Hypotension as a symptom of autonomic neuropathy in patients with advanced malignancies

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Aims. Hypotension can be a symptom of paraneoplastic autonomic neuropathy (PAN). Onconeural antibodies (OA) provide strong evidence for the paraneoplastic origin of neurological syndromes. Our goal was to assess the frequency of PAN among patients with advanced malignancies and hypotension using OA.
Methods. Patients with advanced malignancies and hypotension were screened and enrolled as per protocol. Plasma levels of six classical OAs were assessed in these patients. We prospectively evaluated other symptoms of PAN in these patients.
Results. 31 patients out of 740 screened met the criteria of this cross-sectional study. OAs were present in 4 patients (12.9%). Anti-amphiphysin was found in 1 patient (3.23%), anti- CV2 (anti-CRPM5, anti- collapsin- response mediator protein) was present in 1 patient (3.23%), 1 patient (3.23%) was positive for anti-Hu and anti-Ma2 was present in 1 patient (3.23%). No patient was positive for 2 or more OAs. Normalization of blood pressure in concordance with partial remission occurred in 5 patients. The most used criteria for PAN were fulfilled in 9 patients.
Conclusion. The frequency of PAN may be underestimated in a busy oncology clinic. Assessing OAs may aid in the differential diagnosis of hypotension of unknown origin.

Key words: hypotension, malignancy, onconeural antibodies, neurological disorders

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INTRODUCTION

Hypotension can be a frequent sign in patients with advanced malignancies but the etiology varies and may include low fluid intake and dehydration, advanced tumour kachexia, compression or damage to the organs of the cardiovascular system. Sudden hypotension with symptoms of shock can be associated with emergencies such as pulmonary embolism or significant internal or external blood loss. Deposits of amyloid can be associated with hypotension in patients with plasma cell malignancies.

Paraneoplastic autonomic neuropathy (PAN) is a rare paraneoplastic syndrome that can occur in patients with various malignancies. Most frequently, it is found in patients with small- cell lung cancer (SCLC) and thymomas. Gastrointestinal pseudoobstruction, gall bladder motility disorders, erectile dysfunction and pupillomotoric dysfunction may also be present in patients with PAN. However, hypotension is the most frequent symptom Onconeural antibodies are produced by tumours and damage the autonomic nervous system. Neal et al.[1] presented the case of a patient with advanced SCLC who experienced repetitive collapses caused by orthostatic hypotension as the only symptom of PAN. Positivity of collapse- response mediator protein 5 (CRMP5) was detected in this patient.

Hypotension presents certain challenges in the management of patients with advanced malignancies. The long-term aim is to improve patient's nutritional status and hydration. Cessation of any hypotensive medication is mandatory. Intravenous infusion of normal saline solution may help alleviate symptomatic hypotension. Specific treatment for PAN consists of treatment of the underlying malignancy. Some authors recommend low doses of corticosteroids.

Onconeural antibodies (OA) are the antibodies associated with neurological paraneoplastic syndromes. These antibodies are directed at neuroectodermal tissues[2]. OAs can be divided into two categories according to the strength of their association with primary malignancy.

1. classical or well- characterized OAs strongly associated with primary malignancy

2. non-classical OAs with variable association to primary malignancy. These antibodies may be present in patients without malignancy e.g. in patients with autoimmune disorders. Most common OAs, their association with paraneoplastic syndromes and primary malignancies are summarized in Table 1.(ref.[2-8])

There is lack of relevant data on prevalence of PAN. This might be due to the low frequency and problems with the diagnosis of this paraneoplastic syndrome. To date, no diagnostic criteria have been agreed for PAN.

Table 1. OAs, their association with paraneoplastic syndromes and primary malignancies.

