Pathology of Vulnerable Plaque

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Renu Virmani, MD
CVPath, A Research Service of the International Registry of Pathology
Gaithersburg, MD
<table>
<thead>
<tr>
<th>Plaque Rupture</th>
<th>55 - 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque Erosion</td>
<td>30 - 35%</td>
</tr>
<tr>
<td>Calcified Nodule</td>
<td>2 - 7%</td>
</tr>
</tbody>
</table>

Plaque Morphology of Thrombi in SCD
Clinical and Morphologic Difference in Plaques Associated with Luminal Thrombi

**Plaque rupture**
- Necrotic core
- Thrombus (Th)
- Lumen
- 45-55% thrombi in SCD
- M>F, Older, Ca++
- Eccentric = concentric
- Greater % stenosis
- Macs, T cells, HLA-Dr

**Plaque erosion**
- Lumen
- Thrombus (Th)
- 35-40% thrombi in SCD
- M=F, younger
- Usually eccentric
- Lesser % stenosis
- SMC rich, proteoglycans

**Calcified nodule**
- Lumen
- Thrombus (Th)
- 4-7% thrombi in SCD, calcified plates
- M>F, older, mid RCA
- Usually eccentric
- Stenosis variable
- Nodules of bone
Gross and Light Microscopic Features of Plaque Rupture

60% of Thrombi in Sudden Coronary Death Are from Plaque Rupture

Fig 3-1
Plaque erosion in a 33 year-old female complaining of chest pain for two-weeks and discharged from the emergency room with a diagnoses of anxiety.
Development of Human Coronary Atherosclerosis

Intimal thickening
Intimal xanthoma
Pathologic intimal thickening
Fibrous cap atheroma
Thin-cap Fibroatheroma

Smooth muscle cells
Macrophage foam cells
Extracellular lipid
Cholesterol clefts
Necrotic core
Calcified plaque
Hemorrhage
Thrombus
Healed thrombus
Collagen
What is a Vulnerable Plaque?

- Plaque morphology underlying luminal thrombi represents a vulnerable plaque
  - Thin-cap Fibroatheroma – Plaque rupture
  - Pathologic intimal thickening
  - Fibroatheroma
  - Calcified plates with bone formation – Calcified nodule - surface thrombus

Plaque Erosion
**Thin cap Fibroatheroma is a Precursor lesions of Plaque Rupture**

**TCFA**

(nc) Thin fibrous cap

**Plaque Rupture**

(*Ruptured cap*

(th)

(nc)
Thin-Cap Atheroma (Vulnerable Plaque) Components

- Necrotic core
- Thin fibrous cap (< 65 μm)
- Cap infiltrated by macrophages and lymphocytes
- Cap composition – type 1 collagen and few smooth muscle cells
A Non-Hemodynamically Limiting Thin-cap Fibroatheroma

Fig 2-2
# Morphologic Characteristics of Plaque Rupture and Thin-cap Fibroatheromas

<table>
<thead>
<tr>
<th>Plaque type</th>
<th>Necrotic Core (%)</th>
<th>Fibrous cap Thickness (µm)</th>
<th>MΦs (%)</th>
<th>SMCs (%)</th>
<th>T-lymph</th>
<th>Calcification Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupture</td>
<td>34±17</td>
<td>23±19</td>
<td>26±20</td>
<td>0.002±0.004</td>
<td>4.9±4.3</td>
<td>1.53±1.03</td>
</tr>
<tr>
<td>Thin-cap Fibroatheroma 23±17</td>
<td>&lt;65µm</td>
<td>14±10</td>
<td>6.6±10.4</td>
<td>6.6±10.4</td>
<td>0.97±1.1</td>
<td></td>
</tr>
</tbody>
</table>

P value: 0.01

Mean values are represented ± standard deviation. Abbreviations: MΦs= macrophages, SMCs= smooth muscle cells, T-lymph= T-lymphocytes.

