

Disabling peripheral neuropathy and radiculomyelopathy at the time of presentation in a patient with active acromegaly; A case report

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Abstract

Introduction:

Peripheral arthropathy and entrapment neuropathy are well-recognised manifestations of acromegaly. Distal symmetrical peripheral neuropathy and axial arthropathy producing myeloradiculopathy form a rare combination of manifestations in acromegaly.

Case presentation:

A 61-year-old male presented with progressively worsening upper and lower limb numbness and weakness for eight months. There was pain, swelling and restriction of movements of bilateral knee joints for 30 years. Change in facial appearance with prominent jaws, forehead, and nose as well as hypertension for more than 20 years had not been evaluated for. He was acromegaloid with severe bilateral knee joint osteoarthritis. There was symmetrical quadriparesis with greater involvement of distal muscle groups and glove and stocking type sensory loss. Lower limb reflexes were diminished while an inverted supinator reflex was elicited. Elevated IGF-1 and non-suppressed growth hormone after oral glucose administration confirmed acromegaly. MRI-pituitary showed a pituitary macroadenoma. There was imaging evidence of cervical and lumbar spondylosis with radiculomyelopathy and cauda equina syndrome. Nerve conduction studies suggested sensory and motor axonal polyneuropathy. Nerve cross-sectional areas were increased. He underwent trans-sphenoidal excision of pituitary tumour and anterior cervical discectomy and fusion which partially improved his neurological manifestations.

Conclusions:

This patient's disabling and partly irreversible rare neurological consequences re-iterate the need for early recognition and intervention for this curable endocrinopathy. At this late presentation, diagnostic and management challenges call for careful clinical judgment to avoid expensive and potentially risky interventions without clinical benefit.

Keywords: Acromegaly, peripheral neuropathy, myelopathy, radiculopathy

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Introduction

Acromegaly results from excessive production of growth hormone and insulin-like growth factor -1 (IGF-1) mostly from a growth hormone-secreting pituitary adenoma. There is a delay of about six to ten years between the onset of symptoms and diagnosis even in the developed world due to the slowly progressive nature of the disease(1, 2).

Patients commonly present with characteristic facial and acral features and systemic complications of growth hormone excess or local tumour effects (3). Common skeletal manifestations include acral enlargement, facial disfigurement and peripheral large joint arthropathy, termed acromegalic arthropathy(2). Common manifestations of axial skeleton involvement include degenerative osteoarticular disease, vertebral fractures and diffuse idiopathic skeletal hyperostosis (DISH) (4). Cervical and lumbar spondylosis leading to myeloradiculopathy is less common.

Predominant systemic manifestations are hypertension, diabetes and impaired glucose tolerance, and cardiac dysfunction (5). Peripheral neuropathy mainly includes entrapment neuropathies like carpal tunnel syndrome (6). Peripheral symmetrical polyneuropathy is rare, and most secondary to diabetes mellitus.

Concomitant evidence of rare neurological manifestations of acromegaly, distal symmetrical peripheral polyneuropathy, cervical myeloradiculopathy and lumbosacral radiculopathy leading to functional impairment, evident at the time of diagnosis has not been reported before. Most of the patients are diagnosed before the development of these disabling complications. We report a patient presenting with this rare constellation of clinical features.

Case Presentation

A 61-year-old male presented with insidious onset, progressive upper limb and lower limb weakness for 8 months. He initially noticed numbness in both hands, which progressed to the weakness of fine movements of the hands. Subsequently, he developed numbness in his feet which was followed by gradually progressive weakness. Symptoms worsened to an extent where he started using a wheelchair. There was no sphincter or bulbar involvement. He had back pain for about two years before the onset of these symptoms.

He had been experiencing bilateral knee pain and swelling for about 30 years. Initial symptoms were treated with knee joint aspiration and analgesics, which provided him symptom benefit. Over the last five years, there was marked swelling and deformation of both knee joints with persistent pain and restriction of movements.