Antibody	Paraneoplastic syndrome	Associated malignancies	C/ NC	Ref.
Anti- HU (ANNA-1)	PAN, paraneoplastic cerebellar degeneration, paraneoplastic limbic encephalitis, paraneoplastic sensory neuropathy	SCLC	C	2,3,8
Anti- Yo (PCA-1)	paraneoplastic cerebellar degeneration	Breast cancer, ovarian cancer, cervical cancer, endometrial cancer	C	8
Anti- Ri (ANNA-2)	POMS, paraneoplastic cerebellar degeneration, paraneoplastic brainstem degeneration,	Breast cancer, ovarian cancer, cervical cancer, endometrial cancer, SCLC	C	2,6
Anti-CV2/ CRMP-5	Paraneoplastic encephalomyelitis, paraneoplastic cerebellar degeneration, peripheral neuropathy, PAN	SCLC, thymoma	C	2,8
Anti- Ma1 Anti-Ma2	paraneoplastic brainstem encephalitis, paraneoplastic limbic encephalitis	Testicular germ-cell tumours, lung cancer	C	2,4
Anti- amphiphysin	Stiff- Person syndrome, paraneoplastic encephalomyelitis, PAN	Lung cancer, breast cancer, thymoma	C	2,8
Anti- Tr (DNER)	paraneoplastic cerebellar degeneration,	Hodgkin lymphoma	NC	8
Anti- recoverin	Tumour- associated retinopathy	SCLC	NC	2,8
Retinal anti-bipolar cells antibody	Melanoma- associated retinopathy	Malignant melanoma	NC	2,8
Anti- Zic4	paraneoplastic cerebellar degeneration	SCLC	NC	8
Anti- ANNA3	paraneoplastic sensory neuropathy, paraneoplastic encephalomyelitis	Hodgkin lymphoma	NC	8
Anti- PCA2	paraneoplatic encephalomyelitis, paraneoplastic cerebellar degeneration	SCLC	NC	8
LGI1	paraneoplastic limbic encephalitis,	thymoma	NC	3
mGluR5	paraneoplastic limbic encephalitis,	Hodgkin lymphoma	NC	3
mGluR1	paraneoplastic cerebellar degeneration	Hodgkin lymphoma	NC	8
Anti- VGCC	LEMS	SCLC	NC	7
Anti- ACR	LEMS, PAN	SCLC, thymoma	NC	7
Anti- NMDA	Paraneoplastic encephalitis	SCLC, ovarian cancer	NC	5
Anti- GAD	Stiff- Person syndrome, POMS	Colorectal cancer, thymoma, Hodgkin lymphoma, SCLC, breast cancer, ovarian cancer	NC	6

ANNA – antinuclear antibody; PAN – paraneoplastic autonomous neuropathy; PCA – Purkinje- cell antibody; DNER – Delta/Notch-like epidermal growth factor-related receptor; CRMP5 – collapse response mediated protein; LGI1 – leucine- rich glioma inactivated protein-1; mGluR – metabotropic glutamate receptor; VGCC – voltage-gated calcium channels, ACR – acetylcholine receptor, NMDA – N-metyl-D-aspartate; GAD – glutamate decarboxylase; SCLC – small-cell lung cancer, POMS – paraneoplastic opsoclonus- myoclonus syndrome, LEMS – Lambert-Eaton myasthenic syndrome, C – classical onconeural antibodies, NC – non-classical onconeural antibodies

In 2004, international research group led by Graus et al.[8] provided classification and diagnostic criteria for neurological paraneoplastic syndromes as a whole. Based on these criteria, diagnosis of neurological paraneoplastic syndrome can be made in four following situations:

1. clinical symptoms of well-characterized paraneoplastic syndrome (encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, sensory neuropathy, POMS, LEMS, dermatomyositis), and malignancy occurring within 5 years from diagnosis of this paraneoplastic syndrome

2. known malignancy and clinical symptoms of non-classical neurological paraneoplastic syndrome (not listed above) that alleviate or vanish in concordance with remission of malignancy without using immunosupressive therapy for paraneoplastic syndrome.

3. clinical symptoms of non- classical neurological syndrome (not listed above) and presence of onconeural

antibodies (both classical and non- classical); malignant disease occurring within 5 years from diagnosis of paraneoplastic syndrome.

4. clinical symptoms of non-classical neurological syndrome (not listed above), no clinical symptoms of malignancy, presence of classical onconeural antibodies (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma, anti-amphiphysin).

