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PATHOLOGY MATTERS

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High-sensitivity Cardiac Troponin (hs-cTn)

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Cardiac troponin T (cTnT), C (TnC) and I (cTnI) are constituents of the contractile apparatus of myocardial cells (Figure 1). As per the Fourth Universal Definition of Myocardial Infarction (2018)[1], the preferred biomarker for myocardial injury evaluation is cardiac troponin (cTn) and the high-sensitivity cardiac troponin (hs–cTn) assay is recommended for routine clinical use. Current hs-cTn assays include hs-cTnT and hs-cTnI.

The International Federation of Clinical Chemistry Task Force on Clinical Applications of Biomarkers established the analytical requirements for hs-cTn assays as follows[2]:

- Ability to measure cTn at the 99th percentile upper reference limit (URL) with a coefficient of variation ≤ 10%.
- To detect results above the assay's limit of detection in more than 50% of healthy individuals.

The use of hs-cTn in clinical practice includes the pre-analytical, analytical and post-analytical aspects of hs-cTn. Clinicians need to be made aware of these factors to avoid misinterpretation of results leading to mismanagement of the patient.

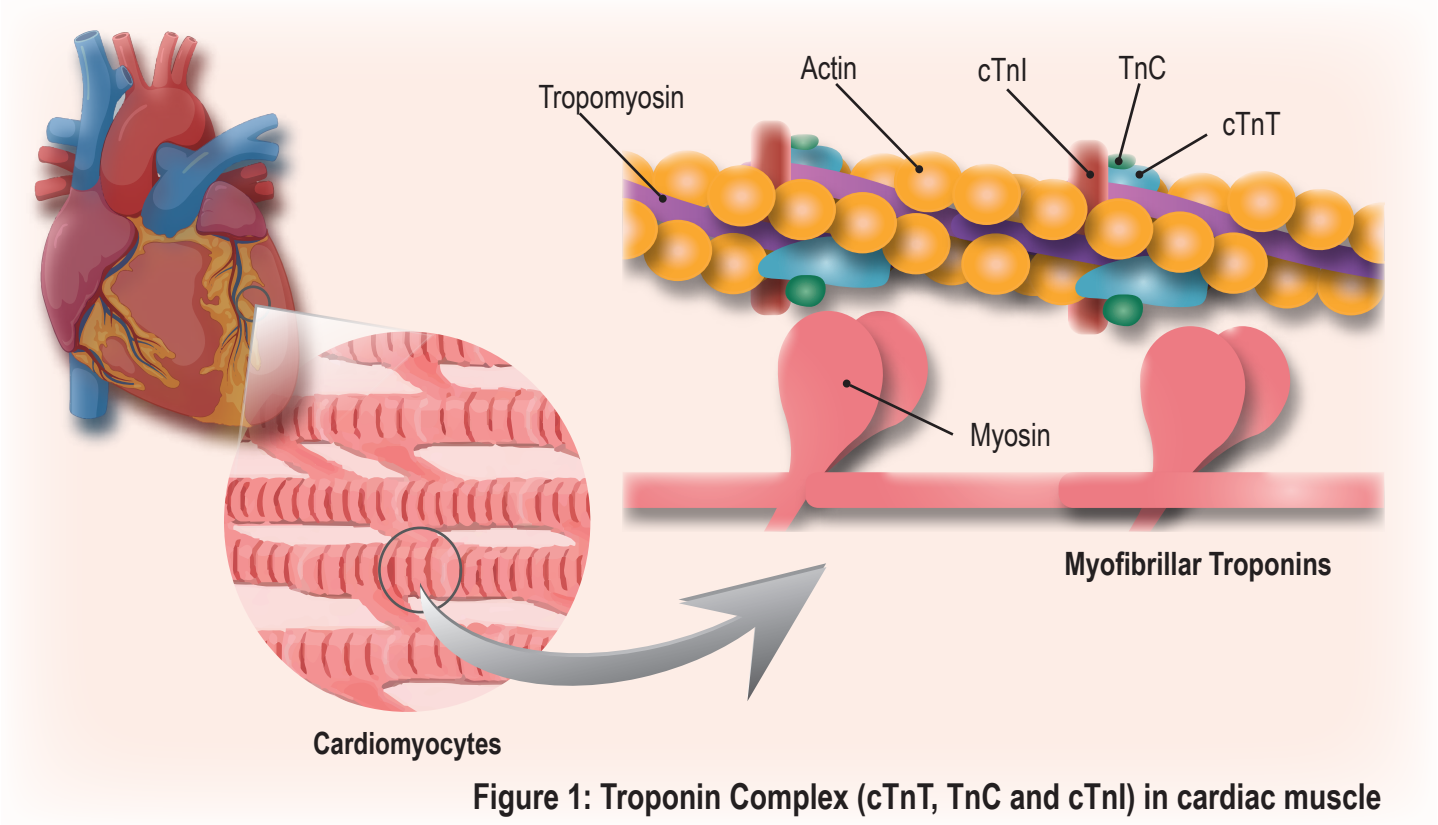

Figure 1: Troponin Complex (cTnT, TnC and cTnI) in cardiac muscle

FACTORS THAT COULD AFFECT hs-cTn TEST RESULTS

Sample collection from the venous central line may lead to insufficient residual volume removal from the catheter and if not flushed properly, adherence of interfering substances to the catheter. Haemolysis can increase cTnI and always lowers cTnT. Minimal changes in absolute cTn concentration (2–4 ng/L) may give rise to inconsistencies in clinical triage.

