Severe central airway stenosis and tracheomalacia in hunter syndrome

Han Loong Tan, MRCP[1], Rozanah Abd Rahman, MMED[1], Noor Aliza Md Tarekh, MMED[1], Mahazir Kassim, MMED Anaesthesiology[2], Narasimman Sathiamurthy, MMED Surgery[3], Amiruddin Nik Mohamed Kamil, MMED Anaesthosiology[4], Lock Hock Ngu, MRCP[5]

[1]Department of Respiratory, Hospital Sultanah Aminah, Johor Bahru, Malaysia, [2]Department of Anaesthesiology and Critical Care, Hospital Sultanah Aminah, Johor Bahru, Malaysia, [3]Department of Surgery (Thoracic Surgery), Hospital Kuala Lumpur, Malaysia, [4]Department of Anaesthesiology and Critical Care, Hospital Kuala Lumpur, Malaysia, [5]Genetic Department, Hospital Kuala Lumpur, Malaysia

SUMMARY

Hunter Syndrome is a genetic disease characterized by deficiency of Iduronate-2-Sulfatase enzyme activity, resulting in accumulation of glycoaminoglycans in various organs including the central airways. We report a case of severe tracheomalacia and airway stenosis at Hospital Sultanah Aminah, Johor Bahru, Malaysia requiring mechanical ventilation in a middle aged gentleman who was previously undiagnosed of mucopolysaccharidosis. The patient underwent emergency tracheostomy for failed intubation, when he presented with shortness of breath and acute respiratory failure. A contrast-enhanced computed tomography of the neck and thorax revealed that the trachea distal to the tracheostomy tube had collapsed with narrowed right and left main bronchus. These findings were confirmed via direct visualization of the airway through a flexible bronchoscopy. Eventually, a tracheal stenting were performed to maintain the airway patency and assist in weaning off from mechanical ventilation. Further investigations to identify the aetiology of the central airway stenosis revealed elevated urinary glycoaminoglycans and the absence of iduronate-2-Sulfatase activity tested on dried blood spots, thus confirming the diagnosis of Hunter Syndrome. Managing mucopolysacharidosis with central airway obstruction requires multidisciplinary team effort in handling the difficult airway, anaesthesiology risk, potential comorbidities and providing genetic counselling.

INTRODUCTION

Mucopolysaccharidoses (MPS) are a group of rare genetic diseases caused by the deficiency of any of the lysosomal enzymes that are involved in the glycoaminoglycans (GAGs) catabolism.[1] The estimated cumulative incidence is approximately 1 in 25,000 newborns. Most cases are diagnosed in the paediatric age group due to the early manifestation of the symptoms. The median age of diagnosis of Hunter syndrome (HS) were 3.5 years, with the age of onset of symptoms at the age of 1.5 years.

In patients with MPS, the accumulation of GAG in various organs and tissues results in a multisystemic clinical picture. Seven distinct clinical types of MPS are known: type I, II, III, IV, VI, VII, and IX. HS or MPS II is caused by deficiency of the lysosomal enzyme iduronate-2-sulfatase. Clinical features and severity of symptoms are widely variable ranging from severe infantile onset disease to an attenuated form, which generally has a later onset with a milder clinical presentation. Symptoms may include coarse facies, short stature, cardiac valvular disease, recurrent respiratory infections, obstructive sleep apnoea, joint stiffness, hepatosplenomegaly, umbilical and inguinal hernias, hearing loss, gingival hypertrophy and developmental delay and regression.[1] Tracheomalacia and tracheal stenosis may present as a result of deposition of storage material in the airways. The attenuated forms of MPS II are more difficult to diagnose since the disease progresses silently over decades and early symptoms are subtle and may be overlooked by physicians who are not familiar with the disease.

