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SUCCESSFUL TREATMENT OF VANISHING BRONCHUS INTERMEDIUS SYNDROME FOLLOWING LUNG TRANSPLANTATION

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The vanishing bronchus intermedius syndrome is a type of peripheral bronchial stenosis that develops in lung recipients within two to nine months after transplantation. Lack of timely diagnosis and effective treatment leads to increased mortality and poor quality of life. The clinical case presented demonstrates the successful long-term treatment of vanishing bronchus intermedius syndrome in a lung recipient using interventional bronchoscopy.

Keywords: lung transplantation, cystic fibrosis, bronchial stenosis, vanishing bronchus intermedius syndrome.

INTRODUCTION

According to leading transplant centers, bronchial complications following a lung transplantation develop in 2–18% of cases [1–8]. Among the complications, the most common is bronchial stenosis, whose frequency varies from 1.4 to 32% [9, 10], which undoubtedly demonstrates a high interest in methods aimed at timely diagnosis and correction.

Bronchial stenosis most often develops within 2–9 months after surgery, but sometimes they can be diagnosed even several years after transplantation [11]. According to the International Society for Heart and Lung Transplantation, bronchial stenosis in the lung graft is divided into central and peripheral. Central bronchial stenosis is located at the bronchial anastomosis or within 2 cm of the anastomosis, while peripheral is at a distance of more than 2 cm from the suture line, in the proximal direction [5].

Bronchus intermedius stenosis is one of the varieties of peripheral stenosis, which is observed in 2–5% of donor lung transplant cases. A condition characterized by a recurrent course due to the absence of a long-term effect of treatment, resulting in intermedius bronchus atresia, is called the vanishing bronchus intermedius syndrome (VBIS) [5, 12–14]. According to S. Shah et al., the mean survival of lung recipients after VBIS diagnosis is about 25.3 months [15]. According to S. Murthy et al, recurrent stenosis after endoscopic correction occurs in 35% of cases, and with repeated intervention can reach up to 70% [3].

Due to the emergence of new transplant centers in Russia and the dynamic development of lung transplantation programs in leading clinics, the VBIS has become undoubtedly a pressing issue, which makes it necessary to systematize the accumulated experience and demonstrate cases of effective treatment. The paper describes a case of successful long-term treatment of recurrent bronchus intermedius stenosis (vanishing bronchus intermedius syndrome), which developed 2 months after lung transplantation, using multimodal interventional bronchology methods.

CLINICAL CASE

In September 2017, a woman born in 1988 (29 years old) was referred to the Shumakov National Medical Research Center of Transplantology and Artificial Organs in Moscow. Her diagnosis was cystic fibrosis (F508del/F508del/3272-16T>A), mixed form, severe course. Chronic suppurative obstructive bronchitis. Diffuse bronchiectasis. Diffuse pneumosclerosis. Type 3 respiratory failure. Chronic pancreatitis. Polypoid rhinosinusitis with nasal polyps, grade 2 – for examination to clarify the indications and exclude contraindications for lung transplantation.

From the patient's medical history, frequent episodes of respiratory diseases were known from early childhood. Cystic fibrosis was diagnosed at the age of 14. Since that time, chronic respiratory infection with Pseudomonas aeruginosa has been diagnosed. In 2005 and 2012, the patient gave birth to two healthy children. Since 2009, chronic respiratory infection with the Burkholderia cepacia complex has been diagnosed. In the period from 2016 to 2017, there was a sharp deterioration in the condition, in the form of progression of respiratory failure phenomena with a need for constant oxygen insufflation (up to 3–4 L/min flow).

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Examination results confirmed the lung injury to be in its end stage. Chest CT scan revealed a bullous-cystic transformation of both lungs with multiple bronchiectasis. Assessment of external respiratory function (ERF) showed: vital capacity (VC) – 1.77 L (47%), forced expiratory volume (FEV_1) – 0.66 (21%), Tiffeneau-Pinelli index – 37.2. Analysis of arterial blood gas composition showed pronounced hypoxemia stage 2–3: pO_2 – 42 mm Hg, pCO_2 – 65 mm Hg. Microbiological analysis of sputum culture revealed a multidrug-resistant Burkholderia cepacia complex. Due to the progressive course of the underlying disease, lack of other effective treatment methods and futility of further conservative therapy, the patient was in September 2017 waitlisted for a deceased-donor lung transplantation. The waiting time for an organ from a deceased donor was 12 months.

