Atypical Graves' Disease: Bradycardia, Paralysis, and Heart Block. Case Report and Literature Review

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ABSTRACT

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In this article, we present a patient with an unusual and potentially fatal presentation of Graves' disease. Typically characterized by tachycardia, tiredness, weight loss, and temperature intolerance, Graves' disease is the most common cause of hyperthyroidism, and in some cases, might manifest in a life-threatening episode of thyrotoxic periodic paralysis (TPP). We report the case study of a patient experiencing his first onset of Graves' disease, who presented solely with TPP without any other symptoms of ongoing thyrotoxicosis. Additionally, he experienced episodes of bradycardia and right bundle branch block (RBBB). The paralysis subsided after potassium replacement, and the RBBB resolved following the initiation of thyreostatic medication. This article describes the patient's clinical evaluation and treatment, outlines measures to prevent rebound hyperkaliemia, and discusses the issue of biotin interference with hormone assays, adrenal insufficiency, and heart blocks resulting from thyrotoxicosis. A review of the literature and the pathophysiology of TPP are also provided.

Keywords: *Thyrotoxic periodic paralysis (TPP), Graves' disease, thyrotoxicosis, right bundle branch block (RBBB)*

STRESZCZENIE

Atypowa prezentacja choroby Gravesa: bradykardia, paraliż i zaburzenia przewodnictwa śródkomorowego. Opis przypadku i przegląd literatury

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Artykuł przedstawia opis przypadku pacjenta z nietypową i potencjalnie zagrażającą życiu postacią choroby Gravesa. Choroba Gravesa, charakteryzująca się tachykardią, zmęczeniem, utratą wagi i nietolerancją ciepła, jest najczęstszą przyczyną nadczynności tarczycy. Jedynie w rzadkich przypadkach może objawiać się ona potencjalnie śmiertelnym tyreotoksycznym paraliżem (thyrotoxic periodic paralysis – TPP). Opisywany pacjent nie prezentował żadnych objawów nadczynności tarczycy poza TPP. Ponadto doświadczył epizodów bradykardii i bloku prawej odnogi pęczka Hisa (right bundle branch block – RBBB). Paraliż ustąpił po dożylnej suplementacji potasu, a RBBB ustąpił po rozpoczęciu leczenia tyreostatycznego. W artykule zwrócono uwagę na problem interferencji biotyny z laboratoryjnymi oznaczeniami hormonów tarczycy oraz omówiono niewydolność nadnerczy i bloki serca wynikające z nadczynności tarczycy. Przegląd literatury i patofizjologia TPP zostały również uwzględnione.

Słowa kluczowe: *TPP, choroba Gravesa, tyreotoksykoza, blok prawej odnogi pęczka Hisa*

Introduction

Thyrotoxic periodic paralysis (TPP) is a rare complication of ongoing thyrotoxicosis, most commonly caused by Graves' disease. TPP symptoms include muscle weakness and paresis, which are more pronounced in the lower extremities.[1] Signs of hyperthyroidism are usually subtle or absent during an attack, which makes TPP a diagnostic challenge.[2] We describe a patient diagnosed with TPP secondary to Graves' disease, exhibiting an atypical presentation that includes bradycardia and right bundle branch block (RBBB) resulting from thyrotoxicosis.

Patient's Information

A 23-year-old male from Ecuador was discovered by his roommate lying on the bathroom floor. The patient presented with acute tetraparesis and reported a recent episode of vomiting. He was transported by an ambulance to the Hospital Emergency Department following the incident. He denied any recent accidents but reported experiencing a similar episode approximately nine months prior. He stated that he did not take any medications or dietary supplements on a regular basis and had no family history of chronic diseases.

The physical examination appeared to be negative for abnormalities in the cardiovascular, respiratory, and gastrointestinal systems. The ECG (Fig. 1) showed sinus intraventricular arrhythmia, prolonged QTc value, wide QRS complex, and a complete right bundle branch block (RBBB). An ABG test demonstrated life-threatening hypokalemia with a value of 1.9 mmol/L (normal range: 3.5-4.5). The CT scan of the head and neck ruled out pathologies of the Central Nervous System; however, a hyperdense thyroid gland in comparison to the surrounding muscles was described. The neurological examination exposed paresis of upper and lower limbs with intact deep reflexes.

