Case Report

A fatal case of native valve endocarditis with multiple embolic phenomena and invasive methicillin-resistant *Staphylococcus aureus* bacteremia: a case report from the Maldives.

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Abstract: Infective endocarditis (IE) is a life-threatening condition caused by infection within the endocardium of the heart, and commonly involves the valves. The subsequent cascading inflammation leads to the appearance of a highly friable thrombus that is large enough to become lodged within the heart chambers. As a result, fever, fatigue, heart murmurs, and embolization phenomena may be seen in patients with IE. Embolization results in the seeding of bacteria, and obstruction of circulation, causing cell ischemia. Of concern, bacteria with the potential to gain pan-drug resistance, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are increasingly being identified as the causative agent of IE in hospitals and among intravenous drug abusers. We retrospectively reviewed de-identified clinical data to summarize the clinical course of a patient with MRSA isolated using an automated blood culture system. At the time of presentation, the patient showed a poor consciousness level, and the calculated Glasgow scale was 10/15. A high-grade fever with circulatory shock indicated an occult infection, and a systolic murmur was observed with peripheral signs of embolization. This case demonstrated the emerging threat of antimicrobial resistance in the community, and revealed clinical findings of IE that may be helpful to clinicians for the early recognition of the disease. The management of such cases requires a multi-specialty approach, which is not widely available in small island developing states like the Maldives.

Keywords: Infective endocarditis; methicillin-resistant *Staphylococcus aureus*; mitral valve

1. Introduction

Before the advent of antimicrobial therapy, infectious diseases were simple ailments to some, but extremely severe ailments to others who fell ill from the pathogens, making infectious diseases the leading cause of death in all age groups.[1] Nevertheless, with the contemporary advancements in medical science, infectious diseases now rank below

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cardio-cerebrovascular diseases, accidents, and malignancies as the top causes of death worldwide.[2] However, the mortality rate still remains high for certain infectious diseases, such as infective endocarditis (IE).[3]

When IE presents acutely, it is a life threatening and complex medical emergency that is inevitably fatal without prompt treatment with broad spectrum antimicrobials[4] in addition to early integral surgical correction of the abnormal excrescence appearing on heart valves.[5] Delayed treatment and management complicate the clinical course, and may result in extra-cardiac embolization, which has been reported to occur in a quarter of patients with IE.[6] The spectrum of clinical manifestations in IE includes the eruption of non-tender hemorrhagic macular purpuric lesions over most distal peripheral sites of the hands and feet, including the appearance of hemorrhage streaks underneath the nails, which result from a vascular phenomenon that transpires in IE. Additionally, erythema over the finger pulps and hematuria may be observed from the deposition of circulating immune complexes, which may also initiate glomerulonephritis. Furthermore, septic seeding due to the formation of breakaway emboli of fibrin-platelet plugs containing bacteria may occur to multiple organ systems, including within the eye, causing surrounding retinal hemorrhage.[7]

Over the past several centuries, IE has been a devastating public health problem burdening apothecaries. However, the invention of medical instruments, such as the stethoscope devised by the French physician René Laënnec in 1816, has allowed findings from auscultation of the heart during illness to be correlated to autopsy findings. The presence of a murmur during a febrile episode is considered to be a hallmark clinical finding of IE, and pathological erosive disruption of the endocardium is commonly referred to as vegetation of the heart valve.[8] Since 1885, IE has been recognized as a pathological entity of an infective process.[9] Some forerunners like Sir William Osler, Edward Janeway, and Mortiz Roth have had pathognomonic findings of IE infamously named after them.[10] Presently, the incidence of IE is increasing in different regions, and IE has been reported to affect up to 7 to 10 people per 100,000 person-years.[11] Several predisposing factors for the development of IE have shifted from conditions like rheumatic heart disease or congenital heart diseases to degenerative valve disease due to the increasingly aging population.[12, 13] In addition, the increased use of prosthesis and intra-cardiac devices or intravenous drug use (IVDU) are factors that predispose an individual to the development of IE.[14] Individuals who are severely immunocompromised or those with a prior history of endocarditis are also considered to be at risk of developing IE.[15]

