CLINICAL VIGNETTE

Three Clinical Scenarios of Acquired Lipodystrophy

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Lipodystrophy, also called lipoatrophy is defined as loss of subcutaneous fatty tissue that is often associated with abnormal fat distribution. Lipodystrophy can be initially categorized into inherited versus acquired and then further differentiated into generalized versus partial/localized. The following three cases discuss two more common causes of acquired lipodystrophy; injection associated and HIV antiviral therapy associated and one less common cause, morphea associated localized involutional lipodystrophy.

Case Presentation

Case 1 – HIV Antiviral Therapy Associated

A 60-year-old female was diagnosed with HIV twenty years ago. She started anti-viral therapy thirteen years ago, which was changed to raltegravir, tenofovir disoproxil fumarate and emtricitabine four years ago. Two years after treatment change, she noticed increased abdominal fat, significant thinning in both arms and legs, and a prominent dorsocervical fat tissue (buffalo hump) despite no changes in diet or exercise. She was otherwise tolerating the medication regimen and her recent HIV RNA quantitative PCR was not detected and CD4 count was 440. Additional tests included elevated hemoglobin A1c of 6.0% and increase in LDL cholesterol from 128 to 280.

Case 2 - Injection Associated

A 56-year-old female with relapsing remitting multiple sclerosis diagnosed in 2005 complicated by urinary incontinence secondary to neurogenic bladder. She was initially treated with subcutaneous interferon beta-1a, but switched to daily subcutaneous glatiramer acetate 5 years ago due to disease progression noted on MRI. Patient rotates her glatiramer acetate injection sites regularly, but over the last 6 months, has noticed a localized area of indention on her left buttock – roughly 5cm x 5cm x 3cm. She denies pain or sensation changes. There is no overlying rash, erythema or warmth.

Case 3 – Morphea Associated

A 31-year-old female with no significant past medical history presented with 9-month history of increasing left lateral thigh indentation, which significantly worsened over the last 3 months. She denies pain, numbness, or extremity weakness and any specific trauma or injury to the location. Patient has no new oral medications, topical creams, massages, cupping or injections in that specific location. She has no family history of lipodystrophy.

On examination, the patient's BMI is normal at 20.7, which was stable over the last year. There is a significant 10 cm linear horizontal depression on her left lateral thigh. There is no pain with palpation. Patient’s extremities were well perfused with normal pedal pulses. There a 4 cm oval, red raised patch with central flattening adjacent to the linear depression.

Nerve conduction and electromyography testing were normal. Blood work to evaluate for systemic autoimmune causes and metabolic causes were all normal. Dermatology was consulted and the patient was diagnosed with morphea localized involutional lipoatrophy. Biopsy confirmation was recommended, but deferred due to upcoming marriage. At dermatology follow up 1 month later, the morphea patch had mostly resolved and her left thigh indentation was no longer increasing in size, and biopsy was declined by patient.

Discussion

Epidemiology

Although inherited lipodystrophy is estimated to occur in one in one million individuals, acquired lipodystrophy incidence has been more difficult to estimate.[1] Estimates of lipodystrophy syndrome frequency occurs in long-term HIV patients on antivirals range from 10 percent to 80 percent. This wide range could be due to the lack of a uniform definition of lipoatrophy.[2] In addition, localized lipodystrophy associated with injections are often not reported.

HIV Medication Associated

Prior to common use of antiretroviral therapy (ART), patients with AIDS were often associated with severe wasting. After ARTs became commonly used, central fat accumulation and progressive peripheral fat loss in cheeks, arms and legs became more prevalent. The first reports were in 1997. These side effects are more commonly noted in females who are greater than 40 years old, have elevated baseline lipids, have lower nadir CD4 cell count, or reach an advanced stage of HIV infection. Symptoms were often associated with intra-abdominal and dorsocervical fat accumulation, subcutaneous lipomas, dyslipidemia, and insulin resistance.[3]

Specific thymidine analog nucleoside reverse transcriptase inhibitors (NRTI) such as zidovudine and stavudine are most commonly associated with lipodystrophy, while tenofovir and abacavir have been shown to prevent worsening.[4] The effects of NRTIs also appear to be more severe when combined with protease inhibitors.[5]