The patient was placed on vital sign monitoring and treated with a total of 40mEq of potassium administered intravenously. The paresis subsided about three hours after the potassium replacement treatment had been initiated. Episodes of bradycardia (heart rate 36/min) occurred while on monitoring. Approximately seven hours after the initiation of potassium administration, mild hyperkalemia was detected with a serum potassium level of 5.1 mmol/L (normal range: 3.5-4.5 mmol/L). The following day, the patient's serum potassium level was 4.6 mmol/L (normal range: 3.5-4.5 mmol/L). Due to the uncertain etiology of the initial hypokalemia and the abnormal image of the thyroid gland observed in the CT of the neck, the patient was transferred to the Internal Medicine Department for further investigation.

Clinical Investigation

Given the patient's lack of regular medication usage and normal kidney function, primary aldosteronism was considered as a potential cause of the hypokalemia. However, plasma renin activity and serum aldosterone concentration were found to be within normal limits. Given the hyperdense image of the thyroid gland revealed in the CT scan of the neck, we opted to test its function: TSH was <0.008 μUI/mL (normal range: 0.35-4.94), free T3 was 16.56 pg/mL (normal range: 1.58-3.91), and free T4 was 3.29 ng/dl (normal range: 0.70-1.48). Further testing indicated an autoimmune cause of the ongoing thyrotoxicosis: TPOAb (thyroid peroxidase antibodies) were >1000 U/mL (normal range: <5.81), TGAb (thyroglobulin antibodies) were 235.92 U/mL (normal range: <4.11), and TRAb (thyroid receptor antibodies) were 12.68 IU/L (normal range: <3.1).

Despite the absence of typical hyperthyroidism symptoms, the patient was diagnosed with thyrotoxic periodic paralysis secondary to Graves' disease. This diagnosis was supported by laboratory findings and the presence of typical autoimmune inflammation observed in thyroid ultrasound. The thyroid gland was enlarged (right lobe: 54x26x22mm; left lobe: 49x23x19mm), hyperechoic, and hypervascular, with heterogenous echotexture and no nodules detected. An ophthalmic examination revealed no signs of thyroid-associated ophthalmopathy.

Furthermore, we observed a decreased serum level of cortisol at 8 am, with values 0.91 μg/dL and 2.96 μg/dL on the following day (normal range: 5-25). ACTH secretion was remained normal, with values of 10.20 pg/mL and 17 pg/mL, respectively (normal range: 7.20-63.30). The absence of antibodies to steroid 21-hydroxylase allowed us to exclude Addison's disease as a cause of hypocortisolemia. No abnormalities were found in the adrenal glands on the abdominal CT scan. The patient's testosterone concentration was notably high, at 1377.70 ng/dl (normal range: 240.24-870.88). A follow-up ECG performed on the fourth day of hospitalization showed no abnormalities (Fig. 2).

Treatment with thiamazole, propranolol, and spironolactone was initiated, and the patient was discharged on the fifth day of hospitalization in good overall condition. Key laboratory results are summarized in Table 1.

Discussion

Thyrotoxic periodic paralysis is a potentially life-threatening complication of ongoing thyrotoxicosis, which can be induced by Graves' disease, toxic nodular

goiter, or excessive iodine/thyroxine use. Elevated thyroid hormone levels increase Na^+/K^+ ATPase activity, leading to an influx of extracellular potassium into muscle cells and subsequent hypokalemia.[3] This potassium overload in muscle cells, coupled with the impaired function of neurons (caused by hypokalemia) results in paralysis-like symptoms in the extremities.

However, it is crucial to acknowledge that patients with TPP may exhibit normal or even elevated plasma potassium levels during an episode.[4] Thyroid hormones enhance cell responsiveness to adrenergic stimulation, further intensifying the potassium shift.[3] Insulin, by altering cellular membrane permeability for sodium and potassium, can precipitate acute paralysis episodes a few hours after the ingestion of a carbohydrate-rich meal. Patients with hyperinsulinemia also are at a significantly greater risk of developing TPP.[5] In addition to hypokalemia, patients may also develop hypophosphatemia and hypomagnesemia.[2]

