Fatal Case Due to Methicillin-Resistant
Staphylococcus aureus Small Colony
Variants in an AIDS Patient

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We describe the first known case of a fatal infection with small colony variants of
methicillin-resistant Staphylococcus aureus in a patient with AIDS. Recovered from
three blood cultures as well as from a deep hip abscess, these variants may have
resulted from long-term antimicrobial therapy with trimethoprim/sulfamethoxazole for
prophylaxis of Pneumocystis carinii pneumonia.

Staphylococcus aureus causes acute and
often fatal infections. Small colony variants
(SCVs), which are subpopulations of S. aureus,
are implicated in persistent and recurrent
infections (in particular osteomyelitis, septic
arthritis, respiratory tract infections in patients
with cystic fibrosis, and deep-seated abscesses)
(1-4). These phenotypic variants produce small,
slow-growing, nonpigmented, nonhemolytic colo-
nies on routine culture media, making correct
identification difficult for clinical laboratories.
Biochemical characterization of these variants
suggests that they are deficient in electron
transport activity (5).

We report a fatal case of a persistent deep-
seated hip abscess due to methicillin-resistant
S. aureus SCVs that led to osteomyelitis and
bloodstream infection in a patient with AIDS.

Case Report

A 36-year-old man with AIDS came to the
Cologne University Hospital, Cologne, Germany,
in June 1997 with fever and progressive pain (of
6 weeks duration) in his right hip. HIV infection
had been diagnosed in 1986. In 1994, his CD4 cell
count was 250/µL, and oral zidovudine therapy
was started. His medical history included
Pneumocystis carinii pneumonia, pulmonary
tuberculosis, and recurrent oral thrush; his
medication included zidovudine, lamivudine,
fluconazole, and trimethoprim/sulfamethoxazole.
In September 1996, he was in a traffic accident
and had severe cerebral trauma resulting in
spastic hemiparesis with occasional seizures.
After an intramuscular injection 2 months before
admission, pus was surgically drained to treat
recurrent abscesses of his right hip. Specimens
for culture were not obtained.

Physical examination found limited mobility
of his right thigh and a tender, nondraining scar
at the site of surgical drainage. Neither warmth
nor swelling was observed over his right hip.
Vital signs were temperature, 38.2°C; respiration
rate, 28; and heart rate, 108. He was awake
and alert and had spastic paresis in his right
arm.

Laboratory studies performed on admission
showed hemoglobin, 10.8 g/dL; leukocyte count,
3,000/µL with a normal differential; CD4 cell
count, 20/µL; platelet count, 131,000/µL;
C-reactive protein, 184 mg/L; and alkaline
phosphatase, 1490 U/L. Radiographs of the chest
and a plain film of the pelvis were normal. A
triple-phase bone scan showed an area of minor
tracer accumulation in the acetabulum region of
the right hip. Blood cultures were drawn, but
antimicrobial therapy was withheld until culture
results became available.

On hospital day 2, one of two blood cultures
drawn on admission yielded nonhemolytic staphylococci that were clumping factor–
negative. The organisms were initially
misidentified as coagulase-negative staphylo-
cocci and were considered contaminants.
Empiric antistaphylococcal therapy with clindamycin (600 mg q8hr) was instituted. On hospital day 4, two sets of blood cultures obtained on hospital day 2 yielded phenotypically identical organisms, which on the basis of a positive tube coagulase test were identified as oxacillin-resistant \textit{S. aureus}. The colony morphology was suggestive of an SCV of \textit{S. aureus}. The patient was started on parenteral vancomycin treatment (1 g q12hr). However, his condition deteriorated rapidly, and he died of refractory septic shock 6 days after admission.

Autopsy showed a large (12 x 10 x 8 cm), deep-seated abscess of the right hip and osteomyelitis of the ischial tuberosity. Both SCVs and typical large colony forms of \textit{S. aureus} were cultured from postmortem specimens of the abscess and the bone.

