Unusual presentation of more common disease/injury

Lambert–Eaton myasthenic syndrome and solitary cerebellar metastasis in a patient with occult small-cell lung cancer: a rare experience

Sayantana Ray, Nikhil Sonthalia, Supratip Kundu, Subhasis Maitra, Manjari Saha, Arunansu Talukdar

Department of General Medicine, Medical College Kolkata, Kolkata, West Bengal, India

Correspondence to Dr Arunansu Talukdar, arka_talukdar@yahoo.com

Summary

The authors describe a case of 60-year-old male patient presented with a 6 month history of progressive weakness of all the four limbs, ataxia, droopy eyelids and bulbar features. Further laboratory and electrodiagnostic studies confirmed the diagnosis of Lambert–Eaton myasthenic syndrome (LEMS). MRI of the brain showed a cerebellar tumour which, following surgery was revealed to be a metastatic small-cell lung carcinoma. Paraneoplastic LEMS together with solitary cerebellar metastasis was diagnosed but no evidence of primary malignancy was detected. An extensive search for related malignancies failed to get any clue. The patient underwent a total surgical excision of tumour and the histopathology revealed a metastatic small cell carcinoma. This case highlights that rarely both paraneoplastic LEMS and cerebellar mass can precede the primary malignancy causing them.

BACKGROUND

Lambert–Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder of neuromuscular transmission. It is characterised clinically by muscle weakness, hyporeflexia or areflexia, and autonomic dysfunction. LEMS develops as a result of antibodies directed at the presynaptic voltage-gated calcium channels (VGCC).^{1–3} LEMS can occur as remote effect of a neoplasm, in the paraneoplastic form (P-LEMS), usually in association with small-cell lung cancer (SCLC), or in the non-paraneoplastic form (NPLEMS).^{4–5} To stamp a case as patient with non-paraneoplastic LEMS needs a long-term follow-up as in paraneoplastic cases neurological symptoms can precede the diagnosis of primary neoplasm.^{1–5–6} Although brain metastasis is present in about 80% of treated cases of SCLC, only a few cases of solitary brain metastasis with occult primary lung tumour at the time of diagnosis has been reported.^{7–8} The most intriguing fact in our case is the presence of both a paraneoplastic syndrome in form of LEMS and a cerebellar metastasis without any evidence of primary causative malignancy that is still not reported in the literature. This case highlights that rarely both paraneoplastic LEMS and cerebellar mass can precede the primary malignancy.

CASE PRESENTATION

A 60-year-old man presented with a 6-month history of progressive weakness of all four limbs followed by difficulty swallowing more with liquid than solid. The weakness was first noticed in proximal lower limb musculature followed by that of upper limbs. He did not give any story of diurnal variation of weakness. Swallowing difficulty was associated with nasal regurgitation of liquid materials. He also mentioned about drooping of eyelids and associated double vision for last 4 months. There was history

suggestive of gait ataxia and bladder involvement. He also complained of a dry mouth during the past 2 months. He had been smoking four packets of bidi daily for last 30 years. On examination, the weakness was found to be of grade 3/5 in all the four limbs. There was predominantly proximal weakness and he had weakness of both flexors and extensors of lower and upper limbs. Prominent weakness of neck flexors was detected. All tendon reflexes were diminished and following voluntary contraction of lower limb muscle for 10 s showed mild improvement. There was generalised wasting of muscles. Plantar reflex was non-responsive bilaterally. Eye examination revealed bilateral, asymmetric partial ptosis and bilateral horizontal jerky nystagmus with fast component towards left side. Further examination revealed signs of cerebellar involvement more on the left side. There were no sensory symptoms. No muscular fasciculations were seen. There was no lymphadenopathy. Fatigability test with forward arm abduction was performed and found to be positive with presence of facilitation. A bedside ice-test showed no resolution of ptosis. Neostigmine test was done which did not show any improvement in muscle strength. Based on these clinical finding we suspected a neuromuscular junctional disorder together with cerebellar involvement and proceed for relevant electrophysiological studies and brain imaging.

