Paraneoplastic Neurological Syndromes in Lymphoid Neoplasms: A Clinical and Laboratorial Challenge

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Dear Editor

I had the great pleasure to read the very interesting paper published recently by Acharya et al. titled “Subacute Sensorimotor Polyneuropathy as Sole Manifestation of Occult Non Hodgkin’s Lymphoma: Infiltrative or Paraneoplastic?” in which the authors tried to ascertain whether the etiology of the neuropathy presented by a patient with a diagnosis of a non-Hodgkin’s lymphoma was due to neural infiltration by the tumor itself or, if it was a paraneoplastic manifestation, with the latter hypothesis being considered the most likely by a diagnosis of exclusion [1]. It was a very challenging case, and several factors hampered the final verdict. Some, were related to the lack/limitation of availability of specific diagnostic tests (no nerve biopsy or search for onconeural antibodies) while others were due to the inherent problems in diagnosing paraneoplastic syndrome itself.

Paraneoplastic neurological syndromes (PNS) are a group of not yet fully understood rare disorders which affect about 0,01 % of cancer patients, with some exceptions such as the Lambert–Eaton myasthenic syndrome which can occur in up to 3 % of small-cell lung cancer [2]. PNS can affect any part of the central and peripheral nervous systems, the neuromuscular junction, or muscles. They are mostly encountered in small lung cancer followed by gynecological tumors (ovarian cancer), breast cancer, thymoma and in a minority of cases in lymphomas (mainly Hodgkin’s lymphomas) [3]. As a general rule, the neurological manifestations precede the clinical onset of cancer, and therefore

can go unnoticed, risking to miss a gold opportunity to detect the cancer at an earlier and curable stage. So, a great index of clinical suspicion is necessary [4].

The very definition of PNS was not always clear. In the past, it was considered neurological syndromes of unknown cause that often associate with cancer, but that description was imprecise, since co-existence of neoplasm and neurological derangement can be merely coincidental, without a direct pathogenic cause-effect relationship. The recent observations that PNS are in many instances an immune mediated disorder, led to the increasing importance given to the onconeural antibodies (ONA) which recognize antigens expressed by the nervous system and by neoplastic cells as a key means to diagnose true paraneoplastic neurological syndromes [5]. This has refined the current definition of PNS to a heterogeneous group of nervous system dysfunctions in cancer patients, which are caused by an immune response to an underlying malignancy and not due to a local effect of the tumor or its metastases [6].

Regarding the ONA, the well characterized ONA (anti-Hu, anti-Yo, anti-CV2, anti-Ri, anti-Ma, anti-amphiphysin) target against intracellular antigens, have a high specificity (>90 %) and are associated with a restricted range of cancer, thus allowing directing the search of the underlying tumor at a stage where it is frequently not clinically overt. However, drawback of ONA, is that antibodies might be detected in the absence of a PNS; in 5–10 % an atypical antibody directed against cell surface antigens is present that is only partially characterized (anti-NMDA, VGKC, AChR, anti-Tr) and is less well linked to a tumor; in about one-third of PNS, no antibodies are even detected. As such, presence of ONA are not the only required condition to catalog a neurological syndrome as paraneoplastic [7].

The spectrum of entities that encompass the PNS can be split into two groups: The “classical syndromes” (the most

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well-known are encephalomyelitis, limbic encephalitis, subacute cerebellar degeneration, subacute sensory neuronopathy, Lambert–Eaton myasthenic syndrome and opsoclonus-myoclonus), which are often associated with cancer and whose diagnosis should not delay the search for an occult neoplasm; and the many other disorders such as Guillain–Barré syndrome, Stiff person syndrome and the subacute sensorimotor neuropathy as described in the case report by Acharya et al., are categorized as “non-classical syndromes”.

Deciding whether a given neurological picture is paraneoplastic depends on the clinical syndrome, presence or absence of cancer and onconeural antibodies, and the time elapsed between onset of neurological symptoms and the detection of the cancer.

In this regard, it was proposed two levels of diagnostic evidence (definite or possible) to consider a neurological syndrome as paraneoplastic [8]. A definite diagnosis includes the “classical syndromes” plus cancer (that develops within five years of the diagnosis of the neurological abnormalities) and presence or absence of ONA; or in the absence of cancer, the presence of well characterized ONA. In the “non-classical syndromes” setting, association with a tumor discovered within five years of diagnosis of PNS and presence of well/partially characterized ONA or, improvement after cancer therapy constitute a definite diagnosis. If no cancer is detected, presence of well characterized ONA is a *sine qua non* requisite for a definite diagnosis. The possible PNS cases involve the “classical syndromes” without detectable cancer plus absence of ONA or presence of only partially characterized antibodies; and “non-classical syndromes” without ONA plus cancer detected within two years of diagnosis (Tables 1, 2).

