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Case Report

Internal Medicine Section

Polyglandular Syndrome with Complications and a Rare Co-existence of Hypercortisolism in a Young Girl: An Internist Approach

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ABSTRACT

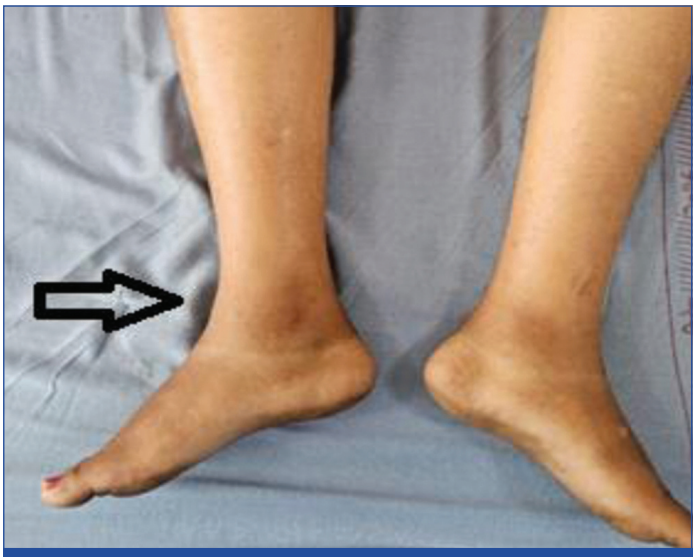
Patients diagnosed with Type 1 Diabetes Mellitus (T1DM) can sometimes manifest as part of broader clinical presentations known as Autoimmune Polyglandular Syndromes (APS). APS refers to a group of rare autoimmune disorders in which multiple endocrine glands are affected by autoimmune attacks. There are four types of APS described so far, including APS1, APS2, APS3 and APS4. In contrast to APS1 and APS2, APS3 does not involve the adrenal cortex. In APS3, autoimmune thyroiditis occurs with other organ-specific autoimmune diseases, excluding Addison's disease. A 20-year-old female with a known case of T1DM, Chronic Kidney Disease (CKD), hypothyroidism, and hypertension recently presented with a hypertensive emergency. On further evaluation, she was also diagnosed as a possible case of APS3 with a rare presentation of hypercortisolism instead of Addison's disease. Various challenges were faced while managing her diabetes due to the brittle diabetes pattern she showed, and also there was a dilemma in the conclusive diagnosis of hypercortisolism in this patient due to the co-existing CKD.

Keywords: Chronic kidney disease, Hypothyroidism, Hypercortisolism, Hypertensive emergency, Type 1 diabetes mellitus

CASE REPORT

A 20-year-old female reported to the Department of Internal Medicine, with a chief complaint of headache associated with 3-4 episodes of vomiting for seven days. The pain was acute in onset, persistent, holocranial in nature with moderate-severe intensity. Vomiting was non-projectile, non bilious, non blood stained, associated with nausea, burning and non radiating pain sensation in epigastrium. The patient also complained of stabbing chest pain of acute onset, persistent, non progressive and non radiating in nature with moderate to severe intensity, with no history of anuria, burning micturition, fever, cough, palpitations, and yellowish discolouration of eyes.