CASE REPORT

A 51-year-old Malay gentleman, who is a chronic active smoker, was diagnosed to have chronic obstructive pulmonary disease (COPD) five years ago and treated with metered-dose inhaler ipratropium bromide/fenoterol 40mcg/100mcg tds, budesonide 400mcg bid and salbutamol 200mcg PRN. His COPD was controlled and only had one episode of acute exacerbation that required hospital admission. He presented at the Hospital Sultanah Aminah, Johor Bahru, Malaysia with fever and cough for two days associated with worsening shortness of breath for the past three months. He also had loud snoring with daytime somnolence and his past medical history include hypertension and herniorrhaphy for umbilical hernia.

Upon arrival in emergency department, he was tachypnoeic with oxygen saturation of 97% under room air, blood pressure 145/86mmHg, pulse rate 97 beats/min, and febrile with temperature of 38.7°C. General examination showed that he has short stature with a thick neck (figure 1a), while lung examination revealed generalized ronchi bilaterally. Besides, he also had a palpable liver of 3 finger breadth below subcostal margin. He was initially treated as acute exacerbation of COPD. Despite being given intravenous hydrocortisone and nebulized bronchodilator, he developed worsening of type I respiratory failure with oxygen saturation of 80% and dropped in conscious level. Multiple attempts for

This article was accepted: 06 April 2021
Corresponding Author: Han Loong Tan
Email: loong1225@hotmail.com

