Case Report

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Woodhouse-Sakati Syndrome: A Case Report from Indonesia

Internal Medicine Section

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ABSTRACT

Woodhouse-Sakati Syndrome (WSS) is an extremely rare autosomal recessive neuroendocrine disease with loss of function mutation of DCAF17 gene, located on chromosome 2q31. This report discusses the first documented case of suspected WSS in Indonesia in a 20-year-old female patient with multiple metabolic abnormalities, delayed puberty, secondary osteoporosis, hydronephrosis, colitis, and recurrent urinary tract infection, possibly due to partial urinary retention. The patient was treated with 6 units of insulin aspart (three times a day) and 8 units of insulin Detemir (once a day) for diabetes mellitus. She also received Levothyroxine for hypothyroidism; calcitriol for osteoporosis; as well as bladder training and antibiotics for recurrent urinary tract infection. Within the last one year, the patient has been admitted to hospital three times due to uncontrolled blood glucose level and clinical manifestation of urinary tract infection and colitis. Although the patient has been treated in a top referral hospital in Indonesia, problems in confirming diagnosis of Woodhouse-Sakati syndrome in this patient still persists due to the absence of facilities for genetic sequence analysis and limitations of financial coverage for the patient and her family.

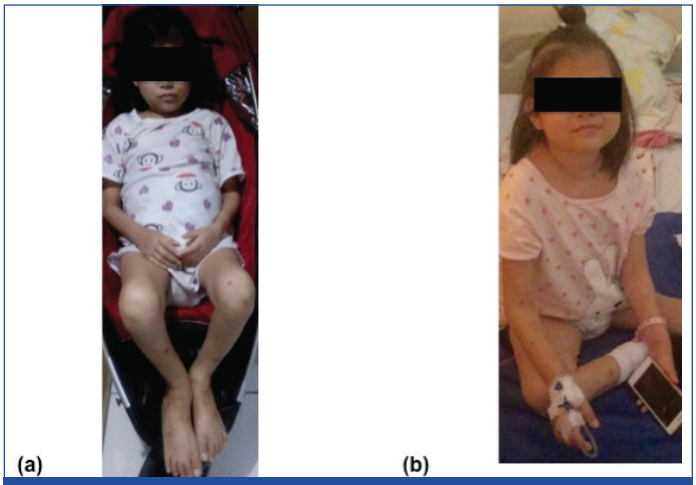
Keywords: Delayed secondary sexual characteristics, Metabolic abnormalities, Young adult

CASE REPORT

A 20-year-old female reported with generalised body weakness since one week prior to hospital admission. She decided to go to hospital only after the weakness of her body worsened, which was three hours prior to hospital admission. Additionally, patient also experienced nausea and vomiting. Upon arrival in the emergency unit, her random blood glucose level was 978 mg/dL. The patient had been diagnosed with type-1 Diabetes Mellitus (DM) since 12 years ago and hypothyroidism since three years ago with regular consumption of levothyroxine. From her medical documents it was found that, the highest random blood glucose level was 1500 mg/dL and the lowest random blood glucose level was 20 mg/dL. Patient was on daily subcutaneous injections of insulin Aspart (6 unit, three times a day) and insulin Detemir (8 unit, once a day, every 10 PM). She was also diagnosed with delayed puberty, which characterised by delay in her growth, as well less developed secondary sexual characteristics and absence of menstrual period.

She also complained of chronic recurrent diarrhoea since two years ago. One year prior to the current hospital admission, patient experienced right lower leg fracture after she slipped on the floor. She initially was only treated with traditional medicines and massages. She was brought to emergency room after two days and was treated with orthopaedic cast. However; possibly due to abnormal bone healing caused by late initial treatment, hypocalcaemia, or secondary osteoporosis; patient was unable to walk properly anymore and needed a wheelchair for her mobilisation.

