Case Report

Treatment of native valve endocarditis due to coagulase negative staphylococci, complicated by a drug reaction with eosinophilia and systemic symptoms (DRESS syndrome)

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Abstract

Coagulase negative staphylococci (CoNS) are a rare cause of native valve endocarditis (NVE). However, they are emerging as important pathogens of NVE. We describe a 61 year old male who developed NVE caused by CoNS and presented with cerebral embolic phenomena. He was treated with vancomycin and subsequently with linezolid. He developed a drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) to linezolid which was managed successfully. The patient's recovery was good after six weeks of treatment with anti-staphylococcal antibiotics.

Keywords: native valve endocarditis, coagulase negative staphylococcus, linezolid, DRESS syndrome, cerebral emboli

Introduction

CoNS are divided into more than 44 species and most have been associated with humans as a major constitute of human skin commensal flora.[1] CoNS is a group of bacteria whose medical importance has emerged in the past decades mainly as devices or prosthetic implant associated infections. CoNS were a rare cause of NVE. However, they are now emerging as an important cause of NVE in both community and healthcare settings.[2] At the same time, DRESS syndrome is a life threatening condition unless diagnosis and management are done promptly and acurately.

We report a case of NVE caused by CoNS, which was treated succesfully after facing a number of challenges and their consequences.

Keywords: Native valve endocarditis, Coagulase negative staphylococcus, Linezolid, DRESS syndrome, Cerebral emboli

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Case report

A sixty one year old, Sinhala retired male teacher from Colombo was admitted with the complaint of a sudden onset of slurring of speech and two episodes of right upper and lower limb involuntary movements followed by mild headache. There was no history of loss of consciousness. On further inquiry, he gave a history of fever of two days.

The patient did not give a history of diabetes mellitus, hypertension or dyslipidaemia. He denied any previous history of a similar neurological problem. However, he gave a history of endocarditis 10 years back in 2005, which was managed medically. Records of microbiological investigations and treatment of this episode was not available. The only history of medical instrumentation was a trans urethral resection of prostate (TURP) done three months before the current illness for a suspected prostatic growth. There was no history of postoperative fever, or cannula or central line infections or catheter associated infections. The patient did not give a history of intra-venous drug use.

On admission, he was afebrile, conscious and rational with no neck stiffness. His blood pressure was 110/70 mmHg with a pulse rate of 100/ minute. There was a harsh pan systolic grade III murmur, best heard at the apex which radiated to the left axilla. He had ataxia, incoordination, and nystagmus and no limb weakness. There was no sensory impairment. His leukocyte count was 9.75 x 10^3 cells/mm^3 with 86% neutrophils. The C–reactive protein was 22 mg/L. The blood picture was suggestive of an infective or inflammatory process.

A transthoracic echocardiogram done two days after presentation was normal with >60% ejection fraction and did not show any vegetations.

