CASE REPORT

Ureaplasma parvum causing life-threatening disease in a susceptible patientAlexander Korytny,¹ Roni Nasser,¹ Yuval Geffen,² Tom Friedman,³ Mical Paul,⁴ Nesrin Ghanem-Zoubi⁴¹Department of Internal Medicine B, Rambam Health Care Campus, Haifa, Israel²Microbiology Laboratory, Rambam Health Care Campus, Haifa, Israel³Department of Cardiac Surgery, Rambam Health Care Campus, Haifa, Israel⁴Infectious Diseases Institute, Rambam Health Care Campus, Haifa, Israel**Correspondence to**

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SUMMARY

A 56-year-old man with lymphoma developed orchitis followed by septic arthritis of his right glenohumeral joint. Synovial fluid cultures were negative but PCR amplification test was positive for *Ureaplasma parvum*. The patient was treated with doxycycline. Two and a half years later, the patient presented with shortness of breath and grade III/IV diastolic murmur on auscultation. Echocardiography revealed severely dilated left heart chambers, severe aortic regurgitation and several mobile masses on the aortic valve cusps suspected to be vegetations. He underwent valve replacement; valve tissue culture was negative but the 16S rRNA gene amplification test was positive for *U. parvum*. He was treated again with doxycycline. In an outpatient follow-up 1 year and 3 months later, the patient was doing well. Repeated echocardiography showed normal aortic prosthesis function.

BACKGROUND

Ureaplasma spp are known to cause epididymo-orchitis. Septic arthritis caused by *Mycoplasmas* and *Ureaplasmas* (members of the family *Mycoplasmataceae*) is very rare, but has been reported in immunosuppressed patients.¹ Recent studies show that a vast majority of *U. parvum* isolates are susceptible to levofloxacin, tetracycline and macrolide antibiotics.²

CASE PRESENTATION

A 56-year-old man was admitted on December 2015 with shortness of breath.

On April 2013, he had been diagnosed with primary central nervous system lymphoma and received chemoradiotherapy.

On June 2013, while being treated with chemotherapy, the patient was diagnosed with orchitis. A urine culture taken before antimicrobial treatment revealed mixed growth, representing contamination. He was treated empirically with ciprofloxacin for 10 days with clinical resolution of symptoms.

Ten days after completing antimicrobial treatment, he was diagnosed with septic arthritis of the right glenohumeral joint requiring hospitalisation. He had leucocytosis of 24,000/ μ L with 90% neutrophils and C reactive protein (CRP) of 197 mg/L. Arthroscopy was performed with evacuation of pus. Synovial fluid aspiration showed a leucocyte count of 108×10^9 /l with 97% neutrophils and glucose of 2 mg/dL. Direct Gram stain, and synovial fluid and blood cultures were negative. A second arthroscopy 2 weeks later

again showed negative Gram stain and culture. A 16S rRNA gene PCR amplification test from synovial fluid was positive with >99% identity for *U. parvum*. The patient was treated with ceftazidime and vancomycin empirically, followed by cefazolin and ciprofloxacin, altogether for 3 weeks with gradual improvement. After the diagnosis of *U. parvum* septic arthritis the patient was treated with oral doxycycline 100 mg twice daily for 6 weeks.

Two and a half years later, the patient was readmitted to our hospital due to shortness of breath. He was in complete remission since July 2013. He was afebrile, and physical examination was normal except for a grade III/IV diastolic heart murmur heard best on the left sternal border. The haemoglobin was 10.3 g/dL, CRP 7.4 mg/L (normal limits 0–5) and troponin I 0.118 ng/mL (normal limits 0–0.028). ECG revealed normal sinus rhythm. Enlarged heart silhouette and accentuated lung hili were noted on chest X-ray. Echocardiography was performed showing severe left atrial and ventricular enlargement, left ventricular ejection fraction of 55%, severe aortic regurgitation (AR) and several mobile masses on the aortic valve cusps (figure 1), with suspected perforation of the left leaflet. The severely dilated left heart chambers were suggestive of a long-standing valvular regurgitation. Blood cultures were negative. The patient was diagnosed with culture-negative endocarditis (CNE) and investigated considering the local epidemiology of CNE in Israel. Q fever indirect fluorescence assay and *Bartonella henselae* ELISA serology tests, were negative. The patient underwent aortic valve replacement surgery for symptomatic severe AR 7 days after admission. Findings on surgery included a ruptured leaflet and several vegetations. Valve pathology yielded calcifications and paucity of lymphocytes. Valve tissue culture was negative but the 16S rRNA PCR gene amplification test from the valve was positive for *U. parvum*.

INVESTIGATIONS

For molecular identification, DNA was extracted from the sample using QIAamp DNA Mini Kit (Qiagen, Valencia, California, USA). Broad-range 16S ribosomal RNA gene was performed using two sets of primers.^{3,4} PCR products were separated by electrophoresis, sequenced using the 3130 genetic analyser capillary electrophoresis DNA sequencer and analysed using a basic local alignment search tool.

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Figure 1 Severe left atrial and ventricular enlargement, mobile mass on the aortic valve cusp (A); severe aortic regurgitation (B).

