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Case report

Primary hyperparathyroidism overlapping with multiple sclerosis: a catastrophic marriage

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Abstract. Primary hyperparathyroidism (PHPT) often leads to neurological or psychiatric disorders, thus mimicking different diseases. Here we present a 77-years old man visited in the Emergency Department complaining for fatigue, multiple falls, nausea, anorexia, and constipation. Symptoms were rapidly worsening, and on admission he appeared sleepy, responsive to verbal stimulus, disoriented, dehydrated, unable to maintain upright position. He suffered from mild, relapsing and remitting Multiple Sclerosis (MS) since the age of 45, at that moment not requiring treatment. The laboratory tests displayed severe hypercalcemia (16.8 mg/dL), slightly decreased level of serum phosphorus (2.8 mg/dL), very high levels of parathyroid hormone (PTH) (508 pg/mL). A parathyroid mass (35x21x32 mm) in left paratracheal position was found with Computed Tomography (CT) of the neck. After correcting hypercalcemia, he was operated on day 18, thus confirming the parathyroid adenoma, that was successfully removed. One month later, the patient was completely well, and able to walk without any help, like three months before. The lab tests' values obtained during the control visit showed complete normalization of calcium-phosphate metabolism. Diabetes, too, was going better, allowing a reduction in metformin dosage. At the best of our knowledge this is the first described case of a clinically significant overlapping between symptoms due to a long-lasting mild MS and an unrecognized, severe, PHPT. This case underlines the importance of a thorough metabolic evaluation of each patient presenting worsening of his neuromuscular and/or neuropsychiatric condition, even when previously known to be affected by a defined neurologic or psychiatric disease. (www.actabiomedica.it)

Key words: hyperparathyroidism, multiple sclerosis, hypercalcemia, demyelinating disease, fatigue

Introduction

Clinical presentation of primary hyperparathyroidism (PHPT) often mimics different diseases, sometimes belonging to the neurologic or psychiatric fields. Among the constellation of presenting symptoms, there are myopathy-like symptoms, such as muscle weakness and fatigability; motor neuron disease-like symptoms, such as hyperreflexia, as well as pyramidal and bulbar signs. PHPT with neuromuscular symptoms has mainly been associated with moderate to severe hypercalcemia in reported cases (1-5). It is also recognized that significant changes in serum calcium levels can lead to neurological disorders such as parkinsonism (6-8), or psychiatric disorders such as psychosis (9).

At the best of our knowledge, however, no cases of significant clinical overlapping between PHPT and Multiple Sclerosis (MS) have been reported to date. Here we present a case of severe worsening of neurological status in a patient affected by mild, relapsing and remitting MS, due to undiagnosed PHPT.

Notably, a dramatic neurological improvement after successful parathyroidectomy was observed.

Case report

A 77 years old man was referred to the Emergency Department (ED) by his General Practitioner (GP) for a recent-onset, severe worsening of his general and neurological status. He complained for fatigue, multiple falls, nausea, anorexia, and constipation. The patient suffered from mild, relapsing and remitting form of MS since the age of 45. He also reported long-lasting arterial hypertension and recently diagnosed type 2 diabetes mellitus. At hospital presentation he was on gabapentin 300 mg b.i.d., amlodipine 5 mg, perindopril 5 mg, and metformin 500 mg b.i.d. After having excluded acute abdomen and stroke, the ED referred the patient to our hospital, closer to his home. It is noteworthy that, about two weeks before this hospital admission, the patient has been admitted in the Neurology ward of a local Hospital, complaining for motor slowdown, uncertain walking, and urinary retention. The patient has been discharged after a one week stay, tributing the symptoms to a progression of the well-known neurological disorder, coexisting with arterial hypertension and newly diagnosed diabetes mellitus. On admission he appeared sleepy albeit responsive to verbal stimulus, slightly disoriented, dehydrated, unable to maintain upright position without help. The laboratory tests are displayed on Table 1. We noted severe hypercalcemia (16.8 mg/dL, or 4.19 mmol/L) accompanied by slightly decreased level of serum phosphorus (2.8 mg/dL); serum glucose was only slightly increased (115 mg/dL, but a few hours before, while in the ED, was 185 mg/dL). Ionized calcium, too, was significantly increased (1.99 mmol/L). The Table 1 also shows the evolution of the main blood tests during hospital stay. On admission, electrocardiogram displayed ST segment abnormalities, mostly marked in leads D1 and aVL, with a slightly shortened QTc segment (340 msec) (Fig. 1, also displaying the electrocardiogram recorded on day 15). Due to the severity of the hypercalcemia, we first of all tried to correct it, giving saline 3000 mL/day, intravenous furosemide 20 mg b.i.d., and intravenous clodronate 300 mg/day, also correcting the associated electrolyte imbalance giving potassium chloride 60 mEq/day and

