Management of Sepsis Patient Aggravated by Diabetic Ketoacidosis

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Abstract**—** *Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host's response to infection. Sepsis can lead to ketoacidosis in diabetes mellitus patients. A 60 years old male complained of headache, mild fever and painful swallowing since 2 weeks prior to hospital admission. History of diabetes mellitus is unknown. Based on examination, the working diagnosis for the patient was sepsis, suspected periapical abscess, type II diabetes mellitus with diabetic ketoacidosis and decreased consciousness. Initial management of sepsis, insulin, and endotracheal intubation were performed. The patient then was admitted to the ICU. Management of sepsis is very important and should be performed based on 1-hour SSC bundle while performing management of DKA. The patient had periapical abscess which is thought to be the source of sepsis. Sepsis then triggers DKA, and several organ dysfunctions in the form of AKI, DIC, and respiratory distress.*

Keywords— Diabetic ketoacidosis, Periapical abscess, Sepsis.

I. INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host's response to infection. Organ dysfunction is identified using the Sequential Organ Failure Assessment score (SOFA score). SOFA score equal to or more than 2 reflect a risk of death of around 10%. This requires prompt and appropriate intervention so that the condition does not get worse[1].

Sepsis can lead to ketoacidosis in diabetes mellitus patients. More than 50% of KAD cases are thought to be triggered by infection. Diabetic ketoacidosis is an acute metabolic disorder characterized by increasing circulating ketone bodies which progresses to ketoacidosis with uncontrolled hyperglycemia due to insulin deficiency. Acidic ketone bodies are produced by lipolysis process. Acidosis occurs when ketone levels exceed the body's buffer capacity. During an infection there will be an increase in the secretion of cortisol and glucagon hence there is a significant increase in blood sugar levels[1].

II. CASE PRESENTATION

60 years old male, complained of headache, not too high body temperature and painful swallowing since 2 weeks before hospital admission and He received antibiotics for a week from an ENT doctor. Three days before hospital admission, the patient experienced decrease in consciousness, slept more often but awoken when called. There are no seizures, vomiting, numbness and weakness of the limbs. The patient also has no history of stroke.

The patient was taken to Hospital B and treated there. During treatment, it was found that there was a tooth infection and an increase in blood sugar levels. The history of diabetes in the patient is unknown, but the family (father, brother and sister) is known to have diabetes. The patient was then referred to RSHS. On examination at the emergency room, it was obtained that the patient has GCS of 9

(E2M5V2), blood pressure 111/67 mmHg (MAP 81 mmHg), pulse rate 127 x/m, respiratory rate 40 x/m with saturation 99% using O2 5 L/m via binasal cannula, and temperature of 37o C. On the Chest examination, it was found that the patient has regular heart sounds, VBS in both lung fields. Normal abdominal examination. On neurological examination, during meningeal stimulation it was found that the patient has stiff neck (+), no resistance on laseque/kernig, brudzinski I/II/III/IV (-). No other neurological deficits were found.

From the laboratory test it was obtained that Hb 14.6 g/dl, Ht 41.8%, Leukocytes 17,870/uL, platelets 49,000/uL, PT 10.20, aPTT 29.10, INR 0.90, Blood Sugar 343 mg/dl, SGOT 31, SGPT 51, total bilirubin 0.290, indirect bilirubin 0.443, Albumin 1.8, Ureum 43 mg/dL, Creatinine 0.93 mg/dl, Na 150 mEq/L, K 3.6 mEq/L, Cl 124 mEq/L, Ca 5.2 mg/dL, Mg 2,2 mg/dL, Fibrinogen 620 mg/dL, D-dimer 5.10 mcg/mL, pH 7.00, pCO2 27.4, pO2 144.4, HCO3 6.8, BE -22 , 5, SpO2 97.5, Lactate 0.9, Urine ketones +3. Radiological abnormalities were not seen on chest and lung radiographs. Panoramic: dental caries on tooth 17, periapical abscess.