On October 2, 2018, bilateral sequential lung transplantation was performed without the use of artificial circulation techniques.

The donor was a 38-year-old woman diagnosed with brain death as a result of acute hemorrhagic cerebral circulation disorder. Brain death was established on the basis of the current legislation (order No. 908n of the Ministry of Health of the Russian Federation, dated December 25, 2014). The donor's lungs were under artificial ventilation for 24 hours; blood gas composition (100% oxygen fraction) in arterial blood – pO_2 – 520 mm Hg., pCO_2 – 36 mm Hg.; there were no episodes of hypotension and cardiac arrest during the donor conditioning period. The donor lungs were harvested according to the standard technique within the framework of multi-organ explantation. Celsior (IGL, France) with a 4-liter volume was used as a preservative solution.

Lung transplantation surgery lasted for 10 hours 3 minutes. The intraoperative period was uneventful. Cold preservation of the right and left lung graft lasted for 6 hours 20 minutes and 9 hours 50 minutes respectively. Due to pronounced mismatch between the diameters of the donor's and recipient's bronchi, bronchial anastomoses were performed telescopically, by intussusception of the donor's bronchial stump into the recipient's main bronchus.

The patient was extubated on postoperative day 2. The early postoperative period was uneventful and without significant clinical events. The drains were removed on postoperative day 3 and day 5. There were no signs of graft dysfunction. During hospitalization, sputum microbiological analysis showed occasional spread in Klebsiella pneumoniae without Burkholderia serasia complex isolation. Laboratory and imaging indicators by the end of postoperative week 3: ERF: VC – 1.88 L (54%), FEV_1 – 1.79 (59%), Tiffeneau-Pinelli index – 83.4; Capillary blood pH (in atmospheric air): pO_2 – 79 mm Hg, pCO_2 – 38 mm Hg, SpO_2 in atmospheric air 96–97%. The patient was discharged on postoperative day 28 in a satisfactory condition with three-component immunosuppressive therapy (tacrolimus, methylprednisolone, mycophenolate mofetil). Concomitant therapy included: antibacterial, antiviral, antifungal and inhaled bronchodilators, gastroprotective therapy. The patient was regularly examined according to the donor lung recipient monitoring protocol.

Two months after transplantation, the patient complained of cough with difficult discharge of scanty amount of sputum, recurrent fever up to febrile digits, and shortness of breath during physical exertion. Outpatient examination revealed a slight decrease in external respiration indicators: (VC – 2.03 L (54%), FEV_1 – 1.76 L (55%), Tiffeneau-Pinelli index – 87). Bronchoscopy revealed cicatricial occlusion of the bronchus intermedius (Fig. 1, a). Chest CT scan revealed an X-ray picture of inflammatory infiltration of the middle and lower lobes of the right lung (Fig. 1, b). Laboratory tests demonstrated an increase in inflammation markers: C-reactive protein 154 mg/L, leukocytosis of up to 12,000 with a left shift in leukocyte formula. Microbiological examination of bronchoalveolar lavage revealed respiratory tract reinfection with Burkholderia cepacia complex and Klebsiella pneumoniae.

Taking into account the clinical and radiological picture of middle and lower lobe obstructive pneumonia, endoscopic balloon bougienage of the intermediate bronchus stenosis (Endo-Flex dilation balloon, 7 Fr, three-step, Germany) was performed in the operating room using rigid bronchoscopy on December 17, 2018. Antimicrobial therapy included antibiotics (meropenem, co-trimoxazole, piperacillin + tazobactam), antifungal drugs (fluconazole), inhalation therapy (colistin, amphotericin). In order to prevent recurrent stenosis, mofetil mycophenolate was converted to everolimus with the target concentration of 4–5 ng/mL. Against the background of the treatment, bronchoscopy and computed tomography showed positive dynamics in the form of formation of a stable bronchus intermedius lumen 5–6 mm in diameter, reduced area and intensity of inflammatory infiltration of the middle and lower lobe of the right lung (Fig. 2, a, b). The patient was discharged on day 12 after balloon bronchoplasty for bronchus intermedius stenosis in a state of positive clinical, laboratory and imaging dynamics. ERF indicators at the time of discharge from the hospital: VC – 2.04 l (58%), FEV_1 – 1.83 L (60%), Tiffeneau-Pinelli index – 89.7.

