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Case study

Paraneoplastic limbic encephalitis with SOX1 and PCA2 antibodies and relapsing neurological symptoms in an adolescent with Hodgkin lymphoma

M. Kunstreich [a,**], J.H. Kreth [b], P.T. Oommen [a], J. Schaper [c], M. Karenfort [b], O. Aktas [d], D. Tibussek [b], F. Distelmaier [b], A. Borkhardt [a], M. Kuhlen [a,*]

[a] University of Duesseldorf, Medical Faculty, Department of Pediatric Oncology, Hematology and Clinical Immunology, Centre for Child and Adolescent Health, Duesseldorf, Germany
[b] University of Duesseldorf, Medical Faculty, Department of Pediatrics and Neonatology, Centre for Child and Adolescent Health, Duesseldorf, Germany
[c] University of Duesseldorf, Institute of Diagnostic and Interventional Radiology, Duesseldorf, Germany
[d] University of Duesseldorf, Medical Faculty, Department of Neurology, Duesseldorf, Germany

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ABSTRACT

Background: Immune cross-reactivity between malignant and normal tissues causes the rare, so called paraneoplastic syndrome (PS). In approximately 60% of the patients, various onconeural antibodies are detectable in the cerebrospinal fluid (CSF) and are associated with typical tumour entities.
Methods: We report an unusual case of paraneoplastic limbic encephalitis (PLE) in a 17-year-old adolescent with classical Hodgkin lymphoma.
Results: He presented with a variety of neurologic and neuropsychiatric symptoms, profound B-symptoms and typical MRI findings including hyperintense lesions with contrast enhancement in the medial temporal lobe and limbic system. Under immunosuppressive therapy and subsequently chemotherapy the neurological situation only temporarily improved and worsened again after interruption of immunosuppression several times. Thus, multiple courses of multidrug immunosuppressive therapy were administered. To date, five years after initial presentation, the young man is able to walk with walking aids and orthoses and is still on oral prednisolone therapy. Analyses of the CSF and serum revealed anti SOX-1 antibodies at initial presentation but PCA-2 antibodies seven months after diagnosis.

Abbreviations: AB, antibodies; CNS, central nervous system; CSF, cerebrospinal fluid; GANS, granulomatous angiitis of the central nervous system; HL, Hodgkin lymphoma; PCA2, Purkinje-antibodies; PLE, paraneoplastic limbic encephalitis; PNS, paraneoplastic neurological syndrome; PS, paraneoplastic syndrome; SCLC, small cell lung cancer.

* *Corresponding author*. Department of Pediatric Oncology, Hematology and Clinical Immunology, Centre for Child and Adolescent Health, Moorenstr. 5, 40225 Duesseldorf, Germany. Fax: +49 211 81 16491/04982.
** *Corresponding author*. Department of Pediatric Oncology, Hematology and Clinical Immunology, Centre for Child and Adolescent Health, Moorenstr. 5, 40225 Duesseldorf, Germany. Fax: +49 211 81 16491/04982.
E-mail addresses: Marina.Kunstreich@med.uni-duesseldorf.de (M. Kunstreich), Michaela.Kuhlen@med.uni-duesseldorf.de (M. Kuhlen).

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Conclusion: Neurologic and/or neuropsychiatric symptoms combined with typical MRI findings should raise the suspicion of PS and lead to further diagnostics for an underlying tumour even in children.

1. Introduction

Paraneoplastic syndrome (PS) is a rare disorder, which arises from immune cross-reactivity between malignant und normal tissues or from tumour secretion of hormones or cytokines. Patients may present with a broad range of endocrine, neurologic, dermatologic, rheumatologic, gastro-intestinal, and haematologic symptoms.[1] It is typical among middle-aged to older patients and most commonly present with cancer of lung, breast, ovaries or lymphoma. Paraneoplastic neurological syndrome (PNS) results from tumour-directed antibodies (so called onconeural antibodies) and associated antigen specific T-lymphocytes, which attack components of the nervous system due to antigenic similarity to developing cancer.[2] PNS can affect the central and peripheral nervous system as well as the neuromuscular junction and is divided into various subgroups. One of them is paraneoplastic limbic encephalitis (PLE) presenting with typical neuropsychiatric symptoms such as acute and subacute mood and behavioural changes, short-term memory deficits, complex partial seizures, and cognitive dysfunction. Hyperthermia, hypersomnia, weight gain, and endocrine dysfunction as signs of hypothalamic dysfunction can likewise occur. In approximately 60% of the patients with PLE, onconeuronal antibodies (ABs) can be detected.[3] The type of autoantibody is mostly characteristic for one distinct tumour entity and, thus, points towards the underlying tumour. E.g. neuronal nuclear anti antigen Hu (anti-Hu) ABs are typically associated with small cell lung cancer (SCLC) and neuronal cell anti antigen Ta/Ma2 (anti-Ta/anti-Ma2) ABs with testicular tumours.[3]

