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Autologous adipose-derived stem cells therapy in COPD treatment: a case report

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Abstract

Here, we describe the clinical course of a patient with chronic obstructive pulmonary disease treated with autologous adipose-derived stem cell therapy. In September 2019, our patient was admitted to Bach Mai Hospital. His post-bronchodilator forced expiratory volume in 1 sec (FEV_1) was 21% and FEV_1/forced vital capacity (FVC) was 40%. He had suffered from two exacerbations of chronic obstructive pulmonary disease (COPD) in the previous year. He received treatment with autologous stem cells from adipose tissue. Follow-up indicated that autologous stem cells from adipose tissue was a safe treatment and improved the patient's dyspnoea and quality of life.

Introduction

Chronic obstructive pulmonary disease (COPD) is causing increasing burden worldwide, being one of the three most common causes of death in the world and 90% of these deaths occur in low- and middle-income countries [1]. In Vietnam, the prevalence of moderate and severe COPD is the highest in Asia Pacific at 6.7% [2]. The prevalence of COPD among adults in northern Vietnam was 7.1%, 10.9% in men and 3.9% in women [3]. Current treatment of COPD often does not prevent disease progression, leading to more severe diseases. Stem cell therapy in COPD is a new treatment approach. Mesenchymal stem cells (MSCs) are pluripotent stem cells that have been found to inhibit the abnormal inflammatory response of the disease and lung cells' apoptosis in COPD. Furthermore, the humoral factor secreted by MSC alleviates COPD symptoms [4–11]. MSCs are present in the stromal tissue of many organs; of these, adipose tissue is a rich and convenient source of cells. This study reports a case report of autologous adipose-derived stem cell (ADSCs) in COPD treatment which have been initially shown to be safe and partly effective. This finding has significant implications for clinical practice.

Case Report

A 57-year-old man living in Bac Ninh province, Vietnam, had been diagnosed with COPD global initiative for chronic obstructive lung disease (GOLD) D for eight years [12]. The patient was a former smoker with 15 pack-years of smoking. He had been treated at the provincial hospital as part of the national project for COPD and asthma with budesonide/formoterol 160/4.5 μg with two puffs two times and tiotropium 2.5 μg with two puffs one time each day. He was referred to Bach Mai Hospital in September 2019, prior to which he had suffered from two non-hospitalized acute exacerbations of COPD.

On admission, he had no sign of COPD exacerbation. His body mass index (BMI) was 20.6 kg/m^2. His modified Medical Research Council (mMRC) dyspnoea scale was 2. His COPD assessment test (CAT) score was 13. The St. George's Respiratory Questionnaire (SGRQ) total score was 45.95. The 6-min walk test (6MWT) was 441 m. The arterial blood gas measurement demonstrated pH as 7.4, partial pressure of carbon dioxide in arterial blood (pCO_2) as 47 mmHg, partial pressure of oxygen in arterial blood (pO_2) as 75 mmHg, HCO_3^- as 27.6, and saturation of oxygen in arterial blood (SaO_2) as 95% on room air. His post-

