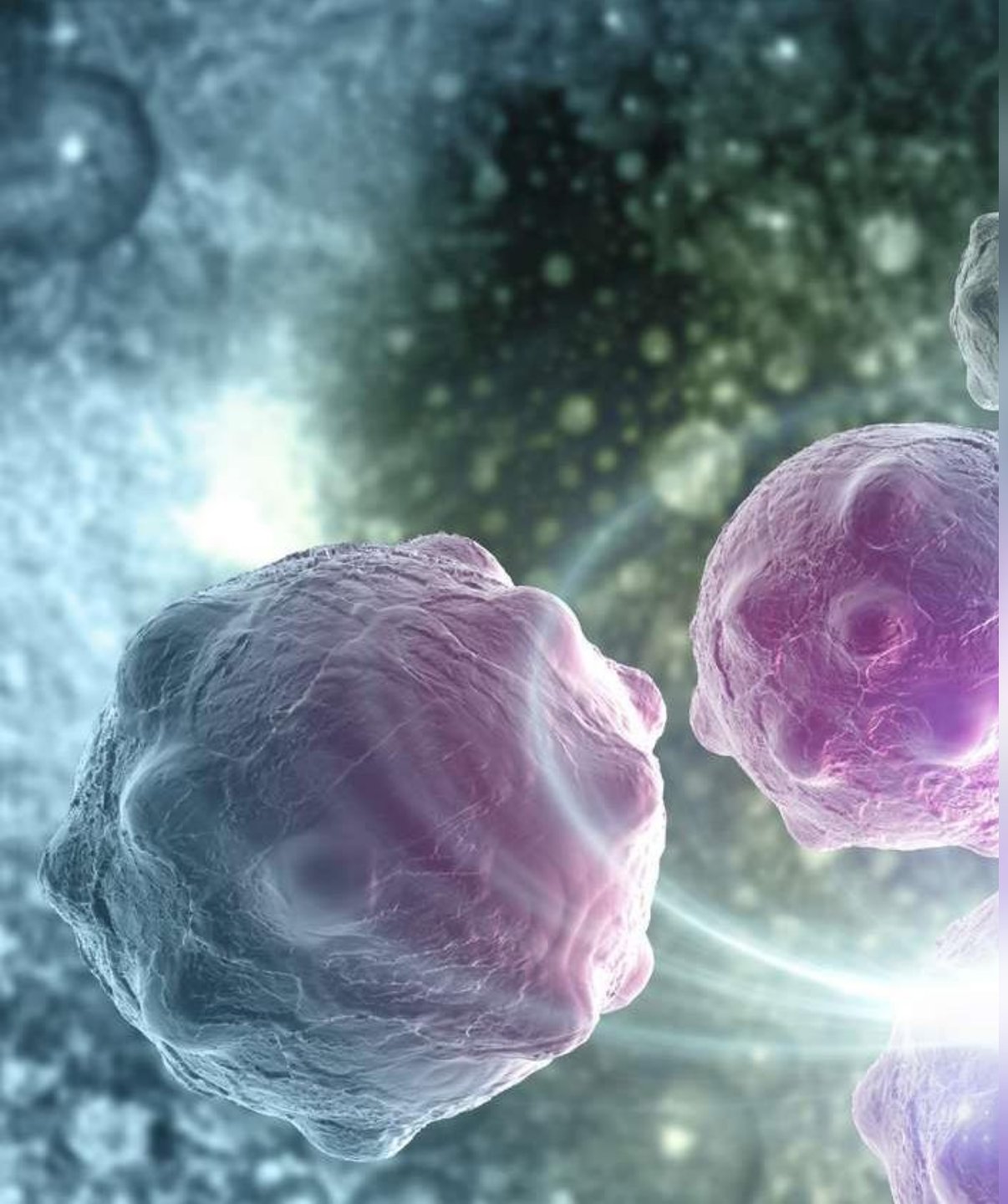
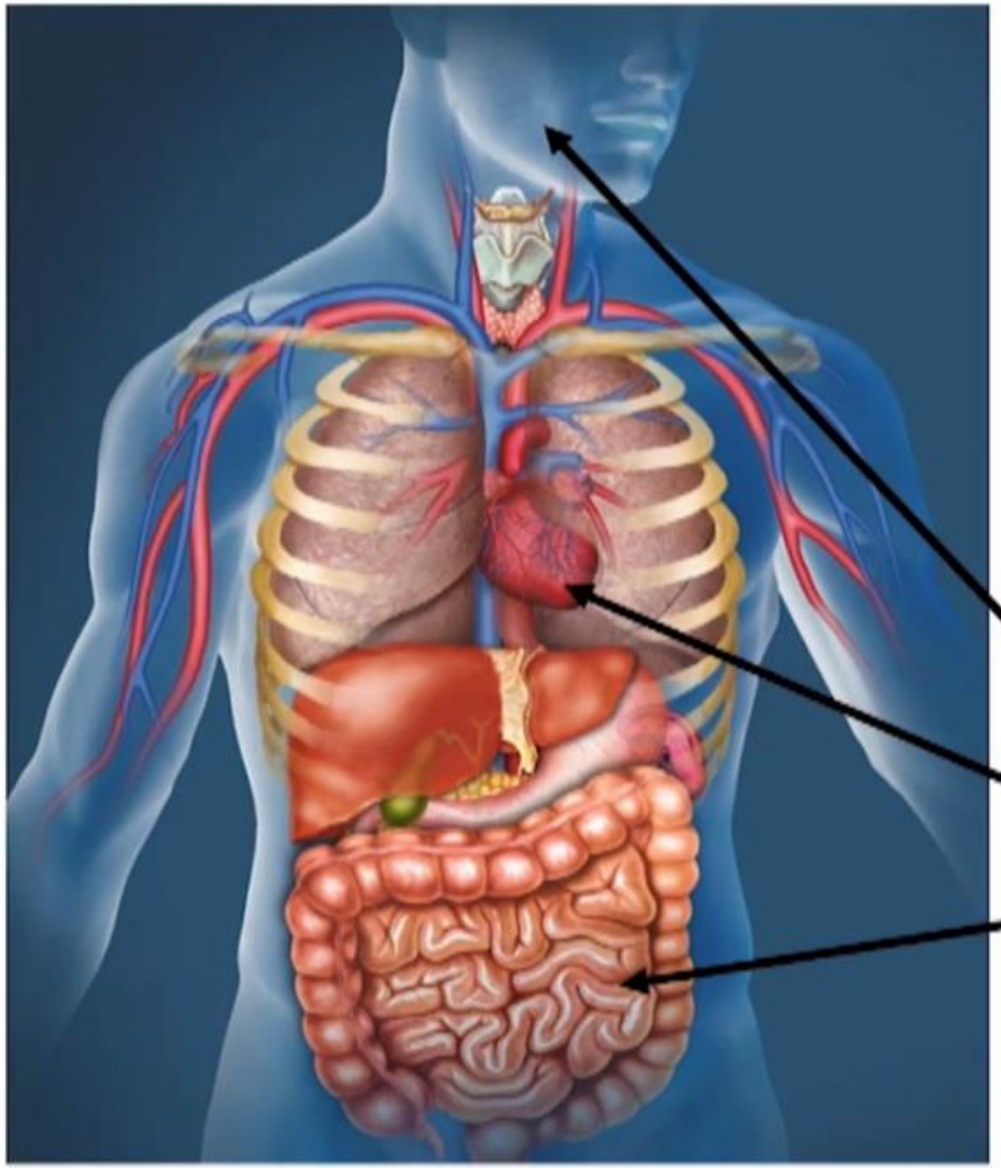


CARCINIOD HEART DISEASE

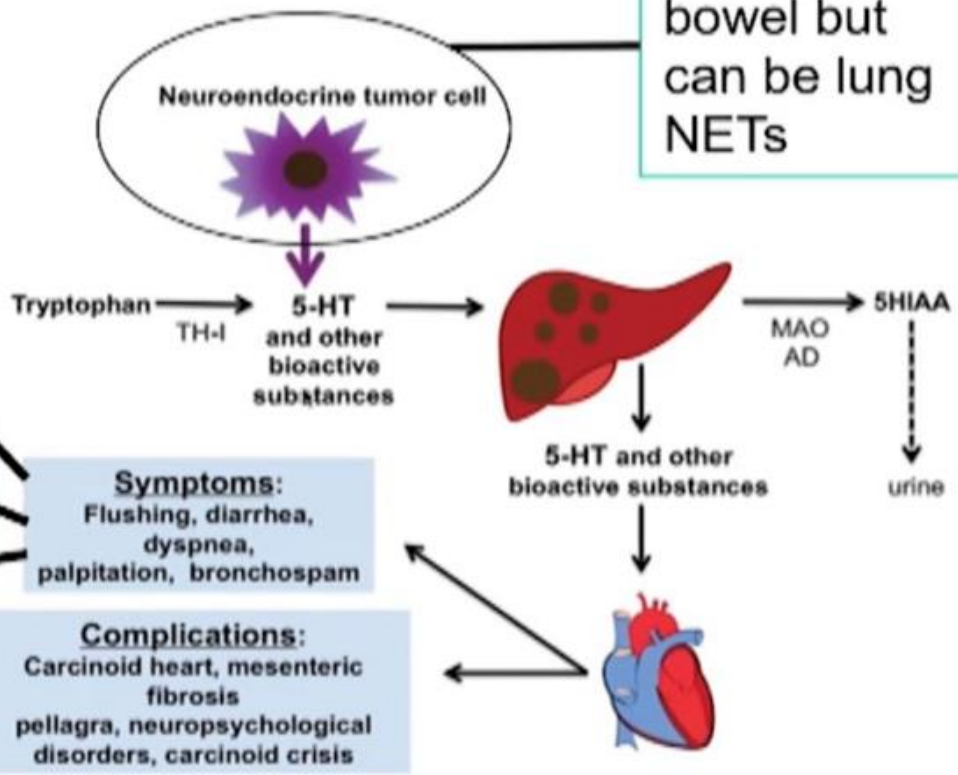
November 2023

‘Carcinoid Syndrome’



Serotonin receptors in gut and heart valves

Most in the bowel but can be lung NETs



Abbreviations: 5-HT: serotonin; TH-I: tryptophan hydroxilase I; MAO: monoamine oxidase; AD: aldehyde dehydrogenase

ocrine

CARCINOID TUMOR

Siegfried Oberndorfer
(1876 – 1944)
German pathologist

In 1907, Siegfried Oberndorfer coined the term ***Karzinoide***
(based on *καρκινώδης* , later anglicized as carcinoid)

Karzinoide Tumoren des Dünndarmes.
[Carcinoid tumors of the small intestine]
Frankfurter Zeitschrift für Pathologie
1907;1:426-429.

Carcinoid = 'carcinoma like'

