ESIM 2015 Case Presentation: Eleven years later…

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Case Presentation: Mr J

- ID: 57 yo male, from South Africa in Canada since 1989
- Reason for Visit:
  - Dyspnea on exertion + leg swelling x 3 weeks
- PMHx:
  - Hypertension
  - Depression
- Medication:
  - Amlodipine 5mg PO Daily, Hydrochlorothiazide 12.5mg PO Daily
- Family History
  - No CAD, No DMII, No Malignancy
- Habits:
  - Non-smoker,
  - 1-2 beers/week
  - No illicit drug use

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- History of Presenting Illness
  - Nov 12th
    - Presented with CP and SOB -> worked up for venous thromboembolism (bilateral leg dopplers and V/Q scan) and MI (Ekg and troponins)-> negative.
    - Discharge dx was panic attack-> discharged home with follow-up with family physician
  - Nov 20th
    - 6 day history of worsening dyspnea on exertion-> unable to climb more than 3-4 steps before SOB
    - Associated with palpitations, bilateral leg swelling
    - + weight loss (20 lbs in 6 months)
    - No chest pain, no PND, no orthopnea, no cough, no fever, no sweats, no chills
    - ROS: + diarrhea (liquid 5-8 x/day x 6-9 month on/off for years), crampy abdominal pain on/off x years

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- Physical exam:
  - Gen: No acute distress
  - VS: BP 161/99 Hr 109 (NSR) Oxygen saturation:96% on room air
  - CVS: JVP 7cm ASA with prominent c-v waves, + right parasternal heave

    S1 and S2 normal, III/VI SEM LLSB, no radiation
  - Resp: GAEB, occasional wheezes, no crackles
  - Abdo: Pulsatile liver, liver span 16 cm, no splenomegaly

    + Shifting dullness, + fluid wave
  - Extremities: 2+ pitting edema bilateral lower extremities
  - Skin: no obvious skin changes

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LIVER PROFILE (MGH)				
BILIRUBIN TOTAL	33.6	umol/L	1.7-18.9	H
BILIRUBIN DIRECT	8.6	umol/L	1.7-8.6	
ASPARATE AMINOTRANSFER...	86	U/L	10-37	H
ALANINE AMINOTRANSFERA...	87	U/L	10-40	H
ALKALINE PHOSPHATASE	133	U/L	53-128	H
GAMMA GLUTAMYL TRANSFE...	50	U/L	7-50	
LIPASE	123	U/L	14-45	H
COAG PROFILE (INR/PT/PTT)				
International Normalization Ra...	1.33		0.89-1.11	H
Prothrombin Time	15.6	s	10.7-13.2	H
PARTIAL THROMBOPLASTIN	24.1	s	23.2-31.0	

TROPONIN-I	0.02	ug/L	0.00-0.06	
COMPLETE BLOOD COUNT				
White Blood Cell	9.20	10^9/L	4.80-10.80	
Red Blood Cell	6.60	10^12/L	4.60-6.20	H
Hemoglobin	165	g/L	140-180	
Hematocrit	0.508	L/L	0.420-0.520	
Mean Cell Volume	76.9	fL	82.0-100.0	L
Mean Cell Hemoglobin	25.0	pg/cell	27.0-31.0	L
Mean Cell Hemoglobin Conce...	325	g/L	320-360	
Red Cell Diameter Width	16.9	cV	12.7-16.0	H
Platelet	207	10^9/L	140-440	
Platelet Hematocrit	0.200			
Mean Platelet Volume	11.2	fL	7.4-10.7	H
Platelet Distribution Width	16.4	cV		
Abs. Lymphocyte Automated	1.60	10^9/L	0.80-4.40	
Abs. Monocyte Automated	0.90	10^9/L	0.08-0.88	H
Abs. Neutrophil Automated	6.50	10^9/L	1.60-7.70	
Abs. Eosinophil Automated	0.20	10^9/L	0.00-0.50	
Abs. Basophil Automated	0.00	10^9/L	0.00-0.22	
Abs. Nucleated RBC Auto	0.18	10^9/L		
CHEMISTRY PROFILE 7				
SODIUM	142	Millimol...	136-147	
POTASSIUM	4.7	Millimol...	3.5-5.0	
CHLORIDE	112	Millimol...	97-109	H
Bicarbonate Level	19	Millimol...	22-27	L
Anion Gap	11	Millimol...	10-15	
GLUCOSE RANDOM	4.8	Millimol...	3.9-11.0	
UREA	5.1	Millimol...	2.1-7.5	
CREATININE	130	umol/L	55-110	H