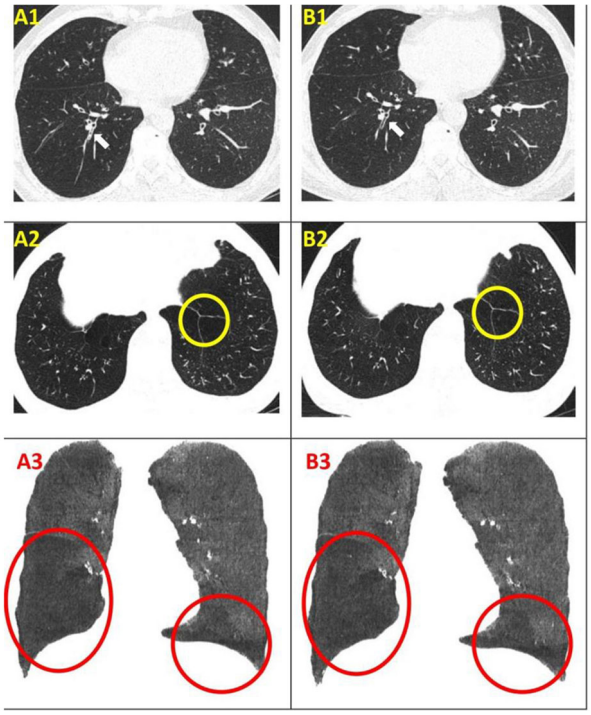

Figure 1. Quantitative computed tomography (CT) of the chest. Before intervention, an inflammation of the bronchus was represented by a thickened bronchial wall, narrow and mucous in the bronchial lumen (white arrow) (A1); bilateral emphysema was concentrated in the basal area of the lung (yellow circle, A2; red circles, A3). After intervention, bronchial wall thickness was reduced, bronchial lumen was wider, and mucous was no longer visible (white arrow) (B1). The emphysema signs did not show much change (yellow circle, B2; red circles, B3).

bronchodilator FEV_1 was 21% and FEV_1/FVC was 40%. The body mass index, obstruction, dyspnea, exercise capacity (BODE) index was 5. His blood eosinophils were 430 cell/μL. C-reactive protein (CRP) was 0.074 mg/dL. Other tests were normal.

Quantitative computed tomography (CT) of the chest (Pulmo 3D software; Pulmo 3D syngovia of Siemens in Germany) showed bilateral diffuse emphysema, more concentrated at the right lung as shown in Figure 1A1–A3.

He was approved for COPD treatment using ADSCs. This procedure was also approved by the Research Ethics Committee of the Ministry of Health of Vietnam. The entire process of liposuction, extraction of stem cells from adipose tissue, and intravenous infusion to the patient as well as preservation of stem cells from adipose tissue are described in Figure 2. This patient was followed up for the next 12 months and had not changed his routine treatment compared with before stem cell therapy.

Table 1 shows the results of cytological analysis in autologous ADSCs obtained from the patient.

Table 2 presents the patient's change in dyspnoea and quality of life in follow-up visit. Interestingly, dyspnoea and quality of life improved at six and 12 months after ADSCs treatment. The 6MWT increased at six- and 12-month follow-up. Meanwhile, the CRP was almost unchanged. Pulmonary function slightly improved at the 12-month follow-up. This patient did not have any acute exacerbation in one-year follow-up.

At 12-month follow-up, a slight increase was found in the patient's inhaled total lung volume in quantitative chest CT. The index of emphysema did not show any difference (Fig. 1B1–B3). Changes of bronchial wall thickness (WT) was assessed by the reduction of WT, wall area (WA), and percentage of WA (% WA), as well as the raise of bronchial inner diameter (ID) and lumen area (LA). Table 3 shows that WT decreased and LA increased at RB1 and RB10 of both lungs (bold indexes) at one year after stem cell treatment.

Discussion

Stem cell therapy in COPD therapy is still limited. Patients selected in clinical trials are severe and very severe COPD patients [13–15]. Stem cell therapy is only considered as an adjuvant therapy, not a replacement for drug therapy. Adipose tissue provides an abundant source of stromal vascular fraction (SVF) for immediate administration. SVF is not cultured but is isolated from adipose tissue using a sterile process. SVF will be delivered via intravenous

