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Case Report

CASE REPORT

Onconeural antigen spreading in paraneoplastic neurological disease due to small cell lung cancer

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Abstract

Cellular and humoral immunity towards distinct onconeural antigens is the hallmark of paraneoplastic neurological diseases (PNDs). Stable formation of immunoglobulin (Ig) G antibodies to particular onconeural antigens occurs in the majority of cases, whereas persistent coexistence of antibodies specific for multiple onconeural antigens is a relatively rare phenomenon of certain malignant tumors like small cell lung cancer (SCLC). We here describe onconeural antigen spreading in a 70-year-old Caucasian male with PND due to SCLC. Onconeural antigen spreading may be promoted by two mutually non-exclusive mechanisms: (i) a switch of antigen expression pattern of the underlying tumor tissue as a result of a mutagenic process caused by the cancer itself and (ii) a self-propagated paraneoplastic immune response with persistent neuronal destruction, liberation, processing and presentation of intracellular neural antigens. This illustrates a potential dissociation between peripheral anti-tumoral immunity and central anti-neural immunity during the course of PND.

INTRODUCTION

Cellular and humoral immunity towards distinct onconeural antigens is the hallmark of PNDs [1]. Stable formation of IgG antibodies to particular onconeural antigens occurs in the majority of cases, whereas persistent coexistence of antibodies specific for multiple onconeural antigens is a relatively rare phenomenon of certain malignant tumors like SCLC [2, 3]. However, onconeural antigen spreading, i.e. the dynamic appearance and disappearance of distinct onconeural antibodies during the course of PNDs in individual patients has not yet been described.

CASE REPORT

A 70-year-old Caucasian male with a long history of smoking and surgically treated urothelium carcinoma 2 years ago, presented 08/2013 with radicular neuralgia and hypesthesia of the legs, disturbed fine motor skills of the hands and extinction of knee and ankle jerks on both sides, accompanied by abnormal posture and ataxic gait. Nerve conduction studies revealed severe demyelinating and axonal polyneuropathy fulfilling the Inflammatory Neuropathy Cause and Treatment (INCAT) criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Initial MRI of the brain and entire spinal

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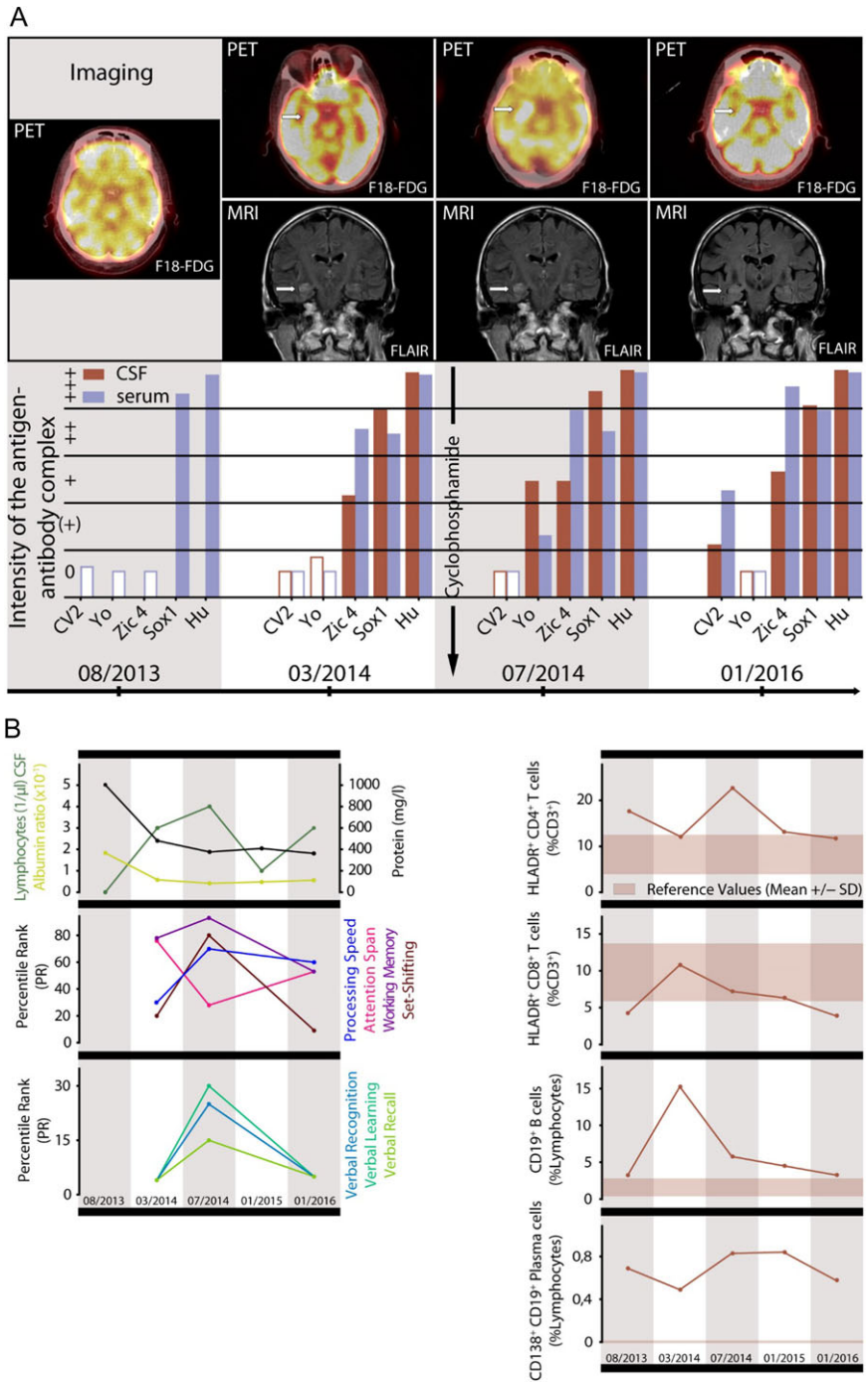

