



## Multiple Possible Causes of Dyspnea in An Unusual Pickwickian Syndrome In The COVID-19 Pandemic: A Case Study

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### Abstract

Pickwickian Syndrome (PS) or obesity hypoventilation syndrome (OHS) is a diagnosis of exclusion with features of obesity, sleep disordered breathing, and chronic daytime hypercapnia. Patients with PS may exhibit general OSA or respiratory failure. We present an unusual case of PS with acute respiratory failure, which resulted in organ failure and death. A 41-year-old male was admitted to the hospital due to shortness of breath. He had sleeping trouble, frequently awaking as the breathing briefly stopped and gasped. There was a history of diabetes melitus (DM) and hypertension for more than ten years, as well as smoking with a moderate Brinkman Index. The patient appeared to be drowsy, tachypneic, hypoxic, and morbidly obese. We diagnosed him with PS, bronchopneumonia, respiratory failure, pulmonary edema, hypertensive heart disease (HHD), DM, acute on CKD. We treated him with medication, oxygen therapy (BiPAP), and hemodialysis. After being transferred from the ICU to the general ward, the patient became apneic and CPR was attempted; nonetheless, the patient died. This unusual case (malignant OHS) was a subgroup of OHS with greater morbidity and multiorgan system dysfunction. There were multiple causes of dyspnea in our patient, which concluded to be a death case. There are three modalities of management for stable PS: positive airway pressure (PAP), weight reduction, and pharmacotherapy. The treatment of respiratory failure in PS was primarily accomplished through the use of positive pressure oxygen therapy. There were multiple causes of dyspnea in this patient. For optimal management, not only should the PS be treated, but other comorbidities should be addressed as well.

**Keywords:** pickwickian syndrome, malignant obesity hypoventilation syndrome

### INTRODUCTION

The term 'Pickwickian Syndrome' was first popularized by a case report from Burwell et al based on the same description

of one character in Charles Dickens' *The Posthumous Papers of the Pickwick Club*, whom the author referred to as "Joe", a fat boy who is always asleep and has a very

extraordinary degree of somnolence.<sup>1,2</sup>

Obesity Hypoventilation Syndrome (OHS), also known as Pickwickian Syndrome (PS), is a diagnosis of exclusion with features of obesity (body mass index/BMI  $\geq 30$  kg/m<sup>2</sup>), sleep disordered breathing, and chronic daytime hypercapnia (PaCO<sub>2</sub>  $\geq 45$  mmHg), with no other causes of hypoventilation or hypercapnia (obstructive airway disease, interstitial lung disease, neuromuscular disease, metabolic-severe hypothyroidism, or chest wall disease-kyphoscoliosis). Almost 90% of OHS patients have obstructive sleep apnea (OSA). However, the presence of OSA is not necessary for the diagnosis of OHS (no need for polysomnography).<sup>3-5</sup> The remaining 10% of OHS patients have sleep hypoventilation, which is described as having oxygen desaturation during sleep unexplained by obstructive apneas or hypopneas.<sup>6</sup>

According to the 2018 Basic Health Research from the Ministry of Health, Republic of Indonesia, the proportion of obese people (BMI  $\geq 27$  kg/m<sup>2</sup>) in the Indonesian population has increased from 10.5% in 2007 to 21.8% in 2018.<sup>7</sup> Unfortunately, the prevalence of OHS is unknown in Indonesia as well as in other countries. Nevertheless, the OHS prevalence can be estimated at 0.15 to 0.3% in the United States (more prevalent than in other nations due to the obesity epidemic).<sup>5</sup> Patients with OHS may present in two ways, each with its own set of medical help routes: as part of the general

OSA population or with rapid deterioration leading to severe respiratory failure (requiring intensive care).<sup>8</sup>

A study by Rasmin et al in Indonesia pointed out that among patients who presented with acute respiratory failure, 44.7% were hypercapnic and about 13.6% had acute on chronic respiratory failure. However, there was no data regarding acute respiratory failure due to OHS in Indonesia.<sup>9</sup> We are presenting an unusual case of Pickwickian Syndrome with signs of acute hypercapnic respiratory failure (AHRF) and multiple possible causes of dyspnea, all of which resulted in organ failure and death.

## CASE REPORT

A 41-year-old Indonesian male was admitted to the hospital due to shortness of breath aggravated by physical activity that started 2 days before admission. The breathlessness was also intensified by position (orthopnea). There was no cough, wheezing, chest pain/discomfort, or fever. Nutritional intake was admitted to be exceptional. Approximately 9 months ago, the patient was hospitalized in another hospital for a same chief complaint and spent 13 days in the ICU.

At the previous hospitalization, the record of chest X-ray (CXR) showed pulmonary edema and the laboratory results indicated renal failure (suspected acute on chronic kidney disease) and mild hypoxemia with compensated chronic respiratory failure from blood gas analysis. The spouse mentioned that this patient

demanded a very huge portion of rice per meal served and that it had been such for a long period of time. She also stated that her husband had sleeping trouble, that was, snoring, could not sleep soundly; frequently awoke as the breathing briefly stopped and gasped.

The latter was neither treated nor diminished after the last hospitalization and was repeatedly observed during this period of inpatient care. The patient had a history of diabetes melitus and hypertension for >10 years, consumed 10 mg of amlodipine once daily and also a combination of 500 mg of metformin and 2 mg of glimepiride twice a day. He had a moderate Brinkmann Index with a history of 25 years of cigarette smoking, 12 cigarettes per day.