Table 1. Main lab tests' results from admission day to day 15. PTH assessed on Siemens chemiluminescence assay, ref. values 18-80 pg/mL. 25-Hydroxyvitamin D3 assessed on Elecsys electrochemiluminescence assay, ref. values during the winter 9.38-44.1 ng/mL.

	Reference. Range Adults	On presentation	Day 3	Day 5	Day 15
Sodium (mmol/L)	135-148	142	147	138	141
Potassium (mmol/L)	3.5-5.3	3.43	2.9	4.09	3.94
Chloride mmol/L)	98-107	110			
Urea (mg/dL)	10-50	63	54	27	37
Creatinine (mg/dL)	0.5-1.36	1.39	1.20	1.14	1.13
Glucose (mg/dL)	60-110	115	112	102	105
Calcium (mg/dL) (mmol/L)	8.5-10.5 (2.12-2-62)	16.8 (4.19)	14.9 (3.72)	11.9 (2.97)	10.8 (2.69)
Ionized Calcium (mmol/L)	1.09-1.30		1.99		
Phosphorus (mg/dL)	2.5-4.8	2.8	2.0	2.1	2.7
Hemoglobin (g/dL)	12-17	14.2			
Parathyroid hormone. (pg/mL)	18-80			508	
Alkaline Phosphatase (U/L)	50-220		82		
25-Hydroxyvitamin D3 (ng/mL)	9.38 – 44.1 (winter)		6.45		

