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Clinical outcome after lipectomy in the management of patients with human immunodeficiency virus-associated dorsocervical fat accumulation

An observational cohort study

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Abstract

Lipo-accumulation of the dorsocervical fat pad ("buffalo hump") is a complication observed in people living with human immunodeficiency virus (HIV). We described the clinical outcome of people living with HIV with "buffalo hump" treated by excisional lipectomy.

From April 2013 to March 2018, medical records of people living with HIV, who received care in our hospital have been evaluated. Among them, patients with dorsocervical fat accumulation treated by excisional lipectomy have been retrospectively assessed.

Nine patients with "buffalo hump" among 2886 people living with HIV (3.1‰, 9/2886) were included. Eight were women with a mean age of 47.9 ± 8.0 years old (range, 36–60). Most of them have been infected by blood transfusion (77%, 7/9) and the mean duration of HIV infection was 14.1 ± 5.5 years (range, 6–22). The mean duration for antiretroviral therapy was 8.8 ± 2.1 years (range, 6–11). The mean pre-ART CD4+ T cell count was 91.3 ± 76.5 cells/μL (range, 4–233) and 477.4 ± 271.8 cells/μL (range, 114–926) at the time of surgery. All 9 patients underwent excisional lipectomy of their hypertrophied dorsocervical fat pad. The mean size of the excised specimens was $14 \times 11 \times 6$ cm. The median follow-up time was 24 months (range, 2–60), all 9 patients reported satisfaction with their results, with no recurrence has been observed.

Corrective surgery used to treat localized fat accumulations in people living with HIV with "buffalo hump" showed a favorable effect and can therefore be considered when necessary. Whereas drugs such as integrase inhibitors may avoid lipo-accumulation related syndrome and should be given to people living with HIV in China.

Abbreviations: 3TC = Lamivudine, AIDS = acquired immunodeficiency syndrome, ART = anti-retroviral therapy, AZT = zidovudine, BMI = body mass index, CT = computed tomography, d4T = stavudine, EFV = efavirenz, FBG = fasting blood glucose, HALS = HIV-associated lipodystrophy syndrome, HBV = Hepatitis B virus, HCV = Hepatitis C virus, HDL-C = high density lipoprotein cholesterol, HIV = human immunodeficiency virus, HPV = human papillomavirus, INIs = integrase inhibitors, LA = lipo-accumulation, LD = lipodystrophy, LDL-C = low density lipoprotein cholesterol, NNRTIs = non-nucleoside/nucleotide reverse transcriptase inhibitors, NRTIs = nucleoside/nucleotide reverse transcriptase inhibitors, NVP = nevirapine, PIs = protease inhibitors, PLWH = people living with HIV, TC = total cholesterol, TDF = tenofovir, TG = triglycerides, WHO = World Health Organization.

Keywords: buffalo hump, human immunodeficiency virus, lipectomy, lipodystrophy

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1. Introduction

Life of persons living with human immunodeficiency virus (HIV) has improved since the introduction of antiretroviral therapy (ART). Nevertheless, as these individuals are receiving ART for long-term, complications are increasingly reported, including the HIV-associated lipodystrophy syndrome (HALS), which is characterized by abnormal fat metabolism and tissue deposition. Several characteristics, such as older age, white race, low body weight, low nadir CD4+ T cell count, long duration of ART and exposure of protease inhibitors (PIs), or some nucleoside reverse transcriptase inhibitors (NRTIs) have been identified as risk factors for HALS.[1] This syndrome is also associated with metabolic abnormalities such as dyslipidemia, insulin resistance, and glucose intolerance. The prevalence of HALS in patients on ART has been reported to be 10% up to 40%.[2,3] Areas of adipose hypertrophy or lipo-accumulation (LA) include the dorsocervical region ("buffalo hump"), the anterior neck, the upper torso, and the abdomen, whereas lipoatrophy occurs in the face and the limbs. In severe cases, LA can be disfiguring, which can cause stigma and discrimination, leading to risks of poor adherence, medication discontinuation, and treatment failure.[4] Surgical or cosmetic corrective treatment is the only intervention with almost immediate esthetical result, as well as the change of

classes of ART when possible. Herein, we described the clinical manifestations and treatment outcome in HIV-infected patients with dorsocervical fat accumulation treated by excisional lipectomy in 1 Chinese clinical center.

