CASE REPORT

Acute inflammatory neuropathy with monoclonal anti-GM2 IgM antibodies, IgM- κ paraprotein and additional autoimmune processes in association with a diffuse large B-cell non-Hodgkin's lymphoma

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SUMMARY

Lymphoproliferative disorders are often associated with autoimmune processes preceding or following the occurrence of a lymphoma. Here, we describe a patient with a history of recurrent diffuse large B-cell non-Hodgkin's lymphoma who suffered from an acute inflammatory neuropathy with specific monoclonal anti-GM2 IgM antibodies and associated IgM- κ paraprotein. It was possible in this case to prove that both, anti-GM2 IgM antibodies and IgM- κ paraprotein, share the same binding characteristic. In addition, the patient possibly suffered from an immune thrombocytopenia and an early-stage bullous pemphigoid with anti-BP-230 IgG antibodies. Intravenous immunoglobulin and plasmapheresis alleviated the acute neuropathy and thrombocytopenia, while the bullous pemphigoid has been aggravated. In summary, the simultaneous occurrence of multiple autoimmune processes was a sign of a dysfunctional immune system preceding the relapse of a B-cell non-Hodgkin's lymphoma.

BACKGROUND

Lymphoproliferative disorders are associated with autoimmune processes, for example, haematologic manifestation, rheumatic disease, renal lesions, skin disease or neuropathy, all of those indicating a dysfunctional immune system. Anti-GM2 IgM antibodies are associated with Guillain-Barré syndrome and often occur after cytomegalovirus (CMV) infection. Bullous pemphigoid 230 IgG antibodies (BP-230 IgG) are associated with bullous pemphigoid, an autoimmune blistering skin disease. Paraproteins are monoclonal immunoglobulins or parts of immunoglobulins excessively produced by clonal proliferating plasma cells, often providing evidence for a lymphoproliferative disorder. Sometimes specific antibodies and paraproteins emerge simultaneously. Here, we describe a patient with a history of recurrent diffuse large B-cell non-Hodgkin's lymphoma who suffered from an acute inflammatory neuropathy with specific monoclonal anti-GM2 IgM antibodies and associated IgM- κ paraprotein. In addition, he had signs of a possible immune thrombocytopenia and an early-stage bullous pemphigoid with anti-BP-230 IgG antibodies preceding the relapse of the B-cell non-Hodgkin's lymphoma. The occurrence of multiple autoimmune processes in the context of a

lymphoma is a challenge regarding differential diagnoses as well as therapeutic perspective. There is no common guideline for therapy decisions in this highly complex framework and differential diagnosis can be difficult, especially when the lymphoma itself is not yet detected. Since there are hints that autoimmune processes and lymphoma share similar pathomechanisms, a detailed analysis of single cases can reveal the underlying mechanism of disease manifestations.¹

CASE PRESENTATION

A 75-year-old man was referred to us because of acute progressive cranial nerve palsies, slight ataxia and weakness of the limbs. These symptoms were more pronounced on the right side of his body and started 10 days prior. Three weeks before he had been bitten by a tick. In addition, he suffered from a history of recurrent diffuse large B-cell non-Hodgkin's lymphoma with known persisting monoclonal IgM- κ paraprotein. Therapy of the initial lymphoma (Ann Arbor stage IIIA) had been done according to the R-CHOP scheme (rituximab, cyclophosphamide, hydroxydaunorubicin, Oncovin, prednisone; six cycles) 2 years before. Since the administration of the chemotherapy, the patient has suffered from numbness of his feet. A relapse of the lymphoma on the right neck side had been confirmed 1 year after the initial diagnosis. The relapse had been treated with rituximab and radiotherapy until 4 months before admission to our hospital.

