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Case report

A mysterious cause of chronic cough

A 15-year-old-girl of African descent with sickle cell anaemia (HbSS) presented with an 18-month history of gradually worsening productive cough. She had a history of a previous pneumonia, acute chest crises and two episodes of acute pancreatitis. She was on regular blood transfusions. She underwent a splenectomy in December 2013. There was no documented history of hypercalcaemia. She had no history of fevers or tuberculosis (TB) contacts.

Physical findings

There was evidence of digital clubbing, a wet cough and huff, bilateral basal crepitations and a polyphonic expiratory wheeze bilaterally. Her initial chest radiograph is shown in figure 1.

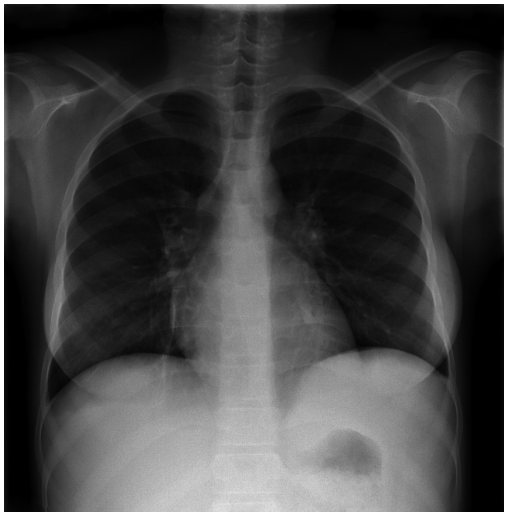

Figure 1 *Normal chest radiograph.*

Task 1
Which of the following investigations would you do next? Choose the most appropriate answer and all that apply.

a) High-resolution computed tomography (HRCT) scan of the chest with contrast
b) Fractional exhaled nitric oxide testing
c) Bronchoscopy
d) Bronchoscopy and bronchoalveolar lavage (BAL)

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This case alerts professionals to take a broad approach when considering childhood chronic cough in sickle cell disease. Certain respiratory conditions are difficult to recognise in childhood, with many children suffering from delayed diagnosis. https://bit.ly/2GZAgmE

Answer 1
a and d.

The long history of a productive cough as well as the digital clubbing would signify bronchiectasis. Bronchiectasis in childhood is rare [1]. Although the chest radiograph is normal, the sensitivity and specificity of picking up bronchiectasis is low [2, 3]. It is important to perform the CT with contrast to check for evidence of hilar lymphadenopathy, or vascular compression, especially with the history of sickle cell disease.

A bronchoscopy is important to check the cause for her symptoms. The cytology of the BAL is required to check for neutrophilia and fat-laden macrophages in case aspiration is the cause of her bronchiectasis. As she is immunodeficient (post-splenectomy and sickle cell disease) it is important to check for atypical organisms, which may need targeted antibiotic treatment, that could be found on a BAL.

Performing an induced sputum could also have been an option. The microbiological yield from expectorated sputum or induced sputum are probably equivalent to that of BAL [4]. It would be less invasive than a BAL. The decision was made to perform a full bronchoscopy and BAL, to check that there were no anatomical abnormalities and to quantify the BAL cytology; therefore, to help rule out aspiration and structural abnormalities as a cause of her symptoms. A pH probe was also passed at the end of the procedure to rule out gastro-oesophageal reflux disease, attempting to rule out reflux aspiration as a cause for her bronchiectasis.

She underwent HRCT with contrast (figure 2).

Task 2
Which of the following statements best describes the findings from the patient's HRCT scan?

a) Cylindrical bronchiectasis
b) Air-trapping and bronchial wall thickening
c) Air-trapping, bronchial wall thickening, bronchiectasis and hilar lymphadenopathy
d) Septal thickening, and bronchial wall thickening