Efforts to isolate the pathogen from valve tissue culture including seeding on blood, chocolate and chromogenic plates in our local microbiology laboratory were unsuccessful. We further sent the valve tissue specimen to a referral laboratory (Unité de Recherche sur les Maladies Infectieuses et Tropicales Émergentes, Marseille, France). Valve cultures were negative in both laboratories.

DIFFERENTIAL DIAGNOSIS

We debated whether his final presentation represented active endocarditis or whether it was the consequence of progressive degenerative changes following undiagnosed endocarditis that developed during or early after the septic arthritis episode. The latter assumption was supported by absence of fever and the paucity of inflammation on excised valve. Persistence of bacterial DNA on valve tissue for years following an episode of infective endocarditis (IE) has been described in *Bartonella* spp⁵ and *Coxiella burnetii* endocarditis,⁶ a finding that does not correspond necessarily with persistence of viable bacteria. On the other hand, the unexplained and severe AR with preoperative echocardiography and intraoperative findings were highly suggestive of active endocarditis.

TREATMENT

After the valve replacement, we recommended doxycycline 100 mg twice daily for 6 months with no evidence to guide the optimal treatment duration. No adverse events were observed throughout the treatment, but the effect of treatment on selection of antibiotic-resistant bacteria was not monitored.

OUTCOME AND FOLLOW-UP

On follow-up 1 year and 3 months later, the patient was doing well. Repeated echocardiography showed normal aortic prosthesis function.

Table 1 Nine cases of infective endocarditis caused by *Mycoplasmataceae*

Patient (reference)	Age, sex	Underlying condition(s)	Valve(s)	Symptom(s)	Diagnostic tool	Pathogen	Surgery	Antibiotic therapy (duration, weeks)	Outcome
1 7	33, M	Mitral valve plasty	Mitral	Heart failure	PCR from cardiac valve	<i>M. hominis</i>	Y	Amo and genta (3); Doxy (4)	Survival
2 7	57, F	Prosthetic aortic valve	Aortic	Heart failure	PCR from cardiac valve	<i>U. urealyticum</i>	Y	Vanco (8); Genta (2)	Death
3 9	21, M	RHD; dental extraction without antibiotic prophylaxis 4 weeks before hospitalisation	Mitral	Fever, anorexia, sore throat, malaise	Serology	<i>M. pneumoniae</i>	N	Benz and genta (6); Oxy (4)	Survival
4 10	25, F	SLE treated with corticosteroids; <i>Streptococcus sanguis</i> endocarditis; prosthetic aortic and mitral valves	Aortic and mitral	Fever	Culture from a portion of valve	<i>M. hominis</i>	Y	Clin and rif (6); Doxy (4)	Survival
5 11	40, M	RHD, aortic and mitral replacement	Aortic and mitral	Abdominal pain, jaundice, fever	16S rDNA PCR, culture	<i>M. hominis</i>	Y	Doxy and clin (8)	Survival
6 12	74, M	Aortic and mitral valve replacement	Aortic	Dizziness, cardiac and kidney failure	16S rDNA PCR, culture	<i>M. hominis</i>	Y	Doxy and clin (9)	Survival
7 13	57, M	Aortic valve replacement, aortic root and mitral repair	Aortic	Dyspnoea, fatigue, chest pain	16S rDNA PCR	<i>M. hominis</i>	Y	Doxy and clin (9)	Survival
8 8	46, M	Mitral valve replacement	Mitral	Dyspnoea, heart failure	Culture	<i>M. hominis</i>	Y	Vanco and amika	Death
9 (PR)	56, M	s/p lymphoma, s/p septic arthritis with <i>U. parvum</i>	Aortic	Dyspnoea, heart failure	PCR from cardiac valve	<i>U. parvum</i>	Y	Doxy (8)	Survival (15 months after surgery)

Amika, amikacin, Amo, amoxicillin, Benz, benzylpenicillin, Clin, clindamycin, Doxy, doxycycline, Genta, gentamicin, Oxy, oxytetracycline, PR, present report, RHD, rheumatic heart disease, Rif, rifampin, SLE, systemic lupus erythematosus, s/p, status post, Vanco, vancomycin

DISCUSSION

Eight previous cases of endocarditis caused by mycoplasmas and ureaplasmas in adults have been reported (table 1).

All patients that were treated with tetracycline (n=6) survived, while two patients that did not receive antimicrobial therapy eventually died.^{7,8} Treatment duration was 4 weeks in three cases and 8–9 weeks in three. The prolonged antibiotic course we recommended after valve replacement is not evidence-based and is based on personal opinion considering the chronic course of the disease and the transplanted biological valve.

We present this case to highlight the importance of nucleic acid-based tests in the investigation of infections of unknown aetiology, including CNE. Physicians should be aware of the fact that ureaplasma infection can cause severe complications in immunosuppressed patients. Close monitoring and follow-up in cases with intracellular invasive infections may lead to early diagnosis of possibly severe complications.

Learning points

- ▶ Immunosuppressed patients have unusual infections caused by common or uncommon pathogens.
- ▶ There is an important role for nucleic acid-based tests in diagnosis of infections caused by intracellular pathogens.
- ▶ Mycoplasmatocae can also cause infective endocarditis with an insidious course.

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Competing interests None declared.

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