After referring to our hospital, the neurological deficits had progressed within the following 2 weeks. At the peak of the symptoms, he suffered from bilateral facial palsy, complete paresis of the right oculomotor nerve and bilateral paresis of abducens nerve. In addition, he showed weakness of the limbs, more pronounced in legs (Medical Research Council Scale grades 3–4), with areflexia on the legs and weak reflexes on the arms. Four days after admission to our hospital, the patient suffered from a medium-sized (10 cm diameter) itchy erythema with papules in the centre of the lower part of his back, which spread during the next few weeks without signs of blisters, but with a consecutive peripheral eosinophilia.

INVESTIGATIONS

Cerebrospinal fluid (CSF) showed an elevated protein level (peak 5 weeks after first symptoms:

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2360 mg/l) and elevated cell count (peak 3 weeks after first symptoms: 72 cells/ μ l). Nerve-conduction studies showed axonal-demyelinating sensorimotor polyneuropathy accentuated in the legs and the sensory system. We conducted a broad search for possible pathogens because of the elevated cell count, the history of tick bite, the lymphoma as an underlying disease and because of the therapy with rituximab. Rituximab as an anti-CD20 antibody causes B cell suppression and therefore an immune suppression. In addition, we monitored the patient for a relapse of the lymphoma including local tumour infiltration and meningeal dissemination. Analysis of CSF, imaging of head, neck, thorax, abdomen and bone as well as bone marrow biopsy only revealed a known cicatricial tissue bulk on the right side of the neck after radiation ending 3 months before. There were no signs for any infection or for a relapse of the lymphoma at that time point.

Antiganglioside autoantibodies were detected using specific ELISA systems (BÜHLMANN Laboratories AG, Schönenbuch, Switzerland) and a line immunoassay for the multiparametric detection of antiganglioside autoantibodies (Generic Assays GA, Dahlewitz, Germany).² We found an elevated IgM-fraction (6.12 g/l), a biconal IgM- κ paraprotein and a high anti-GM2 IgM antibody titre, but no anti-GQ1b (table 1) and no known paraneoplastic antibodies (Immunoblot for anti-Yo, anti-Hu, anti-Ri, anti-CV2, anti-Ma2 antibodies; ravo Diagnostika, Freiburg, Germany) were found. As shown in figure 1, we could demonstrate that not only the IgM, but also IgM- κ bind to GM2.

TREATMENT

Since increasing albuminocytological dissociation in the CSF was proven, as it is typical for acute inflammatory neuropathy, and because of negative pathogen search and negative tumour staging, we started treatment with intravenous immunoglobulins (IVIg, 30 g/day) 3 weeks after first symptoms, despite a non-typically high cell count for an acute inflammatory neuropathy. IVIg was administered for three consecutive days and brought an improvement of the ataxia. Nevertheless, the palsies of the

cranial nerves and limbs progressed. Therefore, we decided to accomplish five courses of plasmapheresis starting 5 days later, which led to fast improvement of the cranial nerve palsies, but initially, only slight improvement of the limb palsy.

In addition, platelet cell count decreased (from 205 to 99 Gpt/l) under therapy with enoxaparin. The search for heparin-induced thrombocytopenia antibodies was negative. Nevertheless, we changed to danaparoid shortly before the start of the plasmapheresis. Under both the regimes, platelet cell count recovered during the following 3 weeks.

OUTCOME AND FOLLOW-UP

Outcome control 8 weeks later demonstrated a nearly complete recovery of the acute neurological symptoms with only a slight paresis of the left abducens nerve and reduced hand force. Sensory deficits, which first had occurred after initial chemotherapy 2 years before, remained unaltered.

Because of the paraprotein-associated anti-GM2 IgM acute inflammatory neuropathy and the spreading itchy erythema with peripheral eosinophilia, we scrutinised a possible forthcoming relapse of the B-cell lymphoma and initiated a new tumour staging. The staging investigations brought forth a suspicious lymph node in the left axilla. Examination of this lymph node histologically confirmed a relapse of the diffuse large B-cell non-Hodgkin's lymphoma. Skin biopsy at that time point demonstrated a beginning of eosinophilic folliculitis with T-cell infiltration, but no signs of a direct lymphoma infiltration. Immunological investigation showed positive anti-BP-230 IgG antibodies (MBL, Nagoya, Japan) as a sign of a possible early stage of bullous pemphigoid.

