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Case Report

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Heteroresistant vancomycin intermediate *S. aureus* (h-VISA) isolated from a patient with orthopedic implant infection treated with glycopeptides: A case report

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ABSTRACT

A 37-year old male patient who had and orthopedic implant after a traffic accident, presented to the Infectious Diseases Clinic. He was accepted as culture negative surgical site infection. Initial empirical treatment was started with clindamycin and then it was changed to the glycopeptides. During the follow-up, implant was removed. Intraoperative culture specimens revealed Methicilline Resistant *Staphylococcus aureus (S. aureus)*. After antibiotic therapy, total hip prosthesis was implanted and was removed for two times. Wound discharge was continued despite restarted the antibiotic treatment and growth of heteroresistant-Vancomycin intermediate *S. aureus* was detected in the aspiration culture. All isolates shared the same clonal properties by pulsed-field gel electrophoresis. The strain was negative for Panton-Valentine-Leucosidine and were shown to carry carried a Staphylococcal Cassette Chromosome mec type–III variant common. After a follow-up lasting eight years, the patient chose to continue his life without prostheses (Girdlestone method). This case was reported for emphasizing how difficult to manage medical treatment of prosthesis infections with developing resistant bacteria and the how important the surgical treatment was.

1. Introduction

The incidence of infections caused by methicillin-resistant staphylococci has increased especially for patients with orthopedic implants (Saleh-Mghir et al., 2002). Compared to methicillin-sensitive strains, infections by these organisms have higher mortality and morbidity rates (Rybak et al., 2008). Due to the multiresistance of methicillin-resistant *Staphylococcus aureus* (MRSA) isolates, glycopeptide antibiotics are among the first-choice drugs in the treatment of patients infected by these strains. However, because of the fact that the isolates have the capacity to develop resistance, the first of cases of vancomycin intermediate (VISA) and heterogeneously vancomycin-intermediate

Staphylococcus aureus (h-VISA) have been reported in Japan in 1996. In 2002, the first case of vancomycin-resistant *S. aureus* (VRSA) was reported (Szabo, 2009; Melo Cristino, 2013). According to the literature, the prevalance of h-VISA is 1.3% (Van Hal and Paterson, 2011). An h-VISA phenotype belonging to an epidemic clone of community-acquired MRSA causing infective endocarditis was reported in Argentina in 2001 (Sola et al., 2011). Some studies from China have reported that 22.1% of the MRSA isolates collected were h-VISA and reports of h-VISA are still continuing (Liu and Chen, 2014). As for VRSA, 12 VRSA cases from the USA have been reported since 2002 (CDC, 2014). Until September 2012, one, three and sixteen cases of VRSA have been reported from Pakistan, Iran and India; respectively (Morawi et al., 2013). In Europe, the first VRSA strain was isolated from a patient who had a diabetic foot infection. Recent studies from Brazil have shown that, community-acquired MRSA has developed resistance against vancomycin after repeated therapies (Rossi et al., 2014). Although an in-vitro study from our country has reported that VISA and VRSA were not determined in MRSA isolates, the fact that some in-vitro studies have reported an h-VISA rate of 0.9% and 17.9%. These strains pose a threat in our country and they especially develop after the glycopeptide administration (Cesur et al., 2012; Sancak et al., 2013). In a study by Sancak et al. (2005) where 175 blood isolates collected in seven universities were tested for sensitivity to vancomycin and daptomycin, the h-VISA prevalence was evaluated and an h-VISA rate of 13.7 was determined. However, the importance of h-VISA in the clinical setting could not be elaborated in those studies since their clinical findings were not sufficient. The current study presentsa case of prosthesis infection where the causative agent was MRSA and h-VISA developed after the use of glycopeptides. After a follow-up lasting eight years, the 37 year-old-patient chose to continue his life without prostheses. The aim of this study is to stress how complicated medical and/or surgical treatment options for prosthesis infections may get with the development of resistant bacteria.

