Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2016:

<table>
<thead>
<tr>
<th>Name of the enterprise / Nature of the interest</th>
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Case 2

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Clinical History

- 4 month-old female
- First child born to consanguineous first cousin parents
- Born 39 weeks
- Growth along the 2nd-9th centile
- Loose skin and significant joint laxity
- Dislocated hips, bilateral talipes, hyperextensible wrists, anterior anus
- Femoral shortening osteotomy, dega acetabuloplasty and capsulorrhaphy
- A diagnosis of cutis-laxa was suggested by clinical genetics
Cutis Laxa

- "Cutis laxa" is Latin for loose or lax skin

- Term used for a heterogeneous group of rare diseases which may be congenital or acquired

- Autosomal dominant, recessive and x-linked

- Systemic involvement with cardiac and respiratory complications

- 100 families affected families in medical literature

- Loose slack skin also seen in Wrinkly Skin Syndrome (WSS) and Geroderma Osteodysplasticum (GO)
Microscopy Report

- Light microscopy on haematoxylin and eosin stained sections showed a light chronic inflammatory cell infiltrate within the dermis.

- Markedly reduced elastic fibre area fraction, volume fraction and mean fibre thickness.
Electron Microscopy Report

- Fibroblasts showing organelle necrosis, moderately expanded and protein filled rough endoplasmic reticulum, and lysosomes expanded and protein filled.
- Elastic tissue severely hypoplastic.
- Moderate amount of flocculent extracellular protein
- No collagen flowers
- Mean collagen fibril diameter, at 72nm, is normal for age
- Variation in collagen fibril diameter at deviation RMS 7.8nm is not excessive.
Differential Diagnosis

- Cutis laxa
- Wrinkly skin syndrome
- Geroderma Oseodysplasticum
Genetics

- Exome sequencing

- Panel of 8 candidate skin-laxity genes were applied (ELN, FBLN5, EFEMP2, LTBP4, ATP6V0A2, PYCR1, ALDH18A1, GORAB)

- Ahomozygous deletion in the GORAB gene

- Four nucleotide deletion is predicted to result in the introduction of a premature termination codon in the third of five GORAB exons

- This gene encodes a member of the golgin family, a group of coiled-coil proteins localized to the Golgi.
Geroderma Osteodysplasticum

- Rare autosomal recessive disorder
- Spectrum of Cutis Laxa Syndromes
- Loose skin
- Hypermobile joints
- Malar and mandibular hypoplasia
- Normal cognition/mentation
- Long term risk of osteoporosis
Histological and EM findings in GO

- The reduction in elastic fibres within the dermis is a common feature noted in GO.
- ‘Fragmentation’ of elastic fibres has also been described in several cases.
- Normal skin biopsies in some GO cases
- There is significant overlap of histological features between GO and other conditions presenting with slack skin, namely Cutis Laxa and WSS.
- The classical histological findings of CL also include loss of, and fragmentation of elastic fibres within the reticular dermis.
- The lack of distinguishable features on light microscopy and electron microscopy highlights the importance of molecular analysis for diagnosis.
Unique finding: Distinct organelle necrosis in fibroblasts, which is a unique finding which has not been previously described.

Significance of organelle necrosis is uncertain:
- Genuinely not present in other cases
- Only a few fields of view were examined
- Not present in plane of section
- Present but not thought to be a significant finding
Summary

- Case history of child with loose slack skin
- Discussed differential diagnosis, namely Cutis laxa, Wrinkly Skin Syndrome
- Histological and ultrastructural features of GO
- Discriminatory clinical features of Geroderma Osteodysplasticum
- Specific genetic mutation – GORAB gene mutation
A case of Geroderma Osteodysplasticum diagnosed by exome sequencing using a panel-based approach

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