DISCUSSION

Autoimmune processes are known complications of lymphoproliferative disorders, and are often designated as being paraneoplastic. However, especially in the case of lymphoproliferative disorders, autoimmune processes are usually a hint for dysfunctional immune system.³ There are reports that autoimmune diseases and lymphoma share similar pathomechanisms, which lead

Table 1 Serological measurement in the time course before and after plasmapheresis

Time point in relation to plasmapheresis	Pre				After 4 weeks	After 8 weeks	After 13 weeks
IgM level (0.4–2.33 g/l)	6.12				1.3	5.69	4.55
Eosinophilia (0–0.5%)	0.05					13	0.07
Autoantibody (EIA standard value)	EIA, IgG	EIA, IgM	IB, IgG	IB, IgM		IB, IgG	IB, IgM
GQ1B (<50%)	1.4	3.1	–	–		–	–
GA1 (<50%)	31	42	–	–		–	–
GM1 (<50%)	0.9	2.5	–	–		–	–
GM2 (<50%)	1.0	99	E	+		E	+
GM3			–	–		–	–
GM4			–	–		–	–
GD1A (<50%)	2.0	27	–	–		–	–
GD1B (<50%)	0.8	15	–	–		–	–
GD2			–	–		–	–
GD3			–	–		–	–
GT1a			–	–		–	–
GT1b			–	–		–	–
MAG-IgM (<1000 BTU)		170	–	–		–	–
BP-230 kDa (<9 U/ml)	5.9				0.8		26
BP-180 kDa (<9 U/ml)							0.7

E, equivocal; EIA, enzyme immunoassay; IB, immunoblot; MAG, myelin-associated glycoprotein.

Figure 1 Analysis of antiganglioside reactivity using a line immunoassay for the simultaneous multiparametric detection of antiganglioside antibodies against GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b and GQ1b employing anti-IgG, anti-IgM, anti- κ and anti- λ secondary antibodies conjugated to alkaline phosphatase. Serum 1 and 2 are samples from the patient before intravenous immunoglobulins and plasmapheresis (PPH), serum 3 is from the patient after intravenous immunoglobulins but before PPH, PPH fluid is from the fifth plasmapheresis.

to uncontrolled lymphocyte growth,¹ and are in some cases triggered by pathogens such as Epstein-Barr virus. In contrast, the typical characteristic of paraneoplastic disease in a closer sense is a specific antibody production against antigens of tumour cells that cross-react with antigens of normal (mainly neurological) tissue.

In the field of autoimmune disorders of the central nervous system there is nowadays a subdivision of neuronal antibodies according to the location of the antigen. Antibodies, which target an intracellular neuronal antigen, are generally associated with paraneoplastic syndromes, as for example anti-Hu antibodies. On the contrary, antibodies against neuronal surface antigens render a different autoimmune pathomechanism more likely. In the case of anti-NMDA (N-methyl D-aspartate) receptor encephalitis, a disease associated with antibodies which are directed against neuronal surface, ovarian tumours can be detected in no more than 60% of the cases, as observed in different case series.⁴

Gangliosides are components of the cell membrane that modulate cell signal transduction and are found predominantly in the

nervous system. Antibody production against different gangliosides has been reported to be associated with neuropathies. The most specific known association is antibody production against GQ1b, which is often triggered by a campylobacter pylori infection, and causes Miller Fisher syndrome. The GM2 ganglioside, also called Tay-Sachs ganglioside, is a minor component of adult nervous tissue. Pathological storage of ganglioside GM2 in neurons leads to motor neuron disease.⁵ Ganglioside expression on malignant cells differs from normal tissue. GM2 is more highly expressed on cell surface of cancers of neuroectodermal origin and lymphoma cells.⁶⁻⁷ In fact, GM2 and its components were the temporary targets for vaccination in human melanoma patients and lymphoma in mouse model.⁸⁻⁹ Autoimmune anti-GM2 IgM antibodies found in Guillain-Barré syndrome are often associated with CMV infection.¹⁰ Two cases are described in the literature, in which antibodies against gangliosides in combination with lung cancer may have triggered paraneoplastic neuropathy in the closer sense.¹¹