Figure 1: Onconeural antigen spreading in paraneoplastic neurological disease due to small cell lung cancer occurs during continued inflammation. (**A**) Cerebral MRI and FDG-PET/CT (upper panels) illustrate spread of paraneoplastic inflammation from the peripheral to the central nervous system, where it persisted throughout the disease course. White arrows demonstrate persistently inflamed and epileptic temporomesial brain regions exhibiting increased FLAIR signal intensities and volumes together with glucose hypermetabolism. Intensity of the antigen–antibody complex for each of the onconeural antibodies (lower panels) detected in serum (blue) and CSF (red). Uncolored bars present negative results. Black arrow indicates start of cyclophosphamide treatment. (**B**) Time course of routine CSF parameters (lymphocyte counts, albumin ratio, protein; left panels) with relative fractions of activated $HLADR^+$ $CD4^+$ and $CD8^+$ T cells, $CD19^+$ B cells and $CD138^+$ $CD19^+$ plasma cells in CSF (right panels; reference values derived from patients with somatoform disorders are displayed in red (n = 14; Ø = 68.0 years): CSF: $HLADR^+CD4^+$ T cells: 8.22 ± 4.28% of $CD3^+$ cells; $HLADR^+$ $CD8^+$ T cells: 7.06 ± 3.92% of $CD3^+$ cells; $CD19^+$ B cells: 1.59 ± 1.21% of $CD45^+$ cells; $CD138^+$ $CD19^+$ plasma cells: 0.00 ± 0.01% of $CD45^+$ cells) with corresponding results of neuropsychological assessments of executive and memory functions (left panels; percentile ranks 16–10 indicate moderate impairment; percentile ranks <10 indicate severe impairment) as indicated.

cord showed moderate contrast enhancement in fibers of the cauda equine an radices only (not shown). Cerebral (as part of a whole-body) FDG-PET/CT was normal (Fig. 1A). Cerebrospinal fluid (CSF) analysis demonstrated albuminocytologic dissociation (cell count of 0/µl; protein 1003 mg/l; albumin ratio 18.4 × 10^{-3}) and presence of elevated fractions of activated $HLADR^+$

$CD4^+$ T cells and $CD138^+$ $CD19^+$ plasma cells (Fig. 1B) without intrathecal Ig-synthesis or oligoclonal bands (type 1 pattern). The detection of serum onconeural anti-Hu and anti-SOX1 IgG antibodies together with the long history of smoking (Fig. 1A) prompted a detailed tumor search especially for SCLC. Chest-CT showed atelectasis of the middle pulmonary lobe with mediastinal lymphadenopathy. However, whole-body FDG-PET/CT and bronchoscopy with bronchoalveolar lavage and biopsy of suspicious mediastinal lymph nodes revealed no malignancy. Sonography of abdomen and pelvis together with detailed urological examination with cystourethroscopy also yielded no evidence for a cancer relapse.