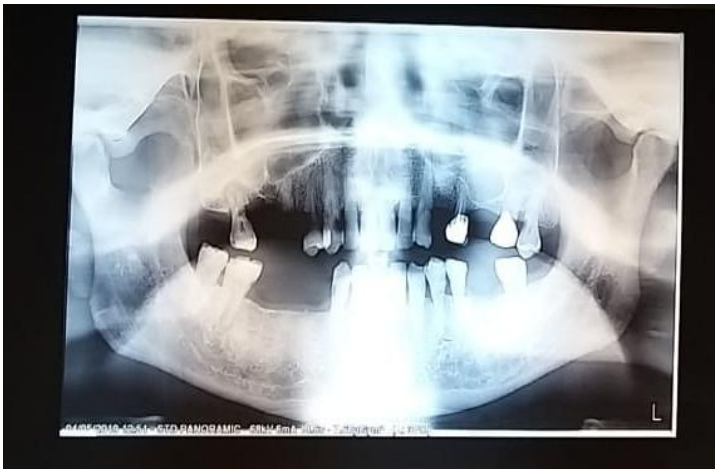


FIGURE 1: Panoramic

Based on this examination, the patient met the criteria for sepsis (SOFA score> 2), which was obtained from the respiratory examination with a PF Ratio of 144.4: 0.41 = 352 (1), platelets of 49,000/uL (3) and GCS of 9 (3) making the total of this patient's SOFA score 7.

Table 1. Sequential Organ Failure Assessment Score

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	PaO_2/FiO_2: > 400 SpO_2/FiO_2: > 302	PaO_2/FiO_2: < 400 SpO_2/FiO_2: < 302	PaO_2/FiO_2: < 300 SpO_2/FiO_2: < 221	PaO_2/FiO_2: < 200 SpO_2/FiO_2: < 142	PaO_2/FiO_2: < 100 SpO_2/FiO_2: < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets x $10^3/mm^3$)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6

According to Sepsis-3, a new (or presumed new) increase in SOFA score above baseline in the presence of infection makes the diagnosis of sepsis. Increasing SOFA scores are associated with incremental increases in mortality.

Abbreviations: GCS, Glasgow coma scale; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, arterial oxygen pressure; SOFA, sequential organ failure assessment (score); SpO_2, oxygen saturation.

FIGURE 2: SOFA Score

The working diagnosis are sepsis, suspected periapical abscess, type II diabetes mellitus with diabetic ketoacidosis, decreased consciousness e.c. metabolic (sepsis and KAD) DD/ e.c. suspected bacterial meningitis, respiratory failure.

Initial management of sepsis according to the recommendations of the Surviving Sepsis Campaign (SSC) is administering crystalloid (RL) 30 ml/kg intravenously, performing blood culture, and administration of antibiotics. Insulin 0.5 U/hour was given. Endotracheal intubation was performed in this patient due to signs of respiratory failure (RR of 40 x/m) and metabolic acidosis in this patient was not well compensated by the patient's respiratory system. The patient was subsequently admitted to the ICU.

III. CARE IN THE ICU

Patient's condition on ICU admission was GCS 6T (E3M3VT), Blood Pressure 110/70 mmHg, HR 120 x/m, Temperature 36oC, Respiration: Ventilator SIMV mode, RR 12 x/m, PC 12, PEEP 5, FiO2 50%, RR actual 12–30 x / m, SpO2 98%. Diuresis 400-500 cc/hour.

Echohemodynamic results: CO: 5.1 L/minute, CI: 3.1 l/minute, SVR: 910 dynes sec cm-5, Distansibility index: 75%, fluid responsiveness (+).

Patient assessment on admission: Sepsis e.c. suspected periapical abscess, type II diabetes mellitus with Diabetic Ketoacidosis, decreased consciousness e.c. metabolic (sepsis and KAD) DD/ e.c. suspected bacterial meningitis, Respiratory Failure.

The treatment plan is aimed at fluid rehydration continuation, overcoming infection and sepsis with antibiotics and source control; management of KAD with administration of fluids, insulin, and electrolyte correction. For respiratory support with ventilator;

The patient was given loading of crystalloid fluid (RL) 300 cc in 1 hour followed by maintenance 2000 cc/24 hours, plasmanate 50 cc/hour, insulin 0.5 - 2 U/hour.

The patient was given meropenem 3 x 1 gr, levofloxacin 1 x 750 mg, ceftazidim 3 x 2 gr, and metronidazole 1 x 1500 mg. In addition, 8 mg/hour of esomeprazole and Paracetamol 4 x 1 gr was also given.

