Chakrabarti B, MBBS, MD, DNB, Assistant Professor
Roy S, MBBS, DMRT, Senior Resident
Malik C, MBBS, MD, Resident Medical Officer, Clinical Tutor
Bhattacharya KS, MBBS, MD, Assistant Professor
Mukherjee S, MBBS, Junior Resident
Department of Radiotherapy, Institute of Postgraduate Medical Education and Research, Kolkata, India

Correspondence to: Somnath Roy, e-mail: drsomnath1980@gmail.com

Keywords: paraneoplastic syndrome, small cell neuroendocrine carcinoma cervix

Abstract
Paraneoplastic syndrome frequently presents before cancer is diagnosed and can be associated with neoplastic disease that is not yet radiographically detectable. We report on the case of a 35-year-old woman who presented at the neurology department with complaints of insidious onset and gradually progressive weakness in all four limbs, which had lasted for the past six months. The weakness originally commenced in both lower limbs and was progressive, ascending in nature from distal to proximal. Both upper limbs were affected seven days later. Magnetic resonance imaging of the dorsal spine revealed long-segment T2 and short T1 inversion recovery (STIR) hyperintensity, suggestive of myelitis. Nerve conduction studies and an electromyogram suggested sensory motor polyneuropathy which affected all four limbs. On gynaecological check-up, a diagnosis of International Federation of Gynaecology and Obstetrics (FIGO) stage IIB carcinoma cervix was made. Histology diagnosed it as a case of small cell neuroendocrine carcinoma. Thus, a diagnosis of chronic inflammatory demyelinating polyneuropathy, arising as a paraneoplastic syndrome in the carcinoma cervix, was made. The patient was treated with chemotherapy, steroids and radical radiotherapy. She recovered partially from her motor deficiencies and completely from her sensory derangement, and was devoid of gynaecological complaints. The cancer growth regressed completely.

Introduction
Neuroendocrine carcinomas of the cervix are an uncommon heterogeneous group of diseases that account for only 0.5-2% of all gynaecologic malignancies. The most common types are ovarian carcinoid tumours and small cell neuroendocrine carcinoma of the cervix. Small cell neuroendocrine carcinoma of the cervix may present with local symptoms, as for squamous cell carcinoma of the cervix, or with systemic symptoms of ectopic hormone production, and may remain occult in some cases. Paraneoplastic symptoms, seen in gynaecological cancers, are commonly ovarian cancer and gestational trophoblastic tumours. Neurological syndromes are common. Peripheral neuropathies, organic dementia, amyotrophic lateral sclerosis-like syndrome and cerebellar ataxia are the most frequent occurrences. Peculiar antibodies that cause difficulties in cross-matching blood can be corrected with prednisone. Cushing's syndrome, hypercalcaemia and thrombophlebitis may occur. Paraneoplastic symptoms which occur in carcinomas of the cervix are a rare presentation.

Chronic inflammatory demyelinating polyneuropathy (CIDP), an acquired immunologically mediated disorder, is clinically similar to that of Guillain-Barré syndrome, except that it has a relapsing or steadily progressive course over months or years. Treatment is usually begun with prednisone, 60 mg daily, continued for 2-3 months, or until a definite response has occurred. Small cell neuroendocrine carcinoma of the cervix carries a dismal prognosis with high mortality, even with early-stage disease that relates to early nodal and haematogenous metastasis. Even though it is a highly aggressive neoplasm, early diagnosis and combined therapeutic modalities may lead to longer survival in some patients. Use of adjuvant chemotherapy
or chemoradiation has been associated with higher survival in patients with cervical cancer.10,11 A high index of suspicion, early diagnosis and proper treatment may prolong survival, and to a major extent, revert paraneoplastic manifestations.

Case report

A 35-year-old nonhypertensive, nondiabetic female with no history of addiction, presented at the outpatient Department of Neurology, Institute of Postgraduate Medical Education and Research, Kolkata, with complaints of an insidious onset and gradually progressive weakness in all four limbs, which started six months prior, having commenced originally in both lower limbs. Thereafter, it was progressive, ascending in nature from distal to proximal. Both upper limbs were affected seven days later.

