

# Severe respiratory failure in a patient with COVID-19 and acromegaly: rapid improvement after adding octreotide

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## SUMMARY

Acromegaly is a rare disorder of unregulated hypersecretion of growth hormone that causes cardiovascular, metabolic and respiratory complications. Herein, we describe the case of a middle-aged man admitted to the hospital with severe COVID-19 found to have clinical and biochemical evidence of acromegaly. His respiratory status declined despite initiation of standard treatments, prompting initiation of subcutaneous octreotide. Following initiation of this therapy, he rapidly improved and was discharged from the hospital 2 days later. Subsequent workup revealed a pituitary macroadenoma that was surgically removed, with improvement in his acromegaly symptoms. COVID-19 disease severity is increased by pre-existing diabetes, lung disease and immunosuppression. Although this patient had obstructive sleep apnoea and pre-diabetes, we hypothesise that our patient's acromegaly contributed to his severe course, as reflected by his rapid improvement after starting treatment with subcutaneous octreotide. Acromegaly may predispose to more severe outcomes in patients with COVID-19.

## BACKGROUND

This report describes a case of severe SARS-CoV-2 infection that occurred early in the global pandemic (March 2020) in a man with recently diagnosed obstructive sleep apnoea, who was found to have acromegaly and pre-diabetes during admission for acute hypoxemic respiratory failure. COVID-19 refers to the syndrome of fever, upper respiratory symptoms, and possible respiratory failure that is caused by the novel SARS-CoV-2 virus, which has risen to pandemic levels worldwide since its initial identification in late 2019.<sup>1</sup> With our knowledge regarding COVID-19 rapidly expanding, an association between underlying endocrinologic comorbidities and disease severity has been revealed.<sup>2</sup> Diabetes has been associated with more severe SARS-CoV-2 infection outcomes, including higher rates of hospitalisation, increased intensive care unit utilisation and higher mortality.<sup>3,4</sup> While there is not yet evidence for an association between pre-diabetes and COVID-19 disease severity, insulin resistance has been associated with similar biochemical markers as advanced diabetes and has been implicated in increased morbidity and mortality from acute viral respiratory infections.<sup>5,6</sup> Elevated triglyceride and glucose index, a proposed marker for insulin resistance, was associated with higher severity and increased mortality of COVID-19,

which also suggested a correlation between insulin resistance and COVID-19 infection severity.<sup>7</sup>

Acromegaly is a rare disorder caused by elevated growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels.<sup>8</sup> Excess levels of these hormones have pathological effects on multiple organs, lead to widespread metabolic, respiratory and cardiovascular complications. Many patients have insulin resistance with pre-diabetes or overt diabetes at the time of acromegaly diagnosis. Respiratory complications arise primarily due to soft tissue changes.<sup>9</sup> Pathological findings include soft tissue and muscle swelling of the nasopharyngeal passages, cartilage and bone hypertrophy, small airway narrowing, derangement of respiratory muscles, and changes to rib and spine architecture. These changes result in impaired air flow, abnormal breathing coordination and lung overgrowth. This frequently manifests as obstructive sleep apnoea, but other respiratory complications can occur. We hypothesised that complications of acromegaly lead to comorbidities that may increase severity of acute respiratory viral infections including COVID-19. Therefore, acromegaly could be a previously unidentified risk factor for more severe COVID-19 infection. As there have been no other reported cases of COVID-19 in patients with acromegaly, we present a case wherein the prompt diagnosis and directed treatment of acromegaly led to rapid recovery from severe disease with respiratory failure.

## CASE PRESENTATION

A fit and previously healthy middle-aged man with a recent diagnosis of obstructive sleep apnoea and without pertinent family or social history presented to an outside hospital emergency department with 2 days of fever and upper abdominal pain. The day before presentation, he had complained of dizziness and a fall after using the toilet, which was witnessed by his daughter. Vital signs were within normal limits. A CT scan of the abdomen and pelvis demonstrated no intra-abdominal abnormality, however, disclosed diffuse, bilateral reticular opacities within the lungs, suspicious for multifocal pneumonia. A head CT was negative for acute intra-cranial abnormality. COVID-19 testing was not available, so the patient was discharged 20 March 2020 with a prescription for oral antibiotics and instructions to self-quarantine. However, later the same day, he presented to our emergency department because of progression of symptoms of persistent fevers,



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**Figure 1** Enlarged hands with deepening of the palmar creases and enlarged feet with elevation of the dorsal–plantar transition on the lateral surface of the foot.

right upper quadrant abdominal pain, dyspnoea and recurrent episodes of presyncope. He also reported fatigue, rhinorrhoea, reduced exercise capacity and non-productive cough. He described several episodes of nausea and diaphoresis associated with bearing down prior to episodes of loss of consciousness. He had no preceding chest pain or palpitations. He denied tongue biting, rhythmic movements or loss of bladder or bowel control with syncopal episodes. Furthermore, he offered that his hands and feet had been growing for the last decade, associated with increased shoe length by two sizes. He had not noticed any vision changes or headaches.

