

## Case report - Thoracic oncologic

# Paraneoplastic extra limbic encephalitis associated with thymoma

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### Abstract

We report the case of a 55-year-old woman with thymoma diagnosed after finding of extra limbic encephalitis. She presented neurologic symptoms as seizure and aphasia; magnetic resonance imaging (MRI) of the brain showed multiple lesions located in insular, parietal and temporal lobes (in cortical and sub-cortical area). Brain biopsies confirmed the diagnosis of encephalitis and CT-scan of the thorax showed an anterior mediastinal mass suspected for thymoma. The patient was submitted to thymectomy through a median sternotomy and we assisted to secondary reduction of cerebral lesions and total remission of symptoms.

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**Keywords:** Thymoma; Paraneoplastic neurologic syndrome; Extra-limbic encephalitis

### 1. Introduction

Paraneoplastic neurologic syndromes (PNS) are a rare group of several disorders resulting from damage to the nervous system in the setting of cancer, remote from the site of tumour and not related to metastasis, infection, or metabolic derangements otherwise associated with cancer [1]. They are considered to be the result of direct damage to neural tissue through an immune-mediated mechanism. PNS may affect either central or peripheral nervous system or both [2].

Thymoma, the most common neoplasm of the anterior mediastinum, is often associated with myasthenia gravis and neuromyotonia, but the association with other PNS is quite uncommon. Thymoma-associated limbic encephalitis is a very rare PNS (about 30 cases reported), but extra-limbic encephalitis was described in literature only exceptionally [3]. Radical surgical resection of thymoma is the mainstay of treatment and assures a good long-term prognosis and remission of symptoms correlated with PNS.

### 2. Case report

A 55-year-old woman was admitted to our hospital with neurologic symptoms as seizure and aphasia; physical examination findings were normal except for an ipotonic areflexive paralysis of the right upper arm secondary to a peri-partum brachial plexus damage. Baseline haematological and biochemical investigations were normal; a lumbar puncture revealed a normal cerebral spinal fluid without cytologic, immunologic or infectious abnormalities. EEG

showed focal epileptic discharges in temporal-parietal left region. Magnetic resonance imaging (MRI) of the brain revealed multiple lesions located in insular, parietal and temporal lobes (in cortical and sub-cortical area) including limbic and extra limbic system (Fig. 1a). Autoimmune serological examinations were negative. Brain biopsies were performed and confirmed the diagnosis of encephalitis. In view of the suspect of a PNS, a total body CT-scan was performed. CT of the thorax revealed a well demarcating anterior mediastinal mass, 5 cm diameter, suspected for thymoma (Fig. 2). Serum anti-acetylcholine receptor antibodies, antineuronal nuclear antibodies (Hu/Ri) anti-Purkinje cell antibodies (Yo) were normal and the patient did not present any myastenic symptoms. Therefore, she was brought to our attention with the diagnosis of paraneoplastic extra limbic encephalitis associated with mediastinal mass. <sup>18</sup>F fluoro-2-deoxy-glucose (FDG)-positron emission tomography scan was positive only in anterior mediastinum with SUV of 6.0. She underwent a radical thymectomy through a median sternotomy. Post-surgical course was uneventful and the patient was discharged on the 7th postoperative day. The histological examination confirmed the diagnosis of A-B thymoma (WHO) with minimal extra capsular invasion of fatty tissue (Masaoka stage II B). A week after the operation we assisted to a total remission of symptoms. One month after surgery, MRI showed a secondary reduction of cerebral lesions (Fig. 1b). Therefore, the patient underwent radiotherapy (50 Gy) to the mediastinum. At the last surgical follow-up, six months after thymectomy, the patient was still asymptomatic and disease free.

### 3. Discussion

PNS may be defined as disorders of the nervous system that occur as a result of malignancy but are not caused by

