultured on CHROMagar (Becton Dickinson, Paris, France), showed membranous colonies that changed color from pink to blue within 48 hours (Figure A). On corn meal agar (Becton Dickinson), pseudohyphae and blastoconidia were seen 24 hours later (Figure B). The yeasts were identified as *Kodamaea ohmeri* (*K. ohmeri*). Drug sensitivity testing showed that this strain was susceptible to voriconazole, fluconazole, itraconazole, and amphotericin B.

Bone marrow aspiration, performed due to the cytopenia, showed phagocytosis of hematopoietic cells by activated macrophages (Figure C). Thoracoabdominal computed tomography revealed splenomegaly and mild bilateral pleural effusion. Transthoracic echocardiography showed a large vegetation (30 mm \times 12 mm) on the aortic valve with mild regurgitation and stenosis.

On hospital day 5, the patient developed persistent pyrexia with a temperature of 39 °C despite antifungal therapy with intravenous voriconazole. Urgent surgery was performed and a large fragile and loose vegetation was found on the aortic valve that almost occluded the orifice (Figure D). The aortic valve was replaced with a 21-mm mechanical prosthesis (St. Jude Medical, St. Paul, MN, United States). Continued blood loss of more than 200 mL/h occurred in the postoperative period. The coagulation profile

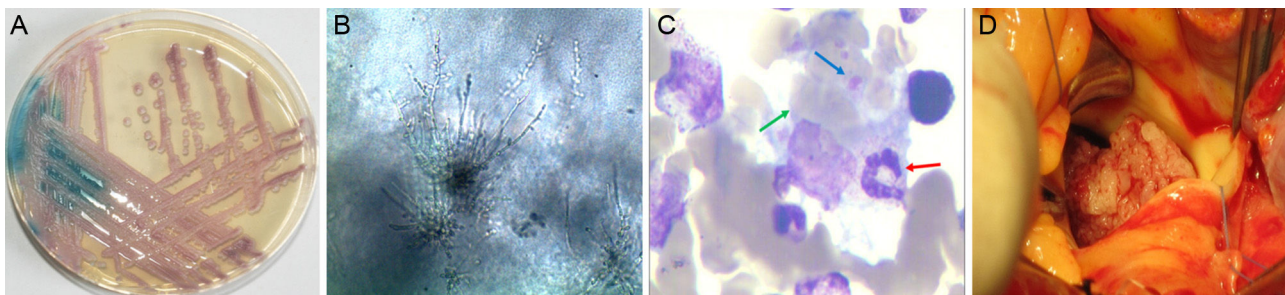


Figure. A: Color change of *K. ohmeri* cultured on CHROMagar Candida medium. B: Subcultured on corn meal agar, the yeast shows pseudohyphae and blastoconidia. C: Bone marrow smear shows macrophage phagocytosis of a band neutrophil (red arrow), multiple red blood cells (green arrow), and platelets (blue arrow) (Giemsa stain; magnification, $\times 1000$). D: Intraoperative view shows a large fragile and loose vegetation on the aortic valve that almost occludes the orifice.

Table
Summary of the Characteristics of the Patients With *K. ohmeri* Endocarditis

Age/sex	Predisposing factor(s)	Duration	Involved valves	Vegetation dimension	Embolic event	Organomegaly	Hemocytopenia	Treatment	Result	Reference
76 y/M	MVR+CABG, pacemaker implantation	1 d	Prosthetic mitral valve	5-cm length	Splenic infarction	No	Thrombocytopenia	MVR, pacemaker removal, AmB lipid complex	Recovered	Reina et al. ³
42 y/M	Heroin addict, hepatitis C, peripheral vasculopathy	2 wk	Mitral valve with rheumatic disease	20 mm in largest diameter	Occlusion of the distal left popliteal artery	No	Erythropenia	Embolectomy, MVR, liposomal AmB	Recovered	João et al. ⁴
43 y/M	Hepatitis B	2 mo	Mitral valve with rheumatic disease	Not described	No	No	Erythropenia	MVR+TVP, itraconazole	Recovered	Yanghua et al. ⁵
40 d/M	Neonatal seizures, necrotizing enterocolitis	20 d	Tricuspid valve	11.1 × 6.4 mm	No	No	Erythropenia	AmB	Death	Sundaram et al. ⁶
57 y/M	Multiple trauma, broad-spectrum antibiotic therapy, long-term use of prednisone	3 mo	Aortic valve	30 × 12 mm	Occlusion of the distal right popliteal artery	Splenomegaly	Pancytopenia	AVR, voriconazole	Recovered	Present case

AmB, amphotericin B; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; M, male; MVR, mitral valve replacement; TVP, tricuspid valve plasty.

showed hypocoagulability with fibrinogen of less than 1.5 g/L and a platelet count of $20 \times 10^9/L$. Hemophagocytic lymphohistiocytosis (HLH) was diagnosed and the patient was started on intravenous methylprednisolone 500 mg/d and immunoglobulin 0.5 g/kg/d for 3 days and transfusion of packed red blood cells, plasma, platelets, cryoprecipitate, and fibrinogen. The treatment effectively stopped the bleeding. The patient eventually recovered well and was discharged.

