The Case of Henry Fork: A Misfolded Mystery

Background

Henry Fork, a 55-year-old man from Rhode Island, presented with severe fatigue and a complex medical history including rheumatoid arthritis and hyperthyroidism. Upon examination, you find Henry is experiencing gastrointestinal pain, upper-left abdominal pain, and edema. Henry Fork mentioned that his brother Jimmy Fork had a similar set of symptoms that sent him to the emergency room a couple of years ago, but he couldn't remember what they diagnosed him with. He did, however, note that his brother also suffers from rheumatoid arthritis. In addition, Mr. Fork admitted that he has been forgetting to take his arthritis medications because of how busy his life has become.

Clinical Findings

Table 1. Initial blood test results for Henry Fork.

Test	Results	Normal Range
C-reactive protein (CRP)	87 mg/L	< 5 mg/L
Fibrinogen	7 g/L	2-4 g/L
Hemoglobin (Hgb)	8 g/dL	♂: 14 – 18, ♀: 12 – 16 g/dL
Platelet Count	500,000 mm^3 (or /μL)	150,000 – 400,000 /mm^3

After the initial blood test, doctors in the emergency room decided to run another blood test, a urine test, and an echocardiogram.

Table 2. Secondary test results for Henry Fork.

Test Category	Specific Test	Finding	Normal
Blood Test	Serum Amyloid A (SAA)	2000 mg/L	Under 3 mg/L
Urine Test	Proteinuria (24-hour collection)	3.0 g/24 h	Under 0.15 g/24 h
Imaging Test	Echocardiogram	Normal Systolic Function	Ejection Fraction (EF) typically 55% or greater
Definitive Biopsy	Renal Biopsy (Congo-Red)	100% Positive for deposits	Zero amyloid deposits present.

Biochemistry:

The serum amyloid A (SAA) protein is a globular, soluble protein made up of mostly alpha helices and regulated by inflammatory cytokines. It responds to immune and inflammation activity as it binds and activates cell-surface receptors. Under normal physiological conditions, the concentration of SAA in the blood is low. However, during prolonged inflammation periods, SAA proteins cleave, resulting in the amyloid A (AA) protein. Since the AA protein is shorter and less stable than the SAA protein, the AA protein misfolds into an anti-parallel beta sheet structure that is insoluble. The accumulation of amyloid A protein deposits in organs is called amyloidosis.

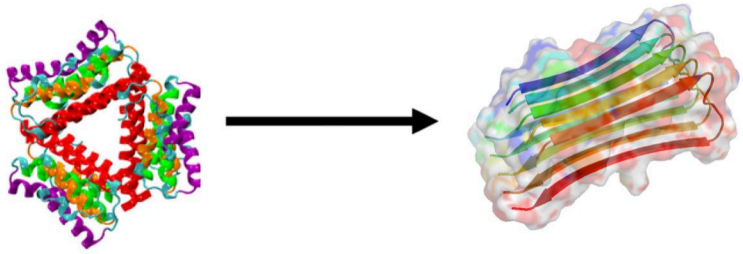


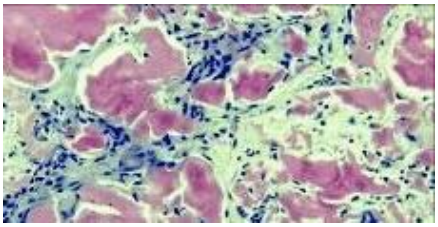
Figure 1. The normal serum amyloid A (SAA) protein transformed into the amyloid A (AA) protein in patients with AA amyloidosis. The SAA protein secondary structure is full of alpha helices and the disease-causing AA protein is rich in beta sheet structures.

Vocabulary: Amyloidosis, proteinuria, rheumatoid arthritis, hyperthyroidism, edema

Analysis:

Q1. Take a look at Table 1. What about Henry's labs is most notable? What about the medical history and biochemistry related to an inflammatory response would make you run the secondary tests (Table 2)?

Q2. The SAA protein is normally soluble and made of alpha helices. When it changes into the AA protein, it stacks in beta sheets and becomes insoluble. Why does this structural change make it more likely to form deposits in tissues?



After getting these test results back, the doctors decided to perform a renal biopsy using Congo-Red stain. Under a polarized light microscope, amyloid aggregates bound to Congo-Red demonstrated an "apple-green" birefringence, confirming an amyloidosis diagnosis.

Figure 2. A renal tissue biopsy using Congo-Red stain. The presence of green-colored birefringence confirms the diagnosis of amyloidosis.

Table 3. Henry Fork's diagnostic test results for amyloidosis.

Test Category	Specific Test	Finding	Normal
Diagnostic Biopsy	Renal Biopsy (Congo-Red)	100% Positive for deposits	Zero amyloid deposits present.

Q3. Rheumatoid arthritis is an inflammatory disease. How did not taking his rheumatoid arthritis medication lead to Henry Fork's amyloidosis diagnosis?

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Answer Key

Vocabulary:

- Amyloidosis: A protein buildup in an organ or throughout the body can result from an unknown cause, a chronic inflammatory disease, or be hereditary. The buildup of misfolded protein aggregates in vital organs which impairs their function
- Proteinuria: An excessive quantity of protein found in the urine
- Rheumatoid arthritis: An autoimmune disease that causes pain, swelling, and stiffness in the joints, and may cause severe joint damage, loss of function, and disability.
- Hypothyroidism: a condition where the thyroid is not producing enough thyroid hormones for the body
- Edema: A type of swelling caused by excess fluid in the body.

NCI Dictionary of Cancer Terms. Cancer.gov
https://www.cancer.gov/publications/dictionaries/cancer-terms.

Analysis:

Q1. Take a look at Table 1. What about Henry's labs is most notable? What about the medical history and biochemistry related to an inflammatory response would make you run the secondary tests (Table 2)?

- Table 1: Shows Elevated CRP, fibrinogen, platelet count
- The rheumatoid arthritis, edema, high inflammation markers and family history of a similar event are indicators for further testing.
- The secondary tests were performed to detect proteinuria and assess kidney involvement, as well as to evaluate the potential for cardiac involvement by conducting an echocardiogram. Running another blood test to check Serum Amyloid A (SAA) can confirm amyloidosis risk based on chronic inflammation.

Q2. The SAA protein is normally soluble and made of alpha helices. When it changes into the AA protein, it forms beta sheets and becomes insoluble. Why does this structural change make it more likely to form deposits in tissues?

- Since the SAA is usually soluble, it can dissolve in the blood stream and gets "cleared" from the body. Since AA protein is insoluble and beta sheets are very stable, they are more prone to stacking or sticking together due to their hydrogen bonding and flat shape. Therefore they do not dissolve in the blood stream and cannot be cleared, leading to an accumulation of amyloid proteins in tissues which impair organ function and cause symptoms like Henry's

Q3. Rheumatoid arthritis is an inflammatory disease. How did not taking his rheumatoid arthritis medication lead to Henry Fork's amyloidosis diagnosis?

- Taking his rheumatoid arthritis medication decreases the inflammatory response in his body. Without this medication, Henry Fork's liver was overproducing serum amyloid A (SAA). Prolonged elevated levels of SAA in the bloodstream led to SAA being cleaved into amyloid A (AA). The unstable structure of AA causes the protein to misfold into insoluble beta sheets that aggregate together. These aggregates then get deposited into organs and result in amyloidosis.