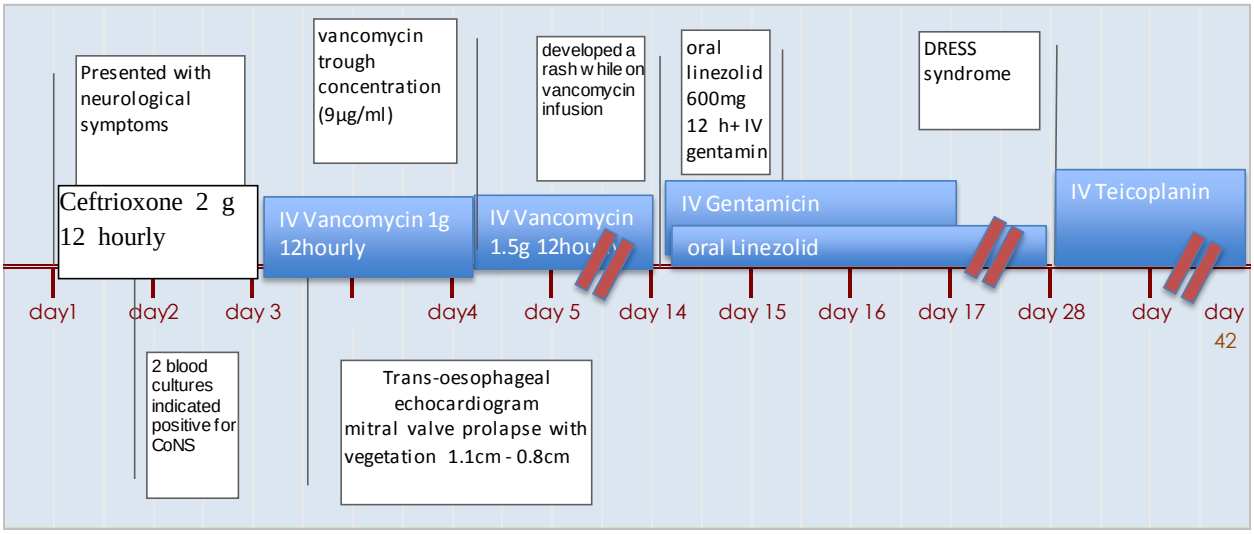
A clinical diagnosis of infective endocarditis was made and ceftriaxone 2 g 12 hourly was started after taking 2 separate blood samples for culture. Both blood cultures indicated positive in the BacT/Alert® automated blood culture system for Gram positive cocci after 22 hours and 24 hours incubation respectively. Sub-culture on blood, chocolate and McConkey agar grew a mixed growth with 2 colony types after 24 hours incubation at 37 ºC from both blood cultures. Both colony types were dome shaped and non-haemolytic and were identified as coagulase negative staphylococci by conventional methods. Species level identification could not be done due to resource constraints. Antibiotic sensitivity testing was performed on both colony types with cefoxitin, ciprofloxacin, clindamycin, erythromycin and vancomycin, using Clinical Laboratory Standards Institute (CLSI) 2015 method. Both isolates gave identical results showing resistance to cefoxitin, ciprofloxacin, clindamycin, and intermediate sensitivity to erythromycin and being only sensitive to vancomycin. As the patient remained febrile after 24 hours of ceftriaxone administration, the blood culture was repeated and the same colony types were re-isolated. As all 4 blood cultures yielded 2 types of isolates with different colony morphology, both types were considered significant. Since, the sensitivity patterns were identical the treatment of the patient was based on this pattern of susceptibility.

A trans-oesophageal echocardiogram done at this point showed mitral valve prolapse with a vegetation 1.1 cm -0.8 cm in diameter attached to the anterior cusp of the pulmonary valve.

There was an associated mild pericardial effusion. Magnetic Resonance Imaging (MRI) scan of the brain showed mid brain infarction. There was no abscess formation.

The vancomycin trough concentration (9 µg/ml) checked after the 5th dose of vancomycin, was less than the recommended value. Renal function being normal, the vancomycin dose was increased to 1.5 g 12 hourly. Repeat blood culture 48 hours after starting vancomycin was negative. After the 14th day of vancomycin, the patient developed an itchy rash while the antibiotic was being administered as a 2 hour infusion. Vancomycin was omitted and oral linezolid 600 mg 12 hourly was started in combination with IV gentamicin 60mg 8 hourly. Gentamicin was omitted after 3 days because the patient developed an itchy rash during administration. While on linezolid, he developed high fever spikes along with a generalized macular papular rash associated with headache together with a dramatic rise in the leucocyte count up to 45000 cells/mm^3 with 28% eosinophils and a rise in serum creatinine from 90 µmol/L to 155 µmol/L. Contrast enhanced CT scan was done and cerebral abscess excluded. He was diagnosed as having a drug reaction to linezolid (the DRESS syndrome). Linezolid was omitted and steroids started along with supportive care. The recommended duration of treatment for CoNS endocarditis is 6 weeks. Since the patient was on antibiotics for only 5 weeks at this point, a further week of treatment with teicoplanin 400mg 12 hourly in 3 doses followed by 400 mg daily was given.

The timeline of the patient's clinical course is given below.



At the end of 6 weeks of treatment, the patient was afebrile with a normal WBC and almost complete recovery of neurological deficits. He was discharged from the ward after education on the risk of recurrence of endocarditis and importance of oral health.

Discussion

CoNS include many species, most of which are non-pathogenic. Although CoNS forms a main part of the normal flora of human skin, they have a great propensity to colonize foreign materials in the human body, causing prosthesis related infections including prosthetic

valve endocarditis. *S. epidermidis* and *S. haemolyticus* are the most frequently isolated staphylococcus species.[2] The most challenging problem in diagnosing infections with CoNS is the assessment of their clinical relevance.