TPP shows a higher prevalence in Asian populations but has been documented in individuals of American Indian/Hispanic and Caucasian ethnicities,[2] as well as in the European, Polynesian, and Turkish populations.[1] Males are significantly more likely to develop TPP than females, with the condition typically manifesting in individuals aged 20 to 40,[5] though cases in children have also been reported.[6]

Research indicates that pathological variants in specific genes, such as those encoding the Kir2.6 ion channel specific to skeletal muscle, which facilitates potassium efflux to the extracellular space, may be associated with TPP. Dysfunctional Kir2.6 channel can lead to increased intracellular potassium storage and subsequent hypokalemia, placing individuals with that pathological variant at a higher risk for TPP.[7]

Prodromal signs of TPP may include muscle aches, cramps, and stiffness. During an attack, patients typically present with sudden episodic paresis or muscle weakness, often more pronounced in the lower extremities. Weakness usually starts in the proximal muscles of the lower limb and may progress to flaccid quadriplegia.[8] Intact deep reflexes are observed in both symmetrical and asymmetrical paralysis. Although rare, respiratory failure due to respiratory muscle weakness can be potentially life-threatening. Symptoms of thyrotoxicosis, such as heat intolerance, palpitations, anxiety, and fatigue, usually precede TPP but may be subtle or even absent during paralysis episodes.[2,8] A typical ECG displays sinus tachycardia, ST-segment depression, U-waves, and AV blocks, characteristic of hypokalemia. Rarely, prolonged QTc values and ventricular tachyarrhythmias are present.[1]

Atypical Presentation of Graves' Disease

In our case, the patient exhibited no symptoms of thyrotoxicosis before or after developing TPP, with no family history of thyroid disease. Thus, the only clinical clues leading us to include thyroid disease as a part of the differential diagnosis were the abnormal thyroid gland image in the neck CT and the occurrence of paralysis in the morning after breakfast consumption. The final diagnosis of TPP was supported by laboratory and ultrasound findings typical for Graves' disease.

It should be noted that biotin (vitamin B_7), commonly found in many dietary supplements, can interfere with thyroid hormone assays. Depending on the laboratory test used, false elevations in free T3, free T4, TRHAb, TPOAb, and TGAb, as well as false decreases in TSH, may occur.[9,10] Such results can biochemically mimic hyperthyroidism and even lead to a misdiagnosis of Graves' disease. In the treatment of a nearly asymptomatic patient with laboratory findings as the only manifestation of thyrotoxicosis, this phenomenon should always be considered.

The thyroid hormone affects the myocardium by increasing heart rate and cardiac contractility.[11] Therefore, a patient in a hyperthyroid state is expected to present with tachycardia and palpitations. Bradycardia due to thyrotoxicosis may occur if the patient suffers from coexisting heart disease, hypercalcemia, or uses beta blockers, calcium channel blockers, or digoxin.[12] RBBB may result from congenital heart disease, ischemic heart disease, and degenerative or idiopathic fibrosis.

However, these factors were absent in our patient since propranolol was added later to the therapeutic regime. Even in the presence of hyperthyroidism, our patient experienced episodes of bradycardia. Moreover, the patient's ECG showed right bundle branch block, which subsided after the thyreostatic treatment was initiated. During our literature search, we encountered only one case report regarding temporary RBBB arising from concurrent thyrotoxicosis.[13] There is also a report of the left bundle branch block secondary to Graves' disease.[14] That is why we believe that RBBB and bradycardia he experienced were directly related to TPP and an asymptomatic, atypical form of Graves' disease we diagnosed him with.

As mentioned above, the excessive activation of Na^+/K^+ ATPase caused by hyperthyroidism plays a central role in TPP. This enzyme's hyperactivity might be linked to cardiac abnormalities observed in our patient. Increased efflux of sodium indirectly decreases cardiac contractility as less substrate is available to the Na^+/Ca^{2+} exchanger. It lowers intracellular calcium concentration, thus, negatively influencing cardiac contractility.[15,16] Increased activity of

Na^+/K^+ ATPase is also responsible for raising resting membrane potential of cardiac myocytes (intracellular potassium levels are elevated while the extracellular K^+ concentration is decreased, which lowers the transcellular electrochemical gradient). This state leads to the action potential and refractory period elongation and enhances automaticity of the heart. Those factors induce QT prolongation and can prompt the development of cardiac arrhythmias.[17] Impairments of depolarization and contraction (resulting from raised resting membrane potential) can also lead to disturbances in cardiac conduction pathways which could explain the transient RBBB observed in our patient.[18]