Initial vital signs were significant for fever to 102°F, a respiratory rate of 27 breaths/min, and normal blood pressure, heart rate and oxygen saturation on room air. His physical exam was significant for mild respiratory distress with diaphoresis, mild scleral injection and coryza, frontal bossing, coarse facial features, bilateral basilar inspiratory crackles, large hands and feet, skin tags throughout and acanthosis nigricans in his axillae (figures 1 and 2). He did not have elevated jugular venous distension, lower extremity oedema, or other evidence of heart failure. His abdominal exam was benign without tenderness to palpation. His visual fields were full without any signs of bitemporal hemianopsia.

## INVESTIGATIONS

Select admission laboratory results are shown in table 1 and were significant for a normal creatinine of 0.86 mg/dL (0.70–1.30 mg/dL), undetectable troponin I, and an initial venous lactate level of 1.2 mmol/L (<2 mmol/L). N-terminal prohormone of brain natriuretic peptide (NT-Pro-BNP) was normal at 53 pg/mL (<125 pg/mL). Complete blood count demonstrated normal leucocyte count. Venous blood gas was normal. PCR testing

**Table 1** Select admission laboratory values

Lab study	Patient result	Normal range
Fasting glucose	122	70–99 mg/dL
Creatinine	0.86	0.70–1.30 mg/dL
Albumin	3.2	3.5–4.7 mg/dL
Venous lactate	1.2	<2 mmol/L
NT-pro-BNP	53	<125 pg/mL
Leucocyte	6.89	3.5–10.8 K/cu mm
% Neutrophils	75%	50.0–70.0%
Haemoglobin	12.1	13.5–17.5 g/dL
C reactive protein	51.8	<10.0 mg/dL
INR	1.07	0.90–1.20
SARS-CoV-2	Detected	Not detected

INR, international normalized ratio.

from a respiratory swab was negative for influenza and respiratory syncytial virus, and positive for SARS-CoV-2.

Endocrinological testing during the patient's initial presentation is shown in table 2 and was significant for a haemoglobin A1c of 6.1% and an elevated IGF-1 level of 447 ng/mL (71–224 ng/mL) with z-score of 4.3 (measured at Associated Regional and University Pathologists Laboratory). Repeat IGF-1 measurement through Esoterix Laboratory verified an elevated IGF-1 level of 311 ng/mL (121–237 ng/mL). A random serum GH concentration was elevated to 29.30 ng/dL (0.05–3.00 ng/mL). Prolactin was slightly elevated at 21.7 (2.1–17.7 ng/mL). Thyroid axis testing was normal and a cosyntropin stimulation test did not reveal adrenal insufficiency.

A portable chest radiograph obtained on admission showed bilateral, diffuse, patchy airspace opacities consistent with a developing multifocal pneumonia (figure 3). A CT chest was not obtained at the time, as it was not felt that it would have changed management with characteristic findings on chest radiography. A brain MRI obtained after resolution of his pneumonia (a month after initial presentation) disclosed a 14×13×10 mm hypoenhancing mass in the inferior portion of the sella turcica consistent with a macroadenoma (figure 4).

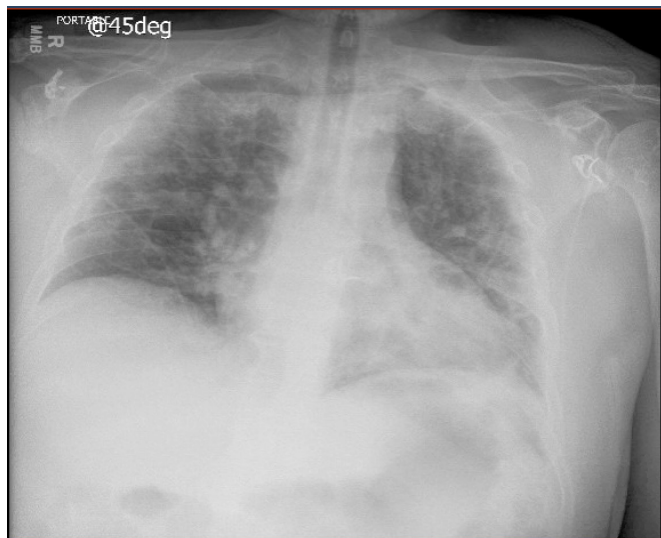


**Figure 2** Dermatological manifestations of insulin-resistance including: (A) acanthosis nigricans in the intertriginous region of the axilla and (B) acrochordons (skin tags) on the neck.

