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A RARE CASE OF PARANEOPLASTIC GUILLAIN-BARRÉ SYNDROME IN A PATIENT WITH ENDOMETRIAL CANCER

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ABSTRACT

Introduction: Guillain-Barré syndrome is an acute, inflammatory polyradiculoneuropathy of autoimmune aetiology. It is a rare disease seen in 1 in 100,000 person-years. Up to 20% of those affected develop severe disability; mortality in Guillain-Barré syndrome is 5%. Guillain-Barré, associated with many malignancies as a paraneoplastic phenomenon, has been reported – especially in haematological malignancies such as lymphoma and leukaemia. Solid tumours associated with paraneoplastic Guillain-Barré syndrome are breast and lung cancers. The association between paraneoplastic Guillain-Barré syndrome and gynaecological malignancies are rare, and only a handful of cases have been previously reported in gynaecological cancers.

Case description: We discuss a 65-year-old Sri Lankan female patient diagnosed with metastatic endometrial carcinoma who presented with paraneoplastic Guillain-Barré syndrome. The patient was treated appropriately and eventually recovered from her condition.

Conclusion: Paraneoplastic Guillain-Barré syndrome is a rare phenomenon that clinicians can easily miss, and it has rarely been described in gynaecological cancers. Our patient was diagnosed with this rare phenomenon. The timely recognition and prompt treatment of this potentially life-threatening condition with multiple complications is essential in managing patients with malignancies and neuropathy. Further studies on paraneoplastic Guillain-Barré syndrome are needed as cases may be underreported.

KEYWORDS

Guillain-Barré syndrome, paraneoplastic, endometrial carcinoma

LEARNING POINTS

- Paraneoplastic Guillain-Barré syndrome e is a very rare phenomenon that can be easily missed by clinicians.
- Paraneoplastic Guillain-Barré syndrome has rarely been described in gynecological cancers.
- The timely recognition and prompt treatment of this potentially life-threatening condition with multiple complications is essential in managing patients with malignancies and neuropathy.

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INTRODUCTION

Neurological paraneoplastic syndromes are a rare subgroup of diseases commonly related to neuroendocrine tumours. However, they have been associated with uterine malignancies. Paraneoplastic neurologic syndromes in uterine cancer patients are very rare and have a variety of clinical presentations, the most common being cerebral degeneration. However, other neurological syndromes present with various symptoms, leading to delayed diagnosis[1]. Rarer paraneoplastic neurological syndromes associated with uterine cancer are Guillain-Barré syndrome, encephalitis, encephalomyelitis, subacute sensory neuropathy, sensory-motor neuropathy and other neurological manifestations. Their presentation often correlates with a cancer diagnosis or recurrence, underlining their clinical significance.

CASE DESCRIPTION

Our patient was a 65-year-old previously healthy female of Sri Lankan ethnicity without any significant medical history or receiving any regular medication. She was investigated for post-menopausal bleeding two months before presentation. She was diagnosed with high-grade endometrial carcinoma and underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy four weeks before the current presentation. Histologically, she was diagnosed with an International Federation of Gynaecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique – FIGO) stage 2 disease. The patient underwent one cycle of adjuvant chemotherapy following surgery and received carboplatin and paclitaxel combination therapy. She tolerated treatment well. One week after the adjuvant chemotherapy was completed, she presented with a history of bilateral hand and foot numbness and tingling for the preceding week. She also complained of lethargy and loss of appetite, but no history of fever or other systemic symptoms. She had progressive bilateral lower limb weakness for three days before the presentation, which gradually and progressively worsened. The patient had difficulty standing from a sitting position and with time, she could not support her weight or ambulate. She also complained of severe lower back pain of a mechanical type simultaneously with the onset of weakness. The back pain was only partially relieved by nonsteroidal anti-inflammatory drugs. She did not have a sensory level, or urinary or faecal incontinence. On admission, physical examination revealed BP 180/100 mmHg, PR 100 bpm, regular and good volume RR 20/min, SpO_2 98% on air, bilateral air entry equal and no added sounds. The abdomen was soft and non-tender, no hepatosplenomegaly and no ascites.

The patient was alert and oriented. Cranial nerves were intact; the patient was able to vocalise and had no dysphagia. Strength testing showed 3/5 weakness in hip flexors and extensors bilaterally; the upper extremities showed 4/5 strength. Deep tendon reflexes were diminished in ankle and knee joints. No muscle fasciculations were noticed, and there was no sensory loss despite subjective complaints of numbness and tingling sensations. There were no cerebellar signs – a Romberg test was negative – and no bladder or bowel impairment.

By the evening of the second day of admission to the ICU the weakness worsened, with power in the lower extremities dropping to 1/5 and upper limb power to 2/5 bilaterally, and absent reflexes in the legs and upper limbs bilaterally. Her cough reflex began deteriorating, progressively reducing vital capacity on testing (<700 cc). She developed mild dysarthria and respiratory distress developed, with the inability to breathe adequately. SpO_2 dropped to 85%. Arterial blood gas was measured, which showed pH 7.38, pO_2 55 mmHg, pCO_2 48 mmHg, lactate level 2). As a result, she was electively intubated, sedated, and ventilated. At this stage, several diagnoses were considered.

