Adenovirus 36 DNA in Adipose Tissue of Patient with Unusual Visceral Obesity

Behrouz Salehian, Stephen J. Forman, Fouad R. Kandeel, Denise E. Bruner, Jia He, and Richard L. Atkinson


Infection with human adenovirus 36 (Adv 36) has been reported to cause a large accumulation of fat in 4 animals (chickens, mice, rats, and monkeys) (1–3). Selective deposition of visceral fat disproportional to total fat deposition was observed in some studies. The increase in visceral fat or total body fat in infected animals compared with uninfected animals was >100% in some experiments (1–3). Of animals that were infected, 60%–100% became obese compared with uninfected animals (1–4). Obesity was defined as a weight or fat content greater than the 85th percentile of the uninfected animals.

Several human studies have shown a correlation of antibodies to Adv 36 and obesity (4–8). In 1 study of >500 persons, 30% of obese persons and 11% of lean persons had antibodies to Adv 36 (4). The body weight of infected persons was ≥25 kg heavier than that of uninfected persons (4). In 26 pairs of twins with discordant Adv 36 antibody status, infected twins were heavier and fatter (4). In a group of obese school children from South Korea, 30% had antibodies to Adv 36, and infected children had higher body mass index z-scores than uninfected children (5). However, in animals and adults in the United States, serum cholesterol and triglyceride levels were paradoxically reduced, despite the obesity (1–4). Recent reports of adults in Italy and children in South Korea support the association of Adv 36 and obesity, and show that Adv 36 is more common in obese persons; prevalence ranges from 29% to 65% (6,7).

The mechanisms responsible for the increased adiposity are changes in gene expression of multiple enzymes and transcription factors by the virus (8–15). In adipocytes, the sterol regulatory element binding protein pathway is increased, resulting in increases in levels of sterol regulatory element binding protein 1 and fatty acid synthase. Because levels of transcription factor CCAAT/enhancer binding protein-β, peroxisome proliferator-activated receptor-γ, and lipoprotein lipase are also increased, lipid transport into cells and fatty acid synthesis within cells is increased (8–15). In muscle cells, gene expression of glucose transporters Glut 1 and Glut 4 and phosphoinositide 3-kinase is increased, which results in noninsulin-mediated increases in glucose transport (14).

These changes are thought to be caused by the action of the Adv 36 open reading frame 1 region 4 gene and may be blocked by small interfering RNA or the antiviral drug cidofovir (11,13). When the open reading frame 1 early region 4 gene was transferred to a retrovirus and inserted into preadipocytes in vitro, the gene was capable of inducing the enzymes and enhancing fat accumulation (13).

Adv 36 DNA persists in multiple tissues of infected animals for long periods after initial infection (3). Viral DNA was isolated from brain, lung, liver, muscle, and adipose tissue of monkeys 7 months after initial infection, long after the active virus has disappeared from blood and feces (3). The virus DNA apparently continues to alter gene expression chronically in tissues.

We report a patient with massive fat deposits in the thorax and abdomen. We postulate that these abnormal adipose tissue deposits were caused by Adv 36 infection.

The Patient

The patient, a 62-year old man who was diagnosed with high-grade large cell lymphoma in 1999, received multidrug (cyclophosphamide, doxorubicin, vincristine, and prednisolone) chemotherapy, central nervous system prophylaxis with cytarabine, and high-dose methotrexate. In February 2000, he underwent autologous bone marrow transplantation and received a conditioning regimen of etoposide, cytoxan, and fractionated total-body irradiation. Hypothyroidism, chemoradiation-induced hypogonadism, and adrenal insufficiency developed in the patient, which required chronic glucocorticoid replacement.

During the next 7 years, prostate cancer, rectal ulcer necessitating colon diversion, hemolytic anemia, thrombocytopenia, myelodysplastic syndrome, and diabetes mellitus developed in the patient; he was treated with insulin for the diabetes. He was hospitalized for respiratory insufficiency in August, 2007, which was thought to be caused or exacerbated by massive intrathoracic and intraabdomi-
nal fat deposits. He had obesity of his neck, lateral chest, and abdomen, but limited subcutaneous fat in his abdomen and upper extremities. He had no buffalo hump, round fa-
cies, or other signs of Cushing syndrome. The patient had
tachycardia with muf
fl
ed heart sounds, dullness in the base
of the right chest, and bibasilar diminished breath sounds.
A computed tomography scan of the chest and abdomen
showed fatty densities extending into the intrabdominal,
intraperitoneal, and retroperitoneal areas and herniating
through the esophageal hiatus (Figure
1). These fatty densities extended within the pericardium
without definite pericardial effusion.