Differences between plasma and serum can also affect the accuracy of cTn results. Sample types are not interchangeable for serial cTn result interpretation. Plasma (EDTA or heparin tubes) is the preferred matrix in the emergency department since clotting time is eliminated, hence reducing turnaround time (TAT).

Analytical problems occur in less than 1% of patients. Clinicians should liaise with the laboratory personnel when the reported hs-cTn value does not correlate clinically as it could suggest potential assay interferences such as heterophile antibodies giving either a false-positive or false-negative result. The presence of macrotroponin can give rise to false-positive hs-cTn results due to delayed renal clearance. In streptavidin-biotin sandwich immunoassays, biotin decreases the signal intensity producing false negative hs-cTn results. This may lead to inappropriate patient discharge and subsequent serious clinical consequences.

Hs-cTn ASSAYS IN ACUTE MYOCARDIAL INFARCTION DIAGNOSIS

Myocardial injury (Figure 2) is considered acute, if there is a newly detected dynamic rise and/or fall of cTn levels > 99th percentile URL, or chronic, if cTn levels are persistently raised. Hence, serial measurements of hs-cTn are significant in clinical-decision making. The reference change value (RCV) objectively determines if the change in hs-cTn level over serial measurements is statistically significant, taking into account imprecision and within-subject biological variation.

