CASE REPORT

What the mind knows but the eyes may still miss: reducing the 'Acromegalic Window'

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SUMMARY

A 46-year-old Asian man was referred to our endocrine unit (April 2013) by his general practitioner for investigation of a neck mass. Ultrasound scan of the neck and serum thyroid-stimulating hormone levels revealed a euthyroid multinodular goitre. He presented with symptoms of frequent headaches, polydipsia, polyuria, perspiration and night sweats and demonstrated classic physical features of acromegaly. In retrospect, the patient's medical history included encounters with numerous physicians from an array of specialties for over 20 years, mostly for symptoms well recognised to be attributed to growth hormone (GH) excess. Random insulin-like growth factor-1 level was elevated at 103 nmol/L (normal 13–37 nmol/L) and oral glucose tolerance test showed non-suppressible GH secretion (15.06 mIU/L at 120 min). MRI revealed a mildly enlarged pituitary gland. The patient has been referred for surgery. This case highlights that, even with classic features of acromegaly, there may be a wide-ranging 'Acromegalic Window' between first presentation and clinical suspicion to eventual diagnosis.

BACKGROUND

Acromegaly is a classic and well-described endocrine condition and medical diagnosis is often performed at first glance from clinical features. The course of disease progression is usually slow, resulting generally in an insidious onset of pathological consequences. These two observations have supported an estimated 7–12 year time lag between the onset of the first disease-related symptom and disease diagnosis.¹ During this time lag, growth hormone (GH) induced pathological changes within body tissues which, if left untreated, may lead to serious complications. It has been suggested that this may account for the 2–3-fold increase in mortality and 10-year reduced life expectancy in patients with acromegaly.¹

Retrospectively, our patient had consulted with a vast array of medical professionals since the onset of his symptoms 18 years ago, and yet his condition was only recently diagnosed in May 2013 by one of our local hospital endocrinology consultants following referral for investigation of a thyroid mass. On examination, our patient presented with textbook features of acromegaly: deep voice, large and protruding tongue, well-documented prognathism, thickened lips, prominent supraorbital ridges and spade-like hands and large feet.

We find it quite staggering that despite our patient having been seen by a whole host of medical and surgical specialties, he remained

undiagnosed for 18 years with resultant chronic exposure and comorbidity from GH excess. Potential confounding factors in his delayed diagnosis may be attributed to his ethnicity and the possibility of gradual involvement of his clinical features over the years.

However, this case clearly illustrates the potential for reduction in the length of the 'Acromegalic Window' (time between first presentation and clinical suspicion to eventual diagnosis) and the subsequent consequences of a delayed diagnosis. Furthermore, our patient's extensive medical history highlights the importance of assessing a patient from a holistic viewpoint and with regard to previous medical symptoms, including a keen eye for recognition and evolution of patterns in symptoms and signs.

CASE PRESENTATION

A 46-year-old Asian man with a 30-pack-year smoking history attended the Birmingham City Hospital Endocrine Unit in April 2013 following a referral from his general practitioner (GP) for an incidental neck mass. Ultrasound scan of the neck and serum thyroid-stimulating hormone (TSH) levels revealed a euthyroid multinodular goitre, the largest measuring 11 mm in diameter and located in the right lobe. The isthmus measured 13 mm in thickness and the inferior limit of the thyroid was situated above the level of the thoracic inlet with no intrathoracic extension. The patient denied any symptoms consistent with thyroid disease. However, the patient had recently been having increasingly frequent and severe headaches, polydipsia and polyuria and excessive perspiration and night sweats.

The patient had previously undergone numerous surgeries and procedures during his childhood and adolescence as a result of perpetual breathing difficulties. Between the ages of 4 and 22, the patient had undergone an adenotonsillectomy and three episodes of cryosurgery to both inferior turbinates in conjunction with antral washouts. Despite these interventions, the patient continued to suffer from laboured breathing.