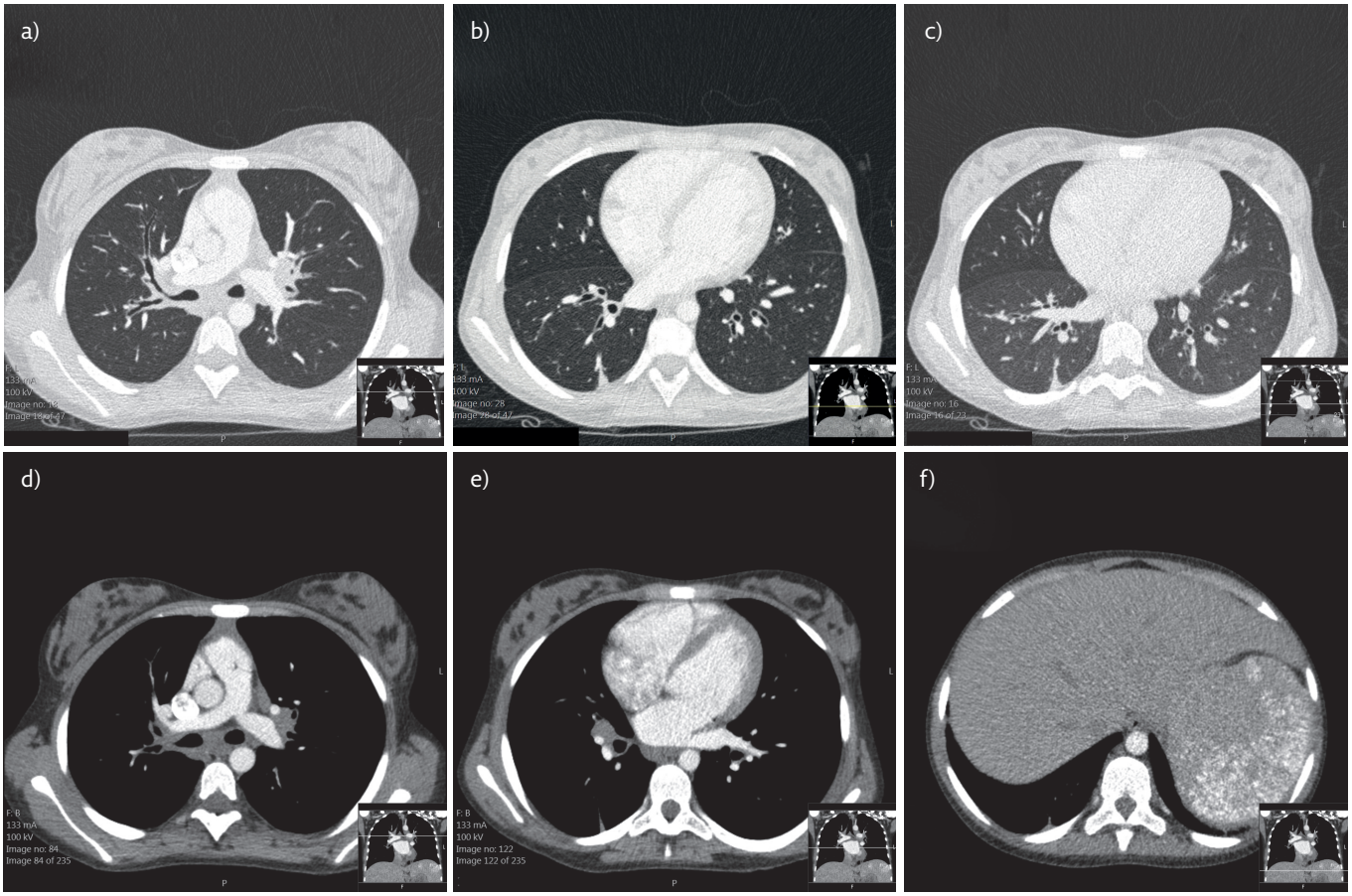

Figure 2 *Chest HRCT scan at presentation.*

Answer 2
c.

There is widening and thickening of the airways, classified as bronchiectasis (figure 2a and b). There is mosaic attenuation (figure 2c), suggesting air-trapping. There is hilar lymphadenopathy (figure 2d and e). Incidentally, there is an enlarged spleen and significant calcification (figure 2f), seen in sickle cell disease.

Fibreoptic bronchoscopy (figure 3) revealed cobblestone appearance of the endobronchial mucosa with increased mucopurulent secretions and erythema bilaterally. BAL cytology revealed 98% macrophages and 2% lymphocytes and was positive for *Staphylococcus aureus*.

The results of further investigations are listed in table 1.