2. Case

The 37 year-old adult patient who was working as a farm labourer and had no comorbid diseases had a traffic accident on January 2007 and subsequently underwent open reduction and plate osteosynthesis due to fracture-dislocation of the left femoral head and acetabular fracture (Fig. 1A). During his follow-up, his implants were removed at our hospital on November 2008 due to avascular necrosis of the femoral head and hip pain (Fig. 1B). Suppurative reaction was observed intraoperatively and all implants could be removed except an extra-articular screw located in the ischiadicum that could not be reached via lateral

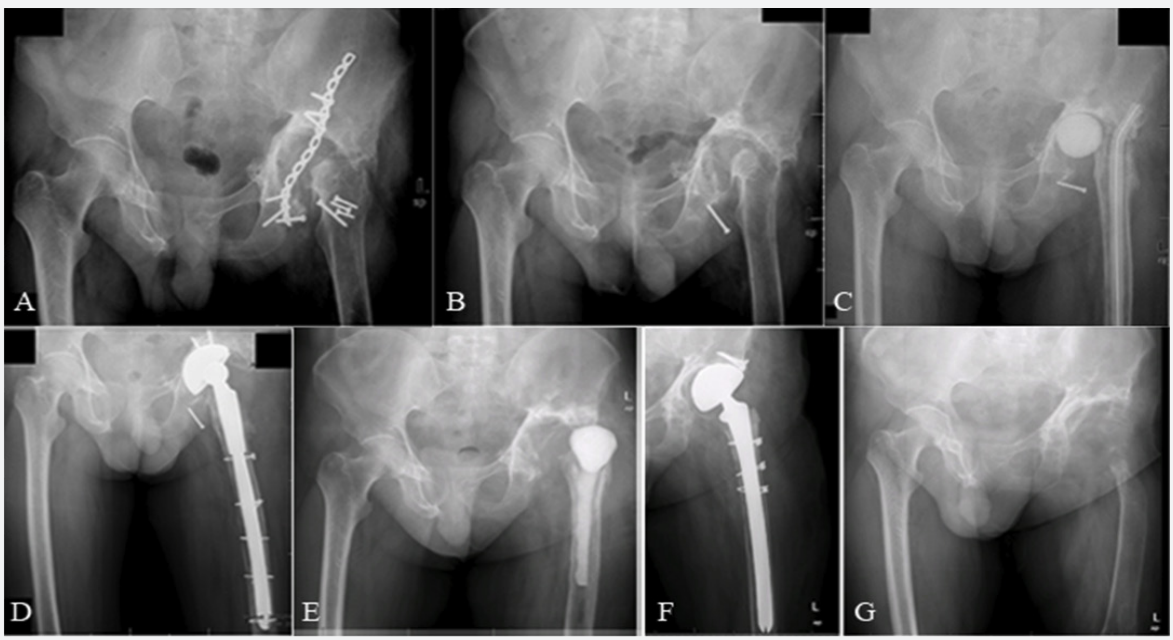

Fig. 1. Radiologic imaging. **A:** The patient's graph of hip at the moment he applied to our center (November 2008); **B:** After the implants were removed except an extra-articular screw (March 2009); **C:** After applying debridement and vancomycin-containing cement (April 2009); **D:** After revision hip prosthesis was applied (January 2010); **E:** The left hip after all the prosthesis equipments and the extra-articular screw were removed (May 2010); **F:** After applying revision left hip posthesis for the second time (November 2011); **G:** The last state after Girdlestone procedure was applied (January 2014)