The physical examination showed a severely-ill general condition, indicated by somnolence, blood pressure of 179/125 mmHg, heart rate of 116 bpm, respiratory rate of 28/min with rapid and shallow breathing, and peripheral oxygen saturation of 67% in room air (escalated to 93% after O<sub>2</sub> supplementation using a non-rebreathing mask/NRM). The temperature was within the normal range. Upon observation, there were periods of snoring and gasping during the first hour in the emergency department (ED).

The patient was morbidly obese with a BMI of 56.64 kg/m<sup>2</sup> (body weight 145 kg and height 160 cm). In the neck area, there was a thick layer of subcutaneous fat that made it difficult to do a neck examination (jugular vein pressure,

presence of lymphadenopathy, and tracheal palpation). Pulmonary examination revealed dull percussion on both hemithorax bases and rales on auscultation, as well as wheezing and prolonged expiration. Heart sounds were regular. Both legs were swollen.

Furthermore, as we were still in the COVID-19 pandemic and the patient had acute dyspnea, we did a swab test as screening. The antigen swab test result was negative, confirmed by a negative SARS-CoV2 PCR test result. The patient was shortly consulted by the internist, pulmonologist, cardiologist, and intensivist, then immediately transferred to ICU after stabilization in the ED.

Arterial blood gas analysis (ABGA) showed AHRF with pH 7.104, PaCO<sub>2</sub> of 117 mmHg, PaO<sub>2</sub> of 53.9 mmHg, HCO<sub>3</sub> of 35.9 mmol/L, normal base excess, and O<sub>2</sub> saturation of 84.5%. Other lab tests were: normal Hb (17 g/dL) and hematocrit (52%), leukocytosis (16,700/μL) with an increased Neutrophil-Lymphocyte Ratio (NLR) of 9.11, normal blood glucose with an increased HbA1c (8.2%), normal liver function but impaired kidney function (ureum of 65 mg/dL, creatinine of 3.30 mg/dL with an estimated glomerular filtration rate/eGFR of 22.1 mL/min/1.73 m<sup>2</sup> and uric acid of 12.4).

Urinalysis indicated proteinuria, glucosuria, and hematuria. The electrocardiography (ECG) showed regular/sinus rhythm, RBBB, with no signs of hypertrophy, ischemic or infarction. The CXR (Figure 1) showed cardiomegaly and

pulmonary edema while echocardiography showed normal ejection fraction (71%) and LVH. Chest CT scan (Figure 2) indicated cardiomegaly with pulmonary vascular congestion, pulmonary edema and pneumonia.

We assessed the patient as having OHS, bronchopneumonia, type 2 DM, hypertensive heart disease (HHD), and acute on chronic renal failure (acute on CKD) with AHRF, low chest expansion, acute pulmonary edema, immobilization, and uncontrolled blood glucose. We managed the patient with oxygen support (positive pressure) and aminophylline (respiratory stimulant) for the AHRF, an antibiotic for pneumonia, insulin to regulate the blood glucose, diuretics and anti-hypertensive drugs for the pulmonary edema and HHD.

In the ICU, we used non-invasive ventilation (NIV) with BiPAP mode ( $P_{\text{insp}}$  10 cm H<sub>2</sub>O, PEEP 8 cm H<sub>2</sub>O, FiO<sub>2</sub> 50%) and did chest physiotherapy to overcome the AHRF. The patient had good clinical responses toward the treatments given, marked by improvements in symptoms, consciousness and vital signs. Nevertheless, the pulmonary auscultation pointed out otherwise. Weaning of NIV was then made from BiPAP to CPAP mode following a better ABGA result taken the day after NIV administration (pH 7.281, PaCO<sub>2</sub> of 64.2 mmHg and PaO<sub>2</sub> of 83.1 mmHg).

During the observation, we found daily fluid balance was always in positive trends with decreased urine output and

finally reached a urine output of 80 mL per day. Worsening kidney function led to acute CKD being established as we looked for an etiology other than diabetic-hypertensive nephropathy. Following a consultation with the nephrologist, the decision was made to begin renal replacement therapy and hemodialysis on this patient. The initial hemodialysis successfully withdrew 1,000 mL and eventually created a negative fluid balance. Two days after, hemodialysis withdrew 2,384 mL, so the daily fluid balance was found to be negative only on days with a hemodialysis schedule. Getting more stable, the patient was then transferred to the regular ward. We had already arranged for plans to perform a spirometry and also to get this patient an NIV for nocturnal use after discharge.

However, 10 hours after being transferred to the regular ward, the patient was agitated and having air-hunger behavior. The spouse acknowledged that the patient leaned forward, tried to breathe, and suddenly took off his oxygen mask. She called the nurse, but unfortunately, the patient appeared apneic and cyanotic with no palpable carotid pulse. The team did cardio-pulmonary resuscitation for 30 minutes, but no response was obtained and he was declared dead.