The endocrine assessment demonstrated an increased plasma level of testosterone, aligning with previous research, which demonstrated a positive correlation between an increased androgen concentration and a higher risk of developing TPP.[19] Graves' ophthalmopathy is typically absent in TPP patients, as observed in our case as well.[8]

Thyroid hormone stimulates both the metabolism and synthesis of steroids, leading to increased metabolic turnover. Consequently, serum cortisol levels are usually within normal ranges in patients with thyrotoxicosis. In some patients, however, early stage of hyperthyroidism may include temporary hypocortisolemia, as adrenal glands adapt slower to increased turnover, and transient functional adrenal insufficiency can occur.[20] Moreover, the adrenal reserve can also be lowered due to ongoing thyrotoxicosis.[21]

We hypothesize that these mechanisms contributed to the hypocortisolemia observed in our patient, as no antibodies to steroid 21-hydroxylase were detected, and the abdominal CT scan revealed no abnormalities. Notably, as described in the literature, a potentially life-threatening adrenal crisis can develop secondary to autoimmune hyperthyroidism.[22]

Treatment

Treatment of the acute TPP should include serum potassium replacement and administration of a non-selective beta-blocker. Adrenolytic medications such as propranolol are to limit the excessive Na^+/K^+ ATPase activity mediated both by adrenergic signaling and thyroid hormones. Intravenous administration of potassium has been demonstrated to alleviate symptoms quicker compared to oral administration. It is recommended to limit the potassium administration to a maximum of 90mEq in 24 hours, as this reduces the risk of rebound hyperkalemia. According to *Lu et al.*, administering 50mEq or less at 10mEq per hour prevents rebound hyperkalemia in most cases. Lower dosages might be seen as equally effective but safer.[23] If paresis persists after potassium replacement, intravenous propranolol of 1mg every 10 minutes up to 3 doses may be administered.[1] Spironolactone can also prevent acute paralysis attacks until euthyroid state is achieved.[5]

Our patient was given 40mEq of potassium, showing rapid improvement, though mild hyperkalemia ensued. Hence, we recommend monitoring serum potassium even when administering lower amounts of KCl.

Definitive prevention of future onsets of TPP should be focused on reducing thyrotoxicosis and achieving an euthyroid state. Thyreostatic medication such as thiamazole, radioactive iodine, or thyroidectomy can be administered based on clinical evaluation.[1]

Conclusions

Graves' disease can manifest present atypically, such as with TPP. Excluding thyrotoxicosis as a periodic paralysis cause is crucial, as it implicates preventive and treatment actions. TPP treatment requires serial serum potassium concentration monitoring to avoid rebound hyperkalemia. The possible development of RBBB should also be taken into consideration while treating a patient with TPP. It might be an advisable clinical practice to exclude adrenal insufficiency, particularly while treating a patient with autoimmune hyperthyroidism. Although rare in TPP patients, Graves' ophthalmopathy examination is necessary. The possibility of biotin interference with hormone assays should always be considered in cases presenting with nearly asymptomatic thyrotoxicosis.

To the best of our knowledge, this is the first case report of mostly asymptomatic Graves' disease presenting with TPP, RBBB and bradycardia episodes.