incision. No growth was detected in tissue specimen cultures that were sent intraoperatively. In the early post operative period, due to temperature increase at the incision line and high levels of acute phase reactants (C-reactive protein, Erythrocyte Sedimentation Rate), wound site infection suggested in the patient. Thus, clindamycin 4x300 mg po was started and used for 4 weeks. The patient has been followed for 12 weeks without antibiotic. At the 12th week, erythema, temperature increase and pain were observed at the incision line, we concluded that the patient did not respond to the treatment. Thus, debridement was performed and vancomycin-containing cement was used (Fig. 1C). The two tissue cultures sent for analysis were negative and since infection could not be excluded and repeated interventions were performed, teicoplanin1x800 mg IV was started empirically. On treatment follow-up, debridement was repeated on July 2009 due to the serious discharge from the incision line. Since MRSA was detected in the two tissue specimens sent for culture intraoperatively, linezolid 2x600 mg was started. Abnormal liver function tests and leukopenia required that the treatment to be cancelled on the second week. Subsequently TMP-SMX (2x160 /800mg) and fusidic acid (3x500 mg) po were started and continued until 8th week. The patient was followed up without antibiotics and any problems for 6 months and on January 2010, revision hip prosthesis was applied to his left hip (Fig. 1D). Although no causative agent were seen by the gram staining of tissue samples taken intraoperatively and frozen section assessment by the Clinical Pathology laboratory was normal, MRSA was isolated in tissue cultures and then tigecycline (starting dose: 1x100 and 2x50 mg, first two weeks) + daptomycin (1.4 mg/kg) + rifampicin (1x600 mg po) therapy was used for 6 weeks. Daptomycin, which is not commercially available in our country, was supplied from abroad. The patient was discharged on March 2010 and rifampicin (1x600 mg)+fusidic acid (3x500 mg) po was prescribed. During this treatment, five aspirate cultures sent from the outpatient clinic were found positive for MRSA. Since MRSA growth was observed repeatedly in tissue of the patient; rectal, bilateral, nasal and axillar swab cultures were sent for analysis and found negative for MRSA colonization. Using pulsed-field gel electrophoresis, it was seen that the 13 MRSA isolates detected between July 2009 and March 2010 belonged to the same clone as determined by identical patterns. Molecular methods revealed that the strain possessed a Staphylococcal Cassette Chromosome mec type III variant which is common in Turkish hospitals (Castillo Ramirez et al., 2012) and was negative for PVL (*S.aureus* results on selected isolates are shown on figures 2a, 2b and 2c). It was suggested that the infections could have resulted from the extra-articular screw that could not be removed. Thus, the removal of all implants was scheduled. On May 2010, all implants of the patient including the prosthesis of the patient and the screw which could not be removed previously were removed (Fig. 1E). The three tissue cultures that were collected intraoperatively, developed colonies varying in size after a 48 hours' incubation. These were screened for h-VISA by the macro-E Test (MET) method and by the GRD gradient strips (E-test TM, bioMerieux Ltd, Biomer İstanbul) (Wootton et al, 2007). The isolates were positive for h-VISA by the two methods. The presence of h-VISA was confirmed later by the PAP-AUC method described by Wootton et al (Wootton et al., 2001). The pin-point colonies, which developed at the end of a 48-hour-long incubation in

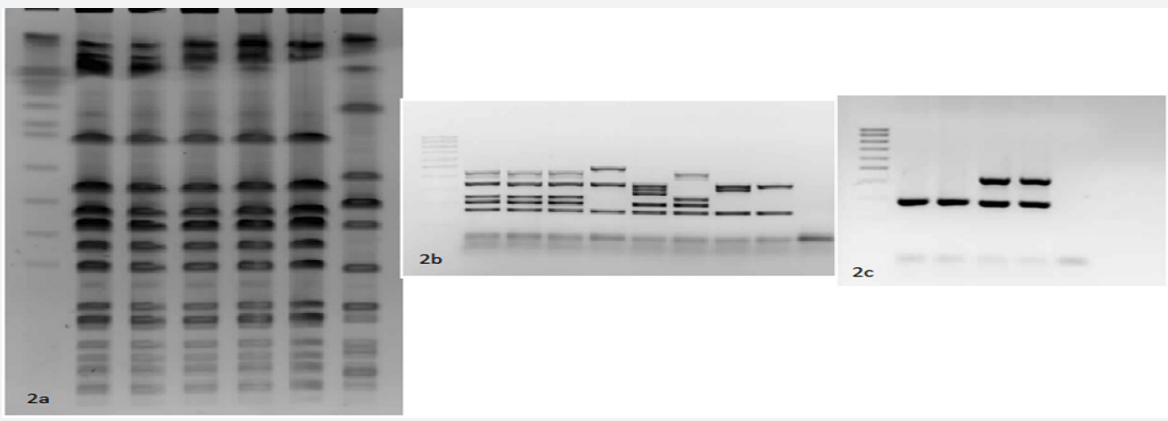

Fig. 2. a: PFGE results of the strains. The PFGE results of strains. 1-Marker, 2-July 2009, 3-January 2010, 4-May 2010, 5-January 2012, 6-June 2012, 7-Control (EMRSA-6); **b:** SCCmec PCR results. The SCCmec PCR results of strains. 1-Marker, 2-July 2009, 3-May 2010, 4-June 2012, 5-SCCmec type I, 6-SCCmec type II, 7-SCCmec type III, 8-SCCmec type IV, 9- SCCmec type VI, 10- Negative control. **c:** PVL PCR results. The PVL PCR results of strains 1- Marker, 2-July 2009, 3-June 2012 4-5 PVL Positive Control, 6-PVL Negative Control