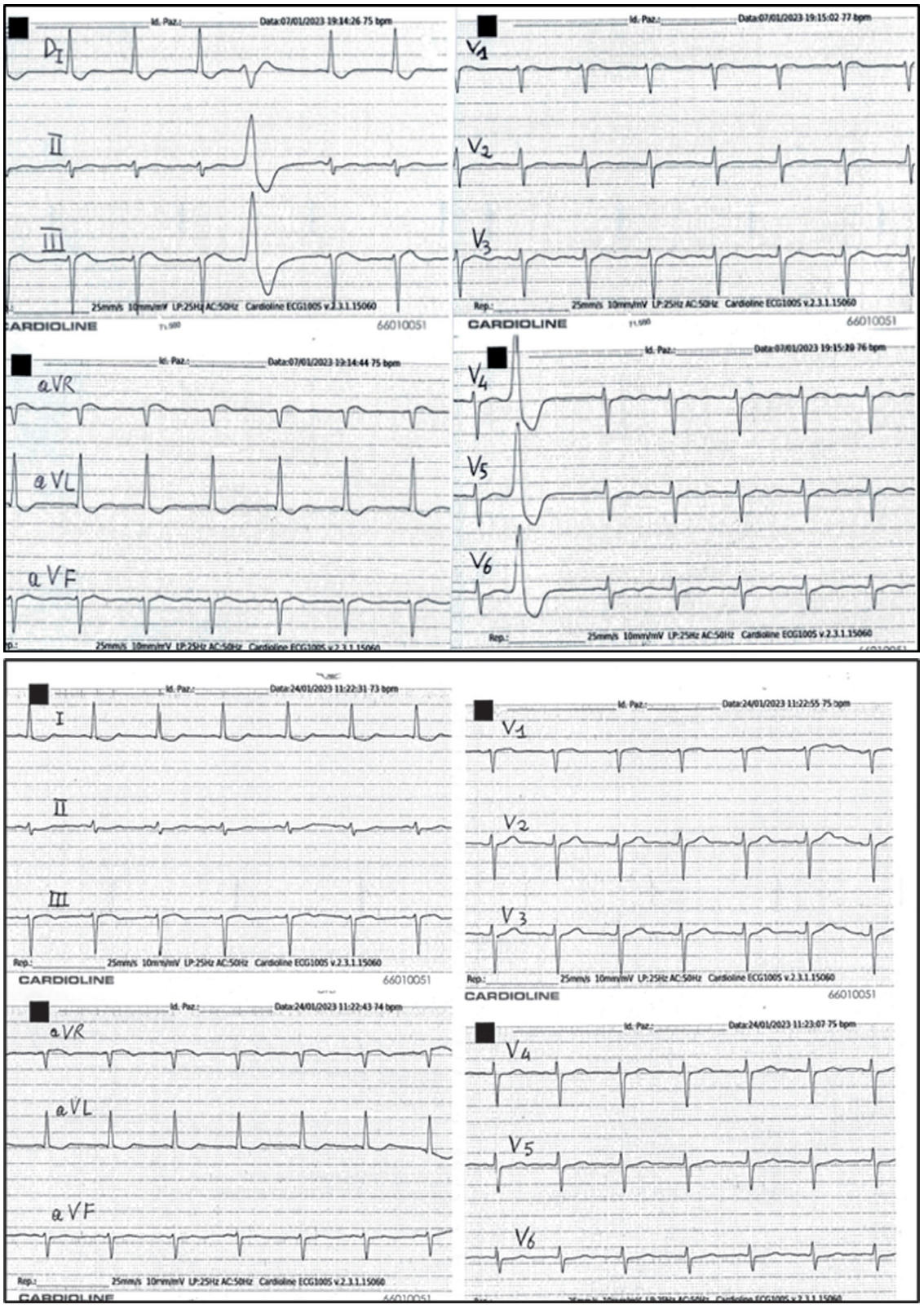

Figure 1. Electrocardiogram (ECG) on admission (left) and on day 15 (right).

magnesium sulphate 60 mEq/day. Due to a slight increase of the blood pressure, maybe due to the volume overload, we increased amlodipine dosage to 10 mg/day for one week (Table 2). Starting from day 5, saline was reduced to 1500 mL/day and furosemide to 20 mg/day. Calcemia displayed progressive reduction, thus achieving a complete normalization on day 15. Significantly, the patient paralleled the lab tests showing a dramatic improvement of his clinical status, particularly of the neurological involvement, and before surgery he was awake, collaborative, and able to maintain upright position.

In the meantime, according to the guidelines of the American Society for Bone and Mineral Research, updated in the year 2022 (10,11), we performed a thorough workup on differential diagnosis of hypercalcemia. Having found very high levels of parathyroid hormone (PTH) (508 pg/mL; Beckman chemiluminescence assay, ref. values 15-88 pg/mL), low levels of 25-hydroxy-vitamin D3 (6.45 ng/mL; Elecsys electrochemiluminescence assay, ref. values during the winter 9.38-44.1 ng/mL), markedly increased 99mTc-MIBI radiotracer accumulation by a parathyroid gland on scintigraphy (Fig. 2) and, finally, a parathyroid mass (35x21x32 mm) in left paratracheal position on Computed Tomography (CT) of the neck (Fig. 3), we were capable to exclude other causes of hypercalcemia, and to diagnose PHPT. On day 15 the patient was transferred to the Surgical Clinic, and was operated on day 18. Surgery confirmed the parathyroid neoplasm (Fig. 4), that was successfully removed. Histology, subsequently, showed that the neoplasm was a parathyroid adenoma, without malignancy features. Significantly, the PTH levels were checked intraoperatively, immediately before surgery, and at 5 minutes and 10 minutes after mass removal. The PTH values are displayed in Table 3. During the staying in Surgical Clinic PTH was assessed on an assay different from the one used in our hospital (i.e. Beckman versus

Table 2. Blood pressure values during hospital stay.

