



EGYPTIAN SOCIETY OF
CARDIOLOGY



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AUTOSOMAL-DOMINANT LEFT-SIDED ARRHYTHMOGENIC CARDIOPATHY (ALSC) PRESENTING AS AN ACUTE CORONARY MASKED AS AN ACUTE CORONARY SYNDROME

Case presentation



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Clinical History

- **GM**, 64 years old female in 2014 (1st presentation)
- Ambiguous history of familiar CAD
- Type II Diabetes Mellitus
- Dyslipidemia
- Previous smoker
- No alcohol
- Menière syndrome, intestinal polyposis



GM 64 yo

Clinical History

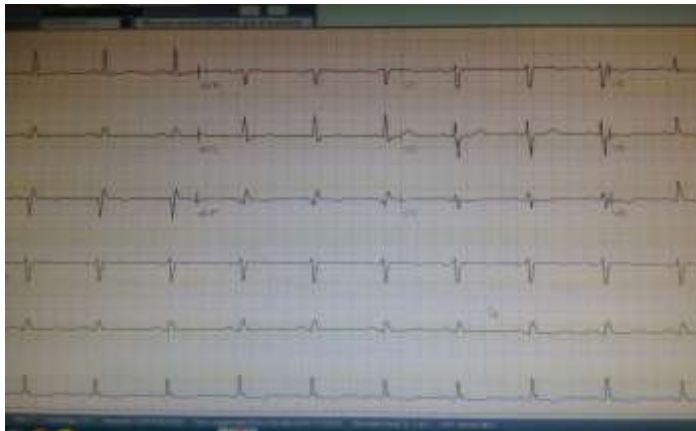
- **September and November 2013** 2 episodes of **typical precordial oppressive pain at rest**, lasting 15 min, with spontaneous resolution
- **December 2013** pre-lipotimic episode linked to dyspnea and vertigo
- **January 2014** frequent episodes of **precordial pain at rest**, linked to diaforesis and tachycardia, with spontaneous resolution in 15 min
- **February 18, 2014** admission to HPG23 ER for several episodes of **precordial pain** in rapid succession

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GM 64 yo

ECG

HR 85 bpm, incomplete left bundle branch block, **Q wave in inferior leads, ST-T abnormalities in infero-lateral leads**



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GM 64 yo

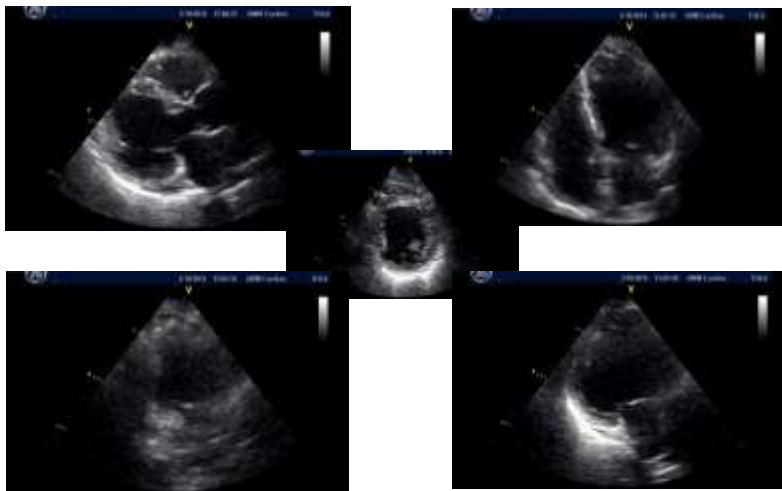
Chest X-ray



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ECHO



Globous and enlarged LV, infero-posterior and lateral hypokinesia, LVEF 40%. Normal RV.