Results of physical examination showed that her body height and facial features did not match chronological age (child-like appearance) [Table/Fig-1]; relatively low blood pressure (94/69 mmHg); tachycardia (117 times per minute, regular, strong, equal upon palpation of both extremities); body height was 117.5 cm; body weight was 23 kg. Further physical examinations found pale conjunctiva in both eyes, reduced visual acuity of both eyes (visual acuity of right eye: 4/6 and visual acuity of left eye: 3/6), less developed secondary sexual characteristics (Tanner stage II), and deformities on both lower extremities accompanied by limited range of motions [Table/Fig-2].



[Table/Fig-1]: Physical appearance of the patient.

[Table/Fig-2]: Current clinical condition of the lower extremities with signs of malunion.

Laboratory examinations showed low haemoglobin (11.3 g/dL) and haematocrit levels (24.5%). Arterial blood gas analysis showed metabolic acidosis. Patient also had high blood ketone level (3.6 mmol/l).

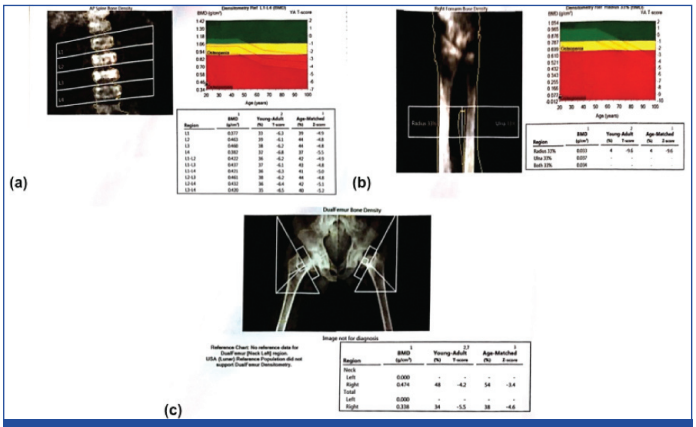
The HbA1c level of the patient was high (8.7%). She had a high morning cortisol serum level (27.85 mcg/dL), high Thyroid-Stimulating Hormone (TSH)-sensitive level (5.050 mcIU/mL), high intact parathyroid hormone level (159.7 pg/mL), low Luteinizsing Hormone (LH) level (1.01 mIU/mL) and low Follicle Stimulating Hormone (FSH) level (1.3 mIU/mL). She had normal free T4, growth hormone, prolactin, estradiol, and progesterone levels. Results of electrolyte examinations showed very low calcium level (1.23 mg/dL) in blood and high blood phosphorus level (4.3 mg/dL).

Reduced renal function was also found based on her high blood urea level (184 mg/dL) and high creatinine level (2.83 mg/dL) in blood. eGFR calculation with CKD-EPI was 23 mL/minute/1.73 m^2.

From her documented medical history, the urinalysis results from three months earlier also showed the presence of proteinuria (+2) and haematuria (24-25) in the urine. The urinary culture from three months earlier also confirmed the infection of Klebsiella oxyloca with sensitivity towards amikacin.

Chest radiograph showed bilateral infiltrates on both lungs. Abdominal ultrasonography also showed bilateral hydronephrosis and bilateral proximal hydroureter with impression of cystitis. From ankle X-Ray, it was concluded that the patient had segmental fracture on metaphysis and distal diaphysis of right tibia and fibula bones with callus formation on the peripheral side, accompanied with angulation of distal fragment of tibia. It also showed subluxation of epiphyseal plate of tibia towards medial side with the widening of space between talotibial joints.

