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Research Article

Multi Bacterial Infection in Immunocompromised Patient

Ummi Nafi'atil Ilmi[1], IGAA Putri Sri Rejeki[2,*]

ABSTRACT

Infection is a major cause of morbidity and mortality in immunocompromised cancer patients due to chemotherapy, radiotherapy, or anti-inflammatory therapy. Approximately 0.9%-39% of cancer patients with febrile non neutropenia has bacteremia and about 7.3% of cancer patients hospitalized have positive bacterial blood cultures. Multi-bacterial infection with Multi Drug Resistant (MDR) in immunocompromised cancer patients complicates therapy and is often fatal. A 6 years old boy diagnosed with left orbital tumor intracranial infiltration. Physical examination: lump in the left eye ± 8 x 10 cm, solid, reddish in color, there was a wound on the left eye ± 12 x 10 cm; Temperature 39^{0}C. Hematology examination Hb 10.3 g / dL; PLT 156 x103 / uL; WBC 28.92 x103 / uL. Blood culture results: Methicillin Resistant *Staphylococcus aureus* (MRSA) resistant to Gentamicin, Amoxicillin Clavulanic Acid, Ampicillin, Penicillin G, Oxacillin and *Enterococcus faecium* resistant to Gentamicin, Ampicillin, Cotrimoxazole, Trimetoprim, Erythromycin, and Clindamycin. Results of pus culture from the left eye wound was *Staphylococcus intermedius* resistant to Gentamicin, Amoxicillin Clavulanic Acid, Ampicillin, Penicillin G, Oxacillin, Chloramphenicol, Ciprofloxacin. Based on the results of blood and pus culture, all bacterial isolates included multidrug-resistant organisms (MDRO). Multidrug resistant organisms are microorganisms, especially bacteria that are resistant to at least 1 antibiotic of three or more categories. Cancer patients are susceptible to infection with multi-drug resistant bacteria because of their decreased immune system, especially after undergoing chemotherapy. Appropriate antibiotic treatment determines patient morbidity and mortality. Infection due to multi-bacteria accompanied by multi-drug resistance in immunocompromised patients is a condition that has to be treated immediately since the onset of the disease to reduce morbidity and mortality.

Key words: Immunocompromised, Sepsis, Multidrug-resistant bacteria (MDR).

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INTRODUCTION

Cancer patients' death may be attributable to several factors, including tumor development and malignancy or other conditions such as sepsis. Cancer patients encounter a relatively higher risk of infections after immunosuppression due to chemotherapy, radiotherapy, or anti-inflammatory therapy. Cancer patients are also potentially exposed to nosocomial infections because they require a long hospital stay. Bacterial infection is one of the most common complications in immunocompromised cancer patients with solid tumors or hematological malignancies.[1]

Several studies have revealed that 0.9%-39% of cancer patients with febrile non-neutropenia experience bacteremia, and an estimated 7.3% who are admitted to the emergency department have positive blood cultures. According to a prospective multicenter study of pediatric cancer patients conducted by Simmon *et al.* in 2005, cancer patients face a relatively higher risk of infections that potentially lead to sepsis. Septicemia is primarily caused by bacterial contamination in venous catheters. Those bacteria include *Staphylococcus aureus*, *coagulase-negative staphylococci* (CoNS), *Klebsiella spp*., *Pseudomonas aeruginosa*, *Escherichia coli*, *Enterobacter cloacae*, *Enterococcus faecium*, and *Klebsiella pneumonia*. In some cases, the infections are caused by more than one bacterium, and many of them are caused by bacteria that are resistant to several drugs.[1]

The colonization rates of multi-drug resistant organisms (MDRO) in various cancer patient populations are 4.7% to 36% vancomycin-resistant *Enterococcus* (VRE), 5% to 10% methicillin-resistant *Staphylococcus aureus* (MRSA), 7% to 18% *Clostridium difficile*, and 3% to 29% multi-drug resistant Gram-negative bacilli (MDR-GNB). In addition, VRE and extended-spectrum β-lactamases (ESBL) increase the risk of bloodstream infections.[2] Multidrug-resistant bacterial infections increase morbidity and mortality rates due to limited therapeutic options, and accordingly these complications reduce survival rates in cancer patients.[2,3]

