Acquired Generalized Lipodystrophy

K30 Case Presentation
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Case presentation

• 2 yo girl admitted 12/31/07 to CHOC
• FUO x 1 week
• nodules along forehead and cheeks
• Evaluation included:
  – Normal CBC, chemistry, UA
  – ESR 22 and CRP 1.9 (<0.75)
  – Negative bone marrow biopsy
  – Excisional forehead nodule biopsy and cheek needle biopsy showed lipophagic panniculitis
Case presentation

- CT scan abdomen: hepatosplenomegaly
- MRI brain: lucency right parietal skull
- Skull biopsy: no histiocytosis
- Mild alopecia- attributed to multiple surgeries
- DC’d home
Case presentation

- From 1/08-2/08: rapid loss of cutaneous fat from face, arms, legs
  - Hepatosplenomegaly
  - Hair grew back curly

- 2/08 AST 516 ALT 560
  - Trial of 1mg/kg steroids x 2 weeks, with taper to off over another 2 weeks
  - No improvement of lipodystrophy
Case presentation

• LFT’s improved to 100’s, hepatosplenomegaly
• Elevated blood glucose 130-140’s (nonfasting)
  – 4+ glucose in urine & polyuria on steroids
  – Hyperphagia off steroids

• 4/08 Evaluation by genetics
  – Progeria: Lamin A (LMNA) mutation not found
  – Farber disease: fibroblast studies negative
Case presentation

• 4/08
  – Fasting glucose 83, insulin 66 (nl 20)
  – Fasting total cholesterol 180
  – Hemoglobin A1c 6.4% (nl <5.4%)

• 9/08
  – Open liver and lymph node biopsy
  – Chronic active hepatitis with 1 cirrhotic nodule, bridging necrosis and lymphocytic infiltrate
  – Lymph node: benign, reactive.
  – AST 91, ALT 147
Case presentation

• 10/08 Rheumatology consultation
  – Exam significant for lipodystrophy everywhere.
    • No fat on palms and soles
    • No abdominal fat
  – Hepatosplenomegaly with abdominal distension
  – No evidence of rash, arthritis, or muscle weakness
  – Development: advanced
Case presentation

• 10/08 Rheumatology consultation
  – ANA negative
  – dsDNA 1:80 (<1:10)
  – Smith/RNP, SSA/SSB, Scl-70, Ribosomal P, RF negative
  – C3: 254, C4: 13 (nl 16-60)
  – Urine prot/cr ratio 0.3
  – Microalbuminuria (albumin/cr) ratio 61 (nl <30)
  – IgG 1890 (929+228)
  – ESR 18 (0-10)
Case presentation

- 10/08 Rheumatology consultation
  - CK & LDH wnl
  - Aldolase 20 (<8)
  - Jo-1, Mi-2 antibodies neg
  - ANCA negative
  - TSH 22 (nl 0.34-5.6), fT4- 0.52 (nl 0.54-1.6)
  - Thyroperoxidase antibodies >6500 (nl<60)
  - Leptin 1 (6-7), adiponectin- undetectable
Case presentation

• 10/08 GI consultation
  – AST 485, ALT 500, GGT 99 (nl <50)
  – Anti-Mitochondrial 1:320 (<1:20)
  – Anti-LKM1 60 (nl <20)
  – Anti-actin negative <1:20
  – HIV non reactive
  – PT/PTT/Fibrinogen wnl
• 2mg/kg prednisolone
Case presentation

- 10/08 Endocrine evaluation
  - AM fasting glucose 170-200 (on steroids)
  - PM post-prandial glucose 290-360
  - Will start on subcutaneous insulin and thyroid hormone replacement
Summary

• 3.5 yo girl
  – Lipophagic panniculitis- resolved.
  – Acquired generalized lipodystrophy
  – Insulin resistance
  – Autoimmune hepatitis
  – Autoimmune thyroiditis
Lipodystrophy

• Acquired
  – HIV related
  – Localized
  – Partial
  – Generalized

• Inherited
  – Congenital
  – Familial partial
  – Mandibuloacral dysplasia

All lipodystrophies may be associated with insulin resistance/diabetes mellitus, dyslipidemia, acanthosis nigricans, & hepatic steatosis
HIV Lipodystrophy

- Face, neck, arms and legs
- Fat deposits in neck, nape and trunk
- Related to >1 y protease inhibitor therapy
- Switching therapy may reverse sx

Double chin

“Buffalo hump”

“Crixivan Belly”
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Garg NEJM 2004;350:1220-34.

- Double chin
- Buffalo hump
- “crixivan belly”
Localized Lipodystrophy

- Can occur after panniculitis, injections, infections, trauma/pressure
- Thighs, abdomen, and ankles most often affected

http://dermatology.cdlib.org/147/case_presentation/lipodystrophy/serrao.html
Localized Lipodystrophy

- Panniculitis
- Injections: steroids, insulin, methotrexate, silicon, drugs
- Pressure:
  - Semicircularis (thighs)
  - Annular (arms, ankles)
  - Centrifugalis abdominalis

Partial Lipodystrophy

- Loss of fat of face, neck, arms, trunk with excess fat deposit on lower extremities
- 20% associated membranoproliferative glomerulonephritis and C3 nephritic factor (low C3)
- F: M 3:1