Patients on antiviral medications should be closely monitored with body mass index, waist circumference and other markers of metabolic syndrome (hemoglobin A1c and lipid panel). Early intervention has been much more effective than later attempts to reverse fat accumulation. Because both lipoatrophy and lipohypertrophy can cause significant impact on a patient's self-image, it is important to discuss treatment options, including alternative ART, initiating use of metformin and/or thiazolidinedione medications to help with insulin resistance, and improving diet and cardiovascular/strength training exercises to reduce visceral fat accumulation.[6]

Injection Associated

Injection-induced localized lipodystrophy has been noted with insulin, antibiotics, corticosteroids and glatiramer acetate. Unlike generalized lipodystrophy, injection associated localized lipodystrophy is not associated with insulin resistance or other metabolic abnormalities. Glatiramer acetate is an immunomodulatory drug commonly used to treat multiple sclerosis, administered by subcutaneous injection. The most common adverse effects, like other injections, are pain, inflammation, and induration at the injection site, reported in 20-60% of patients.[7] Lipoatrophy occurs in an estimated 2% of patients who use glatiramer daily and 0.5% of patients with three times per week dosing. Side effects can occur at various times after treatment onset, as early as several months.[8] Unfortunately, localized lipoatrophy from glatiramer acetate injection is thought to be permanent, so continuing to rotate injection sites for prevention is key.

Morphea Associated Lipoatrophy

Localized involutional lipoatrophy (LIL) is a distinctive idiopathic form of localized atrophy without antecedent inflammation, trauma or injection. LIL can be associated with morphea, lichen sclerosis and atrophoderma. Morphea is an autoimmune disease characterized by sclerotic changes limited to the skin and, therefore, differs from systemic sclerosis. LIL typically presents as a solitary and well demarcated atrophic depression most often located on proximal limbs and buttocks. There is a strong female predominance.[9] Morphea's pathogenesis is poorly understood, but it is thought to be associated with immune dysfunction as histopathology of lesions often show mononuclear lymphocytes, plasma cells and eosinophils.[10]

Morphea is divided into subtypes: circumscribed is most common and generalized and linear. Morphea can often be diagnosed on clinical findings, but tissue biopsy can be helpful to confirm diagnosis. Although morphea is associated with systemic sclerosis, a study of 251 adults with morphea showed only 34% tested positive for antinuclear antibody.[11]

Morphea is typically self-limited. However, if a patient has active disease with continued lesion expansion or involvement with new sites, then treatment with topical or intralesional steroids, topical tacrolimus, topical calcipotriene, or ultraviolet light therapy may be used. These interventions have not shown to be effective for patients with inactive or stable morphea.[12]

Treatment

For patients with generalized lipodystrophy, the drug metreleptin has been approved by the US FDA in addition to continuing with healthy diet and exercise. Unfortunately, metreleptin does not help with acquired partial lipodystrophy or HIV associated lipodystrophy. In addition to the limited treatment options listed above, individuals with acquired lipodystrophies are often encouraged to seek counseling as the physical appearance changes can cause anxiety, stress, and extreme psychological distress. Because the characteristic loss of adipose tissue in patients with acquired lipodystrophy cannot be reversed, cosmetic surgery may be beneficial in improving appearance.