	On presentation	Day 3	Day 5	Day 15
Blood Pressure (mm Hg)	140/80	150/80	160/80	140/70

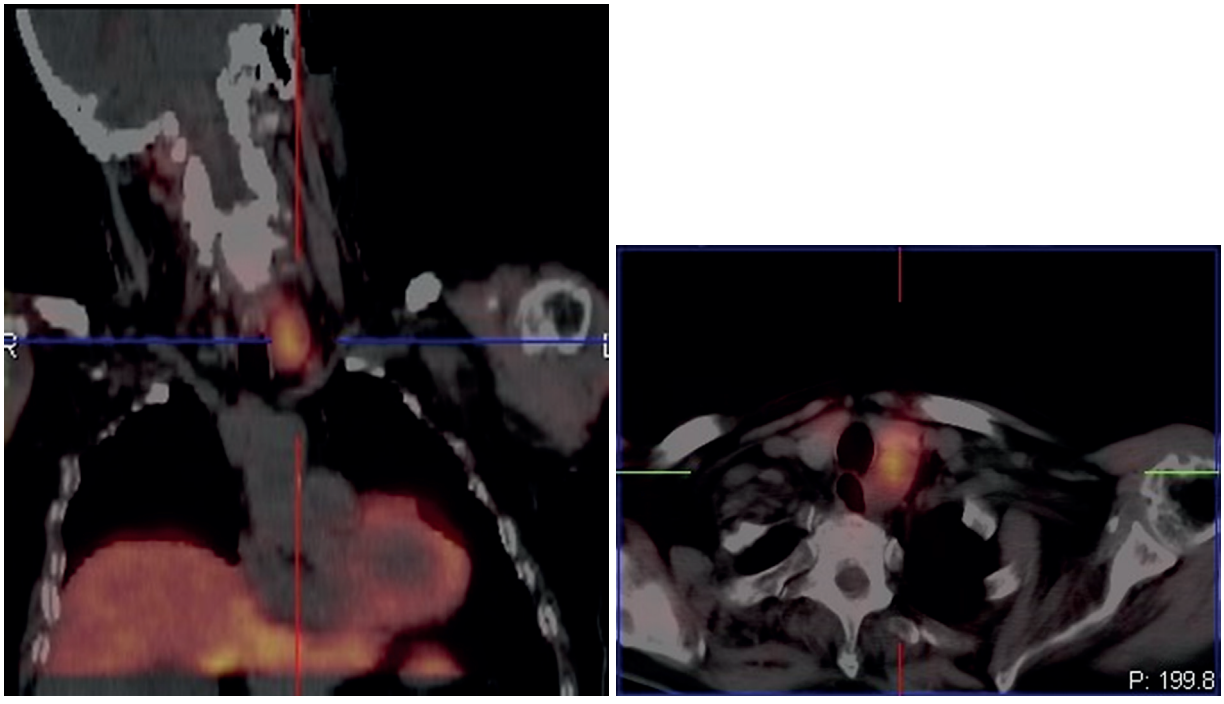

Figure 2. SPECT-CT images of the paratracheal mass characterized by a markedly increased 99mTc-MIBI radiotracer accumulation.

