Clinical Reasoning: A 75-year-old man with parkinsonism, mood depression, and weight loss

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Section 1

A 75-year-old man presented to the emergency department with a 1-year history of 66-pound weight loss and alternating bowel habits. He was admitted to the hospital, where he underwent several examinations to investigate the presence of a malignancy. A colonoscopy, a gastroscopy, an ultrasound of the abdomen, and a contrast-enhanced CT scan of thorax and abdomen did not detect any neoplasia. The only findings consisted of a prostatic hypertrophy and a basal pleural–parenchymal hyperdensity in the left lung, which was described as the result of an infective process. Neoplastic markers CA19.9, carcinoembryonic antigen, neuron-specific enolase, and α-fetoprotein were also negative. Wide-spectrum blood tests were unremarkable, except for hypogammaglobulinemia and elevated β2 microglobulin.

Upon a more thorough collection of the patient's history and examination, progressive stiffness and slowness of movements were reported to have appeared a few months before, along with a longer history of mood depression, apathy, hyporexia, hyposmia, constipation, micrographia, dysphagia, hypophonia, and sleep disturbances including sleeplessness and REM sleep behavior disorder.

A neurologic examination of the motor system revealed a symmetric and severe plastic hypertonia in the trunk and all 4 extremities with cogwheel rigidity at the wrists and marked bradykinesia. In the cranial district, hypomimia, hypophonia, and upward gaze limitation were noticed. Deep tendon reflexes were normal on all 4 limbs. No tremor was recorded. Inducible small-amplitude polyminimyoclonus could be elicited in the upper extremities. The patient could stand aided and walked a few steps with a slow and normal-base gait. Findings on the remainder of the neurologic examination were unremarkable. Family history was negative for neurodegenerative diseases, although a sister had multiple sclerosis and a daughter had depression.

Questions for consideration:

1. What are the main neurologic systems involved?
2. What medical conditions could be considered in the differential diagnosis?

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Section 2

The patient's clinical presentation displayed an involvement of basal ganglia and limbic circuits.

The findings of truncal and limb rigidity, severe diffuse bradykinesia, hypophonia, mask-like facial appearance, and micrographia should direct the diagnostic hypotheses towards a parkinsonian syndrome. This diagnosis is reinforced by the presence of several nonmotor symptoms (i.e., hyposmia, mood depression, sleep disturbances, constipation, weight loss). The age at onset and the clinical presentation may be compatible with an idiopathic form of Parkinson disease (PD) or an atypical parkinsonism, including multiple system atrophy type P (MSA-P), progressive supranuclear palsy, basal ganglia calcification syndrome, or Perry syndrome. The lack of a dominant pattern of inheritance in the family made the latter hypothesis less likely. Given its relatively high prevalence among causes of extrapyramidal disorders, the possibility of a vascular parkinsonism should not be discarded either. Nevertheless, the presence of nonmotor symptoms and the lack of cardiovascular risk factors and of a lower limb–dominant parkinsonism with gait abnormalities are not suggestive of a vascular etiology.

The history of weight loss, even without the finding of a neoplasm, and the subacute onset of symptoms may still suggest a more complex paraneoplastic or dysimmune neurologic syndrome. In this perspective, stiff-person syndrome, a form of parkinsonism and truncal rigidity that may occur in concomitance with a tumor, was considered in the differential diagnosis.

The rapid progression and worsening of symptoms and the presence of mood changes and cognitive decline may also suggest a prion disease. Cortical myoclonus, usually periodic and pseudorhythmic, is also a feature of prion-related encephalopathies, but it is worth noticing that polyminimyoclonus, as noticed in this case, is often found in synucleinopathies (e.g., PD, MSA-P, dementia with Lewy bodies).[1]

Questions for consideration:

1. What further examinations should be prescribed?
2. What therapeutic intervention could be adopted to help in the diagnostic process?

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Section 3

The patient underwent a CT scan of the brain, which excluded the presence of basal ganglia calcification. A brain MRI was performed revealing a few punctiform T2 hyperintense lesions in bihemispheric white matter of probable vascular origin. However, basal ganglia appeared to be spared. T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences showed a hyperintense signal in bilateral mesial temporal lobes (figure, A). T1-weighted images showed mild bilateral hippocampal atrophy (figure, B). EEG was normal.

