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Single Case – General Neurology

Paraneoplastic Autoimmune Limbic Encephalitis Associated with an Atypical Carcinoid Tumor of the Lung: A Case Report

Emma Marull Paretas[a] Claudio De Vito[b] Sabina Catalano-Chiuve[a]
Maria-Isabel Vargas[c] Frédéric Assal[a] Patrice Lalive[a, d] Claire Bridel[a]

[a]Division of Neurology, Department of Neurosciences, Faculty of Medicine, Geneva University Hospitals, Geneva, Switzerland; [b]Division of Clinical Pathology, Geneva University Hospitals, Geneva, Switzerland; [c]Division of Diagnostic Neuroradiology, Department of Radiology, Geneva University Hospitals, Geneva, Switzerland; [d]Division of Laboratory Medicine, Department of Diagnostic, Geneva University Hospitals, Geneva, Switzerland

Keywords
Cancer · Case report · Cognitive dysfunction · Encephalitis · Magnetic resonance imaging

Abstract
We report the case of a patient with a history of an atypical lung carcinoid tumor who developed a rapidly progressive memory impairment. The clinical presentation as well as brain MRI, cerebrospinal fluid, and laboratory tests led to the diagnosis of seronegative paraneoplastic autoimmune limbic encephalitis. To the best of our knowledge, this is the first case in literature of such association. This case also highlights an exceptionally favorable outcome, both clinically and radiologically, after immunosuppression and tumor removal.

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Introduction

Paraneoplastic autoimmune limbic encephalitis (LE) is a rare immune-mediated neurological syndrome frequently associated with lung neuroendocrine tumors (LNET), particularly small-cell lung carcinoma (SCLC). Neurological prognosis critically depends on the ability to treat the accompanying tumor. Here we report the unusual association between seronegative paraneoplastic autoimmune LE and atypical carcinoid (AC) tumor of the lung.

Correspondence to:
Emma Marull Paretas, Emma.MarullParetas@hcuge.ch

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Early recognition of the paraneoplastic nature of LE and prompt oncological treatment allowed a favorable neurological outcome. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000529846).

Case Report

A 75-year-old woman with a history of hypertension and atypical lung carcinoid was referred to our outpatient clinic for assessment of rapidly progressive memory impairment and topographic disorientation over a few months. The neoplastic disease had been diagnosed 8 years earlier, in 2010, and had been treated surgically. In 2015, a tumoral relapse with mediastinal lymph nodes was diagnosed and treated with surgery and radiotherapy. In 2018, a few weeks before visiting our outpatient clinic, the patient was diagnosed with a second relapse, consisting of isolated hepatic and acetabular metastases. The liver metastasis was confirmed by a liver biopsy and subsequently by a metastasis resection. Histology and immunohistochemistry showed tumor cell proliferation with solid and trabecular architecture, focal necrosis, and diffuse positivity for synaptophysin consistent with an AC (shown in Fig. 1).

The initial cognitive assessment showed severe verbal episodic memory impairment and executive dysfunction (Montreal Cognitive Assessment [MoCA] score 16/30). Brain MRI revealed bilateral mesial temporal and insular T2 hyperintensities predominating on the left side, in addition to extensive frontal subcortical vascular leukoencephalopathy (shown in Fig. 2a). An isolated theta element was identified on electroencephalography in the left posterior temporal region. Cerebrospinal fluid analysis revealed mild lymphocytic leucorachia (7 M/L), mild hyperproteinorachia (0.51 g/L), and type 3 oligoclonal bands. Extensive viral workup was unrevealing. Serum and CSF autoantibody screening, including cell surface or synaptic autoantibodies anti-$GABA_B$, -CASPR2, -LGI1 receptor, -AMPA receptor, -NMDA receptor, and intracellular autoantibodies anti-amphyphysin, -GAD65, -Hu, -Cv2/CRMP5, -SOX1, was negative. The diagnosis of definite seronegative paraneoplastic autoimmune LE was retained based on Grau's criteria [1]. The hepatic metastasis was removed, followed by 500 mg of intravenous methylprednisolone daily for 5 days. Radiotherapy was performed on the acetabular metastasis. Infusions of an anti-CD20 monoclonal antibody (rituximab) were initiated and continued for a total of 18 months after metastasis removal, with a total of three doses administered 6 months apart. Three months after surgery and rituximab initiation, the patient's cognitive performance improved significantly (MoCA 25/30). One year after treatment, she was independent in almost all daily activities, requiring help only for administrative tasks. Detailed neuropsychological assessment revealed persistent executive dysfunction but significant memory improvement. Brain MRI showed a notable regression of bilateral mesial temporal lobe hyperintensities (Fig. 2b). Two years after treatment, cognitive performance remained stable despite atrophy of the mesial temporal lobe (shown in Fig. 2c).