She was a known case, presenting with Type 1 Diabetes Mellitus (T1DM) for 15 years on an insulin basal bolus regimen (non-compliant to medication) with poor glycaemic control and primary hypothyroidism for 3 years on regular intake of levothyroxine 75 mg since three years, Chronic Kidney Disease (CKD) for 5 months (non dialysis dependent) and hypertension for 4-5 months on irregular medication. She also had a history of multiple hospital admissions in the last 6 months with Diabetic Ketoacidosis (DKA) episodes, hypertensive emergency, and even the requirement of Intensive Care Unit (ICU) care and mechanical ventilation during her previous admission. While admitting to the hospital, the patient was drowsy but oriented to time, place, and person, with a Glasgow Coma Scale (GCS) score of 14/15 (E4V4M6). On examination, she had a Blood Pressure (BP) recording of 210/120 mmHg, pulse rate 96/minute, and vitally stable otherwise. On palpation, she had bilateral pitting pedal oedema [Table/Fig-1]. Chest examination revealed bilateral infrascapular coarse crackles. She was admitted and evaluated as a case of hypertensive emergency. Labetalol intravenous (i.v.) boluses of 20/40 mg (as per BP recordings) and i.v. diuretics (Torsemide 20 mg i.v. BD) were used to treat her in the initial 2-3 days, after which she was shifted to oral antihypertensives and oral diuretics. This hypertensive crisis was due to incorrect pharmaceutical consumption (self-underdosing) after a review of her medical history. Her antihypertensive medications (Tab Clonidine 0.3 mg TDS, Tab Prazosin 5 mg OD, Tab Nifedipine Retard 30 mg TDS) were adjusted, and her BP was controlled. Simultaneously, Random Blood Sugar (RBS) was found to be 286 mg/dL, and Arterial Blood Gas (ABG) analysis revealed high anion gap metabolic acidosis (pH=7.28, HCO_3=14 mEq/L, $paCO_2$=31.1 mmHg, paO_2=69.1 mmHg) with urine ketone positive, confirmed to be a case of DKA. The patient was immediately started on fluid therapy and insulin infusion, which continued for 48 hours. Strict monitoring of urine output, blood gas parameters, blood sugar, and electrolytes was done to monitor the response, and after 48 hours, she was shifted to a basal-bolus insulin regimen.



[Table/Fig-1]: Pedal oedema (taken after receiving diuretics for two days).

The patient presented with findings of normocytic normochromic anaemia, deranged blood glucose, and kidney profiles. She also had extremely elevated anti-Thyroid Peroxidase (anti-TPO) antibodies and an abnormal thyroid profile with a hypothyroidism picture (details provided in [Table/Fig-2]). Urine Routine/Microscopy (R/M) was abnormal and 24-hour urine protein excretion was highly elevated. Initial Ultrasonography (USG) also suggested the presence of medical renal disease [Table/Fig-2].

Renal artery Doppler was done as part of the investigation of secondary hypertension that revealed normal study. She was also evaluated for Cushing syndrome, as part of secondary hypertension

Investigation (with reference range and units)	Patient's value	Investigation (with reference range and units)	Patient's value
Haemoglobin (F 12.0-16.0 g/dL)	8.23	HbA1c (4% and 5.6%)	7%
TLC (4.5-11.0×103/mm^3)	13.31	Total Cholesterol (less than 200 mg/dL)	177
DLC (N/L/M)	75.3/15.95/6.8	Triglycerides (40-150 mg/dL)	282
Reticulocyte count	0.9%	HDL (40-60 mg/dL)	46
Peripheral smear	RBC- Normocytic Normochromic. WBC- Normal count with normal distribution. Platelets-Adequate.	LDL (<100 mg/dL)	129
Platelet count (130-400×103/µL)	230.9	TSH/FT3/FT4 (0.3-4 mIU/L/1.2-2.8 nmol/L/77-155 nmol/L)	5.0/2.19/1.55
T. Bilirubin (0.0-1.0 mg/dL)	0.97	iPTH/Vit-D (30 to 65 pg/mL/ 20 to 40 ng/mL)	24.3/35.81
D. Bilirubin (0.0-0.4 mg/dL)	0.15	Folic acid (2.7 to 17.0 ng/mL)	>24
SGOT (7-30 U/L)	28	Ferritin (11 to 307 µg/L)	390.1
SGPT (9-25 U/L)	13	Urine R/M	Proteins=100 mg/dL (+2) Glucose=100 mg/dL (+2) PC=0-1 EC=0-1
ALP (30-100 U/L)	107	24 hours urinary protein	8045.1 mg/24 hrs
GGT (40-45 U/L)	42	S. Cortisol (After midnight 1 mg dexamethasone suppression test) (<1.8 µg/dL))	20.40 µg/dL
Total protein (5.5 to 9.0 g/dL)	5.1	S. Cortisol (midnight) (29 ng/dL and 101 ng/dL)	9.09 µg/dL
S. Albumin (3.5-5.5 g/dL)	2.1	S. Cortisol (8 AM Morning) (5 to 25 µg/dL)	15.06 µg/dL
S. Globulin (2.0-3.5 g/dL)	3.0	S. ACTH (between 10 and 60 pg/mL)	7.2 pg/mL
PT/INR (11 to 13.5 seconds/ 0.8 to 1.1	13.9/1.07	Anti-TPO level (below 16 IU/mL)	13,000
Urea/Cr (8-25 mg/dL/0.6-1.8 g/day)	99/5.37	USG abdomen	Right kidney=10×4.5 cm, raised cortical echotexture, CMD maintained. Left kidney=10×2.5 cm, raised cortical echotexture, CMD maintained. Impression- Medical renal disease
Na^+/K^+ (135-145 mmol/L/3.4-5.0 mmol/L)	139/4.4	NCCT brain	Ill-defined area of hypodensity is seen in right frontal region with no surrounding oedema and mass effect
Calcium (8.5 to 10.2 mg/dL)	8.7		
Phosphorus (2.8 to.5 mg/dL)	5.2		