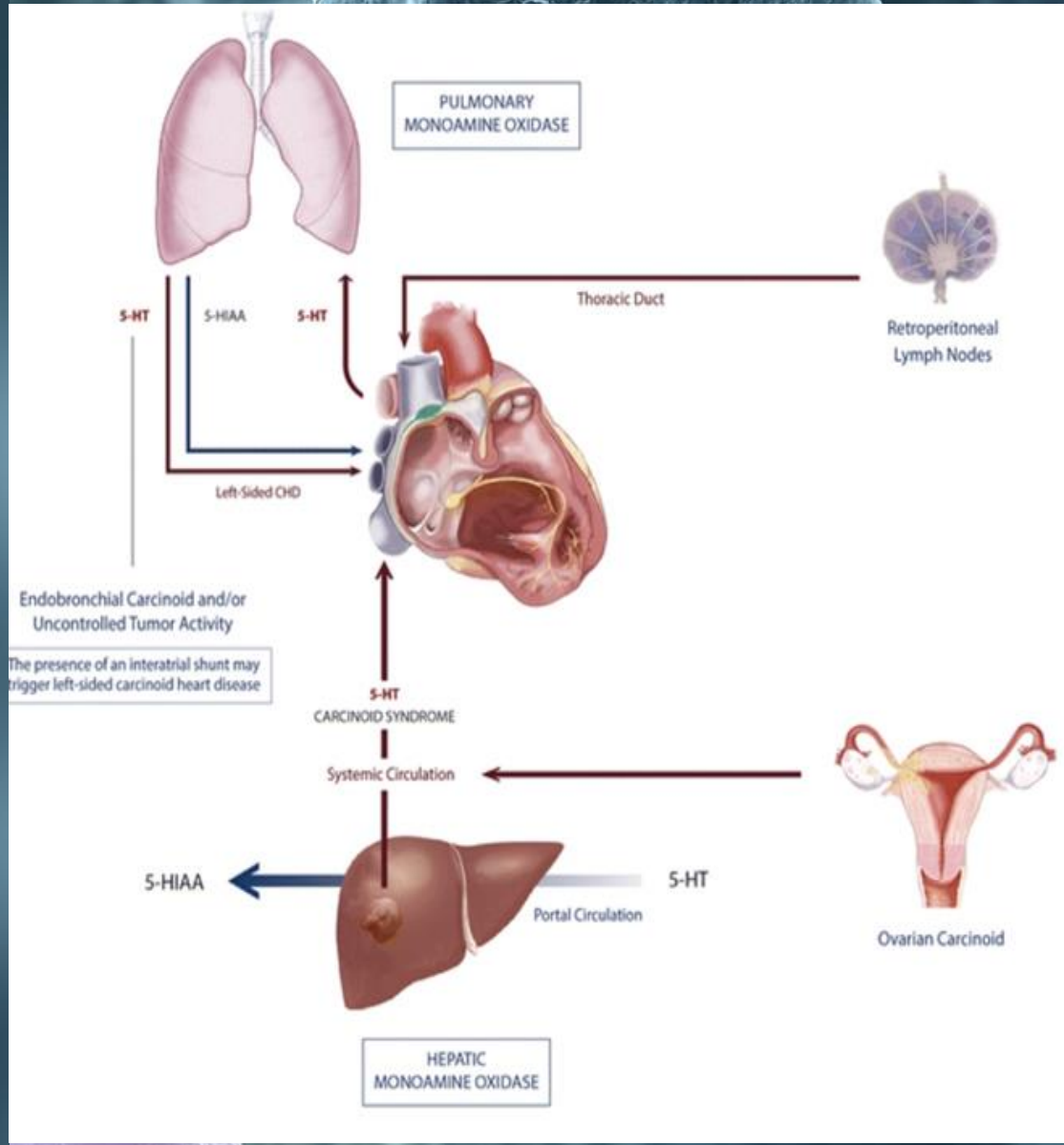
Histologically, a malignant tumor…

… but clinically often behaves like a benign nonmetastatic tumor

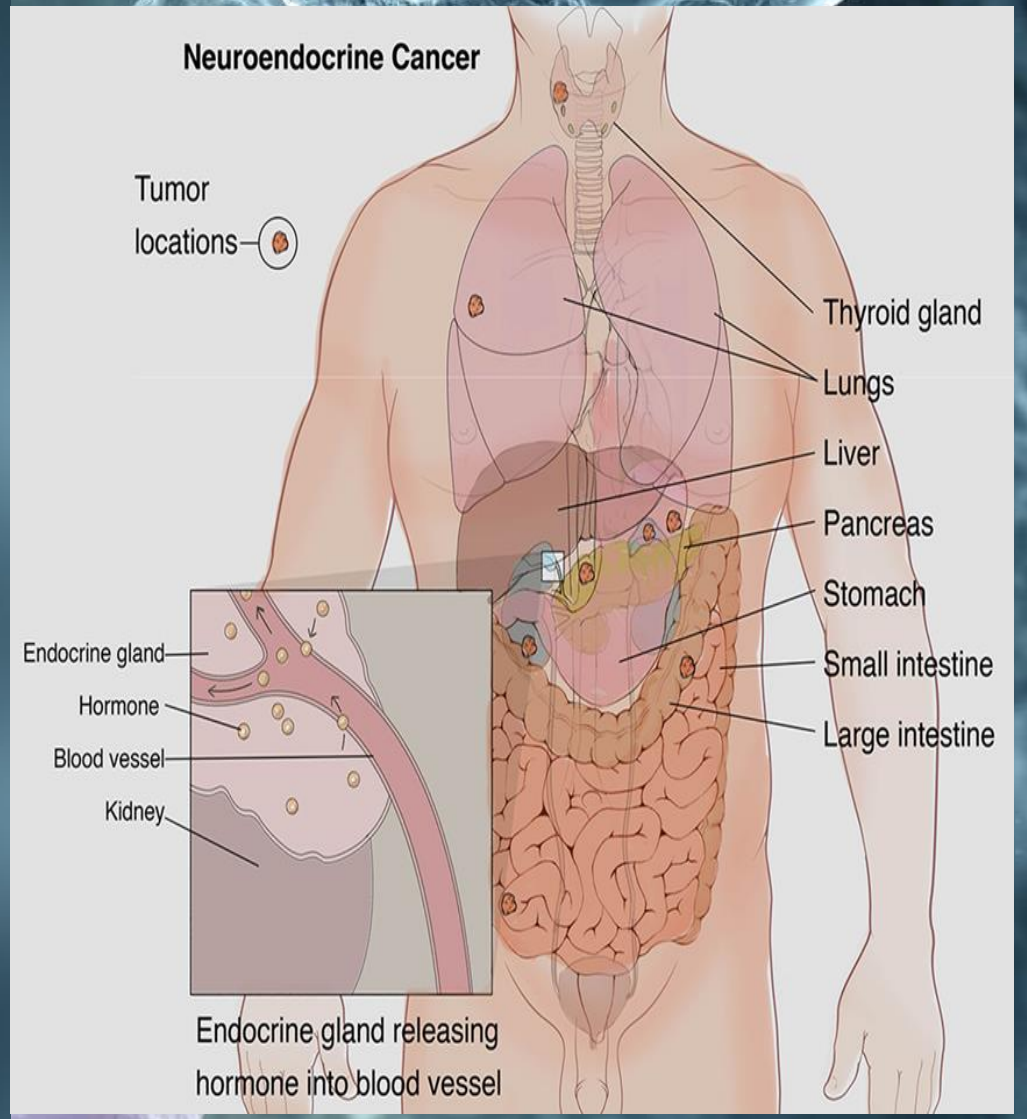
Neuroendocrine Tumors

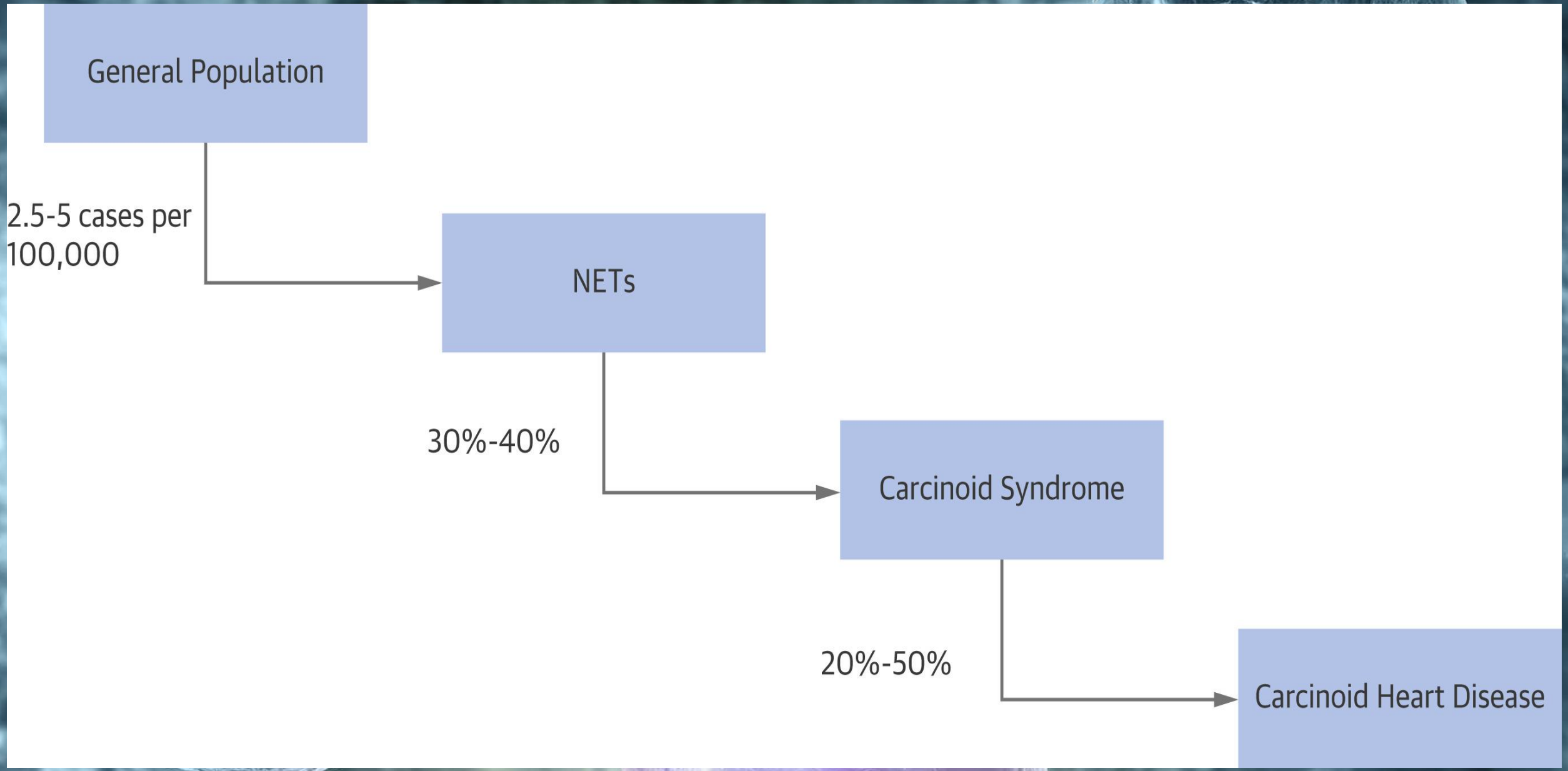
- **Carcinoid** commonly refers to **neuroendocrine tumors** that originate in the:
- GI tract
- Lungs
- Appendix and thymus
- Although they can also occur in the:

lymph nodes, brain, bone, gonads (ovaries and testes) and skin

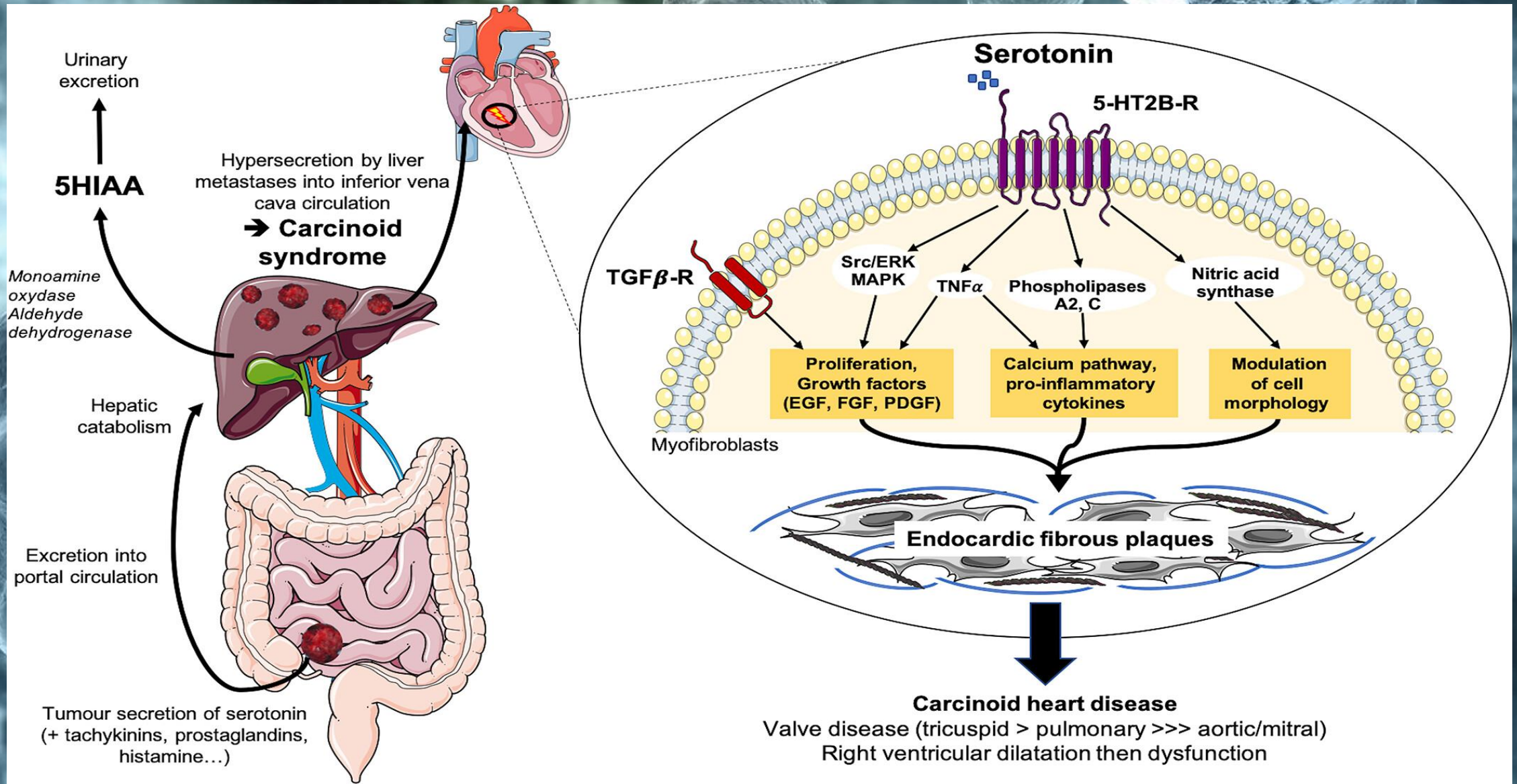


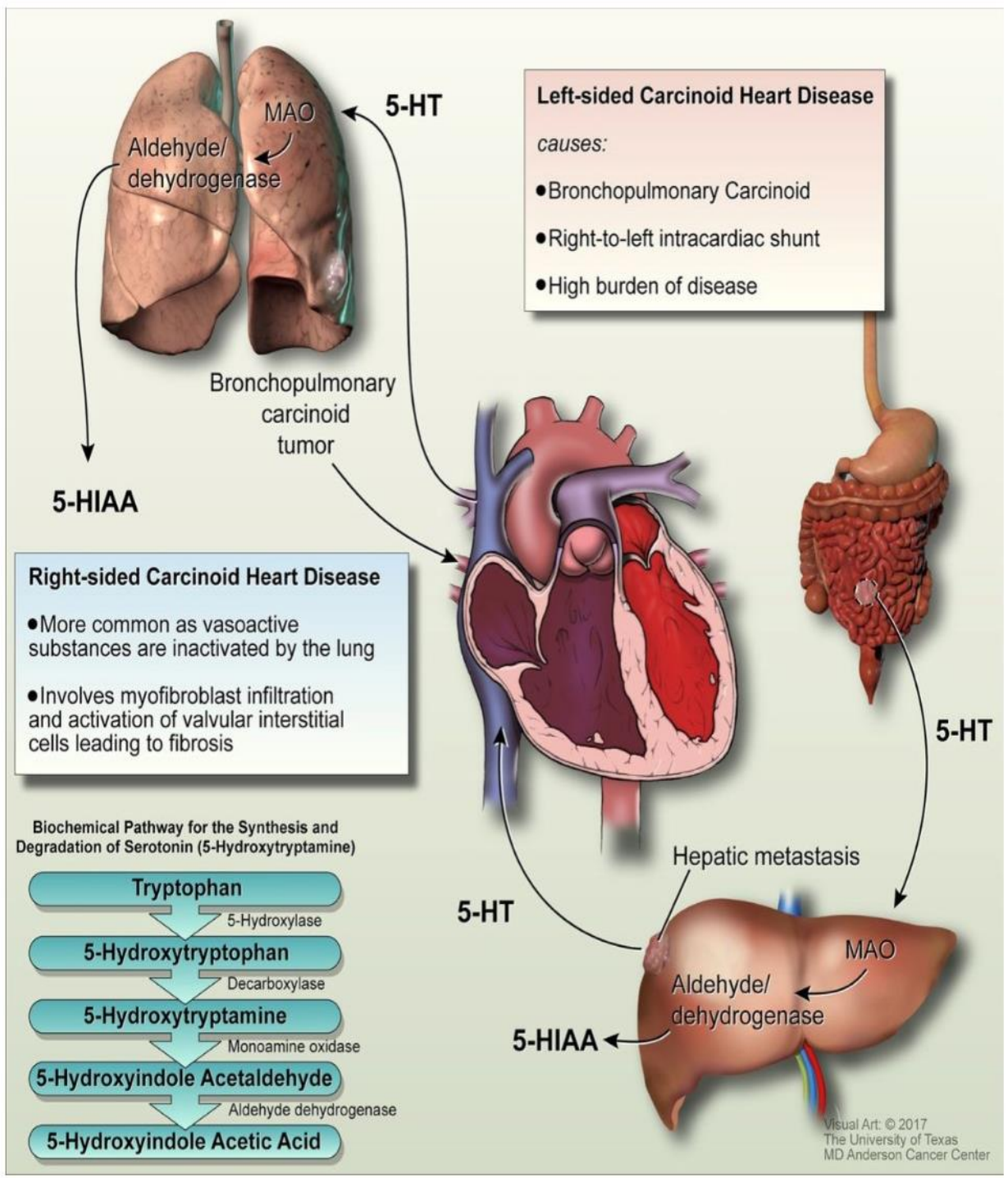
- 30% to 40% of subjects with NETs develop **carcinoid syndrome (CS),** mostly in subjects **with liver metastases.**
- **Approximately 5% of subjects with ovary, lung, or retroperitoneal metastases manifest with CS without having metastases to the liver.**
- 20% to 50% of subjects with CS are diagnosed with **carcinoid heart disease (CaHD or CHD).**
- CaHD is also called **Hedinger's disease (syndrome)**



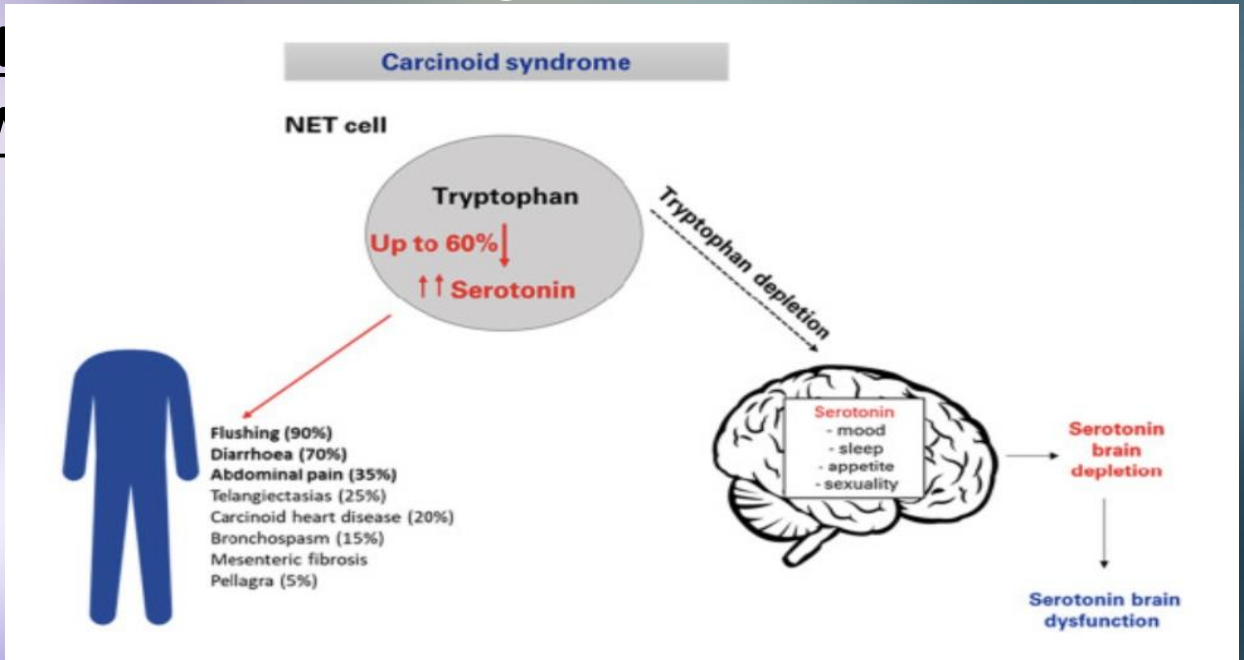

General Population
2.5-5 cases per 100,000
NETs
30%-40%
Carcinoid Syndrome
20%-50%
Carcinoid Heart Disease

Normal results are 2 to 9 milligrams (mg) of 5-HIAA over 24 hours. Women generally have lower levels than men.