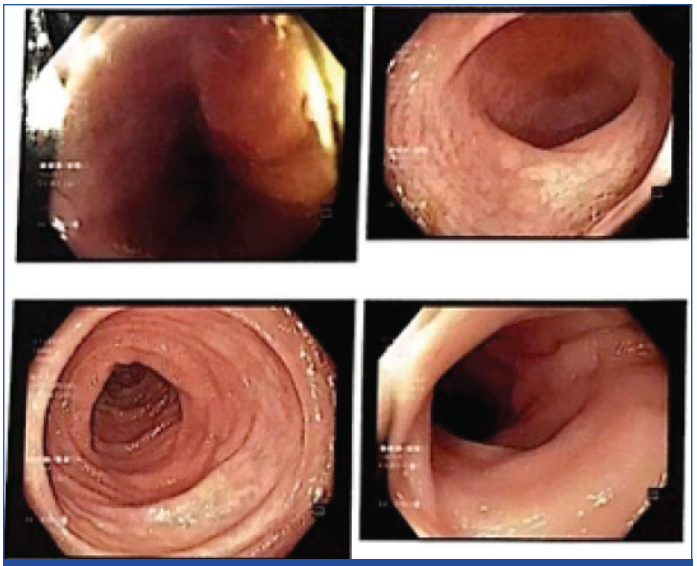
Result of Bone Mass Densitometry (BMD) confirmed the diagnosis of osteoporosis [Table/Fig-3]. BMD examination was conducted on lumbal vertebrae, right forearm, and right neck of femur; suggesting major osteoporosis with possible pathological fractures within the next 10 years. From another documented medical history, it was noted that she had undergone colonoscopy five months earlier and the result showed oedema on the mucosa of descending colon with the impression of colitis [Table/Fig-4].



[Table/Fig-3]: The figures show results of Bone Mass Densitometry (BMD) examination of lumbal vertebrae (a); right forearm (b); and right neck of femur (c). BMD examination was conducted on lumbal vertebrae (bone density: 0.421 g/cm^3; T-score: -6.3); right neck of femur (bone density: 0.474 g/cm^3, T-score: -4.2); and right forearm (bone density: 0.033 g/cm^3, T-score: -9.6). It was concluded that major osteoporosis occurred in these areas.

A standard karyotyping examination was conducted on the patient. The sample was taken from heparinised peripheral blood and was processed with G-Banding technique. The result showed that there were 46 chromosomes with sex chromosome XX in every cell. The patient was then recommended to undergo further examination with Fluorescence In Situ Hybridisation (FISH) to eliminate the possibility of mosaic monosomy in X chromosome. No abnormalities were found from the FISH results.

The patient was diagnosed as having type-1 DM, lower urinary tract infections, community-acquired pneumonia, chronic colitis, acute kidney injury with differential diagnosis of acute on chronic kidney disease stage 4, hypothyroidism, hypercortisolism, myopia of both eyes, unspecified osteoporosis with pathological fracture with malunion and subluxation of joints, delayed puberty, delayed growth, hypogonadism, and hyperparathyroidism. The final diagnosis of Woodhouse-Sakati syndrome was documented based on clinical conditions due to lack of diagnostic confirmation tools, especially related to genetic sequence analysis.

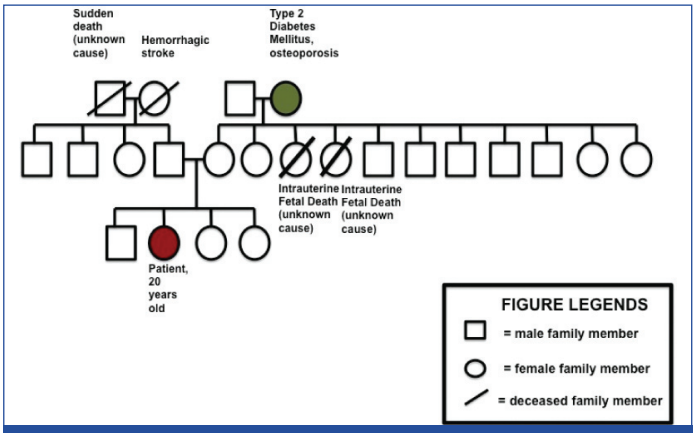


[Table/Fig-4]: Colonoscopy showing oedema on the mucous of descending colon with an impression of colitis.

