Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/pjnns

Case report

Paraneoplastic brainstem encephalomyelitis and atypical form of chronic inflammatory demyelinating polyneuropathy in patient with testicular germinal tumor—Is this an overlap syndrome? A case report

Paweł Gogol [a,*], *Anna Gogol* [a], *Andrzej Opuchlik* [a], *Dorota Dziewulska* [a,b]

[a] *Department of Neurology, Medical University of Warsaw, Warsaw, Poland*
[b] *Department of Experimental and Clinical Neuropathology, Mossakowski Medical Research Institute, Polish Academy of Sciences, Warsaw, Poland*

ARTICLE INFO

Article history:
Received 14 October 2014
Accepted 14 January 2015
Available online 22 January 2015

Keywords:
Paraneoplastic syndrome
Neuropathy
Germ cell tumor

ABSTRACT

Paraneoplastic neurologic syndromes are diagnosed when neurologic symptoms are associated with neoplasm and other causative factors are excluded. They may precede or be simultaneous to various types of neoplasms, mainly malignant. In men up to 45–50 years old the most common cancer causing the paraneoplastic syndrome is testicle tumor, manifesting usually as limbic/brain stem encephalitis and myelitis. Usually effective treatment of underlying neoplasm brings resolution of neurologic symptoms. But corticosteroids and intravenuous immunoglobulins are also used. In the presented case a 37-year-old man was primarily diagnosed and treated for progressive tetraparesis with signs of both upper and lower motor neuron dysfunction, associated with bulbar symptoms. Having various diagnostic procedures performed an atypical form of chronic inflammatory demyelinating polyradiculoneuronopathy was primarily suspected, but eventually a discovery of endodermal sinus tumor in the testicle enabled to state the diagnosis of possible paraneoplastic syndrome. In spite of chemotherapy the patient died shortly after the diagnosis because of infectious complications. Histopathology displayed intense inflammatory changes in the brain stem as well as in cranial nerves and cervical spinal cord. The same immunological process evoked by various pathogenetic factors (infection vs. neoplasm) may cause similar clinical picture and hinder the diagnosis. Most importantly it may delay the proper way of treatment.

* *Corresponding author at*: Department of Neurology, Medical University of Warsaw, Banacha 1a, 02-097 Warsaw, Poland. Tel.: +48 22 599 2858; fax: +48 22 599 1857.
E-mail address: pawelgogol@tlen.pl (P. Gogol).

http://dx.doi.org/10.1016/j.pjnns.2015.01.006

1. Introduction

Yolk sac tumor (YST) is a rare malignant germ cell tumor found in the testis or ovary, and occasionally in extragonadal location. Only single case reports have described the presence of this tumor in the head, lung, stomach, liver, mediastinum, peritoneum, kidney, prostate, vagina, vulva, and presacral regions [1–4]. Like other cancers, YST may be associated with paraneoplastic syndromes. The syndrome most commonly related to YST and other germ-cell cancers of the testis is paraneoplastic encephalitis. The association of the limbic/brainstem encephalitis concurrent with the anti-Ma2 onconeural antibodies was widely described, as well as the presence of testicular tumors as its causative factor in more than 80% of patients, usually men younger than 45–50 years old [5,6].

Paraneoplastic neurologic syndromes are diagnosed when neurologic symptoms are associated with neoplasm and other causative factors are excluded [5]. It is believed that they result from an immune response to an antigen shared between the cancer and the nervous system. They are rare, less than 1% of all patients with various cancers suffer from such disorders. However, depending on the kind of a cancer this may be as high as 30% in small cell lung carcinoma [7,8]. The eight paraneoplastic syndromes most likely to be associated with cancer, the so called ''classic'' syndromes, include encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, opsoclonus-myoclonus, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, Lambert–Eaton's syndrome and dermatomyositis [5].

There are other neurologic syndromes such as acquired neuromyotonia, motor neuron disease, stiff-men syndrome, Guillain–Barré syndrome, and chronic inflammatory demyelinating polyradiculopathy (CIDP) that may be the so-called ''non-classic'' paraneoplastic syndromes. They constitute a peculiar diagnostic challenge.