The patient also complained of sensory changes such as tingling, numbness and a burning sensation in the lower part of her body for the same period. There were no complaints of fever, loss of consciousness, headaches, convulsions, sensory symptoms, bowel or bladder symptoms, cranial nerve deficits, rashes or arthritis, nor was there a family history of neurological disorders.

On examination, her higher functions were normal. On general survey, she had a mild pallor. The pulse and blood pressure were within normal limits with no postural drop. Muscle tone was decreased in all four limbs. Muscle power was 3/5 in the upper limbs and 1/5 in the lower limbs. Deep tendon reflexes were diminished. There was an impaired vibration sensation in the lower limbs. A neurological and systemic examination revealed no more clinical findings.

Magnetic resonance imaging (MRI) of the dorsal spine suggested long-segment dorsal cord T2 hyperintensities. Nerve conduction studies diagnosed CIDP. Other investigations included routine blood tests, fasting and postprandial blood sugar, haemoglobin A1c, a liver function test, renal function tests, a cerebrospinal fluid study, a human immunodeficiency virus test, a venereal disease research laboratory (VDRL) test and antineutrophilic antibody testing. Serum electrophoresis for immunoglobulin was within normal limits. However, an ultrasonography of the abdomen revealed a bulky and heterogeneous cervix and two hypoechoic lymph nodes seen at the right parametrium.

The patient was referred to the gynaecological outpatient department. Following persistent enquiry, the patient disclosed that she had occasional spotting per vagina for the last six months and infrequent passing of white discharge. An ulceroproliferative growth in the anterior lip of the cervix was found that bled on touch.

After proper vaginal and speculum examination, it was clinically suspected to be a case of International Federation of Gynaecology and Obstetrics (FIGO) stage IIB carcinoma of the cervix. Histology diagnosed it as a case of small cell neuroendocrine carcinoma (Figures 1 and 2). Immunohistochemistry showed the presence of chromogranin, synaptophysin and neuron-specific enolase. P16 and p63 were negative, proving it to be a case of small cell neuroendocrine carcinoma of the cervix. A nerve biopsy from the sural nerve showed acute axonal and myelin degeneration. Clusters of lymphocytes and occasional plasma cells were seen in the endoneurium. Sparse perivascular lymphocytes were seen around the epineural venules in the epineurium. Myelin stains highlighted strikingly non-uniform fibre loss, involving the large sector. There was acute myelin breakdown with minimal regeneration. This was suggestive of inflammatory neuropathy.

Figure 1: A microphotograph showing a high-power view of the tumour, comprising small cells with hyperchromatic nuclei, inconspicuous nucleoli and scant cytoplasm arranged in nests and in an organoid fashion (haematoxylin and eosin stain, x 400 magnification)

Figure 2: A microphotograph showing sheets of small cells with hyperchromatic nuclei, together with areas of necrosis (haematoxylin and eosin stain, x 100 magnification)
The patient was treated with three cycles of carboplatin (area under the curve 5 on day 1) and etoposide (100 mg/m² days 1-5) at an interval of 21 days. This was followed by concomitant chemoradiation (external beam radiotherapy of 50 Gy in conventional fractionation, together with weekly concomitant cisplatin 40 mg/m²) and brachytherapy (up to 80 Gy at point A). She was also given oral prednisolone in a tapering dose for the first three months. The patient was put on physiotherapy and supportive care for neurological impairment. She recovered partially from her motor deficiencies and completely from her sensory derangement, and was devoid of gynaecological complaints. The cancer growth regressed completely. She attended a regular monthly follow-up, was asymptomatic, and had been free of disease for over a year.