In recent years, emergence of CoNS as a cause of native valve endocarditis has been described. Of 1635 patients with definite native valve endocarditis and no history of injection drug use, 128 (7.8%) had native valve endocarditis due to CoNS of which *S. epidermidis* was the predominant isolate (80% of 93 speciated CoNS isolates from NVE patients).[3] In a global endocarditis study, *S. lugdunensis* was reported as the second most common CoNS.[4] However, it is quite unusual for this organism to cause endocarditis in an otherwise healthy person who is not an intravenous drug user.

The past history of endocarditis was the most likely risk factor in the present case. His presentation with embolic phenomena manifesting with neurological symptoms is unusual as patients with NVE due to CoNS are less likely to have embolic events, compared with patients with NVE due to *S. aureus*.[3] Dukes criteria were fulfilled with one major and 3 minor criteria[5]. However, he did not have a prosthesis which CoNS are commonly associated with.

The only invasive procedure the patient had undergone was the TURP which was uneventful. Although Gram negative bacilli are common pathogens in the male urogenital tract, surgical breach of the mucosa could have been the portal of entry of the organism to the blood stream.

All 4 blood cultures showed two types of colony morphology. These two types could have been either 2 strains of the same species or 2 different species. CoNS is proven to have small colony variants (a specific phenotype resulting from a switch from normal phenotype) similar to *S. aureus* and hence, it can give appearance of a mixed growth.[3]

The recommendation of the Infectious Diseases Society of America (IDSA 2015) in the management of staphylococcal endocarditis is vancomycin or daptomycin for 6 weeks.[5] These guidelines recommend that vancomycin trough levels be maintained between 10 - 20 µg/ml. The vancomycin dose was increased in the patient to 1.5 g twice a day following which the patient developed reactions to vancomycin which had to be stopped. Due to the unavailability of daptomycin, linezolid was started. Linezolid is a bacteriostatic drug and is not included in the recommendations of IDSA as bactericidal drugs are required to sterilize the vegetations with high bacterial density.[6] However, the British Society for Antimicrobial Chemotherapy documents treatment of individual cases successfully with oral linezolid and recommends oral linezolid as oral bioavailability is close to that achieved with intravenous administration.[7] They do not however recommend it as monotherapy. IV gentamicin was therefore combined with linezolid in treatment of this patient, but had to be omitted after 3 days due to the development of an itchy rash during administration as recommended by the European Society of Cardiology.[8] The latter guideline recommends combination with IV gentamicin for 3 to 5 days for Gram positive coverage. Although failure as well as success of treatment with linezolid in treatment of endocarditis has

been reported,[9] limitations in treatment options dictated the use of this antibiotic in the present case.

Although there was an initial satisfactory response, the patient developed high fever and a raised WBC accompanied by a macular-papular rash which was diagnosed as the DRESS syndrome, the acronym standing for Drug Reaction with Eosinophilia and Systemic Symptoms. It is an entity distinct from other serious adverse drug reactions, and due to dynamic changes in the immune response which occur in the course of the disease, the exact underlying mechanism of which is still unclear.[10] This type of reaction is most commonly seen with several groups of drugs namely anticonvulsants, anti-depressants, anti-inflammatory drugs, anti–infective drugs, angiotensin– converting enzyme inhibitors and beta blockers. It may involve eosinophilic infiltration of several systems including the kidney, lungs, liver and pancreas. Deterioration of renal function in this patient during that period may have been due to eosinophilic infiltration of the kidneys. Some patients suffer with chronic complications and 10% die with visceral organ failure.[10] As recommended,[11] he was managed with steroids and supportive care for this condition with complete recovery.

On discharge, the patient was clinically well, with WBC and CRP in the normal range. He was given advice regarding oral care and oral health and the possible risk of recurrence of endocarditis.

Conclusions

CoNS can cause native valve endocarditis. DRESS syndrome is an adverse event caused by several drugs, including linezolid, which can be managed successfully with steroid therapy, after omitting the likely causative drug.

Informed verbal consent was obtained from the patient for publication of the case report

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