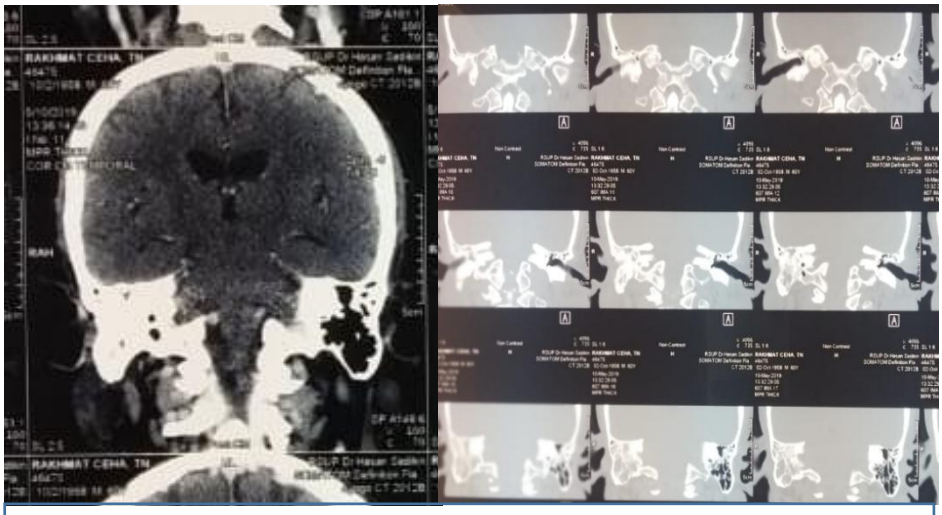
On day 1 in the ICU, the patient's GCS was 6T (E3M3VT), Blood pressure 122/78 mmHg, HR 88-90 x/m, temperature 36.6 0C, CVP 9-11 mmHg, respiration with ventilator mode PS 12, PEEP 6, FiO2 45% with RR of 20-28 x/m, TV 480-520 ml, SpO2 99-100%, Diuresis 200-300-100 cc/hour, Balance: -110/24 hours. Echodynamics: kissing LV with IVC colaps > 50%, fluid responsiveness (+). LVEF 76%, global normokinetics, normal valves, SVR 1040 dyne.s.cm-5. In laboratory examination, there was an increase in creatinine > 1.5 times the baseline, thus it met the criteria for stage 1 AKI (KDIGO).

On day 2 of treatment, on the ENT examination it was found the presence of acute otitis media at the stage of the perforation of the right auricle and a plan to do a temporal CT scan with axial coronal section and aural toilet. Source control action by oral surgeon was performed by extracting tooth 17. On this day, there was also an increase in lactate to 3.7.

During the ICU stay, the patient's hemodynamic was relatively stable without the use of support. The level of conciousness and respiration also showed some improvement. The clinical condition continued to improve after source control measures and hemodialysis measures indicated for sepsis.

TABLE 1
LABORATORY RESULTS DURING TREATMENT IN THE ICU

Laboratory result	Day 0 6/5	Day 1 7/5	Day 2 8/5	Day 3 9/5	Day 4 10/5	Day 5 11/5	Day 6 12/5	Day 7 13/5	Day 8 14/5
Hb	14,6	12,7	14,2	12	12,5	11,2	10,3	9,4	9,2
Ht	41,8	34	37,9	31,9	34,6	31,5	28,5	26,5	26,5
Leucocyte	17870	10240	10,700	8230	10500	9770	10200	8540	8430
Platelet	49000	55000	90000	96000	122000	99000	115000	126000	185000
PT	10,20			12,9	13,5				
aPTT	29,0			22,60	22,7				
INR	0,9			1,16	1,22				
Fibrinogen	620				212,4				
D-Dimer	5,10				3,97				
Blood Glucose	343	248	268/248/219	322	172		155	187	
Urine ketone	+3								
Lactate	0.9		3,7		1,5			1,2	
Natrium	150	154	156/161	156	154	141	143		140
Kalium	3,6	2,4	3,3/ 3,3	2,5	2,4	4,1	3,2		3,9
Chloride	124	124	121	117	113	102	107		
Calsium	5,2	4,09	4,73/4,98	4,13	4,46	4,36	4,74		4,87
Magnesium	2,2	2,0		1,9	1,8	1,4	1,8		1,4
Ureum	43	62	62	75,9	59,1	45	40	43	45
Creatinine	0,93	1,55	1,55	1,74	1,46	1,2	1,06	1,15	1,2
pH	7.00	7,346	7,396	7,47	7,532	7,430	7,439		7,452
pCO2	27,4	19,6	19,0	32	29,1	31,9	38,1		35,5
pO2	144	184	124,0	47,3	134,7	222	212,4		125,2
HCO3	6,8	10,8	11,8	23	24,6	21,4	26		25,1
BE	-22.5	-12,2	-10,2		2,7	-1,9	2,5		1,9
SatO2	97,5	99,7	99,0	84,2	98,3	98,6	99,6		98,2
Albumin	2,1	2,1	2,1		1,89				
SGOT	31								
SGPT	51								
Total Bilirubin	0,733								
Direct Bilirubin	0,290								
Indirect Bilirubin	0,443								
Urine/24 hour	Urine Na 144,7 mmol/L Urine volume 6800 ml/24 hour Urine NA calc 984,0 mmol/24 hour								



- Right
- Bilateral sphenoid sinusitis
- There were no signs of meningitis, intracranial bleeding, ischemic lesions, SOL / neoplasms and vascular malformations.

