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CASE REPORTS

Restless Legs Syndrome as the Presenting Symptom of Multiple Myeloma

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We report a patient affected by restless legs syndrome as the presenting symptom of multiple myeloma, a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow and monoclonal immunoglobulin in the blood and/or urine.

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Restless legs syndrome (RLS) is a sensorimotor disorder[1] occurring often as an idiopathic form; if a concurrent condition known to be associated with RLS is found, it is classified as secondary. The most common conditions highly-associated with RLS include renal failure, iron and folic acid deficiency, peripheral neuropathy, pregnancy, celiac disease, Crohn's disease, and others.[2]

We report here a case of RLS due to iron deficiency in the setting of multiple myeloma (MM), a hematologic malignancy characterized by clonal proliferation of plasma cells in the bone marrow and, usually, the presence of a monoclonal immunoglobulin in the blood and/or urine.[3]

REPORT OF CASE

A 78-year-old right-handed woman was referred to our sleep research center in January 2012 for an 8-month history of uncomfortable sensations in her legs with urge to move, partially relieved by movement. The symptoms were present every day, worsening in the evening; the discomfort forced the patient to get up and walk around at night (with moderate relief). RLS was severe, with a score of 29 at the International RLS rating scale. The patient has not been drinking alcohol (especially in the late evening) or smoke cigarettes. Severe insomnia caused excessive daytime sleepiness (Epworth Sleepiness Scale score 13). The patient underwent a nocturnal polysomnographic (PSG) study, without medication, performed using a complete conventional montage, including bilateral tibialis anterior muscle electromyogram channels. The hypnogram showed abnormal sleep architecture (**Figure 1**), with very low sleep efficiency (30%) and excessive WASO (65.1%) with numerous and long awakenings. The number of periodic leg movements during sleep (PLMS), scored following the WASM/IRLSSG criteria,[4] was abnormally high (PLMS index 80.9/h; PLMS/arousal index 1.6/h; Periodicity index 0.670[5]). The sleep breathing pattern was within the normal limits (apnea/hypopnea index 3.7/h). Family history was negative for RLS.

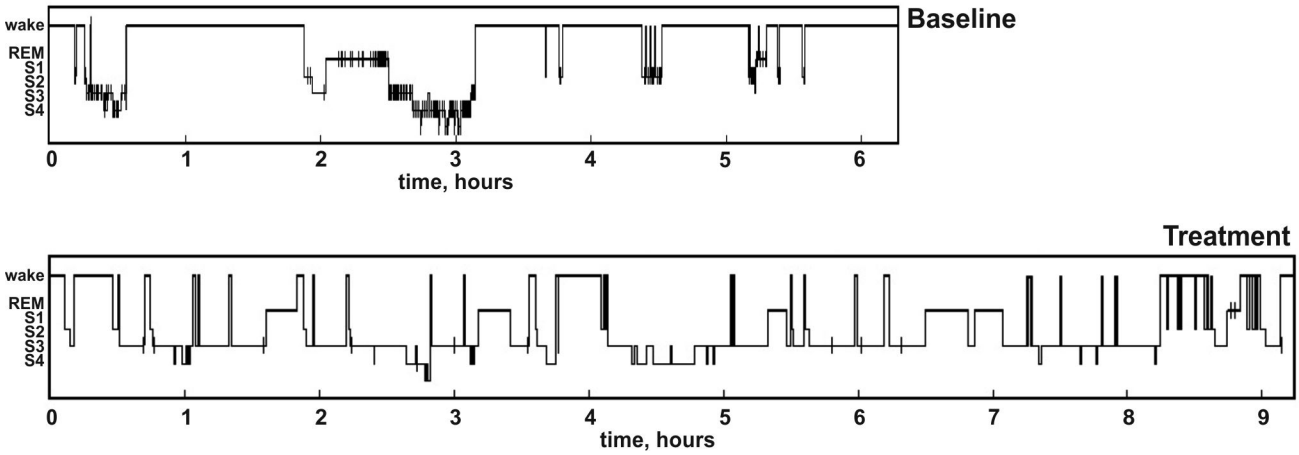
Before our evaluation, the patient had been treated by her general practitioner with prolonged-release pramipexole (0.26 mg); however, this treatment had been suspended before admission to our Centre because of its apparent inefficacy. After our evaluation, gabapentin 400 mg was started together with normal-release pramipexole 1 mg at bedtime.