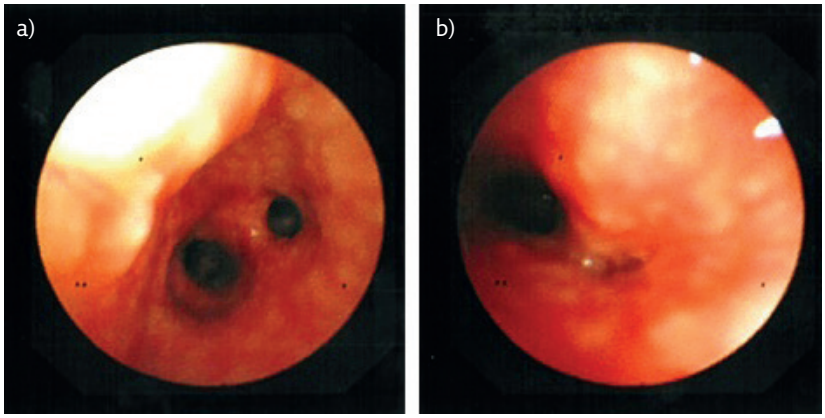

Figure 3 *Fibreoptic bronchoscopy.*

Table 1 *Results of further investigations*

Test	Result
Sweat test	Chloride 17 mmol·L^{-1} (Negative)
Cystic fibrosis genotyping	No mutations detected
Mantoux test	Negative
T spot test	Negative
pH study	Negative
Ciliary studies	Normal
Angiotensin converting enzyme (ACE) level	40 IU·L^{-1} (normal range 8–52 IU·L^{-1})
Anti-neutrophil cytoplasmic antibody	Negative

Task 3
Based on the clinical picture and current results what is the most likely diagnosis?

a) Cystic fibrosis (CF)
b) Bronchiectasis secondary to immunodeficiency
c) Bronchiectasis secondary to aspiration
d) Primary ciliary dyskinesia (PCD)
e) Sarcoidosis

Answer 3
b.

There is evidence of bronchiectasis on the chest CT, and with the previous history of splenectomy leading to immunodeficiency, without any evidence of aspiration, PCD or CF, this is the most likely diagnosis. The lymphadenopathy was thought to be secondary to the sickle cell disease and *S. aureus* infection, and therefore, there was no plan made to perform a lymph node biopsy.

She was subsequently admitted for intravenous antibiotics, and intensive physiotherapy. She required nebulised hypertonic saline. However, her cough persisted, and she required further hospital admissions for *i.v.* antibiotics and chest physiotherapy.

New presentation 1 year later

She presented 1 year later with symptoms of dizziness, and headaches associated with photophobia, persistent fatigue, lethargy, visual disturbances and weight loss. Visual assessment revealed bitemporal hemianopia. She continued to have a productive cough.

Task 4
What would you do next?

a) CT scan of the head
b) Brain magnetic resonance imaging (MRI) scan
c) Both a) and b)
d) None of the above and refer to Neurosurgery
e) None of the above and refer to Ophthalmology

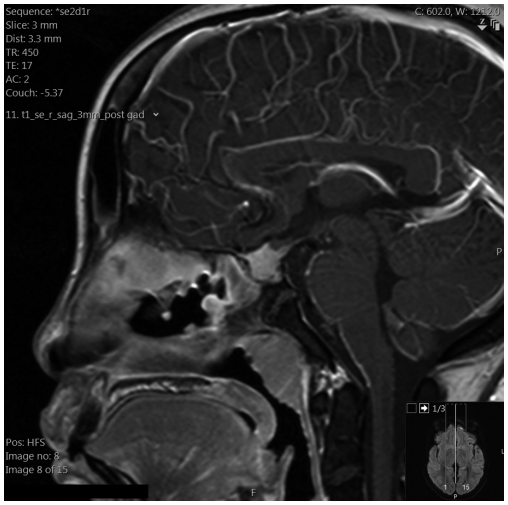

Figure 4 *MRI scan of the brain at presentation.*

Answer 4
b.

These symptoms are suggestive of a pituitary lesion. Brain/pituitary MRI would be the best way to visualise this. MRI scan results shown in figure 4.