CASE

A 6 years old boy was diagnosed with left orbital tumor intracranial infiltration. There were complaints of fluctuating fever, vomiting, cough and shortness of breath after several days of hospitalization in the pediatric hemato-oncology inpatient ward. The physical examination indicated a solid and red lump in the left eye of ±8 x 10 cm, a wound in the left eye of ±12 x 10 cm, and fluid coming out of the left ear. The examination of vital signs displayed a pulse rate of 110x/minute, a respiratory rate of 30x/minute, and a temperature of 39^{0}C. The hematologic examination showed a Hb level of 10.3 g/dL, a PLT level of 156 x10^3/uL, and a WBC level of 28.92 x10^3/uL. The blood culture examination revealed Methicillin-Resistant *Staphylococcus aureus* (MRSA) resistant to Gentamicin, Amoxicillin Clavulanic Acid, Ampicillin, Penicillin G, and Oxacillin; and *Enterococcus faecium* resistant to Gentamicin, Ampicillin, Co-trimoxazole, Trimethoprim, Erythromycin, and Clindamycin. The pus culture examination on the left eye indicated *Staphylococcus intermedius* resistant to Gentamicin, Amoxicillin

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Table 1: Blood culture results.

Susceptibility Test	R: Resistant, I: Intermediate, S: Suscept		
	Culture A	Culture B	Culture C
1. Aminoclycoside			
Amikacin			
Tobramycin			
Gentamycin	S	R	
2. Beta-Lactam Penicillin			
Aztreonam			
Amoxillin			
Amoxillin-Clavulanic Acid	R		
Ampicillin	R	R	
Ampicillin-Sulbactam			
Piperacillin			
Ticarcillin			
Penicillin G	R		
Ticarcillin-Clavulanate			
Piperacillin-Tazobactam			
Oxacillin	R		
3. Beta-Lactam Cephalosporin			
First Generation			
Cepharolin			
Second Generation			
Cefuroxime			
Third Generation			
Ceftazidime			
Cefotaxime			
Ceftriaxone			
Cefoperazone			
Cefoperazone-Sulbactam			
Cefixime			
Fourth Generation			
Cefepime			
Cefpireme			
4. Folate Pathway Antagonist			
Cotrimoxazole	S	R	
Trimethoprime		R	
5. Tetracillin	S		
Tigecycline*			
6. Chloramphenicol	S	R	
7. Macrolides			
Erythromycin	S	R	
Clindamycin	S	R	
8. Quinolone			
Nalidixic Acid			
Ciproflaxacin			
Norfloxacin			
Levofloxacin			
Moxifloxacin			
9. Others			
Fusidic Acid		R	
Mupirocin			
Imipenem*			
Meropenem*			
Ertapenem*			
Vancomycin*	S		
Linezolid*			
Colistin*			
Teicoplanin	S	S	

Culture A: Methicillin Resistant *Staphylococcus aureus*

Culture B: *Enterococcus faecium*

Table 2: Pus culture results.

Susceptibility Test	R: Resistant, I: Intermediate, S: Suscept		
	Culture A	Culture B	Culture C
1. Aminoclycoside			
Amikacin			
Tobramycin			
Gentamycin	R		
2. Beta-Lactam Penicillin			
Aztreonam			
Amoxillin			
Amoxillin-Clavulanic Acid	R		
Ampicillin	R		
Ampicillin-Sulbactam			
Piperacillin			
Ticarcillin			
Penicillin G	R		
Ticarcillin-Clavulanate			
Piperacillin-Tazobactam			
Oxacillin	R		
3. Beta-Lactam Cephalosporin			
First Generation			
Cepharolin			
Second Generation			
Cefuroxime			
Third Generation			
Ceftazidime			
Cefotaxime	S		
Ceftriaxone	S		
Cefoperazone			
Cefoperazone-Sulbactam			
Cefixime			
Fourth Generation			
Cefepime			
Cefpireme			
4. Folate Pathway Antagonist			
Cotrimoxazole	S		
Trimethoprime			
5. Tetracillin	I		
Tigecycline*			
6. Chloramphenicol	R		
7. Macrolides			
Erythromycin	S		
Clindamycin	S		
8. Quinolone			
Nalidixic Acid			
Ciproflaxacin	R		
Norfloxacin			
Levofloxacin			
Moxifloxacin			
9. Others			
Fusidic Acid			
Mupirocin			
Imipenem*			
Meropenem*			
Ertapenem*			
Vancomycin*			
Linezolid*			
Colistin*			
Teicoplanin	S		