Four months after transplantation and 2 months after balloon dilatation for cicatricial stenosis, the patient noted renewed signs of respiratory failure. Bronchoscopy (outpatient examination) revealed recurrent bronchus intermedius stenosis of up to 3–4 mm (Fig. 3, a). Chest CT scan showed the areas of inflammatory infiltration in the middle and lower lobes of the right lung (Fig. 3, b). According to ERF data: VC – 1.85 L (52%), FEV_1 – 1.74 L (54%), Tiffeneau-Pinelli index – 85.9.

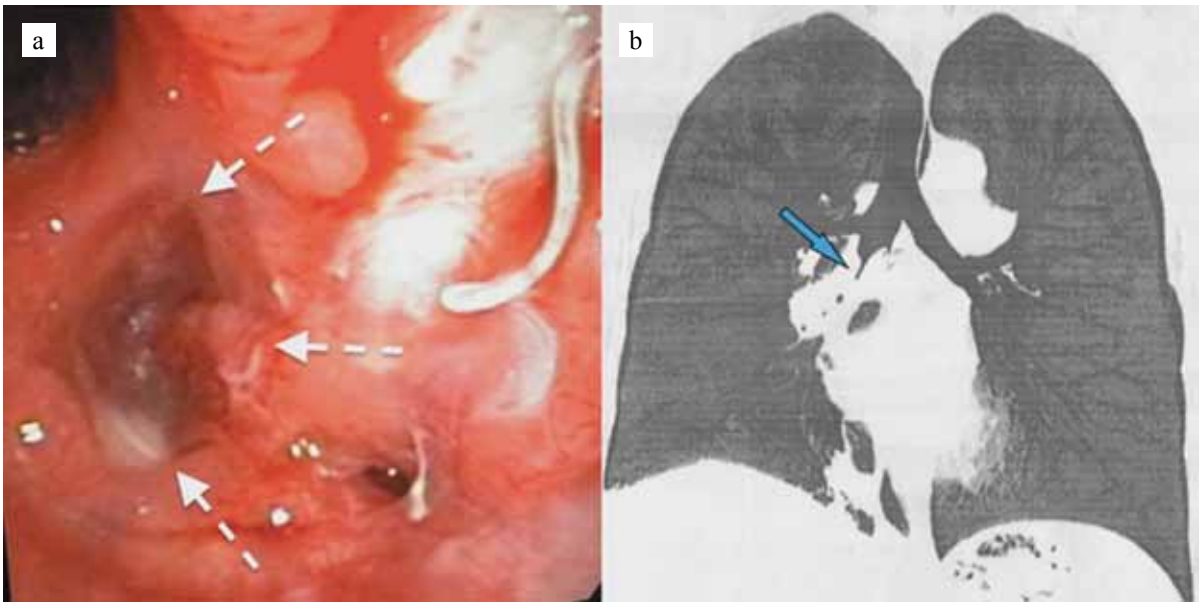

Fig. 1. Cicatricial occlusion of the bronchus intermedius: a – endoscopic picture of the occlusion of the bronchus intermedius (indicated by arrows); b – CT signs of occlusion (indicated by an arrow)