He and his family noticed a change in facial appearance with prominent jaws, forehead, and nose for more than 20 years. He had enlargement of the feet and hands for the same duration. They have not regularly attended any health set-up for further evaluation. He had no headache, visual problems, galactorrhoea, constipation, lethargy, or dizziness.

He was diagnosed to have hypertension 20 years back and was treated with antihypertensive agents. It was well controlled with a single agent. He had no diabetes. He was snoring during sleep resulting in poor quality sleep and daytime somnolence.

There was no significant family history. He has used alcohol occasionally and stopped several years back; there was no other substance use. He was a non-vegetarian, and there was no history of exposure to toxic substances.

He was acromegaloid with prominent supra-orbital ridges, prognathism, interdental separation, macroglossia, and acral enlargement. The skin over the palms and heel was thickened. There were no skin tags.

Upper limb examination revealed bilateral and symmetrical weakness in the distal muscle groups more than the proximal muscle groups (MRC grading: proximally 4 and distally 2) with glove type sensory loss. However, an inverted supinator reflex was elicited. Symmetrical distal predominant weakness was evident in the lower limbs (MRC grading: proximally 4 and distally 3) with absent knee and ankle reflexes, flexor plantar response and stocking type sensory loss up to knee joints. Cranial nerve examination, including visual fields, was normal.

Cardiovascular, respiratory and abdomen examinations were normal. Investigations at the time of presentation are summarised in Table 1.

During the oral glucose tolerance test growth hormone values were 53.6, 52.2, 53.2, 57.4, 57.9 µg/L (normal response <1 µg/L) confirming the diagnosis of acromegaly. Pituitary MRI showed 1.2×1.9×1.2 cm lesion in the pituitary fossa extending into the

Table 1 : Summary of investigations at the time of the presentation

Investigation	Result	Reference range
Haemoglobin (g/dL)	10.7	11 - 16
Mean corpuscular volume (fl)	88.5	80 - 96
White Cell Count (×10 ⁹ /L)	4.38	4 - 11
Platelet Count (×10 ⁹ /L)	140	150 - 450
Erythrocyte sedimentation rate (mm/1st hour)	23	<30
Peripheral blood smear	Normocytic normochromic red cells. Low- normal platelet count. No abnormal cells.	
Urinalysis	Normal	
Ultrasound abdomen	Grade 1 fatty liver. No other abnormalities detected.	
Serum Creatinine (mg/dL)	0.8	0.5 - 1.1
Sodium (mmol/L)	139	135 - 145
Potassium (mmol/L)	3.7	3.5 - 5.1
Aspartate transaminase (U/L)	25	<40
Alanine transaminase (U/L)	12	<40
Fasting blood glucose (mg/dL)	75	<100
Two-hour plasma glucose after 75g anhydrous glucose (mg/dL)	135	<140
HbA1c	5.5%	<5.7%
Thyroid-stimulating hormone (mIU/l)	0.743	0.5 - 4.7
Free T4 (ng/dl)	1.09	0.89 - 1.76
9 am cortisol (nmol/l)	249	118 - 618
Prolactin (mIU/l)	106	59 - 619
Total testosterone (ng/dL)	262	241 - 820
Follicle-stimulating hormone (IU/L)	23	2 - 12
Leutinizing hormone (IU/L)	3	2 - 9
Insulin-like growth factor-1 (ng/ml)	419	94 - 269

the sphenoid sinus (Figure 1).

Nerve conduction studies were suggestive of sensory and motor axonal polyneuropathy. Electromyography revealed features suggestive of chronic neurogenic abnormalities suggesting the possibility of concomitant polyradiculopathy. Ultrasound of the upper limb peripheral nerves confirmed enlargement of the nerves with median

nerve cross-sectional area at wrist being 22 mm² and ulnar nerve cross-sectional area at elbow being 18 mm².