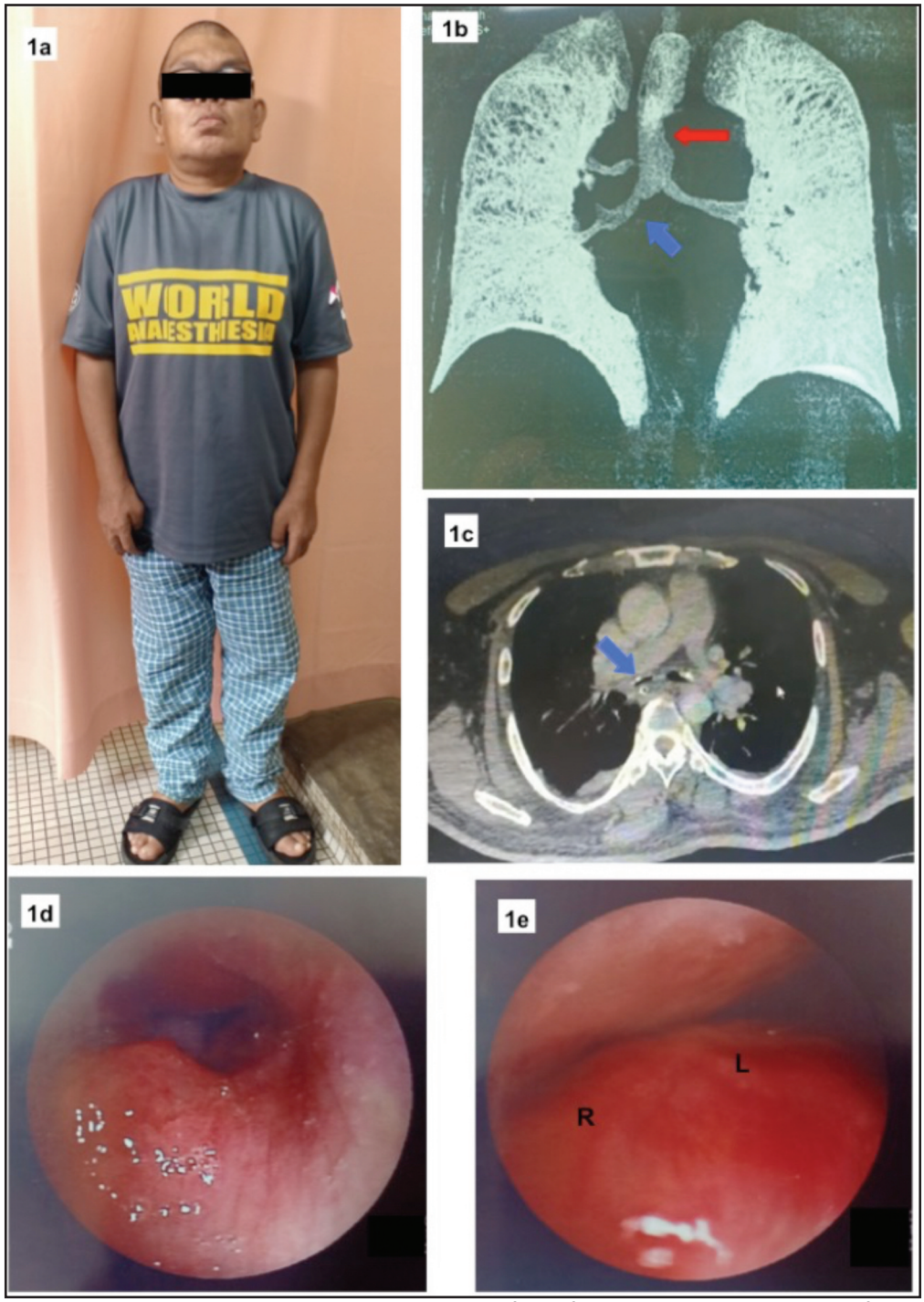

Fig. 1: a) The patient's height is 155cm. He has thick neck and course facial features, which is suggestive of mucopolysaccharide syndrome. Publication of the patient's photo was permitted and consented by the patient b,c) CECT Thorax and reconstruction CT revealed a collapsed trachea (red arrow) inferior to the tracheostomy tube with anterior-posterior diameter of 0.7cm. Both main bronchi are also stenotic, more severe on the right (blue arrow). d) Bronchoscopy through the nasal cavity showed oedematous nasopharynx and the trachea proximal to the trachestomy tube was narrowed with presence of granulation tissue e) Lower third of the trachea and bilateral main bronchi were stenotic. As seen during bronchoscopy, right main bronchus (R) was narrower compared to left main bronchus (L).

intubation failed resulting in an emergency tracheostomy to secure the airway.

A contrast-enhanced CT neck and thorax revealed that the trachea distal to the tracheostomy tube had collapsed with anterior-posterior diameter of 0.7cm (Figure 1b,1c). Both bronchi were also narrowed with the right and left main bronchus measured 0.4cm and 0.5cm respectively. There were bilateral consolidations at the perihilar extending to both lower lobes suggestive of lung infection. Bronchoscopy