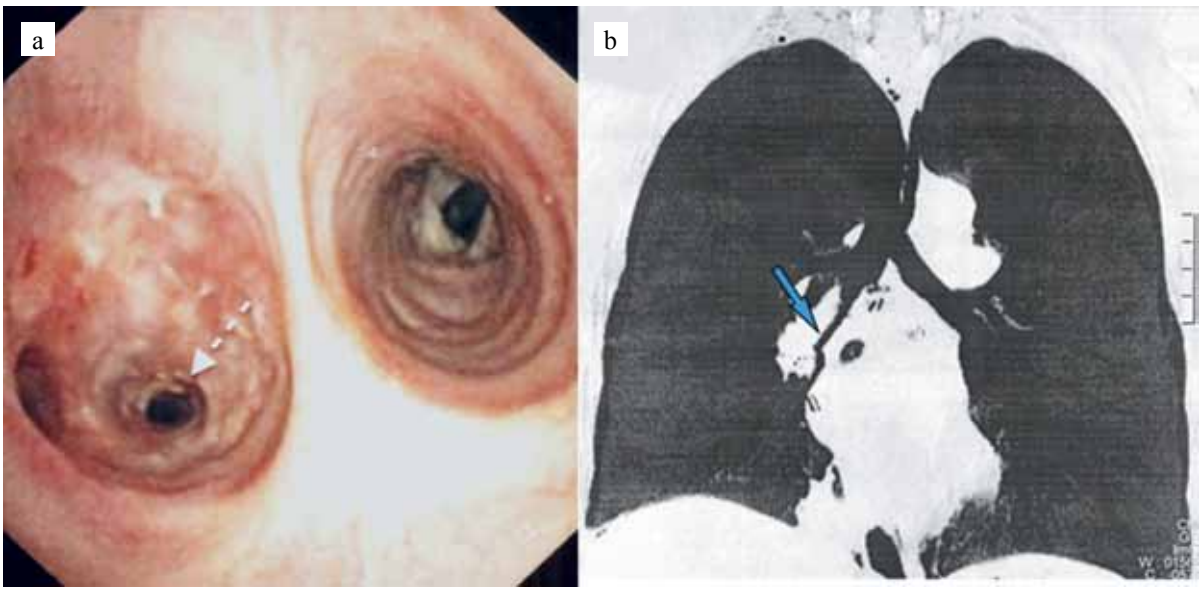

Fig. 2. Resolution of bronchus intermedius stenosis; a, b – lumen of the bronchus intermedius (indicated by arrows)

As part of complex treatment, antibacterial therapy was prescribed according to the scheme: meropenem, cotrimoxazole, piperacillin + tazobactam. Under general anesthesia, with rigid bronchoscopy, two consecutive endoscopic balloon bougienage of stenosis in the bronchus intermedius area were performed on January 31, 2019 and February 11, 2019 in combination with argon-plasma coagulation of scar tissue, until a lumen of 5–6 mm in diameter was achieved.

Within the next month after stenosis correction, while in hospital, the patient suffered recurrent right-sided middle and lower lobe pneumonia associated with multidrug-resistant Burkholderia cepacia complex, complicated by type 2 respiratory failure symptoms (up to 58 mm Hg arterial blood hypoxemia, up to 90% desaturation in the open air).

Six months after lung transplantation and four months after manifestation of recurrent bronchus intermedius stenosis, which required a series of balloon bronchoplasty, it was decided to stent the bronchus intermedius with an uncoated balloon-expanding nitinol stent due to the unstable effect of treatment. This type of stent was chosen due to persistent Burkholderia cepacia – associated pneumonia and the need to maintain effective mucociliary clearance in the stenting area. Stent implantation performed with rigid bronchoscopy (Fig. 4, a, b), made

it possible to carry out long-term scheduled sanitation of the bronchial tree, which was necessary due to persisting right-sided lower and middle lobe pneumonia.

Prolonged implantation of the uncoated bronchial stent (1.5 months) resulted in its partial obstruction due to the growth of scar-granulation tissue in its lumen. On May 27, 2019, the stent was extracted with rigid bronchoscopy (Fig. 5, a, b).

During dynamic observation, the bronchus intermedius with preserved skeletal function and a lumen passable for a 6-mm bronchoscope, which, together with positive clinical, laboratory and imaging dynamics, allowed the patient to be discharged for outpatient observation.

Nine months after lung transplantation, 7 months after the onset of vanishing bronchus intermedius syndrome and 1 month after removal of the uncoated nitinol stent, the patient again began to experience shortness of breath during moderate physical activity. Bronchoscopy revealed recurrent bronchus intermedius stenosis of up to 2 mm (Fig. 6, a). On September 1, 2019, using rigid bronchoscopy, repeated endoscopic restenting of the bronchus intermedius was performed with a self-