[Table/Fig-2]: Routine and advanced investigations of the patient.

evaluation. Serum cortisol after dexamethasone suppression overnight, serum midnight cortisol, and morning cortisol at 8 am were performed and revealed elevated levels (20.40 µg/dL with normal range <1.8 µg/dL). As there are high chances of false hypercortisolemia in CKD patients, midnight salivary cortisol test was planned, but couldn't be done due to financial constraints. Because of the anti-Hepatitis C Virus (anti-HCV) positive status (accidental detection during baseline investigations), an HCV Ribonucleic Acid (RNA) load was tested, which revealed an undetectable target with normal Liver Function Test (LFT) and normal liver in ultrasound. Patient had symptoms of blurring of vision intermittently, eye fundus examination was performed that revealed bilateral non-proliferative diabetic retinopathy and grade-2 hypertensive nephropathy. On neuropathy evaluation, she was diagnosed with severe sensory neuropathy.

She was oligo-anuric with a persistent range of serum creatinine, nephrotic range proteinuria, and eGFR of 11 mL/min/1.73 m^2 during the hospital course. Nephrology opinion was sought and she was treated conservatively as a case of diabetic kidney disease, with diuretics (Torsemide 20 mg PO BD) and adequate fluid management. For diabetes mellitus management, she had undergone seven points RBS charting, a strict diabetic diet, and a basal bolus regimen, and her sugar levels were kept under control during her hospital stay. During the titration of insulin dose, the patient experienced sporadic episodes of hypoglycaemia and very high blood sugar values, hence the possibility of brittle diabetes was also kept in perspective. Tablet Ramipril (2.5 mg BD) was started because of proteinuria and hypertension; however, it was later withdrawn because of hyperkalemia after a three-day course.

Clinically, she improved gradually and blood pressure and sugar got controlled. Hepatitis B and pneumococcal vaccines were started in view of CKD. Proper diabetic education was given to patient and attender, and was discharged with advice of strict compliance to medication and regular follow-up.

The patient was completely well and asymptomatic at discharge. Due to a range of reasons, including non compliance to drug therapy, she was admitted 2-3 times again within a duration of 4-5 months, with similar complaints and eventually lost to follow-up.

DISCUSSION

With a prevalence of >90% among individuals with T1DM and autoimmune disorders, affective thyroid disease is the most common concomitant organ-specific autoimmune illness in adults [1]. T1DM can be part of endocrine syndromes like Autoimmune Polyglandular Syndrome (APS) [1].

These are uncommon medical conditions characterised by the destruction of both endocrine and non-endocrine organs due to the infiltration of T-lymphocytes directed by organ-specific antibodies [2]. There are recognised patterns of polyendocrine deficiencies, which can be attributed to both monogenic and polygenic variations. Historically, this array of clinical characteristics has led to the categorisation of these disorders as Type-1, Type-2, Type-3, or Type-4 APS. Type-3 APS is the most prevalent, primarily characterised by Thyroid Autoimmune Disease (TAD), and it is typically observed in middle-aged females. Within Type-3 APS, there exist several subtypes distinguished by the presence of other

organ-specific autoimmune conditions: Type-3a involves TAD along with T1DM, Type-3b involves TAD along with pernicious anaemia, and Type-3c involves TAD along with conditions such as vitiligo, alopecia, or other organ-specific autoimmune diseases [2].

