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LATE-ONSET MANIA IN A PATIENT WITH A HISTORY OF THYMOMA. CASE REPORT IN COLOMBIA

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Abstract

Late-onset mania is a term that encompasses several possibilities of phenotypic expression, including episodes in the context of early-onset bipolar disorder or latent bipolar disorder with lifetime depression, and episodes in the absence of a history of affective symptoms. In the latter case, the possibility of being a secondary mania increases and consideration of etiopathogenic factors that could variably contribute to the psychopathological presentation is necessary. We present the case of a 75-year-old woman with a history of advanced stage thymoma, who developed subacute neuropsychiatric manifestations generated by affective symptoms that received antidepressant management, as well as a manic episode after the initiation of such treatment. The patient reported no personal or family history of mental disorders. Due to the patient's context, an immune-mediated pathology was considered, in which the antidepressant treatment could contribute to the symptomatic presentation and the corticosteroid to the exacerbation of the affective symptomatology, which made necessary the administration of high doses of psychotropic drugs. This clinical case shows the difficulties involved in the approach to late-onset mania, both diagnostically and therapeutically, in the context of a patient with a history of thymoma.

Keywords: *late-onset mania, antibody-mediated encephalitis, thymoma, paraneoplastic syndrome, manic shift.*

Introduction

Late-onset mania is defined as occurring between the ages of 60 and 65, or even later in life.[1,2]

It is estimated that it affects between 0.5 and 1% of older adults, and that 10% of cases are associated with vascular changes or other brain pathologies, among which paraneoplastic syndromes are relevant in the context of patients with neoplasms. On the other hand, manic-psychotic symptoms tend to be less frequent than depressive episodes.[1] Antibody-mediated encephalitis is the third most common cause of encephalitis.[3] This pathology does not present with homogeneous pathophysiological mechanisms[2], since in some cases, antibodies bind to extracellular surface epitopes generating reversible neuronal dysfunction, while in others, such as those generated in paraneoplastic syndromes, they bind to intracellular epitopes. In this scenario, the antibodies may not be directly etiopathogenic.[3] Thus, it is possible that neuronal loss plays a fundamental role in the syndromic presentation of these cases. Paraneoplastic neurological syndromes are characterized by remote effects of primary neoplasms due to immune-mediated mechanisms that produce direct damage to nervous tissue, either central or peripheral, without invading it.[4] However, there has been an advance in its diagnosis, since nowadays, not only the identification of onconeuronal antibodies is considered, but also the identification of onconeuronal antibodies,[5] and a classification of phenotypes according to the risk of being associated with cancer has been has chosen for a classification of phenotypes according to the risk of being associated with cancer, dividing them into high-risk and intermediate-risk phenotypes. It is also necessary to exclude more prevalent causes, such as neurodegenerative diseases and toxic or metabolic alterations.[5] Finally, the diagnosis is made according to three levels of certainty, according to the findings obtained by means of the PNS-Care Score.[5] It also depends on other criteria to establish the likelihood of autoimmune encephalitis. [6,7] or antiinmune psicosis,[8] and thus improve predictive values. However, the clinical value of these criteria has been questioned in contexts where there is a purely

psychiatric presentation,[9] which represent approximately 4% of the cases.[10]

The absence of alterations in the cerebrospinal fluid does not exclude the diagnosis. In this regard, 60% of patients with alterations at the central nervous system level present antibody titers,[4] and not all of them have the same sensitivity or specificity. There are well-characterized antibodies in the context of paraneoplastic syndromes, which increase the diagnostic suspicion of this entity, even if there is no evidence of the primary neoplasm.[4]

The absence of antibodies may signify the presence of new antibodies to as yet unidentified epitopes, or a T-cell mediated response.[11] In turn, this is associated with other paraclinical alterations: 58-71.8% is related to pleocytosis; 9.4%, to positive oligoclonal bands; 31.6%, to an increased IgG index in the cerebrospinal fluid, and 83% to alterations in the electroencephalogram tracing.[11,12] The prevalence and incidence of this seronegative group are considered to be similar to those of antibody-positive cases,[11,12] i.e., they account for 7 to 11% of cases of autoimmune encephalitis.[13] Given the heterogeneity of this group, there is no clear prognostic picture,[12] which may worsen due to pathophysiological mechanisms involving cytotoxic processes, which in turn may interrelate with other processes, such as aging, generating an altered regulation of microglia that amplifies the inflammatory response.[12] On the other hand, relapses are usually associated with insufficient immune treatment or early withdrawal of immune therapy,[14] and spontaneous resolution is rare.