The patient’s weight was 113 kg, height 183 cm, body
mass index 34, waist circumference 145 cm, and hip cir-
cumference 111 cm. Laboratory tests showed triglycerides
1.356 mmol/L, total cholesterol 2.2015 mmol/L, high-den-
sity lipoprotein cholesterol 0.5957 mmol/L, and low-densi-
ty lipoprotein cholesterol 0.9842 mmol/L. The serum lipids
values represent marked decreases from previous measure-
ments. In December 2002, his low-density lipoprotein cho-

lersterol level was 2.7412 mmol/L. In April 2007, his serum
triglyceride level was 4.92244 mmol/L. The result of a test
for serum immunoglobulin (Ig) M against adenoviruses
was negative (0.07 IU), and the result of a test for serum
IgG was positive (2.18 IU).

Infection with Adv 36 causing disseminated lipomatosis
was suspected. A subcutaneous fat biopsy specimen
was assayed for Adv 36 DNA by nested PCR (4). Three of
4 adipose tissue samples showed a band compatible with
Adv 36 DNA. Water controls in the assay had negative
results. A Hae
III digest of the presumed Adv 36 DNA band
showed digestion at the expected site and yielded 2 bands
equal size (Figure
2). Sequencing of the DNA band by
the Virginia Commonwealth University Massey Cancer
Center Molecular Biology Core (Richmond, VA, USA)
identified the sequence as Adv 36 DNA.

As a control, samples of adipose tissue obtained by
needle fat biopsy from 12 obese persons without abnormal
adipose tissue deposits were evaluated by nested PCR and
quantitative PCR by using proprietary Taqman primers and
probe (Obetech, Richmond, VA, USA). These persons pro-
vided written informed consent. Samples for quantitative
PCR were analyzed with an ABI Step One PCR apparatus
(Applied Biosystems, Foster City, CA, USA). Two of the 8
samples assayed by nested PCR were positive and 5 of 12
samples assayed by quantitative PCR were positive. The
prevalence of Adv 36 infection identified by PCR was simi-
lar to that identified by serum neutralization in obese adults
in the United States (5).

Conclusions
Adv 36 DNA in the adipose tissue of this patient docu-
ments that he was infected with this virus. The propensity

![Figure 1. Computed tomography scans of the patient, showing marked visceral adipose tissue in the abdomen (A) and thorax (B). Diffuse intrabdominal, retroperitoneal lipomatosis, and herniation of the mediastinum can be seen through the esophageal hiatus. Intrapericardial adipose infiltration and adipose tissue bilaterally are seen within the pleura.]

![Figure 2. HaelII digestion of adenovirus 36 (Adv 36) DNA PCR products of the patient. Lane 1, molecular size marker; lane 2, HaelII digest of Adv 36 DNA; lane 3, undigested Adv 36 DNA.]}
of Adv 36 to increase visceral adipose tissue in experimentally infected animals suggests that the abnormal adipose tissue deposits within the abdomen and chest cavities and in the subcutaneous spaces of the chest and neck could be caused by Adv 36 infection. He was being treated with replacement corticosteroids but did not have signs of Cushing syndrome.

More research is needed to determine if Adv 36 plays a role in abnormal adipose tissue deposits/lipomatosis. If Adv 36 is found to be a cause, research is needed to identify effective antiviral agents with a more tolerable side effect profile. Cidofovir is effective against Adv 36 in vitro, but has major side effects in humans.

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Dr Salehian is an associate clinical professor of diabetes, endocrinology, and metabolism in the Department of Diabetes at the City of Hope and Beckman Research Institute, Duarte, California. His primary research interests are glucocorticoid myopathy, thyroid cancer, metabolism and nutrition in patients with critical illnesses, and cachexia.

References


Address for correspondence: Richard L. Atkinson, Obetech Obesity Research Center, 800 East Leigh St, Richmond, VA 23219, USA; email: ratkinson2@vcu.edu

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