Reviewer's report

Title: Gene Expression Analysis Reveals Impaired Mitochondriogenesis and Adipogenesis in Adipose Tissue from a Patient with Acquired Partial Lipodystrophy (Barraquer-Simons Syndrome): a case report

Version: 2 Date: 9 May 2008

Reviewer: yaacov barak

I am familiar with the literature and believe that this case meets one of the 9 criteria for evaluation in the journal: Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

If other, please specify:

Findings that expand the molecular characterization of a disease

Has the case been reported coherently?: Yes

Is the case report authentic?: Yes

Is this case worth reporting?: Yes

Is the case report persuasive?: Yes

Does the case report have explanatory value?: No

Does the case report have diagnostic value?: No

Will the case report make a difference to clinical practice?: No

Is the anonymity of the patient protected?: Yes

Comments to authors:

This is a first of its kind report of gene expression anomalies in subcutaneous adipose tissue from a patient of Barraquer-Simons syndrome (Acquired partial lipodystrophy). The 44-yo patient is newly diagnosed, but described typical symptoms of APL since childhood. The disease itself has therefore gone on for quite a while and is likely full-blown. The authors performed targeted expression analyses of genes associated with adipogenesis, mitochondrial function and inflammation in biopsied material of the patient relative to 10 healthy controls. They found reduced expression of PPARgamma and adiponectin, but not leptin; unchanged levels of markers of local inflammation; and lower levels of genes linked to mitochondrial function without reduction of mtDNA levels. Based on these findings they conclude that the syndrome is associated with impaired
adipogenesis and mitochondrial function, but not with inflammation.

The manuscript and the approach are original and build on the expertise of the corresponding author in analyzing gene expression in HAART-associated lipodystrophy of HIV patients. The observations are new in the context of APL, and transcend a typical case report by presenting molecular analyses that could, in time, shed light on disease mechanism. As such, they fit the scope of the Journal of Medical Case Reports.

The gene expression analyses on which the conclusions are based are targeted and rather limited. The case would have been more exciting, and significantly less biased, if the analyses were of a more global nature, such as microarrays or PCR arrays. However, the underlying fiscal and logistical limitations are understandable. Due to the focused nature of the analyses, the authors’ conclusions are premature at times, and the manuscript would benefit from addressing/discussing these shortcomings.

Specifically:

1. The authors interpret the reduced levels of PPARgamma (and its target adiponectin) as evidence of impaired adipogenesis. However, PPARg functions in multiple aspects of the adipocyte life cycle, and the specific impairment associated with its down-regulation may not necessarily relate to adipogenesis. Another argument that the defect is likely post-adipogenic is that APL develops in patients who originally had a roughly normal complement of adipose tissue. Moreover, one may argue that impaired adipogenesis would have been reflected in a parallel change in the adipogenic C/EBPalpha, whose normal levels in the patient argue against this interpretation. Lastly, the reduction in PPARg may well be an effect and not a cause of the syndrome. The authors should discuss a broader interpretation of these observations.

2. The authors interpret the unchanged levels of pRB and Pref-1 as evidence that the anti-adipogenic activities of neither gene contribute to the syndrome. The relevance of these analyses is questionable, because: A. Pref-1 levels, as presented in Table 1, are minimal, bordering on absent. B. Tying the pleiotropic pRB to the narrow aspect of its anti-adipogenic functions is too contentious. I recommend withdrawing the interpretation due to its minor significance.

3. The finding that two mitochondrial respiratory chain genes are down-regulated, with no parallel decrease in mtDNA, could indeed signify mitochondrial impairment as part of the disease. Three related comments are: A. It would add substantially if the authors could expand their analysis to additional genes to demonstrate the extent of this defect. B. It is too premature to hypothesize that these defects are causative factors in the syndrome (P8, last two lines), and not another one of its effects. In fact, the authors themselves undermine their own case in the last sentence of the discussion, stating that other mitochondrial defects cause lipomatosis, but not lipoatrophy. C. The manuscript title states “Impaired Mitochondriogenesis”, which flies in the face of unchanged mtDNA. This part of the title should probably be changed to: “Impaired mitochondrial
function”.

4. The finding that local levels of TNFalpha, MCP-1, and beta-2 microglobulin stay put is interpreted so as to rule out the involvement of inflammation in the syndrome. Considering that only these markers were tested and that inflammatory processes may assume different manifestations, including some that do not involve overt changes in these three markers, this interpretation is premature. The authors have several options for improving on this aspect: A. Analyze histological properties of adipose tissue from the patients, if such material is available. B. Test additional markers, including, but not limited to other surrogate markers of inflammations observed in other lipodystrophic syndromes, such as the corresponding author’s own work on HAART-associated lipodystrophy. C. Present a more careful and reserved interpretation of the current observation.

The type of interpretations criticized above is common to many papers of a similar scope and nature in the adipocyte field. The authors should not be penalized for following this line. However, there is a growing need to start placing this type of generalizations in the appropriate perspective relative to the evolving knowledge of adipose tissue function.

Minor points:
1. P. 4. The meaning of the statement: “Remarkably a male aspect was noted” is vague. Please elaborate.
2. P. 5, 6 lines from bottom – should be C/EBP#. Please correct.
3. Grammar – P3,L18; P6,L12; P7,L15: Please change “associated to” into either “associated with” or “related to”; P6,L14; P8,L6: Change “respect to” to “relative to”. P3,L3; P3,L13: add article – “the face”; P3, last line, change “which” to “whose”; P8,L22: omit “out”, should read: “This points to altered…”. P8,L19,L26: add article – “the present findings/observations”

Quality of written English: Acceptable

Declaration of competing interests:

I declare that I have no competing interests