Task 5
What does the brain MRI show (figure 4)?

a) Arnold Chiari malformation
b) Hydrocephalus
c) Cerebral oedema
d) A sellar/suprasellar mass compressing the optic chiasm
e) A sellar mass

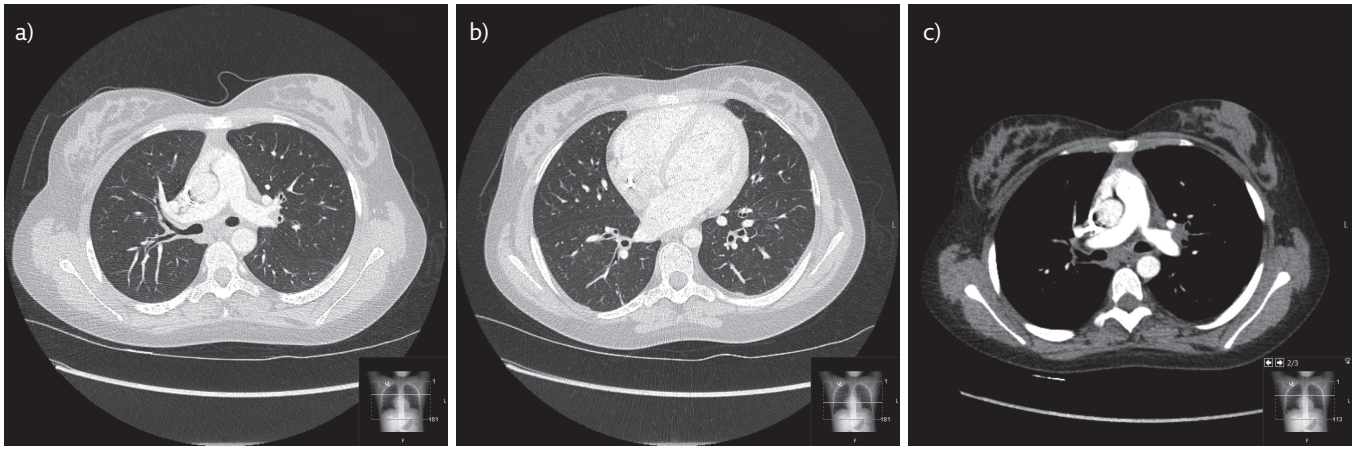

Figure 5 *Repeat chest HRCT.*

Answer 5
d. The brain MRI scan shows a solid enhancing sellar/suprasellar mass (1.5×1.3×1.4 cm) compressing the optic chiasm.

A repeat chest HRCT is shown in figure 5. This showed small-volume mediastinal and hilar lymph nodes, and thick-walled subsegmental airways in both lungs. A few bands of atelectasis in the mid/lower zones, however, some airway thickening. There was a little mosaic attenuation.

Endocrine assessment revealed panhypopituitarism with diabetes insipidus. Multiple hormone deficiencies including hypothyroidism were present. Serum ACE level became elevated during investigation (60 IU·L^{-1}).

A decision was made to biopsy the mass (figure 6). A standard endoscopic transsphenoidal biopsy and debulking of sellar/suprasellar mass was performed. The procedure was uncomplicated without cerebrospinal fluid (CSF) leak but post-operative diabetes insipidus was present which persists, along with pre-existing anterior pituitary hormone deficiencies.

Task 6
What is the lesion suggestive of?

a) Glioma
b) Pilocytoma
c) Spindle cells suggestive of Kaposi's sarcoma
d) Granulomatous lesion and Schaumann bodies

Answer 6
d.

The biopsy shows a granulomatous inflammatory lesion of the adenohypophysis most consistent with the diagnoses of autoimmune granulomatous inflammatory hypophysitis or sarcoidosis. The granulomas were composed of epithelioid macrophages and a large number of T-lymphocytes (mainly CD4 and few CD8 lymphocytes). Stains for CD138 showed a few plasma cells clustered within the granulomatous hypophysis. Stains for acid-fast bacilli, fungi (Grocott) and IgG4 were all negative. The presence of "bare granulomas" whereby fewer lymphocytes surround the granulomatous epithelioid cells and giant cells are typical of sarcoidosis. There were several calcified foci, many of which had a rounded and laminated pattern similar to those described in Schaumann bodies found in sarcoidosis.

A decision was made to perform a biopsy of the lesion in the sellar/suprasellar region. This was to rule out a malignant lesion, which could have been rapidly expanding and may have disseminated.

However, if an endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) or surgical biopsy of one of the hilar lymph nodes had been performed earlier, we may have been able to make the diagnosis before the neurological complication occurred. This may have meant we could have treated the child earlier, and prevented progression of disease. EBUS-TBNA can be safely performed in childhood [5, 6] and has a high diagnostic yield in sarcoidosis [7].