Culture: *Staphylococcus intermedius*

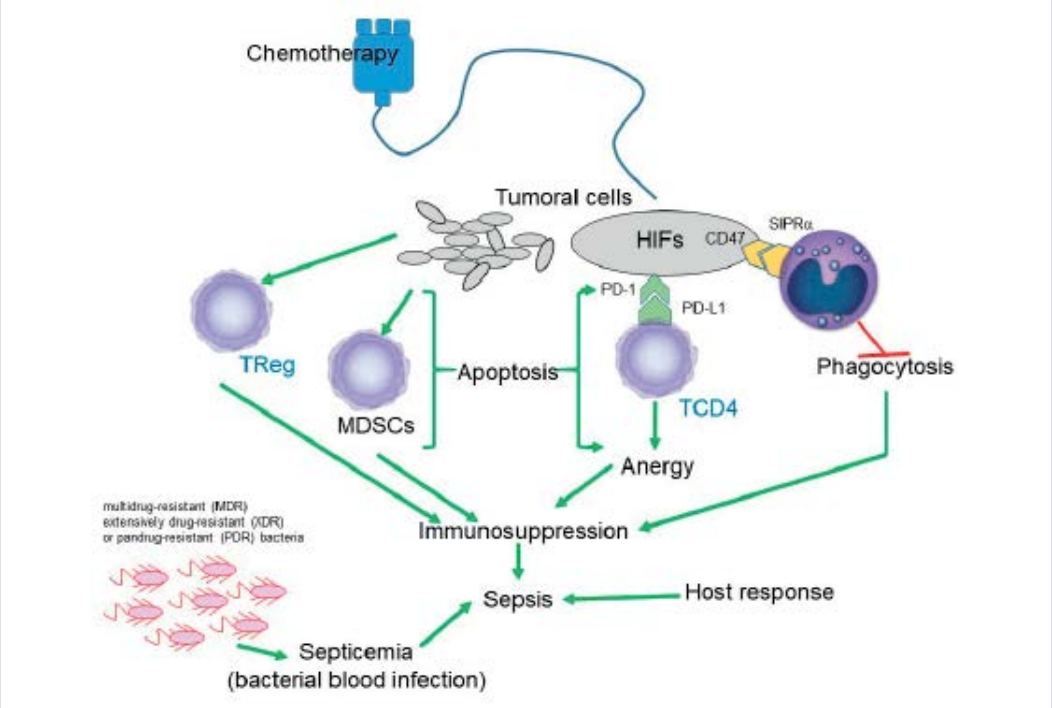

Figure 1: Pathophysiology of sepsis in immunocompromised cancer patients. HIF: hypoxia-inducible factor; MDSC: myeloid-derived suppressor cell; PD1: programmed cell death-1; PDL1: programmed cell death-1 ligand; SIRPα: signal-regulatory protein alpha; TReg: regulatory T cell; TCD4: T lymphocyte CD4 or helper[1].

Clavulanic Acid, Ampicillin, Penicillin G, Oxacillin, Chloramphenicol, and Ciprofloxacin.

Before the pus culture and blood culture examinations, several antibiotics, including Ampicillin sulbactam, Cloxacillin, and Ceftriaxone, were administered to the patient. After the blood culture, several antibiotics, including Gentamicin, Chloramphenicol, and Ampicillin-sulbactam, were also administered to the patient at a higher dose than the previous administration. In addition to antibiotic therapy, the patient also underwent chemotherapy.

DISCUSSION

Blood stream infection (BSI) is a common complication in patients with cancer and the leading cause of high morbidity and mortality. Blood stream infection can be caused by one or more pathogens.[4] Polymicrobial blood stream infection (PBSI) is associated with multidrug resistant (MDR) organisms and poor clinical outcome.[4,5] The definition of PBSI is when two or more organisms are isolated from blood culture specimens collected from patients during a period of <72 hours. Patients confirmed advanced chronic cancer with metastases (Stage IV) and multiple stage III tumors (lung, pancreas, stomach, esophagus, and urothelium) that did not respond to treatment.[4] Polymicrobial bacteremia is a rare case but associated with a high mortality rate.[6,7] Children who experience polymicrobial bacteremia are usually immunocompromised or immune deficiency.[7]

In this patient 2 pathogens were isolated from blood culture, and based on the results of the blood culture and pus culture, all of the bacterial isolates were classified as multidrug-resistant organisms (MDRO). Multi-drug resistant organisms are microorganisms, especially bacteria, that are resistant to at least one antibiotic from three antibiotic classes. Cancer patients are easily infected with multi-drug resistant bacteria since they experience a decrease in their immune system, especially after undergoing chemotherapy.[1,8]

Tumor cells are capable of inducing and activating various immunosuppressive pathways, some of which include regulatory T lymphocytes (Treg) and myeloid-derived suppressor cells (MDSCs) inhibiting the activity of dendritic cells, NK cells, CD8+CTLS cells, CD4+Th cells, and T δγ cells. T. In addition, chemotherapy alone may lead to immunosuppression. Samanta *et al*., 2018 explained that chemotherapy could induce the production of hypoxia-inducible factors (HIF) in tumor cells. HIF could activate CD47, which is a ligand for signal regulatory protein α (SIRPα) in macrophages thereby inhibiting phagocytosis. HIF could also activate the expression of programmed cell death-1 ligand (PDL1) which binds to PD1, thereby inducing T cell anergy.[1]

