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Short communication

Paraneoplastic limbic encephalitis with prominent neuropsychiatric apathy

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ABSTRACT

The spectrum of paraneoplastic neurologic syndromes has increased with the description of encephalitis associated with antibodies against cell surface and synaptic proteins. Subacute cognitive impairment, movement disorders, late onset epilepsy and neuropsychiatric syndromes were recently linked to paraneoplastic encephalitis. Despite that, probably some syndromes and antibodies are yet to be reported. Herein we reported the clinical and neuroimaging pictures of a patient with late onset medial temporal lobe epilepsy, subtle cognitive impairment, psychosis and severe apathy diagnosed with antibody-negative paraneoplastic encephalitis due to colonic adenocarcinoma. The apathy markedly improved after removal of the tumor, without concomitant immunotherapy (steroids, intravenous immunoglobulins, immunosuppressants, plasmapheresis, etc.). Our report highlights the importance of a full clinical and neurologic investigation in cases of atypical neuropsychiatric presentations, particularly in the elderly and with the concomitance of epilepsy and cognitive decline. Even chronic presentations must be considered. Neuroimaging is an important tool to demonstrate structural and functional brain dysfunction in these cases. Colonic adenocarcinoma should be searched for in cases in which a typical tumor related to paraneoplastic neurologic syndromes is not found.

1. Introduction

Over the last decade, the spectrum of paraneoplastic neurologic syndromes (PNSs) has increased with the description of encephalitis associated with antibodies against cell surface and synaptic proteins [1]. Apart from the classical PNS such as limbic encephalitis (LE) and subacute cerebellar degeneration, several unknown manifestations such as subacute cognitive impairment, movement disorders, late onset epilepsy and neuropsychiatric syndromes were recently linked to paraneoplastic encephalitis. Special attention has been given to neuropsychiatric syndromes, with some patients that were previously diagnosed with psychosis or schizophrenia for example, been now recognized to have paraneoplastic autoimmune encephalitis [2–4]. Besides the advances in field and expansion of the concept, probably some syndromes and antibodies are yet to be described [5].

Herein we reported the clinical and neuroimaging pictures of a patient with severe apathy diagnosed with antibody negative paraneoplastic encephalitis due to colonic adenocarcinoma (CoA). We describe the two-year follow-up of the case, review the literature about PNS associated with CoA and discuss probable functional mechanism of the symptoms presented by the patient.

2. Case report

A 64-year-old right-handed previously healthy man presented with refractory apathy. His illness started 5 years ago with abrupt episodes of strange feelings described as “agony in the chest” and fear, followed by loss of responsiveness. Sometimes he described a sensation of numbness in his right arm preceding the loss of contact. His wife reported episodes of unresponsiveness in which he stared for a few seconds, occasionally had some “automatic movements” with the hands. After a few minutes, when he returned to full consciousness, he asked the same question several times “Where am I?” He never had a tonic–clonic seizure or a fall. Concurrently, his wife noted emotional blunting and decrease in his energy. He stopped his previous activities and required external stimulus to do regular activities. An order was needed to bath, to groom and even to eat. He became unconcerned about the family problems, even with his own health state. He used to be an active person, with a good sense of humor. During the appointments, despite his wife and daughter's worries, he remained quiet and did not speak spontaneously. When asked if in his opinion he had some health problem, he answered no. He also denied sadness or depressive feelings. He developed a psychotic syndrome characterized by the delusion that the police would invade his home and arrest him because he was

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stealing water from his neighbors' pipelines. He had also auditory hallucinations of people knocking in his door, and became agitated and aggressive with this.

The patient was diagnosed with epilepsy (with partial complex seizures) and psychotic syndrome and medicated with topiramate 100 mg/day and quetiapine 200 mg/day. The episodes of unresponsiveness, delusion and hallucinations improved, but the apathetic state did not. Several trials of antidepressives (sertraline, duloxetine, venlafaxine) were done in full doses, without any response. Topiramate was changed to lamotrigine, quetiapine dosage was reduced, and modafinil was introduced, but he remained apathetic. He was sent for evaluation in a reference center of behavior and cognitive neurology because of his persistent apathy. The diagnostic suspicion was late onset schizophrenia.

Initial evaluation disclosed a normal general and neurologic examination. Mini mental state examination (MMSE) [6] was 29, and his score in the caregiver version of apathy scale was 42 (range from "0" to "42", greater scores indicating more apathy) [7]. Complete neuropsychological and neuropsychiatric evaluations are shown in Table 1 [7–11].

Serum routine screening for cognitive impairment was non-diagnostic. Cerebrospinal fluid analysis was normal, including IgG index and search for monoclonal bands. Electroencephalogram was normal but prolonged recording showed epileptiform activity with projection in the left temporal regions. Magnetic resonance imaging (MRI) revealed subtle hyperintensity and increased volume of the left amygdaloid nucleus, without contrast enhancement. Both hippocampi were normal in intensity and volume. Positron emission tomography with ^{18}F-fluordeoxyglucose (FDG-PET) disclosed mild reduced metabolism in both anterior temporal lobes, more evident in the left side (MRI and FDG-PET are shown in Fig. 1). After these results, we made the diagnostic hypothesis of LE and started the screening for occult neoplasm and onconeural antibodies. Chest and abdomen computed tomography (CT), upper gastrointestinal tract endoscopy, serum and CSF antibodies to anti-Hu, anti-Yo, anti-NMDA, anti-AMPA and anti-GABAb receptor were negative.