2. Materials and methods

2.1. Patient characteristics and data collection

Zhongnan Hospital of Wuhan University is the largest referral hospital for HIV/AIDS care in Hubei Province, central China. From April 2013 to March 2018, medical records of people living with HIV (PLWH) who received care in our hospital have been evaluated. Among them, we identified 9 patients presenting with dorsocervical fat accumulation treated by excisional lipectomy. Age, sex, weight, height, body mass index (BMI), duration of HIV infection, mode of HIV acquisition, CD4+ T cell count, ART regimens, serum levels of total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and fasting blood glucose (FBG) were collected. Evaluation of liver steatosis was assessed by echography or computed tomography (CT). Patients information on coinfection with hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV) were also collected.

2.2. Ethical consideration

This clinical study was conducted according to the principles expressed in the Declaration of Helsinki. The Ethical approval was granted by the Ethics Committee of Zhongnan Hospital of Wuhan University (NO.2018055).

2.3. Statistical analyses

Continuous variables were described as means, medians, and ranges. We used SPSS 16.0 (Chicago, IL) to perform all statistical analyses.

3. Results

3.1. Characteristics of study participants

From a total of 2886 PLWH (2061 men and 825 women, sex ratio was 2.5:1) hospitalized in our center between April 2013 and March 2018, 9 of them had dorsocervical fat accumulation (3.1‰, 9/2886) were included. Eight were women with a mean age of 47.9 ± 8.0 years old (range, 36–60) (Table 1). Most of them have been infected by blood transfusion (77%, 7/9) and the mean duration of HIV infection was 14.1 ± 5.5 years (range, 6–22). Four PLWH were coinfected with HCV, 1 patient with both HBV and HCV. All the patients have been treated with lamivudine (3TC), among them 7 had a stavudine (d4T) and 2 had a zidovudine (AZT) contained regime, 7 patients received non-nucleoside/nucleotide reverse transcriptase inhibitors (NNRTIs) including nevirapine (NVP) and 2 had efavirenz (EFV). The mean duration for ART was 8.8 ± 2.1 years (range, 6–11). Due to severe toxicity, the Hubei provincial government in 2013 has gradually offered the possibility to replaced d4T by tenofovir (TDF), the only free medicament available in China with reduced metabolic toxicity. At the time of diagnosis of dorsocervical fat accumulation, all patients had limited neck mobility and difficulty to supine before surgery. Their body mass index

Table 1

Characteristics of 9 HIV+ patients undergoing excisional lipectomy for dorsocervical lipodystrophy.