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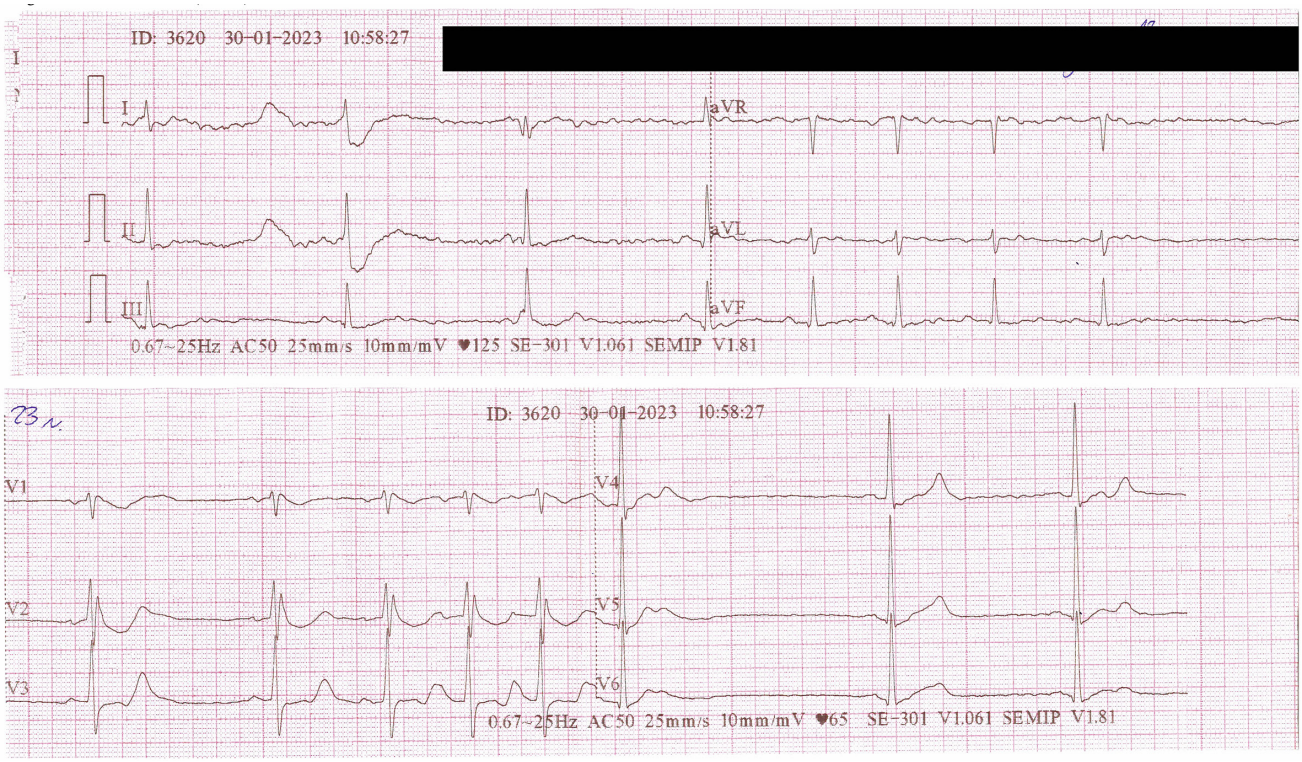

Figure 1. The first patient's ECG showing sinus arrhythmia, prolonged QTc value, wide QRS comlex and a complete right bundle branch block (RBBB)