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GM 64 yo

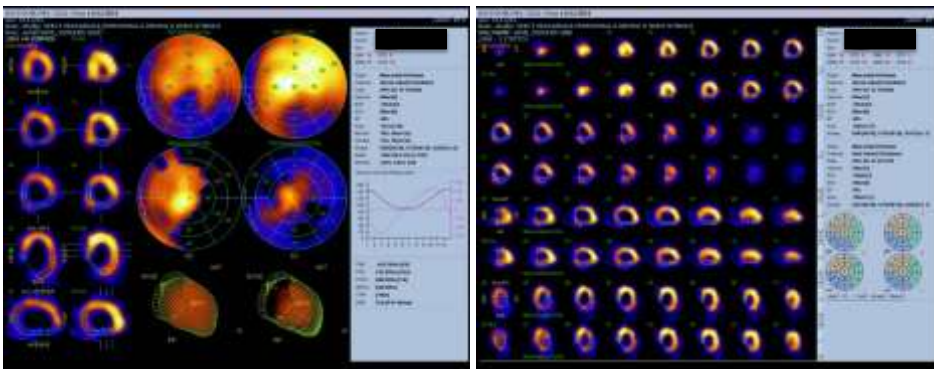
Blood chemistry

- Hb 13.7 g/dl, no iron deficiency
- Creatinine 0.63mg/dl
- eGFR 82 ml/kg/min, BUN 42mg/dL
- Na⁺⁺ 142 mMol/L and K⁺ 4.6 mMol/L
- Total cholesterol 221 mg/dl, LDL 154 mg/dl
- Fasting glycemia 95 mg/dl, glycated Hb 6.5%
- Troponin I 0.07→0.1→0.07 ng/ml
- BNP 98 pg/ml

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GM 64 yo

Perfusional Myocardial Scintigraphy Rest/Stress



Wide infero-lateral ischemia 30% (RC territory)
and mild LV systolic dysfunction (LVEF 40%)

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**GM, 64 yo female, precordial pain,
T2DM, dyslipidemia, previous smoker**

- A: Ischemic Cardiomyopathy?
- B: Diabetic Cardiomyopathy?
- C: Micro-vascular Dysfunction?

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GM 64 yo

Coronary Angiography

- Coronary Angiography: normal coronary arteries
- Ventriculography: enlarged LV, inferior wall aneurysm with inferior akinesis and LV systolic dysfunction (EF 35%)



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GM 64 yo

Cardiac MRI

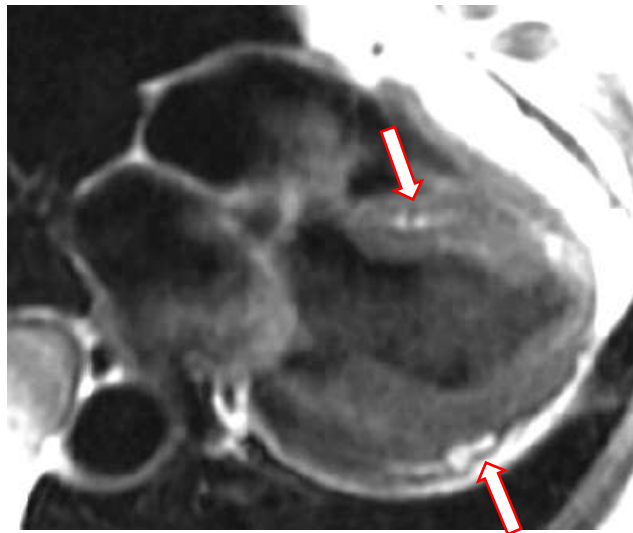


LVEF 36%, primitive hypokinetic dilated cardiomyopathy, LV intramyocardial widespread **fibrosis** (non ischemic pattern) and **adipose tissue metaplasia areas** (inferior and septal wall)

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GM 64 yo

Cardiac MRI



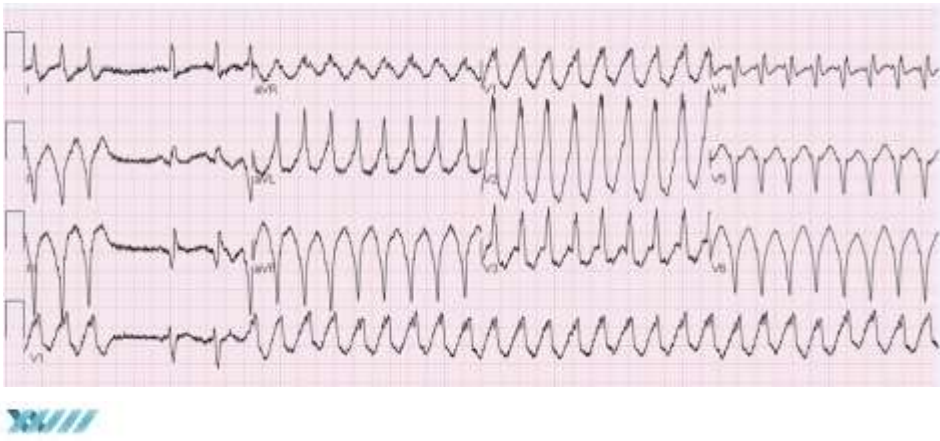
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GM 64 yo

24h HOLTER ECG-MONITORING

Frequent ventricular polymorphic ectopias (>5200), single, couple and hat-trick, also bigeminism.