For cases with the presence of onconeuronal antibodies there is no high quality evidence to guide therapeutic decisions, however, it has been reported that treatment of the underlying neoplasm prevents the progression of neurological symptoms and may even improve them. In cases where onconeuronal antibodies and the syndrome are highly specific, there is evidence in the literature to support empirical oncologic treatments.[4] Finally, there is no reliable evidence to recommend the use of immunosuppressive treatment, which has a poor response rate, or the stimulation of tumor growth.[4]

Presentation of the case study

We present the case of a 75-year-old Caucasian woman with a history of thymoma with pleural involvement undergoing palliative chemotherapy. The patient consulted for a one-month course of sad mood and incoherent speech with floating anxiety and disorientation in public spaces, without delirious ideation. Due to this issuue, it was considered that she was having a depressive episode with anxious symptoms. She was started on escitalopram 10 mg and alprazolam 0.5 mg, both in daily doses. Two weeks after the start of treatment, the patient became irritable and at times presented euphoric affect associated with affective lability. Subsequently, she attended an outpatient follow-up, in which the presence of a major neurocognitive disorder was suspected, so alprazolam was discontinued and the dose of escitalopram was increased in conjunction with quetiapine (20 mg per day and 25 mg per day, respectively). Fifteen days later, the patient returned to the emergency department due to an exacerbation of affective symptoms, presenting logorrhea, hyperthymia, seductive attitude, hyperprosexia and megalomanic delusions.

As pathological history, the patient presented arterial hypertension, hypothyroidism and OSAHS, under management with levothyroxine, valsartan and amlodipine. In the general physical and neurological examination, there were positive findings of dysprosexia, bilateral ideomotor apraxia and perseverative behaviors. On admission mental examination, the patient showed hyperfamiliar and intrusive attitude, logorrhea, hyperprosexia, exalted affect, tachypsychia, loose association of ideas, and megalomaniacal delusions, with marked motor restlessness.

In the paraclinical analysis, a thyroid profile was requested (TSH 0.19 mIU/L, free T4 1.4 nmol/L, free T3 3.27 nmol/L), which revealed positive antithyroid thyroglobulin antibodies (301.36 IU/mL). In the cerebrospinal fluid (CSF) analysis, acellular hyperproteinorrhea with positive oligoclonal bands was found, without identification of antibodies (EUROLINE immunoblot test for paraneoplastic syndrome amphiphysin, CV2, PNMA2, Ri, Yo, Hu, Recoverin, SOX1, Titin, Zic4, GAD65 and indirect immunofluorescence test in HEK293 cells NMDA, AMPA 1 and 2, GABA B1/B2, LGI2-CASPR2, DPPX). MRI with gadolinium showed no intracranial lesions suggestive of secondary neoplastic processes (Figure 1), as well as telemetry, which showed no abnormal traces.

It was concluded that the patient had a late-onset first episode of mania with a Young's scale score of 35 for the evaluation of mania, in the context of an underlying neoplastic disease. As a first diagnostic possibility, an intermediate-risk phenotype paraneoplastic syndrome was considered (Table 1). Therefore, management with methylprednisolone, 1 g daily for 5 days, and immunoglobulin at a dose of 0.4 g/kg/day for 5 days was indicated.