## DISCUSSION

The condition of our patient was complex. The diagnosis of OHS was

accompanied by some other comorbidities which had been experienced by our patients in the long term, most of which also had a role in generating dyspnea. This "unusual" case of Pickwickian Syndrome was mentioned in other studies or reports as "Malignant OHS" (MOHS).<sup>10</sup>

This MOHS is a subgroup among OHS patients with a higher BMI ( $>40 \text{ kg/m}^2$ ) that accounts for greater morbidity and multiorgan system dysfunction. As mentioned in the study by Marik and Desai about MOHS patients' characteristics, all of these patients were admitted to ICU due to AHRF, all had metabolic syndrome and high HbA1c. Some of these patients were also diagnosed with pneumonia, acute or chronic renal failure, sepsis, cellulitis, pulmonary hypertension, and nonalcoholic steatohepatitis (NASH).

From our point of view, there were some causes that possibly induced the symptom of dyspnea in our patient. Some should have been dominant, some were not. There were multiple possible causes of dyspnea in our patient that apparently concluded in a death case, such as OHS, AHRF, bronchopneumonia, acute pulmonary edema, HHD, and acute CKD, which will be individually discussed in the following paragraphs.<sup>11</sup>

### **Obesity Hypoventilation Syndrome and Acute Hypercapnic Respiratory Failure**

Our patient met the features of OHS, which were obesity, sleep disordered breathing, and hypercapnia. Obesity in

Indonesia applies a lower BMI cut-off point than in the US, that is  $>27 \text{ kg/m}^2$ , while our patient was severely obese with a BMI of  $56.64 \text{ kg/m}^2$ . Sleep disordered breathing was also found in our patient, as mentioned by his spouse and observed during treatment in the ICU. Although our patient had a history of smoking with a moderate Brinkman Index (a risk factor of COPD), the diagnosis of acute respiratory failure was mostly led to OHS because such a feature of sleep disordered breathing was commonly absent in COPD.

Diagnosing a potential coexisting COPD from smoking habit in this patient should have been difficult, so spirometry was already planned whenever the patient was stable in an out-patient setting, but the patient died. Marik in a large cohort study of OHS patients revealed that about 43% of OHS patients had been erroneously diagnosed as having COPD.<sup>12</sup> Therefore, the diagnosis of COPD in an OHS patient should be made with caution.

It was quite difficult to demonstrate the presence of daytime chronic hypercapnia in our patient as he was admitted with AHRF, shown by the ABGA with a very high level of  $\text{PaCO}_2$ , mild hypoxemia, and an elevated bicarbonate level. However, elevated bicarbonate levels as a metabolic compensation for respiratory acidosis are quite common in OHS and indicate the chronic nature of hypercapnia. The Hb and hematocrit levels also attained nearly the upper normal limit. There we could see signs of acute and chronic respiratory failure, indicating

intensive treatment. The alveolar to arterial oxygen gradient (AaDO<sub>2</sub>) from the admission ABGA was calculated to be 566.75 mmHg (FiO<sub>2</sub> of 100%). We considered elevated PaCO<sub>2</sub> with high AaDO<sub>2</sub> as signs of hypoventilation, along with another mechanism of hypoxia, that was either a shunt or a V/Q mismatch. As the patient responded well to the NIV and the evaluation of ABGA indicated a correctable PO<sub>2</sub>, then the hypoxia was produced by the V/Q mismatch.<sup>5</sup>

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Patients with OHS have respiratory abnormalities originating from three interacting sources: alteration of pulmonary function related to obesity, changes in central ventilatory drive, and sleep disordered breathing. Obesity in OHS causes more significant changes in reduced lung volumes (total lung capacity/TLC, functional residual capacity/FRC, expiratory reserve

volume/ERV, vital capacity/VC, and forced expiratory volume in one second/FEV<sub>1</sub>) than eucapnic morbidly obese patients. Excess fat deposits in the abdomen, chest wall, and diaphragm may reduce the chest wall and lung compliance aside from decreasing lung volume. Breathing at low lung volumes enhances airway resistance due to small airway closure during exhalation in both sitting and lying positions. All of these, with associated respiratory muscle weakness, increase the work of breathing and if the patient is unable to compensate with elevated ventilatory drive, then OHS occurs.<sup>4,13,14</sup>

The comparison of excess fat deposits on the chest wall and the size of the lungs of our patient can be seen in Figure 2, while the exact objective measurements of lung volumes and capacities from spirometry were not fulfilled. By observing the comparison between excess fat on the chest wall and the lung sizes of our patient, we were assured that restrictive disorder should have taken place from the very beginning of the patient's respiratory problem.<sup>4,13,14</sup>

The majority of morbidly obese patients who maintain eucapnia have intensified respiratory drive as a compensation for abnormal respiratory workload (due to fat deposition). This can be observed similarly to normal subjects whose chest walls are loaded with something heavy. Obese subjects have escalated rates of oxygen consumption and carbon dioxide production; therefore, they have to accelerate minute ventilation



for compensation. If they fail to meet this compensation due to blunting hypercapnic and hypoxemic ventilatory responsiveness, then they could develop hypoventilation and OHS.<sup>4,13,14</sup>

The origin of this blunting response is hypothesized to be a consequence of some causes, namely obesity, genetic predisposition, sleep-disordered breathing, and leptin resistance.<sup>5</sup> Leptin, an adipokine that suppresses appetite, acts on central respiratory pathways as a powerful stimulant to augment ventilation. However, there is increasing evidence that leptin resistance could promote OHS.<sup>13</sup>

Central resistance to leptin (from persistent obesity) may lead to alteration of ventilatory control and deterioration of compensatory mechanisms to increased respiratory workload, culminating in OHS. Chronic hypoxemia and hypercapnia predispose OHS patients to pulmonary hypertension and secondary erythrocytosis.<sup>13</sup>

The latter was found in our patient, as shown in the full blood count result. We believe that leptin resistance has already taken place in our patient, as referred to by a clue gained from the alloanamnesis of the spouse, who confessed that our patient demanded a very huge portion of rice per meal served (high in calories and carbohydrates) and that it has been so for a long period of time. This was a sign of leptin resistance as the suppression of appetite did not occur normally. Hence, ventilatory control was also altered and OHS was sustained.