She received symptomatic treatment for her colitis; consisting of anti-emetics, antacids, anti-reflux agents, and anti-ulcerants. Additionally, she received folic acid, sodium bicarbonate, and calcium carbonate for her chronic kidney disease. Patient also received levothyroxine for hypothyroidism. Routine follow-up was conducted every month, mainly, to control her type-1 DM, hypothyroidism, secondary osteoporosis, and to encourage her to do her bladder training in order to prevent recurrence of urinary tract infection due to partial urinary retention.

DISCUSSION

Woodhouse-Sakati syndrome is an extremely rare autosomal recessive neuroendocrine disease with loss of function mutation of DCAF17 gene (DDB1 and CUL4 associated factor 17), located on chromosome 2q3. Agopiantz M et al., and Koshy G et al., suggested consanguinity as a risk factor of WSS [1,2]. In this patient, no possible consanguinity is observed from genogram analysis of three generations of the family [Table/Fig-5].



[Table/Fig-5]: Genogram of the patient's family (three generations).

Bohlega SA et al., also stated that, other common clinical manifestation in WSS, are hypogonadism and DM. Hypogonadism mainly occurs due to ovarian dysgenesis in female patients and testicular damage and lack of sperm production in male patients. The pathophysiology may be related to disturbed peripheral gonadal process and insufficient hypothalamic-hypophysis responses [3].

From a previous study, 66% of patients with WSS suffered from DM with the onset in adolescence to young adult period [1]. Chronic complications of DM could have contributed to the development of chronic kidney disease and neurogenic bladder in this patient due to reduced IGF-1 levels, which may cause insulin resistance in multiple organs [4].

Unspecified secondary osteoporosis possibly correlates with high level of parathyroid hormone. Physiologically, parathyroid hormone promotes activity of osteoclast; thus increasing bone resorption. Mazzuoli GF et al., describes increased osteoporosis prevalence in early post-menopausal period of female patients with primary hyperparathyroidism [5]. Previous studies showed that cortical and trabecular bone compartments were mainly affected with skeletal damage in patients with primary hyperparathyroidism [6,7].

The presence of hypercortisolism in diabetic patients has also been commonly investigated. Previous literature reported elevation of Adrenocorticotropic Hormone (ACTH) basal level, ACTH level dexamethasone test, and late night salivary cortisol level in diabetic patients. It was also reported that chronic complications of DM were able to disturb Hypothalamic-Pituitary-Adrenal (HPA) axis activities [8]. Chiodini I et al., confirmed these findings by showing that cortisol level was increased without any ACTH reduction in diabetic subjects with chronic complications; suggesting that there is a problem in HPA axis activation or secondary to chronic stress condition in diabetic subjects [9].

Several questions are still unanswered about the mechanisms behind hypothyroidism, and colitis. However, thyroid dysfunction has been shown to exert pre-renal and renal effects by reducing blood flow to kidneys. Thyroid hormones can also increase the activity of sodium-potassium ATP-ase channel; thus affecting sodium reabsorption and tubular potassium permeability [10].

Due to the small number of cases and large variability of clinical symptoms within the same or different families, possibility of involvement of other genes in WSS still needs to be considered. Although diagnosis of WSS can be established with analysis of DCAF17, the knowledge about the encoded protein in this gene is still incomplete. More than 30 isoforms are known to be present in this gene; which may contribute to the variability of phenotypes, preferential nucleolar expression, and cellular activities [1].

CONCLUSION

In Indonesia, to our knowledge, there has not been any documented report about Woodhouse-Sakati syndrome. In the process of arranging this case report, the author also faced several difficulties related to the confirmation of diagnosis of Woodhouse-Sakati syndrome since the availability of recommended genetic examinations was only limited to standard karyotyping and FISH. The availability of sequence analysis and gene-targeted deletion or duplication analysis of DCAF17 is still absent. As a result, diagnosis of Woodhouse-Sakati syndrome in this patient was confirmed only from the clinical manifestation, which suits the symptoms of Woodhouse-Sakati syndrome. Therefore, through the publication of this report, further recommendations from the experts to help with diagnostic confirmation, as well as comprehensive and multi-disciplinary management for such patients are expected.

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