Patients with metastatic malignancy and hypotension were examined in our study for the presence of onconeural antibodies. Following the criteria of Graus et al., the frequency of paraneoplastic autonomic neuropathy in the neurological paraneoplastic syndrome was assessed.

PATIENTS AND METHODS

Approval of the Ethics committee of Faculty Hospital Trencin was obtained before initiation of enrollment.

740 patients treated at the Faculty Hospital Trencin, Department of Oncology from November 1st, 2016 – December 31st 2016 were screened for hypotension. Hypotension was defined as blood pressure below 90/60 mmHg.

Patients with hypotension and metastatic solid tumours were included to our study. The immunoblot technique was used to determine serum levels of classical onconeural antibodies (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma, anti-amphiphysin) in these patients. We used EUROLINE Neuronal Antigen Profile 2 kit (Euroimmun/ PerkinElmer). Tests were done on patient plasma according to the manufacturer's instructions. Briefly, whole blood was spun and plasma separated. Aliquots of the plasma were put onto membrane strips coated with purified onconeural antigens (solid phase). In the case of the presence of examined onconeural antibody, these attached to the antigens (first incubation). Subsequently, we added alkaline- phosphatase labeled anti-human antibodies (second incubation). Finally, chromogen substrate solution was added in order to promote colour reaction. Positivity of onconeural antibody was visualized as dark band at the line of corresponding antigen.

We searched for further symptoms of PAN such as gastrointestinal pseudoobstruction, gallbladder motility disorder, erectile dysfunction, pupillomotoric dysfunction. Patients with lymphoma or multiple myeloma, primary central or peripheral nervous system tumours were excluded. We also excluded patients with clinical symptoms of dehydration, with elevation of serum urea or creatinine or taking antihypertensives.

During the following 12 months after the end of our primary data collection (January- December 2017) blood pressure was measured in patients included to our study during their follow-up visits.

RESULTS

31 patients (15 women and 16 men) out of 740 screened met our inclusion criteria. All patients had stage IV, metastatic disease. Distribution of patients according to site of primary cancer is provided in Table 2.

Table 2. Distribution of patients according to primary malignancy.

Primary malignancy	Number of patients
NSCLC	4
SCLC	3
Breast cancer	1
Cervical cancer	2
Head and neck cancer	2
Ovarian cancer	4
Colorectal cancer	5
Gastric cancer	2
Neuroendocrine tumours	1
Pancreatic and billiary tract cancer	3
Urothelial cancer	1
Cancer of unknown origin	1
Renal-cell cancer	2

NSCLC – non-small-cell lung cancer, SCLC – small-cell lung cancer

No other symptoms of PAN except hypotension occurred in our patients. At least one onconeural antibody was found in 4 patients (12.9%). Anti-amphiphysin was present in 1 patient (3.23%), anti-CV2 (anti-CRPM5, anti-collapsin- response mediator protein) was present in 1 patient (3.23%), 1 patient (3.23%) was positive for anti-Hu and anti-Ma2 was present in 1 patient (3.23%). No patient was positive for 2 or more antibodies. Positivity of anti-amphiphysin was detected in a patient with advanced SCLC, anti-CV2 and anti- Ma2 were detected in patients with colorectal cancer. Finally, 1 patient with pharyngeal cancer was positive for anti-Hu antibody. No anti-Yo and anti-Ri antibodies were detected.

During follow-up, progression of primary malignancy or death occurred in 22 patients (71%). 4 patients paid no further visit to our workplace (12.9%). Finally, partial response (PR) to oncological treatment occurred in 5 patients (16.1%). Complete response (CR) occurred in no patient. Onconeural antibodies were not detected in patients with later partial response. However, in all patients with partial response, normalization of blood pressure occurred.