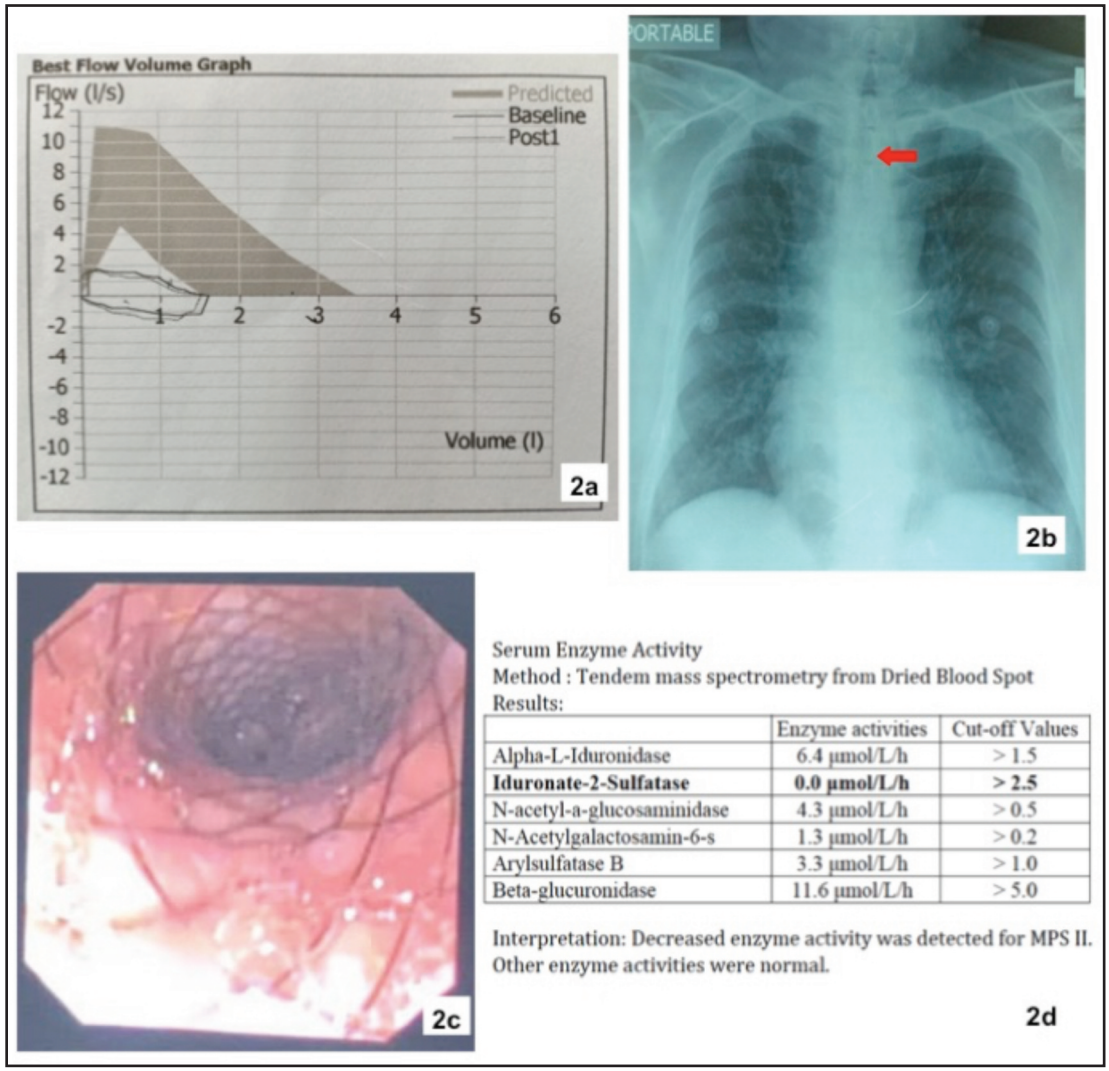

Fig. 2: a) Plateau in both inspiratory and expiratory portion of the flow-volume loop indicates fixed airway obstruction. b) Chest x-ray post tracheal stenting shows stent in-situ (red arrow) with patent trachea. c) Post airway stenting with metallic stent revealed a patent trachea. d) Elevated urine GAG and absence of serum Iduronate-2-Sulfatase activity confirm the diagnosis of Hunter Syndrome. Other enzyme activities are normal.

revealed a stenotic trachea with oedematous mucosa and presence of tracheomalacia. Both main bronchus and all segmental bronchi were narrowed (Figure 1d,1e). Bronchial washing from the right lower lobe were negative for acid-fast bacilli direct smear and the GeneXpert test for tuberculosis. Endobronchial biopsy over the right bronchus intermedius was negative for malignancy or granulomatous lesion. His previous spirometry during clinic visit was reviewed and showed fixed upper airway obstruction with post bronchodilator forced expiratory volume in one second (FEV1) 1.10 litre (44% of predicted), forced vital capacity (FVC) 1.43 litre (51% of predicted) and FEV1/FVC ratio of 0.77 (Figure 2a).

The trachea and bronchial stenosis as well as recurrent lung infection had led to prolonged ventilation. He was treated for influenza pneumonia and later hospital acquired pneumonia secondary to Klebsiella pneumoniae and Stenotrophomonas maltophilia. Besides, he was given one week of intravenous dexamethasone 8mg tds in view of oedematous oropharynx, trachea and bronchi. After a prolonged stay of 34 days in the intensive care unit, he was finally weaned off from ventilator.