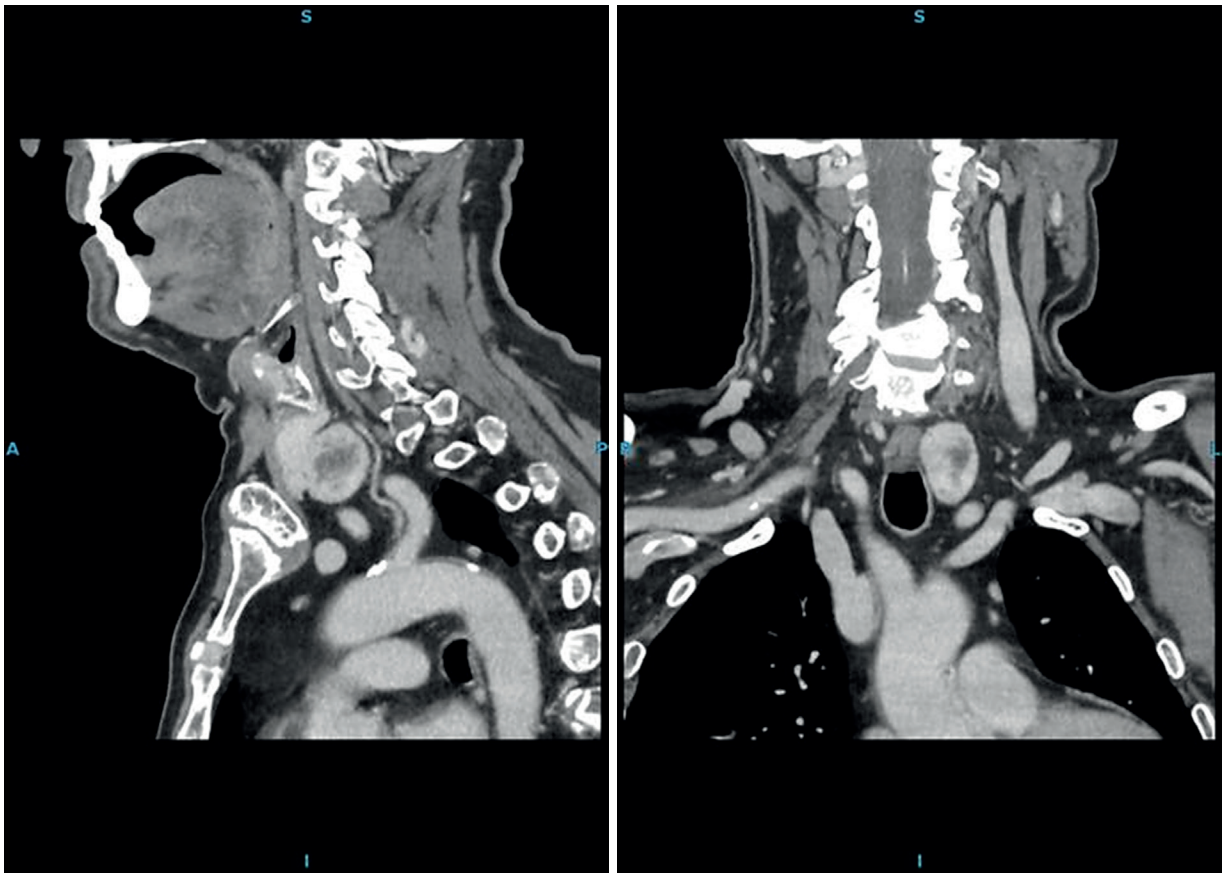

Figure 3. Sagittal and coronal CT images of the paratracheal mass.

Siemens chemiluminescence platform, ref. values, respectively 15-88 pg/mL versus 18-80 pg/mL).

One month after surgery, the patient came to our clinic as an outpatient, for clinical and laboratory re-evaluation. He was completely well, and able to walk without any help, like three months before. The lab tests' values obtained during the control visit are displayed in Table 4, showing complete normalization of calcium-phosphate metabolism. Diabetes, too, was going better, allowing a reduction in metformin dosage.

Discussion

Multiple Sclerosis (MS) is a poorly understood disease of the central nervous system that mostly starts in young adulthood (12). Disease progression is unpredictable and patients may experience a wide range of symptoms, often including fatigue, that is very common, affecting 75–95% of MS-patients at least once in their life (13). Current definitions of fatigue include a subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual activity, an overwhelming sense of tiredness, lack of energy or feelings of exhaustion, distinct from sadness or weakness (14). Fatigue is considered to be the most disabling symptom by many patients, more important than mobility restrictions or pain (15). According to current beliefs, there are primary and secondary mechanisms that lead to fatigue (16). Among the former, axonal loss, reorganization and increased brain recruitment as well as immunological and neuroendocrine factors are the most recognized. Causes of secondary fatigue, at variance, include sleeping problems, depression, stress, side effects of pharmacological therapies and reduced physical activity (17,18).