**Table 2** Select endocrinologic lab values during initial presentation

Lab study	Level	Normal range
Haemoglobin A1c	6.1	<5.7 mmol/L
Estimated average glucose	128	<117 mg/dL
Insulin-like growth factor (IGF-1) (ARUP)	447	71–224 ng/mL
Insulin like growth factor (Esoterix)	311	121–237 ng/mL
Growth hormone	29.3	0.05–3.00 ng/mL
Prolactin	21.7	2.1–17.7 ng/mL
Thyroid stimulating hormone	1.94	0.44–4.75 mIU/L
Free T4	1.0	0.6–1.2 ng/dL
Follicle-stimulating hormone	9	<19 mIU/L
Luteinising hormone	7	<11 mIU/L
Testosterone	87	300–890 ng/dL
Adrenocorticotrophic hormone	62	<46
Cortisol		>21 µg/dL
Baseline	20.2	
Peak (60 min)	35.8	

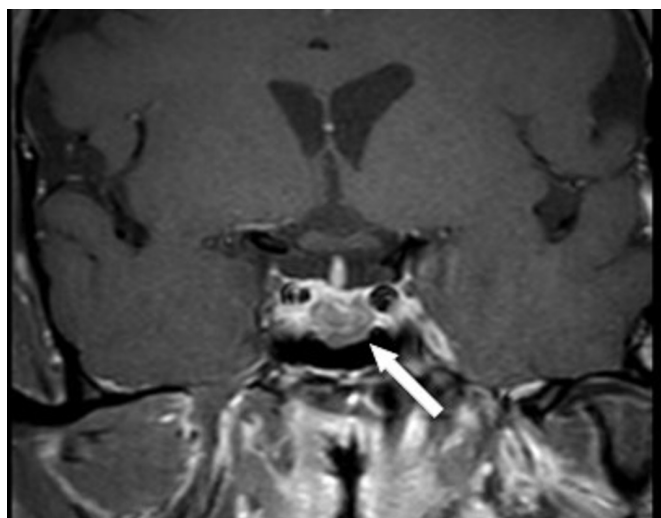
ARUP, Associated Regional and University Pathologists.



**Figure 3** Portable chest radiograph showing bilateral patchy airspace opacities in a peribronchovascular distribution consistent with multifocal pneumonia.

#### DIFFERENTIAL DIAGNOSIS

This patient was initially diagnosed with multifocal pneumonia with respiratory failure and started on empiric ceftriaxone (2 g every 24 hours) and azithromycin (500 mg intravenous every 24 hours), which were continued after SARS-CoV-2 was detected, as concurrent bacterial pneumonia could not be excluded. He received initial resuscitation with 2L of intravenous crystalloid and was placed on 1L per min of supplemental oxygen. On hospital days 2 and 3, he developed recurrent near syncopal episodes with transient oxygen desaturations and hypotension on using the commode, consistent with a diagnosis of vasovagal response, which were effectively treated with a 1L bolus of intravenous crystalloid and increased supplemental oxygen. On hospital day 2, he developed persistent oxygen desaturations requiring a sustained increase to 6L per min of supplemental oxygen, prompting consultation with infectious disease and endocrinology.



**Figure 4** T1-weighted MRI showing a coronal view of a 14×13×10 mm pituitary macroadenoma in the inferior portion of the sella turcica.

While it had been confirmed that the patient had clinical and biochemical evidence of acromegaly, investigation into its source was limited due to his isolation for COVID-19 infection. Because he did not have an urgent indication for MRI of the brain, such as vision changes or severe headache, imaging was postponed until after he had completed a quarantine period and was symptom-free from COVID-19. The most likely source of GH excess was a pituitary adenoma, since ectopic GH release accounts for only 0.5% of cases of acromegaly.<sup>8</sup>

There is little information regarding the impact of the novel coronavirus on overall pituitary function. While a full pituitary hormone evaluation is not urgent, it is important to evaluate the hypothalamic-pituitary-adrenal axis in patients with presumed or diagnosed pituitary adenomas, as untreated corticosteroid deficiency can be life threatening, and may be more so in the setting of an active COVID-19 infection. Our patient had pre-diabetes, central hypogonadism and mildly elevated prolactin related to his GH-secreting pituitary adenoma.

