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LETTER TO THE EDITOR

Paraneoplastic encephalomyelitis revealing burned-out seminoma

Antoine Guilmot[1] · Vincent van Pesch[1] · Thierry Duprez[2] · Philippe Jacquerye[3]

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Dear editor,

Burned-out testicular tumors are characterized by spontaneous regression of the tumor at the primary site [1]. This spontaneous regression has been described in various types of cancer and involve autoimmune mechanisms similar to those induced by immune check-points inhibitors [2]. We herein report a case of a paraneoplastic encephalomyelitis leading to the diagnosis of a burned-out seminoma.

A 52-year-old man without medical history presented with a progressive left hearing loss and vertigo, initially suggesting Meniere's disease. However, further onset of diplopia, balance impairment and a weight loss of 15 kilos required diagnostic re-assessment. Four months after the first symptoms, neurological examination revealed ataxia, multidirectional nystagmus and pyramidal signs. Brain magnetic resonance (MR) examination showed non-enhancing T2/FLAIR hyperintensities in the pulvinar of both thalami (Fig. 1a). Comprehensive infectious work-up, autoimmune, and paraneoplastic serological markers including anti-Ma2 and anti-Ma1 were unremarkable. Cerebrospinal fluid (CSF) examination revealed moderate lymphocytic pleocytosis (26 cells/μL), elevated protein levels (68 mg/dL) and multiple CSF-specific IgG oligoclonal bands. Total-body PET scan showed a single hypermetabolic para-aortic lymph node. The patient was treated by high dose intravenous (IV) corticosteroid pulse-therapy for 5 days and partially improved. Lymph node resection was performed, and histopathology showed seminomatous germ cells. Scrotal ultrasound revealed a right testicular tumor of "burned-out" appearance because of the absence of vascular flow in Doppler mode. Right orchiectomy was performed of which histopathological examination demonstrated a fibrous scar without malignant cells. According to the oncological staging (pT0pN1M0S0, stage II) and considering the patient's clinically altered status, radiation therapy targeting the lumbo-aortic and right iliac lymph nodes was initiated without adjuvant chemotherapy. Two months later, before radiation therapy has been started, the patient was suddenly unable to walk and suffered of arms incoordination. Brain MR revealed an additional T2/FLAIR hyperintense lesion within the brainstem (Fig. 1b) and spinal MR revealed extensive myelitis (Fig. 1c). The patient was re-treated with steroid IV pulse-therapy followed by oral tapering together with cyclophosphamide (1 g monthly for 6 months). The patient developed a weakness of his left arm two months later. Brain MR showed extension of the lesions to the right temporal area (Fig. 1d) and to the homolateral frontal cortex (not shown). A stereotaxic biopsy of the temporal lesion was performed and histology showed moderate T cell infiltration. No oncological recurrence was noted during the follow-up and paraneoplastic screening was again negative. Five sessions of plasmapheresis failed to improve his clinical status. A new relapse occurred five months later with a tonic–clonic seizure. Brain MR showed significant increase in the lesion load (Fig. 1e). Because of the clinical deterioration, palliative care was given. The patient died 3 months later, 16 months after symptom onset.

✉ Antoine Guilmot
antoine.guilmot@uclouvain.be

Vincent van Pesch
vincent.vanpesch@uclouvain.be

Thierry Duprez
thierry.duprez@uclouvain.be

Philippe Jacquerye
philippe.jacquerye@cspo.be

[1] Department of Neurology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium

[2] Department of Radiology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Avenue Hippocrate 10, 1200 Brussels, Belgium

[3] Department of Neurology, Clinique Saint-Pierre d'Ottignies, Avenue Reine Fabiola 9, 1340 Ottignies, Belgium