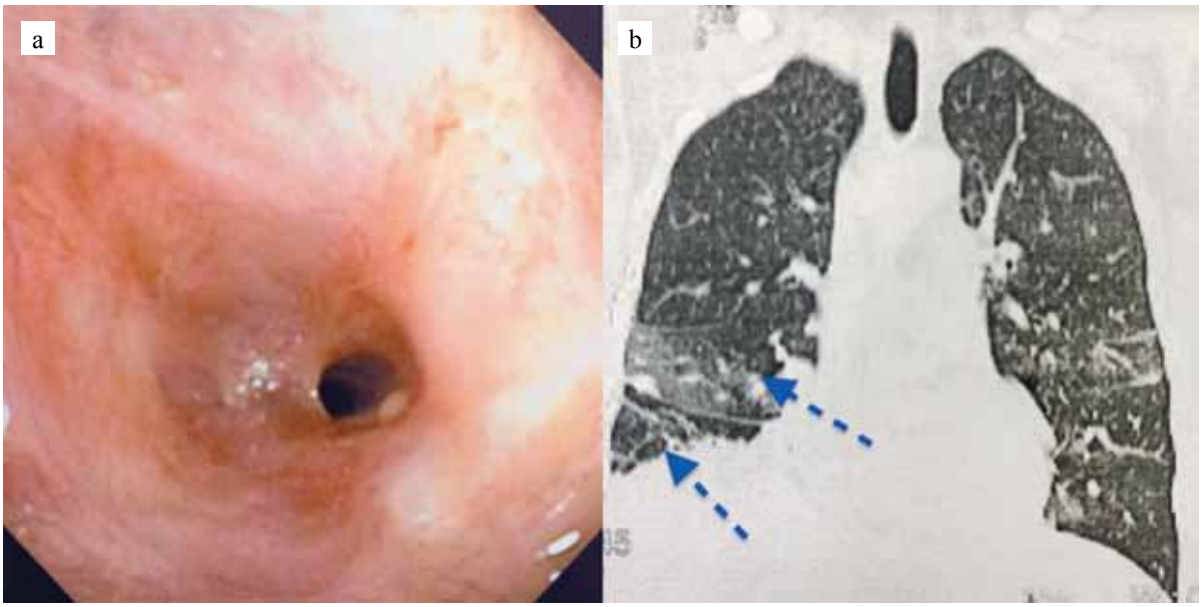

Fig. 3. Development of restenosis after balloon dilatation; a – narrowing of the lumen of the bronchus intermedius; (d ~ 3–4 mm); b – CT signs of pneumonia (indicated by arrow)

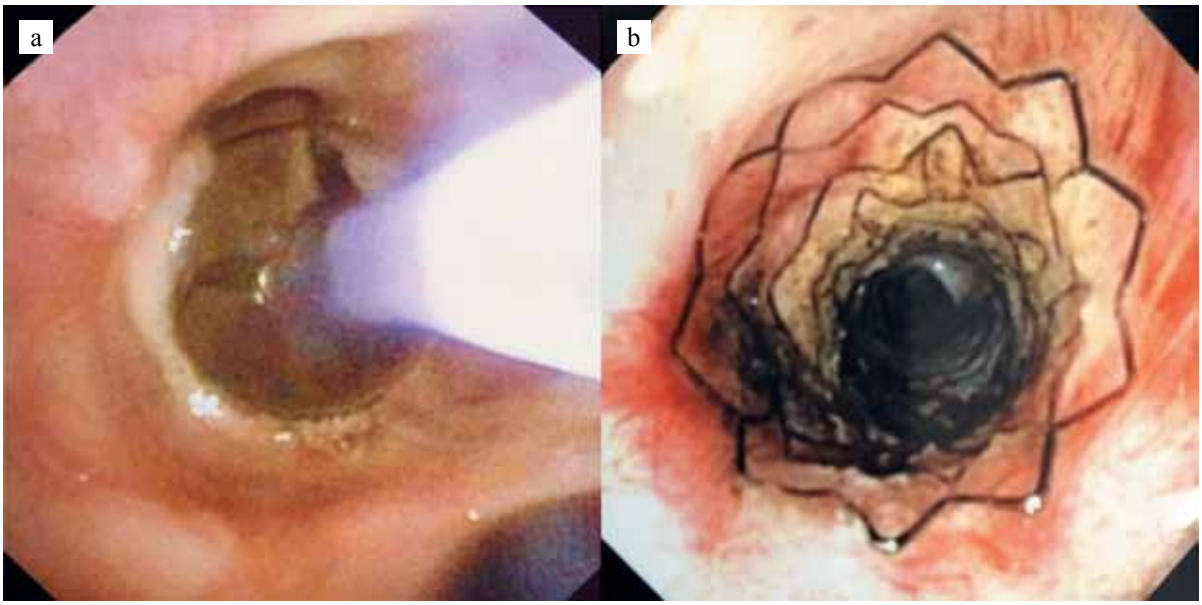

Fig. 4. Stenting of the bronchus intermedius with an uncoated self-expanding nitinol stent; a – balloon dilatation of the bronchus intermedius; b – stent in the bronchus intermedius