In 1995, the patient consulted a dental surgeon with symptoms of a chronically protruding tongue and dry mouth. On examination, it was noted that the patient was 'quite tall at 6 ft 4" and had an altered voice and a mild click on opening of the temporomandibular joints. The patient was also noted to have an anterior open bite from first molars forwards with a class III skeletal relationship consistent with mandibular prognathism.

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The interincisal opening in occlusion was 6 mm. The patient was reported to have marked hypertrophic gingivitis palatal to his upper anterior teeth. There was also some limitation in the elevation of his soft palate. Consequently, a videofluoroscope was undertaken to assess the possibility of a combined orthodontic/orthognathic surgical treatment in order to ameliorate the patient's symptoms.

He was referred to ear, nose and throat (ENT), and during the procedure the ENT surgeon noted an abnormal jaw growth and a large tongue. The videofluoroscope also demonstrated a mass of excess tissue on the tongue base, which was reported to fill the vallecula causing a right-angled downward bend of the epiglottis. It was suggested that this most likely represents exuberant lingual tonsillar tissue, which may be blocking the vocal cord inlet; however, the surgeon wanted to exclude any sinister cause. Nasoendoscopy showed a large mass of adenoidal tissue obstructing the posterior choanae and a large soft tissue mass at the base of the tongue, which was confirmed through biopsy to be consistent with a normal lymphoid tissue. The patient underwent total adenoidectomy and the tissue mass was subsequently resected by laser therapy.

In May 1996, he was referred to a chest physician from the ENT department for shortness of breath and chest tightness, in addition to night-time episodes of sleep apnoea, as described by his wife. He was seen by the chest physician and pulmonary function testing revealed restrictive lung disease with decreased lung volumes but with normal gas transfer (forced expiratory volume in 1 s (FEV₁)=4.10 L, forced vital capacity (FVC)=4.64 L, forced expiratory rate (FER)=88%, total lung capacity=6.22 L). All values were less than predicted except for the FER, and these results suggest a restrictive lung disorder which did not support a diagnosis of obstructive sleep apnoea (OSA). Symptoms persisted and the patient revisited the sleep clinic. Following full polysomnography, results revealed an apnoea-hypopnoea index of 2.6 with no evidence of OSA. While the polysomnography results negated upper airway obstruction, it was concluded that the upper airways were clearly obstructed and the patient was treated with continuous positive airway pressure and followed up in a respiratory clinic for 6 years.

In June 1998, the patient saw a cardiologist for symptoms suggestive of angina and subsequently underwent an exercise tolerance test. He was described as being 'an overweight man' and no evidence of cardiovascular disease was found. He was reassured and discharged, with his symptoms being attributed to anxiety and lack of fitness.

Figure 2 Macroglossia in acromegaly.

In November 1999, the patient was referred to a urologist with left-sided abdominal pain for investigation of left renal colic. He was seen and investigated but no renal stones were found.

In December 2002, the patient was referred by his GP to the gastroenterology unit for symptoms of abdominal pain and a change in bowel habits. Clinical consultations and investigations were reportedly normal, including a normal flexible sigmoidoscopy, and his symptoms were attributed to irritable bowel syndrome. In May 2003, liver function tests suggested a slight increase in bilirubin and Gilbert's syndrome was queried.

He continued under the care of the ENT surgeon, who in September 2004 noted on routine review that the patient had deviation of his nasal septum and some throat hyperaemia suggestive of laryngopharyngeal reflux, and the patient was subsequently discharged.

In November 2004, the patient was found to have a large hiatus hernia with some reflux on endoscopy, for which he was prescribed antireflux treatment.

ENT continued to see this patient throughout 2005 and he was discharged back to his GP in April 2006.

In October 2012, the patient was referred to our endocrinology unit for the first time and was seen by the endocrinology SpR for a multinodular goitre and euthyroidism—acromegaly was not suspected even at this stage and the plan was to conduct some lung function tests and baseline thyroid function tests and discharge the patient.

In April 2013, our endocrinology consultant (PD) saw the patient for the first time and queried the diagnosis of acromegaly.