Morphological Variants of the Thin-Cap Fibroatheroma

- Insignificant Plaque burden
- Large eccentric necrotic core
- Large concentric necrotic core
- Healed Rupture(s)

Vulnerable Plaque Characteristics

Mean % x-sectional area
For TCFA is 60%

80% of thin cap atheromas occur in arteries
with < 75% x-sectional area luminal
narrowing (<50% diameter reduction)
Distribution of Ruptures and Thin-Cap Atheromas by Plaque Area or Lipid Core Size

**A**

Plaque Ruptures (%)

<table>
<thead>
<tr>
<th>Lipid core as % plaque area</th>
<th>&lt;10</th>
<th>10-25</th>
<th>25-50</th>
<th>&gt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>% &lt;10</td>
<td>82 ± 9%*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% 10-25</td>
<td>71 ± 13%*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% 25-50</td>
<td>77 ± 15%*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50%</td>
<td>79 ± 13%*</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**B**

Plaque Ruptures (%)

<table>
<thead>
<tr>
<th>Cross sectional lipid core area, mm²</th>
<th>area&lt;1</th>
<th>area 1-3</th>
<th>area 3-5</th>
<th>area &gt; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean cross sectional area luminal narrowing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81 ± 9%*</td>
<td>73 ± 13%*</td>
<td>77 ± 16%*</td>
<td>78 ± 12%*</td>
<td></td>
</tr>
</tbody>
</table>

**C**

Thin-Cap Fibroatheromas (%)

<table>
<thead>
<tr>
<th>Thin-Cap Fibroatheromas</th>
<th>&lt;10</th>
<th>10-25</th>
<th>25-50</th>
<th>&gt;50%</th>
<th>65 ± 17%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=106</td>
<td>71 ± 17%*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>77 ± 9%*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>76 ± 14%*</td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**D**

Thin-Cap Fibroatheromas (%)

<table>
<thead>
<tr>
<th>Thin-Cap Fibroatheromas</th>
<th>area&lt;1</th>
<th>area 1-3</th>
<th>area 3-5</th>
<th>area &gt; 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=106</td>
<td>65 ± 15%*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>74 ± 15%*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>78 ± 12%*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>77 ± 13%*</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = mean cross sectional area luminal narrowing
Do TCFAs lead to plaque progression?

Movat pentachrome

Sirius red

Sirius red with polarized light
Mean % Stenosis Increases with Number of Prior Rupture Sites but the Increase with Each New Rupture is Small (<20%)

Healed Rupture Sites

Acute Rupture Sites

Percentage of Cross-Sectional-Area Narrowing by Plaque Morphology

**Fig 2-6**

A) Bar chart showing Cross-Sectional-Area Narrowing (%) for different categories of plaque morphology:
- Thin cap
- Acute rupture
- Healed rupture

B) Bar chart showing the comparison between Occlusive and Non-Occlusive Thrombus with a p-value of 0.05.

C) Bar chart showing the New lumen - Old lumen (%) for different numbers of Healed Ruptures.

- P= 0.05
- N=12
- N=19
Necrotic core size, sum mm², independent of plaque area, morphometrically determined, at maximal luminal narrowing of 3 major epicardial arteries

Mean necrotic core area mm²

- Normal TC/HDL-C
- TC/HDL-C > 7

P=0.03
P=0.01
Relationship of Fibrous Cap Thickness to Macrophage Infiltration

Cell Mean for % Kp-1

- Less than 65 µm
- 66 - 200 µm
- 201 - 300 µm
- More than 300 µm

P = 0.03
P = 0.06
Correlation of Fibrous Cap Thickness and Macrophage Infiltration

R² = .117
P = <0.001
Relationship of Fibrous Cap Thickness to Underlying Percent Necrotic Core

% Necrotic Core

- Less than 65 μm
- 66 - 200 μm
- 201 - 300 μm
- More than 300 μm
Correlation of X-Ray Calcification with Plaque type

A

B
Speckled

C
Fragmented

D
Diffuse
Calcified Matrix Determined Histologically

Severe Coronary Artery Disease, n=36, 64±14 yrs
Coronary Arteries Serially Sectioned
Proportion and types of “unstable” plaques, by approximate distance from ostium

- Fibroatheroma
- Hemorrhage into plaque
- Thin cap acute rupture
- Healed rupture