FIGURE 3: Temporal CT Scan

IV. DISCUSSION

Bacterial meningitis is a medical emergency with significant morbidity and mortality, requiring immediate recognition and immediate treatment. In bacterial meningitis there is inflammation of the meninges, especially arachnoid and piamater, due to bacterial invasion in the subarachnoid space. Meningitis is a syndrome consistent with the classic triad of fever, headache and meningismus. Patients usually present with two out of three symptoms and a possible change in mental status.[1,2,3] Acute bacterial meningitis occurs due to bacteria entering the bloodstream and migrate to the brain and spinal cord. Bacteria can also invade the meninges due to ear or sinus infections, skull base fractures, or after brain surgery. Diagnosis in this patient is based on complaints of headache, fever, decreased consciousness and the presence of neck stiffness on physical examination. The source of infection in this case was probably from dental infection with periapical abscess and ear infection with acute otitis media and sinusitis sphenoidalis[2-4].

Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host's response to infection. Organ dysfunction can be identified as an acute change in total SOFA score (Sequential Organ Failure Assessment) $\geq$ 2 due to the presence of infection. The baseline SOFA score can be assumed to be zero in patients with no known previous organ dysfunction. A SOFA score of more than 2 reflects a risk of death of approximately 10%. This requires prompt and precise intervention so that a worsening condition does not occur[1].

Meanwhile, septic shock is a part of sepsis in which circulatory and cellular/metabolic disorders that underlie it can increase mortality. Patients with septic shock can be identified if there is sepsis accompanied with persistent hypotension requiring vasopressors to maintain MAP $\geq$ 65 mmHg and serum lactate levels > 2 mmol/L despite adequate fluid resuscitation.[4]

In this case the diagnosis of sepsis was based on impaired organ function in the form of respiratory distress (PaO2/FiO2= 144.4/0.4= 361), decreased consciousness GCS = 9 (E3, M3, V3), a hematological disorder in the form of thrombocytopenia (49,000/uL). SOFA score = 7.

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Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
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FIGURE 4: SOFA score

Diabetic ketoacidosis (KAD) is a metabolic disorder caused by absolute or relative insulin deficiency, characterized by hyperglycemia, acidosis, and ketosis. KAD and Hyperosmolar Hyperglycemia State (HHS) are 2 serious and life-threatening complications of acute metabolic diabetes mellitus. Both of these conditions can occur in type 1 and type 2 diabetes mellitus (DM), but KAD is more common in type 1 diabetes.

Ketoacidosis is the result of a deficiency or ineffectiveness of insulin that occurs along with an increase in counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormones). This increased activity will break down triglycerides into glycerol and free fatty acids (FFA). Glycerol is an important substrate for gluconeogenesis in the liver, while the excessive production of free fatty acids is the main precursor of ketoacids. In the liver, free fatty acids are oxidized into ketones, which are mainly stimulated by glucagon.

Hyperglycemia occurs due to increased hepatic and renal glucose production (gluconeogenesis and glycogenolysis) and decreased glucose utilization in peripheral tissues. Hyperglycemia and high ketone levels cause osmotic diuresis which will result in hypovolemia and decreased glomerular filtration rate.

There are about 20% of KAD patients who are only known to have DM for the first time. The most common precipitating factor for KAD is infection, and it is estimated that it triggers more than 50% of cases of KAD. In infection there will be an increase in the secretion of cortisol and glucagon so that there is a significant increase in blood sugar levels. Other factors include cerebrovascular accidents, alcohol abuse, pancreatitis, heart infarction, trauma, pheochromocytoma, drugs, recently recognized type 1 diabetes and discontinuity (adherence) or inadequate insulin therapy.