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- dDx Right sided heart failure
  - Left-sided heart failure.
  - Right ventricle myocardial infarction
  - Primary tricuspid regurgitation
  - Mitral stenosis or regurgitation.
  - Stenosis of the pulmonic valve or pulmonary artery
  - Primary pulmonary disease – cor pulmonale, pulmonary embolism, pulmonary hypertension of any cause.
  - Left to right shunt – atrial septal defect, ventricular septal defect, anomalous pulmonary venous return..
  - Hyperthyroidism

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- Cardiac Echo:
  - 1. Degenerative changes of the aortic and mitral valves with mild aortic and mitral regurgitation.
  - 2. Normal left sided chamber dimensions. **The ventricular septum is paradoxic consistent with a right sided volume overload. The remaining walls contract normally and global LV systolic function is normal with an estimated LV EF of 55-60%.**
  - 3. Right sided chamber enlargement with preserved right ventricular systolic function.
  - 4. The **tricuspid valve leaflets are thickened** with significant restriction in motion and incomplete closure in systole. There is **severe tricuspid regurgitation.**
  - 5. The **pulmonic valve is thickened** with peak/mean systolic gradients of 13/6mmHg and mild pulmonic regurgitation (not clinically significant).
  - 6. Normal right ventricular systolic pressure estimated at 36mmHg (RAP=8mmHg).
  - 7. Trivial posterior pericardial effusion.

Case presentation: Mr J

- Causes of primary TR include:
  - Ischemic heart disease affecting the right ventricle with papillary muscle dysfunction or rupture
  - Infective endocarditis.
  - Rheumatic fever
  - Myxomatous degeneration associated with tricuspid valve prolapse
  - Connective tissue disorder (eg, Marfan syndrome)
  - Marantic endocarditis in systemic lupus erythematosus or rheumatoid arthritis.
  - Chest trauma.
  - Drug-induced disease-> anorectic drugs

Case Presentation Mr J

- Abdominal US
  - **Multiple hyperechoeic nodular lesions** in the bilateral liver lobes.
  - **Number of the lesions are significantly increased as compared to previous ultrasound study of May 2000.**
  - In view of interval increase in the number of echogenic lesions in the hepatic parenchyma, possibility of metastatic lesions appears.
  - The **thickened bowel loop in the right lower quadrant** needs to be further evaluated by contrast enhanced CT scan with triple phase CT for liver lesions.
  - Moderate ascites

Case Presentation: Mr J

- Right sided heart failure
- Chronic diarrhea
- Liver lesions (present for at least 10 years)
- Bowel lesion

?

Carcinoid Tumors

- Rare neuroendocrine malignancies arising from neural crest cells.
- 90% of all carcinoid tumours are located in the gastrointestinal system
- The most malignant of the carcinoid tumours tend to arise from the ileum and must be invasive or metastasise to produce the carcinoid syndrome
- Carcinoid syndrome is characterised by facial flushing, intractable secretory diarrhoea, and bronchoconstriction.
- Many carcinoid tumours are slow growing and follow a prolonged course of up to 20 or more years from the development of the carcinoid symptoms

Carcinoid symptoms and their putative mediators

Organ	Symptom	Frequency (%)	Putative mediator
Skin	Flushing	85	Kinins, histamine, kallikreins, other
	Telangiectasia	25	
	Cyanosis	18	
	Pellagra	7	Excess tryptophan metabolism
Gastrointestinal tract	Diarrhea and cramping	75 to 85	Serotonin
Heart	Valvular lesions		Serotonin
	Right heart	40	
	Left heart	13	
Respiratory tract	Bronchoconstriction	19	Unknown

Carcinoid Heart Disease

- Once the carcinoid syndrome has developed, approximately 50% of these patients develop carcinoid heart disease
- The cardiac manifestations are caused by the effects of vasoactive substances released by the malignant cells rather than any direct metastatic involvement of the heart.
- Usually, the vasoactive products are inactivated by the liver, lungs, and brain, but the presence of hepatic metastases may allow large quantities of these substances to reach the right side of the heart without being inactivated by the liver.

