Rare disease

A case of cranial multinevritis: from the onset to the diagnosis of primary neurolymphomatosis

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Summary

Neurolymphomatosis (NL) is a rare peripheral or cranial neuropathy caused by non-Hodgkin's lymphoma (NHL). Diagnosis is often delayed and prognosis is poor. The authors described a woman in her 70s with a facial left peripheral palsy, complete right abducent palsy, left hypoacusia and balance deficit. Then she presented with low progressive hyposthenia at four limbs and cognitive impairment, sudden facial right peripheral palsy and complete left abducent palsy. The authors performed brain and spinal MRI, cerebrospinal fluid (CSF) analysis and extensive haematological examinations for infections, autoimmune and neoplastic diseases. All the results were not diagnostic. Only repeating for the third time a spinal tap, CSF presented neoplastic B cells suggestive for large B-NHL. The authors diagnosed primary NL. The patient was treated with R-CHOP but she died 2 months later. In front of rapidly progressive neuropathy, a NL has to be considered performing different examinations, especially and repeating them after a short period.

BACKGROUND

Neurolymphomatosis (NL) is a rare syndrome determined by nerve infiltration of haematologic neoplastic cells. Usually, it is a manifestation of an unknown or known B cell non-Hodgkin's lymphoma (NHL). Clinical feature is described as a peripheral or cranial neuropathy. Patients with NL present with different types of onset, so diagnosis is often difficult and delayed.¹ Our case needed a repeated set of diagnostic examinations.

CASE PRESENTATION

A woman in her 70s presented a facial left peripheral palsy, treated with steroids and not completely disappeared. Two months later, the patient reported vertigo, postural instability and left hypoacusia. This last symptom got worse in few months with complete left deafness (VIII cranial nerve). After 5 months, a right lateral diplopia (VI cranial nerve) complicated the case history and she was admitted in our department in the suspicion of a cranial neuritis.

Her previous medical history presented two episodes of transient global amnesia and *Helicobacter pylori* gastritis with peptic ulceration at about 60-year-old. Seven years before, occasional discover of serum monoclonal immunoglobulin IgG λ , not investigated at that moment. Until 10 years ago, the patient presented several episodes of sciatic pain as she had multiple disc protrusions and herniations especially to the lomber spine. She was recommended to wear a girdle. A month before the admission, she complained lumbar pain irradiated to the antero-lateral part of the right leg and tingling sensations at the upper part of the anterior right thorax irradiated to radial side of the right arm and the first three fingers.

The patient was also affected by diverticular disease, dyslipidemia and multiple allergy. Patient's chronic therapy was atorvastatin 10 mg.

At the time of admission, clinical examination showed an incomplete left facial palsy (moderate asymmetry of the mouth and difficult of closing right eye), left hypoacusia and balance deficit with no side-prevalence (Romberg sign negative) and complete right abducent palsy. Other findings: mild postural instability, precautious gait, normal cerebellar signs, very quick fatigable nystagmus with head motion in left gaze direction, very mild global weakness and fatigue (strength was 4–5/5 at Medical Research Council (MRC) scale at four limbs), normal-weak reflexes (except for right patellar reflex who was diminished), paresthesias predominant at the lower part of right C4 dermatome and weaker at right C5–C6–C7 dermatomes, reduced pallesthesia at lower limbs. Neuropsychological assessment demonstrated time and space orientation, normal personal autobiographical memory and attention.

INVESTIGATIONS

We first performed a spinal tap. Cerebrospinal fluid (CSF) examination showed 10 cells per μ l (90% polyclonal lymphocytes), proteins 34.6 g/dl, glucose 60 mg/dl, identical oligoclonal bands in CSF and serum. Additionally, we found not significant CSF cytology (extremely rare irregular polylobated non-specific cells, not diagnostic for haematologic malignancies), and cytofluorometry (14% B cells). It was negative for neurotropic viruses and *Mycobacterium*. Haematological examination excluded HIV, tuberculosis, borreliosis, syphilids, Epstein-Barr and cytomegalo viruses. All autoimmune markers (antinuclear antibodies, anti-dsDNA antibodies and antiextractable nuclear antigen, cytoplasmic antineutrophil cytoplasmic antibodies (c-ANCA) and p-ANCA) were in the range of normality. ACE and chest radiography were not altered. Blood cytofluorometry presented 20% B lymphocytes (4% of total white blood

cells) polyclonal and κ/λ ratio 1, 7. We confirmed the presence of serum monoclonal immunoglobulin IgG λ (1070 mg/dl) and diagnosed monoclonal gammopathy of undetermined significance. We excluded multiple myeloma performing a bone marrow biopsy and finding 11488 cells per μl , 9% polyclonal lymphocytes, 25% B cells (4% of total white blood cells) polyclonal and κ/λ ratio 1, 2. First brain MRI showed a few millimetric subcortical periventricular lesions (most probably ischemic). There was no pathological enhancement with gadolinium. Spinal cord MRI evidenced retrolisthesis L2-L3, diffuse cervical, thoracic and lumbar spondylo arthrosis, disc protrusions and herniations. Imaging, performed with contrast enhancement sequences, did not show infiltration of the roots. Vertebral somas L2 and L3 showed a gadolinium enhancement areas at MRI images, but normal bone structure with a CT -scan. We supposed that these alterations could be degenerative. Then, we searched for occulted neoplasia. Neoplastic markers were in the range of normality. We studied chest and abdomen CT imaging, mammography and thyroid ultrasound scan with no significant finding. Fluoro-2-dexoy-d-glucose-positron emission tomography CT and vertebral bone scintigraphy evidenced a focal area at L2-L3 vertebrae. An audiogram reported left side hypoacusia, and auditory brainstem evoked potentials indicated a left side peripheral damage. Nerve conduction studies demonstrated a subclinical motor neuropathy of lower limbs.