Although the pathogenesis of IE has not yet been fully elucidated, it was postulated that it is initiated by the activation of endocardial endothelial cells by an antigen or denudation from contaminants introduced into the circulatory system. The inflicted injury to the endothelial cell lining frequently involves the endothelial layer of the heart valves. Endotheliitis initiates a hyper-coagulant state via an enzymatic process, depositing fibrin and webbing the anterior surfaces of the heart valvular structures (cusps and leaflets), and further trapping platelets and other blood cells and components of blood in the site.[16] This causes blood flow turbulence within the heart chambers, promoting the ongoing endothelial injury.[17] Concurrently, the translocated bacterium adheres to the site, triggering an inflammasome response and up-regulation of pro-inflammatory cytokines.[18] Additionally, a pedunculated mass is formed by the snowballing effect of the vegetative excrescence within the heart chambers. In large vegetation, visualization of its oscillative motion is possible by transthoracic echocardiography.[19] The soft vegetative excrescence is highly friable, and can break loose into the circulatory system as an embolus that can subsequently obstruct the distal microvascular circulatory system, and seed bacteria into other organs.[20]

As mentioned earlier, IVDU is a predisposing factor that substantially increases the risk of developing IE. Small island developing states like the Maldives face an increasing rate of drug abuse. The United Nations Office of Drug and Crime reported from a survey

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conducted in 2013 across the atolls that 22.9% of the 13,714 respondents were active drug users, of which 2.3% were identified as IVDU.

Here, we present a fatal case of native valve IE due to intravenous drug use in adolescence.

2. Materials and Methods

The present case was referred from a peripheral hospital in Maldives to Indhira Gandhi Memorial Hospital (IGMH), Malé, Maldives, in April 2022. The patient was subsequently admitted to the National Cardiac Center with the diagnosis of native valve IE. De-identified clinical and laboratory data were retrospectively reviewed to summarize the clinical course of the presented case. Blood culture and susceptibility testing were performed using an automated culture system (bioMerieux, Durham, NC, USA). Additional bloodborne pathogen screening was performed using an electrochemiluminescence immunoassay (ECLIA; Roche, Mannheim, Germany) for hepatitis B surface (HBs) antigen and anti-hepatitis HBs antibody, (Humasis, Gyeonggi-do, Korea) for anti-HCV antibody, ECLIA (Roche) for HIV antibody/antigen, and RT-PCR (Liferiver, San Diego, CA, USA) for SARS-CoV-2.

Case Report

A 31-year-old male with a provisional diagnosis of sepsis was promptly medically evacuated from a peripheral health center to a central referral tertiary care hospital (IGMH) in Maldives. At the time of arrival to the emergency department, the patient was unconscious, showed a poor response to pain stimulus, and exhibited peripheral cyanosis. Anisocoria was present, and the pupils did not react to light stimulus. Ptosis of the right eye was seen. The pupils measured 3 mm in the right eye, and 2 mm in the left eye. The palpebral conjunctivae appeared pale without conjunctival hemorrhage. Furthermore, there was no neck stiffness, signs of meningeal irritation, or evidence of cervical lymphadenopathy. No jaundice, edema, or bleeding was apparent during the physical examination. Additionally, no abnormality was observed within the oral cavity, and the posterior pharyngeal wall, tonsils, and gag reflex appeared to be normal. No suspicious rash, localized ecchymosis over the trunk, or other visible physical abnormality on the body was observed, except for obvious multiple track marks over the right cubital fossa, in addition to clubbing of the terminal phalanges, Janeway lesions, and splinter hemorrhages, as shown in Figure 1.

(**a**) (**b**)

Figure 1. Peripheral stigmata of IE (**a-b**) Both the left and right hands showed multiple Janeway lesions and splinter hemorrhages.

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The recorded vital signs at presentation included a biometric thermal body temperature of 38.1° C, a pulse rate of 142 beats per minute, and a blood pressure reading of 88/58 mmHg, with a prolonged capillary refilling time (>2sec) and a respiratory rate of 52 breaths per min.

Examination of the cardiovascular system revealed prominent tachycardia, and both heart sounds (S1 and S2) were acoustically distinct on a background of a pan-systolic murmur of grade III intensity, which plateaued before disappearing at diastole. The high-pitched rumbling was audible over the left apex region, corresponding to the fifth left intercostal space, laying adjacent to the mid-clavicular line. In this region of the chest wall, the sound of murmurs can be more easily heard by maneuvering the patient laterally on the left decubitus position with radiation to the axillar region. No other murmurs, including other cardio-adventitious heart sounds, such as S3, S4, opening snaps, ejection clicks, or pericardial rubs, were audible over the tricuspid, aortic, pulmonary, and Erb's areas of the anterior chest wall.