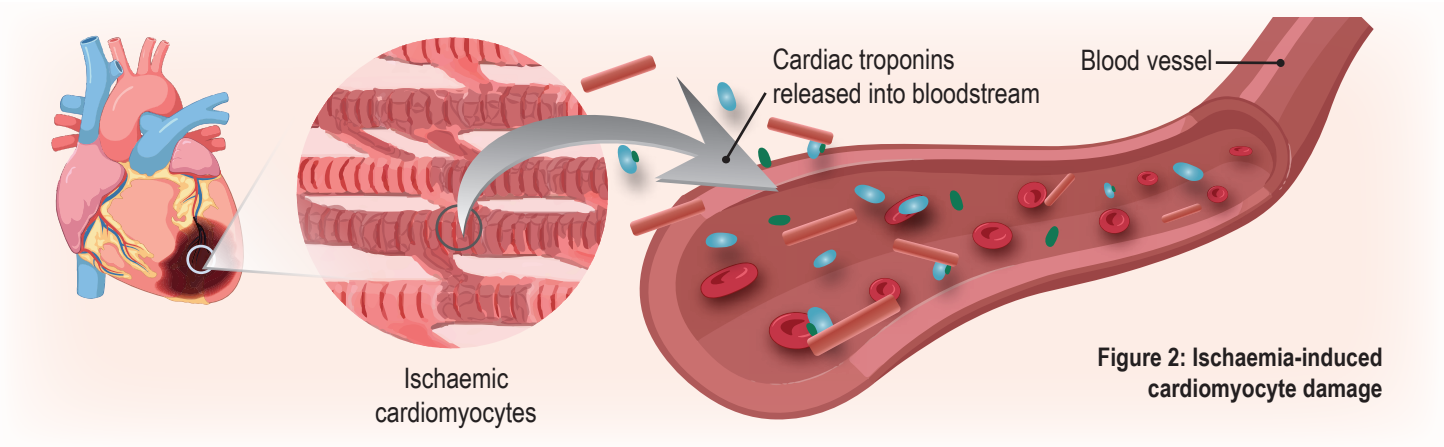

Figure 2: Ischaemia-induced cardiomyocyte damage

The optimal RCV is dependent on whether the diagnosis is made to rule-in AMI, i.e., the need for high specificity, or to rule out AMI, i.e., the need for high sensitivity. The use of an absolute RCV (in ng/L), which is assay specific and timing interval dependent, is considered superior to the relative RCV (in %) because it offers a varying set of criteria depending on the baseline value, hence maintaining sensitivity.

Key considerations for interpreting RCV are: the bigger the RCV, the higher the specificity (i.e. the lower the sensitivity) and the smaller the RCV, the higher the sensitivity (i.e. the lower the specificity) for AMI. Absolute changes in cTn concentrations are ideal for hs-cTn assays when cTn levels are low whereas a relative RCV (%) is preferred when cTn concentrations are high. In summary, hs-cTn assays are extremely sensitive and precise in the diagnosis of AMI, but caveats and limitations should be considered.

The TAT for cTn should be ≤ 60 minutes for the employment of recommended accelerated algorithms. To avoid misinterpretation, hs-cTn should also be reported as whole numbers. While acknowledging the differences between assays, sex-specific 99th percentiles (with URL for female being less than that of male) are also recommended as it enhances the diagnostic specificity of hs-cTn for acute myocardial infarction (AMI).

References:

1. Thygesen K, Alpert JS, AS Jaffe et al. Fourth Universal Definition of Myocardial Infarction. Circulation 2018
2. Wu AHB, Christenson RH, Greene DN et al. Clinical Laboratory Practice Recommendations for the Use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical Applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine. Clinical Chemistry 2018

Gastric Amyloidosis, A Case Report

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Amyloidosis is a rare disease that occurs when insoluble fibrillary protein, called amyloid, builds up in the organs and may result in organ dysfunction. This disease can be localized or systemic with amyloid accumulating in the heart, kidneys, liver, spleen, nervous system, and digestive tract.

Amyloid is not normally found in the body, but it can be formed from several different types of protein. Some amyloidosis occur in association with other diseases and these types may improve with treatment of the underlying disease. Other types of amyloidosis may lead to life-threatening organ failure[1,2].

Localized primary gastric amyloidosis is a rare disorder characterized by the extracellular deposition of insoluble fibrillary protein in the stomach and can mimic various diseases both in presentation and endoscopic examination.

CASE PRESENTATION

We reported a case of a 57-year-old Chinese lady who presented with dyspepsia and bloating. Gastroscopy showed a *Helicobacter pylori*-like gastritis.

Histologically, the biopsy showed multiple fragments of antral and body type glands covered by foveolar epithelium. Amorphous deposits pinkish material was seen in the lamina propria, muscularis mucosa and in blood vessel walls (Figure 3a, 3b & 3c). A moderate infiltrate of small lymphocytes and plasma cells was noted in the lamina propria. A few of the glands showed evidence of intestinal metaplasia. No *H. pylori* organisms were identified. There was no evidence of dysplasia or malignancy. Additionally, Congo red staining via polarized light microscopy showed apple-green birefringence in the deposits (Picture 3d & 3e). A diagnosis of Gastric Amyloidosis was made with advice to do perform further investigations for subtyping and to determine manifestations at other sites.