Subsequently, he underwent tracheal stenting under totally intravenous anaesthesia and spontaneous ventilation. Flexible bronchoscopy findings revealed tracheomalacia and tracheal stenosis 3cm below the vocal cord and 6 cm in length. The distal end of the stenosis situated at 1 cm above the carina. Balloon dilatation was performed over both the bronchi and post dilatation a 5.2mm bronchoscope could easily pass through the bronchus. A fully covered metallic stent (Hanarostent trachea) with a diameter of 16mm and a length of 6cm was deployed into the tracheal stenotic segment (Figure 2b, 2c) through the tracheostomy opening using flexible bronchoscope as guidance. The oxygenation was maintained via a nasal cannula and spontaneous ventilation. After stent adjustments, the tracheostomy tube was removed. The stent could not be inserted through the vocal cord due to severely narrowed larynx. Although he

required re-intubation one week later due to excessive secretion causing airway compromise, he was finally discharged home well with Modified Medical Research Council (mMRC) dyspnoea scale I.

Since discharge, the patient had recovered gradually and was scheduled for regular chest physiotherapy. He was taught about effective cough technique to expectorate the airway secretion. He is able to perform the activity of daily living and four months later, he resumed his duty in his workplace.

The unusual trachea and bilateral bronchial stenosis has prompted an effort to identify the underlying aetiology. He did not have past history of intubation, airway trauma, recurrent chest infection or symptoms of autoimmune disease. Pulmonary tuberculosis was ruled out based on the bronchial washing result and absence of typical symptoms. The central airway stenosis together with the presence of short stature, short neck, umbilical hernia and hepatomegaly raise the suspicion of MPS, which was later confirmed to be HS with the elevated urine GAGs of 35.5g/mol creatinine and absence of serum Iduronate-2-Sulfatase activity in dried blood spots (Figure 2d). Other sulfatase enzymes were normal, thus excluding the diagnosis of multiple sulfatase deficiency.

DISCUSSION

Tracheobronchial stenosis can result from malignant and benign causes. Prolonged intubations or tracheostomy is the commonest cause of non-neoplastic stenosis of proximal airways. Besides, granulomatous infection such as tuberculosis, and aspergillosis need to be ruled out in patients with tracheobronchial stenosis. Other causes include systemic diseases such as relapsing polychondritis, amyloidosis, sarcoidosis and inflammatory bowel disease. Due to the rarity of the disease, diagnosis of MPS with proximal airway stenosis requires high index of suspicion in a patient with facial dysmorphism and skeletal dysfunction, followed by laboratory confirmation.

Airway obstructions particularly in patients with MPS types I, II, and VI may lead to fatal complications in emergency cases, during surgical procedures or during intubation.[2] Large amount of storage material deposition may lead to upper airway obstruction as well as bronchial and tracheal stenosis. Besides, tracheomalacia and bronchomalacia are commonly seen, resulting in complete major airway collapse. These airways stenoses occurred around adolescence and are progressive, leading to almost complete obstruction of a bronchus or the trachea.

There is no standard management guidelines available regarding the treatment of upper airway obstructions in patients with MPS. Many MPS patients with upper airway obstruction are treated with tracheostomy. However, in patients who underwent tracheostomy, when the auto-positive end-expiratory pressure (PEEP) function of the glottis is reduced, airway collapse caused by the malacia will become apparent.[2] Jeong et al reported that infrastomal tracheal stenosis (85.7%) and stomal narrowing(71.4%) are frequent in patients with MPS type II post tracheostomy, resulting in difficult cannula care and need for revision.[3]

There are few case reports on performing airway stenting in patients with MPS complicated with airway stenosis and tracheomalacia. Davitt et al. reported a case of a 22 year-old male with HS who had drastic improvement in his symptoms and functional status after insertion of plastic and metallic stents for major airway obstruction. Another two patients with mucopolysaccharide storage disorders (Maroteaux–Lamy syndrome and HS) with tracheal stenosis and tracheomalacia were reported to be weaned off from prolonged ventilation after stenting of the trachea. During the subsequent 2-year follow up period, no further requirement for mechanical ventilation was reported.2 However, Karl et al. concluded that the short-term benefit of airway stenting needs to be weighed against the possible long-term stent-related complications and morbidity in patients with MPS and airway stenosis.[4]