Examination of the respiratory system revealed symmetrical chest movements that were rapid and consistent with a thoraco-abdominal breathing pattern. Bronchial breath sounds with equal air entry into both lung fields were present on auscultation without the presence of stridor, wheeze, crepitations, or pleural rubs.

Inspection of the abdomen revealed no evidence of an enlarged liver or spleen. The abdomen was soft to palpation without guarding or tenderness in any of the major quadrants, including the posterior flanks. An *in situ* Foley catheter showed the presence of a small amount of residual urine. Bowel sounds were present and normal.

A central nervous system examination revealed a Glasgow coma scale of 10/15, which represented an eye-opening response only to pain stimulus, inappropriate verbal responses, and motor responses limited to movements of the limbs in response to localized pain stimuli. Muscle tone appeared to be intact with no weakness or flaccidity in the extremities, including normal reflexes and normal plantar response resulting in a negative Babinski sign. Other neurological deficits observed involved cranial nerves II and III. The other cranial nerves (I and IV-VIII) were not assessable, except for cranial nerves IX and X, which remained intact. Additionally, lagophthalmos was present in both eyes with exposed corneas. The anterior segment of the right eye had minimal conjunctival injection when compared to the marked conjunctival injection with a corneal infiltrate at the limbal 4 o'clock position (Figure 2) with anterior chamber findings of globular infiltrates and Roth spots.

Figure 2. A hypopyon caused by septic embolization in the left eye that was suggestive of uveitis.

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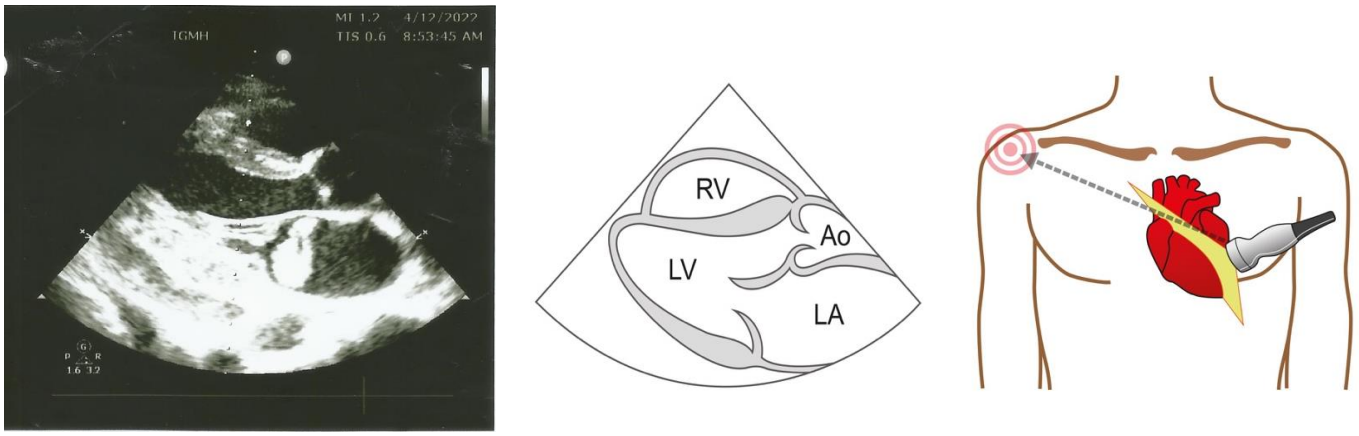
Bedside ultrasound demonstrated a >50% collapsible inferior vena cava on the longitudinal axis and an oscillating vegetation >10mm in the left atrium. Several boluses of intravenous crystalloid had no impact on the low blood pressure, and noradrenalin was started for inotropic cardiac functioning and peripheral vasoconstriction. The finding of a large vegetation was suggestive of IE, and blood was collected by venipuncture from three different sites prior to the administration of targeted empiric antibiotic. Vancomycin was administered up to 1g/day to maintain the vancomycin trough levels at 20 mcg/mL. Further management included transthoracic echocardiography (Figure 3), and hematological and biochemical investigations, as shown in Table 1.