In the present case, the patient had a history of T1DM for 15 years and later on she developed hypothyroidism and hypercortisolism which is attributed to autoimmunity considering the age of presentation. High cost of blood investigations to assess the pancreatic autoantibodies prevented from doing the same. However, young age of onset, absence of family history, and absence of signs of insulin resistance were conclusive for a clinical diagnosis of T1DM. To check for autoimmune thyroiditis, serum Anti-TPO level was evaluated, which came out to be significantly raised.

A case report published by Lakhotia M et al., from India reported a case of a 29-year-old male presented with Type-2 APS. However, his first presentation with hypothyroidism preceding the adrenal insufficiency was a rare occurrence, and also the co-existence of celiac disease was another rare thing [3]. A retrospective study conducted by Shaikh SB et al., across 100 T1DM patients showed that 29% of T1DM subjects had autoimmune thyroid disorder (Hashimoto's or Graves' disease), 5% were diagnosed with vitamin B_{12} deficiency, 4% had Addison's disease, and 6% showed vitiligo. A 28% had a family history of autoimmune endocrinopathy. These all were pointing towards high prevalence of APS in T1DM patients [4]. It is worth noting that CKD is recognised to induce physiological hypercortisolism, which can lead to a clinical presentation resembling that of Cushing's disease. However, the exact cause and timing of symptom presentation in these two conditions are not clearly distinguishable. Furthermore, certain aspects of CKD may complicate the accurate interpretation of biochemical findings that would typically diagnose Cushing's disease in patients with normal renal function [5].

The APSs manifest as distinct clusters of endocrine irregularities, which exhibit discernible patterns in individuals with immune dysregulation. Recognising these patterns allows for the treatment and anticipation of associated systemic or other hormonal deficiencies [6]. Notably, approximately 20% of patients diagnosed with T1DM present with Thyroglobulin (TG) and TPO antibodies. However, only a minority of them progress to clinical or biochemical hypothyroidism, rendering APS3 (also known as APS2b) relatively common [7]. In the context of this case, APS 1 and APS 2 were ruled out due to the absence of adrenal insufficiency. Currently, there is no universally accepted set of guidelines for the diagnosis and management of APS Type-3. Nevertheless, it would be prudent to consider this diagnosis in patients with TAD, as other studies have indicated that as many as 52% of individuals with TAD could potentially meet the criteria for an APS Type-3 diagnosis [7]. It is worth noting that this case represents a rare presentation due to the presence of hypercortisolism instead of Addison's disease in association with all these autoimmune conditions.

Overt endogenous glucocorticoid excess (Cushing's syndrome) is a well-recognised cause of hyperglycaemia [8]; however, due to the low prevalence (1/500,000) in the general population [9], its epidemiological role on diabetes development is trivial. Subclinical hypercortisolism is a recently defined entity, characterised by impaired ACTH/cortisol homeostasis without classical signs or symptoms of Cushing's syndrome as in present case [10]. Preliminary reports have suggested that these patients are at high risk of T2DM [11] and, most importantly, those who are diabetic are expected to experience clinical improvement after hypercortisolism removal [12], whereas in T1DM, Addison's disease is most commonly associated. Addison's disease occurs more frequently in patients with T1DM as part of the APS [13]. Conversely, in some patients, diabetes may be attributed to insulin resistance due to hypercortisolism too. In this case, the patient was presenting with a rare presentation of T1DM being associated with subclinical hypercortisolism.

However, the occurrence of hypercortisolism is infrequent in APS. Simultaneously, it was essential to take into consideration that elevated levels of plasma cortisol represent a well- documented characteristic of CKD. It has been suggested that the heightened inflammatory state in CKD leads to increased activation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, resulting in escalated cortisol secretion [14,15]. Additionally, the extended half-life of plasma cortisol and its metabolites in CKD, partially attributable to reduced renal excretion, may contribute to this phenomenon. Furthermore, the presence of higher concentrations of glucuronide conjugates and steroids (aside from cortisol) in the serum of CKD patients can cross-react with antisera used in cortisol immunoassays [14,15]. Any combination of these factors could potentially increase the likelihood of obtaining false-positive results when measuring plasma cortisol levels for the diagnosis of Cushing's disease. To address this diagnostic challenge, the measurement of midnight salivary cortisol, while not entirely specific to CKD, is recommended over several evenings in such cases. The circadian rhythms of cortisol and ACTH prove to be the most accurate indicator for guiding a definitive diagnosis in this context. Additionally, thorough attention should be paid to signs, symptoms, and clinical history [5].