Patients No.	1	2	3	4	5	6	7	8	9
Gender	M	F	F	F	F	F	F	F	F
Age, y	50	36	56	47	52	60	49	37	44
BMI, kg/m²	23.3	21.9	22.0	24.1	22.4	18.1	24.0	23.9	28.8
Duration of HIV infection, y	11	15	17	6	12	20	22	7	17
Duration of ART, y	9	6	11	6	11	11	10	7	8
ART regiments	3TC+d4T+NVP	3TC+d4T+EFV	3TC+d4T+NVP	3TC+AZT+NVP	3TC+d4T+NVP	3TC+d4T+NVP	3TC+d4T+NVP	3TC+AZT+EFV	3TC+d4T+NVP
Nadir CD4+, cell/μL	126	12	233	6	96	74	4	141	130
CD4+ before surgery, cell/μL	468	522	800	300	926	137	114	542	488
CD4+ at follow-up, cell/μL	566	441	729	485	700	694	140	479	540
Coinfection	-	HCV	-	HPV	HCV	-	HBV+HCV	HCV	HCV
TG, mmol/L, N<1.70	4.14	6.67	3.72	3.66	1.71	3.8	0.49	2.06	1.88
TC, mmol/L, N<5.18	3.48	4.08	5.21	4.72	3.39	5.28	2.21	3.98	5.69
LDL-C, mmol/L, N<3.63	1.52	1.55	2.66	2.64	1.58	2.21	1.49	2.16	3.53
HDL-C, mmol/L, N>1.04	0.88	0.76	1.18	1.13	0.86	1.39	0.84	0.83	1.11
FBG, mmol/L, N<6.1	5.39	6.06	4.18	4.93	5.35	7.22	5.33	4.63	5.32
Liver imaging	Steatosis	Normal	Normal	Steatosis	Normal	Normal	Cirrhosis	Normal	Normal
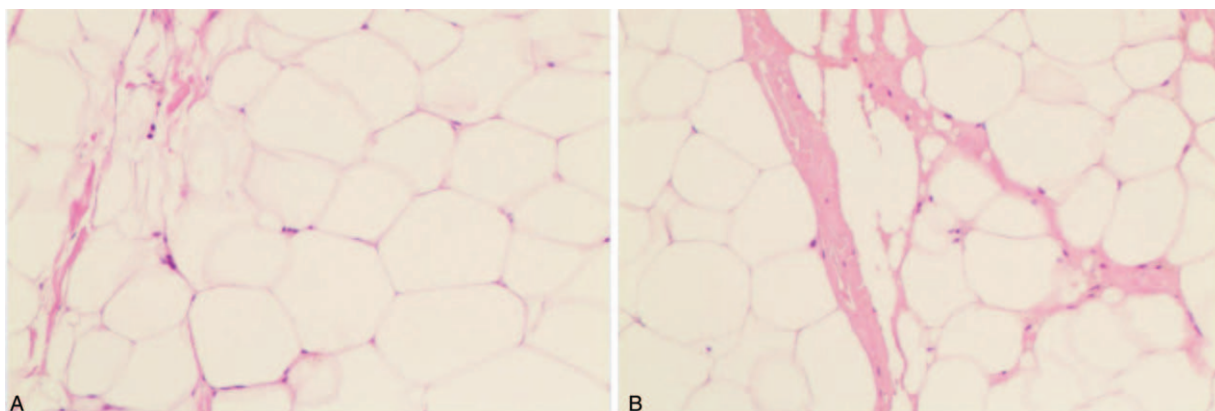
Figure 1. Histologic specimen of abnormal fat from lipodystrophy excision demonstrating fibrous septae and significant variability among adipocytes (A) fibrous septae; (B) adipocytes.

(BMI) ranged from 18.1 to 28.8 kg/m². The liver radiological examination showed steatohepatitis in 2 patients, whereas cirrhosis has been detected in 1 patient associated with HBV and HCV coinfection. The results of the laboratory examinations revealed a 2 to 3-fold increase of the serum TG over normal values in 8 PLWH (89%), and 1 (11%) had an increased fasting glucose. The mean pre-ART CD4+ T cell count was 91.3 ± 76.5 cells/μL (range, 4–233) and 477.4 ± 271.8 cells/μL (range, 114–926) at the time of surgery.

3.2. Surgical procedures

All 9 patients underwent excisional lipectomy of their hypertrophied dorsocervical fat pad. The mean size of the excised specimens was $14 \times 11 \times 6$ cm. There was no clear boundary between aggregated fat and surrounding adipose tissue in all patients. Pathological examination did not show capsule or pseudo-capsule, the tissue was composed of fibrosclerotic zones and significant variation in the shapes and sizes of adipocytes (Fig. 1). The majority of patients (7/9, 78%) underwent surgery without complications and recovered after surgery, the mean duration of hospitalization was 23.4 ± 14.3 days (range, 7–54). Whereas 2 patients (2/9, 22%) underwent additional procedures, including one with seroma complicated by infection and another with wound dehiscence. Patient with seroma were managed by aspiration and drain placement, whereas delayed wound healing was treated by daily dressing changes. For the patient with wound dehiscence, resuturing had been done at the 9th day after

surgery. In these 2 patients, intravenous infusion of antibiotic was given. The median follow-up time was 24 months (range, 2–60 months), all 9 patients reported satisfaction with their results, and no recurrences have been observed (Table 2), with the mean CD4 + T cell count was 536 ± 142.8 cells/μL (range, 140–779) at the time of follow-up (Table 1) whereas the HIVRNA viral load were all under detectable level (<20 copies/mL).