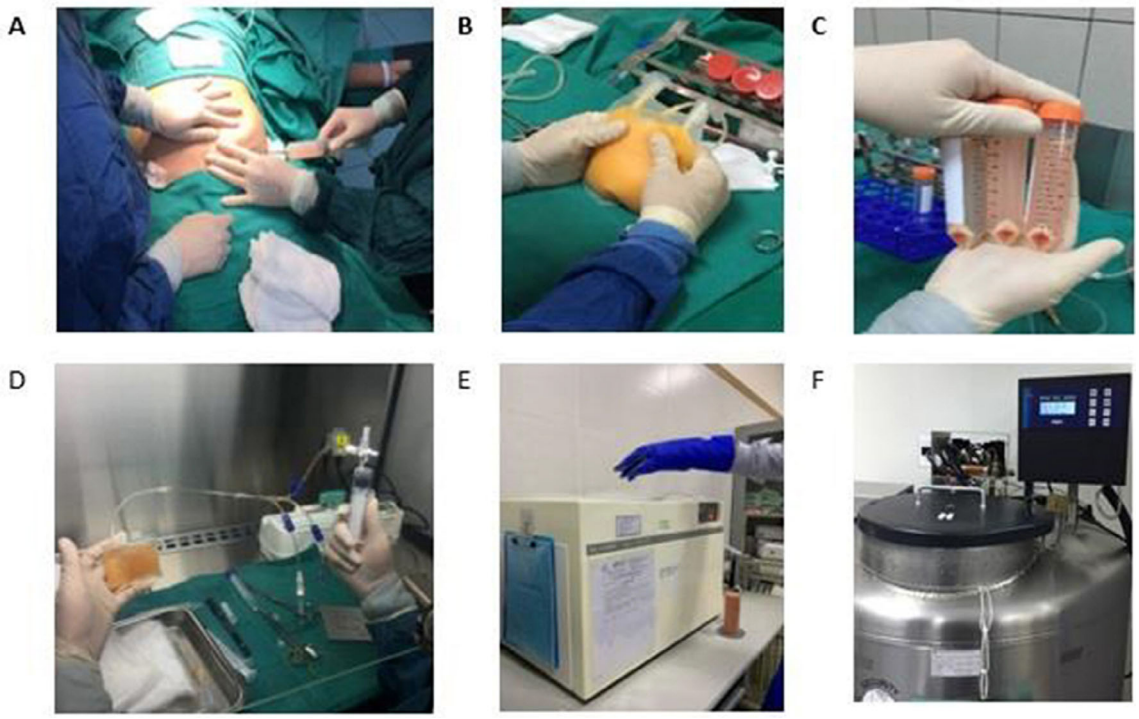

Figure 2. Technique of autologous adipose-stem cell in chronic obstructive pulmonary disease (COPD) treatment. Liposuction in subcutaneous fat tissue around the navel was done with lidocaine local anaesthesia, resulting in 80 mL of fat (A). Stromal vascular fraction (SVF) was isolated from lipoaspirate by AdiStem Large Kit and platelet-rich plasma solution was produced by using AdiStem's PRP kit to process 20 mL of whole blood (B). SVF was obtained (C). Adipose-derived stem cells (ADSCs) was divided into two parts. One part was mixed with PRP and light-activated with AdiStem™ (Stemcell of AdiStem in Australia/HongKong) AdiLight LED and then given intravenously to the patient. The other part was mixed with platelet rich plasma (PRP) and Dimethyl sulfoxide (DMSO), freezed down, and cryopreserved in liquid nitrogen at −196°C for six months. At the point of six months, after a follow-up visit, the remaining stem cells were given immediately intravenously to the patient after defrosting (D–F).

infusion for patients. SVF contains multiple cellular components, including ADSCs, which are similar to other types of MSCs. The main mechanism of MSCs in COPD includes inhibition of excessive inflammatory response, correction of protease-resistant imbalance, inhibition of alveolar apoptosis, changes in oxidative stress, epithelial repair, lung tissue and endothelium, antibacterial, and reduction in pulmonary arterial pressure [4–11]. Therefore, when using autologous ADSCs to treat our patients, we did not expect to see major improvements in lung function. Instead, we aimed at inhibiting systemic inflammatory responses to reduce the frequency of exacerbations, improve dyspnoea symptoms, increase exercise capacity, and improve quality of life. Previous studies showed that there have been no complications of autologous ADSCs infusion [16,17], which was confirmed in our case. Our patient was carefully prepared and followed up through the intervention. Pain at liposuction sites usually goes away after a few days. It is difficult to unravel the mechanism of stem cell therapy for the improvement of symptoms with only one case report. In this patient, the only adjuvant treatment was stem cell therapy while he maintained his routine treatment as before. Comparing after and before stem cell treatment, we found improvement of patient's symptoms and dyspnoea level by the CAT score, mMRC, and

Table 1. Results of cytological analysis in autologous stem cell from adipose tissue.

Characteristics	Adipose-derived stem cells
Adipose tissue (mL)	80
% Viability	99
Nucleus cells ($\times 10^6$)	532.8
CD34 marker cell concentration (cell/μL)	0
CD34 marker cell count	0
%CD34/nucleus cells	0
MSC concentration (cell/μL)	2.1
MSC count	100,800
%MSC/nucleus cells	0.000189

MSC, mesenchymal stem cell.