#### TREATMENT

Following his lack of recovery with empiric antibiotics and progression of hypoxia, the patient met our institution's criteria at the time (March 2020) for administration of hydroxychloroquine (400 mg two times per day × 1 day followed by 200 mg two times per day × 4 days). Despite initiation on hydroxychloroquine and continuation of empiric antibiotics (which were considerations at the time but are both now inconsistent with current evidence and treatment guidelines<sup>10</sup>), his supplemental oxygen requirement progressively increased to 6L per minute. While acromegaly is typically only treated urgently if there is concern for a pituitary mass effect or visual compromise, it was hypothesised that the adverse effects of excess GH and IGF-1 on soft-tissue swelling and airway function were negatively impacting his respiratory status. Accordingly, the endocrinology team recommended initiating treatment with octreotide with monitoring for possible improvement in respiratory status.

On hospital day 6, treatment with octreotide 50 µg subcutaneously two times per day was initiated. His oxygenation gradually improved, and within 12 hours his supplemental oxygen requirement had decreased to 0.5L/min. A decrease in his hand size reflected the octreotide-mediated decrease in soft-tissue swelling (figure 5). He was able to discontinue supplemental oxygen the evening of day 7 and he was discharged home off oxygen on hospital day 8. Follow-up chest imaging was not obtained, as it was not felt that it would have changed management.

#### OUTCOME AND FOLLOW-UP

One month after discharge, our patient returned for an MRI of his brain, which showed the aforementioned macroadenoma (figure 4). The adenoma was subsequently resected via transphenoidal hypophysectomy 3 months after discharge. Tissue histology revealed findings consistent with a mixed somatotroph and lactotroph adenoma.

His IGF-1 level dropped but remained elevated off of octreotide therapy following tumour resection, prompting initiation of lanreotide therapy. Seven months after diagnosis, his symptoms of acromegaly (including swelling in his hands and feet and joint pain) have improved.

#### DISCUSSION

This case, which is the first to describe treatment of a patient with coexisting acromegaly and respiratory failure from the novel SARS-CoV-2 virus, highlights the complex interplay



**Figure 5** Dorsal hands prior to (above) and after (below) treatment with octreotide showing a reduction in finger size and reduced ring tightness.

between endocrinopathies and respiratory disease in COVID-19. The most notable aspect of this case is the rapid improvement in respiratory status that occurred after initiation of treatment with octreotide, an intervention that is known to reduce soft swelling in patients with acromegaly.

The first indications of acromegaly in our patient were his acral overgrowth and characteristic facial features (figure 1), including prognathism, frontal bossing, large nose and thickened lips.<sup>11</sup> Patients with acromegaly typically have increased insulin resistance, which can progress to secondary diabetes mellitus. This can dermatologically manifest as acanthosis nigricans and acrochordons (skin tags), as seen in our patient (figure 2).<sup>12</sup> Dermatological changes can even progress to include hirsutism and androgenic alopecia.<sup>12</sup> Other common sequelae of acromegaly include cardiovascular disease (often biventricular hypertrophy and diastolic dysfunction, which was not present in our patient), hypertension, severe obstructive sleep apnoea (which was present in our patient and affects up to 80% of patients), colon polyps and cancer, orthopaedic disease (such as arthropathy and carpal tunnel syndrome, absent in this case), and a higher incidence of menstrual irregularities and infertility in women.<sup>13</sup>

Acromegaly is associated with increased morbidity and mortality, but the diagnosis is often delayed by 10 years or more. Early diagnosis and appropriate management of acromegaly and associated conditions help reduce complications of the disorder. Guidelines suggest evaluation of IGF-1 levels when there is evidence of typical clinical manifestations of acromegaly, especially acral and facial features, or in patients without typical physical features who have several associated conditions (ie, sleep apnoea syndrome, type 2 diabetes, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis and hypertension), and to rule out acromegaly in patients who have a pituitary mass.<sup>14</sup> In our patient, testing was initiated due to the presence of classic

### Patient perspective

I have worked hard all of my life and sacrificed my body doing manual labor to provide for my family. Before, many people would comment that my hands were large, and I thought that was the price I paid for working in physical demanding fields. I didn't go to the doctor regularly because for one thing, I didn't have health insurance, and also it is not in my nature to try to take care of myself. When I contracted COVID-19, I was delivering heavy machinery all over the Portland Metro area. When I deliver the machinery, it takes a lot of physical work.