Likewise, management with escitalopram and quetiapine was suspended, and the administration of valproic acid, 750 mg per day, and olanzapine, 5 mg per day, whose doses were increased to 1000 mg per day and 25 mg per day, respectively, for the control of manifest symptoms, was started. Secondary to the treatment with corticoids, exacerbation of the affective symptomatology was evidenced, with increase to 38 points in Young's scale, which presented improvement at the end of such management without psychopharmacological adjustments. Considering the adequate clinical evolution and the improvement of symptoms, hospital discharge is indicated with maintenance of valproic acid, 1000 mg per day, and olanzapine, 20 mg per day. The patient was discharged with a Young scale score of 11. No neurocognitive tests were performed during hospitalization. Since discharge, the patient presented resolution of affective and psychotic symptoms. The dose of olanzapine was progressively reduced to 5 mg daily due to somnolence. Additionally, during outpatient follow-up, the Montreal Cognitive Assessment (MoCA) was performed, in which the patient obtained a score of 23/30, with presence of failures in working memory and executive functions that do not compromise basic activities of daily living.

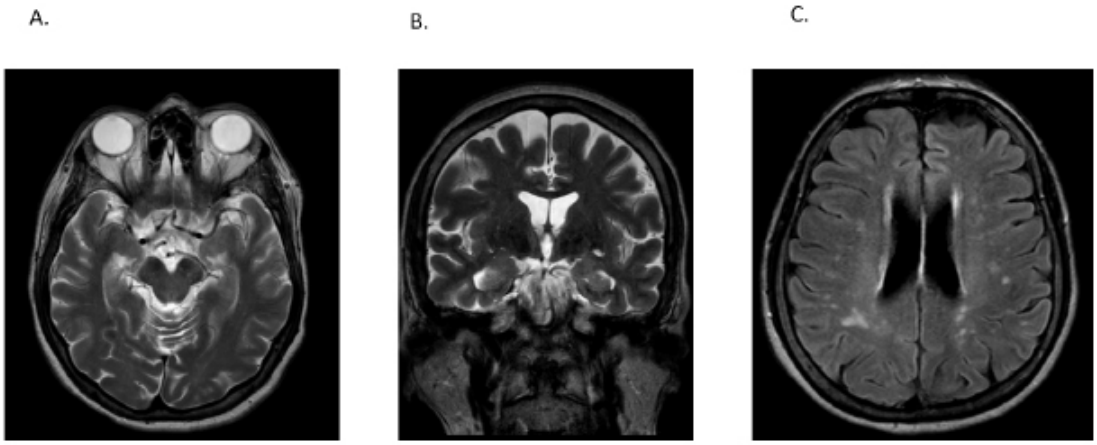

Figure 1. Brain magnetic resonance imaging. A) Axial T2-weighted view without evidence of hyperintensities at the temporal level and without appreciable volumetric alterations. B) Coronal T2 scan without evidence of hyperintensities at temporal level. C) Axial FLAIR section with evidence of multiple hyperintensities in white matter of posterior predominance Fazekas I.

Discussion

This case shows the appearance of a manic picture with late-onset psychotic symptoms in a patient with an unresectable neoplastic process under palliative and antidepressant management, without chemotherapy and without brain invasion. This patient had no personal or family history of affective disorders. As part of the diagnostic process, it was considered unlikely that this episode was part of a primary mental disorder, so secondary causes were sought,[2] particularly neurological, due to evidence of high correlation with neurological conditions in the patient's age group.[1] The diagnostic evaluation ruled out the possibility that the patient was in delirium and that she had metabolic or toxic alterations or vitamin deficiencies as possible causes of the picture. Additionally, metastatic brain involvement or primary infectious processes at the cerebral level were ruled out. Previous medications taken by the patient were also reviewed, and the possibility was raised that antidepressant management was a contributing factor in the turnaround, since antidepressant-induced mania represents a latent risk. However, there is not much evidence that this occurs in later stages of life, and it is considered that the early ages are those at greatest risk for turning,[15] and that this risk depends on the antidepressant used.[16]

At a neuroimaging level, hyperintensities of occipital predominance were evidenced, without the presence of concomitant acute or subacute processes. Because of this, the possibility of vascular mania was contemplated.[17] However, there are limitations in the clinical use of this concept due to the limited availability of case reports, which do not always present a relationship between the development of neurological symptoms and the manifesting symptoms, nor uniform criteria on what to consider as significant lesions. Because the patient had lesions characterized as Fazekas I, and given the possibility of confounding factors due to the association between