MRI of the cervical spine showed thecal sac indentation at C3/C4, C5/C6 and C7/T1 levels and myelopathic changes at C3/C4 level (Figure 2). Dorsal spine images showed indentation at T6/T7 and T8/T9 levels. MRI lumbosacral spine revealed

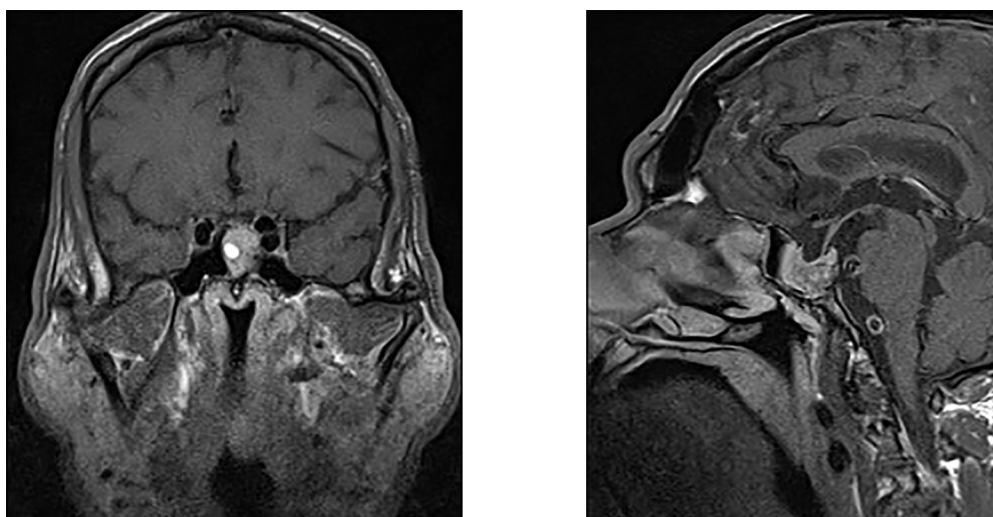


Figure 1 : Fat suppressed, post-contrast T-1 weighted coronal and sagittal MR images of the sellar region showing pituitary macroadenoma with internal haemorrhage extending into the sphenoid sinus.

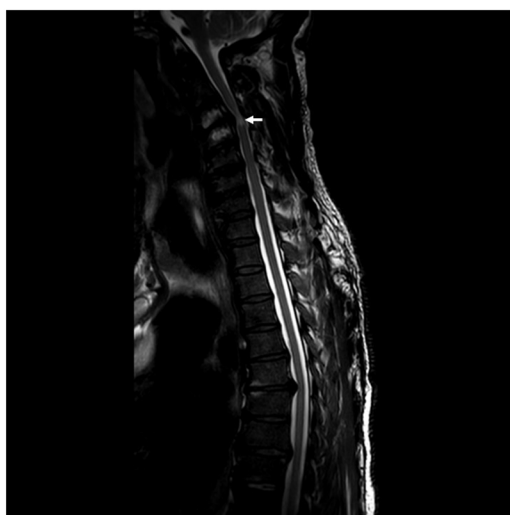


Figure 2 : Sagittal T2 weighted MR image of the cervical spine showing thecal sac indentation at multiple level with myelopathic changes at C3/C4 level.

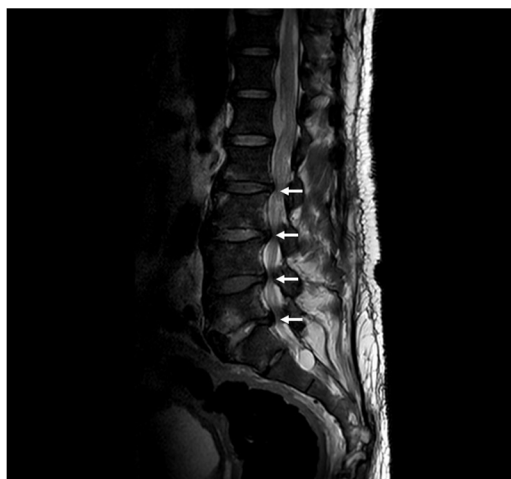


Figure 3 : Sagittal T2 weighted MR image of the lumbosacral spine showing disc bulging at multiple level with cauda equina compression.

disc bulging at L2/L3, L3/L4, L4/L5 and L5/S1 levels with cauda equina compression (Figure 3).