Carcinoid Heart Disease

- The characteristic pathological findings are endocardial plaques of fibrous tissue that result in distortion of the valves leading to either stenosis, regurgitation, or both.
- The preferential right heart involvement is most likely related to inactivation of the vasoactive substances by the lungs

Carcinoid Workup

Biochemical

- 24 hour urinary 5-HIAA
  - High sensitivity and high specificity
  - Requires strict avoidance of foods containing serotonin and tryptophan as well as certain drugs for three days prior to the urine collection
- Chromogranin A
  - Proteins that are stored and released in a variety of neuroendocrine tissues.
  - Not recommended as a screening test for carcinoid (not specific)
  - Tumor marker to assess disease progression, response to therapy, or recurrence after surgical resection.
- Other hormones
  - Gastrin, glucagon, insulin, adrenocorticotropic hormone (ACTH), parathyroid hormone, and calcitonin.

Tumor localization

- CT abdo
- Octreoscan
  - Many carcinoid tumors express high levels of somatostatin receptors and can therefore be imaged with a radiolabeled form of the somatostatin analog octreotide (111-indium pentetreotide)

Management

- In the early non-metastatic phase
  - Surgical resection of the carcinoid tumour can be curative.
- In those with the carcinoid syndrome and carcinoid heart treatment tends to be palliative
  - Without treatment, the median duration of survival is 12 to 38 months from the onset of systemic symptoms
  - Symptom control usually with a somatostatin analog
    - Octreotide is an eight amino acid peptide that, by binding to somatostatin receptors, has the direct effect of reducing the vasoactive peptides that provoke the carcinoid syndrome
  - Can consider debulking the tumour, and sometimes, in those with hepatic metastases, by hepatic artery ligation or embolisation.
  - Cardiac surgery (tricuspid valve replacement)
    - Should be considered for symptomatic patients whose metastatic carcinoid disease and symptoms of carcinoid syndrome are well controlled.
    - Indications: impaired exercise capacity, progressive fatigue, and progressive decline in ventricular function in the presence of controlled metastatic carcinoid disease

Back to Mr J

5 HIAA 24 H URINE	70	umol/d	0-50	H
CHROMOGRANIN A	>3084.0	Nanogr...	<=180.0	H

LIVER, BIOPSY:
- WELL-DIFFERENTIATED NEUROENDOCRINE TUMOR, MOST CONSISTENT WITH METASTASIS. SEE COMMENT.
- REMAINING NON-NEOPLASTIC LIVER SHOWS CENTRILOBULAR CHOLESTASIS AND SINUSOIDAL CONGESTION AND DILATATION CONSISTENT WITH RIGHT HEART FAILUREBUT NO STEATOSIS OR FIBROSIS .
- STAINABLE IRON IS ABSENT AND THERE ARE NO PAS-D POSITIVE GLOBULES.

- Octreotide scan :
  - There are multiple foci of uptake of different sizes and different intensities involving the right and left lobes of the liver.
  - There is a large focus of intense uptake with lobulated contour involving the ascending colon
- Started on octreotide and diuretics
- Symptoms well controlled x 4 years

Carcinoid heart disease: key points

- Carcinoid tumours are rare neuroendocrine malignancies mostly arising within the gastrointestinal system, particularly the ileum and appendix
- The carcinoid syndrome, characterised by cutaneous flushing, secretory diarrhoea, and bronchospasm, occurs secondary to vasoactive tumour products such as serotonin and only occurs in the presence of metastatic spread
- Elevated 24 hour urinary excretion of 5-hydroxyindole acetic acid (5-HIAA), an end product of serotonin metabolism, is a key diagnostic finding
- Carcinoid heart disease occurs in approximately 50% of patients with the carcinoid syndrome and usually indicates a worsening prognosis. The majority of patients with carcinoid heart disease develop right heart failure secondary to caused by dysfunction of the tricuspid and pulmonary valves
- Palliation of symptoms and prolonged survival can be achieved with appropriate medical treatment and valvular surgery in selected patients with carcinoid heart disease

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