(**a**) (**b**) (**c**)

Figure 3. (**a**) Two-dimensional echocardiogram showing a large echogenic mass in the left atrium (**b**) Normal anatomical landmarks seen in the long axis view (RV: right ventricle; LV: left ventricle; LA: left atrium; Ao: aorta) (**c**) Parasternal position of the probe for transthoracic echocardiography.

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Table 1. Laboratory investigations performed over the course of the illness

Day of illness (days)	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 12
Hospitalization (days)		**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Leukocytes (5000-10,000/μL)	13,700	21,000	21,600	20,800	18,500	26,000	25,000	48,100
Neutrophils (40-60%)	79.1	68.0	82.8	76.7	74.8	77.8	77.7	78.7
Lymphocytes (12.2 - 47.1%)	3.4	14.0	6.3	12.6	16.1	11.0	12.8	7.4
Eosinophils (0.0 - 4.4%)	0.9	0	0.2	0	0	0.1	0.3	0.1
Basophils (0.0 - 0.7%)	0.5	0	0	0	0	0	0	0
Monocytes (4.4 - 12.3%)	16.1	17	6.4	6.3	5.4	3.9	3.9	4.6
Hemoglobin (11.9 - 15.4 g/dL)	13.1	12.7	10.5	9.9	9.7	9.2	8.0	7.9
Hematocrit (36.2 - 46.3%)	38.6	39.9	32.4	28.8	29.5	24.9	24.0	23.2
Platelets (151,000 - 304,000/μL)	230,000	4,700	3,500	37,300	33,400	26,600	25,000	29,000
Creatinine (0.7-1.2 mg/dL)	2.67	3.13	1.95	1.26	1.21	1.09	1.19	1.07
Urea (19.0-44.1 mg/dL)	209.0	258.9	222.5	192.6	175.4	158.3	145.5	115.5
Sodium (136-145 mmol/L)	138	142	150	157	153	151	152	148
Potassium (3.5-5.1 mmol/L)	3.6	4.0	3.5	3.3	4.9	4.1	4.0	4.2
Total bilirubin (0.2-1.2 mg/dL)		3.6	2.1	1.4	0.8	1.0	1.3	1.3
Direct bilirubin (0.0-0.5 mg/dL)		2.3	1.4	0.9	0.3	0.4	0.8	0.9
Albumin (35-5.2 g/dL)		2.6	2.1	2.2	2.2	2.1	2.0	1.9
Protein (6.4-8.3 g/dL)		6.0	5.0	5.1	5.7	5.7	5.6	6.2
Aspartate aminotransferase (5.0-34.0 IU/L)		104	124	63	38	26	45	85
Alanine aminotransferase (0.0-55.0 IU/L)		49	52	37	31	25	36	71
Alkaline phosphatase (40.0-150.0 IU/L)		78	58	69	61	79	94	223
INR (2.0-3.0)		1.2	1.3	1.1		1.1		1.3
APPT (24.6-38.8 sec)		37.6	41.7	38.2		38.9		42.6
PT (11.1-13.1 sec)		14.6	15.8	13.0		13.7		16.5
CRP (0.0-0.5 mg/dL)	45.5	43.4	46.5	39.0	30.7	25.3	26.8	29.2
CK (30-200 IU/L)		382	476					
CKMB (0.0-24.0 IU/L)		25	51					
LDH (140-280 IU/L)		681						
Troponin I (0.0-0.3 ng/mL)		3.6						
Lactate (4.5-19.8 mg/dL)		69						
Hepatitis B surface Ag	positive							
Anti-hepatitis B surface Ab	positive							
Anti-hepatitis C Ab	negative							
RPR	non-reactive							
Anti-HIV Ag/Ab	negative							
SARS-CoV-2 RT-PCR	negative							
Blood culture	positive			positive				

INR: international normalization ratio; APPT: activated partial thromboplastin time; PT; prothrombin time; CRP: c-reactive protein; CK: creatinine kinase; CKMB: creatinine kinase myoglobin-binding; LDH: lactate dehydrogenase; RPR: rapid plasma regain; Ag: antigen; Ab: antibody; RT-PCR: real-time polymerase chain reaction

Transthoracic echocardiography demonstrated vegetation in the mitral valve with ruptured chordae tendineae and acute mitral regurgitation. The blood culture was positive for MRSA that was resistant to oxacillin with a vancomycin minimal inhibitory concentration of 1.0μg/mL (Table S1). Additionally, neuroimaging revealed multiple bilateral hyperdense lesions in the occipital region that were suggestive of hemorrhagic transformations (Figure S2). The presented case subsequently required

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endotracheal intubation and mechanical ventilation with worsening of the consciousness level, and was managed in the intensive care unit without any clinical improvement until the clinical trajectory rapidly deteriorated with fatal irreversible atrial fibrillation.