Approximately 7 months after a short period of symptom improvement under treatment with methylprednisolone pulse therapy and oral taper, the patient presented 03/2014 with progressive gait disorder and cognitive impairment together with temporal lobe seizures. Neuropsychological assessment showed severe memory impairment and executive dysfunction (Fig. 1B). Cerebral MRI exhibited increased T2/fluid-attenuated inversion recovery (FLAIR) signal intensities without contrast-enhancement, and cerebral FDG-PET/CT demonstrated glucose hypermetabolism of the right more than left temporomesial brain region (Fig. 1A). Interictal EEG showed right- more than left-sided temporal slowing in the theta-delta band together with sharp waves and sharp-slow-waves. CSF analysis revealed normal cells counts (3/µl) with normal protein (481 mg/l) and no disruption of the blood/CSF barrier (albumin ratio 5.8×10^{-3}), but intrathecal IgG synthesis (55%) and ≥3 CSF-specific oligoclonal bands (type 3 pattern) together with persistently elevated fractions of activated $HLADR^+$ $CD4^+$ T cells, $CD19^+$ B cells, and $CD138^+$ $CD19^+$ plasma cells (Fig. 1B) [4]. In addition to anti-Hu and anti-SOX1, anti-Zic4 IgG antibodies became detectable in serum and CSF (Fig. 1A). These findings established paraneoplastic limbic encephalitis in addition to demyelinating and axonal polyradiculoneuropathy and illustrate a spread of the paraneoplastic immune response from the peripheral to the central nervous system. Repeated searches for malignancy using FDG-PET/-CT, chest-CT, abdominal sonography, oesophagogastro-duodenoscopy and colonoscopy were unremarkable. Hence, long-term immunosuppressive treatment was initiated using cyclophosphamide (750 mg/m^2 every 4–6 weeks) together with anticonvulsive treatment with levetiracetam (starting with 2 × 500 mg/day).

Clinical and paraclinical follow-up examinations during 22 months of immunosuppressive and anticonvulsive treatment after initial amelioration revealed deteriorating memory and executive functions (Fig. 1B) together with progressive sensory and also cerebellar ataxia and continued temporal lobe seizures prompting enhanced anticonvulsive treatment with levetiracetam (up to 2 × 1000 mg/day). MRI showed persistent hyperintense T2/FLAIR signals of the right more than left mesial temporal lobe without contrast-enhancement together with progressive cerebral and cerebellar atrophy (Fig. 1A). FDG-PET/CT illustrated persistent right temporomesial hypermetabolism (Fig. 1A). Another FDG-PET/CT scan of the whole body did not provide evidence of cancer.

Remarkably, throughout the disease course antigen spreading of the humoral paraneoplastic immune response could be observed. Anti-Hu, anti-SOX1, and anti-Zic4 IgG antibodies persisted whereas anti-Yo IgG antibodies switched to anti-CV2 IgG antibodies in both serum and CSF (Fig. 1A). In 01/2016, ~30 months after disease onset and initial detection of onconeural IgG antibodies, SCLC was confirmed from another biopsy of the previously suspicious middle pulmonary lobe, which at that point showed distinct tracer-enrichment upon the fifth FDG-PET/CT scan. Additional staging yielded limited disease, and the patient received combined radio-chemotherapy with cisplatin and etoposide.

DISCUSSION

Our case represents a typical PND with associated onconeual antibodies which appears a few years ahead of the related malignancy [5]. Multiple coexisting onconeural antibodies are rare, however such clusters of antibodies occur more frequently than previously assumed [2]. Nevertheless, a dynamic switch between distinct onconeural antibody entities during the course of individual PND has not been reported thus far.

In that regard, two pathophysiological scenarios explaining such antigen spreading seem conceivable: First, (mainly peripheral) antigen spreading may be promoted by a switch of antigen expression pattern of the underlying tumor tissue as a result of a mutagenic process caused by the cancer itself [6]. This would explain the appearance of anti-Zic4 and anti-CV2 IgG antibodies (at higher concentrations in serum compared to CSF) adding to anti-Hu and anti-SOX1 IgG antibodies which are all frequently associated with PNDs and typical for SCLC [7]. Second, (mainly central) antigen-spreading may be promoted by a self-propagated paraneoplastic immune response with persistent neuronal destruction, liberation, processing and presentation of intracellular neural antigens. This may be enhanced by persistent epileptic activity of the affected brain tissue and (transient) spread of the intrathecal immune response to other sites of the brain and spinal cord i.e. from the limbic system to the cerebellum in this case. This would explain the transient detection of anti-Yo IgG antibodies (at higher concentrations in CSF compared to serum), that are usually not associated with SCLC and mainly expressed by cerebellar Purkinje neurons [1, 5, 7].

Moreover, a contribution of immunotherapies like cyclophosphamide to the appearance of novel onconeural antibodies during the treatment course due to cytotoxic effects especially on tumor cells (less so on neurons) cannot be excluded.

This illustrates a potential dissociation between peripheral anti-tumoral immunity and central anti-neural immunity during the course of PND which should to be considered for the choice of treatment strategies.

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CONFLICT OF INTEREST STATEMENT

All authors declare no relevant conflicts of interest.

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