Figure 1 Prognathism in our patient with acromegaly.

Figure 3 Skin tags in our patient with acromegaly.

Figure 4 Spade-like hands in acromegaly.

Figure 5 Sagittal section of MRI of the pituitary showing enlargement.

The patient's medical history also includes osteoarthritis of the left knee, bilateral hips and spine. A CT scan showed moderate degenerative changes within both hips and advanced degenerative changes at the L5/S1 spinal level. Owing to continuing bowel problems, the patient sought colonoscopy privately in 2012, which showed a very long and enlarged colon. This was

suggested to be caused by Hirschsprung's disease during fetal development.

The patient lives with his wife and children, works part time, does not drink any alcohol and has a 30-pack-year history of smoking. He has a strong family history of heart disease and diabetes. He does not have any drug allergies.

On examination, the patient was found to be tall with a body mass index of 27 with prominent supraorbital ridges and prognathism (figure 1—prognathism in acromegaly). He has an enlarged protruding tongue (figure 2—macroglossia in acromegaly) and thickened lips. There was no hand tremor or sweating. The patient's hands were large and spade-like (which has prevented him from wearing his wedding ring, figure 3—spade-like hands in acromegaly). A multinodular thyroid goitre was present. He had skin tags superficial to his neck (figure 4—skin tags in acromegaly) with scarring from previous neck surgery.

Systemic examination was otherwise unremarkable apart from a one finger hepatomegaly.

INVESTIGATIONS

Full blood count and biochemistry, including renal, hepatic function and bone profile, were normal. He had an elevated IGF-1 level of 103 nmol/L (normal 13–37 nmol/L).

Oral glucose tolerance test revealed GH levels as follows: 20.04 mIU/L at 0 min, 18.06 mIU/L at 30 min, 15.87 mIU/L at 60 min, 15.27 mIU/L at 90 min, 15.06 mIU/L at 120 mins, 13.56 mIU/L at 150 min and 13.35 mIU/L at 180 mins (normally GH should suppress to <2 mIU/L 2 h following the glucose load). The patient's blood glucose level at 2 h following the glucose load was 8 mmol/L, suggestive of impaired glucose tolerance.

The pituitary profile showed normal FT4 20 pmol/L, TSH 0.28 mIU/L, normal luteinizing hormone, follicle-stimulating hormone, testosterone and prolactin levels. The short Synacthen test revealed a subnormal 30 min cortisol level of 458 nmol/L (a normal adrenal response should show a rise in cortisol >550 nmol/L).

MRI of the pituitary (figure 5—sagittal section showing a pituitary enlargement in our patient with acromegaly) showed a moderate enhancement throughout the pituitary which measures approximately 1.3×0.5×1.5 cm (AP×CC×transverse diameter). The pituitary gland appeared to abut the clinoid processes and was almost in contact with the internal carotid arteries in this region. There was no optic chiasm compression or bony erosion. No other gross intraparenchymal lesion in the

Table 1 The prevalence of signs and symptoms in patients with acromegaly and the medical/surgical specialties likely to encounter them

Our patient's symptoms/signs	Prevalence within acromegaly	Specialisms likely to encounter these symptoms/signs
Excess soft tissue and bone growth increased size of hands and feet, tongue, lips; prognathism; supraorbital ridges; deepened voice with sonorous resonance	Ubiquitous ¹⁰	General practice, dental surgeon, ENT, maxillofacial surgery, orthopaedics, rheumatologist
Goitre	25–90% ¹⁰	General practice, endocrinology, ENT, general medicine and surgery
Respiratory complications	60–80% ¹⁰	General practice, ENT, general medicine, respiratory medicine
Skin tags	70% ¹⁰	General practice, dermatology, ENT, plastic surgery
Hyperhidrosis	70% ¹⁰	General practice, cardiologist, endocrinologist
Myalgia and arthralgia/arthropathy	30–70% ^{10 11}	General practice, endocrinologist, general medicine, orthopaedics, rheumatologist
Impaired glucose tolerance	16–46% ¹⁰	General practice, cardiologist, endocrinologist, general medicine
Headache	8% ¹²	General practice, general medicine, neurologist

brainstem or around the craniocervical junction was seen. The cerebral hemispheres and posterior fossa were noted to be normal in appearance. It was concluded that the pituitary gland was perhaps at the upper limit of normal size.