Garg NEJM 2004;350:1220-34.
Partial Lipodystrophy

- 250 cases reported to date
- Associated with other autoimmune diseases: (dermatomyositis, hypothyroidism, rheumatoid arthritis, celiac dz, pernicious anemia, SLE, leukocytoclastic vasculitis)
- Less likely to have metabolic abnormalities

Garg NEJM 2004;350:1220-34.
Generalized Lipodystrophy

4.5 months

6 months

Generalized Lipodystrophy

8 months

10 months

Generalized Lipodystrophy

- Females 3:1 males
- Fat loss everywhere except bone marrow and retroorbital areas
- 20% risk of cirrhosis from hepatic steatosis or autoimmune hepatitis

Generalized Lipodystrophy

- Dyslipidemia common
- High risk of insulin resistance/diabetes
- Low leptin and adiponectin
- Increased linear growth
- 3 subtypes

Acquired Generalized Lipodystrophy

- Panniculitis Variety (Type I)
- Autoimmune Variety (Type II)
- Idiopathic Variety (Type III)

80 cases reported (to date)

Acquired Generalized Lipodystrophy

Associated Autoimmune diseases:
- Juvenile Rheumatoid Arthritis
- Scleroderma
- Systemic lupus erythematosus
- Type I Diabetes
- Autoimmune Hepatitis
- Thyroiditis

Pathogenesis

- CD95 (fas, APO-1) mediated apoptosis of adipocytes
  - Mechanism of endocrine cell apoptosis in Type I DM and Hashimoto thyroïditis
- Increased CD95
  - TNF alpha and IFN gamma

The diagram illustrates the activation of executioner caspases, apoptosis, and caspase-independent cell death through the FasL-Fas and RIP pathways.

- **FasL** and **Fas** are involved in the death signaling pathway.
- **c-FLIP** and **Pro-caspase-8** are components of the death receptor pathway.
- **DISC** (Death-Induced Signaling Complex) is the site of caspase activation.
- **RIP** interacts with caspase-8 and is involved in caspase-independent cell death.

**Legend:**
- **Red** represents the death domain.
- **Blue** represents the death-effector domain.
Treatment

• Lipodystrophy
  – No medical therapy available
  – Plastic surgery
    • Autologous fat transplant
    • Synthetic implants/fillers
• Metabolic abnormalities
  – Thiazolidinediones (glitazones)
  – Recombinant leptin
Adipoinsular axis

Adipose organ

ADIPOSE TISSUE AS AN ENDOCRINE ORGAN

http://www.cardiometabolic-risk.org
Leptin therapy

The New England Journal of Medicine

LEPTIN-REPLACEMENT THERAPY FOR LIPODYSTROPHY

Elif Arioglu Oral, M.D., Vinaya Simha, M.D., Elaine Ruiz, N.P., Alexa Andewelt, B.S., Ahalya Premkumar, M.D., Peter Snell, Ph.D., Anthony J. Wagner, Ph.D., Alex M. DePaoli, M.D., Marc L. Reitman, M.D., Ph.D., Simeon I. Taylor, M.D., Ph.D., Phillip Gorden, M.D., and Abhimanyu Garg, M.D.

(N Engl J Med 2002;346:570-8.)

9 patients with lipodystrophy
• 5 with congenital, 3 with acquired, and 1 familial lipodystrophy
• decreased hyperglycemia significantly, increased insulin sensitivity
• improved triglyceridemia
• reduced fatty liver
• reduced appetite
• reduced basal metabolic rate
Leptin therapy

10 patients with lipodystrophy
- 6 with congenital, 2 with acquired, and 2 familial lipodystrophy
- patients had increased CD3 T lymphocyte counts
- Improved cytokine production (TNF alpha, IFN gamma)
- 2 developed membranoproliferative glomerulonephritis
Leptin & Immune system

**Innate immunity**
- Activation of neutrophils
  - ↑ Chemotaxis
  - H$_2$O$_2$, O$_2^-$
- Cytokine induction by monocytes/macrophages
  - ↑ Acute-phase response
  - ↑ Inflammatory anorexia
  - ↑ Fever
  - TNF, IL-1, IL-6
- Activation of APCs
  - ↑ MHC molecules
  - ↑ Adhesion molecules
  - ↑ Phagocytosis
  - Leukotriene B$_4$,
  - Cyclo-oxygenase 2
  - Macrophage
- Cytotoxicity
  - ↑ Perforin
- NK
- IL-2

**Adaptive immunity**
- Thymic homeostasis
  - ↑ Thymocyte number
  - ↑ CD4$^+$CD8$^+$ cells
  - ↑ CD4$^+$CD8$^-$ cells
  - ↓ Apoptosis
- Proliferation
  - Naive T cells → IL-2
- $T_H^1$-cell stimulation
  - ↑ DTH
  - ↑ IgG$_2$α switch
  - ↑ CD8$^+$ T-cell help
  - ↑ Macrophage activation
  - TNF, IFN-γ, Leptin
- $T_H^2$-cell inhibition
  - IgG$_1$ switch
  - IL-10, IL-4

Leptin therapy

• Ob/ob mice are protected against experimental autoimmune diseases:
  – Encephalomyelitis
  – hepatitis/colicitis
  – Type I diabetes
  – Arthritis

• Leptin treated ob/ob mice are not protected unless anti-TNF alpha given
What’s on the horizon

• Leptin for treatment of congenital lipodystrophy
  • Dr. Kristina Rother @ NIH

• Experimental
• Anti-TNF?
• Fat transplant?
Thank you.