Obese subjects have altered physiological conditions on supine sleep. Significant upper airway narrowing is linked to excessive fat depositions surrounding upper airway and nocturnal fluid shift from the lower extremities (fluid overload and edema in the obese) to the neck. Both causes decrease pharyngeal size and promote collapsibility. This narrowing or closure of upper airway contributes to obstructive events during supine sleep. Same matter also applies to OHS patients, where they experience long-lasting apneas and hypopneas with insufficient ventilatory compensation owing to reduced control from the respiratory centres.<sup>4</sup>

It leads to a significantly greater oxygen desaturation on apnea episodes compared to obese eucapnic patients. Recurrent nocturnal hypoxemia elevates arousal threshold then may blunt the hypoxemic ventilatory response and conclude to hypoventilation.<sup>13</sup> Likewise, blunted hypercapnic ventilatory response occurs if compensation for acute CO<sub>2</sub> loading was diminished which gave a progressive rise in PaCO<sub>2</sub>, accompanied with compensatory renal bicarbonate retention. Daytime hypercapnia due to obstructed nocturnal breathing develops when appropriate ventilatory and renal compensatory response are compromised.<sup>14</sup>

Our patient had a very thick fat deposits on his neck, generating difficulty in examining neck area and also producing

obstacle if tracheostomy is indicated for him. His legs were also swelling, therefore we never put him on supine position to minimize the worsening of sleep disordered breathing. Sleep disordered breathing on our patient was observed during treatment in ICU in the form of sudden choking or gasping. As stated before, OHS could be diagnosed either when a patient reaches an acute-on-chronic exacerbation with acute respiratory acidosis, leading to admission to the ICU, or during a routine out-patient evaluation by a pulmonologist or sleep specialist.<sup>4</sup> A study from Marik pointed out that 63% of OHS patients were hospitalized with an admission diagnosis of respiratory failure.<sup>12</sup>

Chebib et al. stated that about 32.1% of OHS patients (37 out of 115) in their study were admitted to the ICU for AHRF.<sup>15</sup> There was no exact data in Indonesia regarding AHRF that emerged from OHS. The only Indonesian data on acute respiratory failure was studied by Rasmin et al., who pointed out comparable proportions of hypoxemic (55.3%) and hypercapnic (44.7%) acute respiratory failure, with pneumonia as the most common cause (58.7%) of acute respiratory failure.<sup>9</sup> Our patient was admitted for strict monitoring and treatment in the ICU due to AHRF and other diagnoses.

### **Bronchopneumonia and Screening for COVID-19**

Our patient also had pneumonia based on the clinical symptoms, physical

examination, and chest CT. Dyspnea, or breathing discomfort, is one of several symptoms of pneumonia. Seeing that we are still in a COVID-19 pandemic and the chest CT indicated signs of pneumonia (even though it was not specific for viral pneumonia), we carried out evaluation for COVID-19 from antigen swab and isothermal PCR swab; both results were negative. Strausz et al. identified that OSA was associated as a risk factor for severe COVID-19 manifestation (OR=2.37) besides other already identified-risk factors such as older age, male sex, obesity, diabetes, cardiovascular disease, and poor lung function.<sup>16</sup>

Our patient might already have at least 5 of those severe COVID-19 risk factors mentioned. Luckily, he was tested negative for COVID-19. The pneumonia seemed to be of bacterial origin and responded well to antibiotics, as seen in the reduction of leukocyte number (12,200/ $\mu$ L) three days after the antibiotic was administered. Pneumonia was found as an admission diagnosis in 20% of patients with OHS and 15% of MOHS.<sup>11,12</sup> Pneumonia was also reported as a complication in a third of all cases of acute renal failure (ARF).<sup>17</sup>

### **Hypertensive Heart Disease and Type 2 DM**

Patients with OHS should already have comorbidities. Cardiometabolic comorbidities compromise the outcome of OHS patients and certainly cause dyspnea. Some of those comorbidities were found in



our patient, namely hypertension (HHD) and type 2 DM. The prevalence of essential hypertension in OHS patients ranged from 55–58%, while half of the OHS patients had pulmonary hypertension.<sup>4</sup> In a study comparing OHS patients with obese and OSA patients, Basoglu discovered that the rates of cardiometabolic comorbidities were higher in OHS patients, such as coronary artery disease (20.3% vs 15.3%), congestive heart failure (15.3% vs 10.2%), hypertension (67.8% vs 53.2%), and diabetes mellitus (35.6% vs 25.1%).<sup>18</sup>

