



## CASE REPORT / CASO CLÍNICO

# Organic Psychosis in a Patient with an Atypical Carcinoid Tumor of the Lung Psicose Orgânica em Doente com Tumor Carcinoide Atípico do Pulmão

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### Abstract

Psychiatric manifestations are present in at least one third of cancer patients. Notwithstanding, less than 50% are properly followed-up. This article contributes to the scarce existing literature on psychotic symptoms in patients with neuroendocrine tumors - a rare presentation of a rare disease. It emphasizes a possible association between carcinoid tumor of the lung and psychotic symptoms, discusses the differential diagnosis and presents an effective psychopharmacological therapeutic option, never published before, to the best of our knowledge.

We report the case of a female 69-year-old patient with an atypical carcinoid tumor of the lung and no previous psychiatric history. The clinical picture was characterized by paranoid and reference delusional ideas, with acoustic-verbal hallucinatory activity, with secondary depressive mood and extreme anxiety. An organic psychosis was admitted with probable relationship with her neoplastic disease and was treated with aripiprazole, with good response and tolerance.

### Resumo

Manifestações psiquiátricas estão presentes em pelo menos um terço dos doentes com cancro. Apesar disso, menos de 50% são devidamente acompanhados. Este artigo contribui para a escassa literatura existente sobre sintomas psicóticos em doentes com tumores neuroendócrinos - uma apresentação rara de uma doença rara. Enfatiza uma possível associação entre tumor carcinoide do pulmão e sintomas psicóticos, discute o diagnóstico diferencial e apresenta uma opção terapêutica psicofarmacológica eficaz, nunca publicada, até onde sabemos.

Relatamos o caso de uma doente de 69 anos com um tumor carcinoide atípico do pulmão, sem história psiquiátrica prévia. O quadro clínico caracterizou-se por ideias delirantes paranoides e autoreferenciais, atividade alucinatória acústico-verbal, humor depressivo e ansiedade extrema secundários. Foi admitida uma psicose orgânica em provável relação com a sua doença neoplásica, que foi tratada com aripiprazol, com boa resposta e tolerância.

**Keywords:** Aripiprazole; Carcinoid Tumor/complications; Carcinoid Tumor/psychology; Lung Neoplasms/complications; Psychotic Disorders/drug therapy; Psychotic Disorders/etiology

**Palavras-chave:** Aripiprazol; Neoplasias do Pulmão/complicações; Perturbações Psicóticas/etiologia; Perturbações Psicóticas/tratamento farmacológico; Tumor Carcinoide/complicações; Tumor Carcinoide/psicologia

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## INTRODUCTION

Lung carcinoid tumors are rare tumors originating in lung neuroendocrine cells.<sup>1</sup> Although infrequent, their incidence has been increasing in the recent decades,<sup>2</sup> currently 2 per 100 000 inhabitants.<sup>3</sup> About 30% are functionally active due to the release of biogenic amines into the bloodstream, giving rise to carcinoid syndrome.<sup>2,4</sup>

Cancer patients are more likely to have psychiatric comorbidities compared to the general population.<sup>2</sup> Psychiatric manifestations are present in at least one third of these patients. Nevertheless, it is estimated that less than 50% are identified and properly followed-up.<sup>5</sup> This potentially worsens global outcome due to its association to worse quality of life and increased mortality.<sup>6</sup> In the evaluation of psychiatric symptoms in cancer patients, the first aim should be to clarify whether the symptoms represent: a normal reaction to a life-threatening disease; a psychiatric disorder; a manifestation of the neoplasm itself or a consequence of its treatment.<sup>5</sup>

Some studies have examined the presence of psychiatric symptoms in patients with carcinoid tumors, most of which have shown a relationship with anxiety and depression, although there is very little information about association with psychosis.<sup>2,6</sup> In articles that report a relation between carcinoid tumors and psychosis, most of them are caused by carcinoid syndrome<sup>7</sup> or hypercortisolism. There are two cases in which there was no association with these causes, but whose resolution of psychotic symptoms was obtained with surgical removal of the tumor and not with psychotropic drugs.<sup>8,9</sup> There is only one published case report in which a previously diagnosed neuroendocrine tumor associated with psychotic symptoms was treated with an atypical antipsychotic. However, this article does not describe which work up or etiological investigation was made.<sup>10</sup> Primary psychiatric disorders are generally an exclusion diagnosis, so we think that it is crucial to run an investigation in order to exclude a treatable underlying cause for psychotic symptoms.<sup>11</sup>

Although psychiatric symptoms/syndromes may arise during any phase of neoplastic disease,<sup>5</sup> many of the published papers report psychiatric symptoms that arise before the diagnosis of the neoplasm.

The present clinical case contributes to the scarce existing literature on psychotic symptoms in patients with neuroendocrine tumors - a rare presentation of a rare disease. It emphasizes a possible association between carcinoid tumor of the lung and psychotic symptoms, discusses the differential diagnosis and presents an effective psychopharmacological therapeutic option (aripiprazol), never published before, to the best of our knowledge.