Discussion

This 35-year-old female patient had decreased tone, with loss of deep tendon reflexes and posterior column senses, suggesting a lower motor neuron type of weakness that could either have been radiculopathy or neuropathy. The MRI of her dorsal spine revealed long-segment T2 and short T1 inversion recovery (STIR) hyperintensity, suggestive of myelitis. Nerve conduction studies and an electromyogram suggested sensorimotor polyneuropathy that was affecting all four limbs. Anatomical localisation was central, with peripheral demyelination with an axonal component. The possible causes of such a presentation, like diabetes mellitus, plasma cell disorders, human immunodeficiency virus, vasculitis and infective aetiology, were all excluded. The patient was a histologically proven case of small cell neuroendocrine carcinoma of the cervix.

Immunohistochemistry showed positivity of chromogranin, synaptophysin and neuron-specific enolase. P16 and p63 were negative. This further confirmed a case of small cell neuroendocrine carcinoma of the cervix. A nerve biopsy from the sural nerve showed acute axonal and myelin degeneration.

Paraneoplastic syndrome frequently presents before cancer is diagnosed and can be associated with neoplastic disease that is not yet radiographically detectable. An autoimmune pathogenesis has been demonstrated for some of these disorders, and specific antibodies are associated with many of the paraneoplastic disorders. These antibodies are generated as an antitumor response and are directed against the patient’s tumour. They are thought to cross-react with specific neuronal subgroups to produce neurological dysfunction and the clinical syndrome. As a part of this syndrome, neurological manifestations include cerebellar degeneration, opsoclonus myoclonus, retinopathy, limbic or brainstem encephalitis and neuropathies. It may present as an exclusively motor disorder, or with a mixed sensorimotor disturbance. The diagnosis is often suspected clinically because the neurological syndrome is highly specific.

CIDP is an acquired immunologically mediated disorder. It is clinically similar to that of Guillain-Barré syndrome. It may present as an exclusive motor disorder or with a mixed sensorimotor disturbance. Electrodiagnostic studies show marked slowing of motor and sensory conduction, and focal conduction block. Signs of partial denervation may also be present, owing to secondary axonal degeneration. A nerve biopsy may show chronic perivascular inflammatory infiltrates in the endoneurium and epineurium, without accompanying evidence of vasculitis.

Treatment is usually begun with prednisone, 60 mg daily, continued for 2-3 months, or until a definite response has occurred. If no response has been noted despite three months of treatment, a higher dose may be tried. The dose is gradually tapered in responsive cases, but most patients become corticosteroid-dependent, often requiring prednisone 20 mg daily on alternate days, on a long-term basis. Intravenous immunoglobulin is best used as the initial treatment in pure motor syndromes. It is unknown whether or not combined treatment with intravenous immunoglobulin and steroids offers added benefit.

The diagnosis of small cell neuroendocrine carcinoma of the cervix depends on the combination of light microscopic and immunohistochemical analysis. Immunohistochemical findings were positive 81.8% for neuron-specific enolase and 81.8% for protein gene product 9.5 (PGP 9.5); 72.7% for synaptophysin; 63.6% for chromogranin A; and 54.5% for neural cell adhesion molecule.

Various markers have been suggested to differentiate small cell neuroendocrine carcinoma of the cervix from similar diseases. P63 is of value in distinguishing small cell neuroendocrine carcinoma (p63-negative) from small cell squamous carcinoma (p63-positive), and in confirming that a poorly differentiated carcinoma is squamous in type. In our case, p63 was negative.

Despite the reported retrospective studies and case reports in the literature, the best modality of treatment remains controversial. Early-stage patients should be treated with extensive hysterectomy and pelvic lymphadenectomy in combination with pre- and/or postoperative adjuvant chemotherapy and radiotherapy. Concurrent chemoradiation could be used to treat patients with advanced-stage disease, despite their poor prognosis. Use of adjuvant chemotherapy or chemoradiation has been
associated with higher survival in patients with small cell neuroendocrine cervical cancer.\textsuperscript{10}

\textbf{Conclusion}

Small cell carcinoma of the cervix, occurring either as a variant of squamous cell carcinoma or as a neuroendocrine carcinoma, imparts a poor outcome. Presentation with paraneoplastic syndrome, as in our case, may misdirect and delay diagnosis. All physicians should keep in mind the paraneoplastic syndrome as a differential diagnosis and search for a possible hidden cancer whenever such cases are seen. A high index of suspicion, early diagnosis and proper treatment may cure this cancer and to a major extent, revert the paraneoplastic syndrome.