5. Discussion

IE can rapidly progress to cause deteriorating organ functioning after the onset of symptoms. The clinical trajectory is associated with the virulence of the IE-causing bacterium.[21] Although a plethora of bacteria can cause IE, Gram-positive bacteria, such as *Staphylococcus* and *Streptococci* species, are the most frequently encountered causative agents, and are thus presently the most clinically relevant commensal bacteria causing IE.[22, 23] *Streptococci* bacteria, such as viridans streptococci and beta-hemolytic streptococci, used to be the most commonly isolated organisms, but with the paradigm shift in the prevalence of isolated organisms, *Streptococci* species is now second to *Staphylococci* species, largely due to exposure and acquisition from hospitals and healthcare settings.[24] Both of these bacteria are present in the normal human microbiota, with *Streptococci* species colonizing the upper respiratory tract, and *Staphylococci* species, including coagulase-negative staphylococci, colonizing skin surfaces and the nares of asymptomatic carriers.[25]

The resistance of *Staphylococci* to methicillin was first detected in 1961, and since then, several repertoires of genes responsible for virulence factors and resistance to antibiotics, antiseptics, and heavy metals in *Staphylococcus aureus* have been described.[26,27] Over the subsequent decades, MRSA has caused periodic epidemics, and is considered to be an emerging nosocomial pathogen, *i.e.*, a cause of infections in healthcare settings, with the potential to cause severe diseases, such as bacteremia, pneumonia, endocarditis, and osteomyelitis.[21]

The resistance to antibiotics resulted from the horizontal transfer of a mobile genetic element onto *Staphylococcus* species.[26] The gene encoding methicillin resistance (*mecA*), which confers resistance to beta-lactams, has one of four classes of the staphylococcal cassette chromosome *mec* (SCC*mec*), which produces low-affinity penicillin-binding proteins that are abbreviated as PBP2 or PBP2a. In contrast to MRSA strains found in healthcare settings, other virulence factors, such as Panton-Valentine leucocidin (PVL), a pore-forming bacterial leukotoxin that causes the lysis of leukocytes and cell necrosis, were observed to cluster among strains of MRSA outside of healthcare and community settings; such strains include strains USA100-400.[28] Nevertheless, the present spillover of strains blur the distinction between healthcare-associated and community-acquired MRSA infections.[29]

In the present case, the blood cultures collected at the time of presentation to the hospital yielded MRSA. To our knowledge, there has been no recent documentation of MRSA in any patient at our institution prior to the present case, not even among patients with severe diseases, such as IE. The reason for this may be that diseases caused by MRSA do not need to be reported, and there is no surveillance system for MRSA within the institution or at a national level. Hence, although IE was clinically suspected in the present case, MRSA as the causative agent was an unexpected finding.

This case demonstrates the threat of MRSA to public health as the bacterium has the potential to cause detrimental consequences. Furthermore, it is anticipated that similar cases may be encountered in the future. Thus, clinicians should be more vigilant, and advocate to public health authorities to implement a surveillance system for blood stream infections. There were several limitations in this case study. First, were unable to determine whether the isolated MRSA strain carried genes, such as *PVL*, that could have supported our hypothesis that the isolated strain was community-acquired rather than healthcare-associated. Furthermore, we were unable to determine whether any virulence factors, such as immune evasion, were at play, although it could have explained the overwhelming sepsis that may have contributed to the disease's fatal trajectory.[30] Finally, due to the retrospective nature of this report and the unavailability of stored specimens, we were unable to conduct further analyses.