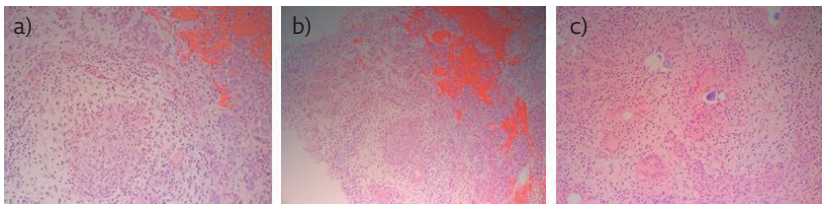

Figure 6 *Histological studies of the pituitary biopsy.*

Further management

Endoscopic transsphenoidal debulking was performed. Oral hydrocortisone, desmopressin, and levothyroxine replacement therapy were commenced. Oral prednisolone (30 mg·day^{-1}) was commenced. Unfortunately, her compliance with corticosteroid therapy was suboptimal.

A repeat brain MRI scan 6 months later is shown in figure 7; it showed some regression in volume of the mass to 1.2 x1.0 x1.1 cm.

Following prednisolone therapy, her chest symptoms were much improved. Serum ACE levels showed some reduction, although her compliance was suboptimal and the reduction was not as marked as expected (figure 8).

An alternative to oral corticosteroids would be to use *i.v.* methylprednisolone, and this is used first line in some centres to treat sarcoidosis [7]. This would have addressed the adherence issue. In our centre oral corticosteroids is the first-line therapy for sarcoidosis, as it reduces the need for hospital stay and reduces complications. As her compliance was intermittent, and scans showed eventual regression, she was not switched to *i.v.* pulses of methylprednisolone.

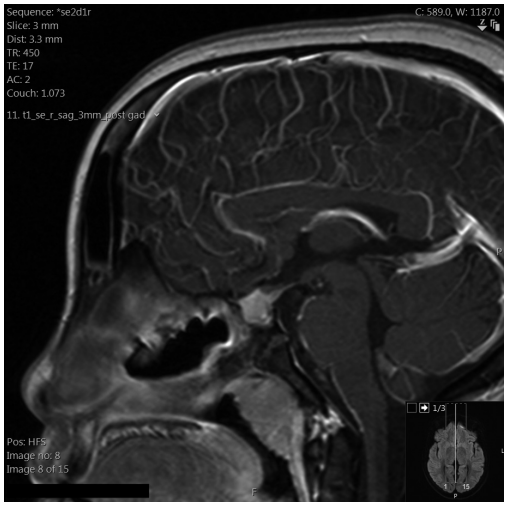

Figure 7 *MRI scan of the brain 6 months after the initiation of prednisolone treatment.*

Task 7
Was there an indication in patient's past medical history which could have made sarcoidosis one of the differential diagnoses from the beginning?

a) Splenectomy
b) Previous severe pneumonia
c) Previous episodes of acute pancreatitis
d) No indication in patient's past medical history

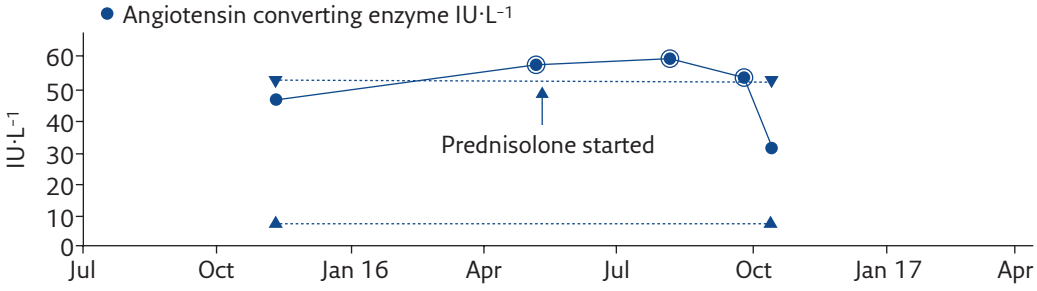

Figure 8 *Serum ACE levels over a year, showing reduction in levels following prednisolone treatment.*

Answer 7
c.