\textbf{References}

1. Rekhi B, Patil B, Deodhar KK, et al. Spectrum of neuroendocrine carcinomas of the uterine cervix, including histopathologic features, terminology, immunohistochemical profile, and clinical outcomes in a series of 50 cases from a single institution in India. Ann Diagn Pathol. 2012;24. [Epub ahead of print]

2. Kuc-Rajca M, Dariska-Bidzińska A. Contemporary management of neuroendocrine neoplasms of the female genital organs. Ginekol Pol. 2011;82(9):685-689.

3. Rhiem K, Possover M, Gossmann A, et al. “Occult” neuroendocrine component and rare metastatic pattern in cervical cancer: report of a case and brief review of the literature. Eur J Gynaecol Oncol. 2007;28(2):139-141.

4. Qin JC, Li L, Yang ZJ, Yao DS, et al. Clinico pathologic analysis of small cell neuroendocrine carcinoma of the cervix. Zhonghua Fu Chan Ke Za Zhi. 2011;46(5):360-363.

5. Boyle E, Nzewi E, Khan I, et al. Small cell cervical cancer: an unusual finding at cholecystectomy. Arch Gynecol Obstet. 2009;279(2):251-254.

6. Liu J, Li Y, Li S, et al. Clinico pathological features and prognosis of small cell carcinoma of the cervix. J Huazhong Univ Sci Technolog Med Sci. 2010;30(5):626-630.

7. Lee SW, Nam JH, Kim DY, et al. Unfavorable prognosis of small cell neuroendocrine carcinoma of the uterine cervix: a retrospective matched case-control study. Int J Gynecol Cancer. 2010;20(3):411-416.

8. Watanabe Y, Nakai H, Imaoka I, et al. Carcinomatous meningitis during systematic chemotherapy in a patient with advanced small-cell neuroendocrine carcinoma of the uterine cervix. J Obstet Gynaecol Res. 2012;38(1):336-339.

9. Kim YM, Jung MH, Kim DY, et al. Small cell carcinoma of the uterine cervix: clinicopathologic study of 20 cases in a single center. Eur J Gynaecol Oncol. 2009;30(5):539-542.

10. Cohen JG, Kapp DS, Shin JY, et al. Small cell carcinoma of the cervix: treatment and survival outcomes of 188 patients. Am J Obstet Gynecol. 2010;203(4):347, e1-e6.

11. Lee JM, Lee KB, Nam JH, et al. Prognostic factors in FIGO stage IB-IIA small cell neuroendocrine carcinoma of the uterine cervix treated surgically: results of a multi-center retrospective Korean study. Annals of Oncology. 2008;19(2):321-326.

12. Joint Task Force of the EFNS and the PNS. 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. J Peripher Nerv Syst. 2005;10(3):220-228.

13. Jolles S, Sewell WAC, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol. 2005;142(1):1-11.

14. Deng GH, Zhang X, Wu LY. Clinico pathological analysis of nine cases of small cell carcinoma of the uterine cervix. Zhonghua Liu Za Zhi. 2010;32(3):199-202.

15. Chatterjee S, Chakravorty S, Kapoor P, Chattopadhyay D. Small cell neuroendocrine carcinoma of cervix: a case report. Indian J Pathol Microbiol. 2005;48(3):410-412.

16. McCluggage WG. Immunohistochemistry as a diagnostic aid in cervical pathology. Pathology. 2007;39(1):97-111.

17. Bifulco G, Mandato VD, Giampaolino P, et al. Small cell neuroendocrine cervical carcinoma with 1-year follow-up: case report and review. Anticancer Res. 2009;29(2):477-484.