Diagnosis of KAD in this patient was based on the finding of hyperglycemia conditions (GDS 343 mg/dl), acidosis conditions (Blood Gas Analysis: pH 7.00, pCO_2 27.4, pO_2 144.4, HCO_3 6.8, BE -22.5, $satO_2$ 97.5) and the presence of ketones in the urine (urine ketones +3). This condition is also supported by clinical conditions, namely: decreased consciousness (although the bias is caused by the patient's meningitis and sepsis conditions), Kussmaul's breathing, and tachycardia.

Dissaminated Intravascular Coagulation (DIC) is a condition in which bleeding and thrombosis occur. DIC is characterized by systemic activation of blood clots, which results in the formation and deposition of fibrin, which leads to microvascular thrombi in various organs and contributes to multiple organ dysfunction syndromes (MODS). DIC is a complication or effect of the development of another underlying disease and generally involves activation of systemic inflammation such as sepsis, trauma, organ destruction (such as pancreatysis), malignancy, severe transfusion reactions, obstetric complications, heatstroke.

Sepsis is a clinical syndrome defined as a systemic response to infection. It is often exacerbated by coagulopathy and by DIC in 35% of severe case. During sepsis, inflammation diffusely activates the coagulation system, consuming multiple blood clotting factors and producing DIC. In infection-induced SIRS, both disrupted endothelial cells and activated mononuclear cells produce proinflammatory cytokines that promote coagulation. In sepsis-associated DIC, antibiotics and treatment of the underlying disease are the main things in DIC therapy[1].

Acute Kidney Injury (AKI) is a serious complication that often occurs in critical illness. The incidence of AKI in patients hospitalized in the ICU is around 20 - 67%. Sepsis and septic shock are the main precipitating factors for AKI. AKI mortality rate in septic shock can reach 60%. Based on KDIGO criteria, AKI is diagnosed if the serum creatinine level increases by at least 0.3 mg/dL (26.5 µmol/L) in 48 hours or increases at least 1.5 times the baseline value in 7 days[1,5].

KDIGO Definition of AKI

AKI is defined as any of the following (*Not Graded*):

- Increase in SCr by ⩾0.3 mg/dl (⩾26.5 µmol/l) within 48 hours; or
- Increase in SCr to ⩾1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5 ml/kg/h for 6 hours.

KDIGO AKI Staging

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 µmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 µmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

FIGURE 5. KDIGO

In this case, the diagnosis of AKI was based on an increase in creatinine levels. Initial creatinine on admission was 0.93 which increased within 24 hours to 1.55 (increase of more than 0.3 mg/dL or $\geq$ 1.5 times).

In this case, the mechanism of AKI formation can be caused by pre-renal (polyuri) and renal due to sepsis.

Stage 1 AKI management

- Stop drugs that are nephrotoxins

- Improve body fluid volume status:
  - Correction of hypovolemia, hydration, improve hemodynamics
  - Maintain MAP> 65 mmHg or SBP > 100 mmHg
  - Consider vasoactive use if hypotensive persists despite sufficient fluids.
  - Maintain a urine output of 0.5 ml / kg / hour

- Treatment of infection if present

- Manage and improve the risk factors that contribute to the disease.

V. PATIENT MANAGEMENT

The patient's problems stemmed from infection, presumably from periapical abscess of tooth 17, and acute otitis media of the right auricle. The causative bacteria infect the meninges through blood or direct invasion. The inflammatory reaction caused by this infection leads to sepsis which aggravates the general condition of the patient. Organ dysfunction that occurs includes thrombocytopenia and DIC, respiratory distress, and AKI. Sepsis also triggers KAD.

Therefore, the management of sepsis in this patient become is paramount, based on the hour-1 SSC Bundle:

1. Check the lactate level, recheck if the initial lactate level is > 2mmol/L
2. Take blood cultures before giving antibiotics.
3. Give broad spectrum antibiotics
4. Start giving 30 ml/kg body weight of crystalloid fluid immediately to patients with hypotension or lactate levels $\geq$ 4 mmol/L
5. Use vasopressors if hypotension is present during or after fluid resuscitation to maintain MAP $\geq$ 65 mmHg.

Management of patients in the emergency room was carried out following the h-1SSC.

DKA management targets:

1. Fluid resuscitation
2. Correction of acidosis and ketosis
3. Returning glucose levels to normal limits
4. Correction of electrolytes and fluid deficits
5. Identify and treat the causative factors

VI. CONCLUSION

In this case, a patient had a dental infection that progressed to periapical abscess, and acute otitis media with sphenoid sinusitis and mastoiditis. This is thought to be the source of spread of meningitis and sepsis. Sepsis then triggers KAD, and several organ disfunction in the form of AKI, DIC and respiratory distress.

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