Impression was that his neurological manifestations were due to a combination of peripheral neuropathy and compression of the cord and multiple roots. Peripheral neuropathy was considered to be predominantly contributing to the disability. Clinical and biochemical evaluation for alternative causes of peripheral neuropathy, including leprosy, monoclonal gammopathy and retroviral infection were negative. There was no evidence of toxin or heavy metal exposure. Though vitamin B12 levels could not be tested, there were no other features of B12 deficiency.

He underwent trans-sphenoidal excision of pituitary adenoma. Histology confirmed the presence of pituitary adenoma. Immunohistochemistry showed

a 0.4% Ki index. (Figure 4) MRI-pituitary on post-operative day one did not reveal any residual pituitary tumour (Figure 5). Post-op 3-month IGF-1 was 283.1 ng/mL (51-209 ng/mL). He was started on levothyroxine and hydrocortisone replacement due to post-operative deficiency. He is awaiting further assessment with growth hormone day curve, repeat pituitary functions and follow up MRI-pituitary.

Three months after pituitary surgery, he underwent anterior cervical discectomy and fusion for treatment of cervical myeloradiculopathy. Though there was evidence of cauda-equina involvement, a joint decision was made with the patient not to intervene at this point since his sphincter function is normal.

The patient had improvement of upper limb power two months after surgery (MRC grading: proximally 4

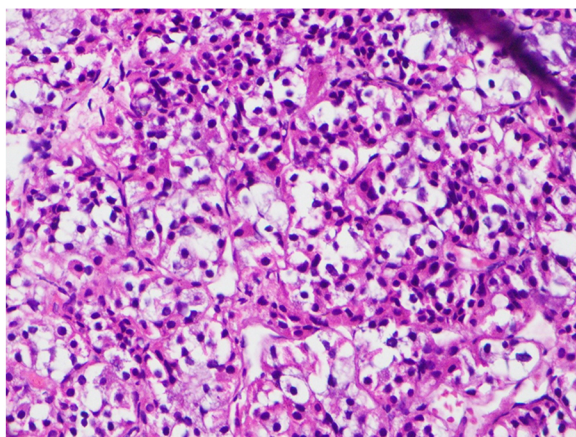


Figure 4 : High power ($\times 400$) Haematoxylin and Eosin-stained light microscopy of the specimen showing nests of cells with intervening fine vasculature. Cells contain round nuclei with stippled chromatin. The cytoplasm is abundant and clear to pale eosinophilic. Mitoses are not seen.

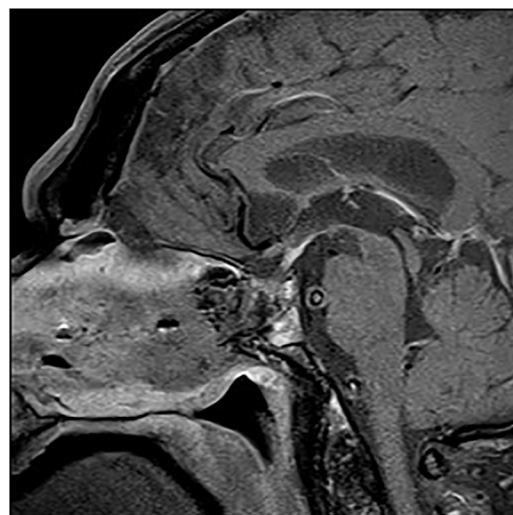
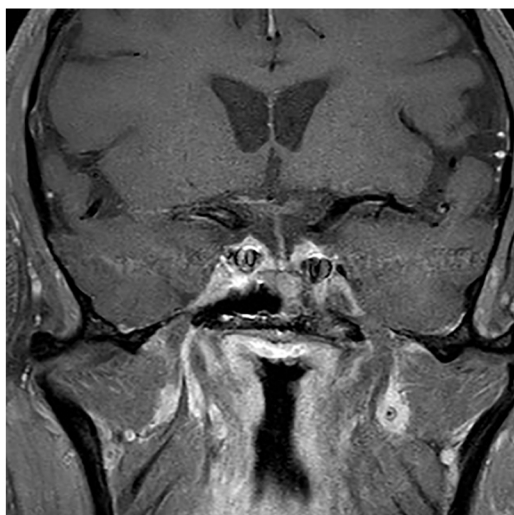