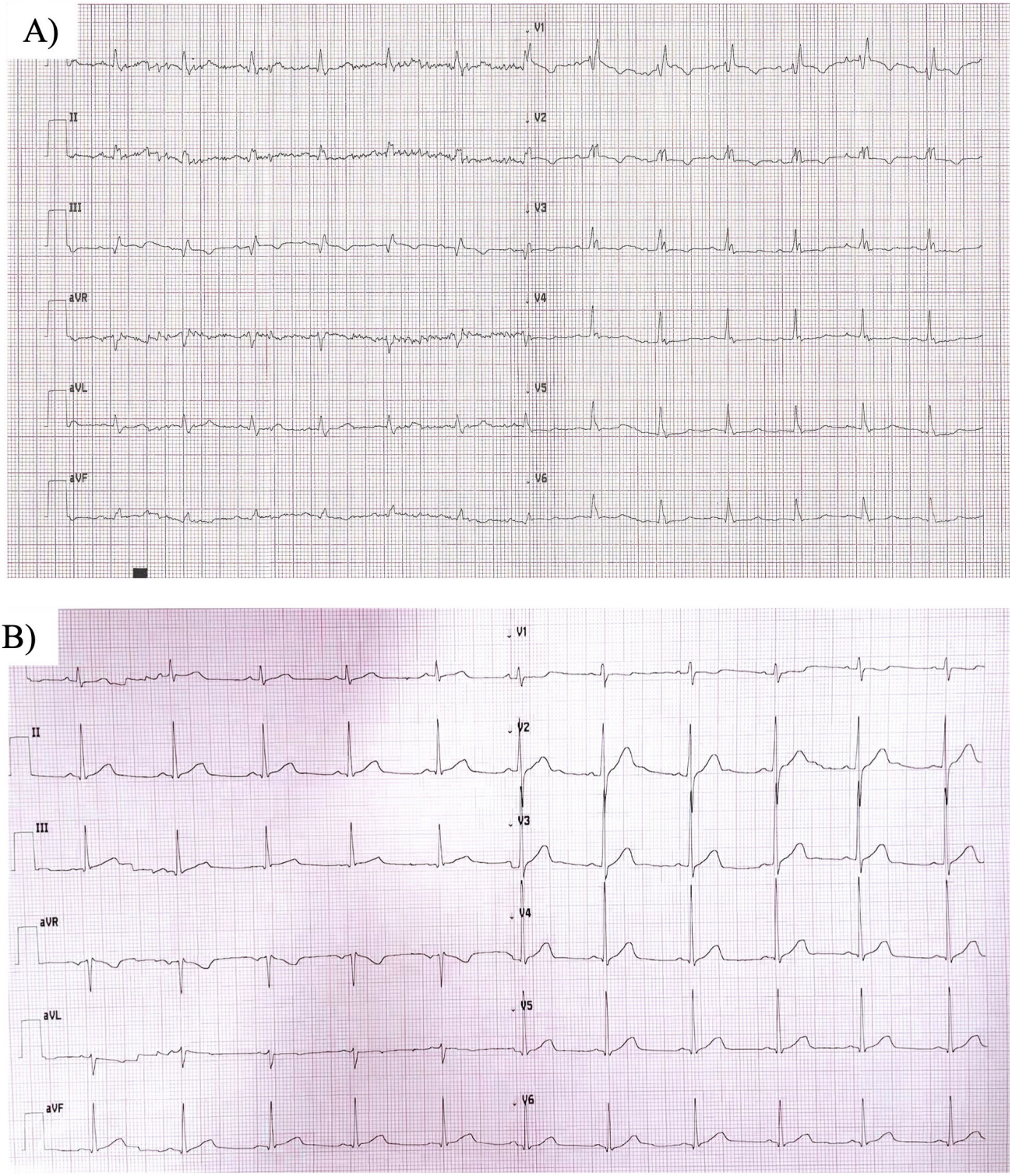

Figure 2. A) Patient's ECG after normalization of serum kalium level, B) Patient's ECG on 4th day of hospitalization showing no abnormalities

Table 1. Summary of laboratory testing

Days of Hospitalization	1st Day	2nd Day	3rd Day	4th Day	3 weeks later	*Normal ranges*
TSH [μIU/mL]	–	<0.008↓	–	<0.008↓	<0.005↓	*0.350-4.940*
fT3 [pg/mL]	–	16.56↑	–	10.47↑	5.85↑	*1.58-3.91*
fT4 [ng/dL]	–	3.29↑	–	1.80↑	1.68↑	*0.70-1.48*
TPOAb [U/mL]	–	>1000↑	–	–	–	*<5.81*
TGAb [U/mL]	–	235.92↑	–	–	–	*<4.11*
TRAb [IU/L]	–	12.68↑	–	–	–	*<3.1*
Cortisol at 8am [μg/dL]	–	0.91↓	2.96↓	–	–	*3.70-19.40*
ACTH [pg/mL]	–	10.20	17.00	–	–	*7.20-63.30*
Plasma Renin Activity [ng/mL/h]	–	3.18	–	–	–	*0.06-4.69*
Testosterone [ng/dL]	–	1377.70↑	–	–	–	*240.24-870.88*
LH [mIU/mL]	–	5.82	–	–	–	*0.57-12.57*
FSH [mIU/mL]	–	6.66	–	–	–	*0.05-11.05*
PTH [pg/mL]	–	35.0	–	–	–	*18.50-88.00*
Creatine [mg/dL]	0.50↓	–	–	0.60↓	–	*0.70-1.30*[1]

[1] Abbreviations: TSH – thyrotropin; fT3 – free triiodothyronine; fT4 – free thyroxine; TPOAb – thyroid peroxidase antibody; TGAb – thyroglobulin antibody; ACTH – adrenocorticotropin hormone; PTH – parathyroid hormone; LH – luteinizing hormone; FSH – follicle-stimulating hormone; ↑ – above normal value; ↓ – below normal value.

Patient's Consent
Patient's written informed consent was obtained for publication of this case report.

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