First of all, we considered Guillain-Barré syndrome. Other diagnostic considerations were acute myelopathy due to cord compression, chemotherapy-induced neuropathy, acute polyneuropathy due to vasculitis and acute vitamin B1 deficiency. The patient's history suggested Guillain-Barré syndrome with acute ascending paralysis with areflexia, relative symmetry, and absence of objective sensory loss or sphincter involvement. There was a history of underlying malignancy; the patient had no clinical symptoms or signs to suggest an antecedent infection. Investigations including full blood count, C-reactive protein test, stool cultures, chest radiograph, urinalysis and cultures were normal, making paraneoplastic Guillain-Barré syndrome highly likely. We planned nerve conduction studies and lumbar puncture, and an MRI to exclude compressive myelopathy as a differential diagnosis.

She had hyponatraemia with an average potassium level. Renal, hepatic and thyroid functions and vitamin B12 levels were normal; fasting blood sugar and HBA1c levels were within normal range. The vasculitis screening was negative, as were HIV, HBsAg, CMV and IgM. Cerebrospinal fluid analysis showed cyto-protein dissociation (with a protein level of 200 mg/dl, no polymorphs and five lymphocytes). No features are suggestive of meningitis. Nerve conduction studies showed decreased amplitudes and slow velocities of compound muscular action potential, suggesting acute inflammatory demyelinating neuropathy-type Guillain-Barré syndrome. An MRI spine T1 weighted sagittal scan without contrast of the complete spine demonstrated the absence of fracture, subluxation and abnormal cord signal in the cervical, thoracic and lumbar spine. There were no features of metastatic disease or cord compression. In the ultrasound scan of the abdomen there was a 3.2 cm × 2.1 cm hypoechoic lesion noted in the right iliac region adjacent to the iliac vessels, highly suggestive of the metastatic lymph node. With her clinical presentation and investigations, the patient was diagnosed with Guillain-Barré syndrome and was started on intravenous immunoglobulin (IVIg) 0.4 mg/kg for five doses, resulting in minimal improvement. Lower limb muscle power was 2/5; upper limb power was 2/5;

neck muscle power was 2/5. She had poor tidal volumes and diminished cough reflex. As there was minimal recovery initially one week after the IVIg course, plasmapheresis was initiated with seven cycles, as recommended by the neurologist. There was a gradual improvement of motor power in the limbs. The patient also had severe lower back pain associated with Guillain-Barré syndrome. Her back pain was treated with gabapentin, PCM and fentanyl SOPs. During the ICU stay, she also developed fluctuating blood pressure, with very high BP from her baseline. As she was not known to be hypertensive, this can be associated with autonomic dysfunctions in Guillain-Barré syndrome. The very high blood pressure readings were initially treated with labetalol infusion, titrated according to blood pressure. Later, she had persistent hypertension and was treated with prazosin and amlodipine.

During the hospital stay, the patient also developed low serum sodium with low serum osmolality, high urine osmolality and urine sodium, and a diagnosis of syndrome of inappropriate antidiuretic hormone (SIADH) was made. Guillain-Barré syndrome is a well-known cause of SIADH. The patient was treated with fluid restriction, and her sodium levels recovered. She underwent a percutaneous tracheostomy on day 12 of her ICU stay for liberation from the ventilator and underwent seven cycles of plasmapheresis as recommended by the neurologist. There was a gradual improvement of motor power in the limbs. Physiotherapy was continued, and speech and occupational therapy was initiated. By day 28 of the ICU stay, the patient could ambulate and was transferred to the neurology ward. An oncology review was arranged on discharge. Contrast-enhanced computed tomography of the chest, abdomen and pelvis were arranged to assess the stage of metastasis. Two months after discharge, the patient is fully mobile and able to carry out her day-to-day activities. She is on oncology follow-up for her malignancy, undergoing chemotherapy for the metastatic disease of endometrial cancer.

DISCUSSION

The typical presentation of Guillain-Barré syndrome is rapidly progressing ascending paralysis[2]. Weakness typically begins in the lower limbs and progressively ascends. Typically, there is hypo- or areflexia in the affected limbs. Additional supportive features include symptom progression over days or weeks, predominant motor involvement, symmetrical distribution, autonomic dysfunction and cranial nerve involvement. Usually, there is an antecedent history of diarrhoea or respiratory tract infection 1–2 weeks before the onset of symptoms. Commonly involved organisms include *Campylobacter jejuni*, Epstein-Barr virus and cytomegalovirus. This antecedent history of infection is absent in paraneoplastic Guillain-Barré syndrome, such as in our patient. Intravenous immunoglobulin or plasmapheresis given early (within two weeks) reduces functional deficit and accelerates recovery. Our patient responded to this treatment, which was started promptly after early diagnosis.

