OBSERVATION

"Bullfrog Neck," a Unique Morphologic Trait in HIV Lipodystrophy

Case Series and Review of the Literature

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Background: Human immunodeficiency virus (HIV)-associated lipodystrophy is a syndrome that occurs primarily in individuals who are being treated with highly active antiretroviral therapy (HAART).

Observations: We describe 3 patients with an 8- to 15-year history of HIV disease and HAART who presented a unique feature of HIV lipodystrophy, the "bullfrog neck." In addition to their features of facial lipoatrophy and "buffalo hump," patients had the unique feature of circumferential enlargement of the neck. All patients were undergoing treatment with the same non–nucleoside reverse-transcriptase inhibitor (NRTI) medication, efavirenz.

Conclusions: We present a novel finding of the bullfrog neck in 3 patients with classic features of HIV lipodystrophy. The dysmorphic features of HIV lipodystrophy present a significant therapeutic challenge because the current repertoire of treatments is only modestly effective, and the disease in patients who continue HAART regimens over the long term will progress. Review of the recent literature suggests that the individual protease inhibitors and NRTIs used may play a role in the development and progression of HIV lipodystrophy.

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TEN YEARS AGO, SHORTLY AFter the US Food and Drug Administration approval of protease inhibitors for the treatment of human immunodeficiency virus (HIV), clinicians began reporting unique changes in distribution of body fat in patients treated with these medications. The first reports of what came to be known as lipodystrophy noted fat loss in the face, arms, legs, and buttocks along with concomitant fat gain or lipohypertrophy in the abdomen and sometimes in the breasts and back of the neck ("buffalo hump"). Patients also were noted to have elevated triglyceride, cholesterol, and blood glucose levels with concerns about associated risks of diabetes and atherosclerotic heart disease.

Lipodystrophy is a condition characterized by abnormal fat distribution that can lead to either lipoatrophy (fat loss in the face, buttocks, arms, and legs)[1] or lipohypertrophy (fat accumulation in specific areas of the body such as the neck, belly, upper torso, and breasts). The term *HIV-associated lipodystrophy* refers to both abnormal central fat accumulation (lipohypertrophy) and localized loss of fat, most commonly in the mid portion of the face (lipoatrophy); however, some patients present only lipohypertrophy or lipoatrophy.[2]

While the exact mechanisms underlying HIV lipodystrophy are unknown, there are several hypotheses based on human and in vitro studies that attempt to explain the unique pathophysiologic characteristics of this condition. Protease inhibitors and nucleoside reverse-transcriptase inhibitors (NRTIs), especially stavudine and zidovudine, have been suggested to inhibit both cytoplasmic retinoic acid–binding protein and low-density lipoprotein receptor–related protein.[3-12]

In HIV-associated lipohypertrophy, the most typical areas for fat accumulation include the buffalo hump secondary to an enlarged dorsocervical fat pad, breast enlargement, and central truncal adiposity due to abdominal visceral fat accumulation (often referred to as "crix belly" or "protease paunch" for fat accumulation secondary to indinavir and other protease inhibitors).[13,14] Rarer presentations of lipodystrophy include multiple symmetric and asymmetric lipomatoses (symmetric

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Table. Study Patient Characteristics

Patient No./ Sex/Age, y	HIV Duration, y	CD4 Count and VL at Start of HAART	HAART Medications/ HAART Duration, y[a]	Features of Lipodystrophy
1/M/38	10	NR	Atripla (Sustiva, Viread, Emtriva)/8	Facial lipoatrophy, bullfrog neck, buffalo hump extending from posterior neck to mid back
2/M/42	8	CD4, <300/μL VL, 77 000/mL	Sustiva ×3 y then switched to Reyataz and Epzicom ×2	Facial lipoatrophy, bullfrog neck
3/M/52	15	CD4, <250/μL VL, 50 000/mL	Sustiva and Norvir/8	Facial lipoatrophy, bullfrog neck

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; NR, not reported; VL, viral load.
[a] Atripla is manufactured by Bristol-Myers Squibb & Gilead Sciences LLC, Foster City, California; Emtriva, Gilead, Foster City; Epzicom, GlaxoSmithKline PLC, Brentford, England; Norvir, Abbott Laboratories, Abbott Park, Illinois; Reyataz, Bristol-Myers Squibb, New York, New York; Sustiva, Bristol-Myers Squibb; Viread, Gilead.

