CASE REPORT

Unusual cause of paraparesis in a patient with Cushing's syndrome

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SUMMARY

Paraparesis is a rare manifestation in patients with Cushing's syndrome and the causes include vertebral compression fracture, hypokalaemia, spinal epidural lipomatosis, paraneoplastic syndrome and metastasis to the vertebrae and spinal cord. We report an unusual cause of paraparesis due to radiation-induced myelomalacia in a patient with adrenocortical carcinoma-associated Cushing's syndrome, who are predisposed to radiation-induced injury.

BACKGROUND

Paraparesis is a rare manifestation in patients with Cushing's syndrome. Aetiology of paraparesis in patients with Cushing's syndrome include vertebral compression fracture, hypokalaemia, spinal epidural lipomatosis and paraneoplastic syndrome due to adrenocorticotrophic hormone (ACTH) producing malignant carcinoids. We report an unusual cause of paraparesis in a patient with Cushing's syndrome due to adrenocortical carcinoma (ACC).

CASE PRESENTATION

A 31-year-old woman presented with weight gain, excessive facial hair growth and secondary amenorrhoea for 6 years. On examination she had moon facies, acanthosis nigricans (grade III), multiple skin tags, hirsutism with Ferriman-Gallwey score of 26/36, pink violaceous striae >1 cm wide over abdomen, cuticular and pulp atrophy. She was known to have had primary hypothyroidism for the past 6 years, diabetes mellitus for 4 years and hypertension for 2 years. Biochemical investigations showed Na⁺ 143 mmol/L, K⁺ 4.3 mmol/L, Mg²⁺ 2.4 mmol/L, Cl⁻ 103 mmol/L, urea 25 mg/dL, creatinine 0.82 mg/dL, phosphate 3.6 mg/dL, calcium 9.5 mg/dL, total serum proteins 6.8 mg/dL, albumin 4.43 mg/dL, serum bilirubin 0.85 mg/dL, aspartate aminotransferase 27 U/L, alanine aminotransferase 34 U/L and alkaline phosphatase 98 U/L. Haemogram showed haemoglobin 12.2 g/dL, total leucocyte count 9400/mm³ and platelet count of 332×10⁹/L. Hormonal evaluation revealed, 08:00 plasma cortisol 771 nmol/L (Normal (N) 171–536), 08:00 plasma ACTH <1 pg/mL (N: 5–60), dehydroepiandrosterone sulfate 972 µg/dL (N: 98–340), testosterone 6.63 nmol/L (N: 0.2–2.9), tri-iodothyronine (T3) 1.8 ng/mL (N: 0.8–2.0), tetra-iodothyronine (T4) 10.2 µg/dL (N: 4.8–12.7), thyroid-stimulating hormone (TSH) 3.5 µIU/mL (N: 0.27–4.2), prolactin 7.7 ng/mL (N: 4.7–23), luteinizing hormone 1.04 mIU/mL (N: 2.4–12.6), follicle-stimulating hormone 0.155 mIU/mL

(N: 1.5–12.4), overnight dexamethasone suppression test (ONDST) 331 nmol/L (<50), low-dose dexamethasone suppression test (LDDST) 894 nmol/L (<50) and glycated hemoglobin 6.4%. Contrast-enhanced CT (CECT) abdomen showed 6.0×4.5 cm right adrenal heterogeneous mass with increased vascularity without any evidence of metastasis.

A provisional diagnosis of ACTH-independent Cushing's syndrome due to ACC was considered and patient was subjected to right laparoscopic adrenalectomy. Resected mass weighed 66 g, size 6×5×4 cm and macroscopic capsular invasion suggestive of R2 resection. Histopathological examination was suggestive of ACC with modified Weiss score of 6/7, Ki 67 index <5% and immunohistochemistry showing positivity for melan-A and calcitonin. Patient received conformal radiotherapy to the tumour bed after 2 months of surgery at the dose of 45 Gy delivered in 25 fractions over 5 weeks, followed by boost of 9 Gy in 5 fractions, while adequately sparing the spine, and limiting the maximum point dose to 45 Gy without any significant adverse events.

Patient remained asymptomatic until 6 months postradiotherapy when she presented with gradually progressive ascending spastic paraparesis (power 3/5), associated with sensory symptoms and signs, urinary incontinence and constipation. Differential diagnoses of metastatic disease involving vertebrae and spinal cord, radiation-induced myelitis, paraneoplastic syndrome and neuromyelitis optica were considered. Hormonal profile during this admission showed 08:00 plasma cortisol 132 nmol/L, TSH 4.02 µIU/mL, T4 8.7 µg/dL, T3 1.11 ng/mL, testosterone 0.08 nmol/L and prolactin 10.3 ng/mL. Other routine workup was unremarkable. Cerebrospinal fluid (CSF) analysis revealed proteins 56 mg/dL, glucose 83 mg/dL, and absence of leucocytes or malignant cells. Visual evoked potential was normal. CECT abdomen and chest revealed hypodense soft tissue of size 2.2×1.3 cm in right suprarenal region.