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The diagnosis of IE primarily involves correctly identifying the etiological agent through serial blood cultures and the use of molecular techniques to identify fastidious pathogens.[22] Conventionally, it is recommended to collect venous blood for culture in three separate culture sets, at three different sites, and at three periodic intervals. This helps to determine the persistence of the bacteremia, which is vital for the diagnosis and management of the disease. In the present case, MRSA was identified in all blood samples collected at three time points, which reflected the protracted bacteremia.

Apart from *Staphylococci* and *Streptococci* species, which are the typical bacteria associated with IE, other relevant Gram-positive bacteria to be considered in cases with IE include *Enterococcus faecalis*, a commensal bacterium of the gastrointestinal tract, and Gram-negative bacteria belonging to the *Enterobacteriaceae* family.[31] Similarly, the oral microbiome also includes organisms that can cause IE with a low pathogenicity; these include *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella*, and *Kingella* (HACEK) species.[32] Other than bacteria of the HACEK group, which are fastidious and challenging to culture, the other bacteria that causes IE are generally easily cultivable for species identification. Nevertheless, bacterial growth may be impacted by prior antibiotic use or the presence of vector-borne bacterial species, such as *Coxiella brunetii* and *Bartonella* species.[33]

As epidemiological tools, the Von Reyn and Duke clinical criteria have been demonstrated to work well for the diagnosis of IE, and they are presently widely used. The present case had clinical findings that met the two major criteria required for a definitive diagnosis of IE: i) the presence of a typical microorganism that causes IE, and ii) evidence of endocardial involvement, demonstrated by the presence of vegetation by echocardiography. Two approaches were utilized for optimizing the field of view, *i.e.*, a transthoracic approach and a transesophageal approach; the latter has been reported to be more sensitive in identifying vegetation than the less invasive transthoracic echocardiography. In addition to the two major criteria, four of the five minor criteria were also met, including i) a predisposing factor, such as IVUD, ii) an elevated body temperature above 38°C, iii) the presence of a vascular phenomenon, such as Janeway lesions, and iv) an immunological phenomenon, such as Oslers nodes and Roths spots, which are classic micro-embolic lesions that are considered to be specific to IE, but are now fairly rare due to early detection and treatment. The presence of multiple embolic lesions in the present case reflected the chronic course of the disease at the time of presentation.

As alluded to earlier, IVDU is a predisposing factor that substantially increases the risk of developing IE. In cases with IVDU, the characteristic cardiac involvement is involvement of the right-sided heart valves, which increases the risk of embolization to the lungs, causing pulmonary embolism.[34] Conversely, in the present case, the vegetation was located on the mitral valve without any involvement of the valves on the right side of the heart. Hence, we considered that the pathophysiology of IE in the present case may not have been directly due to IVDU, but was rather indirectly due to the introduction of MRSA through unsterile injection techniques. Additional predisposing factors, such as a congenital pathology of the mitral valve leaflets, may have been present, but undetectable, in the present case. Involvement of the mitral and aortic valves poses a much greater risk of severe complications, leading to a poor prognosis and reduced survival after embolic events causing infarcts in multiple organs. In the present case, embolization to the brain was observed at multiple locations, including septic seeding to the eye. Due to the severe disease at the time of presentation, early endovascular interventions were performed.

We described herein the clinical findings of a fatal case of IE. Early recognition of the disease is essential to avoid complications and fatal outcomes. Although the isolated MRSA strain was still sensitive to several antimicrobials, which could be used in salvage therapy, proper preventative measures, such as hand hygiene and contact precautions, are pivotal and fundamental to control and contain the spread of MRSA.

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Supplementary Materials: The following supporting information can be downloaded at www.mdpi.com/xxx/s1: Table S1 Antibiotic sensitivity pattern of *S. aureus* isolated from blood culture after 72 hours of incubation. Figure S1. Computed tomography images depicting the coronal view of the brain (**a)** Bilateral multiple subcortical hypodense foci representing infarctions (**b**) Unilateral hyperdense foci consistent with hemorrhagic transformation.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. For this case report, approval was obtained from the Institutional Review Board (National Healthcare Academy) of Indhira Gandhi Memorial Hospital (137-B(NHA)/MISC/2022/45, June 21st, 2022), and an exemption was obtained from the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (MUTM-EXMPT 2022-005) on October 25th, 2022.

Informed Consent Statement: Written informed consent was obtained from the next of kin of the patient for the publication of this paper.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available to ensure the privacy of the study participant.

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