Heart valve disease and pulmonary hypertension, in pts with carcinoid tumors and people who used the fenfluramine-phentermine combination for weight control, have been associated with high levels of serotonin in blood. The mechanism by which serotonin i
v



Hypothesis

- Serotonin induces oxidative stress in human heart valves, and may increase reactive oxygen species.

- A nonspecific inhibitor of flavin-oxidases (diphenyliodonium), or inhibitors of monoamine oxidase [MAO (tranylcypromine and clorgyline)], prevented the serotonin-induced increase in $O_2^{\cdot -}$.

- Dopamine, another MAO substrate that is increased in patients with carcinoid syndrome, also increased $O_2^{\cdot -}$ levels in heart valves, and this effect was attenuated by clorgyline.

Cases

Case 1

Case 2

Case 3

CASE 1

- A 62 years old women experienced a progressive increase in bowel movement in the past 6 months, presenting with up to eight stools per day prior to the admission.

- The patient had undergone several gastroenterology consultations, but no organic cause of the accelerated bowel movement had been identified.

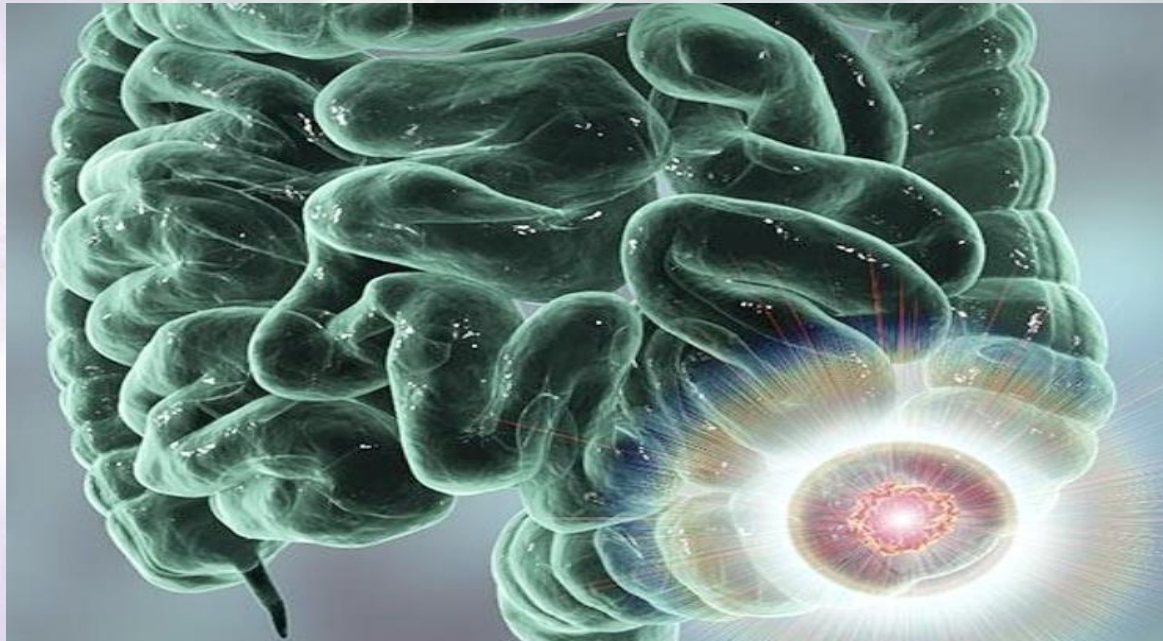
- She started to experience shortness of breath and fatigue at progressively lower levels of exercise and had lost around 25 kg.

Physical exam

- Normal blood pressure (130/80 mmHg) and heart rate (80/min)
- Tricuspid regurgitation (TR) murmur, a loud P2
- Slightly decreased blood oxygen saturation (93% in room air)
- Skin flushing around the cheekbones and the upper torso
- Hepatomegaly (4 cm below the costal margin)

PARACLINIC FINDINGS

- ECG ---→ LBBB with no other remarkable features
- Mild rise of AST & ALT , slightly raised serum creatinine levels, and elevated NT-pro-BNP were found
- The chest X-ray was within limits.

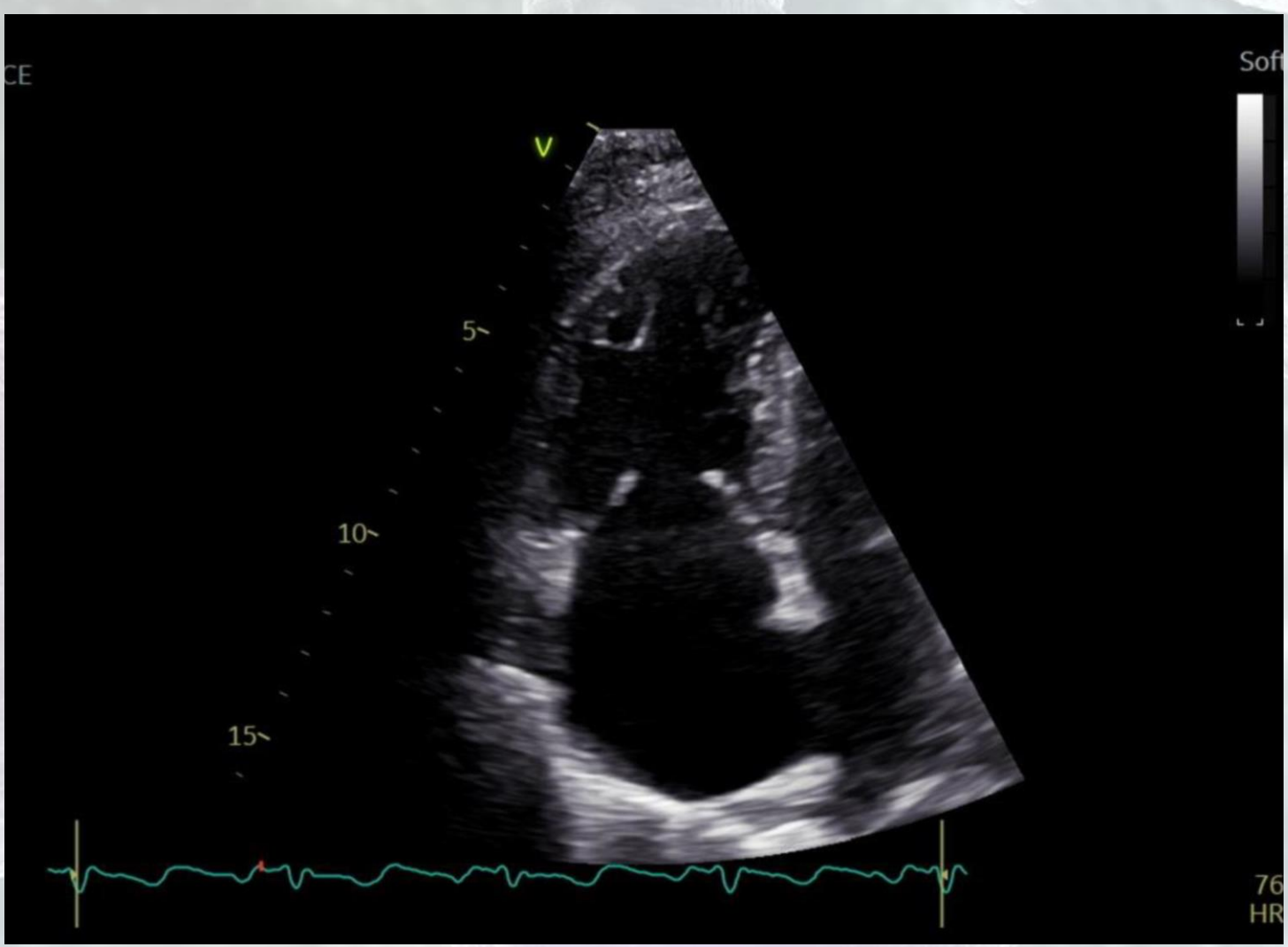


ECHOCARDIOGRAPHY (TTE)

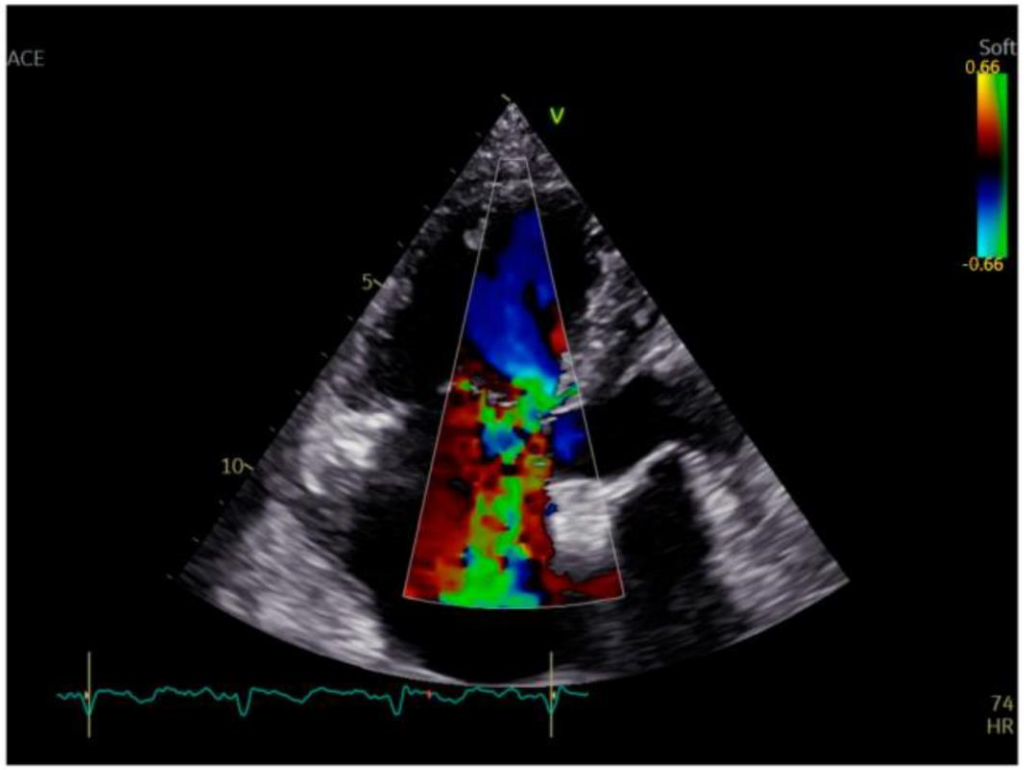
- Retracted and thickened tricuspid valve (TV) with reduced mobility during both opening and closure , severe TR (vena contracta = 18 mm), moderate TS , dilated right heart chambers with preserved systolic function, moderate pulmonary regurgitation, and mild pericardial effusion.

- The insertion of the septal leaflet of the tricuspid valve was identified as being below the insertion of the mitral valve (7.5 mm/m^2) suspicious for Ebstein like anomaly [not fulfilling the Ebstein anomaly criteria ($\geq$8 mm/m^2)].

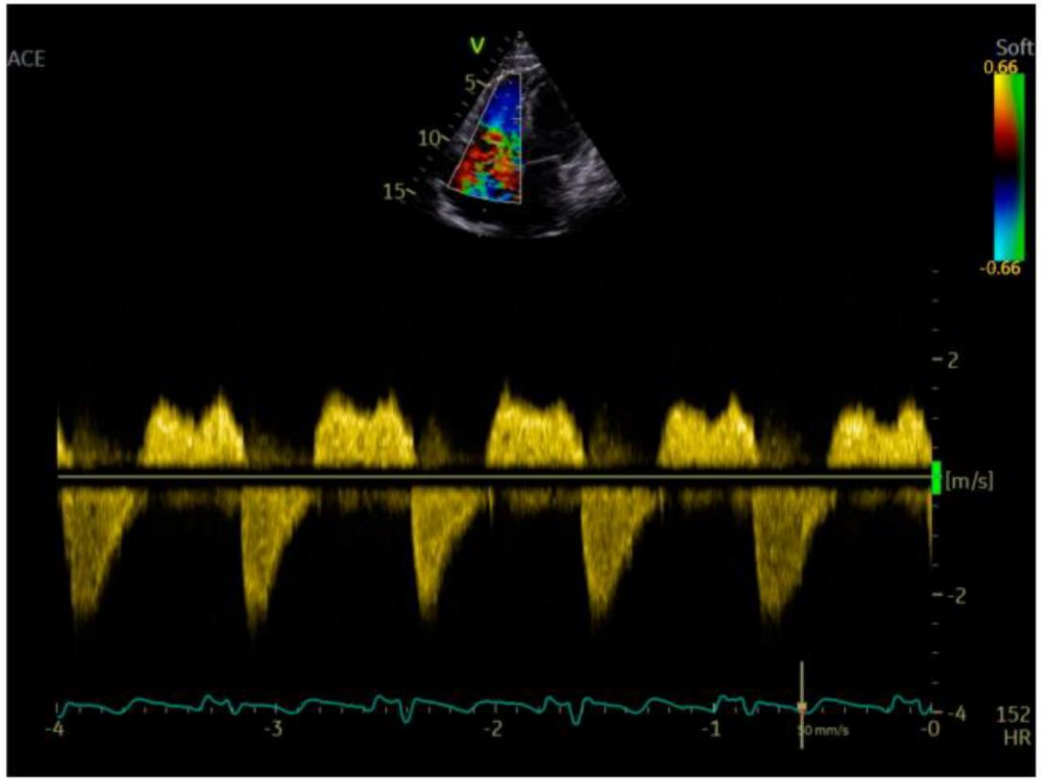
Retracted and thickened tricuspid valve with reduced mobility in our case



(a) Severe tricuspid regurgitation; (b) Severe tricuspid regurgitation and moderate tricuspid stenosis