4. Discussion

As one of the manifestations of HALS, dorsocervical fat accumulation called "buffalo hump" can become painful with lager size, leading to restricted neck movement, and can be associated with abdomen fat accumulation leading to sleep apnea.[5] Stigma and discrimination, may lead to low adherence to the treatment, accompanying with depression and social withdraw.[6] Several studies have attempted to better understand the pathogenesis, yet the precise mechanism of HALS has not been well determined. However, several factors have been identified which include HIV infection, ART, the genetic background, and host metabolic factors.[7–9] The development and severity of HALS have been initially associated with the duration of HIV infection, and low CD4+ T cell count.[10,11] More recently, Lo et al[12] first reported on contribution of cumulative exposure to ART as one of the strongest factors for dyslipidemia, especially with protease inhibitors (PIs). Whereas now it is well established that each class of drugs has a different effect on fat metabolism, even drugs of the same class may have

Table 2

Surgical complications and the follow-up of HIV+ patients undergoing excisional lipectomy for dorsocervical fat pad.

Patients No	Date of operation, yy/mm	Size of the lipoma, cm	Postoperative complications	Treatment of complications	Duration of hospitalization, d	Duration of follow-up, mo
1	2013.04	$15 \times 12 \times 4$	-	-	24	60
2	2013.09	$20 \times 18 \times 6$	-	-	12	54
3	2014.06	$10 \times 10 \times 4$	-	-	17	45
4	2015.01	$15 \times 13 \times 6$	-	-	27	38
5	2016.03	$11 \times 8 \times 7$	-	-	7	24
6	2017.09	$15 \times 12 \times 5$	-	-	18	6
7	2017.10	$14 \times 7 \times 5$	-	-	16	5
8	2017.12	$12 \times 10 \times 6$	Seroma	Aspiration	54	3
9	2018.01	$13 \times 10 \times 7$	Wound dehiscence	Resuturing	36	2

different effects. In addition, combination of certain drugs acts synergistically to cause dyslipidemia.[13–15] For nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), dyslipidemia has been associated with exposure to stavudine, zidovudine, and abacavir, whereas tenofovir and lamivudine showed minimal or even a favorable lipid influence.[16] In the NNRTIs, efavirenz has been associated with increases in TC and TG, whereas rilpivirine has been shown to have less effect on lipids compared with efavirenz.[17] Among PIs, lopinavir, ritonavir, and nelfinavir have been associated with lipo-accumulation whereas atazanavir has limited effect.[18] The integrase inhibitors (INIs) class have a little or no effect on lipid, which makes it one of the best choices for patients. Most of our patients had been treated by the combination of 2 NRTIs and 1 NNRTI drugs and no PIs have been used, as recommended by the Chinese therapeutic guideline proposed for first-line choice regimen. Our findings further revealed that patients with dorsocervical fat pad under NRTIs and NNRTI regimens had a significantly greater increased plasma levels of TG than TC. The relationship between changes in body fat and lipid levels is not yet well understood because alterations in the lipid profile do not clearly correlate with body tissue fat deposition. Proposed hypotheses including local effects of increased glucocorticoid production, inhibition of adipocyte differentiation, impaired activity of glucose transporters, mitochondrial toxicity, and more recently the effect of gut dysbiosis.[19–22] In recent years, as the number of HIV infections continues to increase and the duration of ART prolonged, the utilization of PIs (i.e., Kaletra) as the second-line treatment in China is increasing. Apart of the morphologic changes, accompanied cardiovascular diseases in this population may also increase, and prevention of these conditions has become a concern. At the same time, other classes of antiretroviral drugs such as integrase inhibitors, which has been proposed by World Health Organization (WHO) and has been widely used in western countries should be integrated as first-line treatment in China.