TREATMENT

The patient was started on hydrocortisone 10 mg twice daily following a slightly subnormal Synacthen test result.

OUTCOME AND FOLLOW-UP

The patient has subsequently been referred to the Regional Neurosurgery Centre for further investigations and consideration for surgery.

DISCUSSION

This case report illustrates an 18-year acromegalic window—the lengthy period between the onset of the first acromegaly-related symptom and the diagnosis of the condition. Based on retrospective analysis, there have been numerous patient case-inspired postulations accounting for the acromegalic window.

Importantly, acromegaly is a rare condition, and thus medical professionals may not have sufficient exposure to the subtle acromegalic features to support an early diagnosis. Initial symptoms may be non-specific and include headache, joint pain, amenorrhoea, dental irregularities and sleep apnoea, while the characteristic signs of GH excess may take years to develop.^{2 3} The former limitation is well depicted in a patient case reported by Abdo *et al*,⁴ where a patient who presented with hirsutism was later found to have acromegaly as the source of her excess hair growth. As the authors point out, the differential diagnosis for hirsutism is very broad and it is easy to simply attribute a common sign to a commonly associated cause. However, it is prudent to undertake further investigations in order to exclude a more sinister origin.

The diagnosis of acromegaly can be further complicated by interpreting GH and IGF-1 levels in the presence of insulin-dependent and non-insulin dependent diabetes.^{5 6} Evidently, an undiagnosed or overlooked state of hyperglycaemia can cloud the true results of an oral glucose tolerance test.

The literature also documents two atypical presentations of acromegaly. Castro *et al*⁷ describes the medical pathway of one patient who presented with an acute onset of central diabetes insipidus which was later attributed to acromegaly following physical examination, and of another patient who presented with a short history of generalised seizures caused by the extension of a pituitary tumour into the patient's temporal lobe.

In a case report written by Danzig,⁸ the patient describes his experience of a 4-year period of undiagnosed acromegaly and how his life was radically altered by the condition. He discusses his disappointment with the latency of his diagnosis. Despite having consulted an array of medical professionals for numerous physical symptoms during this time period, the patient explains that it was he who arrived at his own diagnosis, which was subsequently supported by a consultant unknown to his case.

Interestingly, a case by Cohen *et al*⁹ depicts a patient with apertognathia as the initial presenting symptom of acromegaly. The patient's inability to incise and a progressive open bite prompted a dental examination and further case work up.

Notwithstanding these diagnostic difficulties, our case underlines the importance of the fundamental principles of clinical medicine—a comprehensive patient history, thorough clinical examination and diligently recorded patient notes.

Undeniably, our patient's symptoms had slowly developed throughout his lifetime; he did not initially present with the

same symptoms and signs as he does today. Equally important, however, the constellation of signs and symptoms that now comprise our patient's acromegalic demeanour did in fact initially manifest at some point in time, and the patient has had more than adequate exposure within the healthcare system for his symptoms and signs to have been recognised by clinicians. It should be within every doctor's remit to question and record unusual symptoms and signs, particularly if they do not fit a recognisable clinical picture.

Furthermore, it is not the sole responsibility of any one specific specialty to make the ultimate diagnosis of a disease, especially if the condition affects the whole body, as in acromegaly.

Patient's perspective

Upon reflection, the patient is angry because he feels his condition could have been diagnosed many years earlier based on the symptoms with which he had originally presented. He feels that most of his medical problems were attributed to unrelated causes, and he uses his diagnosis of sleep apnoea as an example; while the patient was not overweight or obese at the time of the onset of his symptoms of sleep apnoea, the attending physician suggested that because most patients with sleep apnoea suffer from weight problems, this patient's symptoms were likely to be attributable to his weight.