Table 2. Follow-up data 12 months after adipose-derived stem cell therapy in COPD.

Characteristics	Baseline	Three-Month follow-up	Six-Month follow-up	Nine-Month follow-up	12-Month follow-up
CRP (mg/ml)	0.074	0.048	0.060	0.040	0.067
FEV_1 (L)	0.61	0.57	0.62	0.70	0.66
FEV_1 (%)	21	20	21	24	23
CAT score	16	13	11	11	10
mMRC score	2	2	1	1	1
SGRQ score					
Symptom	44.24	31.24	15.88	8.92	12.84
Activity	60.36	59.44	53.52	59.45	47.55
Impact	38.26	24.02	23.59	12.40	17.87
Total	45.95	35.96	31.38	26.08	26.03
6MWT (m)	441	498	561	528	546

6MWT, 6-min walk test; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FEV_1, forced expiratory volume in 1 sec; mMRC, modified Medical Research Council Dyspnoea Scale; SGRQ, St. George's Respiratory Questionnaire.

SGRQ. In addition, his exertion capacity improved, with 6MWTs increasing from 441 to 546 m. He did not have any acute exacerbation during one-year follow-up. The inflammation in the lumen decreased after one year of stem cell treatment. The overall results suggest that the patient's improvement is related to the stem cell

Table 3. Quantitative CT scan at baseline and one year after stem cells therapy.

		%LAA < − 950				
Index	TLV (mL)	UL	LL	UR	MR	LR
Baseline	5414	31.2	29.5	36.7	40.6	42.6
12-Month follow-up	5489	29.8	32	36.9	39.8	44.9

Index	Baseline	12-Month follow-up	Index	Baseline	12-Month follow-up
RB1—R			RB1—L		
WA (mm^2)	25.34	22.36	WA (mm^2)	20.64	22.61
% WA (%)	76.82	73.5	% WA (%)	73.85	69.7
LA (mm^2)	**7.65**	**8.06**	LA (mm^2)	**7.31**	**9.83**
ID (mm)	2.99	3.14	ID (mm)	3.01	3.49
WT (mm)	**1.7**	**1.51**	WT (mm)	**1.47**	**1.44**
RB4—R			RB4—L		
WA (mm^2)	19.12	19.8	WA (mm^2)	26.17	27.91
% WA (%)	77.8	76.87	% WA (%)	73.94	76.84
LA (mm^2)	5.45	5.96	LA (mm^2)	9.22	8.41
ID (mm)	2.58	2.67	ID (mm)	1.64	3.25
WT (mm)	1.48	1.5	WT (mm)	1.64	1.76
RB10—R			RB10—L		
WA (mm^2)	16.86	20.5	WA (mm^2)	27.6	25.74
% WA (%)	76.66	67.81	% WA (%)	71.1	66.53
LA (mm^2)	**5.85**	**9.73**	LA (mm^2)	**11.22**	**12.95**
ID (mm)	2.68	3.48	ID (mm)	3.74	4.01
WT (mm)	**1.46**	**1.34**	WT (mm)	**1.62**	**1.48**

CT, computed tomography; ID, inner diameter; LA, lumen area; LAA, low attenuation area; LL, lower left; LR, lower right; MR, medial right; RB, respiratory bronchioles; TLV, total lung volume; UL, upper left; UR, upper right; WA, wall area; WT, wall thickness.

therapy. However, more well-designed and long-term trials are necessary to prove about the efficacy of stem cell therapy.

In summary, this case report showed that the autologous stem cells from adipose tissue was safe and effective in improving the COPD patient's dyspnoea and quality of life. Further research is needed to explore this hopeful direction for patients with COPD.

Disclosure Statement

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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Author Contribution Statement

All authors have made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. Thuy Thanh Nguyen was involved in drafting the manuscript or revising it critically for important intellectual content. Chau Quy Ngo, Phuong Thu Phan, and Giap Van Vu have given final approval of the version to be published. All authors read and approved the final manuscript.

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