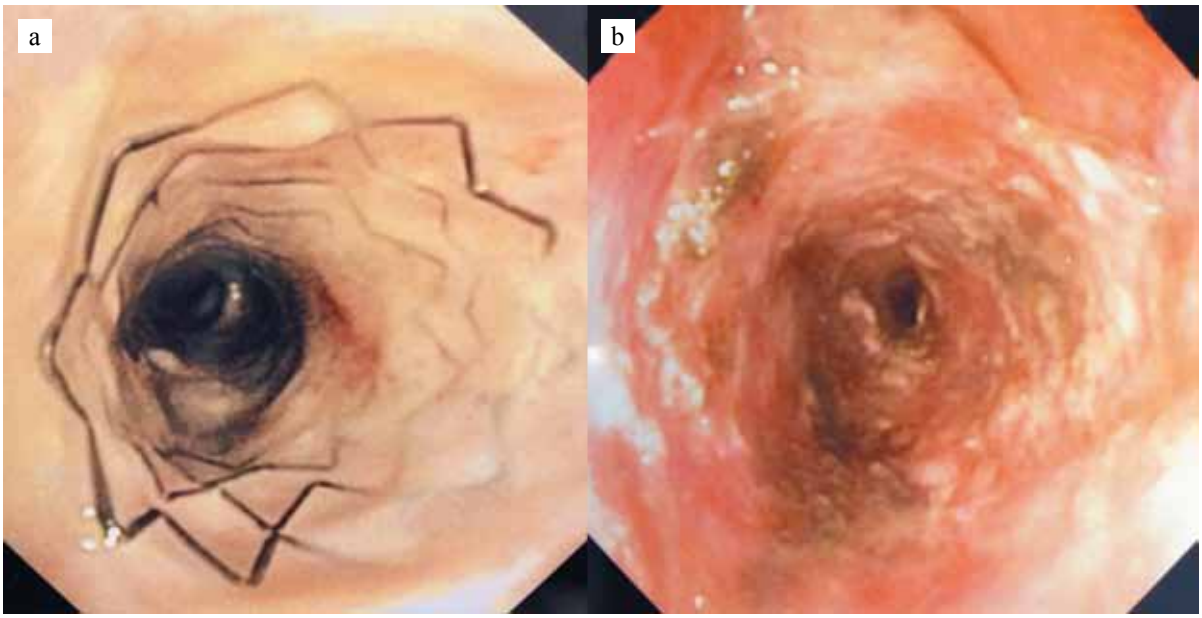

Fig. 5. Extraction of uncoated nitinol stent; a – cicatricial-granulation tissue in the stent lumen; b – after stent extraction

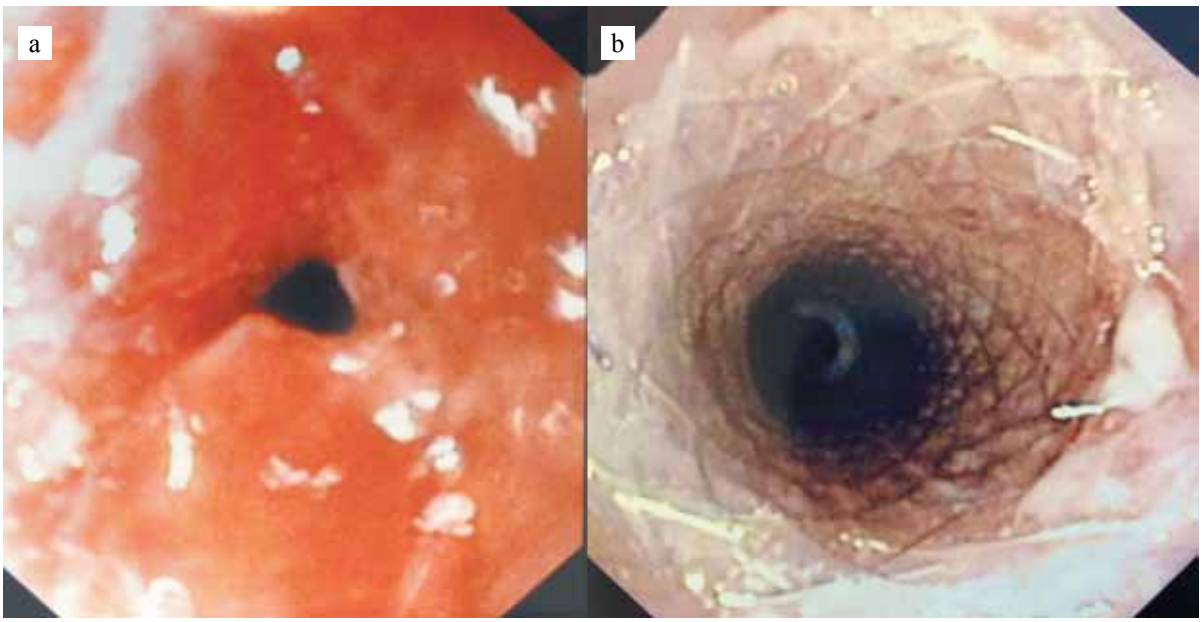

Fig. 6. Stenting of bronchus intermedius restenosis; a – up to 2 mm bronchus intermedius restenosis; b – re-stenting of the bronchus intermedius with a self-expanding nitinol stent d = 8 mm