## CASE REPORT

We report the case of a 69-year-old Caucasian female patient, without personal or family history of psychiatric disease, with an atypical carcinoid tumor of the lung, diagnosed in 2013, with slow progression, with intercostal invasion and severe chronic pain. Her daily medication included: zolpidem 10 mg id, everolimus 10 mg id, fentanyl

75 mcg 3/3 days, gabapentin 2400 mg / day, duloxetine 60 mg bid; and fentanyl 400 mcg SOS – this medication had been started several years ago without recent changes or *abuse* of the SOS drug that the patient avoided using. Her disease was stable according to recent biological markers, thoracic computed tomography (CT) scan and PET exams. A brain magnetic resonance imaging (MRI) with contrast was recently performed, showing that there were no changes in the cerebral, cerebellar or brainstem parenchyma, suggestive of secondary neoplastic lesions.

The patient was clinically stable, without psychiatric symptoms until 29/11/2019 when, without any identified precipitant, she first felt like being followed by cars and people. The patient was not observed or treated until she reported at a Psychiatry appointment, at the Psychiatry and Mental Health department of Hospital Garcia de Orta, on February 12<sup>th</sup>, 2020, at 9h30 a.m., that “People go to the stairs of my house. They show up with wigs... but nobody sees or believes me” sic. She accuses her husband, daughter and granddaughter of being involved in a scheme. She heard them make comments, when she is alone, like “she is not well, let’s go!” sic to which she replied, “don’t hurt me!”. She has run away from home, on two occasions, out of fear. She also complained about a depressive mood with decreased appetite and energy, intermediate insomnia and a progressive increase in anxiety, present for one week, without weight loss or other depressive symptoms. The depressive and anxiety symptoms seem to have arisen after feeling hit by this scheme.

At the appointment the patient was alert, oriented in all spheres and collaborating, although extremely anxious, showing marked signs of onychophagy. Attention and concentration were not disturbed. Her mood was depressive. She had no speech/language changes and no formal/course though disorder, but showed paranoid and reference delusional ideas, delusional interpretations, acoustic-verbal hallucinatory activity in the form of a commentary and possible visual hallucinations, with significant behavioral and emotional impact. Her insight was partial, recognizing the depressive and anxious symptoms but not the psychotic symptoms, accepting treatment with direct transition from de psychiatry appointment to the psychiatry ward, in a general hospital. The psychotic symptoms and the antipsychotic treatment efficacy were assessed using the positive and negative syndrome scale (PANSS). At admission her PANSS total score was 68.

In the Psychiatric inpatient unit, we carried out an extensive research on the possible etiology of her psychosis, with collaboration with Neurology, Oncologic Pneumology and Endocrinology. Hypercortisolism/altered ACTH, thyroid dysfunction, changes in vitamin B12 and folic acid levels, creatinuria or 24-hour urinary cortisol were excluded. The electroencephalogram concluded mild to moderately slow electrogenesis, diffusely and posed the possibility of brain metabolic disorder. The electrocardiogram did not show any variations.

We excluded infectious diseases (HIV, syphilis and hepatitis B and C), vitamin deficits, toxic substances and causes of delirium in cancer patients such as delirium related to

disease progression, to pharmacological changes, especially opioids and to infectious causes, among others.

A lumbar puncture was performed and cytochemical, microbiological and anatomopathological exams revealed no changes. The workup for autoimmune paraneoplastic encephalitis was negative in both serum and cerebrospinal fluid, including neuronal antibodies: ribosome, Hu, Yo, Ri, CV2, PNMA2, amphiphysin, recoverin, SOX1, titin, Ig-LON5, GAD1 (67kD), NMDA, AMPA 1, AMPA 2, DPPX-6, GABA-b, LGI 1 e CASPR 2.

Considering the patient's comorbidity and to minimize the interference between antipsychotic treatment and the neoplastic condition, as well as drug-to-drug interactions (pain medication), the chosen antipsychotic was aripiprazole, initiated with 10 mg per day, at breakfast. Everolimus, fentanyl, gabapentin and duloxetine were kept at the usual dose, and zolpidem was switched by lorazepam 2.5 mg. Seven days later, due to good tolerability and partial response (PANSS total score of 59), aripiprazole was titrated to 20 mg per day. After 20 days her PANSS total score reduced approximately 50%, to 38, with no side effects of the treatment.

At the time of discharge, thirty-three days later, the patient was euthymic, with no anxiety. She kept delusional memories regarding the episode that motivated the hospitalization, but without affective or behavioral impact, with reestablished family bonds. She recognized most of her symptoms (psychotic and anxious) and therapeutic benefits. She was discharged with a PANSS total score of 33 points.

Her oncological situation remained stable and no relationship between psychopathology and everolimus was proved. Curiously, her pain also showed significant improvement since admission, starting at 9 points (in 10) with frequent oral fentanyl, at the psychiatric ward, and 5 points (in 10) at discharge, with no SOS needed. This is probably due to better control of anxiety and depressive mood.