In the suspicion of immune-mediated origin or vasculitic damage by neoplastic cells determining cranial neuropathy, we immediately started prednisone 50 mg with an improvement of the right abducent palsy. Two weeks after we started to decrease steroid treatment. During this period, the patient presented low progressive hyposthenia at four limbs, especially legs with tendon reflexes reduction. She started to be quite confuse (probably as a deterioration of general intellectual functions) and electroencephalogram showed diffuse slow waves θ . We repeated spinal tap with similar findings. Electromyography (EMG) evidenced motor neuropathy of lower limbs, almost symmetric. Then, the patient presented with sudden facial right peripheral palsy and complete left abducent palsy (almost a month after the onset of the contralateral). A second brain MRI (3 weeks later) evidenced thickness of the left acoustic-facial pedicle with gadolinium enhancement. We supposed to perform a cranial nerve biopsy but we did not because of the worsening condition of the patient. We analysed CSF for the third time showing 110 cells per μl (90% monoclonal lymphocytes), proteins 184.6 g/dl, reduced glucose 16 mg/dl and serum oligoclonal bands. At cytofluorometry all white blood cells were lymphocytes, 95% cells κ monoclonal. Similar findings in bone marrow biopsy with 7384 cells, 11% lymphocytes B κ monoclonal (5% of total white blood cells). Both blood and CSF cytology evidenced big lymphocytes with irregular nucleus and with the same CD-subtype phenotype. These findings were suggestive for large non-Hodgkin B lymphoma. We diagnosed primary NL.

TREATMENT

The patient was treated with intratecal and systemic chemotherapy R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone).

OUTCOME AND FOLLOW-UP

During the first month, she had a mild recovery of the cranial neuritis, but she presented a progressive global worsening of global weakness, hyposthenia at four limbs (strength was 3/5 at MRC scale) and cognitive decline. In particular, she developed a progressive subacute consciousness impairment, gradually evolved to comatose state. The R-CHOP treatment was stopped switching to palliative cares. She died 2 months later with heart failure.

DISCUSSION

NL is an uncommon neurological manifestation, extremely rare as the presentation of malignancy. Grisariu *et al*² described only 11 patients with systemic NHL who manifested a primary NL at onset. Frequently more than one neural structure is involved during the disease course and peripheral sensorimotor neuropathy is the main clinical features. In fact, our patient developed a polyneuropathy, as demonstrated by EMG, but she particularly presented with a multi-cranial nerves involvement.

Diagnosis of NL is often delayed and needs an integration of clinical, radiological and biological finding, as remarked by the International Primary Central Nervous System Lymphoma Collaborative Group report.² However, Levin³ indicated that CSF and MRI could be not diagnostic for NL, as in our case. Bower⁴ described a case of NL with cranial presentation, whose diagnosis was elusive despite extensive investigations. We especially experimented the necessity of repeating in a short time diagnostic examinations to obtain significant results.

Usually, imaging studies have a great utility in disease definition. Kim presented a case of rapidly progressive secondary NL with cranial onset, diagnosed with MRI and PET-CT findings.⁵ However, in our case neither brain and spinal MRI nor PET-CT revealed diagnostic features. Brain MRI showed a nerve enlargement only on the right side, whereas our symptoms were prevalent on the other one. Spinal MRI and PET-CT evidenced no specific findings for NL in the lumbar tract, as our patient was also affected by arthrosis. Although, Gan⁶ suggested that abnormalities on the images, in particular PET-CT scanning, could indicate a target for a biopsy. We were intentioned to perform a vertebral biopsy, but a rapid worsening of the patient's condition abolished this possibility. However, Grisariu's paper² suggested the high diagnostic yield of nerve biopsy, especially with inconclusive MRI and CSF findings. We did not consider biopsy of any spinal nerve root or plexus, as no suspicious infiltration of roots was evidenced at spinal cord MRI and PET-CT did not show any enhancing lesion in plexuses. Although we had found a motor neuropathy that was probably manifestation of NL, we did not perform peripheral nerve biopsy (but in our report this clinical feature was not the presenting and most impressive one). We evaluated cranial nerve biopsy after second cranial MRI findings, but we decided to avoid as risks of the procedure were too high in such an impaired patient.

In our report, the clue element for diagnosis was CSF analysis, but we had to repeat three times a spinal tap to finally detect malignant cells. Cytological examination of the first and second spinal taps could be considered suspicious, described twice as a non-specific and rare findings.

The delay in diagnosis, and consequently, in therapy could contribute to the poor prognosis. Treatment is mainly based on chemotherapy with a response rate of 82%, lasting from 2 weeks to 9 years.⁷

Learning points

- ▶ Primary NL is extremely rare presentation of NHL.
- ▶ A high suspicion of NL is necessary in front of rapidly progressive neuropathy.
- ▶ To perform many diagnostic examinations and to repeat them after a first negative result.

Competing interests None.

Patient consent Not obtained.

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