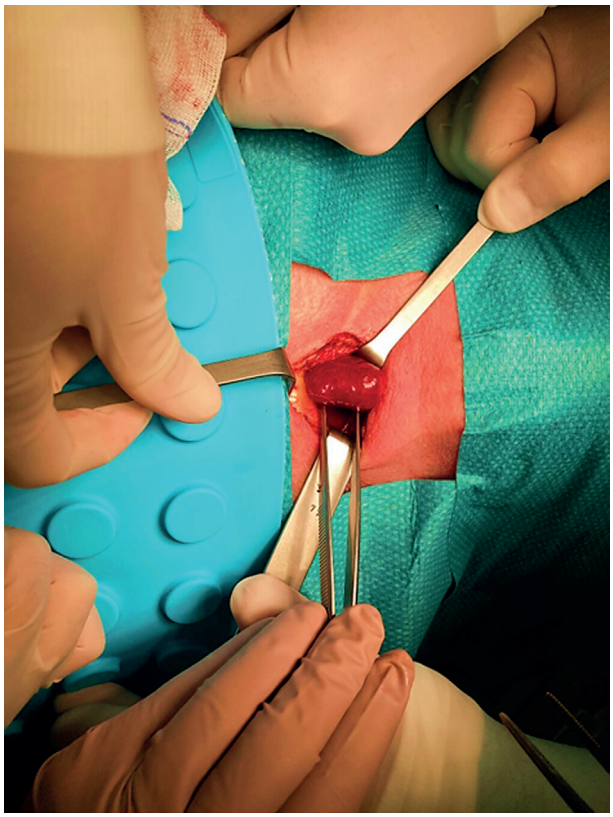

Figure 4. Intraoperative image during the removal of the tumor.

Table 3. Paratyroid hormone (PTH) levels during and after parathyroidectomy. PTH assessed on Beckman chemiluminescence assay, ref. values 15-88 pg/mL.

	At anesthesia induction	5 mins after parathyroidectomy	10 mins after parathyroidectomy
PTH (pg/mL)	1562	635	346

Hypercalcemia, defined by a serum calcium value above the upper limit of the normal range, affects approximately 1% of the general population and approximately 2% of patients with cancer (19-22). The pathophysiology of hypercalcemia varies by etiology, being increased bone resorption, reduced kidney calcium clearance, and increased gastrointestinal calcium absorption the leading ones. Approximately 90% of patients with hypercalcemia have PHPT or malignancy-related hypercalcemia. In PHPT, excess PTH,

Table 4. Lab tests' values 1 month after parathyroidectomy. PTH assessed on Siemens chemiluminescence assay, ref. values 18-80 pg/mL.

	Reference range	Values
Sodium (mmol/L)	135-148	143
Potassium (mmol/L)	3.5-5.3	4.5
Creatinine (mg/dL)	0.5-1.36	1.13
Glucose (mg/dL)	60-110	118
Calcium (mg/dL) (mmol/L)	8.5-10.5 (2.12-2-62)	9.2 (2.3)
Ionized Calcium (mmol/L)	1.09-1.30	0.97
Phosphorus (mg/dL)	2.5-4.8	3.2
PTH (pg/mL)	18-80	68.4

typically secreted by a single benign parathyroid adenoma, acts on its target tissues, notably bone, kidney, and the gastrointestinal tract. PTH stimulates bone resorption, as well as conversion of calcidiol to calcitriol, which in turn increases gastrointestinal calcium absorption. In humoral hypercalcemia of malignancy, instead, tumors secrete parathyroid hormone–related protein (PTHrP), a protein with homology to PTH, which activates the PTH receptor (23). In some hematologic malignancies and lymphomas, at variance, hypercalcemia is caused by ectopic overproduction of calcitriol from macrophage 1α-hydroxylase activity induced by malignant cells (24). Milk-alkali syndrome from excess calcium carbonate ingestion results from increased intestinal absorption and reduced kidney excretion of calcium (25-26). Thiazides too can cause hypercalcemia by promoting increased kidney calcium reabsorption, but many patients continue to have hypercalcemia after thiazide discontinuation, indicating underlying PHPT (27).

The symptoms and signs of hypercalcemia are determined by the severity of hypercalcemia and the rate of increase in serum calcium. The presence of symptoms suggests a more severe and rapidly progressive condition. According to a widely used classification, mild hypercalcemia is defined by total calcium of less than 12 mg/dL (<3 mmol/L); moderate hypercalcemia by total calcium of 12 to 13.9 mg/dL (3-3.5 mmol/L); and severe hypercalcemia by 14 mg/dL or greater (>3.5 mmol/L) (28). Interestingly, low albumin levels

may mask hypercalcemia, while high albumin may result in "pseudo-hypercalcemia" (23).