expanding nitinol stent with 8 mm diameter and 19 mm length (Boston Ultraflex, USA) (Fig. 6, b).

For 6 months after restenting, the patient's condition remained stable, with no signs of respiratory failure. Regular endoscopic examinations showed adequate lumen throughout the bronchus intermedius.

At 16 months after lung transplantation, 14 months after the onset of vanishing bronchus intermedius syndrome, and 7 months after repeated restenosis with routine endoscopic follow-up, signs of recurrent stenosis were revealed in the proximal edge of the previously implanted stent (Fig. 7, a, b).

On February 1, 2020, with rigid bronchoscopy, the stent was removed from the bronchus intermedius, cryoablation of the cicatricial stenosis area was performed. In order to achieve hemostasis after stent extraction, we used electrosurgical methods. After 5 days, after achieving clear positive dynamics in the bronchial mucosa repair processes after application of electrosurgical methods of hemostasis, repeated stenting was performed using a similar self-expanding nitinol stent with a 10 mm diameter (Fig. 7, c).

Within six months after the last restenting, there were no signs of recurrent bronchus intermedius stenosis du-

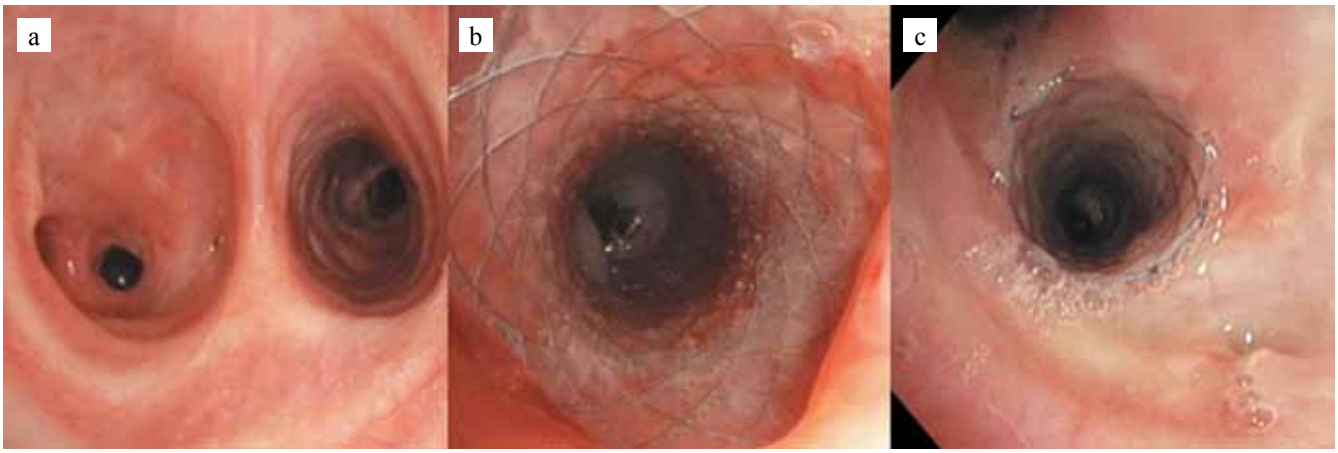

Fig. 7. Conversion of an 8 mm-diameter nitinol stent to a 10 mm-diameter nitinol stent; a – proximal edge of the stent (d ~ 4–5 mm); b – distal and middle third of the stent (d ~ 8 mm); c – after placement of a self-expanding nitinol stent (d = 10 mm)