Despite the nature of my work, I never felt tired because I always focused on working to provide for my family. When I got sick with COVID-19, I noticed that for the first time I was extremely fatigued. Every time I got back in my truck, I felt like I needed to take a nap and I was so winded with my normal activity. When I got home in the evening, I went straight to bed. Normally, I converse with my wife and share a meal with her, but I could not muster the energy for that. I woke up after a few hours to go to the bathroom and felt like I was going to die. I felt hot, short of breath, and lightheaded. I attempted to call out to my wife, but I couldn't. Suddenly, I fell, lost consciousness, and woke up on the floor having just cut my nose. My daughter called the medics and my wife prayed for me. When the medics arrived, I felt better, so I didn't get transferred to the hospital. I didn't understand why I was so sick when I had always been healthy. I had another episode that night and my daughter drove me to the hospital. The doctor told me I might have COVID-19 but they didn't have the test for it. When my symptoms got worse, I decided to go to OHSU because I had delivered machinery there many times. I knew it was a big hospital and that they would have the resources to help me.

I was very ill in the hospital. My family could not visit me, but I called them every day. My oxygen level kept going up and I was scared I was going to die. I found strength in my faith. I prayed to God to spare me because I wanted to be there for my family. I called my wife and had her read my bible to me. One night, my chest felt so tight, I was worried I was not going to get better. I don't remember what treatments I was getting at that time to help me, but I prayed all night and the next day I finally started getting better. I was not too concerned that I could not get the imaging I needed to diagnose my pituitary adenoma. I knew that God brought me through my infection, and I had confidence that I would continue to get the assistance I needed. I am so glad they found the tumor when they did. It could have been worse if it was found later. The octreotide medication made my hands and feet smaller quickly. I am doing so much better after surgery and I am optimistic my acromegaly will be cured. I am so grateful for my team of doctors, in the hospital and afterward.

Financially, things are still stressful. I lost my job when I was sick with COVID-19 and haven't started working again. I don't have health insurance, so the medical costs worry me. My daughter has been helping me fill out financial aid paperwork. I realize that I cannot put my health off anymore. I am working on getting a primary care doctor and know I need to take time for myself. I think it is non-negotiable that all humans need medical insurance, so they do not ignore their health like I did.

physical features, pre-diabetes, and recently diagnosed obstructive sleep apnoea. MRI imaging of the pituitary is recommended after elevated levels of IGF-1 are identified; however, this was postponed in our case due to COVID-19 precautions. Diagnosis

of acromegaly during the COVID-19 pandemic is especially complex, with reduced access to imaging and extensive endocrinological testing, and experts have released consensus guidelines regarding its evaluation and treatment in this unprecedented era.<sup>15</sup> Guidelines otherwise recommend screening for comorbidities at time of diagnosis including obtaining echocardiography, colonoscopy and thyroid exam with a thyroid ultrasound if there is a palpable thyroid nodularity. Definitive management for most patients with pituitary tumours is resection via transsphenoidal surgery, which was undertaken in this patient following quarantine and recovery from COVID-19.

Adjunctive treatment for GH hypersecretion typically involves somatostatin analogues, such as octreotide and lanreotide, both preoperatively and postoperatively given the ability of these drugs to reduce secretion of GH from somatotroph cells and thus reduce hepatic production of IGF-1.<sup>16</sup> This is necessary in part because of the difficulty in achieving complete surgical resection of large GH-secreting pituitary adenomas. It has been hypothesised that rapid glycometabolic and immunomodulatory control of untreated acromegaly is key to successful treatment of patients who contract COVID-19, and that somatostatin analogues are the drug of choice for treatment of respiratory failure in such patients given their potentiation of chemoreceptor response to hypoxia.<sup>17 18</sup> We hypothesise that it was the elevated GH, IGF-1 and the immunomodulatory effects from his untreated acromegaly that contributed to both his severe presentation and rapid recovery following initiation of octreotide. This case also underscores the importance of early multidisciplinary consultation in patients with COVID-19 and complex multi-system comorbidities.

### Learning points

- ▶ Guidelines recommend testing for acromegaly with insulin like growth factor-1 when characteristic clinical features (such as acral enlargement and skin findings of insulin resistance) are present.
- ▶ Insulin resistance seen in acromegaly may be a predisposing factor for severe disease from COVID-19 and other respiratory viral illnesses.
- ▶ Acromegaly is a chronic illness that can change respiratory mechanics and cause soft tissue swelling that may aggravate respiratory illness. Somatostatin analogues can be considered as an adjunctive treatment for respiratory failure in patients with untreated acromegaly.
- ▶ Early multidisciplinary consultation is warranted for all patients with COVID-19 with complex multisystem comorbidities.

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