Figure 1. A 38-year-old man with a 10-year history of human immunodeficiency virus and highly active antiretroviral therapy. A, In frontal view, face and neck demonstrate facial lipoatrophy and circumferential neck lipohypertrophy. B, In lateral view, lower face and neck demonstrate facial lipoatrophy and circumferential neck lipohypertrophy.

lipomatoses extending from the breasts to the axillae have been reported) and suprapubic fat pads (pubic lipomas), which were reported in nearly 10% of patients with lipodystrophy.[15-17] Involvement of the face is the most stigmatizing form of HIV-associated lipoatrophy, substantially reducing patient quality of life and inhibiting compliance with antiretroviral therapy.[18] While a number of reports in the literature have described the dysmorphic features of the buffalo hump resulting from the enlargement of the dorsocervical fat pad, we present herein a case series of a rarer, less-reported feature of the increase in neck circumference or "bullfrog neck"[19] in patients with HIV lipodystrophy.

REPORT OF CASES

CASE 1

A 38-year old white man with a 10-year history of HIV disease HAART was seen in our clinic for desired improvement of body dysmorphism associated with HIV lipodystrophy. He demonstrated classic features of facial wasting through the mid-malar region and lower cheeks associated with HIV lipoatrophy in addition to buffalo-hump lipohypertrophy of the lower posterior neck and upper half of the back (**Table**). The patient had undergone liposuction 6 years previously at another institution for desired improvement of the enlargement of the dorsocervical fat pad of the neck and upper back. According to the patient, while he reported initial improvement of the buffalo hump in the posterior neck and upper back after the procedure, several months later, uneven distribution and texture of fat in the neck and back resulted in increased lumpiness and greater prominence of the lipohypertrophy than prior to the procedure.

In addition to the dysmorphism of the face, posterior neck, and back, he had the unique finding of circumferential enlargement of the neck, extending from the base of the mandible to the base of the clavicle. Given the substantial circumferential enlargement of the neck, loss of the mandibular-cervical and mental-cervical angles at the superior pole of the neck and loss of the sternoclavicular angle at the base of the neck were both noted (**Figure 1**). The patient was undergoing treatment with an antiretroviral cocktail called Atripla (Bristol-Myers Squibb & Gilead Sciences LLC, Foster City, California), which is a combination therapy of efavirenz, 600 mg; tenofovir DF, 300 mg; emtricitabine, 200 mg.

CASE 2

A 42-year-old man with an 8-year history of HIV disease was seen in our clinic for desired improvement of facial lipoatrophy associated with HIV disease. He demonstrated classic features of facial wasting through the mid-malar region and lower cheeks associated with HIV lipoatrophy. In addition to the dysmorphism of the face (similar to patient 1), he had circumferential enlargement of the neck extending from the base of the mandible to the base of the clavicle. The changes in the neck seen in case 1 were seen also in case 2 (**Figure 2**).

The patient first underwent antiretroviral treatment with efavirenz (Sustiva; Bristol-Myers Squibb, New York, New York) immediately after diagnosis of his HIV disease. One year after the initiation of efavirenz treatment, the patient noticed the simultaneous evolution of facial lipoatrophy (predominant loss of the malar fat pad) and circumferential enlargement of the neck. The patient's infectious disease specialist discontinued efavirenz therapy and began a regimen of atazanavir, lamivudine, and abacavir. After

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switching from efavirenz to HAART, the patient reported substantial slowing in the progression of both the facial wasting and neck enlargement.

CASE 3

A 52-year-old man with a 15-year history of HIV disease was seen in our clinic with facial lipoatrophy associated with HIV disease. He demonstrated classic features of facial wasting through the mid-malar region and lower cheeks associated with HIV lipoatrophy. In addition to the dysmorphism of the face, he presented with the circumferential enlargement of the neck extending from the base of the mandible to the base of the clavicle (**Figure 3**).

The patient's antiretroviral medication regimen included efavirenz and ritonavir (Norvir; Abbott Laboratories, Abbott Park, Illinois). Approximately 2 years after initiation of this unusual regimen, the patient reported noticing the simultaneous evolution of facial lipoatrophy (predominant loss of the malar fat pad) and circumferential enlargement of the neck.