REFERENCES

1. **Garg A**. Clinical review: Lipodystrophies: genetic and acquired body fat disorders. *J Clin Endocrinol Metab*. 2011 Nov;96(11):3313-25. doi: 10.1210/jc.2011-1159. Epub 2011 Aug 24. PMID: 21865368; PMCID: PMC7673254.
2. **Jacobson DL, Knox T, Spiegelman D, Skinner S, Gorbach S, Wanke C**. Prevalence of, evolution of, and risk factors for fat atrophy and fat deposition in a cohort of HIV-infected men and women. *Clin Infect Dis*. 2005 Jun 15;40(12):1837-45. doi: 10.1086/430379. Epub 2005 May 6. PMID: 15909274.
3. **Baril JG, Junod P, Leblanc R, Dion H, Therrien R, Laplante F, Falutz J, Côté P, Hébert MN, Lalonde R, Lapointe N, Lévesque D, Pinault L, Rouleau D, Tremblay C, Trottier B, Trottier S, Tsoukas C, Weiss K**. HIV-associated lipodystrophy syndrome: A review of clinical aspects. *Can J Infect Dis Med Microbiol*. 2005 Jul;16(4):233-43. doi: 10.1155/2005/303141. PMID: 18159551; PMCID: PMC2095035.
4. **Wohl DA, McComsey G, Tebas P, Brown TT, Glesby MJ, Reeds D, Shikuma C, Mulligan K, Dube M, Wininger D, Huang J, Revuelta M, Currier J, Swindells S, Fichtenbaum C, Basar M, Tungsiripat M, Meyer W, Weihe J, Wanke C**. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis*. 2006 Sep 1;43(5):645-53. doi: 10.1086/507333. Epub 2006 Jul 27. PMID: 16886161.
5. **Mallal SA, John M, Moore CB, James IR, McKinnon EJ**. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS*. 2000 Jul 7;14(10):

1309-16. doi: 10.1097/00002030-200007070-00002. PMID: 10930144.
6. **Guzman N, Vijayan V**. HIV-associated Lipodystrophy. 2020 Jun 1. In: *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2021 Jan–. PMID: 29630235.
7. **Lebrun C, Mondot L, Bertagna M, Calleja A, Cohen M**. Endermology: a treatment for injection-induced lipoatrophy in multiple sclerosis patients treated with sub cutaneous glatiramer acetate. *Clin Neurol Neurosurg*. 2011 Nov;113(9):721-4. doi: 10.1016/j.clineuro.2011.07.012. Epub 2011 Aug 11. PMID: 21839580.
8. COPAXONE® (glatiramer acetate injection) Current Prescribing Information Parsippany, NJ. Teva Neuroscience, Inc. https://www.copaxonehcp.com/about-copaxone/safety.
9. **Chang CH, Fang KT, Hong, SJ**. Morphea-like localized involutional lipoatrophy - A case report associated with family history. *Dermatologica Sinica*. 2010; 28:113-116.
10. **Badea I, Taylor M, Rosenberg A, Foldvari M.** Pathogenesis and therapeutic approaches for improved topical treatment in localized scleroderma and systemic sclerosis. *Rheumatology (Oxford).* 2009 Mar;48(3):213-21. doi: 10.1093/rheumatology/ken405. Epub 2008 Nov 20. PMID: 19022832.
11. **Dharamsi JW, Victor S, Aguwa N, Ahn C, Arnett F, Mayes MD, Jacobe H**. Morphea in adults and children cohort III: nested case-control study--the clinical significance of autoantibodies in morphea. *JAMA Dermatol*. 2013 Oct;149(10):1159-65. doi: 10.1001/ jamadermatol.2013.4207. PMID: 23925398; PMCID: PMC4153681.
12. **Knobler R, Moinzadeh P, Hunzelmann N, Kreuter A, Cozzio A, Mouthon L, Cutolo M, Rongioletti F, Denton CP, Rudnicka L, Frasin LA, Smith V, Gabrielli A, Aberer E, Bagot M, Bali G, Bouaziz J, Braae Olesen A, Foeldvari I, Frances C, Jalili A, Just U, Kähäri V, Kárpáti S, Kofoed K, Krasowska D, Olszewska M, Orteu C, Panelius J, Parodi A, Petit A, Quaglino P, Ranki A, Sanchez Schmidt JM, Seneschal J, Skrok A, Sticherling M, Sunderkötter C, Taieb A, Tanew A, Wolf P, Worm M, Wutte NJ, Krieg T**. European Dermatology Forum S1-guideline on the diagnosis and treatment of sclerosing diseases of the skin, Part 1: localized scleroderma, systemic sclerosis and overlap syndromes. *J Eur Acad Dermatol Venereol*. 2017 Sep;31(9):1401-1424. doi: 10.1111/jdv.14458. Epub 2017 Aug 9. PMID: 28792092.