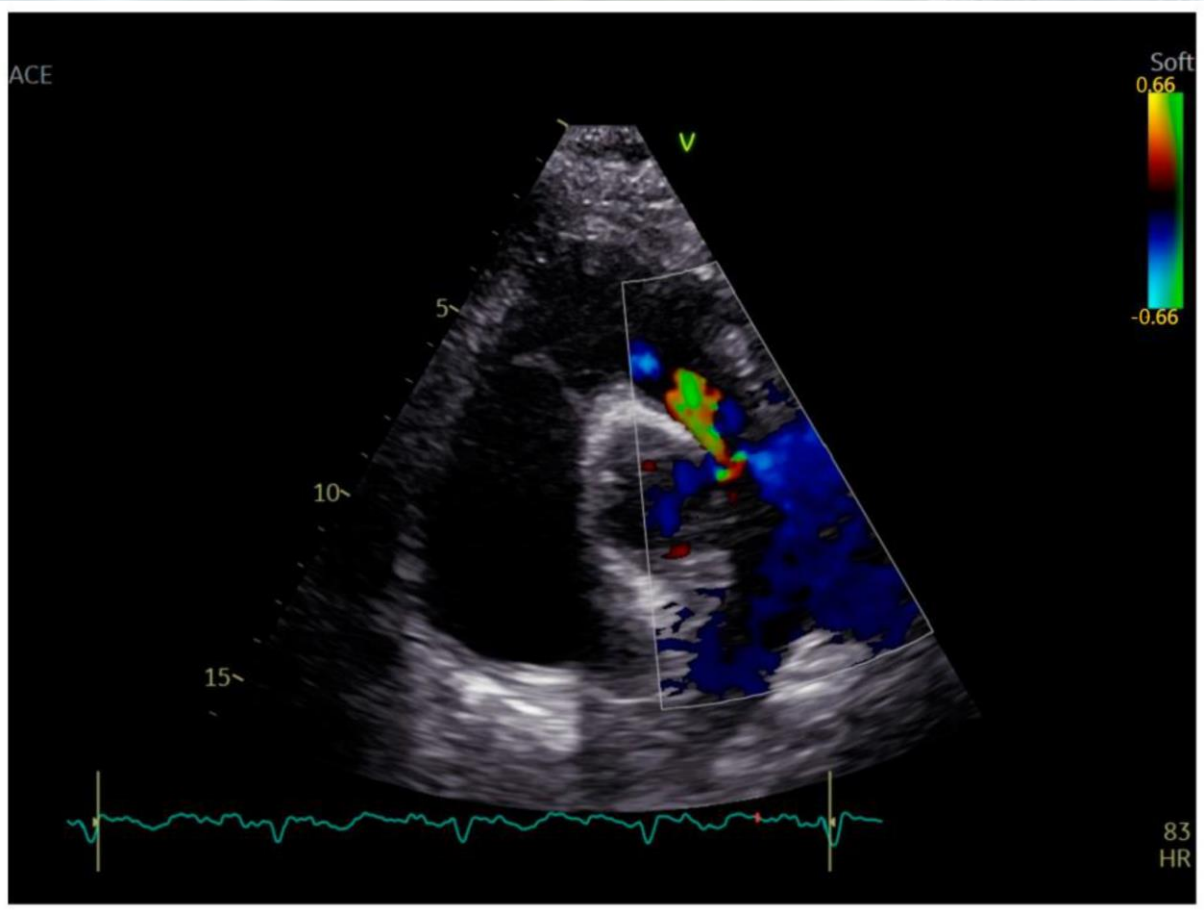


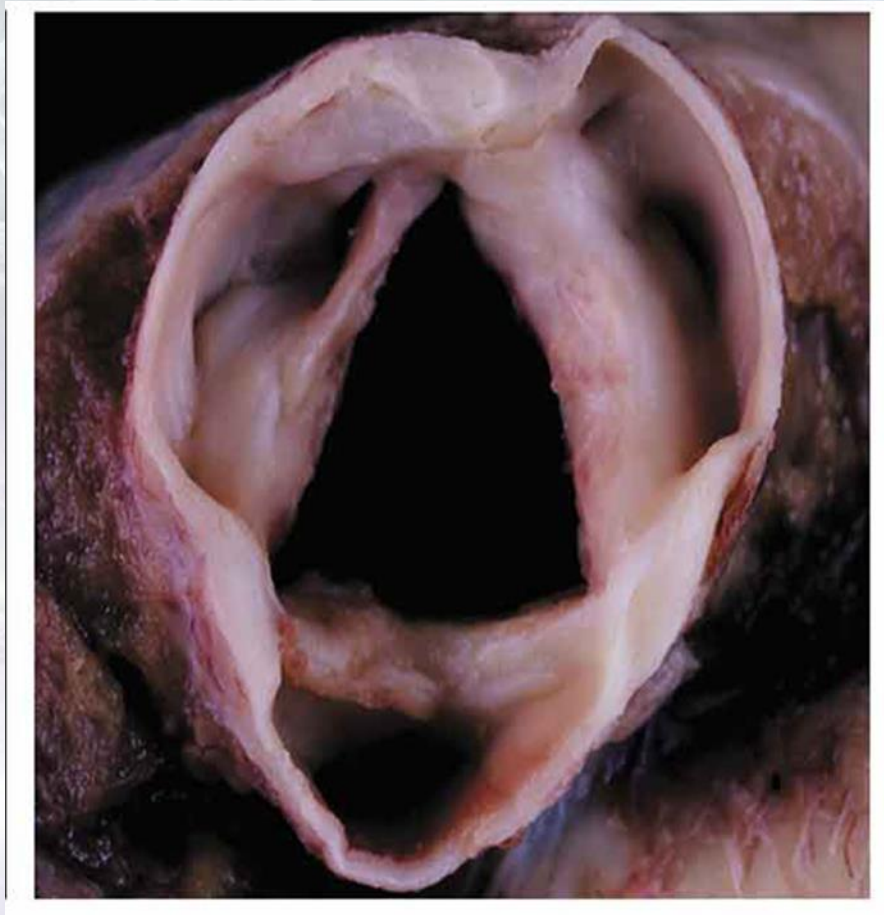
(a)



(b)

Moderate pulmonary regurgitation

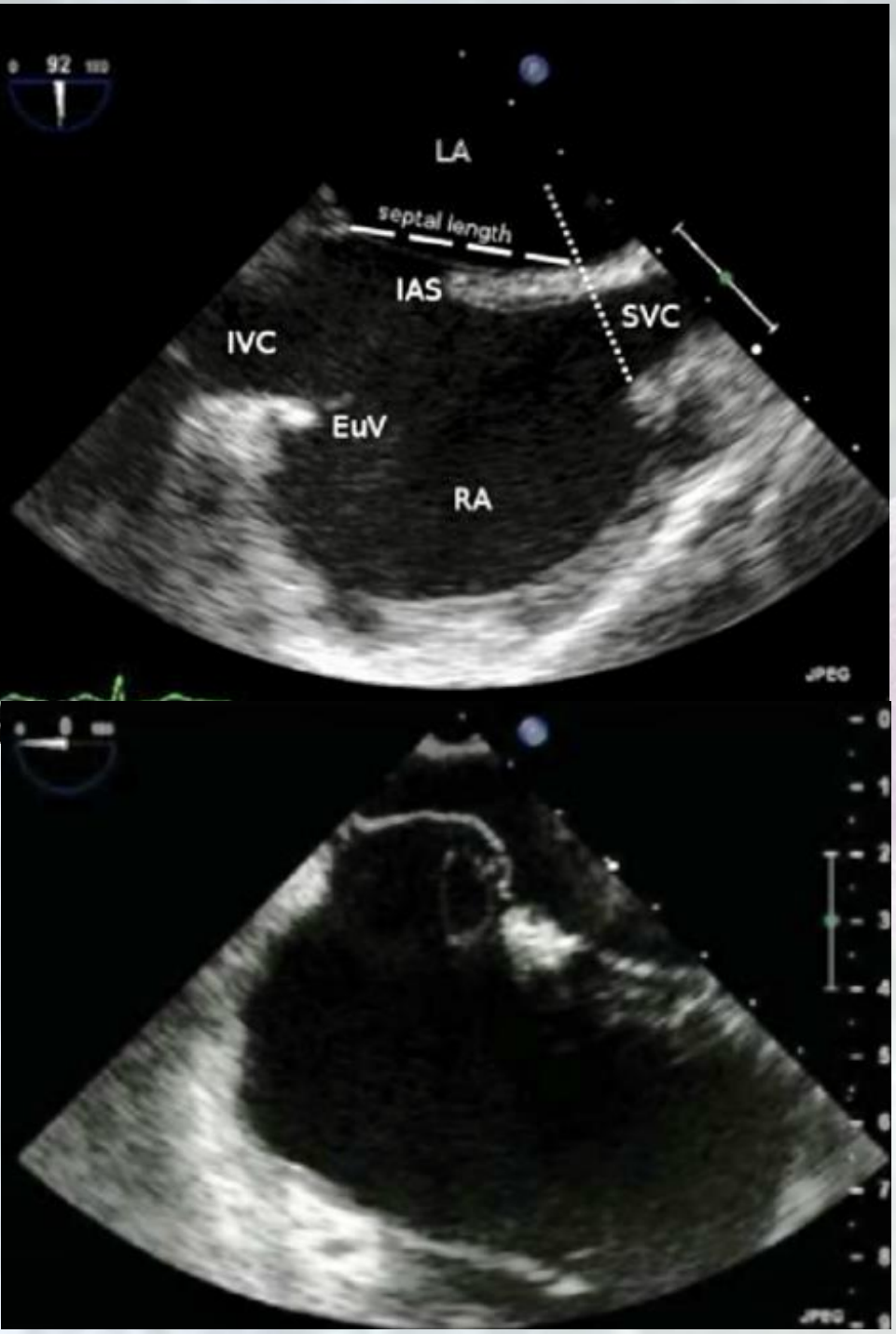


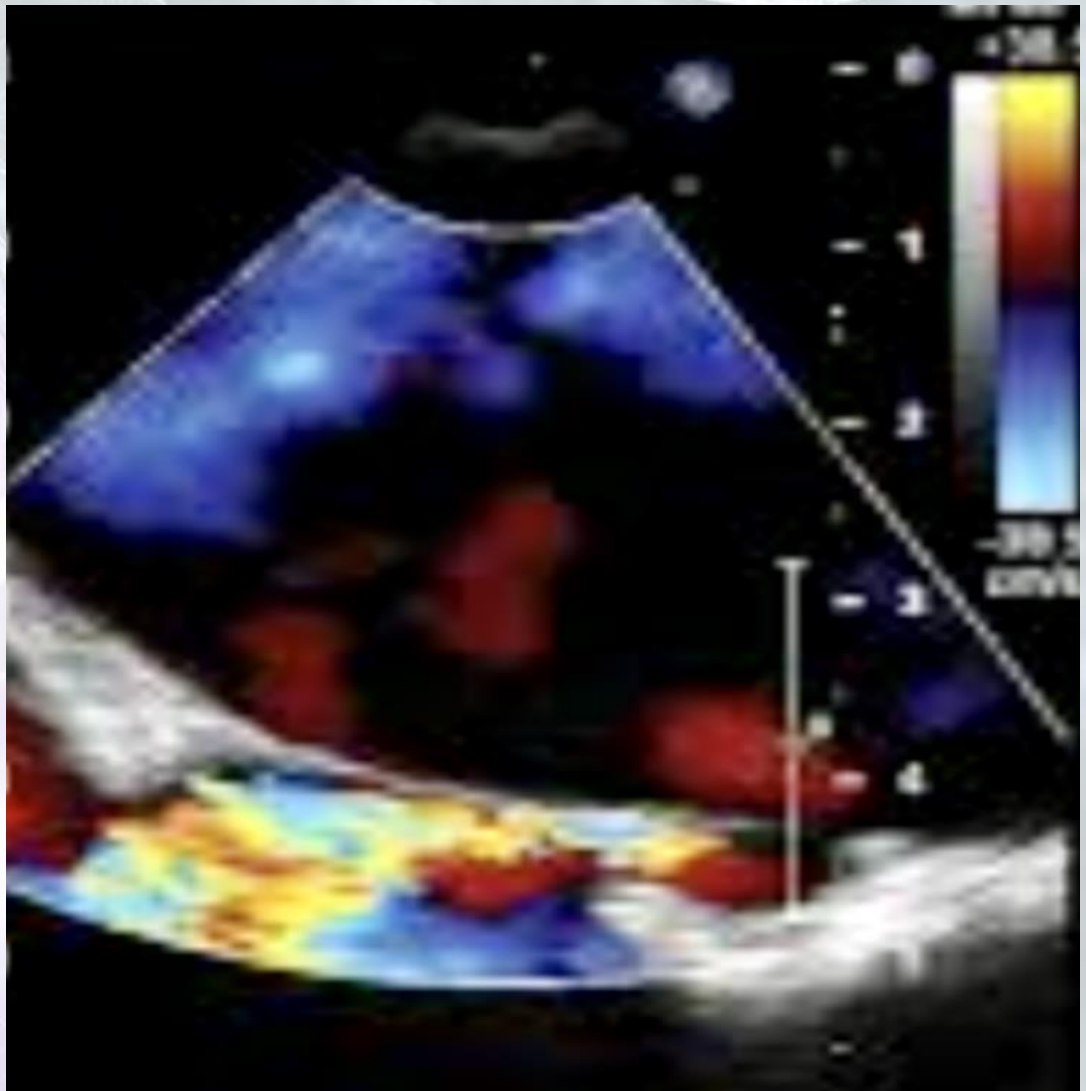


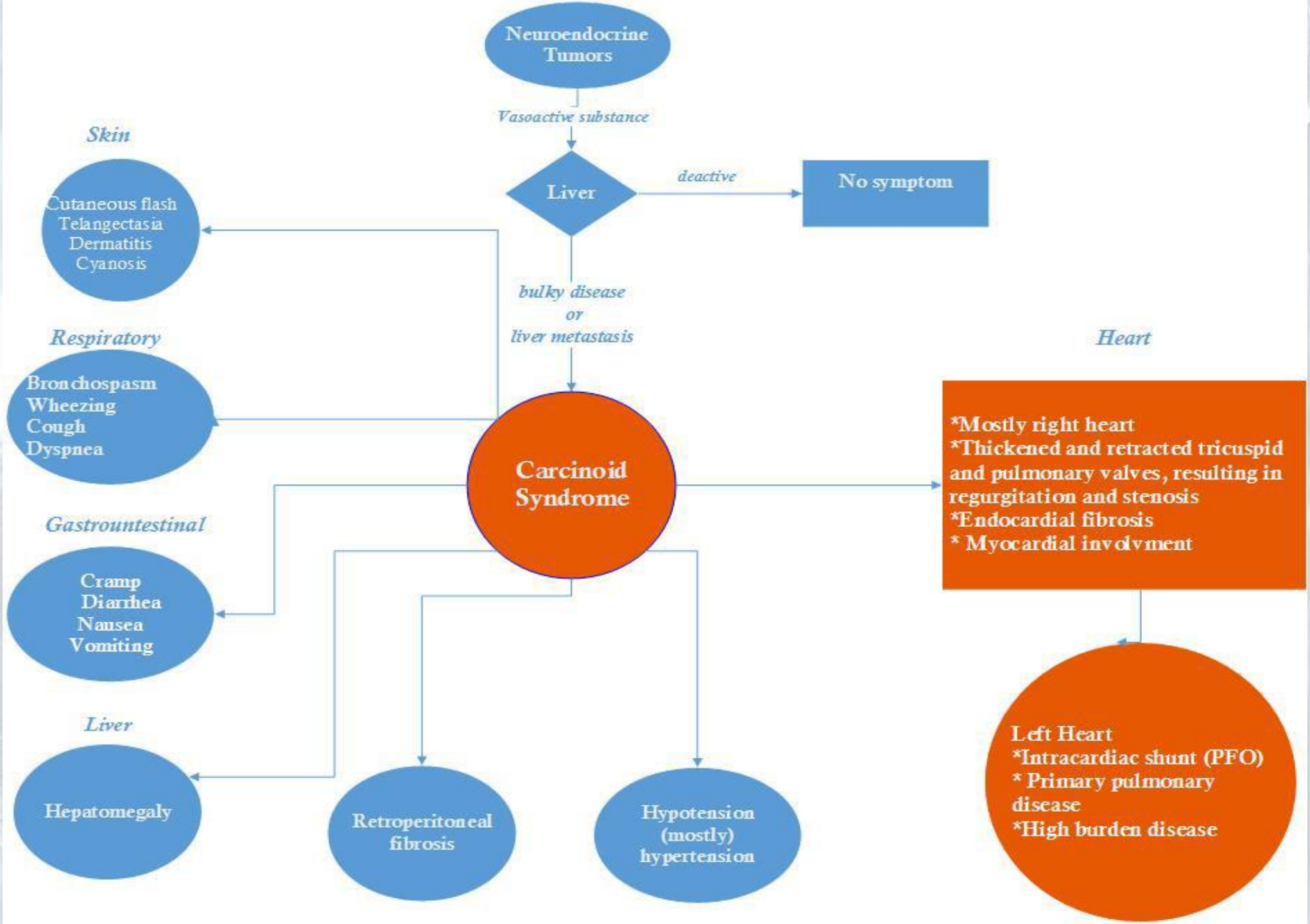
Transesophageal Echocardiography (TEE)

- It confirmed the structural abnormalities described by TTE and the previous measurements.
- Better showed the infiltrated aspect of the tricuspid and pulmonary valves and their restricted mobility, which, when integrated with the patient history and the physical examination findings, indicated carcinoid syndrome.
- Also observed a patent foramen ovale and not an ostium secundum atrial septal defect, as well as a restrictive sub-aortic ventricular septal defect.
- A cardiac MRI also reaffirmed the TEE findings.