## DISCUSSION

In the reported case, the clinical features were anxiety with onychophagia, depressive mood with decreased appetite and energy, visual hallucinations, and the most prominent clinical features, persecutory and reference delusional ideas, with delusional interpretations, as well as acoustic-verbal hallucinations. No other signs or symptoms of other organ/system were detected; neither changes in state of consciousness, attention, orientation or memory. Floating course and severe changes in the sleep-wake cycle were excluded. According to clinical findings, the considered first diagnostic hypothesis was an Unspecified Organic Psychosis – F09, ICD-10. The presence of anxiety and intermediate insomnia was interpreted as secondary to the described psychotic state.

The late age of occurrence of the first psychotic episode and the absence of personal or family history of psychosis in this clinical case<sup>11</sup> were not suggestive of a classic, functional psychotic illness. Depression with psychotic features was also excluded because depressive symptoms were not the

most prominent, compared to psychotics, and appearing secondary to them both in the form of their appearance and in the resolution associated with the resolution of psychotic symptoms. In addition, the clinical case did not meet criteria for a major depressive disorder. Thus, we tried to clarify the etiology of the psychotic episode. Sudden onset of symptomatology (the patient even reports a specific day for the onset of symptoms) and possible visual hallucinations also point out to the organicity of the clinical picture, notably related to the underlying oncologic disease - carcinoid tumor of the lung - diagnosed about six years ago.

Carcinoid tumors of the lung are usually diagnosed in the fifth or sixth decade of life,<sup>10</sup> corresponding to 1%-5% of all lung tumors<sup>12</sup>; they are more common in women and in Caucasians.<sup>13</sup> Associated psychiatric symptoms occur mainly in the metastatic form of the disease, and depressive symptoms are reported in up to 50% of cases.<sup>10</sup> The onset of psychotic episodes was reported in four cases in the literature,<sup>7-10</sup> showing a rare manifestation.

In neuroendocrine tumors, the etiology of psychosis may be associated to different mechanisms, which may include hormonal effects of the tumor, hormonal effects of octreotide treatment, and possible consequences of systemic metabolic dysfunction.<sup>10</sup> The pathophysiological processes underlying psychosis in these patients may relate to high serotonin levels, particularly when there is carcinoid syndrome, in which large amounts of biogenic amines, such as serotonin, are produced.<sup>4,10</sup> When tryptophan is diverted to this serotonin production, its deficiency can affect the formation of nicotinic acid and protein, precipitating psychiatric manifestations.<sup>14</sup> Another important aspect relates to a deficit in niacin synthesis. The impaired synthesis of niacin is due to the fact that tryptophan - also its metabolic precursor - is mobilized for the production of serotonin in carcinoid syndrome.<sup>10</sup> In this context, some patients may develop pellagra, which can be associated with psychotic symptoms.<sup>10</sup> Despite the understanding of the described aspects, the precise mechanisms for the onset of psychiatric symptoms in these patients have not yet been identified.<sup>10</sup> Research suggests that atypical antipsychotics may be adequate and safe in the treatment of such symptomatology.<sup>10</sup> In our patient, complementary diagnostic tests allowed the exclusion of important disorders, particularly central nervous system metastasis, ~~carcinoid syndrome~~, hypercortisolism and paraneoplastic autoimmune encephalitis. Measurements of serotonin, its metabolites and other catecholamines were not performed as showed no benefit to the presented case, according to multidisciplinary consultation, since the patient had no systemic signs compatible with an increase in amines, because the systemic levels may not reflect imbalances in the central nervous system and because it would not change our approach. Nonetheless without these measurements it is not formally possible to exclude the presence of carcinoid syndrome.

In view of the evidence, the diagnosis at discharge was unspecified organic psychosis, probably associated with neoplastic disease, due to inexistent prior psychiatric history, age of onset, clinical evolution and EEG findings. The

patient was treated with aripiprazole, with good therapeutic response and tolerance.

With this case report, the authors intend to reinforce the possibility of psychotic symptoms in patients with carcinoid tumors, as well as the role of atypical antipsychotics as an effective therapeutic measure. We also suggest

further case studies, since it has not yet been possible to clarify the exact mechanism causing psychosis.

In conclusion, we want to emphasize on the fact that people with similar clinical conditions to those of the patient whose case we reported, are preferably to be committed in a Psychiatric Service, provided that there is support from a multidisciplinary team.

### Declaração de Contribuição

**RG:** Análise e interpretação de dados; concepção do projeto; redação do manuscrito e revisão

**CS:** Análise e interpretação de dados; redação do manuscrito e revisão

**FM:** Análise e interpretação de dados; concepção do projeto; revisão do manuscrito e das suas várias versões

**AR:** Análise e interpretação de dados; revisão do manuscrito e das suas várias versões

### Contributorship Statement

**RG:** Literature searches and analyses; conception of the project; manuscript writing of the first draft and review.

**CS:** Literature searches and analyses; manuscript writing of the first draft and review.

**FM:** Literature searches and analyses; conception of the project, manuscript review and critique.

**AR:** Literature searches and analyses; manuscript review and critique.

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