Although extremely rare in lymphoid neoplasms, PNS involve a large range of central and peripheral nervous

Table 2 Diagnostic criteria for a “Possible PNS”

Type of PNS	Classical	Classical	Non-classical	Non-classical
Parameters				
Cancer	Negative	Negative	Positive	Negative
Onconeural antibodies	Negative	–	Negative	–
Well characterized	–	–	–	–
Partially characterized	–	Positive	–	Positive
Level of diagnostic evidence	Possible	Possible	Possible	Possible

system manifestations. [9]. In Hodgkin’s lymphoma (HL), the central nervous system paraneoplastic subacute cerebellar degeneration (manifested as dysarthria, nystagmus, truncal ataxia, and appendicular ataxia) is the most common and best characterized PNS, with a strong correlation with the ONA anti-Tr and in very rare instances to auto-antibodies against the metabotropic glutamate receptor (mGluR1). Males are more affected than females, with a median age of 49 years and in almost all cases the PNS develops before the diagnosis of the lymphoma and the outcome appears to be good after cancer treatment. Other PNS that may occur in this lymphoid malignancy include: limbic encephalitis, which may be associated or not with the autoantibodies anti-NMDA; the peripheral nervous system paraneoplastic encephalomyelitis, chronic inflammatory demyelinating polyradiculoneuropathy, sensory neuropathy, sensory neuronopathy and myotonia, in all of which the neurologic syndrome antedates the cancer diagnosis and no onconeural antibodies were detected. [9, 10]. While central nervous system paraneoplastic manifestations are more prevalent in HL, on the other side, peripheral nervous system demyelinating polyradiculopathies and motor neuron involvement are more predominant in non-Hodgkin’s lymphoma (NHL), followed by autonomic neuropathies and Lambert–Eaton myasthenic syndrome, and to date no association with ONA have been detected. Nonetheless, among the central nervous system paraneoplastic manifestations in this group of lymphoid neoplasms, cerebellar degeneration is the most frequent manifestation. Contrary to HL, it affects female sex predominantly, with a median age of 58 years and besides anti-Tr, the anti-GAD was also identified. It is followed by motor neuron disease, brainstem encephalitis, and limbic encephalitis. In most cases, the neurological symptoms precede the neoplasia diagnosis too. [9, 11]. In NHL, paraneoplastic peripheral nervous system diagnosis is more tricky since multiple etiologies might be responsible for the neuropathy and the differential diagnosis should exclude other more common

Table 1 Diagnostic criteria for a “Definite PNS”

Type of PNS	Classical	Classical	Non-classical	Non-classical
Parameters				
Cancer	Positive	Negative	Positive	Negative
Onconeural antibodies	Positive or Negative	Positive	Positive	Positive
Well characterized	–	–	Positive	–
Partially characterized	–	–	Yes	–
Improvement after therapy	Definite	Definite	Definite	Definite
Level of diagnostic evidence	Definite	Definite	Definite	Definite

factors such as neoplastic root infiltration, iatrogenic causes, infection, amyloid or paraprotein deposition, etc.

Neurological improvement is more frequently seen in patients with HL than in NHL. However, in both groups, the survival rate appears to be good after cancer treatment. [9].

In the case reported by Acharya et al., the patient presented a non-classical syndrome and cancer that developed three months after the neurological manifestations. However, no nerve biopsy was performed, screening for ONA was not possible and also no documented neurological response after the first cycle of treatment for the cancer was observed. At this current state, the level of evidence of PNS is only possible. If no neoplastic nerve infiltration was documented or if either ONA were detected and neurological manifestations improved after cancer chemotherapy, PNS in that case would be upgraded to a definite level diagnosis.

The cornerstone of therapy of PNS is the identification and treatment of the underlying malignancy. Rapid detection and immediate treatment of the underlying tumor appears to offer the best chance of stabilizing the patient and preventing further neurological deterioration [12, 13].

The chemotherapy regimen used in the case reported by Acharya et al. was CHOP instead of R-CHOP which is associated with a higher tumor response rates in B cell NHL. Furthermore, since many PNS are an auto-immune disease, adding a monoclonal antibody drug like Rituximab could have resulted in a rapid improvement of the neurological disease too [14].

Conflict of interest Nothing to declare

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