Large Stretched PFO in our case






Neuroendocrine Tumors
Vasoactive substance
Liver
deactive
No symptom
Skin
Cutaneous flash
Telangectasia
Dermatitis
Cyanosis
bulky disease
or
liver metastasis
Respiratory
Bronchospasm
Wheezing
Cough
Dyspnea
Heart
Carcinoid Syndrome
*Mostly right heart
*Thickened and retracted tricuspid and pulmonary valves, resulting in regurgitation and stenosis
*Endocardial fibrosis
* Myocardial involvment
Gastrountestinal
Cramp
Diarrhea
Nausea
Vomiting
Liver
Hepatomegaly
Retroperitoneal fibrosis
Hypotension (mostly) hypertension
Left Heart
*Intracardiac shunt (PFO)
* Primary pulmonary disease
*High burden disease

CMR

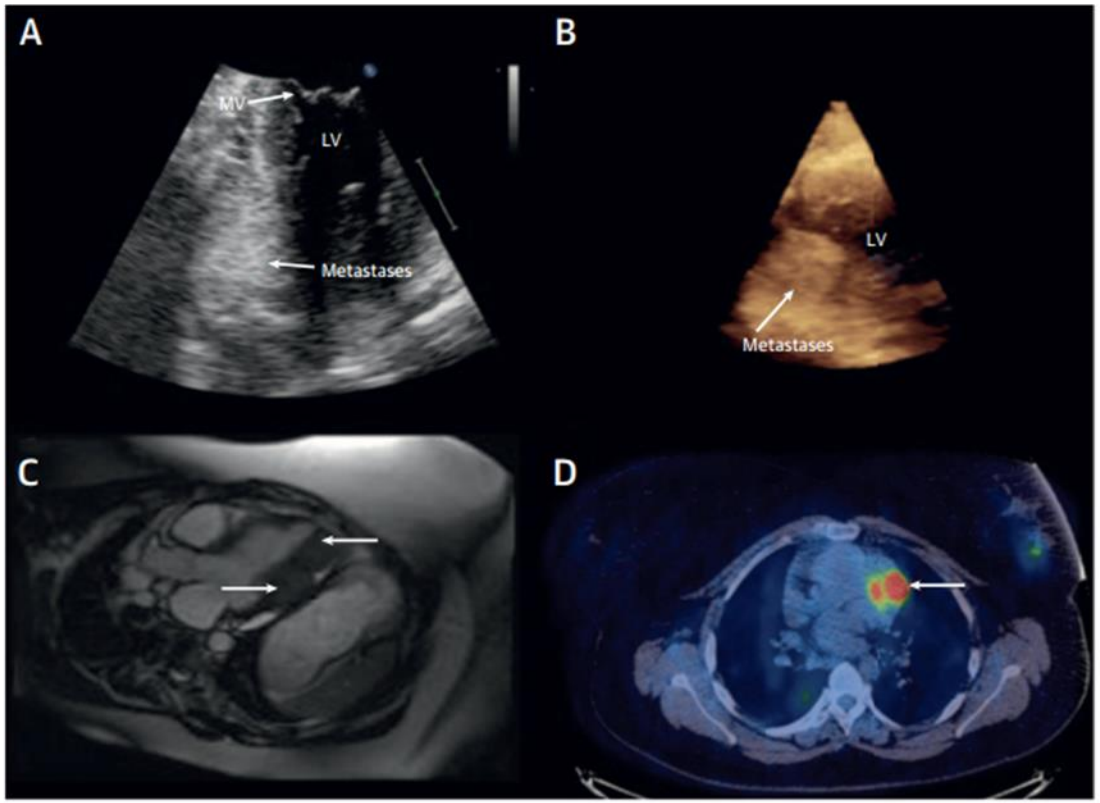
- **Cardiac magnetic resonance** enables functional, volumetric, and structural characterizations of the right-sided heart valves; specifically, PV involvement.

- Cardiac carcinoid metastases and structural infiltration appear clearly.

- So CMR is recommended to evaluate **PV involvement, RV function, and metastasis in carcinoid HD.**

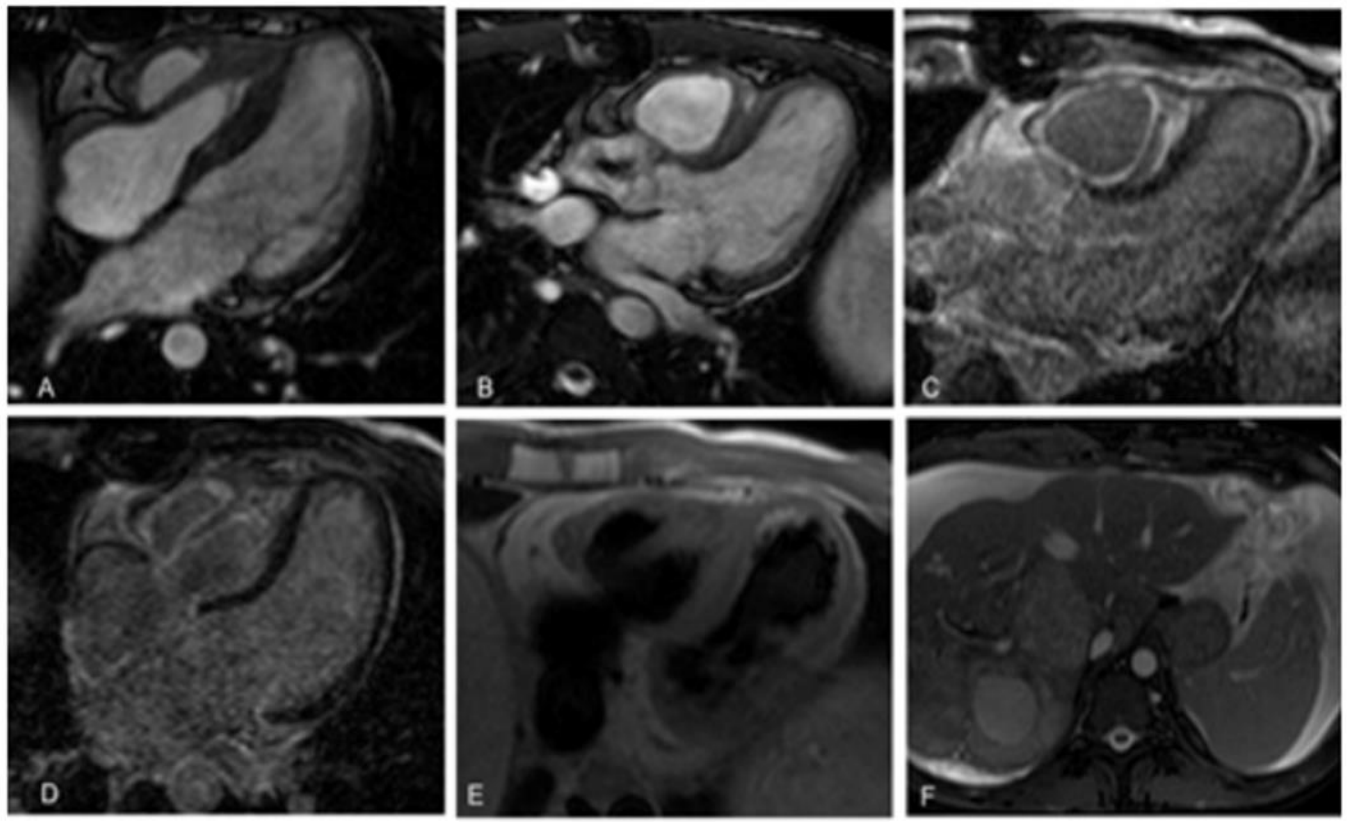
CMR & tissue characterization

- **CMR** results provide a unique opportunity for tissue characterization using conventional non-contrast (T1- and T2-weighted sequences with or without fat saturation) and contrast-enhanced (late gadolinium enhancement) techniques for identifying localized pathologies, such as cardiac metastases.



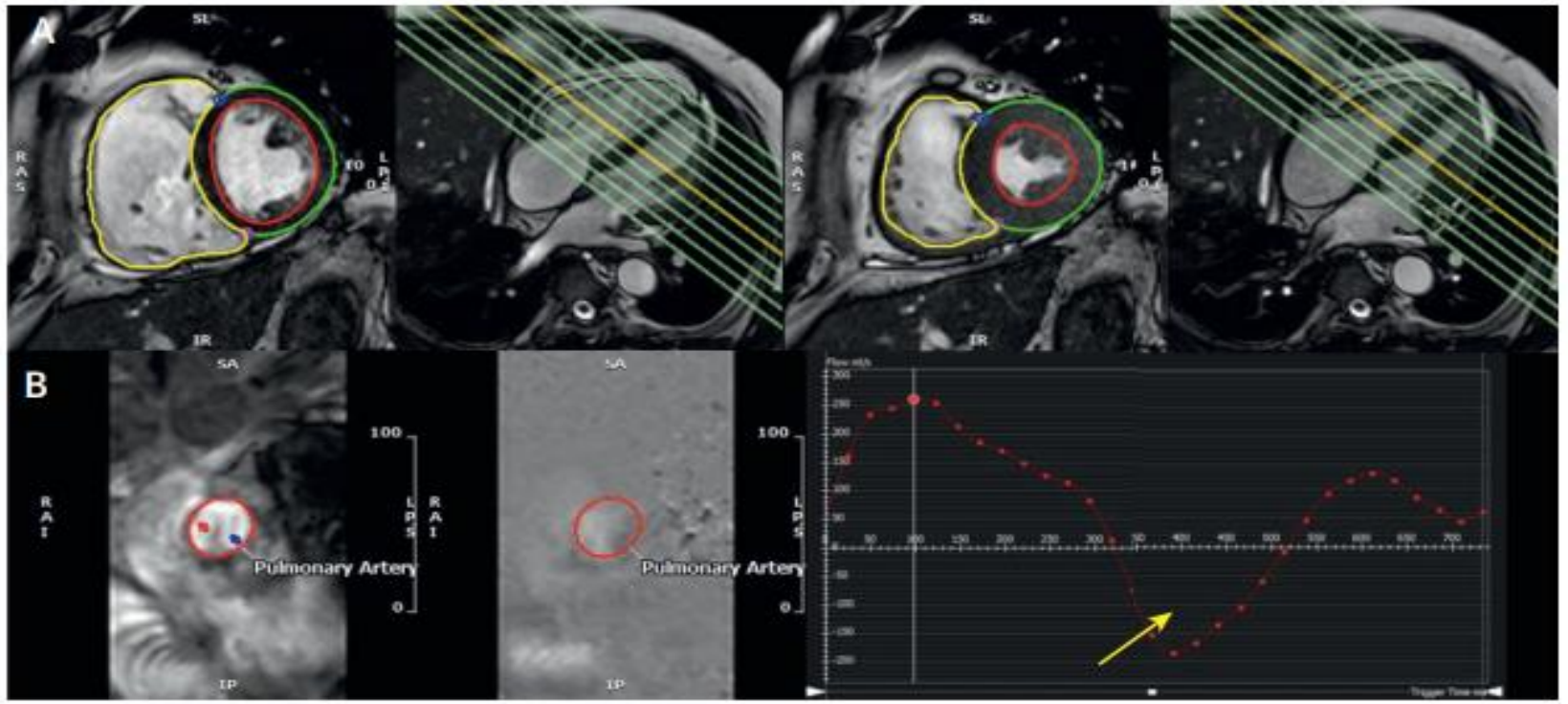
(A) Transesophageal echocardiogram demonstrating large mass in mid to distal inferior wall of the left ventricle. **(B)** 3-dimensional TTE shows rounded mass **(arrow)** in the posterior wall of the LV. **(C)** CMR demonstrating 2 masses in the mid inferolateral wall extending to the apex **(arrows)**. Masses are limited to myocardium with no extra cardiac extension. **(D)** Gallium-68-labeled octreotide PET demonstrates avid focal uptake of tracer in the region of the 2 masses **(arrow)**, suggesting metastatic carcinoid tumor. Reprinted with permission from Bhattacharyya et al. (5). CMR = cardiac magnetic resonance; LV = left ventricle; PET = positron emission tomography; TTE = transthoracic echocardiogram.

LGE in the subendocardial region of the free wall, papillary muscle and interventricular septum



A and B) cine resonance magnetic imaging in 4-chamber and 3-chamber, respectively; there is **an increase in the thickness of the free wall of the RV and papillary muscle and a retracted TV. The RA and the RV appear as a single chamber**. The interventricular septum is displaced to the LV, suggesting an increased volume of the RV. C and D) show the presence of LGE in the subendocardial region of the free wall, papillary muscle and interventricular septum. There was no LGE in the LV. E) dark blood sequence with **increased thickness of the RV myocardium and absence of edema**. F) images of the thoracoabdominal transition showing **hepatomegaly, multiple hepatic nodules and ascites**, characteristic of neuroendocrine tumors

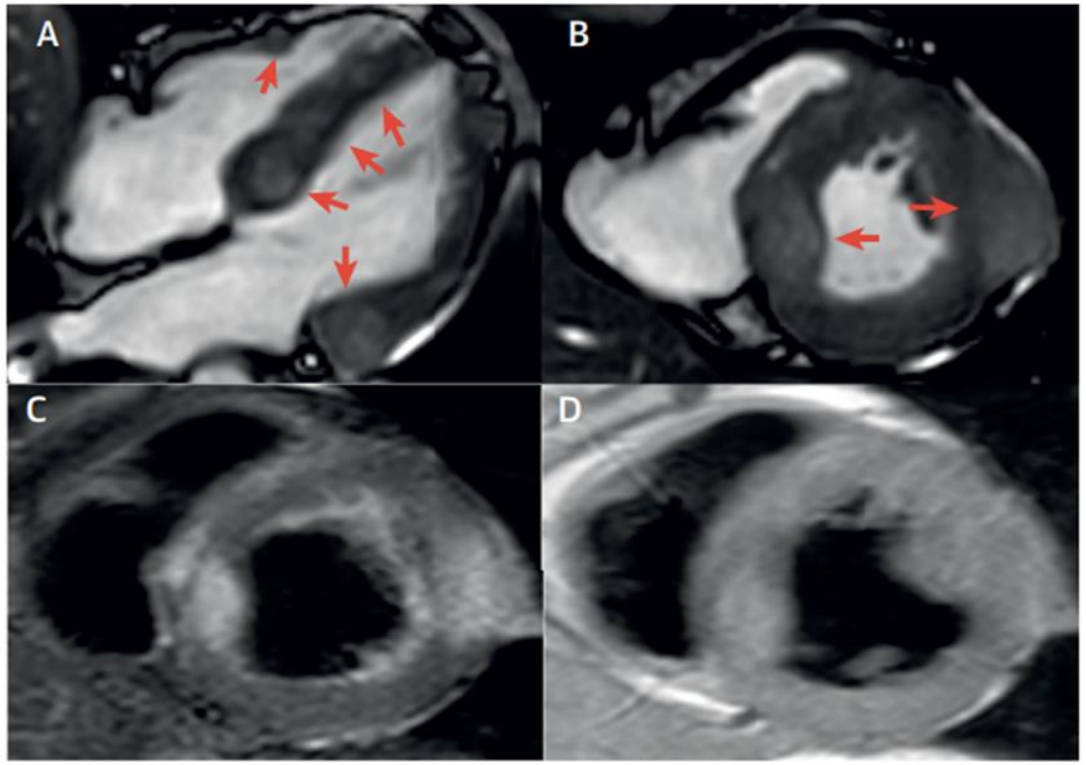
CMR Estimation of Tricuspid and Pulmonary Reg-V in a Carcinoid Patient With Involvement of Both the Tricuspid and Pulmonary Valve



(A) Calculation of RV stroke volume using short-axis cine stack with SSFP sequence. Example of contouring of the ventricles in short axis in end-diastole **(left)** and end-systole **(right)** with corresponding 4-chamber images. **(B)** Measurement of pulmonary stroke volumes using phase-contrast imaging. Magnitude image for anatomy **(left)** and corresponding phase-contrast image **(middle)** with a section of main pulmonary artery in the center **(red contour)**. Flow time curve is shown across the main pulmonary artery **(right)**. The part of the **curve** below the baseline illustrates backflow in the pulmonary artery during diastole **(yellow arrow)**. Total RV stroke volume was 156 ml; pulmonary forward flow volume, 72 ml; calculated tricuspid, RegVol, 84 ml; and RegF, 54%. Pulmonary RegVol 21 ml and RegF 30%. Tricuspid regurgitation was considered severe and pulmonary regurgitation moderate. CMR = cardiac magnetic resonance; RegF = regurgitant fraction; RegVol = regurgitant volume; RV = right ventricle; SSFP = steady-state free precession.