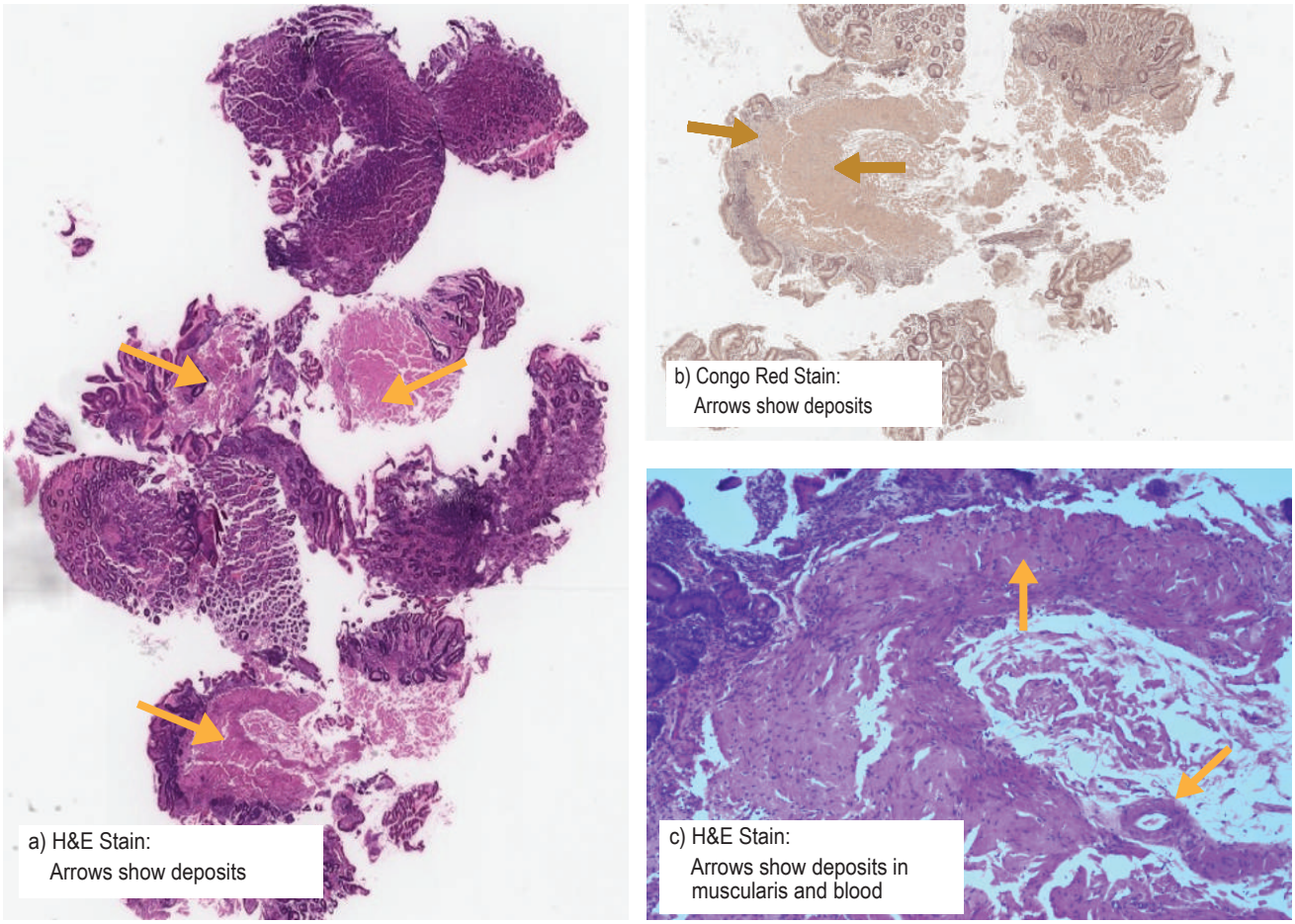

Figure 3: Amyloidosis in Tissue Biopsy

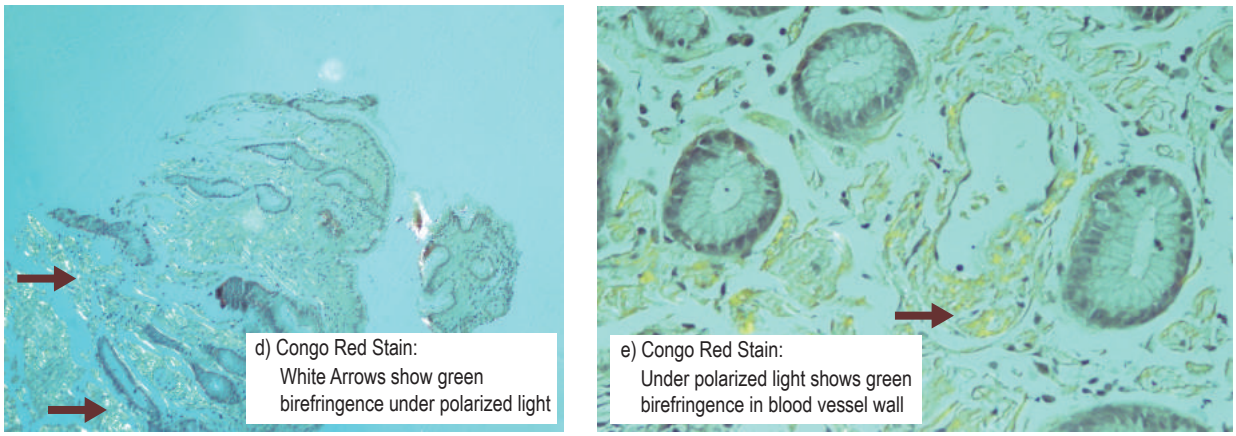

Figure 3 (con't) : Amyloidosis in Tissue Biopsy

DISCUSSION

Amyloidosis is defined by the extracellular deposition of abnormal proteins in organs. The six types of Amyloidosis include: Primary (AL), Secondary (AA), Haemodialysis-related, Hereditary (Familial), Senile (Wild-type), and Localized. The two most common types in clinical practice are Primary amyloidosis and Secondary amyloidosis. Patients with primary type have monoclonal light chains in the serum and/or urine, and a few (15%) may present with multiple myeloma. On the other hand, the secondary type is associated with inflammatory, infectious, and neoplastic diseases. Amyloidosis usually involves gastrointestinal tract (GI), liver, kidney, and spleen and are sometimes associated with the onset of inflammatory bowel disease. In the GI tract, the duodenum and stomach are the most common sites of such protein deposition. GI involvement is common in cases of systemic amyloidosis. The symptoms of GI Amyloidosis include nausea, vomiting, hematemesis, and epigastric pain.

Patients with systemic amyloidosis may present with purpura, macroglossia, joint swelling, congestive heart failure and hepatomegaly. Our patient presented with dyspepsia and bloating, and further investigations are needed to determine if this a localized primary amyloidosis in the GI tract which is rare.

Histopathological (HPE biopsy) examination is the gold standard for the diagnosis of gastric amyloidosis. In our case (on H&E staining) there was abundant amyloid deposition in the lamina propria and muscularis mucosa. The Congo red staining revealed the characteristic apple-green birefringence in the lesions; however, we were unable to perform Congo red staining with potassium permanganate pretreatment for the confirmation of the primary type. For patients diagnosed with amyloidosis, it is important to determine whether they have systemic or localized disease as the treatment and prognosis are different for each disease entity. Further investigations like serum and urine immunoelectrophoresis (for the determination of monoclonal immunoglobulin or free light.

References:

1. Liu XM, Di LJ, Zhu JX et al. Localized primary gastric amyloidosis: Three case reports. World J Clin Cases 2020
2. Amyloidosis, Overview: https://www.mayoclinic.org/diseases-conditions/amyloidosis/symptoms-causes/syc-20353178. Accessed on 25th November 2021