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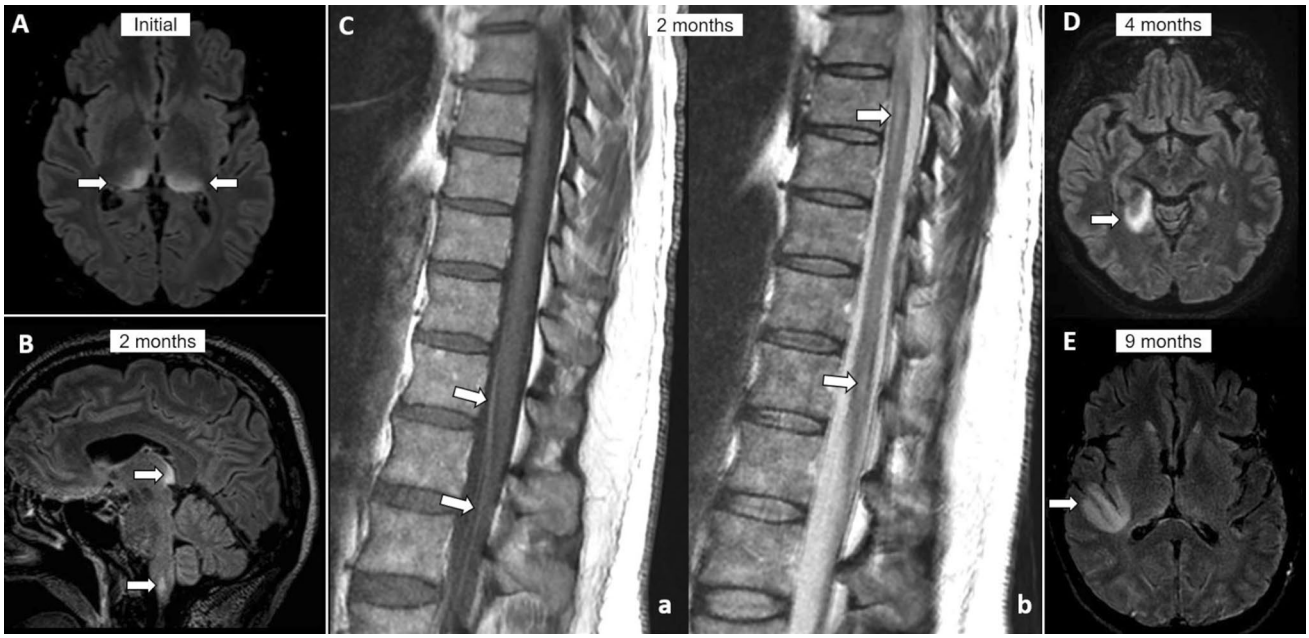

Fig. 1 Neuroimaging evolution**.** On initial brain MR, 4 months after onset of the first symptoms, axial (**a**) post-contrast FLAIR views demonstrated bilateral hyperintensities of the pulvinar (arrows), the posterior area of the thalami. At 2 months, sagittal (**b**) postcontrast T2/FLAIR revealed an additional hyperintense focus in the left medulla oblongata (lower arrow) and unchanged hyperintense signal in the thalami (upper arrow). Sagittal contrast-enhanced T1-weighted view of the dorso-lumbar spinal cord and cauda equina showed abnormal periconal pial and radicular enhancement (arrows in **c**a). Corresponding sagittal T2-weighted view demonstrated abnormal hyperintensities within the cord (arrows in **c**b). Axial post-contrast FLAIR view revealed the extension of the hypersignal to the right para-hippocampic gyrus (arrow) at 4 months (**d**) and to the right insular cortex (arrow) at 9 months (**e**)

Our patient presented a burned-out seminoma associated with encephalomyelitis compatible with a PNS, a cancer-related immune-mediated disorder. Tumors of the testis are commonly associated with anti-Ma2 or Ma1 antibodies, targeting intracellular antigens [3]. It is currently admitted that PNS can occur with a negative antibody screening [2, 4]. Anti-Ma2/Ma1 related-syndromes usually consist of either limbic, diencephalic or brainstem encephalitis or, less frequently, of encephalomyelitis [2–4]. Paraneoplastic autoantibodies to intracellular antigens (onconeuronal) are not thought to have a major pathogenic role but their presence is a marker of an immune-mediated mechanism involving cytotoxic T lymphocytes (CTL) resulting in early and irreversible neuronal cell death [2–4]. Immunomodulatory treatments are therefore less effective compared to disorders related with antibodies against cell-surface antigens [2, 4]. Treating the underlying tumor remains the most effective treatment approach [4]. The same CTL response have antitumor effect which explains that patients often have a more indolent tumor course or even spontaneous regression [2].

Despite complete oncological treatment and immunosuppression, our patient had a persistent and uncontrolled inflammatory disease of fatal issue. This contrast with the generally better prognosis reported in anti-Ma2 associated-PNS and among the very few cases of burned-out seminoma associated-PNS described in the literature [1, 3]. A potential explanation could be the delay before symptom onset and the start of the treatment. It seems that the initial favorable antitumor CTL response turned into a self-sustaining deleterious inflammatory process, given there was no sign of cancer recurrence during the follow-up. This underlines the importance of an early and aggressive immunosuppression therapy to preserve the "neuronal reserve". Scrotal ultrasound should be performed in front of subacute neurological syndrome in men, even if older and with negative screening for paraneoplastic antibodies. Another hypothesis to explain the poor outcome of our patient is a genetic predisposition. Association between specific human leukocyte antigen (HLA) and PNSs have been described and provide an insight into their pathogenesis [5]. Nevertheless, further investigations are needed, for example, through a systematic HLA genotyping and immunophenotyping of such patients. A better understanding of the mechanisms underlying "favorable" (spontaneous regression) versus "deleterious" (autoimmunity) immune reactions is crucial to improve treatment and prognosis of PNS.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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