Interestingly, we noticed that even more male PLWH were initially included in our study (male: female = 2.5:1), however, in the group of patients with reported "buffalo hump" underwent surgery, there were far more women than men (male: female = 1:8), whereas the patients were mainly men in other studies.[23–25] Is the women more prone to "buffalo hump" formation than men? We think one of the reasons for this discrepancy is the lack of consensus on diagnostic criteria of HALS.[26] The diagnosis is usually based on the patient's self-report of regional body fat changes and physical examination. But it is obviously that an individual's awareness and acceptance of body fat gain may be different. For example, an obese person may not be as concerned with increasing central adiposity, in contrast the women maybe more conscious to their body image and more eagerly to seek for medical attention. In the literature, the formation of "buffalo hump" was merely associated with the infection of HIV. Since in our study, 7 out of the 9 patients have been infected by blood transfusion, 1 patient has been coinfected with HBV whereas the HBVDNA was negative as a result of ART, but 5 out of 9 patients has been coinfected with HCV, which were not the case in other studies, so, does HCV play a synergistic role with HIV in the formation of "buffalo hump," or especially has an influence on the women should be exploited further.

A study including 72 patients from the Asia-Pacific region showed that the patients receiving ART for >3.8 years had a significantly higher prevalence of HALS than those receiving ART for <3.8 years (16% vs 5%; odds ratio [OR], 4.01; $P = .001$).[2] In an Indian cross-sectional study, the mean duration of ART was 5 years for the development of fat redistribution group.[27] In our study, the average time of HIV infection was 14.1 ± 5.5 years (range, 6–22) and the average time of duration for antiretroviral therapy was 8.8 ± 2.1 years (range, 6–11), which was much longer than the other studies. Tracking the causes, we found that since it remains difficult to accurately define HALS, many clinicians did not make an early diagnosis, and some patients may have been treated surgically late. Hence, in resource-limited regions, apart from ART switching and lifestyle change strategies, the surgical treatment in patients with dorsocervical fat pad are still the cornerstone of the management.[24,25,28] Although the cosmetic and functional results of the surgery are often fulfilled, the main drawback is recurrence of the fat accumulation, with a reported relapse rate up to 50% over a follow up of 12 to 30 months.[29] In our study, during a median of 24 months (range, 2–60) of follow-up, all 9 patients reported satisfaction with their results, there have been no recurrences reported, and the CD4+T cell count were stable for all the patients at the time of follow-up with the viral load under detectable level. This may benefit from drug switch from d4T to TDF. Additionally, our relatively short follow-up time of certain patients could not be ignored, so the long-term effect of surgery needs further observation.

Although 2 surgical options for the treatment of dorsocervical fat pad are proposed which including traditional surgical dermolipectomy and non-invasive ultrasound-assisted liposuction. While the "buffalo humps" are usually composed by fat tissue that is hard, with trabecules and fibrous as shown in our study,[30,31] making passage of the lipoplasty cannulas into the region quite difficult, some studies recommended excisional lipectomy in order to maximal remove the fibrous fatty tissue and theoretically reduce the rate of recurrence.[25,32] Taking together, we suggested to use excisional lipectomy as the primary treatment, with liposuction added when necessary for better contouring of the periphery of the excision, especially when the fat pad is >10 cm.

5. Conclusion

Globally, corrective surgery used to treat dorsocervical fat accumulations in patients experiencing considerable physical or psychological discomfort shown a favorable effect and can therefore be considered when necessary. Whereas more drugs with favorable lipid profile should be used to PLWH in the country like China and more prevention strategies should be initiated to control the metabolite effect of ART.

Author contributions

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