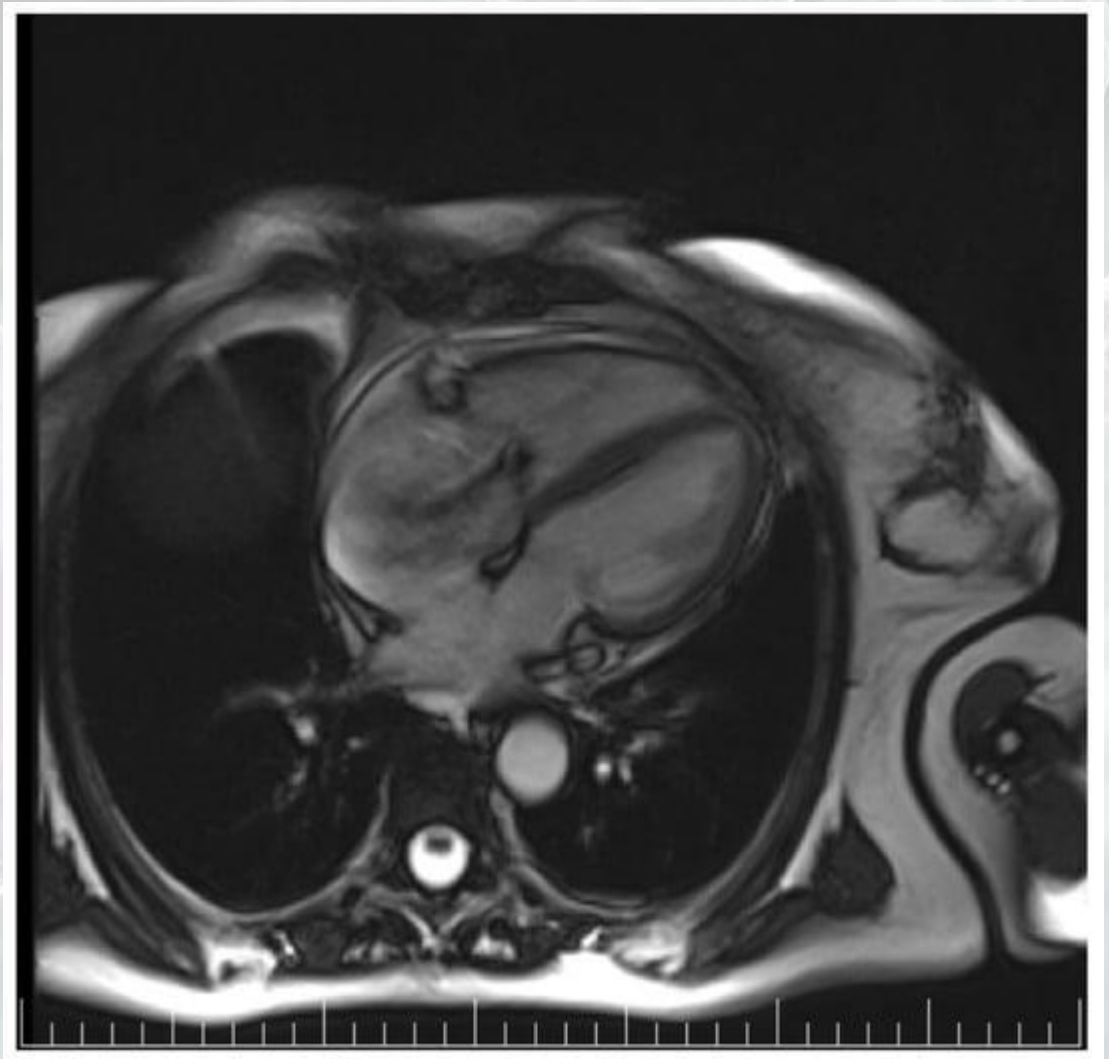
CMR Images From a Patient With Cardiac Carcinoid Metastases of a Pulmonary Carcinoid

CMR useful in:
****identify and quantify the fibrosis**
****diagnose the myocardial metastasis**
****assist in defining the surgical treatment**



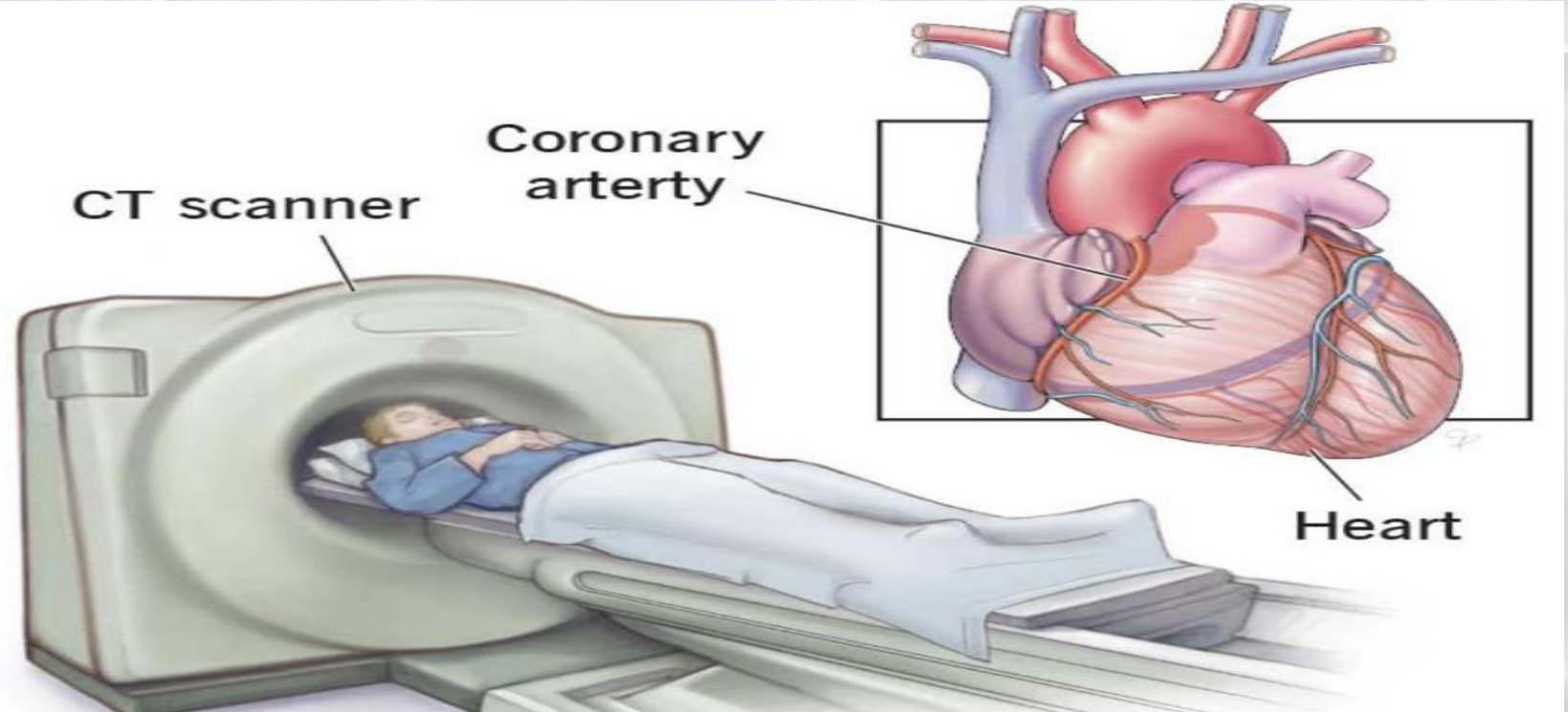
Initial evaluation with echocardiography revealed mild concentric LV hypertrophy without valve engagement. CMR showed normal chamber dimensions with both left and right ventricular function. In the LV walls, multiple round masses, 6 to 23 mm in diameter, were seen, involving the septum, apex, and lateral wall, localized both intramurally, subepicardially, and subendocardially; and 1 single mass of 5-mm diameter was observed in the mid RV free wall **(red arrows)**. **(A and B)** 4-chamber and short-axis views, respectively. The masses displayed a hyperintense signal compared to that of neighboring myocardium on T2-weighted sequences **(C)** and an isointense signal on T1-weighted sequences **(D)**. CMR = cardiac magnetic resonance; LV = left ventricle.

Cardiac MRI in this case—severe tricuspid regurgitation.



Computed tomography (CT)

- In addition to allowing for pre-operative, noninvasive coronary angiography in candidates for cardiac surgery, computed tomography (CT) is rarely performed to study CaHD lesions.



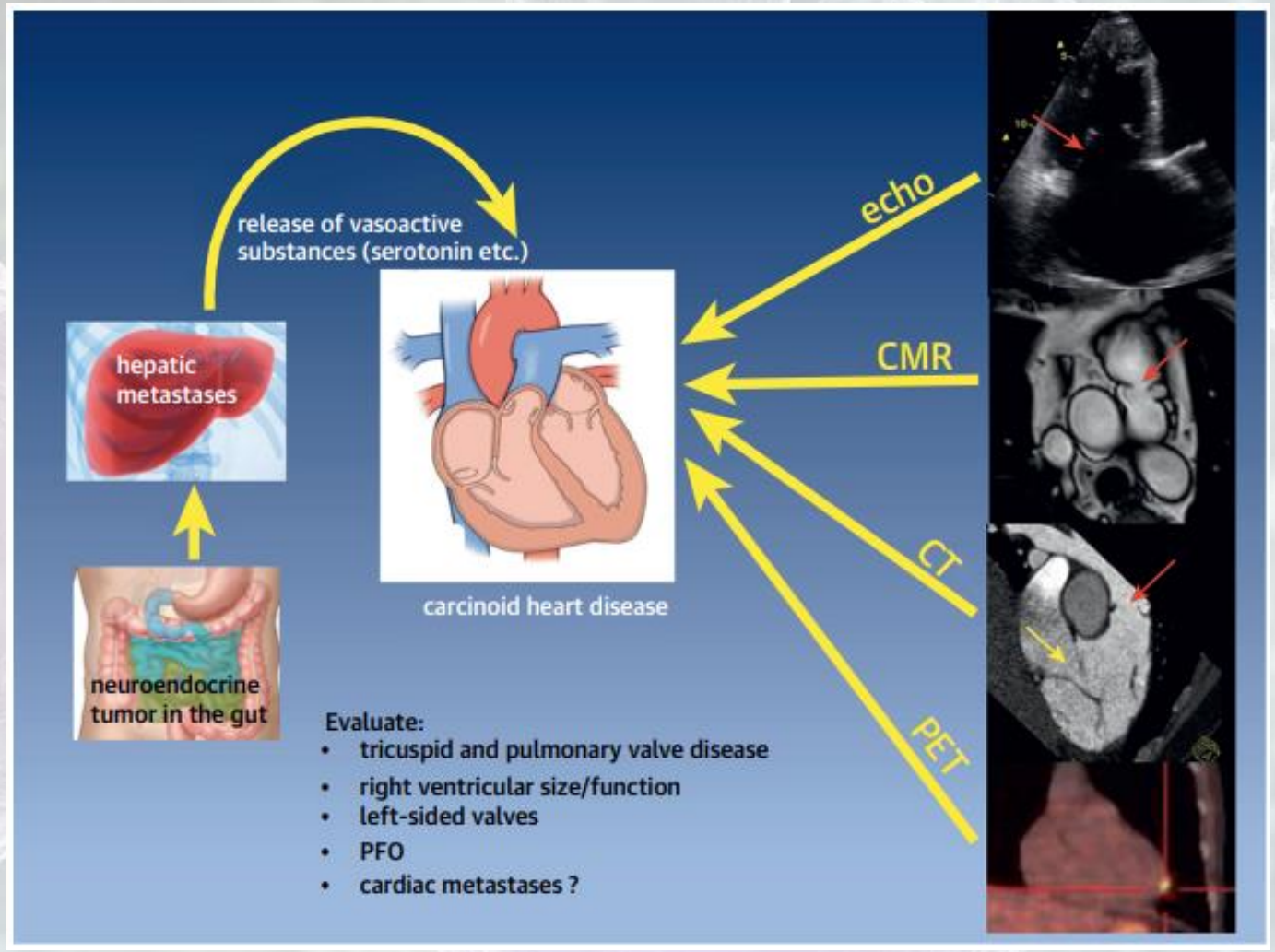
Diagnosis of our CASE

- The diagnosis was confirmed by very elevated levels of 5-hidroxi-indolacetic acid (>60 mg/24 h), chromogranin A (763 μg/L), and serum serotonin (>1000 μg/L).

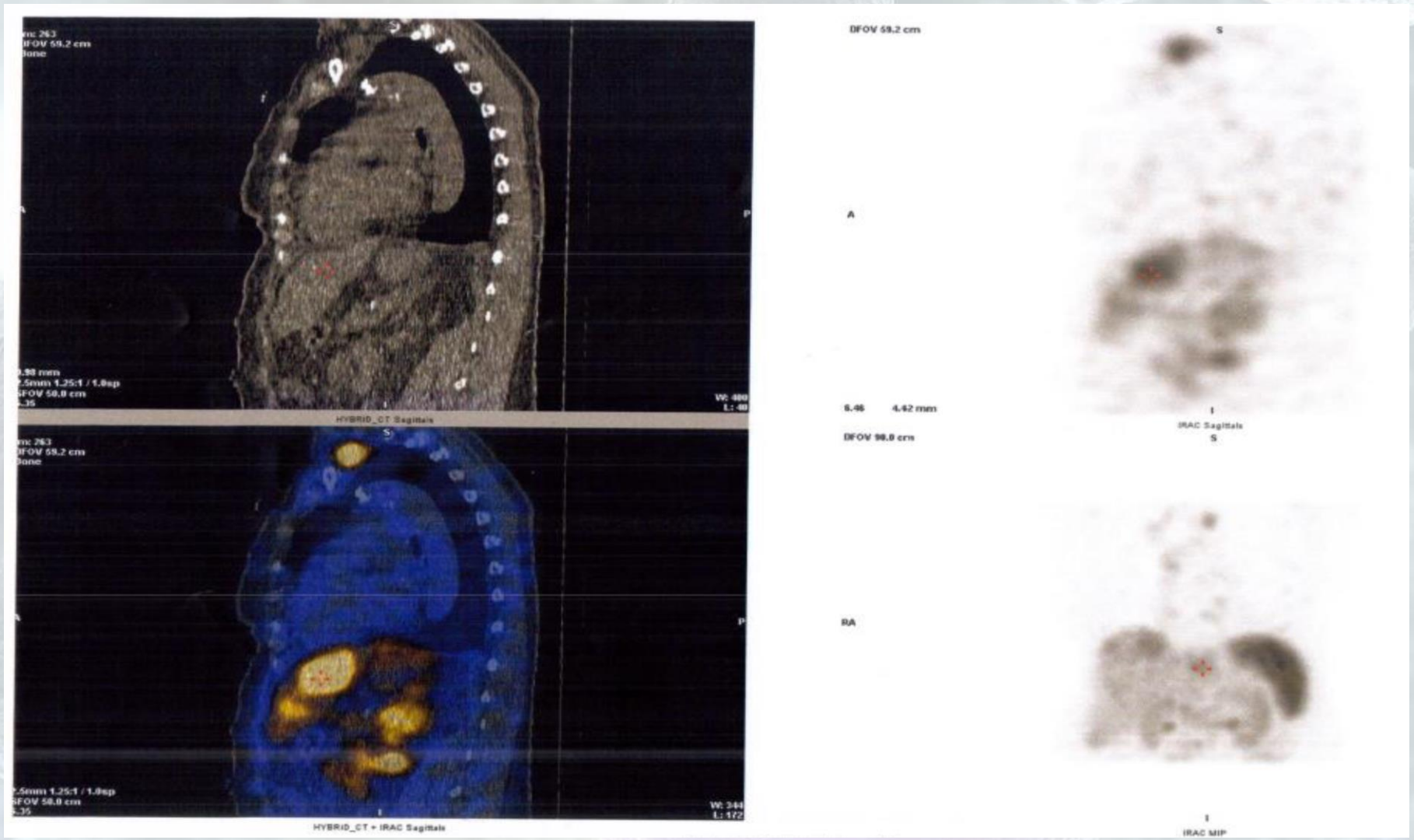
- A 99mTc- Tektrotyd scintigraphy and SPECT-CT were performed in order to identify the site of the carcinoid tumor.

- It showed multiple metastases in the supraclavicular, mediastinal, and retroperitoneal lymph nodes, as well as liver and bone metastases, without distinguishing the primary lesion.

PET; ONE of THE IMAGING MODALITIES



99mTc-Tektrotyd scintigraphy and SPECT-CT in our case showing multiple metastases in the supraclavicular, mediastinal, and retroperitoneal lymph nodes & liver and bone metastases.