At present, the patient is quite exasperated with the outcome of his delayed diagnosis. He clearly expresses angst and worry for the future and is nervous about how the long-term effects of his untreated condition will present to him in years to come. The patient is well aware of the potential complications and long-term effects of unmanaged acromegaly, which understandably cause him distress, seeing how he has presented with many of these signs and symptoms for several years now.

As an example of the arthritis and joint destruction associated with acromegaly, this Muslim patient used to avidly pray on his knees, but can no longer do so because the unilateral flexion of his left knee causes him too much pain. Moreover, following recurrent bowel symptoms and previous CT results which suggest a megacolon, the patient has been referred for a colonoscopy to investigate for any sinister cause of his recent change in bowel habits.

When looking to the future, the patient is undecided on how he plans to deal with his condition. While both surgery and participation in a clinical trial have been offered to him as management options, the patient is neither keen for surgery, as he has once been resuscitated during a previous operation and is apprehensive to undergo treatment with a drug that has yet to be clinically approved. While he awaits the joint decision of the multidisciplinary team meeting, the patient continues to work self-employed and care for his family despite feeling quite poorly in himself. Having been recently treated with steroids, he now complains of weight gain and lethargy which he feels is exacerbated by having to work (for financial reasons) and finding very little time to exercise, which he foresees becoming more challenging as the number of hospital appointments increase in the near future.

The patient is very grateful that a cause has been ultimately established but frustrated that the underlying cause of his symptoms was not discovered sooner. Having been under the care of numerous consultants trained in a variety of specialties for two decades, he is surprised that the signs and symptoms of his condition were missed for so long.

Learning points

- ▶ Acromegaly is a classical endocrine condition and although rare, diagnosis is mostly based on clinical suspicion.
- ▶ Long-term non-resolving medical or surgical issues or a constellation of symptoms should always be investigated for a potential underlying cause.
- ▶ Patients should always be assessed from a holistic viewpoint and in the context of their medical history (including symptoms and signs) in order to facilitate pattern recognition.
- ▶ Awareness of this very apparent spot diagnosis (albeit a rare condition) needs to be reinforced to doctors at every level of training.
- ▶ The potential for reduction in the length of the 'Acromegalic Window' is the key to preventing subsequent consequences of a delayed diagnosis.

If this were the case, many conditions would be left undiagnosed and go untreated. Wider awareness and clinical suspicion along with involvement of multidisciplinary specialist teams is the key to success in medicine as is evident in so many specialties these days.

In order to solve the diagnostic puzzle, medical professionals have been specifically trained to ask themselves why their patients have particular presenting signs/symptoms at a specific point in time. While patients do not present to the clinic with a labelled diagnosis, if we carefully listen to our patients, examine them prudently and have a questioning mind, most clinical diagnoses can usually be made, although there will always be exceptions. Although individual symptoms may not immediately point to the diagnosis, changing trends in presentation and a watchful review of new symptoms/signs would undoubtedly point any generally trained physician towards making a reasonably correct diagnosis. Table 1 below indicates the prevalence of common symptoms and signs in patients with acromegaly and the specialism that is most likely to initially encounter them.

In summary, in light of the rarity of acromegaly, its insidious onset, lengthy latency period and potential confounding factors, acromegaly is often a diagnosis of clinical suspicion. More importantly, however, our patient case demonstrates that by undertaking a holistic view of the patient and taking into consideration their medical history, the culpable diagnosis of most medical conditions, including acromegaly, is much more likely to be evident and may prompt early investigation and hopefully the correct diagnosis and treatment.

Contributors DRGF performed the literature search, contacted the patient and gathered his details, arranged for patient's perspective, wrote and revised the manuscript. PD came up with the idea of the case report, gathered details about the patient from the case notes, edited and revised the manuscript and provided overall guidance.

Competing interests None.

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