Enzyme replacement therapy and bone marrow transplantation are two treatment options for MPS type II. Idursulfase are enzymes produced by recombinant deoxyribonucleic acid (DNA) technology for treating patients with MPS type II via catabolism of accumulated GAGs. In a double-blind, placebo-controlled trial involving 96 MPS II patients, those who were given weekly idursurface reported a 37-m increase in the 6-minute-walk distance and 160mL increase in absolute FVC compared to placebo group. Besides, patients on ERT have decreased urinary GAGs level, improved elbow mobility, reduced hepatomegaly and better quality of life.[5] However, to date, no evidence of ERT benefit on airway stenosis or tracheomalacia has been reported. Data on the effect of bone marrow transplantation in HS is limited. Reported benefits include stabilization of cardiovascular abnormalities, resolution of hepatosplenomegaly as well as improvement in joint stiffness and hearing defect.[5]

As seen in our patient, central airway obstruction can be misdiagnosed as COPD. Both conditions presented with shortness of breath and may have cough and chest tightness. The initial presenting signs and symptoms of shortness of breath, ronchi on auscultation and no audible stridor in a chronic smoker resulted in the diagnosis of COPD. Eventually, the unusual tracheal and bronchial stenosis with facial dysmophism, elevated urinary GAGs and absence of iduronate-2-sulfatase revealed the true pathology behind the symptoms. A careful evaluation of the flow volume loop from spirometry would guide us in differentiating between COPD and fixed airway obstruction. The former shows concave-shaped maximal expiratory flow-volume curve, whereas flattening of both the inspiratory and expiratory flow-volume loop is seen in the latter.

Most of the cases of HS are diagnosed during childhood. We report here a case of MPS type II diagnosed at middled age man after he presented with severe tracheal and bilateral bronchial stenosis requiring mechanical ventilation. The basis of tracheal stenting is on the intention to treat, since he was difficult to be weaned off from ventilator and tracheostomy initially. Managing MPS patients with central

airway stenosis can be challenging as it involves multidisciplinary team in handling the difficult airway, anaesthesiology risk, potential comorbidities such as obstructive sleep apnoea, cardiac valvulopathy, skeletal dysfunction and the need for genetic counselling.

CONCLUSION

This is an unusual case of severe tracheobronchial stenosis and tracheomalacia leading to the diagnosis of HS in adulthood. In addition to genetic counseling, ERT and bone marrow transplantation, tracheal stenting and tracheostomy remain the important strategies in maintaining airway patency in this rare genetic disease.

REFERENCES

1. Giugliani R, Federhen A, Rojas MV, Vieira T, Artigalas O, Pinto LL et al. Mucopolysaccharidosis I, II, and VI: Brief review and guidelines for treatment. Genet Mol Biol 2010; 33(4): 589-604.
2. Kampmann C, Wiethoff CM, Huth RG, Staatz G, Mengel E, Beck M, et al. Management of Life-Threatening Tracheal Stenosis and Tracheomalacia in Patients with Mucopolysaccharidoses. JIMD Rep 2017; 33: 33-9.
3. Jeong HS, Cho DY, Ahn KM, Jin DK. Complications of tracheotomy in patients with mucopolysaccharidoses type II (Hunter syndrome). Int J Pediatr Otorhinolaryngol 2006; 70(10): 1765–9.
4. Karl R, Carola S, Regina E, Thomas N, Huber RM. Tracheobronchial stents in mucopolysaccharidosis. Int J Pediatr Otorhinolaryngol 2016; 83: 187-92
5. Scarpa M, Almassy Z, Beck M, Bodamer O, Bruce LA, De Meirleir L, et al. Mucopolysaccharidosis type II: European recommendations for the diagnosis and multidisciplinary management of a rare disease. Orphanet J Rare Dis 2011; 6: 72.