Table 1. The follow up of the case with medical and surgical treatment chronologically

Growth data	Specimen/ Number	Bacteria	Medical treatment	Operation & Debridement	Vancomycin μg/ml	Daptomycin μg/ml
Jan 2007	Underwent open reduction and plate osteosynthesis at an another center					
Nov 2008	Tissue/1	No growth	Clindamycin	Implant removed at our hospital	-	-
April 2009	Tissue/1	No growth	Teikoplanin	Debridement+ vancomycin-containing cement	-	-
July 2009	Tissue/1	MRSA	Linezolid → TMP–SMX + Fusidic asid	Debridement	1	0.094
Jan 2010	Aspiration /1	MRSA		Revision of left hip prosthesis	1.5	0.125
Feb 2010	Aspiration/1	MRSA	Tigecyclin + Daptomycin + Rifampicin		1.5	0.125
	Aspiration/2 Tissue /4				1.5	0.125
	Aspiration	MRSA			1.5	0.125
	Aspiration/2	No growth			2	0.125
March 2010	Aspiration/2	MRSA	Rifampicin + Fusidic asid		1.5	0.125
	Tissue /1	MRSA			1.5	0.125
Aug 2010	Synovial fluid/1	h-VISA	Rifampicin + Fusidic asid	Debridement	2	0.125
Nov 2011	Applying revision left hip prosthesis for the second time at an another center					
Jan 2012	Aspiration /4	h-VISA	Linezolid + Tigecyclin		2	0.125
Feb 2012		h-VISA	→ Rifampicin + Fusidic asid		2	0.125
March 2012	Aspiration/2	h-VISA	TMP–SMX + Fusidic asid		2	0.5
June 2012		h-VISA	Rifampisin + Fusidic asid		2	0.5
Aug 2012	Removing the second revision left hip prosthesis at an another center					

the specimens mentioned above and which had the same antibiogram pattern with the parent strain, were deemed to be small colony variants. Daptomycin (1x6 mg/kg) and rifampicin (1x600 mg) treatment were continued for 8 weeks. The patient was discharged after being prescribed rifampicin (1x600 mg)+fucidic acid (3x500 mg) therapy. On August 2010, the second debridement was performed on the patient who applied with complaints of erythema and discharge. h-VISA was isolated from the intraoperative cultures collected during debridement. The daptomycin therapy (1x6 mg/kg) was restarted and continued for 8 weeks. The patient was discharged after being prescribed rifampicin (1x600 mg)+fusidic acid (3x500 mg). The patient was followed up without any clinical problems for 8 months. During this period no discharge was observed at the incision site and his acute phase reactant levels decreased. However, he underwent revision hip implantation surgery in another medical center (Fig. 1F) and applied to our clinic 3 months later due to recurring discharge at the incision site. MRSA growth was observed in the aspirate cultures collected. Linezolid and tigecycline were administerated for 6 weeks. On August 2012, the patient's prosthesis was removed since the discharge at the incision site did not regress and the patient was discharged from our clinic after being prescribed rifampicin (1x600 mg)+fusidic acid (3x500 mg) therapy. The minimal inhibitory concentration levels of all isolates are given on the Table 1. The patient who endured a total of nine interventions and had his prosthesis removed currently refuses to undergo another prosthesis implantation surgery and in the absence of a prosthesis (Girdlestone method), his follow-up still continues without any clinical problems (Fig. 1G).