A study by Castro-Aón et al also confirmed that OHS patients had higher BMI and more frequent histories of arterial hypertension, heart failure, and arrhythmia than OSAS patients, significantly. Patients with OHS had twice the risk of mortality and almost twice the risk of cardiovascular events than those of OSAS patients.<sup>19</sup> Patients with OHS tended to have more impaired endothelial dysfunction, which led to atherosclerosis and cardiovascular events. This was due to higher C-reactive protein (CRP) levels and a lower level of adiponectin, an antiatherogenic and insulin-sensitizing adipokine. Obesity causes low-grade chronic systemic inflammation and inflammatory changes in adipose tissue.<sup>20</sup>

In a previous study by Chebib et al, 54% of patients with OHS had congestive heart failure as the leading cause of AHRF for ICU admission in 54% of patients.<sup>15</sup> Our patient had a history of hypertension for more than 10 years with signs of congestive heart failure due to

hypertensive heart disease as seen radiologically by the size of the heart (cardiomegaly), congestion of the pulmonary vasculatures and LVH on echocardiography. Edema on the legs was also observed. This could be compelling evidence that hypertension in our patient was uncontrolled, yet the medication all this time might also be neither adhered nor optimal.<sup>4,21</sup>

However, blood pressure was observed to be stable and respond to treatments given. It was fortunate that no signs of coronary artery disease or arrhythmias were found during monitoring in the ICU, but the sudden agitation and declines in vital signs of our patient in the regular ward were considered to be of heart attack origin. Compared with patients with eucapnic OSA and similar BMI, patients with OHS are more prone to manifesting cor pulmonale and pulmonary hypertension (PH).<sup>4,21</sup>

Almeneessier revealed that the prevalence of PH was in the range of 59% to 88% among OHS.<sup>21</sup> A study conducted to evaluate echocardiography and ECG in OHS patients emphasized that the prevalence of LV systolic and diastolic dysfunction was 25% and 60%, respectively, with 61.5% of them having normal ejection fraction. The prevalence of RV dysfunction and PH was 63.3% and 52%, respectively.<sup>22</sup>

Isolated nocturnal hypoxemia could establish permanent PH. Both pulmonary vasoconstriction and pulmonary vascular bed remodelling in the alveolar hypoxia of

OHS rendered PH the same way as COPD.<sup>23</sup> Either HHD or PH/cor pulmonale might produce dyspnea. According to the echocardiography result, we concluded that our patient had LVH with normal ejection fraction and no cor pulmonale or PH were inspected, so HHD was thought to be the cardiogenic cause of dyspnea in him.

OSA causes insulin resistance (lower insulin sensitivity and higher fasting insulin levels) as well as an increase in gluconeogenesis (higher levels of epinephrine, norepinephrine, and cortisol). Insulin resistance in OSA is also related to elevated CRP, TNF- $\alpha$ , and IL-6.<sup>24</sup> Intermittent hypoxia, which corresponds to obesity, leads to sympathetic activation, chronic inflammation, and oxidative stress, which bring about a reduction of insulin sensitivity, augmentation of gluconeogenesis, and beta cell dysfunction (decrement of insulin secretion). Intermittent hypoxia is also involved in lowered glucose uptake by the muscles, altered gut microbiota, and leptin resistance. All of these give rise to insulin resistance and glucose intolerance (type 2 DM).<sup>25</sup> This insulin resistance in OSA is not only noticed in obese subjects but also in non-obese subjects.<sup>26</sup>

Furthermore, patients with OHS demonstrated higher resistance to insulin and a higher level of glycated Hb.<sup>20</sup> Despite the fact that CPAP (continuous positive airway pressure) has been shown to reduce intermittent hypoxia and inflammatory markers in OSA and OHS,

some meta-analysis studies concluded that CPAP had no place in significantly correcting HbA1c and fasting glucose, but may improve insulin sensitivity.<sup>27–29</sup>

Most studies pointed out that the prevalence of DM was higher in OHS than in OSA.<sup>18,19,30</sup> Our patient had a history of type 2 DM for more than 10 years without any history of insulin application. The HbA1c level was high and appeared to be higher than the previous hospitalization (9 months ago, HbA1c=6.0%), indicating uncontrolled blood glucose caused by either treatment non-compliance (irregular use) or suboptimal treatment (combination of oral hypoglycemic medications when insulin might already be indicated). Chronic intermittent hypoxia and leptin resistance (escalated appetite) had a role in insulin resistance in our patient that concluded he had type 2 DM. Furthermore, it had already occurred more than 10 years ago. Although type 2 DM may cause dyspnea if metabolic acidosis occurs and triggers the Kussmaul breathing pattern, nevertheless, the ABGA of our patient resulted only in respiratory acidosis.