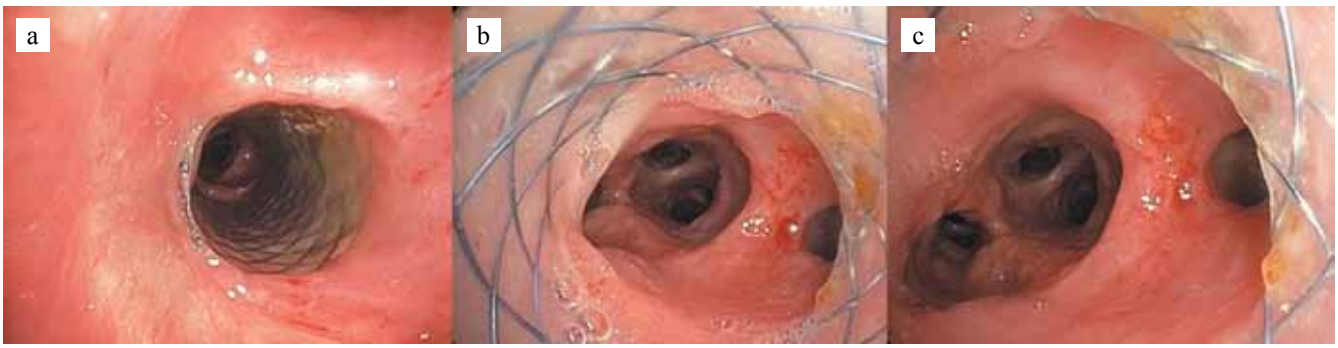

Fig. 8. View of the stent in the bronchus intermedius 6 months after implantation; a – proximal edge of the stent; b – distal edge of the stent; c – area of bifurcation of the bronchus intermedius

ring routine examinations, the function of the transplanted lungs was satisfactory (VC – 2.93 L (84%), FEV1 – 2.16 L (71%), Tiffeneau-Pinelli index – 74%), clinical, laboratory and imaging parameters were within normal range. During endoscopic examination, the stent in the bronchus intermedius was correctly positioned, the stent lumen was passable, there were no marginal scar and granulation changes (Fig. 8).

DISCUSSION

Stenoses are the most common type of bronchial complications in the long term after lung transplantation [9, 16, 17]. To date, there is no consensus and comprehensive understanding of the mechanisms of development of bronchial stenosis and, in particular, vanishing bronchus intermedius syndrome. The opinion of the majority of authors leans in favor of telescoping bronchial anastomosis and highly virulent infection persisting in the tracheobronchial tree as the main factors in the development of bronchus intermedius stenosis. Other authors note the importance of such factors as duration of artificial ventilation, duration of cold ischemia of the lung graft, ischemia-reperfusion injury of the graft, impaired blood supply to the tissues of the bronchial tree as a result of bronchial artery transection [2, 4, 16, 18].

The main causes for the development of VBIS in our observation were: telescoping bronchial anastomosis (used due to marked differences in the lumen diameters of the recipient's bronchus and the donor's bronchus) and presence of chronic respiratory infections Pseudomonas aeruginosa and Burkholderia cepacia, and later Klebsiella pneumoniae.

Within 2 months after VBIS manifestation in the form of obstructive pneumonia, our treatment strategy was limited to staged balloon bougienage. Shortening of the duration of the positive effect of the interventions threatened the re-development of bronchial obstruction with an outcome of middle and lower lobe pneumonia. In order to preserve an adequate bronchus intermedius lumen, providing effective evacuation of the airway contents of the middle and lower lobes of the right lung, stenting of the recurrent stenosis area with an uncoated nitinol stent was performed. Despite the risks of infiltration, up to complete obstruction, uncoated metal stent was chosen, which made it possible to maintain effective mucociliary clearance in the implantation area and thereby avoid aggravating the course of the infectious process and achieve

resolution of inflammatory-infiltrative changes in the right lung. Removal of an uncoated metal stent partially overgrown with cicatricial-granulation tissue naturally required the use of endoscopic electrosurgical methods of hemostasis. Repeated interventions in the form of staged balloon or electrosurgical bronchoplasty with implantation of stents made it possible to achieve stable long-term effect in the form of preserving the bronchus intermedius lumen, sufficient for satisfactory external respiration indicators. Thus, as of August 2020, the duration of effective correction of the vanishing bronchus intermedius syndrome is 21 months. Clinical, laboratory and imaging assessment showed no signs of respiratory failure and graft dysfunction.

Strict outpatient and remote monitoring, together with active use of observational and interventional bronchology techniques, are effective measures for the timely diagnosis and surgical correction of severe bronchial complications threatening the development of lung graft dysfunction and reduction in the quality and life expectancy of lung recipients.

The authors declare no conflict of interest.

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