Uterine amyloidosis causes fetal death in goats

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Cases

- 3 breeds of goats: Toggenburg, Saanan and La Mancha
- 2 counties in N. CA : Yolo and Sacramento
## 10 goats from ages 3-8 years old

<table>
<thead>
<tr>
<th>Animal #</th>
<th>Breed</th>
<th>County</th>
<th>Age (years)</th>
<th>Parity</th>
<th>Fetus# (condition)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toggenburg</td>
<td>Yolo</td>
<td>5</td>
<td>5</td>
<td>(dead)</td>
</tr>
<tr>
<td>2</td>
<td>Toggenburg</td>
<td>Sacramento</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Toggenburg</td>
<td>Yolo</td>
<td>4</td>
<td>4</td>
<td>3 (2 mummified, 1 live birth)</td>
</tr>
<tr>
<td>4</td>
<td>Toggenburg</td>
<td>Yolo</td>
<td>7</td>
<td>6</td>
<td>3 (1 mummified, 2 live births)</td>
</tr>
<tr>
<td>5</td>
<td>Toggenburg</td>
<td>Sacramento</td>
<td>5</td>
<td>4</td>
<td>3 (2 dead, 1 viable)</td>
</tr>
<tr>
<td>6</td>
<td>La Mancha</td>
<td>Yolo</td>
<td>8</td>
<td>7</td>
<td>1 (dead)</td>
</tr>
<tr>
<td>7</td>
<td>Toggenburg</td>
<td>Yolo</td>
<td>3</td>
<td>3</td>
<td>3 (dead)</td>
</tr>
<tr>
<td>8</td>
<td>Toggenburg</td>
<td>Sacramento</td>
<td>7</td>
<td>5</td>
<td>3 (dead)</td>
</tr>
<tr>
<td>9</td>
<td>Saanen</td>
<td>Sacramento</td>
<td>3</td>
<td>2</td>
<td>3 (dead)</td>
</tr>
<tr>
<td>10</td>
<td>Saanen</td>
<td>Yolo</td>
<td>4</td>
<td>3</td>
<td>2 (dead)</td>
</tr>
</tbody>
</table>
Clinical presentation

(1) Abortion in mid-to-late term pregnancy and a clear uterine discharge
(2) Failure to kid beyond due date with agalactia and clinical diagnosis of fetal death
(3) Live kids and mummified fetuses, often occurring repeatedly over multiple years
Clinical signs in goat abortions

Normal, blood tinged membranes

Abnormal clear discharge
Gross lesions: pale uterine carcuncles
Gross lesions: pale uterine carcuncles
Histology – Interstitial Caruncular Amyloid

Interstitial protein

Congophilic / Green birefringence

H&E

Congo red
What is amyloid?

Non-branching, fibrillar, Congo red binding, extracellular protein aggregates

Highly insoluble

*Reports of uterine amyloidosis are rare*
What is the amyloidogenic protein?

Mass spectrometry analysis of the insoluble proteins
Insoluble caprine uterine peptides match ovine serum amyloid A

QGWGTFLREAGQGAKDMWRAYRDMKEANYKGADKYFHARGNYDAAQRGPGGVWAAEV

T1  T2  T3

REALQGITDPLFKGMTRDQVREDTKADQFANEWGQSGKDPNHFGPADLPDKY

T4  T5
Insoluble caprine uterine peptides match ovine serum amyloid A

58     80
Bovine  DARENIQRFTDPLFKGTTSGQGQ
Ovine   NGREALQGITDPLFKGMTRDQVR
Caprine EALQGIDPLFKGMTR
SAA confirmed by immunohistochemistry using an SAA antibody
SAA amyloidosis

• Reactive/Secondary

• Serum amyloid A (SAA) protein
  – Acute phase protein
  – ↑1000 fold

• SAA
  – 104-112 amino acid (SAA protein) extracellular
  ↓
  Acute phase response
Causes of high SAA

- Chronic infection
- Neoplasia
- Other sources of chronic inflammation

- Uterine SAA has occurred with uterine tumors in women (endometrial carcinoma)

*Here the pathogenesis is unknown*
Conclusions

• New syndrome of amyloidosis in goats in Northern California

• 3 breeds, multiple locations across 2 counties

• Clinical presentation is fetal death and mummification or abortion

• Amyloid is restricted to the uterus and has been identified as serum amyloid A (SAA)

• The uterine endometrium is producing high levels of SAA transcripts, suggesting local production of SAA
Detailed description of the clinical pattern:

Dr. Joan Rowe
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Uterine amyloid in other species
What are protein misfolding diseases?

Protein folding is normally assisted by chaperones.

Diseases can occur when proteins cannot adopt the correct architecture and aggregate:
- loss of function
- gain of function

Exogenous or endogenous factors can lead to:

Increased production:
- genetic (ie, mutations)
- aging
- reactive oxygen species

OR

Decreased clearance of misfolded proteins.
Type II diabetes: Islet Amyloid Polypeptide
Caprine SAA protein has 4 isoforms

- Position  Amino Acid
  43      R / Q
  66      L / I
  80      Q / R
  105     A / P

- No isoform unique to + vs – cases
- No unique amino acids compared Ov or Bov
What is the amyloidogenic protein?

- No reports of uterine amyloidosis
- SAA IHC – inconclusive
- Protein sequencing
  - 1 positive case: ~15kD band
  - 3 positive cases, 1 negative case: insoluble pellet
Insoluble protein from goat uterus contains SAA peptides in amyloidogenic region

Bovine  DARENINQRFTDPLFKGTTSGQGQ
Ovine   NGREALQGITDPLFKGMTRDQVR
Caprine EALQGITDPLFK
        EALQGITDPLFKG
        EALQGITDPLFKGMTR
        QGITDPLFK

87% (306/352) ID’ed peptide fragments