We would like to present a case report of a patient with a non-classic paraneoplastic syndrome or an overlap syndrome associated with testicular germ-cell tumor.

2. Case report

Thirty-seven year-old man, physical worker and current smoker, complained of progressive four-limb weakness (at first lower then upper limbs) followed by swallowing and speech problems, which he attributed to the upper respiratory tract infection that preceded symptoms by one month and was treated with antibiotics.

First neurologic examination (in another hospital) revealed triparesis – proximal in the right upper limb and distal in lower limbs – with decreased muscle tone, but brisk reflexes, muscle atrophy corresponding with the sites of paresis and bilateral Babinski sign. Deep sensation in the lower limbs was disturbed and bilateral Laseque's sign was noted. Involvement of cranial nerves resulted in right-sided facial and tongue muscles paresis, dysarthria and dysphagia.

Lumbar puncture revealed albuminocytologic dissociation in the cerebrospinal fluid (discreet cell count elevation of 14 μl, with preponderance of lymphocytes and monocytes and almost threefold elevation of protein concentration of 129 mg/dl). Electrophysiology showed acute axonal-demyelinating poliradiculoneuropathy of the motor fibers with acute denervation and reinervation in muscles. Performed twice MRI scans of the brain with contrast enhancement were negative, and central nervous system diseases such as boreliosis, herpes simplex and HIV infections were excluded. Based on clinical picture and results of additional tests the diagnosis of post-inflammatory encephaloradiculoneuropathy was stated and pharmacological treatment was introduced. Initially, high-dose intravenous corticosteroids (1.0 g per day for five days of methylprednisolone) were administered, and slight improvement in the muscle strength was observed.

On admission to our clinic (four months later) further aggravation of clinical symptoms was observed especially considering bulbar symptoms (left abducens nerve palsy). Treatment with intravenous immunoglobulin was started as the second-line treatment (maximum dose of 2.0 g/kg body weight), which again resulted in the improvement in muscle strength and swallowing problems. Afterwards, long-term oral therapy with prednisolone was initiated with the starting dose of 1.3 mg/kg body weight and the patient was discharged home. Meanwhile the neoplastic markers (AFP, total PSA, CEA, CA-15-3, CA 19-9) were investigated as well as CT scans of the chest and abdomen, and physical examination and USG of the testis, but none showed abnormalities.

Three months after the first one, the EMG investigation showed pure axonal motor polyneuropathy.

Nearly one year later the patient was again admitted to our clinic with deterioration of symptoms. This time external ophtalmoparesis was notable (only vertical eye movements were spared) and other cranial nerves damage of the bulbar origin. Due to respiratory failure he needed non-invasive mechanical ventilation by means of facial mask (Bi-level Positive Airway Pressure). Once again the MRI scans of the brain showed no abnormalities that could explain the symptoms.

The patient informed on the left testicle swelling and pain that he had consulted by urologist and had treated with antibiotics for the last two months. Performed USG showed the presence of a pathological mass in the left testicle suggestive of a cancer. It was associated with the highly elevated alpha-fetoprotein level in the blood (around 52 times upper limit). The mass was surgically removed and the histopathology investigation revealed yolk sack tumor with foci of embryonic carcinoma. The patient underwent chemotherapy with cisplatin and ethoposide. Unfortunately, shortly after the first course he developed severe leukopenia with agranulocytosis, which was complicated by pneumonia and sepsis. The patient eventually died.

The necropsy was performed. Post-mortem examination revealed pneumonia but not metastases of the testis tumor. Microscopic examination of the brain and spinal cord showed inflammatory process involving both the central and peripheral nervous systems particularly severe in the brain stem, cervical spinal cord and cranial nerves. The most evident morphological manifestation of the inflammation was vasculitis involving small-sized arteries (Fig. 1A) and capillary vessels. Inflammatory mononuclear cells infiltrating vessel