Unfortunately, we were unable to conduct these investigations due to their unavailability. Consequently, we cannot rule out hypercortisolism induced by CKD in this case, and we could not definitively diagnose Cushing's syndrome under these circumstances. The hypercortisolism observed in various screening tests had to be attributed to the phenomenon of false hypercortisolism often seen in CKD patients.

Another diagnostic fallacy we faced in this case was the glomerular range proteinuria associated variations of endocrine hormone levels. Urinary loss of T4 binding globulin and various proteins can cause false low values of thyroid hormones. At the same time, nephrotic range proteinuria can cause urinary loss of cortisol binding globulin, leading to false low levels of serum cortisol, which is exactly reverse in this case.

Another challenge faced during treatment of this patient was the high variability of blood glucose levels. She had past history of DKA episodes, RBS values up to 500 mg/dL range, and hypoglycaemic episodes during the hospital course. Brittle diabetes, which represents the most severe phenotype of high glucose variability was kept as possibility. Historically, brittle diabetes was described as severe glycaemic instability of blood glucose levels with frequent and unpredictable episodes of hypoglycaemia and/or DKA that disrupt life activities, often requiring frequent and/or prolonged hospitalisations [16]. These patients usually have T1DM or pancreatic diabetes (e.g., post-pancreatectomy). Risk factors include duration of diabetes (cognitive impairment, advanced renal disease). Patient had various risk factors as above, which led her to this condition. The basal bolus regimen had to be blocked, and to switch to continuous insulin infusion with hourly strict monitoring for a better control. Later her daily insulin requirement was calculated and shifted to basal bolus regimen. Strict adherence to diabetic diet, and proper diabetic education helped to achieve target range sugars later. Hypertension is both a cause and effect of CKD and contributes to its progression [17]. As estimated Glomerular Filtration Rate (eGFR) declines, the incidence and severity of hypertension increase [18]. Additionally, hypertension and CKD are both independent risk factors for Cardiovascular Diseases (CVD). When both exist together the risks of CVD morbidity and mortality are substantially increased [19]. As seen in this patient, whether hypertension or CKD is the first event, is a matter of mystery. However, the long-standing history of diabetes, normal sized kidneys, nephrotic range proteinuria, diabetic retinopathy all were in favour of diabetic kidney disease, and CKD may be considered as the triggering agent for the young age hypertension presentation.

As seen in patients having multiple arrays of diseases, this patient too was under a multitude of medications for her treatment. Multimorbidity,

commonly defined as the co-existence of two or more chronic health conditions, is common in the older population [20]. Managing multiple chronic conditions presents significant challenges for both healthcare providers and patients, and it exerts a detrimental impact on overall health outcomes. Multimorbidity is associated with a range of adverse consequences, including diminished quality of life, self- reported health, mobility, and functional capacity. It also leads to an increased likelihood of hospitalisations, physical discomfort, greater utilisation of healthcare resources, higher mortality rates, and elevated healthcare costs [21].

In the case of this young female patient, it was noteworthy that she was prescribed numerous medications, a condition commonly referred to as polypharmacy, which is more prevalent among older individuals with multiple chronic conditions. Polypharmacy carries its own set of unfavourable effects, encompassing increased mortality risk, heightened susceptibility to falls, severe medication-related reactions, prolonged hospitalisation, and a greater likelihood of hospital readmission shortly after discharge [22].

CONCLUSION(S)

The APS3 comprises autoimmune endocrine disorders like hypothyroidism and T1DM but typically lacks Addison's disease, and may include hypercortisolism. Diagnosing Cushing's syndrome in CKD patients remains challenging due to frequently false-positive test results. Patients with T1DM and concurrent renal issues require diligent monitoring, diabetic education, and strict dietary adherence to manage their condition. Autoimmune conditions often underlie the development of multiple chronic health issues in young patients. Polypharmacy is a concern not only among the elderly but also among younger individuals with multiple health conditions.

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