One episode of NSVT.

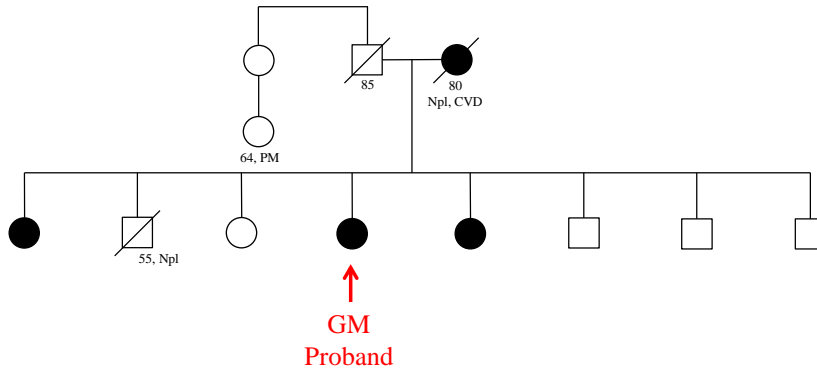


**GM, 64 yo female, precordial pain,
T2DM, dyslipidemia, previous smoker**

- A: Dilated Cardiomyopathy?
- B: Arrhythmogenic Ventricular Cardiomyopathy?
- C: (ongoing) Myocarditis ?

24h

Extended evaluation of the Family Tree



→ Cardiological evaluation + ECG + ECHO

→ Next Generation Sequencing (NGS) analysis of all known genes (n. 113) associated with cardiomyopathies was performed.

GM 64 yo

Next Generation Sequencing (NGS) analysis

Report for mutation **RP_004415.2(DSP)c.1867C>A**

Warning: The report is based on knowledge and data that are not fully established. Consequently, medical decisions must not be made on the basis of this report.

Class 3 - Unknown pathogenicity

Transition from C to A in exon 5.
Reference substitution:
The nt position 2567 is changed to A.

This variant is reported as pathogenic by HGMD - Phenotype: Dilated cardiomyopathy, weakly fac. hereditary. [View in HGMD](#)

This variant is known to ClinVar [AC008412.1](#) | ClinVar significance* - not provided.

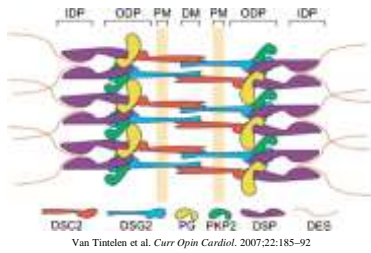
HGVS v2.2 nomenclature

cDNA Level:	RP_004415.2:c.1867C>A
gDNA Level:	(374538337)p.176769C>A
Protein Level:	p.1867S60Y

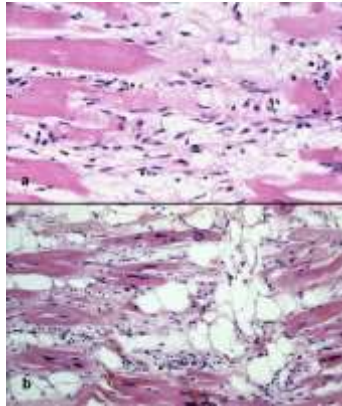
Pathogenicity clues

- Highly conserved nucleotide (PhastP: 6.52 [14, 15, 4])
- Highly conserved amino acid, up to Chicken (conserving 33 species)
- Moderate physicochemical difference between Thr and Leu (Swanther et al., 19 [3-21])
- The variant is in protein domain: SpectrinAlpha-actin
- Age-ONSD: CAS (501 - 500 - 50) - 73.7%
- OP%: Inheritance (score: 5, median: 4.5)
- Multifactor: Disease causing (p-value: 1)

Desmoplakin: normal



Ongoing myocyte death (a) with early fibrosis and adipocytes infiltration (b).