DISCUSSION

Out of 740 patients (154 patients with advanced cancer) treated in our hospital during 2 months (November 1st, 2016- December 31st, 2016), only 31 patients were enrolled. As mentioned above, anti-amphiphysin, anti-Hu and anti-CV2 may be present in PAN. These antibodies were positive in 3 patients (9.7%). However, anti-Ma2 was detected in 1 patient. This antibody can be positive in patients with limbic, hypothalamic or brain stem encephalomyelitis. These rare paraneoplastic syndromes can be present in patients with germ-cell tumours and lung cancer. Our collection of patients is rather heterogeneous.

Patients with 13 different malignancies and hypotension were enrolled. In line with the literature, anti- amphiphysin was positive in a patient with advanced SCLC. However, positivity of anti- Hu was present in patient with advanced pharyngeal cancer. Moreover, anti-CV2 was positive in a patient with advanced colorectal cancer. Reviewing the published literature, the presence of OAs (anti- Hu and anti-CV2) did not match the expected malignancy in the last two patients.

Diagnostic criteria of neurological paraneoplastic syndromes provided by Graus et al.[8] were met in 9 cases (29%). 4 patients (12.9%) were treated for known malignancy, they presented with clinical symptoms of non-classical neurological paraneoplastic syndrome (hypotension) and were OA positive. 5 patients (16.1%) had known malignancy without OAs and or the non-classical paraneoplastic syndrome, the clinical symptoms of which alleviated or vanished after specific oncological treatment in accord with remission of the underlying malignancy.

Positivity of onconeural antibodies and hypotension are symptoms that can be evaluated by objective methods. However, we admit that the frequency of hypotension could have been biased. Besides possible mismeasurement of blood pressure, patient's hydration status could have been assessed incorrectly. Moreover, antihypertensive therapy may not have been disclosed by the patient.

CONCLUSION

PAN is rare paraneoplastic syndrome that can be common to various malignancies. Generally, it is assumed that frequency of PAN is rather underestimated in oncology practices. At least multi-institutional cooperation would be necessary to obtain relevant data on prevalence of these rare syndromes. Despite existing general diagnostic criteria for neurological paraneoplastic syndromes there is a need for diagnostic criteria for PAN.

Hypotension and other symptoms of autonomic neuropathy of unknown origin should lead us to search for underlying malignancy. OAs may be useful in differential diagnosis as their presence provides strong evidence in favour of a paraneoplastic origin of an otherwise non-specific clinical syndrome.

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Compliance with ethical standards: All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration (7th revision, 2008). Signed informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Neal AJ, Qian MY, Clinch AS, Le BH. Orthostatic hypotension secondary to CRMP-5 paraneoplastic autonomic neuropathy. J Clin Neurosci 2014;21(5):885-6.
2. Zhang H, Zhou C, Wu L, Ni F, Zhu J, Jin T. Are Onconeural Antibodies a Clinical Phenomenology in Paraneoplastic Limbic Encephalitis? Mediators Inflamm 2013;2013:e172986.
3. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: neurological symptoms, immunological findings and tumour association in 50 patients. Brain J Neurol 2000;123(Pt 7):1481-94.
4. Barnett M, Prosser J, Sutton I, Halmagyi G, Davies L, Harper C, Dalmau J. Paraneoplastic brain stem encephalitis in a woman with anti-Ma2 antibody. J Neurol Neurosurg Psychiatry 2001;70(2):222-5.
5. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10(1):63-74.
6. Laroumagne S, Elharrar X, Coiffard B, Plojoux J, Dutau H, Breen D, Astoul P. "Dancing Eye Syndrome" Secondary to Opsoclonus-Myoclonus Syndrome in Small-Cell Lung Cancer. Case Rep Med 2014;2014:1-4.
7. Hülsbrink R, Hashemolhosseini S. Lambert–Eaton myasthenic syndrome – Diagnosis, pathogenesis and therapy. Clin Neurophysiol [Internet] [cited 2014 Sep 11]; Available from: http://www.sciencedirect.com/science/article/pii/S1388245714003459
8. Graus F, Delattre J, Antoine J, Dalmau J, Giometto B, Grisold W, Honnorat J, Smitt PS, Vedeler Ch, Verschuuren JJ, Vincent A, Voltz R. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004;75(8):1135-40.