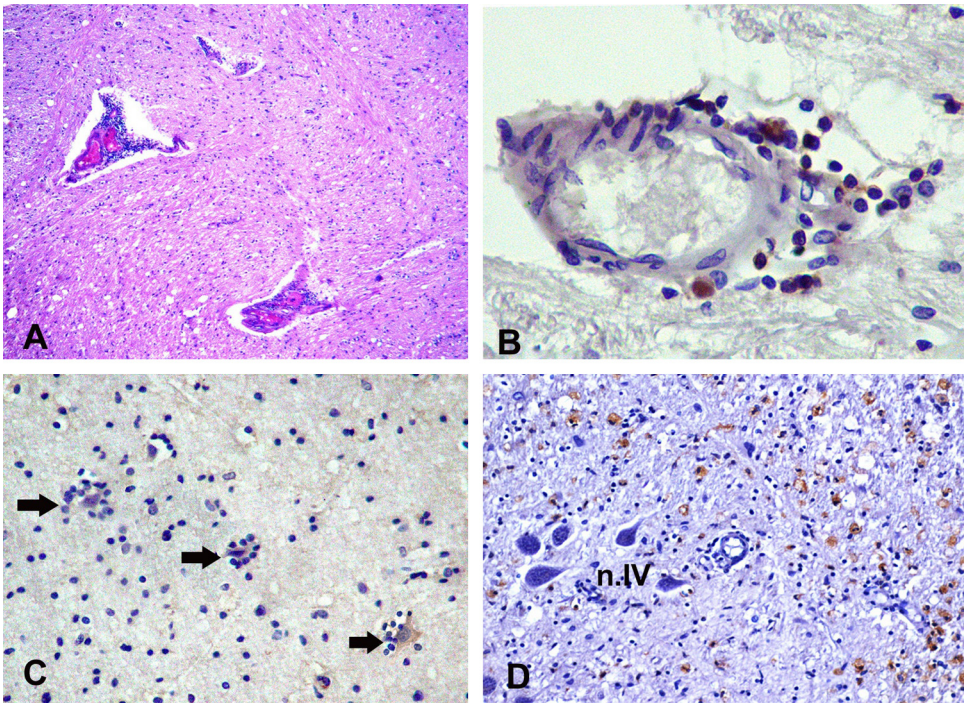

Fig. 1 – (A) Cuffs of the inflammatory infiltrates around small arteries in the posterior horn of the cervical spinal cord, H&E. (B) CD3+ lymphocytes T within inflammatory infiltrate of the midbrain artery, anti-CD3. (C) Mononuclear cells around neurons in the frontal cortex (arrows), H&E. (D) Numerous macrophages in the midbrain parenchyma; visible delicate perivascular inflammatory infiltrates and well preserved neurons in the trochlear nerve nucleus, anti-ferritin

wall and perivascular space were mainly composed of CD3+ lymphocytes T (Fig. 1B) while lymphocytes B were only occasionally noted. Parenchymal lymphocytic infiltrates were found in the brain stem, spinal cord, spinal roots as well as in cranial nerves, particularly in the oculomotor nerve, but not in the cerebral and cerebellar parenchyma. Although evident loss of neurons was not observed in any of the examined structures, increased perineuronal satelitosis and neuronophagy (Fig. 1C) were seen sporadically in the cerebral cortex and basal ganglia. In the brain stem and spinal cord, microglia activation and numerous macrophages accompanied the inflammatory changes (Fig. 1D).

3. Discussion

Histopathologic investigation of the nervous system in the patient with germ-cell tumor associated with inflammatory encephaloradiculoneuropathy displayed paraneoplastic inflammation of brain stem, spinal cord and cranial nerves.

The fact that the first symptoms were preceded by the upper respiratory tract infection probably delayed identification of the cancer, as the patient was presumed to present a non-typical form of the chronic inflammatory demyelinating polyneuropathy. His clinical presentation fulfilled the criteria of the atypical CIDP according to EFNS/PNS guidelines elaborated in 2010 [9]. A post-inflammatory beginning, gradually progressing limb paresis and cranial nerve dysfunction supported this notion. Even though such symptoms like bilateral Babinski sing and asymmetric limb paresis are not the usual presentation of this disease, similar cases in the literature were described [9,10]. The diagnosis of CIDP was supported by the presence of albuminocytologic dissociation in cerebrospinal fluid examination, axonal-demyelinating damage to motor fibers with assisting acute denervation and reinervation features in EMG, and above all, by the lack of changes in the brain MRI, specially scans of the brain stem and limbic system, despite three investigations dispersed in time.