Discussion

The association between subacute limbic system dysfunction and bronchial carcinoma was first characterized in 1968. In this seminal paper, Corsellis et al. [2] described the brain post mortem findings of 3 patients who presented with subacute short-term memory deficits and neuropsychiatric symptoms in the context of small- or large-cell lung carcinoma and revisited an additional 8 earlier cases. They found extensive neuronal loss, astrogliosis, and

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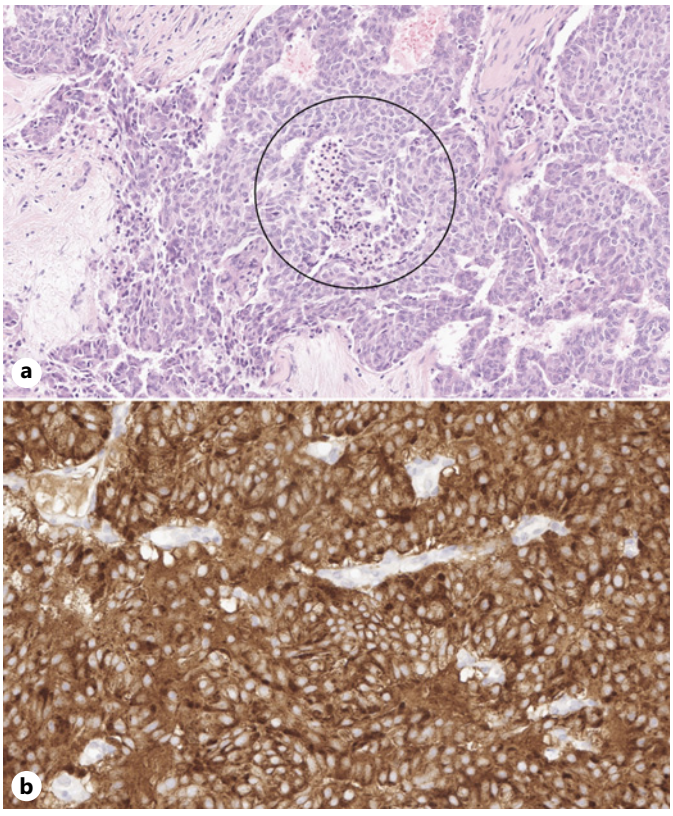

Fig. 1. Histopathological findings. **a** Tumor cell proliferation with solid and trabecular architecture with focal necrosis, consistent with an AC (H&E stain; ×200). **b** Tumor cells stain diffusely for synaptophysin (×400).

mild lymphocytic perivascular inflammatory infiltrates focused in the limbic gray matter bilaterally. Importantly, no spread of tumor cells to the nervous system was identified, and the hypothesis of an immune-mediated etiology was formulated. The identification of autoantibodies directed against antigens shared between the tumor and the nervous system in a majority of patients brought further evidence to support a paraneoplastic autoimmune etiology. Paraneoplastic autoimmune LE is now a well-characterized neurological syndrome, and its prevalence is increasing, probably due to better recognition. In the right clinical and paraclinical setting, detection of an autoantibody is not necessary to retain the diagnosis of definite paraneoplastic autoimmune LE, provided alternative causes have been excluded. Early recognition of its paraneoplastic nature is critical, as the neurological prognosis depends largely on the ability to treat the accompanying tumor promptly.