Basso et al. *Cardiovasc Pathol* 2005

Desmoplakin: p.Thr356Lys

Loss of desmosomal integrity can substantially affect gap junctions, sodium channel function and electrical propagation, thereby promoting ventricular arrhythmias



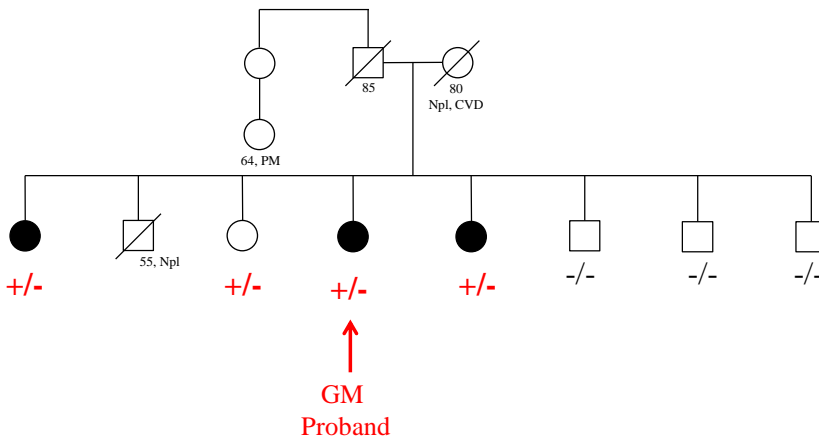
Chronic (and acute) inflammation as a response to myocardial injury



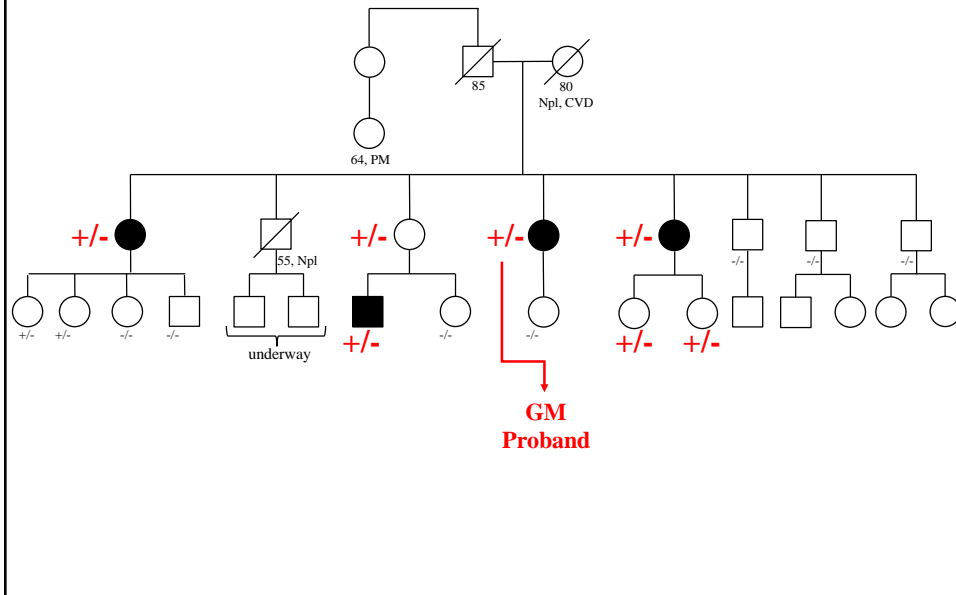
Myocyte cell death may occur via apoptosis or necrosis



Genetic analysis of proband's extended family



Genetic analysis of proband's extended family



GM 64 yo

Key points

- An atypical “acute coronary syndrome-like” manifestation of Left Dominant Arrhythmogenic Cardiomyopathy (LDAC), with arrhythmias of LV origin, lateral T-wave inversion and late gadolinium enhancement in the LV on C-MRI
- In the absence of CAD, inferior-lateral T-wave inversion is often considered a benign condition.
- Chest pain with enzyme release might be attributed to myocarditis.
- We hypothesized that these abnormalities might be manifestations of the "left-dominant" subtype of AC based on C-MRI findings.
- The extended familial screening allowed to identify other three asymptomatic LDAC cases, deserving a careful and regular follow-up

➔ **Final diagnosis:** Autosomal-dominant left-sided arrhythmogenic cardiomyopathy caused by mutation in desmoplakin.

$M_{A(LDAC)} O_H G_{AD} E_{G-DSP(p.Thr356Lys)} S_{BII}$

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Thank you for the attention



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