Mild hypercalcemia is typically asymptomatic or characterized by nonspecific symptoms, and even moderate hypercalcemia may be well tolerated when chronic or with a slow onset (usually months). In contrast, large or abrupt increases in serum calcium (over days to weeks) frequently cause multisystemic symptoms, such as fatigue, anorexia, polyuria, and polydipsia, as well as neuromuscular manifestations (hyporeflexia, lethargy, muscle weakness), psychiatric and cognitive symptoms (depression, anxiety, altered mental status, psychosis, delirium, personality changes, dementia, stupor, and even coma), slowed peristalsis causing gastrointestinal symptoms (nausea, vomiting, and constipation), and cardiovascular problems (such as prolonged PR interval, ST segment modifications, QT interval shortening, arrhythmias). The prevalence of type 2 diabetes mellitus has been reported to be increased in patients with PHPT in some studies, and a meta-analysis indicated greater insulin resistance in PHPT patients versus controls (29). It is also well recognized the association between PHPT and hypertension (30).

In the last 50 years, the phenotype of PHPT has dramatically changed with an evolution from a symptomatic to a largely asymptomatic disease, mainly due to routinary assessment of calcemia and consequent early diagnosis (31). Parathyroid carcinoma, in contrast, presents most often in the setting of severe hypercalcemia and should be considered in the differential diagnosis of patients who present with markedly high serum calcium levels (32).

Conclusion

At the best of our knowledge this is the first described case of a clinically significant overlapping between symptoms due to a long-lasting mild, relapsing and remitting, form of MS and an unrecognized, severe, PHPT. Our patient, in fact, well known for being affected for about 30 years by a mild form of MS, displayed a severe worsening of his clinical status in a couple of months. The recognition of the disease, and the medical (as a first step) and surgical (definitive treatment) control of the endocrine-metabolic derangement, allowed the patient returning to his previous normal life. He only continued to need antihypertensive and antidiabetic drugs, as well as gabapentin.

As such, this case underlines the importance of a thorough metabolic evaluation of each patient presenting worsening of his neuromuscular and/or neuropsychiatric condition, even when previously known to be affected by a defined neurologic or psychiatric disease. Look at the calcium!

References

1. Patten BM, Bilezikian JP, Mallette LE, et al. Neuromuscular disease in primary hyperparathyroidism. Ann Intern Med 1974;80:182-193
2. Carnevale V, Minisola S, Romagnoli E, et al. Concurrent improvement of neuromuscular and skeletal involvement following surgery for primary hyperparathyroidism. J Neurol 1992;239:57
3. Patten BM, Pages M. Severe neurological disease associated with hyperparathyroidism. Ann Neurol 1984;15:453-456
4. Ghosh M, Bhattacharya A, Ghosh K, et al. A commonly overlooked motor neuron disease mimicker. Endocrinol Diabetes Metab Case Reports 2014:14-17
5. Siqueira Carvalho AA, Vieira A, Simplício H, et al. Primary hyperparathyroidism simulating motor neuron disease: Case report. Arq Neuropsiquiatr 2005;63:160-162
6. De Rosa A, Rinaldi C, Tucci T, et al. Co-existence of primary hyperparathyroidism and Parkinson's disease in three patients: an incidental finding? Parkinsonism Relat Disord. 2011;17:771-773
7. Hirooka Y, Yuasa K, Hibi K, et al. Hyperparathyroidism associated with parkinsonism. Internal Medicine 1992;31:904-907
8. Guimaraes Augusto CM, Sobral de Morais N, Palmeira Santana R et al. Parkinsonism as an atypical manifestation of primary hypoerparathyroidism. AACE Clinical Case Report 2019;5:e244-e246
9. Singh P, Bauernfreund Y, Arya P, Singh E, Shute J. Primary hyperparathyroidism presenting as acute psychosis secondary to hypercalcaemia requiring curative parathyroidectomy. J Surg Case Rep. 2018;2018:rjy023
10. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the fourth international workshop. J Clin Endocrinol Metab. 2014;99: 3561-3569
11. Bilezikian JP, Silverberg SJ, Bandeira F, et al. Management of Primary Hyperparathyroidism. J Bone Mirer Res 2022;37:2391-2403