HLH is rare and has a mortality of 41%. It is characterized by defective cytotoxic cell control of an initial immune response that progresses to uncontrolled macrophage activity and hypercytokinemia. This activation produces an exaggerated inflammatory response and hypersecretion of cytokines in a so-called cytokine storm.¹

According to the HLH-2004 diagnostic guidelines, our case fulfilled 6 of the 8 criteria, namely, fever, splenomegaly, cytopenia, fibrinogen ≤ 1.5 g/L, hemophagocytosis in the bone marrow, and ferritin ≥ 500 $\mu\text{g/L}$. After reviewing 2197 adult HLH cases, Ramos-Casals et al.¹ determined that viral infection was the most common cause of HLH (34.68%); fungus (1.68%) was a less frequent trigger. *K. ohmeri* is a rare fungal pathogen in humans. There is no published report of secondary HLH related to *K. ohmeri* infection and we believe it to be a new trigger of HLH.

K. ohmeri is commonly used in the food industry for its fermentation ability. The first case of human infection was reported in 1998, and the pathogen, isolated from pleural fluid, was considered a contaminant.² *K. ohmeri* endocarditis has thus far only been reported in 4 patients.^{3–6} The characteristics of all 5 cases (including the present patient) are described in the Table. The patients were all male with predisposing factors. The mitral valve was the most commonly involved valve. The present patient is the first reported case with aortic valve involvement. Vegetations were larger than 10 mm in 4 of the 5 patients. This feature is associated with fungal endocarditis and favors the occurrence of embolic events. A combination of valve replacement and an antifungal drug was used to treat *K. ohmeri* endocarditis in 4 of the

5 patients. One patient, treated by antifungal therapy alone, died before planned surgery could be performed; consequently, we believe that surgery should be urgently performed to treat *K. ohmeri* endocarditis. Compared with the previously reported cases, the present patient had a longer duration that induced more severe multiorgan injuries, which may be the potential cause of the associated HLH.

In the present case, *K. ohmeri* emerged as a rare infectious fungus and was accompanied by a life-threatening HLH, which undoubtedly complicated endocarditis diagnosis and treatment. We believe that multidisciplinary collaboration can favor early recognition and diagnosis and will eventually result in a specific therapy.

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Association Between Mutations in the NKX2.5 Homeobox, Atrial Septal Defects, Ventricular Noncompaction and Sudden Cardiac Death



Asociación entre mutaciones en el homeodominio de NKX2.5, desarrollo de defectos del tabique interauricular, falta de compactación ventricular y muerte súbita

To the Editor,

Phenotypic overlapping of congenital heart disease, noncompaction cardiomyopathy, and arrhythmogenic cardiomyopathy is uncommon. In *Revista Española de Cardiología*, Bermúdez-Jiménez et al.¹ published an article describing a family with a mutation in the *NKX2.5* gene (p.Glu167Lys) showing this phenotype. We consider it appropriate to further highlight the risk of sudden death associated with *NKX2.5* mutations related to this phenotype. To this end, we describe a family attended in our center

The *NKX2.5* gene codes for a transcription factor containing 3 domains that are implicated in cardiac development.² The homeobox domain is needed for interactions with DNA and other transcription factors. *NKX2.5* mutations have been associated with cardiac septal defects, conduction defects, and noncompaction cardiomyopathy.

We present the case of a 30-year-old woman, whose paternal grandfather had died suddenly in his sleep at the age of 40 years. She was referred to our center for study after her brother experienced cardiac arrest. Her sister had died suddenly in childhood in the postoperative period following atrial septal defect (ASD) repair. Her brother experienced cardiac arrest in his

sleep, with asystole followed by ventricular fibrillation after resuscitation maneuvers. Echocardiography detected mild left ventricular dilation, with evidence of noncompaction, moderate-severe systolic dysfunction, and an atrial septal aneurysm with no shunting. Electrocardiography findings were normal. He ultimately died due to hypoxic-ischemic encephalopathy. Autopsy was not performed. His father and mother showed no abnormalities on echocardiography or 24-hour Holter monitoring.

Our patient had undergone surgical repair of an ostium secundum ASD in infancy. Cardiac magnetic resonance showed left ventricular noncompaction, with a left ventricular ejection fraction at the lower limit of normal. First-degree atrioventricular block was observed, with no other abnormalities on Holter monitoring.

The patient is the mother of 2 children (5 and 4 years of age) diagnosed with ostium secundum ASD and hypertrabeculation on echocardiography, with no evidence of noncompaction and a prolonged PR interval for their age. The defects have not been treated to date.

Genetic study of her deceased brother was performed, using a new-generation sequencing panel. Exons from 268 genes were included, and the analysis was focused on 16 of them: *ACTC1*, *CASQ2*, *DMD*, *DTNA*, *HCN4*, *LDB3*, *LMNA*, *MYBPC3*, *MYH7*, *NKX2-5*, *SCN5A*, *TAZ*, *TNNI3*, *TNNT2*, *TPM1* and *VCL*. A variant in heterozygosity was identified in *NKX2.5* (p.Lys183Asn). The mutation has not been described previously in public databases of the general population nor has it been indicated as deleterious by bioinformatic predictors. The p.Lys183Asn variant affects a residue with high evolutionary conservation (Figure 1). Our patient, her children, and her father are all carriers of the mutation, whereas her mother is not a carrier.



Figure 1. Graphic representation of the p-Arg142Cys mutation in *NKX2-5*. Nucleotide sequence and protein sequence, showing their conservation.