3. Discussion

According to the Clinical and Laboratory Standards Institute (CLSI) guidelines, VISA is defined as the isolate having a MIC of 4-8 μg/ml, whereas h-VISA is defined as the isolate having a MIC level of 1-2 μg/ml along with a sub population with a MIC >4μg/ml. Reduced growth/reproduction kinetics due to changes in surface protein/muropeptide and altered accessory gene regulator functions in the VISA strains are responsible for the resistance (Saleh-Mghir et al., 2002). The most important risk factor for the development of h-VISA, VISA and VRSA is the use of vancomycin. Complications and persistent infections caused by these strains are more common compared to vancomycin-sensitive *S.aureus* strains. Infections are particularly difficult to treat in patients who have cardiac vegetation or have foreign bodies implanted, such as plates, screws or prostheses. Even though additional appropriate antibiotherapy (linezolide, quinupristin, dalfopristin, TMP-SXT, daptomycin and tigecycline) is used, the lack of sufficient amount of antibiotic concentration in the bone tissue, phenotypical alterations in the microorganism (biofilm formation and small colony variants) and antibiotic resistance

render the treatment more difficult. During the follow-up of the patient presented in the current case report, we concluded that it was necessary to remove all foreign objects including a screw that was placed on May 2010 during the first surgery and left inside through all the surgeries performed until today (Fig. 1). After all orthopedic materials were removed, it was seen that h-VISA was isolated in the 3 intraoperative cultures. It was suggested that the growth could originate from the use of multiple antibiotics and/or glycopeptides for treatment, long hospital stay including long hospitalization in the intensive care unit and insufficient infection source control. Since it is known that MRSA has humans as the primary reservoir, commonly found on environmental surfaces and associated with health care; even methicilline susceptible *S. aureus* was not detected at all on collected nazopharyngeal, rectal, bilateral nazal and axillary swab specimens of the patient. However, since the patient applied to multiple medical centers and was hospitalized a few times, the members of the staff who took care of the patient could not be screened. It was determined that all MRSA pathogens collected from the patient were of the same clone (Figures 2a, 2b, 2c). In spite of appropriate antibiotherapy and surgical interventions, the patient did not respond to the treatment. Whenever a foreign object (plate, screw, prosthesis etc.) was implanted, infection developed and required a medical treatment lasting 2 to 6 months.

It was concluded that source control was insufficient and the patient who received many antistaphylococcal antibiotics during the follow-up did not respond to the medical treatment. It may be appropriate to repeatedly question the indications of all antibiotics including glycopeptides in patients whose cultures are negative for prosthesis infection. Additionally, if source control is not carried out, treatment failure is inevitable for all infections, regardless of which antibiotics are used. In this case, if eight months after the removal of all foreign bodies and the management of the infection, the same pathogen still grew in cultures collected during prosthesis insertion, this suggests that the problem may have multiple causes. The importance of the characteristics of the microorganism and/or the host and the dynamics between the host and the pathogen should be taken into consideration. It has been reported that the characteristics of the bacteria regarding DNA polymorphism and genomic sequence are important in terms of antimicrobial resistance and virulence (Dubee et al., 2013). The strain isolated from the patient possessed a SCCmec Type III-like genetic element and was PVL-negative. These genomic characteristics suggest that the strain is not community-acquired. Although the patient was not immunosuppressed, it was suggested that the long hospital stay involving a long period of hospitalization in the intensive care unit and the intense use of antibiotherapy and empirical glycopeptyde use combined with repeated interventions within the same region might have contributed to the lack of response to treatment. All these factors are health care-related. Many studies conducted in our country report that SCCmec Type III is the most common hospital-acquired MRSA strain (Karahan et al., 2008; Gill, 2009; Gülmez et al., 2012). However, in these studies, the clinical findings and the data on infection management presented are not sufficient. In order to elaborate the dynamics between the host and the pathogen, studies that evaluate clinical and microbiological findings with together are needed. According to the sources that we could access, in a case study where a patient in whom h-VISA was detected for the first time in our country using the Macro E-test method, clinical and microbiological findings were evaluated together and the result was in favor of the pathogen. In parts where antibiotic penetration is low, treatment of infections caused by resistant bacteria like h-VISA is particularly more difficult and patient compliance is reduced. This finding is supported by the fact that the patient refuses to undergo prosthesis implantation surgery. In such cases; multidisciplinary follow-up and covering clinical and microbiological findings in unison may both elucidate the dynamics between the host and the pathogen further.

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