Table 1. Differential diagnoses according to various criteria[5,7,8]

	Present	Absent
Possible autoimmune encephalitis (must meet all three criteria	Rapid progression (less than 3 months) of psychiatric symptoms. At least one of the following: pleocytosis (leukocyte count > 5 cells/mm3), de novo CNS focalization, de novo seizures, MRI findings suggestive of encephalitis. Reasonable exclusion of alternative causes.	
Probable autoimmune encephalitis (negative antibodies)	Rapid progression (less than 3 months) of psychiatric symptoms. Absence of specific antibodies in serum and CSF. Pleocytosis, oligoclonal bands or increased CSF IgG index. Exclusion of other well-defined types of autoimmune encephalitis.	Absence of specific antibodies in serum and CSF, and at least two of the following: - MRI abnormalities suggestive of autoimmune encephalitis. - Brain biopsy showing inflammatory infiltrates and excluding other syndromes.
Psicosis autoinmune posible (primer criterio + uno de los siguientes)	Current or recent diagnosis of paraneoplasia. Current psychotic symptoms of abrupt onset (< 3 months).	At least one of the following: - Movement disorder (catatonia or dyskinesia). - Adverse response to antipsychotics, suspicion of neuroleptic malignant syndrome. - Severe or disproportionate cognitive dysfunction. - Decreased consciousness. - De novo seizures. - Clinically significant dysautonomia.
Hashimoto's encephalitis	Normal MRI or with non-specific abnormalities. Positive antithyroid antibodies. Absence of specific neuronal antibodies in serum and CSF.	Subclinical or mild thyroid disease (usually hypothyroidism). Encephalopathy with seizures/myoclonus/hallucinations/stroke-like episodes. Reasonable exclusion of other alternative causes.
PNS Care Score: 6 points (intermediate risk phenotype 2 and presence of cancer 4).	Probable paraneoplastic neurological syndrome.	

cardiovascular risk factors, late-onset mania, and late-onset mania, the patient's neurological symptoms were not always related to the development of neurological symptoms and the development of neurological symptoms.[18] and white matter hyperintensities, not specific to manic syndrome,[17] this has not been considered as an etiological factor, but rather as a vulnerability factor.

On the other hand, the presence of positive anti-thyroglobulin antibodies was evidenced, which raised the possibility of Hashimoto's encephalopathy, which implies difficulties at the time of diagnosis, since its clinical presentation may be similar to other autoimmune encephalitis. However, the patient did not meet the criteria for this pathology, which occurs in 13% of the healthy population.[6]

Due to these factors, immune-mediated etiology continued to be one of the most probable.[8]

The patient, when evaluated according to the PNS-Care Score, reached a classification of possible encephalitis with an intermediate risk phenotype (Table 1). She also presented findings suggestive of inflammation at the CSF level. One of the difficulties involved in these criteria is the need for compliance with autoimmune encephalitis without considering autoimmune psychosis as part of the criteria,[5] as well as the potential limitations in purely psychiatric presentations.[9] On the other hand, there were difficulties in the treatment, since it should have included resection of the neoplasm and management with chemotherapy, which, due to the characteristics of the involvement, were not performed.

Conclusions

Late-onset mania poses a challenge to the clinician due to its high association with general health comorbidities, such as cardiovascular risk factors and neurological diseases, as well

as its heterogeneous presentation within a clinical spectrum with multiple etiological possibilities. Such challenges are heightened in the context of a concomitant neoplastic process. Due to the age of onset and the subacute course, with no significant history of vulnerability, the search for secondary causes is central in this case.

However, the determination of the etiologic agent was hampered due to the multiple factors that interact centrally to assign the phenotype. As a first working diagnosis, an immune-mediated etiology is presented, in which the absence of antibodies could be a reflection of the lack of knowledge of the underlying pathophysiological mechanisms, and lead to the underestimation of this type of cases.5 This raises the importance of continuing the description and study of this type of pathologies, in which psychiatric symptoms predominate,19 without presence of seizures, with alterations in the neurological examination not explained by psychiatric symptomatology and no evidence at the time of a concomitant neurodegenerative process.

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