After the results, we had planned to do a steroid pulse empirically targeting possible immune mediated LE, but before that, the patient had a lower gastrointestinal bleeding. Investigation with colonoscopy showed a polyp in the hepatic angle of the colon. Biopsy showed well differentiated adenocarcinoma that originated from a high-grade dysplastic tubular adenoma. The patient was submitted to a surgery for resection of the tumor (partial colectomy and termino-terminal anastomosis). Anatomopathological analysis of resected tissue disclosed neoplastic infiltration to the submucosa, preserving the muscle layer of the colon wall, without dissemination to adjacent lymph nodes (N0, Stage 1). After a convalescence period, the patient started to improve from the apathy. He gradually returned to his usual behavior. He returned to do things spontaneously and became concerned about his health. His wife described him as the man he used to be before the illness. His psychotic symptoms disappeared even with the withdrawal of antipsychotics. Table 1 shows neuropsychological and neuropsychiatric evaluation after the resection of the colonic tumor. His score in the apathy scale improved to 5. Despite the improvements in apathy, he still needs an antiepileptic drug (lamotrigine) to control the seizures. In an attempt to progressively taper off the drug, he returned to have the partial complex seizures with exactly the same characteristics of the initial presentation. MRI and FDG-PET (Fig. 1) done 2 years after surgery did not show changes from the first examinations. The patient continues to be followed up in our ambulatory clinic, and remains well after 2 years of the surgery.

3. Discussion

Our patient presented with a LE syndrome with temporal lobe seizures, subtle cognitive impairment and severe neuropsychiatric symptoms (apathy and psychosis). Despite the presence of seizures, mild cognitive impairment and psychosis, the most important and difficult to treat symptom was apathy. Neuroimaging helped in the investigation by showing structural and metabolic abnormalities in limbic regions. Despite initial non-diagnostic investigation, a lower gastrointestinal bleeding was the clue to search for a bowel neoplasm. The final diagnostic was paraneoplastic LE due to CoA.

According to the current diagnostic criteria for PNS, our patient is included in one of the definitions of definite PNS; "A non-classical syndrome that resolves or improves after cancer treatment without concomitant immunotherapy, provided that the syndrome is not susceptible to spontaneous remission" [12]. Despite the unusual clinical presentation (severe apathy) and lack of detectable antibodies, the symptoms markedly improved after identification and resection of the CoA, without immunotherapy (steroids, intravenous immunoglobulins, immunosuppressants, plasmapheresis, etc.). Before that, several drugs had shown to be unsuccessful in improving the apathy. This case demonstrates that even a chronic, atypical neuropsychiatric manifestation may be caused by a PNS and that the spectrum of PNS is still open. Probably, several "atypical" presentations are yet to be reported. A high index of suspicion is necessary when evaluating elderly subjects with late-onset behavioral symptoms, particularly with concomitant epilepsy and cognitive impairment. Even tumors that are not commonly related to PNS need to be extensively searched for to exclude malignant disease. Another aspect to be pointed is the duration of the clinical presentation. Our patient had 5 years of duration when first evaluated in our service. This would be atypical for PNSs that usually have a subacute presentation.

PNSs are more commonly associated to certain tumors, such as small cell lung cancer, breast and ovarian cancer, thymoma and Hodgkin's lymphoma [12]. CoA was seldom reported to cause paraneoplastic syndromes [13–15]. Classic LE, subacute cerebellar degeneration, subacute

Table 1
Patient's performance before and after the colonic adenocarcinoma resection.

	Performance before CA resection	Performance one year after the CA resection	Performance two year after the CA resection	Normal values (M and SD)
DRS_Total [8]	121*	129	136	132.5 ± 9.4
Attention	36	37	37	35.3 ± 1.8
I/P	25*	32	32	33.8 ± 4.2
Construction	06	06	06	5.8 ± 0.6
Conceptualization	31	30*	36	35 ± 4.7
Memory	23	24	25	22.5 ± 2.5
FAS [9]	22	25	32	25.3 ± 11.1
RAVLTt [10]	40	41	47	35.8 ± 7.8
RAVLTdr [10]	8	6	9	6.9 ± 2.3
GDS [11]	2	9	4	≤5
Apathy scale [7]	42	20	5	†

AS: Apathy scale; DRS: Dementia Rating Scale; CA: Colonic adenocarcinoma; FAS: Phonemic fluency of words with "F", "A" and "S" in 1 min; GDS: Geriatric depression scale; I/P: Initiative and perseveration subscale of DRS; M: Mean; RAVLTt: Rey auditory verbal learning test total score (sum of learned words in five trials); RAVLTdr: Rey auditory verbal learning test delayed recall (after 30 min); SD: Standard deviation.*Abnormal results in DRS. †Range from "0" to "42", greater scores indicating more apathy.