Immunocompromised cancer patients experience more critical sepsis and worse prognosis because of the inability of the body to produce an adaptive immune response against various microorganisms. The condition becomes more dangerous in these patients if the infecting bacteria becomes multidrug-resistant (MDR).[1]

A correlation between multi-bacterial infection with multi-drug resistance and poor outcome has been reported. The selection of appropriate empiric therapy within the first 48 hours of initial symptoms and within the first 24 hours after a positive blood culture is critical to the outcome of patients with such infection. Antimicrobial administration should be initiated at the onset of sepsis symptoms, at least within the first 60 minutes after the identification, because studies have shown that the mortality rate increases every hour without adequate therapy. In hospitalized patients, early catheter removal and injection site rotation have been proven to be beneficial in reducing the mortality rate.[2,9]

Based on the suspected pathogen, adding a glycopeptide antibiotic, such as teicoplanin, should be considered for treating MRSA and ampicillin-resistant enterococci. If the environment has an MRSA level of more than 20%, empiric therapy with teicoplanin should be

considered. However, it is important to monitor teicoplanin therapy as it exhibits high inter-patient variability. A combination of teicoplanin with a fifth-generation cephalosporin, such as ceftaroline, may be preferred for treating MRSA but not for enterococci. In environments where vancomycin-resistant *Enterococcus* (VRE) are endemic, the administration of ampicillin or piperacillin as anti-enterococcal agents may be considered because VREs tend to be susceptible to aminopenicillin treatment, and conversely, ampicillin-resistant *Enterococcus* are frequently proven to be sensitive to glycopeptide treatment.[9]

Treating MDR bacterial infections has been a clinical challenge since the therapeutic options are often limited, and antibiotics that can fight MDR bacteria have some limitations. Implementing an antibiotic surveillance program and infection control measures is essential to avoid the development and spread of antimicrobial resistance.[2,3]

Differentiating blood culture results of a contaminant from a true pathogen is challenging because some of these microorganisms are an increasing source of true bacteremia. According to the World Health Organization, true infection should be suspected in the following situations: if the same organism is grown in two vials of the same blood specimen, if the same organism is grown in culture from more than one specimen, if growth is rapid (within 48 hours), if different isolates of the same species show the same biotype and antimicrobial susceptibility profiles.[10] All culture results should be reported to the physician, including suspected contaminants. Identification of two or more agents may indicate polymicrobial bacteremia, which can occur in debilitated patients, but may also be due to contamination.[10] In this case only one blood culture was used, making it difficult to determine the cause of bacteremia in this patient.

CONCLUSION

Multi-bacterial infection with multi-drug resistance in immunocompromised cancer patients requires immediate treatment even from the beginning of the disease course to reduce the morbidity and mortality rates.

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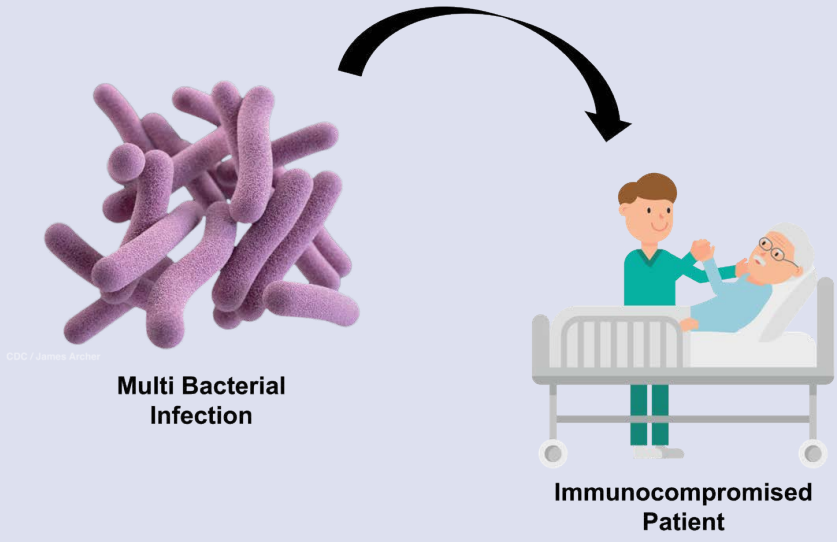
GRAPHICAL ABSTRACT



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