Paraneoplastic syndromes occur in association with multiple neoplasms, predominantly SCLC, a type of LNET. LNETs are a group of tumors with multiple grades of malignancy originating from pulmonary neuroendocrine cells, also known as Kulchitsky cells, in the bronchial epithelium. The World Health Organization (WHO) classification of 2021 includes low- and intermediate-grade typical carcinoid and AC, respectively, and high-grade carcinomas, such as SCLC [3]. Carcinoid tumors represent approximately 1–3% of all primary lung neoplasms, ACs being the least common and having worst prognosis compared to typical carcinoids [4]. However, the 5-year survival rate is overall higher for carcinoid tumors compared to SCLC, regardless of their stage [5].

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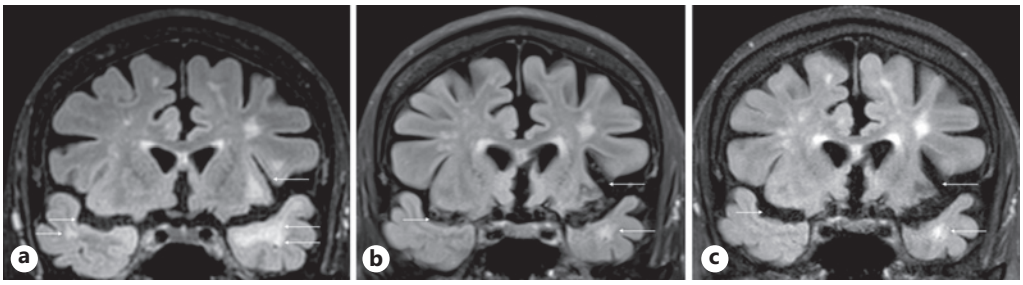

Fig. 2. Coronal FLAIR sequences show a hypersignal in the left and right temporal lobes as well as a cortico-subcortical atrophy of both temporal lobes, which are subtle in the baseline MRI (**a**) and increase on a 13-month (**b**) and a 21-month (**c**) follow-up MRI.

We report the case of an unusual association between a seronegative paraneoplastic autoimmune LE and an AC tumor of the lung with a favorable outcome after metastasis resection performed 4 months after onset of neurological symptoms and rituximab treatment. Significant cognitive improvement 3 months after surgery was observed, particularly in memory, and it continued to improve up to 1 year after treatment. We found 3 other cases of an association of LE and carcinoid tumors. In the first report of LE and midgut carcinoid, no autoantibodies were searched [6]. In the second, anti-Ri antibodies were detected in a patient with lung carcinoid tumor [7], whereas in the third report describing an association with thyroid carcinoid, none was identified despite extensive screening [8]. Together, these reports underscore the importance of considering paraneoplastic autoimmune LE in tumors not classically associated with such syndromes.

Paraneoplastic LE has also been described in two cases of squamous cell carcinoma [9, 10], another non-SCLC. In both, the course was favorable immediately after cancer treatment. However, the course proved fatal in the first case after 8 months due to cancer progression and a LE relapse. In the second case, no information is provided regarding the long-term course. This suggests that the better outcome of our case might also be linked to a less aggressive oncologic disease.

Conclusion

Our case showcases an exceptionally favorable outcome of a paraneoplastic LE associated with a carcinoid tumor of the lung after a combination of tumor removal and immunosuppression with rituximab. This result is even more remarkable given that paraneoplastic LE usually shows a poor response to immunosuppressive agents.

Statement of Ethics

All authors declare that this study was performed in line with the principles of the Declaration of Helsinki. Ethical approval was not required for this study in accordance with local guidelines. A written informed consent was obtained from the patient for publication of the details of her medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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This case report did not receive any funding.

Author Contributions

Emma Marull Paretas and Claire Bridel prepared the manuscript and reviewed the patient data. Maria-Isabel Vargas provided and reviewed patient imaging. Claudio De Vito performed the histological examination of the sample and provided one of the figures. Sabina Catalano-Chiuve and Frédéric Assal provided the neuropsychological assessment results and reviewed the manuscript. Patrice Lalive reviewed and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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