Figure 5 : Fat suppressed, post-contrast T1 weighted coronal and sagittal MR images show no residual tumour.

and distally 3). Lower limb power remained the same. He still requires a wheelchair to mobilise. He expressed subjective improvement of sensory symptoms. The median nerve cross-sectional area at the wrist has reduced to 17 mm², but the ulnar nerve cross-sectional area at the elbow remains 18 mm². Rehabilitation with physiotherapy and occupational therapy was commenced.

Discussion

Key problems that resulted in disability in this patient include peripheral neuropathy and multiple roots and cord compression. This combination of severe neurological manifestations without other systemic effects like diabetes and cardiac disease is not commonly observed in acromegaly.

Spinal involvement in acromegaly is considered a part of acromegaly arthropathy. Common manifestations include degenerative osteoarticular disease, vertebral fractures, and DISH(7). Changes that were evident in our patient include degenerative osteoarticular disease. Growth hormone excess causes chondrocyte proliferation and increased production of bony matrix. This mostly affects the facet joints of the cervical and lumbar spine. Ossification of ligaments and periarticular pyrophosphate deposition is also seen (2). These bony deformities can lead to narrowing of the spinal canal and foramina, causing compression of the spinal cord and the roots(8). Our patient has had similar changes in the cervical and lumbar spine with consequent root and cord compression. He had disabling bilateral knee joint osteoarthritis, which has a similar pathophysiological process.

These changes are thought to occur in two stages; the first stage predominates with articular cartilage thickening, which is at least partially reversible with treatment of acromegaly. During the second stage, ossification, osteophyte formation, and destruction of bones and joints occur. This is considered to be irreversible (9). The long course of our patient close to 30 years and established damage evidenced by radiological studies suggest that his changes are likely irreversible. Therefore, our primary treatment targeting acromegaly is unlikely to reverse the disability created by his spinal pathology. This led to the clinical decision of pursuing spinal surgery independent of treating acromegaly.

The commonest type of neuropathy described in acromegaly includes entrapment neuropathies such as carpal tunnel syndrome. Widespread peripheral neuropathy is also described in patients with

acromegaly. The commonest cause is diabetes mellitus and impaired glucose tolerance (IGT)(10). Interestingly, our patient did not have any evidence of IGT. Peripheral neuropathy without diabetes is recognized in acromegaly and is thought to be associated with nerve fibre hypertrophy (10, 11). The increased cross-sectional area of the nerves has been demonstrated in acromegaly and partial improvement in nerve enlargement has been observed with the disease control (12, 13). In the absence of hypothyroidism, underlying malignancy, frequent alcohol consumption or any other cause that could give rise to an axonal polyneuropathy, our patient likely had acromegalic hypertrophic peripheral neuropathy. The presence of enlarged peripheral nerves, partial improvement of neurological symptoms and nerve thickness following surgery supports this diagnosis.

Delayed presentation in our patient could have led to the development of this degree of severe, mostly irreversible neurological manifestations, which are not reported to be seen at the time of diagnosis of acromegaly.

Conclusions

A rare combination of disabling neuromuscular manifestations in this patient emphasises the need for early identification of acromegaly to prevent irreversible neurological deficits. In a situation where neurological manifestations are already established, careful assessment is required in deciding treatment interventions that are likely to be clinically beneficial.

Abbreviations

DISH	- Diffuse idiopathic skeletal hyperostosis
IGF-1	- Insulin-like growth factor-1
IGT	- Impaired glucose tolerance
MRC	- Medical research council
MRI	- Magnetic resonance imaging

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