Figure 2. A 42-year-old man with an 8-year history of human immunodeficiency virus and highly active antiretroviral therapy. A, In frontal view, lower half of the face and neck demonstrate circumferential neck lipohypertrophy. B, In lateral view, lower half of face and neck demonstrate circumferential neck lipohypertrophy.

Figure 3. A 52-year-old man with a 15-year history of human immunodeficiency virus and highly active antiretroviral therapy. A, In frontal view, the lower half of the face and neck demonstrate facial lipoatrophy and circumferential neck lipohypertrophy. B, In lateral view, the lower half of the face and neck demonstrate circumferential neck lipohypertrophy.

COMMENT

We report herein a series of cases with the unique bullfrog neck[19] morphologic trait in patients with HIV lipodystrophy. This unique finding is characterized by circumferential enlargement of the neck extending from the base of the neck at the clavicle to the superior pole of the neck at the angle of the mandible. While the buffalo hump characterized by enlargement of the posterior base of the neck and upper back (resulting from increase in the dorsocervical fat pad) has been well characterized, the bullfrog neck[19] is a novel finding in patients with HIV lipodystrophy.

Interestingly, all of our patients developed HIV lipodystrophy while undergoing treatment with the same nonNRTI, efavirenz. This agent has been reported in the HIV literature to increase risk of lipodystrophy and systemic hyperlipidemia. A study comparing the incidence of lipodystrophy during treatment with varying combinations of HAART medications, reported that combinations including efavirenz were significantly more likely to be associated with both increased lipid levels and greater incidence rates of HIV lipodystrophy.[20] A total of 753 subjects (median CD4 count, 182/μL median HIV-1 RNA, 100 000 copies/mL) were observed for a median of 112 weeks. By week 96, 12% of subjects undergoing treatment with lopinavir plus an NRTI required a lipid-lowering agent, as did 26% of subjects undergoing treatment with efavirenz plus an NRTI. Lipodystrophy was significantly more common in the patients being treated with efavirenz than in those treated with lopinavir. Patients treated with efavirenz plus NRTIs had a 32% incidence rate of lipoatrophy compared with an incidence rate of 17% among patients treated with lopinavir plus 2 NRTIs ($P < .05$).

Review of the recent literature suggests that the specific combination of protease inhibitors and NRTIs may have a significant effect on the incidence of HIV lipodystrophy.[13,14,20-24] In addition, early modifications to the HAART cocktail can have a significant impact on slowing the progression of lipodystrophy. The importance of early initiation of HAART in prevention of lipodystrophy is illustrated in our second patient, for whom delayed diagnosis of HIV disease resulted in initiation of HAART at a low CD4 count (<300/μL) and resulted in the development of lipodystrophy in the first year of HAART.

While HAART is highly efficacious, the substantial negative impact on patient quality of life of the associated lipodystrophy reduces patient compliance. In a recent study of patients with HIV lipodystrophy, 90% of patients attributed the lipodystrophy to their HIV medications; 20% had thoughts of suicide secondary to the condition; and 20% stopped taking their HIV medications owing to concerns about development of the syndrome.[18] Given the substantial effect of this condition on patient's lives and well-being, in addition to the metabolic consequences of hyperlipidemia and diabetes, further investigation into prevention and treatment for this devastating condition is greatly needed.

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Correction

Errors in Abstract and Table 2. In the Study by Ryan et al titled "The Effect of Narrowband UV-B Treatment for Psoriasis on Vitamin D Status During Wintertime in Ireland," published in the August 2010 issue of the *Archives* (2010;146[8]:836-842), the first sentence of the "Results" section in the abstract should have read as follows: "Levels of serum 25(OH)D increased significantly ($P<.001$) from a median (range) of 23 (9-46) ng/mL at baseline to 51 [rather than 59, as given in the originally published article] (32-112) ng/mL at the end of NB–UV-B treatment compared with no change in the control group." In Table 2, the final 25(OH)D level for the treatment group and the baseline 25(OH)D level for the control group were transposed and should have read 51 (32-112) and 13 (7-33) ng/mL, respectively.

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