Acute pancreatitis is a rare presentation of sarcoidosis, and has been described in childhood [8]. The episodes of pancreatitis were legitimately thought to be related to biliary sludging due to the high red cell turnover seen in sickle cell disease. However, this along with her ethnicity, the initial hilar lymphadenopathy and slightly raised serum ACE could be suggestive of sarcoidosis. It is easier to reflect upon this in retrospect, but maybe the serum ACE could have been followed up more closely. However, eventually even with all this in mind, tissue diagnoses was the only way to diagnose such a tricky case.

Discussion

This is a complex case of a child with sickle cell disease with a chronic cough. Her cough was thought to be caused by bronchiectasis secondary to relative immunodeficiency from her splenectomy and sickle cell disease. Her sickle cell disease meant that she had had previous acute chest crises. Sickle cell disease itself can lead to chronic chest changes and sickle cell lung disease (SCLD) and interstitial lung disease. Sickle cell disease can also be associated with asthma, and these can contribute to chronic cough. The diagnosis was therefore formed by a process of elimination initially, and subsequently revised when she presented with her neurological symptoms. A diagnosis of sarcoidosis was made following this, but in retrospect if a hilar lymph node biopsy had been performed earlier, possibly the diagnosis could have been made at an earlier stage, thus preventing disease progression.

Acute pancreatitis is a rare presentation of sarcoidosis, and the history of such was an early pointer to this diagnosis. The pancreatitis was thought to be related to increased biliary sludge seen in sickle cell disease, but in retrospect, with her history, ethnicity and mildly raised serum ACE, possibly we could have followed this more carefully and made the diagnosis earlier.

Sarcoidosis is a multisystem noncaseating granulomatous inflammatory disease, with pulmonary involvement being the most common manifestation [9]. The nervous system is affected in approximately 5–13% of cases [10], with presentations ranging from cranial and peripheral neuropathies to acute or chronic meningitis, and hypothalamic–pituitary dysfunction as seen in this case [7, 11, 12]. Hypothalamic–pituitary involvement, though extremely rare, is linked to severe sarcoidosis [13]. Corticosteroid therapy is the first line treatment [12], which helps improve MRI lesions but does not necessarily result in normalisation of endocrine function in the majority of the cases [13].

We report this case because it is the first case, to our knowledge, whereby a child's respiratory diagnosis has been revised following the presentation of a pituitary hypophysitis. Secondly, this case illustrates the complexities of chronic cough in paediatric individuals, and alerts us to consider other causes of chronic suppurative lung disease; assessing possible involvement of other systems through history, examination, and targeted investigations. Thirdly, the case illustrates the benefit of EBUS-TBNA which, if carried out early, could lead to earlier diagnosis and prevent disease progression.

This case illustrates how difficult sarcoidosis can be to diagnose, that acute pancreatitis can be an early sign of sarcoidosis and that serum ACE can be only moderately raised in children. In fact, only 50% of children with sarcoidosis have an elevated level [14, 15]. Her level at first testing was within the normal range, but did become elevated subsequently (figure 8). There are a number of ACE polymorphisms, notably the ACE D allele is linked with higher serum ACE levels. This is the case in normal patients as well as patients with sarcoidosis [16]. Some polymorphisms are likely linked to lower levels. Possibly, there should be different reference ranges depending on the genotype a child has. Unfortunately, we were unable to perform a genotype for our patient. However, as there are so few children with sarcoidosis, accurate reference ranges for different genotypes do not exist. Monitoring levels over a longer period is more helpful. A large number of symptomatic children with sarcoidosis remain undiagnosed for years [17]. Eventually, biopsy is the only definitive way to diagnose this condition.

In this case, we had to perform a neurosurgical biopsy of the lesion, as the suprasellar/sellar lesion could have been malignant in nature. However, if sufficient an EBUS-TBNA done at an earlier stage could have prevented the progression of her disease to involve the pituitary gland. This procedure is well described in childhood [5, 6] including as a diagnostic aid in childhood sarcoidosis [7].

In conclusion, this multi-system case highlights the importance of precise history taking, the difficulty in diagnosing sarcoidosis in childhood, with many children suffering from delayed diagnosis. It is important to consider a lymph node EBUS-TBNA in a child with unexplained lymphadenopathy. This case reminds us that half of children with sarcoidosis can have a normal serum ACE level, and it is important that we think of this condition even in patients with other chronic illnesses such as sickle cell disease.

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Conflict of interest

None declared.

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