% distribution
Frequency and Location of Unstable Lesions: Thin-cap Atheromas, Acute and Healed Ruptures in the Coronary Circulation

**Thin-cap Fibroatheroma**

- Frequency (%)
- Total Lesions = 131

**Acute Plaque Rupture**

- Frequency (%)
- Total Lesions = 68

**Healed Plaque Rupture**

- Frequency (%)
- Total Lesions = 136

Frequency of Thin-Cap Fibroatheromas by Decades

A. Mean Number of TCFAs

B. Frequency of Thin-Cap Fibroatheromas by Decades

Fig 2-7
Number of Thin-Cap Atheromas in Various Coronary Syndromes in Males and Females

Fig 2-11
Frequency of thin cap atheroma, by mechanism of death

Number of thin cap atheromas

- noncoronary
- erosion
- stable plaque
- healed rupture
- acute rupture
43-year old WM collapsed at work and could not be resuscitated.

Fig. 11
### Comparison of the Length, Necrotic Core Area and % Necrotic core/plaque Area

<table>
<thead>
<tr>
<th>Dimensions</th>
<th>Fibroatheroma</th>
<th>Thin-cap Atheroma</th>
<th>Plaque Rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length, mm, mean/Range</td>
<td>6 mm (range 1-18 mm)</td>
<td>8 mm (range 2-16 mm)</td>
<td>9 mm (range 2.5-22 mm)</td>
</tr>
<tr>
<td>Necrotic core area mm²</td>
<td>1.2 ± 2.2</td>
<td>1.7 ± 1.1</td>
<td>3.8 ± 5.5</td>
</tr>
<tr>
<td>% necrotic core/plaque area</td>
<td>15 ± 20 %</td>
<td>23 ± 17 %</td>
<td>34 ± 17 %</td>
</tr>
</tbody>
</table>
Serial Sections of a Thin-Cap Fibroatheroma
Cut 250 mm apart

Fig 2-16
Serial Coronary Sections (mm) Demonstrating Multiple Vulnerable Plaques and Rupture Sites

Proximal LCx

Distal
Remodeling in Varying Coronary Lesion Morphologies

IEL-Expected IEL (mm²)

A.

IEL-Expected IEL (plaque area)

B.
Mean Number of Thin Cap Fibroatheromas and Serum Cholesterol in Men

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Population</th>
<th>Whites</th>
<th>Blacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC &lt; 210 mg/dl &amp; ratio &lt; 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC &gt; 210 mg/dl &amp; ratio &gt; 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TC &gt; 210 mg/dl &amp; ratio &gt; 5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cases</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig 2-17
Mean Number of Thin-Cap Fibroatheromas in 51 Women with SCD and Severe Coronary Disease
A Comparison of Risk Factors

Age

Cholesterol

Diabetes

Smoking

Fig 2-18
Serum hs-CRP correlated with Immunohistochemical staining intensity of Plaques and with TCFA

<table>
<thead>
<tr>
<th>CRP</th>
<th>CRP staining intensity of plaques*</th>
<th>Mean number of thin cap atheroma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CRP group (&lt;1.0µg/mL)</td>
<td>2.9 ±0.5</td>
<td>0.95 ±0.22</td>
</tr>
<tr>
<td>High hs-CRP group (&gt;3.2µg/mL)</td>
<td>6.2±0.6</td>
<td>3.0 ±0.3</td>
</tr>
</tbody>
</table>

*Grading of staining intensity was assessed on macrophages and Lipid core. A quantitative score of 0 to 4 was applied to each. A sum of the 2 scores resulted in overall grading system of 0 to 8.
Thin Cap Fibroatheroma-
A plaque vulnerable to rupture?

- Definition
- Frequency is higher in AMI than SCD, >males than females
- Higher prevalence in the presence of high TC, low HDL-C, high TC/HDL-C ration, high hs CRP (>3.2 mg/dl)
- Location in SCD, proximal and mid LAD, RCA, and LCX
- Length 2-22 mm (mean 8 mm)
- % luminal narrowing (80% of TCFAs occur in lesions <50% diameter stenosis)
- % necrotic core is <25% of plaque area in 70% of TCFAs
- Calcification is not a marker of TCFA