**Findings**

\textit{S. aureus} SCVs were recovered from one of two blood culture sets obtained on admission and from two of four blood culture sets obtained on hospital day 2. Growth was not detected until the blood culture bottles had been incubated 24 hours. \textit{S. aureus} with a normal phenotype was recovered from nose and throat specimens but not from blood cultures, whereas both SCVs and typical \textit{S. aureus} phenotypes were isolated from the deep hip abscess (Figure 1) before death, as well as from a postmortem specimen. All isolates were clumping factor–negative but showed a delayed positive reaction in the tube-coagulase test at 24 hours. The results of the ID 32 staph test did not unambiguously identify SCVs as \textit{S. aureus} because the tests for urease and trehalose were negative. Both the \textit{nuc} gene and the \textit{coa} gene were identified by polymerase chain reaction (PCR) amplification. Methicillin resistance was confirmed for both small and large colony forms by PCR amplification of the \textit{mecA} gene.

When cultured without supplementation, all SCVs were nonpigmented and nonhemolytic. Supplementation with hemin, thymidine, or menadione identified two SCVs showing thymidine auxotrophy and a combined thymidine and menadione auxotrophy, respectively. All SCVs were stable on repeated subculturing.

Epidemiologic typing by PCR analysis of inter-IS256 spacer length polymorphisms (Figure 2) and pulsed-field gel electrophoresis of genomic DNA (data not shown) showed identical banding patterns for both SCVs and large colony forms, which indicates that the phenotypically different \textit{S. aureus} isolates represented a single strain. Antimicrobial susceptibility testing was performed by microbroth dilution, according to the National Committee for Clinical Laboratory Standards guidelines. Susceptibility to trimethoprim/sulfamethoxazole was tested with Etest (AB Biodisk, Solna, Sweden). In contrast to current standards, the MICs for SCVs were determined after 48 hours of incubation at 35°C. Susceptibility testing showed that all \textit{S. aureus} isolates were resistant to penicillin (MIC, >8 µg/mL), ampicillin (MIC, >32 µg/mL), oxacillin (MIC, >8 µg/mL), erythromycin (MIC, >32 µg/mL), clindamycin (MIC, >32 µg/mL), ciprofloxacin (MIC, >8 µg/mL), gentamicin (MIC, >500 µg/mL), and trimethoprim/sulfamethoxazole (MIC, >32 µg/mL) and susceptible to vancomycin.
Dispatches

Proctor and colleagues recently reported five cases in which SCVs of *S. aureus* were implicated in persistent and relapsing infections. They identified only a single case reported in the previous 17 years and ascribed this to insufficient ability of laboratories to identify these organisms (8). In most cases, patients had received antibiotics. Aminoglycoside treatment may have selected for *S. aureus* SCVs (10), and in cases of osteomyelitis or deep-seated abscesses, persistence of these variants in the intracellular milieu may have permitted evasion of host defenses and allowed for the development of resistance to antimicrobial therapy (7,11). Von Eiff and colleagues recently reported four cases of chronic osteomyelitis due to SCVs of *S. aureus* in patients who had received gentamicin beads as an adjunct to surgical therapy for osteomyelitis (2). Kahl et al. described persistent infection with *S. aureus* SCVs in patients with cystic fibrosis (4). All these patients had received long-term trimethoprim/sulfamethoxazole prophylaxis. It may be tempting to speculate that administration of trimethoprim/sulfamethoxazole for prophylaxis against *P. carinii* pneumonia may have selected for SCVs within the patient’s large hip abscess. Further prospective studies are needed to assess the role of *S. aureus* SCVs in HIV-infected patients on long-term antimicrobial therapy.

Dr. Seifert is assistant professor at the Institute of Medical Microbiology and Hygiene, University of Cologne, Germany. His research interests include the molecular epidemiology of nosocomial pathogens, in particular *Acinetobacter* species, catheter-related infections, and antimicrobial resistance.

References