At our observation, she also complained a generalized pruritus, worsening at night. The pruritus started almost contemporaneously with RLS and was treated with topical steroids and antihistamine agents with scarce benefit. It is important to note that antihistamine agents were started when RLS symptoms were already present and that they did not modify its severity. Several scratching lesions were evident on forearm and legs. Moreover the patient had a second-degree obesity (body mass index 35) and reported severe widespread bone pain and lower back pain, together with generalized weakness and fatigue.

The patient had a past medical history of hypertension, previous depression (not evident at examination), osteoporosis, and spondyloarthrosis; diabetes was not reported. The patient had two uneventful pregnancies, during which no RLS symptoms were reported. Neurological examination only showed bilateral, asymmetrical, distal hypopallesthesia of the lower limbs. Mini-mental state examination was normal (27).

The patient underwent a complete set of blood analyses and the following abnormal values were found (normal limits within brackets): triglycerides 150 mg% (35-135), hemoglobin 9.9 g% (11.5-16.5), glycosylated hemoglobin 6.8% (4.5-5.7), creatine phosphokinase 252 U/l (24-173), hematocrit 31.8% (38-48), ferritin 12 ng/mL (13-150), transferrin 373 mg% (200-360), Katz index 54 mm (3-15). Serum protein electrophoresis showed a peak in the gamma zone. Serum albumin was 50.60 mg/L (52-65.1), alpha-2 macroglobulin 14.6 mg/L (9.5-14.4), β_2 microglobulin 3 mg/L (1-2.9). Bone marrow biopsy showed monoclonal plasma cells (25-30%). Electrocardiogram and thyroid function were normal, as well as renal function and calcemia. Brain and spine computerized tomography was normal but, for the lumbar-sacral region, disclosed the presence of ab-

Figure 1—Hypnogram before and after treatment with gabapentin; the occurrence of leg movements is indicated by small vertical bars superimposed over the hypnogram



normally small intervertebral spaces with a clear protrusion of the L3-L4 disc, together with signs of diffuse arthritis. Electromyography showed signs of peripheral neuropathy depending on lumbar-sacral radicular involvement.

All these results allowed us to reach the diagnosis of multiple myeloma in this patient, who was referred to a hematology clinic.

The patient came back to our institute for a follow-up visit in February 2012. The treatment of iron deficiency, started by the hematologist had resolved the anemia, and the patient reported a notable reduction of RLS symptoms (International RLS severity scale 4); gabapentin and pramipexole were also regularly and continuously taken. A second PSG was carried out and the resulting hypnogram appeared to be significantly improved and practically normalized (**Figure 1**), and there was a clear decrease of PLMS number (PLMS index 0.13/h; PLMS/arousal index 0.1/h). The respiratory pattern continued to be normal.

DISCUSSION

The first important consideration from this case report is that the patient was referred to our sleep center because of her severe RLS symptoms dramatically reducing her quality of life. However, our clinical study clearly demonstrated that RLS was not the primary disease but was most probably secondary to a series of factors known to cause it. In this patient, radiculopathy was likely present before the onset of RLS and MM; conversely, iron deficiency and severe bone pain probably started with MM and induced the appearance of severe and apparently dopamine agonist-resistant RLS symptoms.

With our data, it cannot be established if RLS should be considered as a paraneoplastic condition heralding the malignant disease or just a secondary form depending on the development of MM, possibly exacerbated by the association with radiculopathy. Paraneoplastic syndromes are conditions that can have several clinical expressions. They can precede neoplasia or be contemporaneous; they can disappear with the treatment of neoplasia and possibly reappear with the subsequent development of metastases. Interestingly, pruritus often represents the onset symptom of neoplasia and can also precede it by several years. On the other hand, some RLS patients also describe their subjective symptoms as pruritus.

Considering the information available for this patient, we believe that the most likely possibility is that RLS was secondary to iron deficiency, a very well-known and established cause of RLS in the literature.[6] This belief is strongly supported not only by the clear results of our blood analyses but also by the important clinical and PSG improvement observed after the correction of iron deficiency while MM was still evident. It should also be mentioned that our patient was taking gabapentin for its known effects on both RLS and pain[7] and pramipexole, a first-line treatment for RLS.[8]

Beside the speculations on the reciprocal interactions and cause/effect relationship between the numerous factors considered in this patient, the most important message from this case report is that RLS symptoms can sometimes be the sign of a life-threatening condition that should be suspected if symptoms do not respond promptly to dopamine agonists; if so, careful and complete collection of clinical and laboratory data should be carried out. In particular, if RLS onset coincides with pruritus and bone pain, a complete blood count should be checked along with ferritin and iron studies; if anemia is found, serum protein electrophoresis should then be checked.

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DISCLOSURE STATEMENT

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