Contrast-enhanced MRI (CEMRI) spine showed segmental cord signal changes with patchy incomplete peripheral enhancement diffuse and mild expansion of spinal cord from T10 to conus medullaris which was suggestive of postradiotherapy changes (figure 1A–D). A 18-fluorodeoxyglucose positron emission tomography (¹⁸FDG PET)-CT revealed non-FDG-avid ill-defined density in the right suprarenal region and no evidence of FDG-avid lesion elsewhere in the body (figure 2A, B).

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Figure 1 (A–D) Sagittal T2 (A) and (B) contrast-enhanced MRI spine showing segmental altered signal intensity with patchy incomplete peripheral enhancement extending from T10 level to conus medullaris corresponding to the irradiated segment confirmed on T2 axial (C) and postcontrast T1 axial (D) images. Note the vertebral marrow signal changes at the corresponding level (white arrows).

Figure 2 (A and B) 18-Fluorodeoxyglucose positron emission tomography—CT postoperative showing only physiological tracer uptake and no evidence of any hypermetabolic tissues suggestive of metastasis anywhere in the body.

OUTCOME AND FOLLOW-UP

Patient was initiated on prednisolone 60 mg/day and is currently on tapering doses of the same. Urinary incontinence did improve however, no clinically appreciable improvement of power in lower limbs was observed after 2 weeks of therapy. Follow-up CEMRI is planned after 3 months of steroid therapy.

DISCUSSION

ACC is a rare malignancy with an incidence of 0.7–2 cases/million population per year, more frequent in women with highest incidence in fourth and fifth decade of life.^{1 2} Most adult patients (40–60%) present with signs and symptoms of hormone excess and rapidly progressing Cushing's syndrome

with or without virilisation. Non-functioning ACC presents with abdominal discomfort or pain, back pain, fever, weight loss and loss of appetite.^{3 4} Open adrenalectomy is regarded as standard treatment for ACC with aim of R0 resection with locoregional lymph node dissection, however, even with R0 resection both local and distant recurrence is common with recurrence rates of up to 85%, clearly indicating need for adjuvant treatment options.^{5 6} According to European Society for Medical Oncology clinical practice guidelines on adrenal cancers adjuvant radiotherapy is indicated in incomplete/R1 resection or Rx resection.⁷

Adjuvant radiotherapy is usually given to tumour bed and locoregional lymph nodes within 3 months of surgery in fractionated doses of 1.5–2 Gy/day for 5 days/week over 4–6 weeks with total dose range from 40 to 60 Gy. Common adverse events after radiotherapy include gastrointestinal disturbances, dermatological manifestations, fatigue, anorexia, pneumonitis or pulmonary fibrosis and haematological side effects.^{8–11}

Radiation-induced myelitis is one of the most dreaded complication of radiotherapy and it is a diagnosis of exclusion. Criteria's for radiation-induced myelitis are (1) spinal cord must have been included in the radiation field, (2) main neurological lesion must be within the segment of cord exposed to radiation and (3) metastasis or other primary spinal cord neoplasm must be ruled out as the cause of the neurological disorder.¹² Radiation-induced myelomalacia may have four different presentations: first, an acute transient myelitis distinguished by the presence of Lhermitte's sign; second, syndrome due to infarction of spinal cord defined by acute onset paraplegia or tetraplegia; third, selective paralysis of second motor neuron and fourth, the most frequent syndrome is chronic progressive radiation myelopathy.¹³ Radiation myelitis has become a rare complication in recent times, due to expertise in dose prescription and delivery with sophisticated techniques and is more common with single high dose or reirradiation.^{14–16}

Patients with hypercortisolemia are predisposed to radiation-induced nervous tissue damage.¹⁷ The higher incidence of radiation sequelae in patients with hypercortisolemia may be explained by increased capillary permeability and capillary thrombosis caused by hypercortisolemia.¹⁸

Index patient presented with chronic progressive myelopathy after 6 months of radiation therapy. She received total dose of 50 Gy in 30 fractions with 1.8 Gy in each fraction over 7 weeks which is well within the tolerated dose for spinal cord described in the literature, however myelopathy has been reported with

lower doses also.¹⁹ This is the first case report showing that radiation-induced myelomalacia can occur following tumour bed radiotherapy for ACC even after sparing the spinal cord. We are certain about the diagnosis because of typical MRI findings which include lack of disproportionate perilesional oedema, complete rim enhancement and no significant mass effect (cord expansion) that favour radiation myelopathy rather than metastasis. Normal ¹⁸FDG PET-CT and CSF cytology denies the diagnosis of metastasis. The mainstay of treatment is steroid therapy for prolonged period; however, therapies such as hyperbaric oxygen and monoclonal antivascular endothelial growth factor-A (bevacizumab) have been tried with limited success.^{20 21}

Contributors KDJ wrote the manuscript. CKA helped in the radiological investigations and confirming the diagnosis. SM edited the manuscript and helped in management of the case. AB identified the case and supervised the treatment of the patient.

Competing interests None declared.

Patient consent Obtained.

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Learning points

- Radiation myelopathy can occur despite fractionated bed radiotherapy for adrenocortical carcinoma.
- It is a diagnosis of exclusion and metastatic disease must be ruled out.
- Hypercortisolemia predisposes to radiation-induced nervous tissue injury.
- Treatment is mainly steroid therapy for prolonged period with limited success and the role of other therapies such as bevacizumab is still limited.

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