Paraneoplastic Guillain-Barré syndrome is an uncommon but well-documented entity. Most documented cases are associated with haematological malignancies such as lymphoma and leukaemias[3]. Common solid tumours include breast and colon cancer. Only a handful of cases of paraneoplastic Guillain-Barré syndrome in endometrial and other gynaecological cancers have been reported. The relationship between cancers and Guillain-Barré syndrome is not coincidental, as demonstrated by Vigliani et al.[4] in a population study of 435 Guillain-Barré syndrome patients over nine years. This showed that the incidence of a simultaneous or later diagnosis of malignancy within six months of Guillain-Barré syndrome was statistically significant ($P<0.01$).

Tho et al.[5] presented a case where a woman with uterine adenocarcinoma showed rapidly progressing symptoms compatible with an acute demyelinating neuropathy diagnosis. Imaging studies did not produce abnormal results, and the lumbar puncture showed an elevated protein content. The significant temporal correlation with the patient's malignancy explained the paraneoplastic nature of the syndrome.

The pathogenesis of Guillain-Barré syndrome is thought to be due to the inflammatory damage to the neuronal myelin sheath, which is immune-mediated through humoral and cell-mediated mechanisms. The immune process is initiated due to molecular mimicry. Antigens expressed on the cell membrane of the infective agent induce an immune response that cross-reacts with similar antigens in the nerve sheath. For example, *C. jejuni* isolated from Guillain-Barré syndrome patients have identical antigens to gangliosides in human myelin. The immune response to the infection leads to inflammatory damage to the nerve myelin sheath. A similar mechanism is thought to cause paraneoplastic Guillain-Barré syndrome in malignancies. However, the lack of specific serum and cerebro-spinal fluid markers for malignancies highlights the need for further investigation. Many theories have been postulated to explain paraneoplastic Guillain-Barré syndrome in malignancies, but one of the most plausible ones is that tumour cells express onco-neural antigens that stimulate the production of antibodies against these once-neuronal antigens, similar to molecular mimicry in infective processes. Various onconeural antibodies have been discovered over the years, supporting this theory. However, only 50% of patients diagnosed with paraneoplastic syndromes have onconeural antigens, although the absence of these antigens does not rule out paraneoplastic syndromes. There are other non-immune mechanisms of paraneoplastic Guillain-Barré syndrome, such as toxic metabolites and cytokines formed from the tumours damaging nerve tissue, and competition between tumour and the nervous system for specific substrates such as tryptophan, which may lead to paraneoplastic manifestations.

Frequently, paraneoplastic Guillain-Barré syndrome is associated with cancer treatment (vincristine, carboplatin,

daunorubicin), as this is an immunosuppressive state and can lead to immunologically mediated demyelination[6]. Platinum therapy can cause an increase in cytokines such as TNF-ALPHA and IL-6, which enhances neural sheath damage. Despite this mechanism, platinum-based treatments mainly cause sensory neuropathies. Neurotoxicity occurs in up to 50% of people receiving platinum-based chemotherapy drugs. This predominantly affects large-diameter sensory neurons – motor neurons are frequently spared. This patient had pure motor neuropathy inconsistent with carboplatin damage, which mainly causes sensory neuropathy, and its clinical course was rapid and responsive to immunoglobulins in keeping with Guillain-Barré syndrome. The severity of carboplatin neurotoxicity is recognised to be dose-related, and the low dose of carboplatin used with this patient would have been unlikely to cause such disabling neuropathy.

Even though not used in our patients, immune checkpoint inhibitors (pembrolizumab) are increasingly used to treat gynaecological malignancies[7]. The bulk of data on neurotoxicity from immune checkpoint inhibitors comes from melanoma and lung cancer research. Immune checkpoint inhibitors are relatively new drugs to gynaecological oncology. Clinicians need to be familiar with the adverse effects of this treatment, including rare but potentially fatal events. Immune checkpoint inhibitors may cause a variety of immune-related adverse effects. The two main pathways these new drugs target are cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1, or its ligand PD-L1) inhibition. This mechanism is hypothesised to reduce peripheral tolerance of self-antigens, promoting cross-reactivity through molecular mimicry by tumour cells and resulting in autoimmunity. One reported Guillain-Barré syndrome/acute inflammatory demyelinating polyneuropathy is due to immune checkpoint inhibitor therapy in a gynaecological malignancy. The Guillain-Barré syndrome in our patient is not due to this treatment; she only had carboplatin and paclitaxel as adjuvant chemotherapy.

CONCLUSION

Our case is another demonstration of paraneoplastic Guillain-Barré syndrome associated with cancer. It was essential to diagnose paraneoplastic Guillain-Barré syndrome promptly and treatment led to good functional recovery. Paraneoplastic Guillain-Barré syndrome is a very rare phenomenon. However, it is an essential diagnosis in patients with malignancies, including gynaecological malignancies, who present with neuropathy. The timely recognition and prompt treatment of this potentially life-threatening condition with multiple complications is essential in managing patients with malignancies and neuropathy. Further studies on the paraneoplastic Guillain-Barré syndrome are needed as cases may be underreported.

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