The clinical presentation of the acute inflammatory neuropathy in the present case revealed symptoms more typical for the Guillain-Barré syndrome (progressive weakness of the limbs) combined with additional symptoms more typical for the Miller Fisher syndrome (palsy of the muscles of the orbit, ataxia). There were also signs for a toxic sensible symmetric neuropathy (numbness of the feet), which occurred with the initial administration of chemotherapy (R-CHOP), 2 years prior. Especially, Oncovin (also called vincristine) causes toxic peripheral neuropathy as a side effect. We observed a response to therapy (IVIg/plasmapheresis) exclusively for the recent motor symptoms, whereas the sensory deficits stayed unaffected.

The appearance of a paraprotein of the IgM- κ class per se indicates a dysfunctional cell clone producing immunoglobulin debris in significant amounts. There are other examples with simultaneous appearance of a specific antibody and an associated paraprotein, for example, paraprotein with myelin-associated glycoprotein or antidisialosyl antibodies.¹² Since we prove that the IgM- κ paraprotein and the anti-GM2 IgM antibody share the same binding properties, we suppose the same B-cell clone to be their origin. In this case, it is more likely that what we discovered is an autoimmune process within a dysfunctional immune system rather than a paraneoplastic disease in the closer sense. In addition, the occurrence of a second specific autoantibody—the anti-BP-230 IgG antibody against adhesion molecules of the epidermis—is a further hint of immune system dysfunction instead of paraneoplastic causes. Nevertheless, there are reports that especially the GM2 ganglioside is a possible candidate for a paraneoplastic process in lymphoma.⁹⁻¹¹

In the present case, both, clinical presentation of autoimmune neuropathy and skin affection, started before immune modulating therapy. In addition, an autoimmune process may also have caused the observed thrombocytopenia. Neuropathy and thrombocytopenia improved after administration of intravenous immunoglobulins and conducting several courses of plasmapheresis, but skin affection worsened over time with increasing anti-BP-230 IgG antibody titre (table 1).

Originally, we considered it unlikely that the patient's symptoms are caused by an autoimmune process because of the recently maintained therapy with rituximab, which as an anti-CD20 antibody resulting in B-cell suppression. Therefore, an infectious origin of the symptoms as a side effect of rituximab was thought to be more probable in the beginning. On the other hand, after confirming the diagnosis of an autoimmune process, a palliative therapy with rituximab as a B-cell suppressor was discussed, since this could on one hand improve the

autoimmune processes, and on the other hand can be used as a treatment for a relapse of the lymphoma.

In summary, this case report emphasises that different autoimmune processes may respond differently to immune modulating interventions. This makes it difficult in clinical routine to determine the best solution for the individual patient, when more than one autoimmune process is present at the same time, especially in the context of malignancy. For a deeper understanding of the underlying pathomechanisms of autoimmune, lymphoproliferative and paraneoplastic diseases, it will be necessary in the future to further characterise individual courses of disease with complete clinical and serological presentation over time and their response to immune modulating therapy, especially when having the chance to identify specific antibodies and their targets.

Learning points

- Identifying specific antibodies and knowing their targets can support differential diagnosis.
- Autoantibodies against surface targets make an autoimmune process more likely.
- Lymphoma and autoimmune processes share common pathomechanisms.
- Multiple autoimmune processes emerging simultaneously indicate a dysfunctional immune system and make the occurrence of a lymphoma or relapse of a lymphoma likely.

Competing interests Dirk Roggenbuck is a shareholder of GA Generic Assays GmbH and Medipan GmbH. Both companies are diagnostic manufacturers.

Patient consent Obtained.

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