12. Patti F, Vila C. Symptoms, Prevalence and Impact of Multiple Sclerosis in Younger Patients: A Multinational Survey. Neuroepidemiology 2014; 42:211–218
13. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: mechanisms, evaluation, and treatment. Sleep. 2010;33:1061–1067
14. Mills RJ, Young CA. A medical definition of fatigue in multiple sclerosis. QJM. 2008;101:49–60
15. Vucic S, Burke D, Kiernan MC. Fatigue in multiple sclerosis: mechanisms and management. Clin Neurophysiol. 2010;121: 809–817
16. Krupp LB, Serafin DJ, Christodoulou C. Multiple sclerosis-associated fatigue. Expert Rev Neurother. 2010; 10:1437–1447
17. Bol Y, Duits AA, Hupperts RM, Vlaeyen JW, Verhey FR. The psychology of fatigue in patients with multiple sclerosis: a review. J Psychosom Res. 2009;66:3–11
18. Kos D, Duportail M, D'hooghe M, Nagels G, Kerckhofs E. Multidisciplinary fatigue management programme in multiple sclerosis: a randomized clinical trial. Mult Scler. 2007;13:996–1003
19. Minisola S, Pepe J, Piemonte S, Cipriani C. The diagnosis and management of hypercalcaemia. BMJ. 2015;350:h2723
20. Palmér M, Jakobsson S, Akerström G, Ljunghall S. Prevalence of hypercalcaemia in a health survey: a 14-year follow-up study of serum calcium values. Eur J Clin Invest. 1988;18:39-46
21. Gastanaga VM, Schwartzberg LS, Jain RK, et al. Prevalence of hypercalcemia among cancer patients in the United States. Cancer Med. 2016;5:2091-2100
22. Balasubramanian P, Majumdar SK. Albumin-corrected calcium and the prevalence and categories of hypercalcemia in hospitalized patients with 1-year follow-up of undiagnosed cases. Endocr Pract. 2021;27:279-285
23. Donovan Walker M, Shane E. Hypercalcemia, A review. JAMA 2022;328(16):1624-1636
24. Hewison M, Kantorovich V, Liker HR, et al. Vitamin D-mediated hypercalcemia in lymphoma: evidence for hormone production by tumor-adjacent macrophages. J Bone Miner Res. 2003;18:579-582
25. Beall DP, Scofield RH. Milk-alkali syndrome associated with calcium carbonate consumption: report of 7 patients with parathyroid hormone levels and an estimate of prevalence among patients hospitalized with hypercalcemia. Medicine (Baltimore). 1995;74:89-96
26. Machado MC, Bruce-Mensah A, Whitmire M, Rizvi AA. Hypercalcemia associated with calcium supplement use: prevalence and characteristics in hospitalized patients. J Clin Med. 2015;4:414-424
27. Griebeler ML, Kearns AE, Ryu E, et al. Thiazide-associated hypercalcemia: incidence and association with primary hyperparathyroidism over two decades. J Clin Endocrinol Metab. 2016;101:1166-1173
28. Carroll MF, Schade DS. A practical approach to hypercalcemia. Am Fam Physician. 2003;67:1959-1966
29. Sun Q, Zhang T, Chen P, Nan-Wei T, Zhang M. Glucose metabolic disorder in primary hyperparathyroidism: a systematic review and meta-analysis. Int J Clin Exp Med. 2019;12:11964-11973
30. Kalla A, Krishnamoorthy P, Gopalakrishnan A, Garg J, Patel NC, Figueredo VM. Primary hyperparathyroidism predicts hypertension: results from the National Inpatient Sample. Int J Cardiol. 2017;227:335-337
31. Minisola S, Arnold A, Belaya Z, et al. Epidemiology, pathophysiology, and genetics of primary hyperparathyroidism. J Bone Miner Res. 2022;37:2315-2329
32. El-Haji Fuleian G, Chakhtoura M, Cipriani C, et al. Classical and Nonclassical Manifestations of Primary Hyperparathyroidism. J Bone Miner Res. 2022;37:2330-2350

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