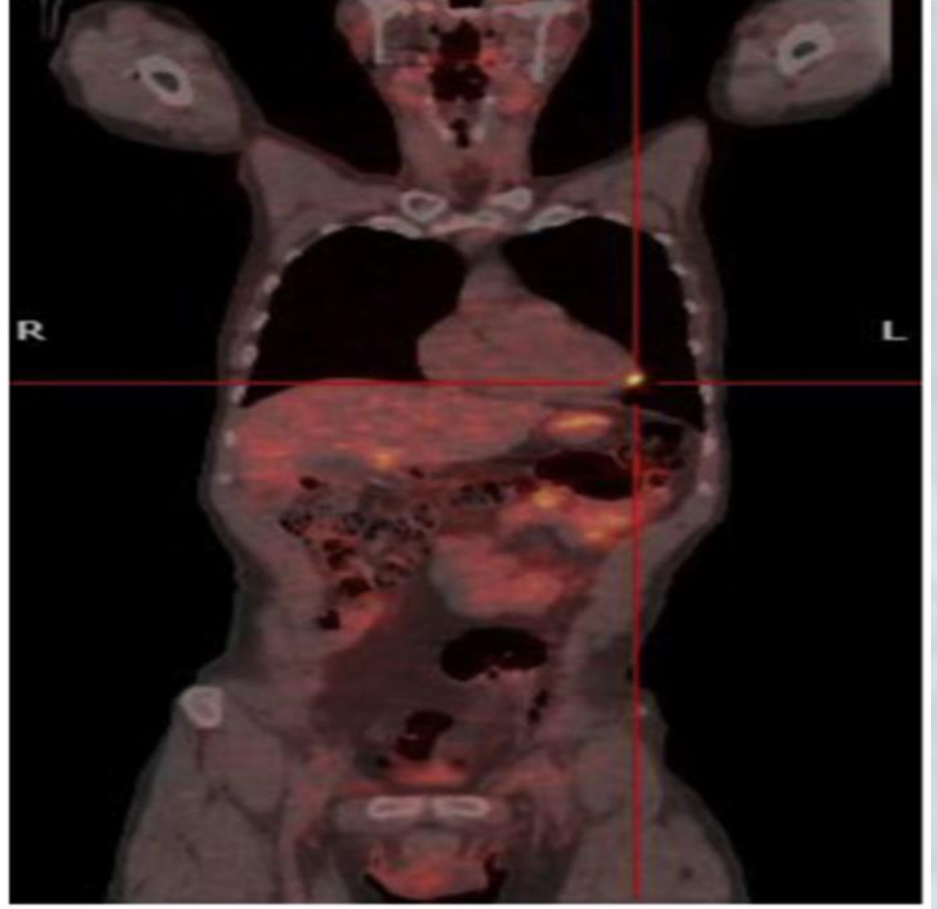
Nuclear imaging

- Several radiolabeled somatostatin analogs, such as gallium-68- or indium-111-labeled octreotide, which are taken up by neuroendocrine tumor cells.
- Used to detect and localize neuroendocrine tumors and their metastases by PET and can occasionally detect metastatic cardiac lesions
- The somatostatin analogs are superior to [18F] fluorodeoxyglucose-based markers for the detection of neuroendocrine tumors.
- Furthermore, PET is better than single-photon emission tomography imaging in this regard, showing higher sensitivity to small lesions, especially when performed together with CT

Direct Myocardial Involvement

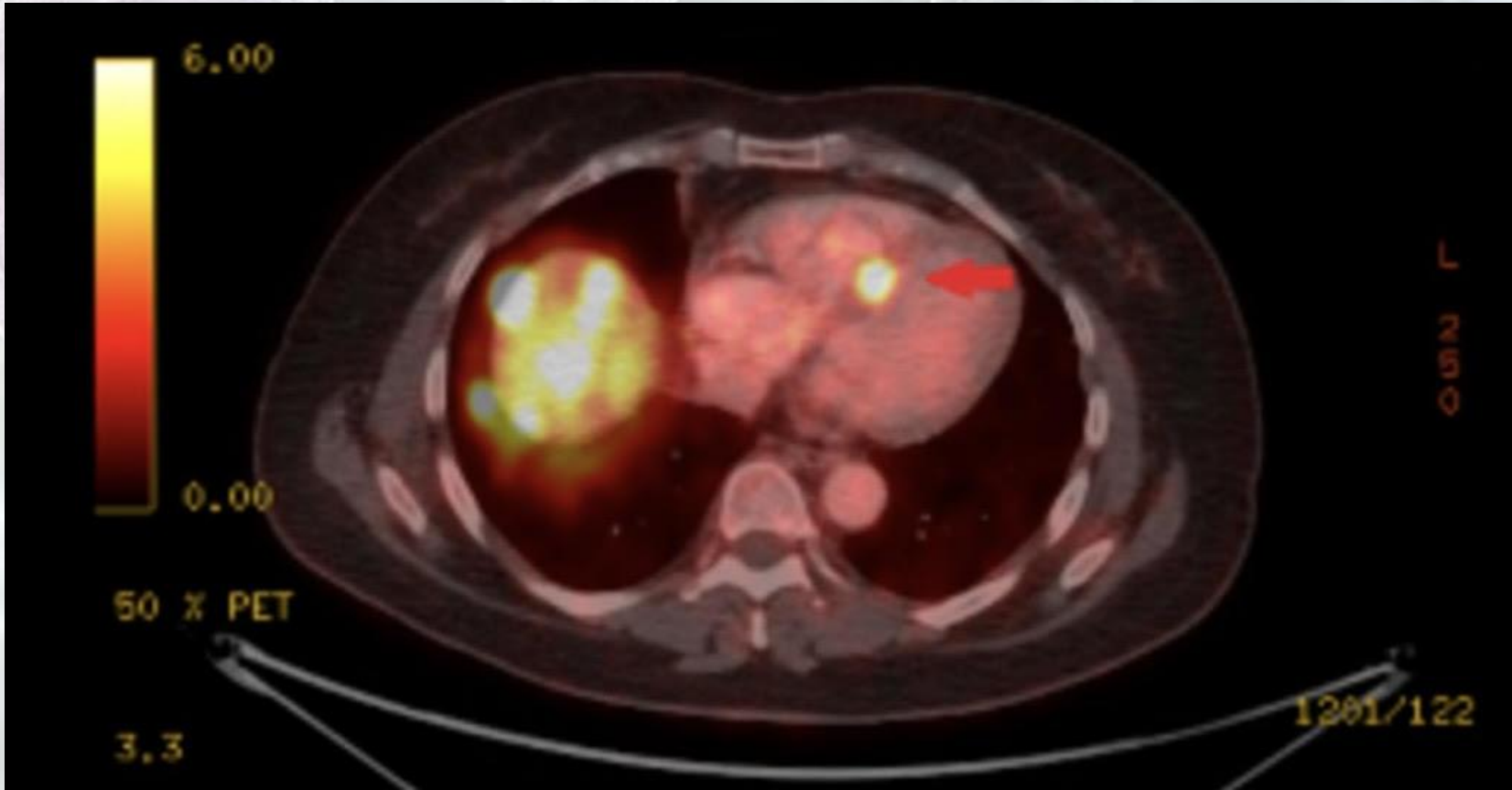
- In one series(incidence of metastasis, 3.8%), most of the tumors were on either ventricle (including the ventricular septum), and all were circumscribed, homogeneous, and non-infiltrative on echocardiograms.

- Lesions smaller than 1 cm are usually not detectable on echocardiograms, and positron-emission tomography/computed tomography (PET/CT) may prove more useful.



Small pericardial metastasis from midgut carcinoid tumor visualized with [11C]5-hydroxytryptophan (5-HTP) PET/CT. 5-HTP is the precursor of serotonin which accumulates in serotonin-producing tumors, and PET identifies lesions with high accuracy. Note the absence of uptake in normal myocardium.

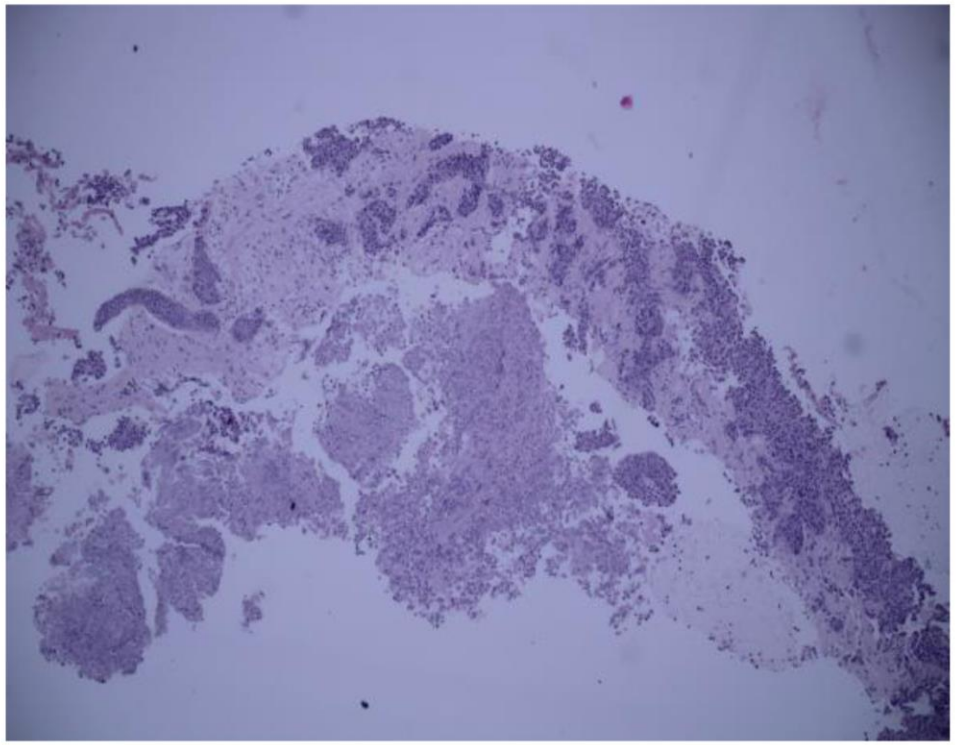
- Occurrence of cardiac metastases did not seem to correlate with valvular CaHD.
- Note, however, that the valvular lesions typical of CaHD do not take up somatostatin analogs, and thus nuclear imaging plays no routine role in evaluating valvular CaHD.



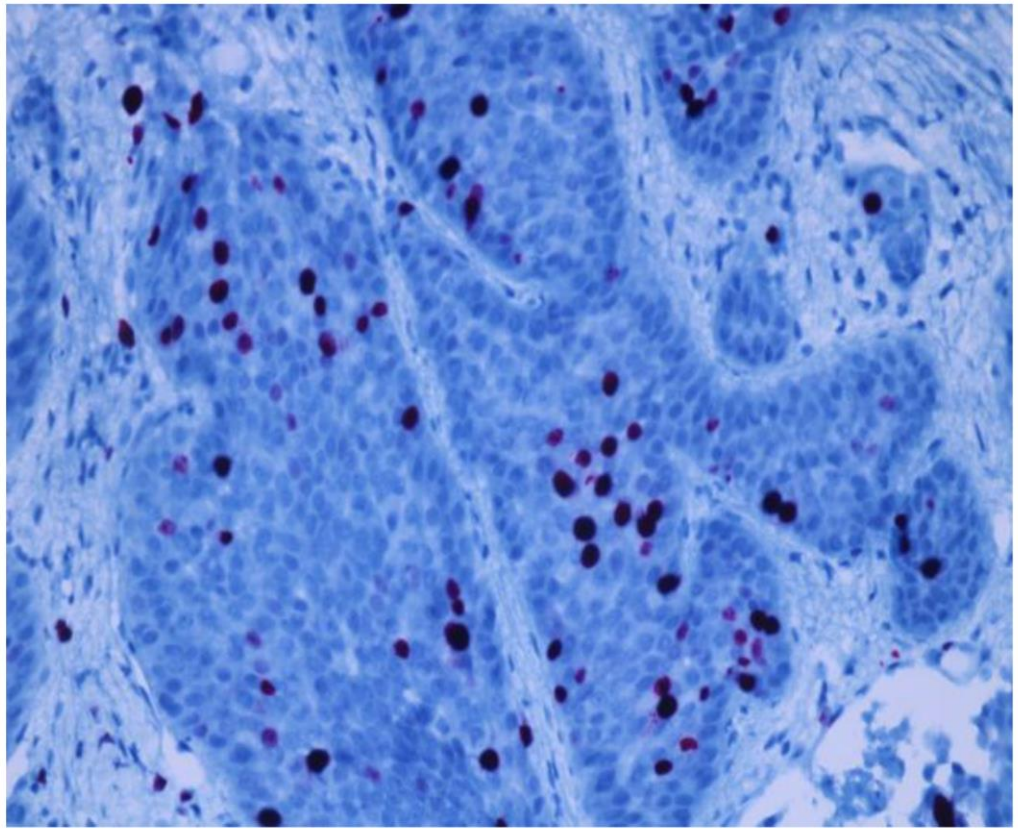
Biopsy & pathology diagnosis of our patient

- The patient underwent a surgical biopsy of the supraclavicular lymph nodes.
- Pathology report : monomorphic cells with hyperchromatic, round-oval nuclei and pale eosinophilic cytoplasm.
- The IHC showed intense and diffusely positive chromogranin, CDX2, CK19, mildly positive synaptophysin, and membrane-positive CK56.
- The above-mentioned findings were suggestive of a G2 moderate-grade neuroendocrine tumor

(a) Hematoxylin and eosin staining showing numerous small monomorphic cells with salt-and-pepper chromatin; (b) immuno-histochemical staining for Ki67 labeling index.



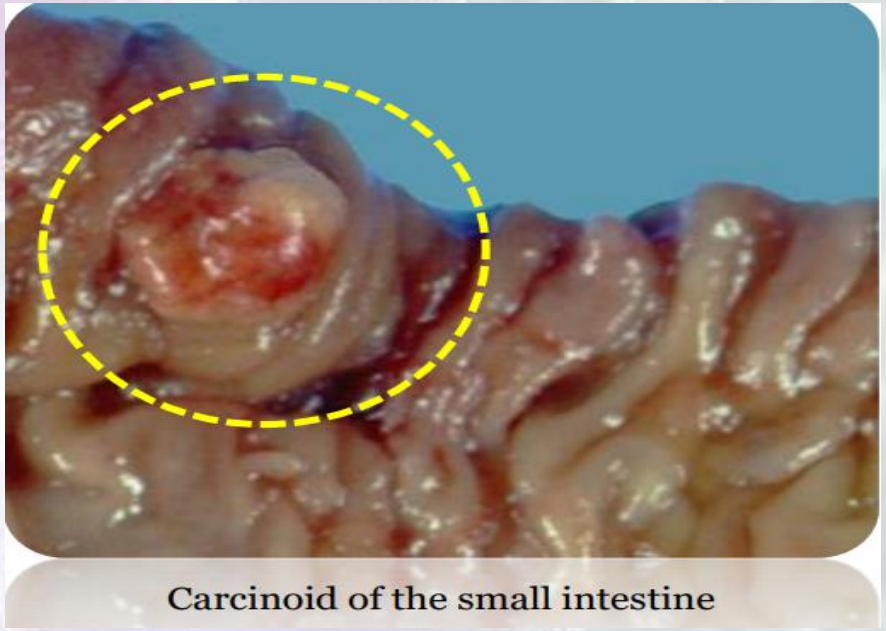
(a)



(b)