### **Acute on Chronic Renal Failure and Acute Pulmonary Edema**

Chronic kidney disease is described by the continuing presence of reduced kidney function. Obesity is associated with direct and indirect risk factors for CKD, some of which are major risk factors, namely type 2 DM and hypertension.<sup>31</sup> Overweight and obese individuals had a relative risk for developing CKD of 1.87 and

7.07, respectively, when compared to normoweight individuals. It was also thought that obesity was linked to CKD from hyperfiltration due to increased metabolic demands.<sup>32</sup> Sivam et al compared the prevalence of CKD in OHS and OSA. Stage 1-3 CKD was more frequently present in OHS (46%) than in OSA (22%).<sup>31</sup> The prevalence of CKD was higher among subjects with sleep-related breathing disorders (30.5%) compared to control subjects (9.1%).<sup>33</sup> Vice versa, sleep-related breathing disorders were also observed among CKD patients.<sup>34</sup>

Hypertension and type 2 DM, which our patient had had for more than 10 years, could bring many complications. In this topic, hypertensive nephropathy or diabetic nephropathy, Both lead to CKD through their complex pathogenesis. It can be considered so as he already had a record of worsening kidney function since the last hospitalization (9 months ago) but refused to have renal replacement therapy. Our patient was known to have CKD nine months ago and apparently had an acute deterioration of CKD, or so-called "superimposed ARF" (acute on chronic renal failure/ACRF).

Hsu et al defined superimposed ARF having both a peak inpatient serum creatinine greater than the last outpatient serum creatinine by >50% and receipt of acute dialysis.<sup>35</sup> Ali et al and Zhou et al described ACRF using the classification as follows:<sup>36,37</sup>

1. Risk (R-ACRF): serum creatinine level elevated by 50% or more from index

serum creatinine but had not reached 350  $\mu\text{mol/L}$  (3.96 mg/dL) or GFR reduced by 25% or more.

2. Injury (I-ACRF): serum creatinine level elevated by 100% or more from index serum creatinine but had not reached 350  $\mu\text{mol/L}$  (3.96 mg/dL) or GFR reduced by 50% or more.
3. Failure: serum creatinine increased by 200% or more from index serum creatinine or serum creatinine had increased to 350  $\mu\text{mol/L}$  (3.96 mg/dL) as recommended by Acute Dialysis Quality Initiative (ADQI) group.

In his previous hospitalization, our patient had a creatinine result of 2.5 mg/dL, and in this current hospitalization, the creatinine was 3.3 mg/dL with an eGFR of 22.1 mL/min/1.73 m<sup>2</sup> and even worsened to the level of 7.0 mg/dL with an eGFR of 9.1 mL/min/1.73 m<sup>2</sup> on 3 days. Our patient did have an elevated serum creatinine by >50%. We also performed dialysis to overcome the worsening creatinine and eGFR, and also to counterbalance the anuria (his urine output reached 80 mL per day).

Therefore, according to Hsu et al, our patient met the criteria of superimposed ARF. For the ADQI recommendation, our patient fulfilled the criteria of ACRF (failure). Acute chronic renal failure and/or fluid overload could produce dyspnea through non-cardiogenic pulmonary edema, which should be responsible for defective gas transfer in the alveoli in the form of a shunt.

Pulmonary edema that correlates with renal disease is generally classified as having secondary renal-cardiac consequences and primary renal/non-cardiogenic pulmonary edema. The latter corresponds to accumulation of excess extracellular fluid following impairment of water and solute excretion (fluid overload) or to increased pulmonary capillary permeability due to reduction of oncotic pressure in the plasma.<sup>17</sup>

In our patient, pulmonary edema was very evident on physical and radiological examination (CXR and chest CT). Fluid overload was also pronounced from daily fluid balance, which was frequently positive. Normal ejection fraction and LVH from echo portrayed cardiac compensation, so the pulmonary edema in our patient was mainly of primary renal origin (non-cardiogenic). As a result, daily fluid balance became negative only on the days when dialysis was scheduled, and clinical improvements became more apparent. By all means, the multimodal treatment combination for our patient brought about good progress until the unexpected abrupt decline in the regular ward.

### **Treatments: Three Modalities**

There are three modalities of management in stable OHS patients: reversal of sleep-disordered breathing through positive airway pressure (PAP), weight reduction (medically or surgically), and pharmacotherapy (respiratory stimulants).<sup>5,6,14</sup> Treatment using PAP is

recommended for medium to long-term use in either NIV or CPAP. The NIV uses bi-level pressure settings while CPAP has continuous pre-set pressure during the respiratory cycle to prevent obstructive apnea. The NIV provides additional ventilatory support, while CPAP enables carbon dioxide unloading.<sup>4,5,38</sup>

The effectiveness of CPAP is identical to that of NIV, but NIV is more costly and requires more resources and equipment training. Both were equally effective for correcting sleep hypoxemia, hypercapnia, gas exchange, daytime sleepiness, sleep quality, quality of life, and obstructive events (sleep disordered breathing). However, the use of each modality was not superior to the other and should be individualized for each patient.<sup>4,5,38</sup> In addition, both NIV and CPAP significantly reduced mortality in OHS and OSA patients at 5-to-10-year follow-up. The mortality rate in untreated OHS patients was higher than in treated OHS patients.<sup>39</sup>

The effectivity of weight loss through a comprehensive program (motivational counseling, diet and exercise) or bariatric surgery was described in a systematic review by Kakazu et al. The comprehensive program reduced body weight but had no clinically significant effects, whilst bariatric surgery lowered more weight and was correlated with improvement in OHS, gas exchange, daytime sleepiness, and pulmonary arterial pressure. However, bariatric surgery had post-operative negative effects that lasted from one month to a year.<sup>40</sup> Perioperative mortality

is about 0.5% to 1.5%. Intestinal leak occurred in 2–4% of patients, with pulmonary embolism occurring in 1%.<sup>5</sup>