To further investigate the paraneoplastic hypothesis, the patient underwent a total body FDG-PET scan, which revealed a hyperfixation of pulmonary bases and a few thoracic lymph nodes, which were again interpreted as basal pneumonia, for which the patient was started on antibiotic therapy. Bronchoscopy was performed to better investigate the radiologic abnormalities in the lung bases, without evidence of malignant cells. FDG-PET cerebral scans showed a diffuse cortical hypermetabolism, with a stronger signal in the basal ganglia (figure, C and D).

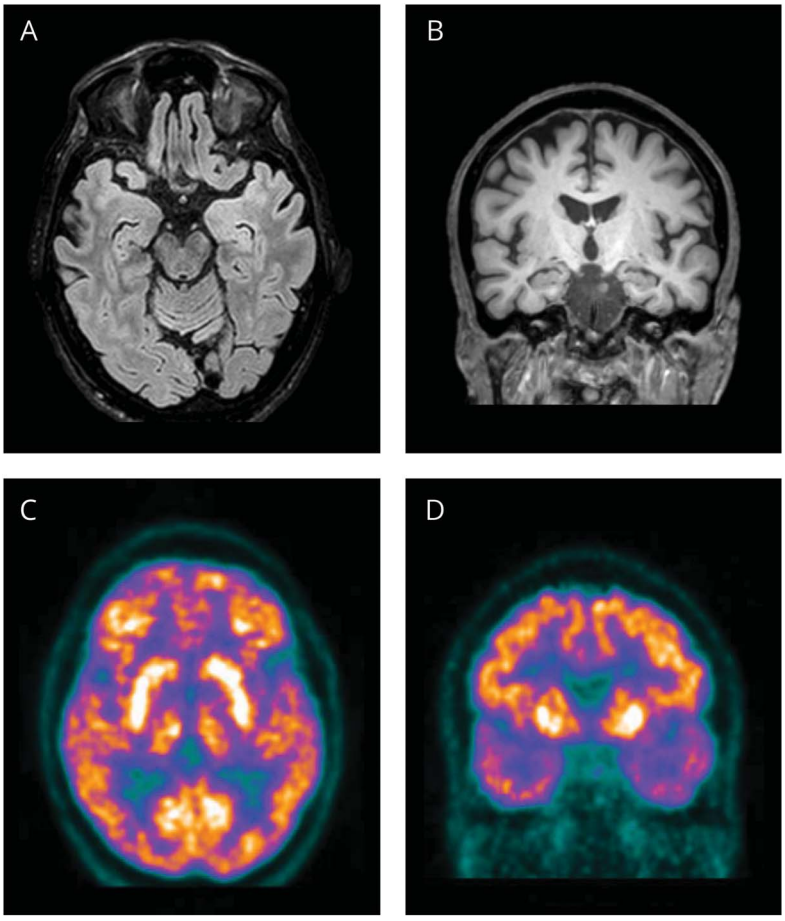
During hospitalization, the patient developed acute leukopenia, which regressed spontaneously in a few days. For a full characterization of the hematologic status of hypogammaglobulinemia, elevated β2 microglobulin, and the recent episode of leukopenia, bone marrow biopsy was performed, with the detection of chronic B-cell leukemia. Concomitantly, the patient presented an acute episode of gastroparesis, followed by hypovolemic shock, which was treated with a fluid load, and supraventricular tachycardia, which regressed spontaneously.

Meanwhile, the patient was started on ex adjuvantibus therapy with levodopa and baclofen and soon showed a moderate decrease of muscular rigidity and bradykinesia and a good response on hypomimia.

Questions for consideration:

1. Given this new evidence, what is the most probable diagnostic orientation?
2. What examinations would be of additional value to the diagnostic hypothesis?

Figure Structural and functional brain imaging



(A) Axial fluid-attenuated inversion recovery image shows hyperintense signal in left mesial temporal lobe. (B) Coronal T1-weighted image shows mild bilateral hippocampal atrophy. (C, D) Axial and coronal brain FDG-PET images show basal ganglia and cortical hypermetabolism.