As a consequence a treatment with high-dose intravenous methylprednisolone infusions were introduced followed by intravenous human immunoglobulins (maximum dose of 2 mg/kg body weight fractioned in five portions). The treatment resulted in slight regression of the symptoms and temporary stabilization of the neurologic status.

Clinical picture suggestive of CIDP did not determine the workup regarding neoplasmatic disorder. According to the literature, it is highly uncommon for CIDP to be associated with malignancy [11,12]. During the patient first stay in our clinic routine procedures including chest, abdomen and pelvis examinations were performed. However, testicular germ-cell tumor found during his second stay strongly suggests, that all the demonstrated symptoms might have been the symptoms of a paraneoplastic syndrome interfering with inflammatory polyneuropathy.

According to the recommendations from 2004 elaborated by PNS Euronetwork, if the non-typical paraneoplastic syndrome with or without well-defined onconeural antibodies is followed by a diagnosis of the cancer within two years of observation, it falls into a category of the certain paraneoplastic syndrome [5] (*criteria of the certain and possible*

Table 1 – Diagnostic criteria of the paraneoplastic syndrome (PNS).

Certain paraneoplastic syndrome
1 Classic PNS[a] + malignancy diagnosed within 5 years from PNS diagnosis
2 Non-classic PNS, which improves or resolves after neoplasm treatment, without immunotherapy being used; except – spontaneous PNS remission
3 Non-classic PNS with positive onconeural antibodies (well[b] or not well defined) + malignancy diagnosed within 5 years from PNS diagnosis
4 Neurologic syndrome (classic or non-classic PNS) + positive well-characterised onconeural antibodies + no neoplasm
Possible paraneoplastic syndrome
1 Classic PNS + no onconeural antibodies + high risk of malignancy
2 Neurologic syndrome (classic PNS or not) + partially characterized onconeural antibodies + no malignancy
3 Non-classic PNS + no onconeural antibodies + malignancy diagnosed within 2 years after the PNS

[a] Classic PNS: encephalomyelitis, limbic encephalitis, subacute cerebellar atrophy, opsoclonus-myoclonus, subacute sensory neuronopathy, chronic gastrointestinal pseudo-obstruction, Lambert–Eaton's syndrome, dermatomyositis.
[b] Well-characterized onconeural antibodies: anti-Hu, anti-Yo, anti-Ri, anti-CV2/CRMP5, anti-Ma/Ta, anti-amphiphisin.

paraneoplastic syndrome are shown in Table 1). It is why no onconeural antibodies were investigated in this 37-year-old man after the testis tumor had been found, as it was not necessary for the diagnosis.

It is well known that the diagnosis of the paraneoplastic syndrome poses a diagnostic challenge until the malignancy is found. As six well-characterized onconeural antibodies have rather high specificity (>90%) [13], they may help establishing the diagnosis. On the other hand, they are found in only 50% of the patients with PNS [5]. What is more, in up to 20% of patients with classic paraneoplastic syndrome none of the well-characterized onconeural antibodies is found.

Regarding our patient, it remains uncertain whether all the symptoms present from the very beginning may have resulted from the underlying paraneoplastic syndrome or from inflammatory demyelinating polyradiculoneuropathy, which later were joined by cross-link immunologic reaction to cancer antigen. The fact that despite repeated brain MRI scans no lesion of the brain stem and limbic system was found neither exclude the diagnosis of the paraneoplastic syndrome nor confirm CIDP. Various studies showed that MRI changes are found in 70–80% patients with paraneoplastic syndromes [14] and in 20% of patients with CIDP [15,16]. EFNS Task Force guidelines on management in PNS edited in 2006 [17] give the value of 60% of patients with paraneoplastic limbic encephalitis and positive MRI investigation. But in the same time the authors highlight the notion that using specific MRI imaging such as FLAIR may result in the higher number of positive results.

As a conclusion, clinical picture of the syndromes originating from immunologic reaction to various antigens (cancer vs. infective agent antigens) may resemble each other and thus significantly hinder the process of establishing the proper diagnosis.