INVESTIGATIONS

Electrophysiological studies demonstrated low amplitude of compound muscle action potential (CMAP) in orbicularis oculi and in upper and lower limb muscles. Repetitive nerve stimulation at low rate (3 Hz) revealed a decremental response (figure 1a). However, 30-Hz stimulation resulted in a 300% increase CMAP highly suggestive of LEMS (figure 1b). Anti-P/Q-type VGCC antibody

Figure 1 (a) Repetitive stimulation at 3 Hz demonstrating a 21.97% decrement between stimulus 1 and 5. Gain is 3 mV per division and a sweep speed of 5 milliseconds. (b) An incremental response as manifested by increase in area under curve for amplitude of about 300% at high-rate stimulation (30 Hz). Gain is 1 mV per division and a sweep speed of 5 milliseconds.

titre was raised (>45 pM). CT scan of chest was normal. Antiacetylcholine receptor antibody test was negative. A fiberoptic bronchoscopy showed normal study with bronchoalveolar lavage fluid analysis negative for malignant cells. Ultrasound of abdomen showed normal echogenicity of both the kidneys. An endoscopic examination of colon revealed no abnormality. Thyroid profile was within normal limits and there was no clinical or ultrasound evidence of thyroid gland enlargement. MRI of brain revealed peripherally enhancing mass in the left cerebellar hemisphere with diffusion restriction at periphery suggestive of secondary (figure 2a,b). The tumour was completely excised and histopathology revealed metastatic small cell carcinoma (figure 3). A panel of immunohistochemical stains including AE1/AE3, cytokeratin 20, cytokeratin 7 and synaptophysin were used. The tumour showed a dot-like staining pattern with pan-cytokeratin antibody AE1/AE3. Tumour cells showed positivity for cytokeratin 7 but were immunonegative for cytokeratin 20. Neuroendocrine differentiation was demonstrated using immunopositivity for synaptophysin.

All these features points towards small cell cancer of pulmonary origin. In view of the presence of a paraneoplastic syndrome that has strong association with SCLC, we consider it to be a metastasis from occult SCLC.

DIFFERENTIAL DIAGNOSIS

- ▶ Lambert–Eaton syndrome
- ▶ Myasthenia gravis
- ▶ Guillain–Barré syndrome
- ▶ Demyelinating neuropathy.

TREATMENT

3, 4 diaminopyridine (3, 4 DAP) was not commercially available to us, so we put the patient on oral pyridostigmine (60 mg four times daily) and oral prednisolone (1 mg/kg) on alternate days. As the weakness was worsening with evidence of respiratory compromise, intravenous immunoglobulin (IVIG) at dose of 1 g/kg for 2 consecutive

days was administered. Two weeks after IVIG the patient showed satisfactory improvement in strength. The patient received whole brain irradiation at a total dose of 30 Gy in 10 fractions with good tolerance following the complete excision of the tumour.

OUTCOME AND FOLLOW-UP

Two weeks after IVIG the patient showed satisfactory improvement in strength. He could walk without assistance and there was improvement in ptosis with disappearance of bulbar features. Unfortunately the patient was lost to follow-up and we could not investigate further for the evidence of primary lung tumour that had given rise to the paraneoplastic syndrome and cerebellar metastasis.

DISCUSSION

LEMS is rare with a prevalence of about 1 per 100 000, equally common in men and women. It is associated with small cell lung tumours, lymphoproliferative disorders and rarely with other malignancies like papillary carcinoma of thyroid, thymoma, colonic carcinoma, renal cell carcinoma etc. There are two types of LEMS—LEMS associated with carcinoma and LEMS without carcinoma. Patients with either type have disease on autoimmune basis.⁹ VGCC are blocked in patients with LEMS. Antibodies against the P/Q VGCC type inhibit acetylcholine release from the motor nerve terminals, resulting in muscular weakness.¹⁰ Our patient was 60 years old, corroborating with the mean age (57.9) of patients with LEMS associated with carcinoma. However, 80% of patients with LEMS are older than 40 years.¹¹ The disease is usually subacute in onset as seen in our case. He presented with proximal limb weakness of 6 month's duration, which is characteristic of patients with LEMS. Our patient had cranial nerve symptoms (eg, diplopia, ptosis and dysphagia) which may be present in 70% of patients with LEMS.¹² He also complained of a dry mouth and had orthostatic hypotension. Such autonomic symptoms are seen in 80% of patients with LEMS.¹² Results of electrodiagnostic studies in our patient were characteristic

Figure 2 (a) Coronal T1W MR showing a focal rounded heterogenous mass ($2.7 \times 2.9 \times 2.6$ cm) in the left cerebellar hemisphere with patchy and perifocal enhancement after contrast. (b) Axial T2W fluid attenuated inversion recovery MR shows image peripherally enhancing rounded space-occupying lesion with perifocal oedema.