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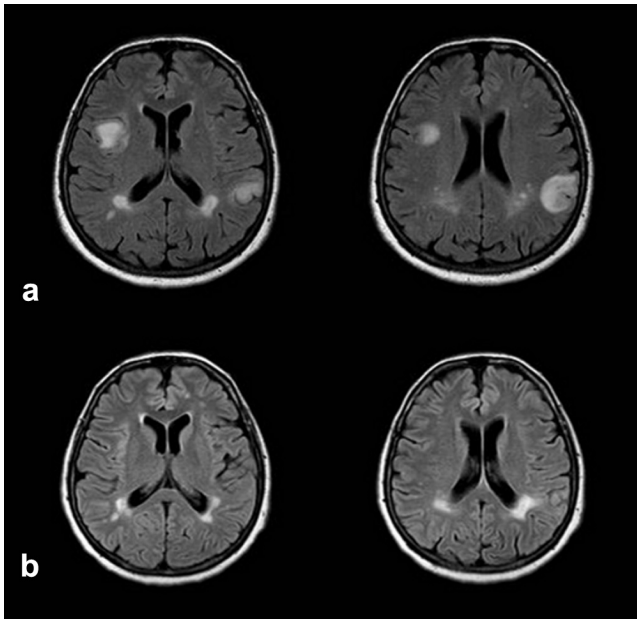


Fig. 1. Magnetic resonance imaging (MRI) of the head T2 flair (a) before therapy revealed multiple lesions. (b) After thymectomy resolution of cerebral lesions.



Fig. 2. Computed tomography (CT) of the thorax: a well demarcating anterior mediastinal mass, histology will confirm a thymoma.

direct tumour growth, metastases or metabolic or infectious complications [4].

Thymoma occurs often with paraneoplastic myasthenia gravis, but is rarely associated with encephalitis with brain lesions that usually are confined to the limbic system. We reported what seems to be the 5th case of a biopsy proven extra-limbic encephalitis associated to thymoma. None of the four previous reported cases, as in our case, had over encephalitis myasthenia gravis too, but three were positive for AchR antibodies [3]. The brain biopsy should not be necessary in all cases and the knowledge of the possibility

of inflammatory lesions associated with neoplasm should lead to research it. Nevertheless, it is not always simple to make a precise diagnosis on MRI images and the biopsy can help in differential diagnosis.

Symptoms are not specific, as well as seizure and aphasia in our case, and it is important to rule out metastatic central nervous system disease and multiple sclerosis. Actually, the treatment is very different and there is the necessity to discover and treat the primary cancer. Prompt detection and treatment of the underlying tumour offer the best chance of cure and the neurologic symptoms may improve with the eradication of the primary disease [5].

The pathogenesis of PNS is not well known: apparently these uncommon group of disorders are caused by immune responses primarily directed against onconeural antigens of an underlying neoplasm that cross-reacts with proteins expressed in the peripheral or central nervous system [6]. Over the years certain clinical presentations have been found to represent classic PNS and to be associated with certain malignances and well-characterized antibodies (e.g. myasthenia gravis and thymoma) [2]. There is, however, significant variability: not all patients with PNS have paraneoplastic antibodies, as in our case, and not all patients with paraneoplastic antibodies have PNS.

Besides the more frequent myasthenia gravis other PNS associated with thymomas are limbic encephalitis, neuromyotonia, peripheral neuropathy, inflammatory myopathy, subacute hearing loss, psychosis and sleep disorders [2]. In these cases, in our opinion, it is mandatory to investigate a mediastinal mass and research immunological markers such as antibodies anticollapsin response mediator protein (CV2-CRMP5), antiampiphysin or neuropil antibodies of the hippocampus or cerebellum.

In conclusion, treatment for extra-limbic encephalitis secondary to a PNS should be directed at underlying disease; a radical resection should be the target to obtain local control and clinical improvement.

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#### References

- [1] Darnell RB, Posner JB. Paraneoplastic syndromes affecting the nervous system. *Semin Oncol* 2006;33:270-298.
- [2] Toothaker TB, Rubin M. Paraneoplastic neurological syndromes: a review. *Neurologist* 2009;15:21-33.
- [3] Okita K, Matsukawa N, Hattori M, Yamada K, Takada K, Yamawaki T, Yoshida M, Hashizume Y, Ojika K. Recurrent limbic and extralimbic encephalitis associated with thymoma. *Clin Neurol Neurosurg* 2007;109:206-209.
- [4] Chaudhry MS, Waters M, Gilligan D. Paraneoplastic limbic encephalitis attributable to thymoma. *J Thorac Oncol* 2007;2:879-880.
- [5] D'Avino C, Lucchi M, Ceravolo R, Mussi A, Malandrini A, Annunziata P, Siciliano G. Limbic encephalitis associated with thymic cancer: a case report. *J Neurol* 2001;248:1000-1002.
- [6] Darnell RB. Onconeural antigens and the paraneoplastic neurologic disorders: at the intersection of cancer, immunity, and the brain. *Proc Natl Acad Sci USA* 1996;93:4529-4536.