Conflict of interest

None declared.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

REFERENCES

[1] Cao D, Liu A, Wang F, Allan RW, Mei K, Peng Y, et al. RNA-binding protein LIN28 is a marker for primary extragonadal germ cell tumors: an immunohistochemical study of 131 cases. Mod Pathol 2011;24(February (2)):288–96. http://dx.doi.org/10.1038/modpathol.2010.195

[2] Gupta R, Mathur SR, Arora VK, Sharma SG. Cytologic features of extragonadal germ cell tumors: a study of 88 cases with aspiration cytology. Cancer 2008;114(December (6)):504–11. http://dx.doi.org/10.1002/cncr.23983

[3] Mei K, Liu A, Allan RW, Wang P, Lane Z, Abel TW, et al. Diagnostic utility of SALL4 in primary germ cell tumors of the central nervous system: a study of 77 cases. Mod Pathol 2009;22(December (12)):1628–36. http://dx.doi.org/10.1038/modpathol.2009.148

[4] Toner GC, Geller NL, Lin SY, Bosl GJ. Extragonadal and poor risk nonseminomatous germ cell tumors. Survival and prognostic features. Cancer 1991;67(April (8)):2049–57.

[5] Graus F, Delattre JY, Antoine JC, Dalmau J, Giometto B, Grisold W, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004;75(August (8)):1135–40.

[6] Mathew RM, Vandenberghe R, Garcia-Merino A, Yamamoto T, Landolfi JC, Rosenfeld MR, et al. Orchiectomy for suspected microscopic tumor in patients with anti-Ma2-associated encephalitis. Neurology 2007;68(March (12)):900–5.

[7] Dalmau J, Rosenfeld MR. Paraneoplastic syndromes of the CNS. Lancet Neurol 2008;7(April (4)):327–40.

[8] Monstad SE, Knudsen A, Salvesen HB, Aarseth JH, Vedeler CA. Onconeural antibodies in sera from patients with various types of tumours. Cancer Immunol Immunother 2009;58(November (11)):1795–800. http://dx.doi.org/10.1007/s00262-009-0690-y

[9] Van den Bergh PY, Hadden RD, Bouche P, Cornblath DR, Hahn A, Illa I, et al. European Federation of Neurological

Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – first revision. Eur J Neurol 2010;17 (March (3)):356–63. http://dx.doi.org/10.1111/j.1468-1331.2009.02930.x

[10] Zéphir H, Stojkovic T, Latour P, Lacour A, de Seze J, Outteryck O, et al. Relapsing demyelinating disease affecting both the central and peripheral nervous systems. J Neurol Neurosurg Psychiatry 2008;79(September (9)): 1032–9. http://dx.doi.org/10.1136/jnnp.2006.108290

[11] Antoine JC, Camdessanché JP. Peripheral nervous system involvement in patients with cancer. Lancet Neurol 2007;6 (January (1)):75–86.

[12] Giometto B, Grisold W, Vitaliani R, Graus F, Honnorat J, Bertolini G, et al. Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol 2010;67(March (3)):330–5. http://dx.doi.org/10.1001/archneurol.341

[13] Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. J Neurol 2010;257(April (4)):509–17. http://dx.doi.org/10.1007/s00415-009-5431-9

[14] Lawn ND, Westmoreland BF, Kiely MJ, Lennon VA, Vernino S. Clinical, magnetic resonance imaging, and electroencephalographic findings in paraneoplastic limbic encephalitis. Mayo Clin Proc 2003;78(November (11)):1363–8.

[15] Mendel JR, Kolkin S, Kissel JT, Weiss KL, Chakeres DW, Rammohan KW. Evidence for central nervous system demyelination in chronic inflammatory demyelinating polyradiculopathy. Neurology 1987;37(August (8)):1291–4.

[16] Thomas PK, Walker RW, Rudge P, Morgan-Hughes JA, King RH, Jacobs JM, et al. Chronic demyelinating peripheral neuropathy associated with multifocal central nervous system demyelination. Brain 1987;110(February (Pt 1)): 53–76.

[17] Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Hart IK, et al. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. Eur J Neurol 2006;13(July (7)):682–90.