Hence, bariatric surgery should be considered only when the benefits outweigh the risks. Pharmacotherapy in OHS was adjunctive therapy as it was poorly studied; therefore, it could not replace oxygen therapy (PAP). Medroxyprogesterone and acetazolamide were known respiratory stimulants used as pharmacotherapy in OHS. Medroxyprogesterone affects the hypothalamus through the estrogen-dependent progesterone receptor. It could correct daytime hypoxemia and hypercapnia by increasing hypoxic respiratory drive, yet it had no significant effects on hypercapnic respiratory drive. The adverse effects are venous thromboembolism, decreased libido in women, and erectile dysfunction in men. Acetazolamide is believed to be beneficial by inducing metabolic acidosis, which then augments the minute ventilation.<sup>5,6</sup>

The use of both medications should be closely monitored. We already planned to administer the continuous use of PAP as maintenance therapy and also a weight reduction program for our patient following hospital discharge if he could survive. We recognized that the study of aminophylline in OHS was very limited, although it was notable as a respiratory stimulant.<sup>41,42</sup> In a case report, aminophylline was used as a respiratory stimulant to manage OHS.<sup>43</sup>

The management of AHRF in OHS mainly involved oxygen therapy with

positive pressure to overcome the hypercapnia. The success rate of NIV in treating AHRF was claimed to be 91% in a retrospective study. The median time to correct the respiratory acidosis was 2.9 days. High success rates were found in OHS subjects with acute decompensation and also with high PaCO<sub>2</sub>.<sup>15</sup> Nevertheless, a systematic review by Nicolini et al pointed out that NIV failure in OHS patients with AHRF ranged from 2% to 60.5%. NIV failure and mortality were associated with pneumonia and multi-organ failure.<sup>44</sup>

Although there were no RCTs investigating the efficacy of NIV in OHS, it has been listed as standard practice for managing AHRF in this case. Access to NIV should be available for a maximum of an hour from the acute onset of the patient in the emergency department. Administration of NIV should be applied as much as tolerated during the first 24 hours of admission, and once the respiratory acidosis has been corrected and hypercapnia has resolved, weaning of NIV will be performed. The decision to continue home therapy using PAP should be considered based on the presence of ongoing respiratory failure, stability of NIV, and local care pathways.<sup>4</sup>

The NIV is recommended for OHS patients experiencing AHRF. Full-face oronasal masks are generally recommended for less air leakage and higher tidal volume. Both are necessary to enhance alveolar ventilation. In addition, oronasal masks are better tolerated in acute settings because OHS patients with

AHRF tend to breathe using their mouth. Nonetheless, nasal masks are preferred for long-term use as oronasal masks are less efficient and are correlated with poor adherence plus great side effects.<sup>3</sup>

There are no guidelines regarding the use and titration of NIV. However, BaHammam proposed an algorithm for that matter. Treatment initiation is recommended using BiPAP with an Expiratory PAP (EPAP) of 4-6 cm H<sub>2</sub>O and an Inspiratory PAP (IPAP) of 8-10 cm H<sub>2</sub>O. The EPAP should be escalated gradually until there are improvements in snoring, witnessed apneas, and oxygen saturation, whereas IPAP should be gradually increased to achieve SpO<sub>2</sub>>90%. The response to NIV was evaluated by monitoring the vital signs, level of consciousness, respiratory pattern, and arterial blood gases in the first 6 hours. Intubation should be considered if there

was deterioration in the monitoring, NIV intolerance, instability of the hemodynamics, agitation, abdominal distention, inability to clear secretions, or if there was upper gastrointestinal bleeding.<sup>13,45</sup>

Endotracheal intubation in OHS patients must be very challenging because of their limited mouth opening and neck mobility. The NIV should be used continuously during the daytime and at night. It could be weaned for night use and 6-8 hours of daytime use whether or not improvements were observed. The weaning could also be performed for night use only once acid-base stability was already achieved (pH>7.35).<sup>13,45</sup> The use of BiPAP in our patient was already appropriate according to the algorithm. It was evidenced by improvements in symptoms, consciousness, vital signs, and ABGA. The other comorbidities for causes of dyspnea were also managed properly.