Figure 3 H&E, 400×, small-cell carcinoma, brain metastasis.

of LEMS, with a low CMAP amplitude at rest, a decremental response at low stimulation frequency, and an incremental response at high-rate stimulation.

3,4-DAP is recommended as first-line symptomatic treatment in LEMS and it should be offered to all patients suffering from this rare disease. Patients with paraneoplastic LEMS may be unresponsive to 3, 4-DAP and further immunotherapy should be considered in this context. Other treatment consists of pyridostigmine bromide, prednisone, azathioprine and guanidine- all of which are associated with significant side effects and poor responses.¹¹ IVIG infusion has been studied more recently in patients with LEMS. Bain *et al*¹³ reported an onset of effect of IVIG

in their patients at 2 to 4 weeks. The severity of symptoms in our patient prompted us to go for a therapy which has quicker onset of effect and lower side effect profile, so we started a course of IVIG. The patient showed marked improvement in the weakness and bulbar symptoms following one course of IVIG.

Our patient had solitary cerebellar metastasis with no evidence of primary. Surgery followed by histopathology revealed a metastatic small-cell carcinoma. Recently a simple clinical score has been developed and validated to identify the presence of SCLC early in the course of LEMS.¹⁴ It can be derived allocating one point for the presence of each of the following parameters at or within 3 months from

onset: age of onset ≥ 50 years, smoking at diagnosis, weight loss $\geq 5\%$, bulbar involvement, erectile dysfunction and Karnofsky performance status lower than 70. Our patient had a score of five which correlates with 96.6% chance of an associated SCLC even if the primary was not detectable at the time of diagnosis. Similarly there are studies to show that in majority of the patients with brain metastasis with unknown primary, the primary detected during clinical course is bronchogenic carcinoma.^{15 16} LEMS is initiated by an immune reaction to VGCC expressed on the surface of the SCLC. The resulting antibodies react with VGCC at the presynaptic nerve terminal of the neuromuscular junction.¹⁷ Similarly, VGCCs are expressed in the cerebellum and patients with SCLC, with or without LEMS, may also have cerebellar dysfunction. The long-term survival in these patients despite presence of highly malignant tumour implies that the anti-VGCC antibodies may be playing a role in controlling tumour growth or, alternatively, that the small cell cancers that provoke LEMS may be slower growing.¹⁸ Similarly there are cases reported to show that the prognosis in a patient of solitary brain metastasis and occult small cell lung carcinoma is not always as dismal as compared with the patients with brain metastasis occurring after the evidence of SCLC and synchronous metastasis to other sites.^{7 8} These facts bring to the front that though a small cell lung carcinoma is a highly malignant disease with poor prognosis, early detection and treatment of the paraneoplastic syndrome and metastasis even in absence of the detectable primary tumour can significantly improve the survival in these patients.

In our case the neurological symptoms of the patient improved with IVIG and patient tolerated the radiotherapy well but unfortunately long-term response evaluation and further investigation with bronchoscopy and rescanning with positron emission tomography (PET) study could not be contemplated as the patient was lost to follow-up.

Learning points

- ▶ Both paraneoplastic and neoplastic LEMS though have similar clinical feature they have a different natural history and should be identified early during the course of the disease.
- ▶ It is possible to predict the possibility of having an associated cancer in patients with LEMS on the basis of δ -P score.
- ▶ Rarely both a metastasis and a paraneoplastic syndrome associated with a cancer can occur in a person without the diagnosis of the primary cancer.
- ▶ These patients are ideal candidates for long-term follow-up with bronchoscopy, rescanning with PET study for the detection of primary at least for 2 years from the initial diagnosis of the paraneoplastic syndrome.
- ▶ Prognosis is better in patients having brain metastasis with occult primary small cell lung carcinoma than in patients developing the metastasis after the full blown development of SCLC.

Competing interests None.

Patient consent Obtained.

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