Paraneoplastic syndromes and especially the devastating subgroup of PLEs are very rare during childhood and adolescence.

2. Case study

A 17-years old young man presented with marked reduction of short-term memory, cognitive deficits, disorientation, headache, diplopia, paraesthesia of the right arm and leg, and, subsequently, spastic paraparesis and profound B-symptoms including weight loss, night sweats and fever. Magnetic resonance imaging (MRI) of the central nervous system (CNS) and spinal cord showed hyperintense lesions with contrast enhancement in the medial temporal lobe and limbic system, thus, suggesting limbic encephalitis (Fig. 1A). At that time, blood count, renal and liver function, coagulation and serum electrolytes were within normal range. Erythrocyte sedimentation rate (ESR) was elevated. ANA and ENA screening were positive without proof of specific autoantibodies. Cerebrospinal fluid (CSF) tests revealed pleocytosis (296 cells/μl) and an elevated protein. Viral and microbiologic tests (in blood, CSF, and tracheal secretion) yielded exclusively negative results. His clinical course rapidly worsened with respiratory insufficiency and signs of septic shock needing mechanical ventilation and catecholamine therapy. Various antibiotics were administered empirically. He subsequently suffered from a generalized seizure and developed tetraparesis, neurogenic bladder dysfunction, bowel incontinence, and motoric axonal polyneuropathy. Under immunomodulatory therapy with two courses of high-dose corticosteroids and intravenous immunoglobulins symptoms improved. As paraneoplastic syndrome was suspected, whole body MRI was performed and showed a mediastinal mass. Surgical excision and subsequent histopathological examination revealed Hodgkin lymphoma (HL) of the nodular sclerosis subtype. Treatment according to the EuroNet-PHL-C1 protocol was initiated in risk group II including four cycles of chemotherapy [2x OEPA (vincristine, etoposide, prednisone, adriamycin) and 2x COPDAC (cyclophosphamide, vincristine, prednisone, dacarbazine)] and local radiotherapy to the mediastinum. No intrathecal chemotherapy was administered. The clinical condition profoundly improved under treatment. Retrospective analyses revealed SRY-related HMG-box (SOX) 1 antibodies (according to the testing methods described by Graus et al.[4]) in the CSF and serum from initial diagnostics, whereas anti-Tr, PCA2, ANNA 1/2, Ma1/2, CRMP5, amphiphysin, NMDAR, GABARB1, AMPAR1/2, CASPR2, and LGI2 ABs were tested negative.[3–5] After two cycles of chemotherapy, SOX1 ABs were negative.

Seven months from initial presentation, the patient again presented with neurologic deterioration. MRI revealed new lesions. Relapse of HL was excluded by whole body MRI and PET-CT. Both, CSF and serum were still negative for SOX1 ABs. However, PCA2 (Purkinje-antibodies) anti-neuronal ABs were demonstrated (serum and liquor). Immunomodulatory therapy comprising methylprednisolone and 6 cycles of plasmapheresis improved neurologic symptoms and was followed by immunosuppressive therapy including 2 cycles of cyclophosphamide. Four weeks after start of therapy, PCA2 ABs were tested negative in liquor and serum.

10 months after disease onset, symptoms worsened again. Under 7 cycles of plasmapheresis, the patient's clinical condition improved again but worsened immediately when plasmapheresis was stopped. Thus, intravenous methylprednisolone pulse-therapy (1 g/die for five days) was