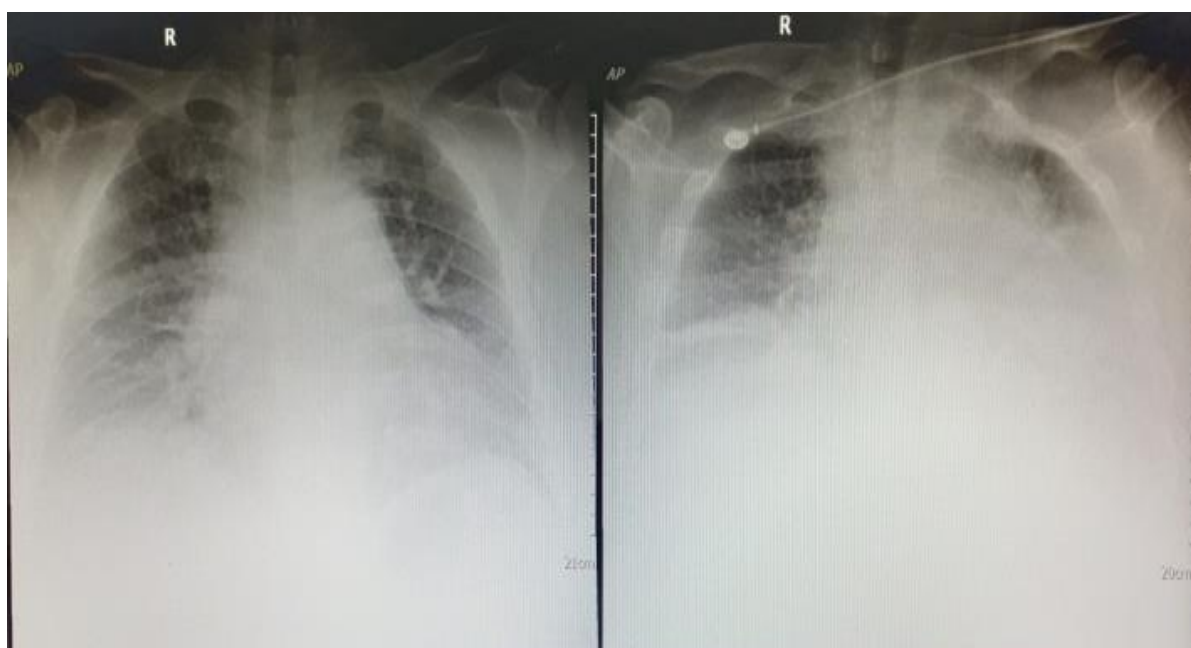


Figure 1. Left. Chest X-Ray: Cardiomegaly with pulmonary vascular congestion and interstitial pulmonary edema; Right. Chest X-Ray 6 days later: Increased lung opacity (worsening)



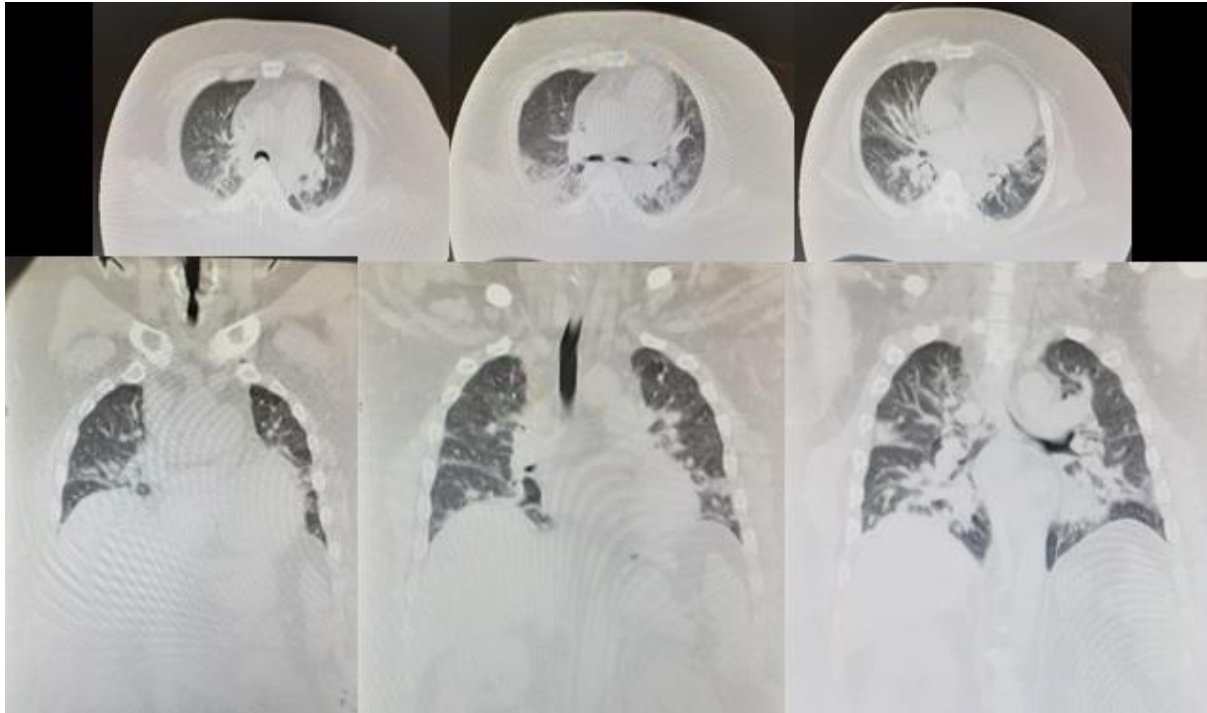


Figure 2. Chest CT-Scan: cardiomegaly with pulmonary vascular congestion, pulmonary edema and pneumonia

## CONCLUSION

Based on our findings, there were multiple possible causes of dyspnea in this patient. We believe that this unusual Pickwickian syndrome or so called malignant obesity hypoventilation syndrome which has more comorbidities and/or organ dysfunctions will be found more often in the future, notably in the population with increasing prevalence of obesity. We should also not omit the possibility of COVID-19 as a concurrence in malignant OHS case. Management of patient ought to treat not only the OHS but also all the comorbidities. In consequence, by identifying each of the possible comorbidities (especially those producing dyspnea) and treating them plus the OHS itself, the management will be optimal and should be minimizing mortality in OHS patients.

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