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Section 4

The detection of an increased fixation of FDG in the cerebral cortex and, particularly, in the basal ganglia may be suggestive of an autoimmune disorder with involvement of the CNS.

The occurrence of gastroparesis and tachyarrhythmia suggests an impairment of the autonomic nervous system. To discriminate the central or peripheral nature of dysautonomia, EMG was performed. Results showed a prominent chronic sensory-motor axonal polyneuropathy, which could be considered the cause of autonomic dysfunction.

In order to rule out possible autoimmune processes, a lumbar puncture was performed. CSF pressure, cell count, protein, and glucose levels were normal. Oligoclonal bands were absent in serum and CSF. A wide-spectrum antibody assay was conducted on CSF and serum to evaluate the presence of autoantibodies associated with paraneoplastic neurologic syndromes (i.e., antibodies anti-Hu, Yo, Ri, amphiphysin, Ma1/2, CV2, SOX1, Tr[DNER], ZIC4, CASPR2, leucine-rich glioma-inactivated 1 [LGI1], GAD65, and GlyR). Serology results showed the presence of anti-LGI1 antibodies in serum.

The patient was started on steroidal therapy, first with IV methylprednisolone 1 g for 5 days, followed by oral administration of lower doses of prednisone. After initial improvement of bradykinesia, rigidity, hypophonia, and facial mimicry, the clinical presentation remained stable, with an important parkinsonian syndrome. The patient's general condition worsened rapidly upon reduction of steroidal therapy and led to death a few weeks later, probably due to an exacerbation of the underlying leukemia.

Discussion

Anti-LGI1 antibodies–associated encephalitis is an autoimmune disorder usually characterized by epileptic seizures, memory deterioration, behavioral changes, sleep disturbances, and hyponatremia.[2] Few cases of unusual presentation of LGI1-related syndrome have been described to be accompanied by a multitude of movement disorders, including prominent akinetic-rigid parkinsonism,[3] progressive encephalomyelitis with rigidity and myoclonus,[4] chorea,[5] dystonia, and neuromyotonia.[6]

In the diagnostic reasoning, the history of weight loss, rapid and symmetric parkinsonism, and behavioral changes were red flags for a paraneoplastic or dysimmune encephalopathy. Cerebral imaging was supportive of an autoimmune process, with the evidence of hyperfixation of FDG in basal ganglia. Brain MRI scans showing hippocampal atrophy and increased FLAIR/T2 signal in mesial temporal cortices were consistent with LGI1 encephalitis.[7,8] The finding of LGI1 antibodies in serum confirmed the immune-mediated etiology of the syndrome.

A few case reports have found that LGI1 encephalitis is mainly nonparaneoplastic, with negativity of tumor markers and radiologic examinations.[8,9] In this case, it was speculated that the severe loss of weight could be attributed either to chronic B-cell leukemia or to hyporexia inscribed in the context of mood depression.

LGI1 encephalitis has been described to be responsive to immunotherapy: a combination of high-dose corticosteroids, IV immunoglobulin (IVIg), and plasma exchange seems to be more effective than corticosteroid monotherapy in improving the degree of recovery.[10] In this case, methylprednisolone only was administered, since the presence of hypogammaglobulinemia and the history of a previous cardiac arrhythmia contraindicated the use of IVIg and plasmapheresis.

The case described here falls into an atypical presentation of LGI1 encephalitis, due to the absence of epileptic seizures and the prevalence of parkinsonism, mood depression, and dysautonomic neuropathy, along with the possible association with a systemic malignancy.

Author contributions

Emanuele Frattini: study concept and design, analysis and interpretation of data, acquisition of data. Edoardo Monfrini: analysis and interpretation of data, acquisition of data. Giacomo Bitetto: analysis and interpretation of data, acquisition of data. Barbara Ferrari: analysis and interpretation of data, acquisition of data. Sara Arcudi: analysis and interpretation of data, acquisition of data. Nereo Bresolin: analysis and interpretation of data, study supervision. Maria Cristina Saetti: analysis and interpretation of data, acquisition of data. Alessio Di Fonzo: study concept and design, critical revision of manuscript for intellectual content.

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Disclosure

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