Treatment

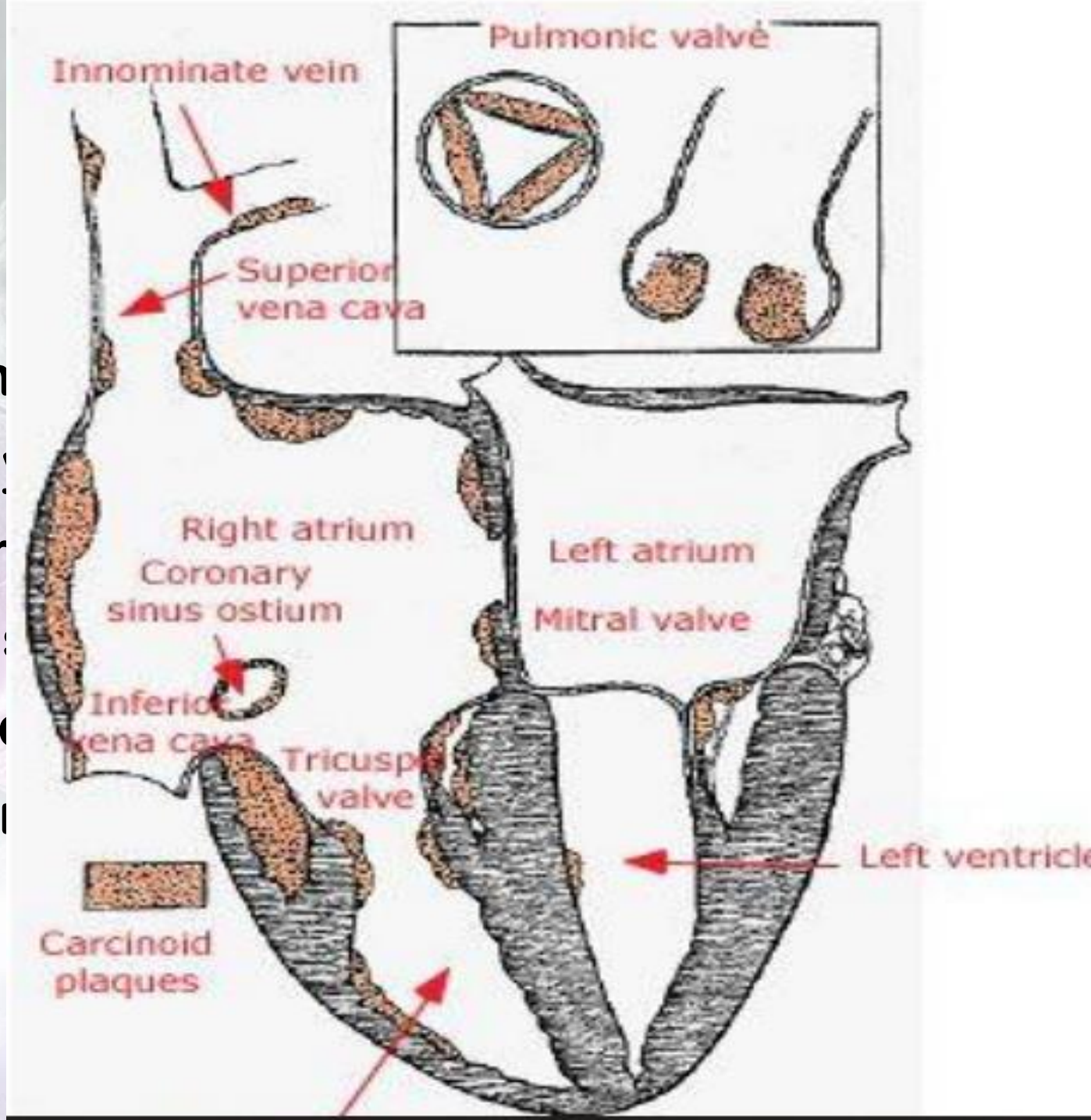
- The patient's clinical condition had severely declined over time.
- Specific treatment with Lanreotide 120 mg s.c. was initiated, but the patient passed away just 3 months after the echocardiography raised the suspicion of a carcinoid tumor.



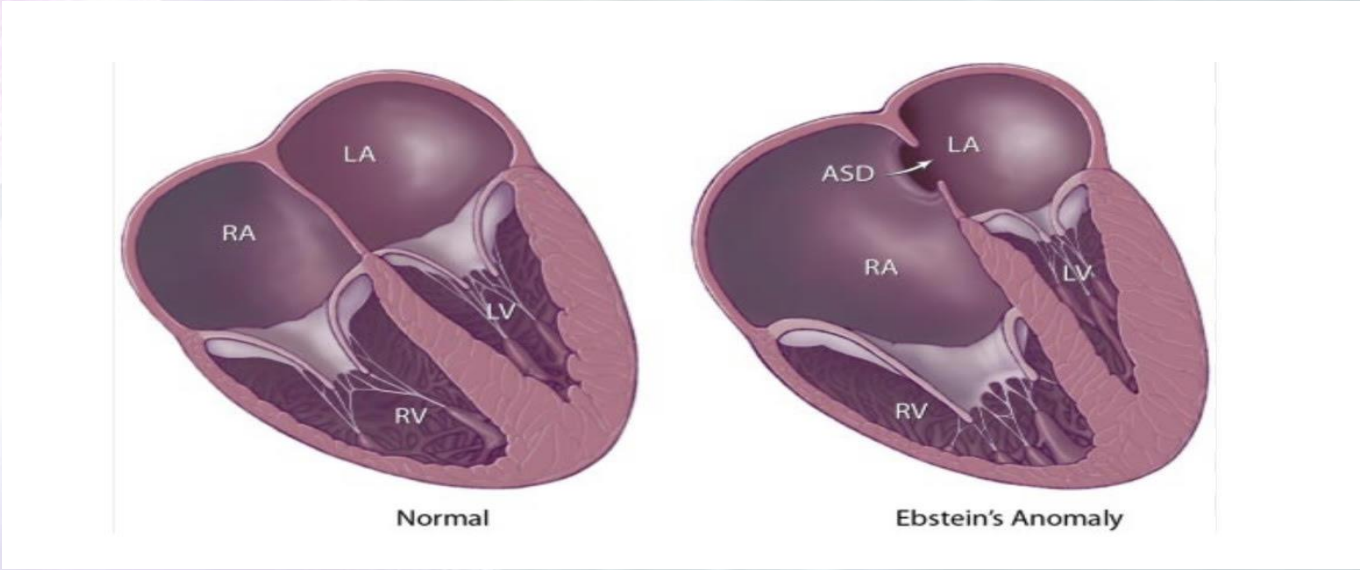
Carcinoid of the small intestine

Discussion

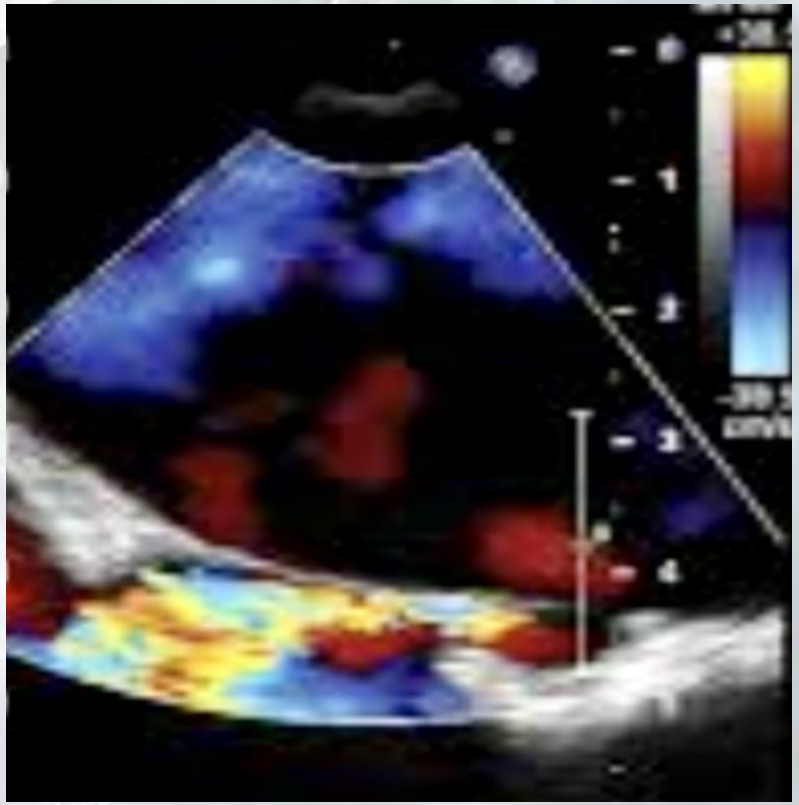
This case with malignan carcinoid tumors, which rarel first reveal as carcinoid hear disease, making the diagnosi even more challenging an having a detrimental effect o the patient's survival



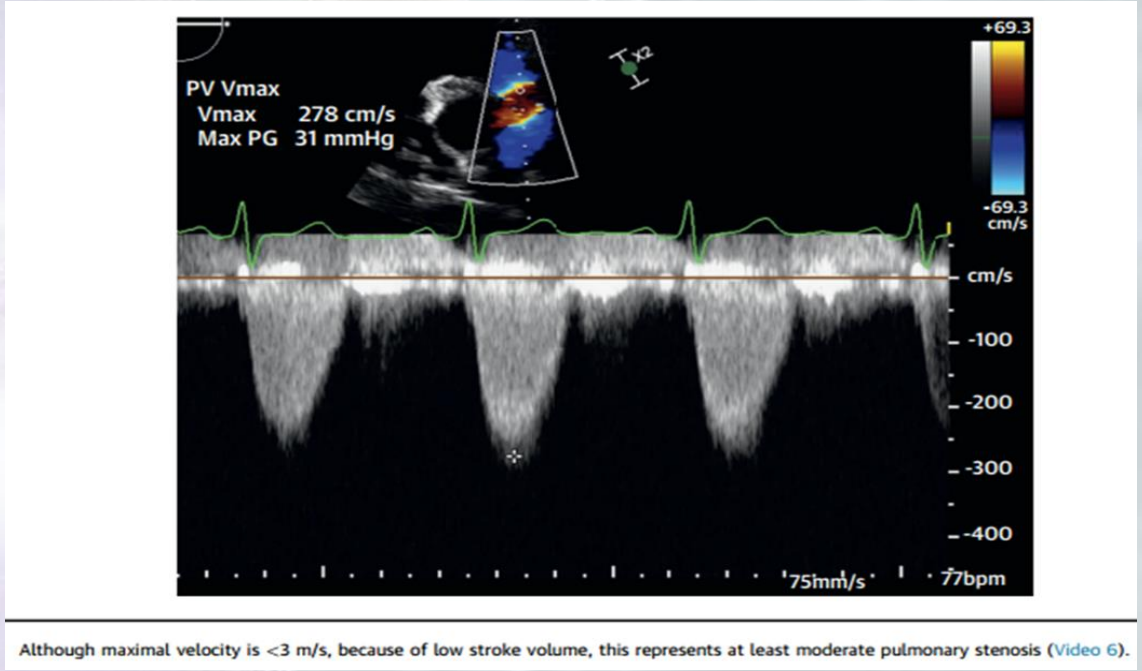
- This case highlights the additional difficulties that can appear in the diagnostic process, when a concomitant disease is also suspected.
- The patient was first diagnosed with a possible Ebstein anomaly, which is a relatively rare congenital cardiac malformation characterized by an antero-caudal displacement of the TV annulus and atrialization of the RV, leading to right heart dysfunction and tricuspid regurgitation .



- The condition is also commonly associated with PFO and a ventricular septal defect, which were both identified in our patient, but no left sided involvement was detected.



- A report by Pellikka PA et al. noted the frequency with which these and other findings occurred in 74 patients with CHD in whom detailed echocardiography was conducted:
- Tricuspid regurgitation (100%, which was moderate to severe in 90% of the cases),
- Pulmonic stenosis (53%),
- Pulmonic regurgitation (81%),
- Left-sided valvular involvement (7%),
- Small pericardial effusion (14%).



Although maximal velocity is <3 m/s, because of low stroke volume, this represents at least moderate pulmonary stenosis (Video 6).

Valvular Heart Disease

- In carcinoid HD, **valvular involvement**—specifically isolated **TV regurgitation**—is seen most often.
- In most patients, the leaflets were also fixed in a half-open position, which led to **TV stenosis**.
- Up to 80% of patients have had **PV regurgitation or stenosis**.
- These structural and valvular lesions eventually lead to **right-sided heart failure** with **symptoms** such as **lower-extremity edema** and **early satiety**.
- **Left-sided cardiac valves** may be involved in the setting of an **intracardiac shunt** (such as a **PFO**) , **extensive liver metastasis**, or **bronchial carcinoid tumors**

STRUCTURE	CHARACTERISTIC FEATURES
Tricuspid valve	Thickening of valve leaflets and subvalvular apparatus Diminished normal concave curvature of leaflets Altered dynamic motion of leaflets during diastole Fused and shortened chordae Retraction and reduced excursion of valve leaflets Tricuspid regurgitation, ranging from mild to severe
Pulmonary valve	Diffusely thickened valve cusps Straightening of cusps Fixed, retracted, and thickened cusps Pulmonary regurgitation and/or stenosis
Aortic valve	Diffuse thickening of valve cusps Fixed, retracted, and thickened cusps Aortic regurgitation
Mitral valve	Diffuse thickening of valve leaflets Thickened papillary muscles and shortened chordae Restricted leaflet mobility Tenting of leaflets Mitral regurgitation
Right ventricle	Dilated chamber Impaired function

Patients with confirmed advanced carcinoid heart disease should be examined every 3–6 months by echocardiography

Tricuspid valve	• Most valvular diseases
	• Thickened, retracted leaflets with reduced mobility and subvalvular involvement
	• Mostly presenting with isolated regurgitation; smaller cases presenting with mixed stenosis and regurgitation
	• Different degrees of tricuspid regurgitation
	• "Dagger-shaped" in the Doppler profile in severe tricuspid regurgitation (an increase in early peak pressure with a subsequent rapid drop)
Pulmonary valve	• Thickened, retracted leaflets with reduced mobility
	• Mostly a combination of stenosis and regurgitation
	• Short pressure half-time with no flow time in the Doppler profile in severe pulmonary insufficiency
Right atrium/right ventricle	• Enlargement with dysfunction
	• Right ventricular outflow tract obstruction may occur.
	• Reduced right ventricular strain (regardless of valvular disease, in some cases even reduced global left ventricular strain)
Left heart valve	• Mostly regurgitation with mild-to-moderate severity
Metastasis	• Direct metastasis into the myocardium as a well-defined mass

Discussion

- In subjects with established CHD, echocardiography is recommended when the clinical status is significantly changing or every 3–6 months.
- Therapies that reduce circulating serotonin levels (somatostatin analogs, antitumor therapy) have not been shown to reverse valve disease.
- Surgical valve replacement is the current standard of care when intervention is indicated, and it represents the only effective therapy for CHD. It should be considered for symptomatic patients with severe valve impairment and well-controlled metastatic carcinoid disease and symptoms.

Take home message of case 1

- Echocardiography can be an important tool in the timely diagnosis of CHD and carcinoid syndrome.
- Its reliability and affordability warrant a reevaluation of its place in the diagnostic protocol for CHD, to the detriment of more expensive and less widespread investigations.
- Especially if surgical therapy is considered, evaluate the patency of the foramen ovale by using contrast (agitated saline) echocardiography or TEE for possible intraoperative closure is REC.

Proposed recommendations for diagnosis, follow-up and prognosis evaluation of carcinoid heart disease in patients with neuroendocrine tumours.

Examination	Indication (frequency)	Pathological features
Clinical assessment		
Physical examination	All patients (every 6 months)	Asthenia, dyspnoea, jugular vein distension, hepatomegaly, peripheral oedema, ascites, left-sided heart failure symptoms
Circulating biomarkers		
Screening and Prognosis		
24-h urinary (or plasmatic) 5HIAA	All patients (every 6 months)	≥300 µmol/24 h
NT-proBNP	Patients with carcinoid syndrome (every 6 months)	≥260 pg/mL
Prognosis		
Chromogranin A	Non-systematic	≥120 µmol/L
Cardiac imaging		
Screening		
Transthoracic echocardiography	Patients with 5HIAA urinary level >300 µmol/24 h (every 6–12 months)	Evaluation of heart valvular disease, in particular tricuspid and pulmonary valves involvement, patent foramen ovale, ventricular volumes and function
	Patients with carcinoid syndrome (every 6–12 months)	
	Non-functioning NET with liver metastases (every 1–2 years)	
Diagnosis/follow-up		
Transthoracic echocardiography	Confirmed CHD or NT-proBNP ≥260 pg/mL (every 3–6 months)	Evaluation of heart valvular disease, in particular tricuspid and pulmonary valves involvement, patent foramen ovale, ventricular volumes and function
Transoesophageal echocardiography/3D transthoracic echocardiography	Non-systematic but recommended for preoperative work-up	Evaluation of heart valvular disease, in particular pulmonary valve involvement
Cardiac computed tomography/ cardiac magnetic resonance imaging	Non-systematic recommended for preoperative work-up	Evaluation of heart valvular disease, in particular pulmonary valve involvement, ventricular volumes, detection of myocardial metastases and assessment of coronary arteries
Nuclear medicine imaging	Non-systematic (confirmation of suspicion on morphological imaging)	Detection of myocardial metastases

CASE 2

- A 35-year-old female with no significant past medical history presents to the cardio-oncology clinic for evaluation after a recent diagnosis of Stage IV neuroendocrine carcinoid tumor.

- The patient admits to having gastrointestinal and cardiac related symptoms for many years.

- Her symptoms began 12 years ago with abdominal pain, for which she was treated with cholecystectomy .

FINDINGS

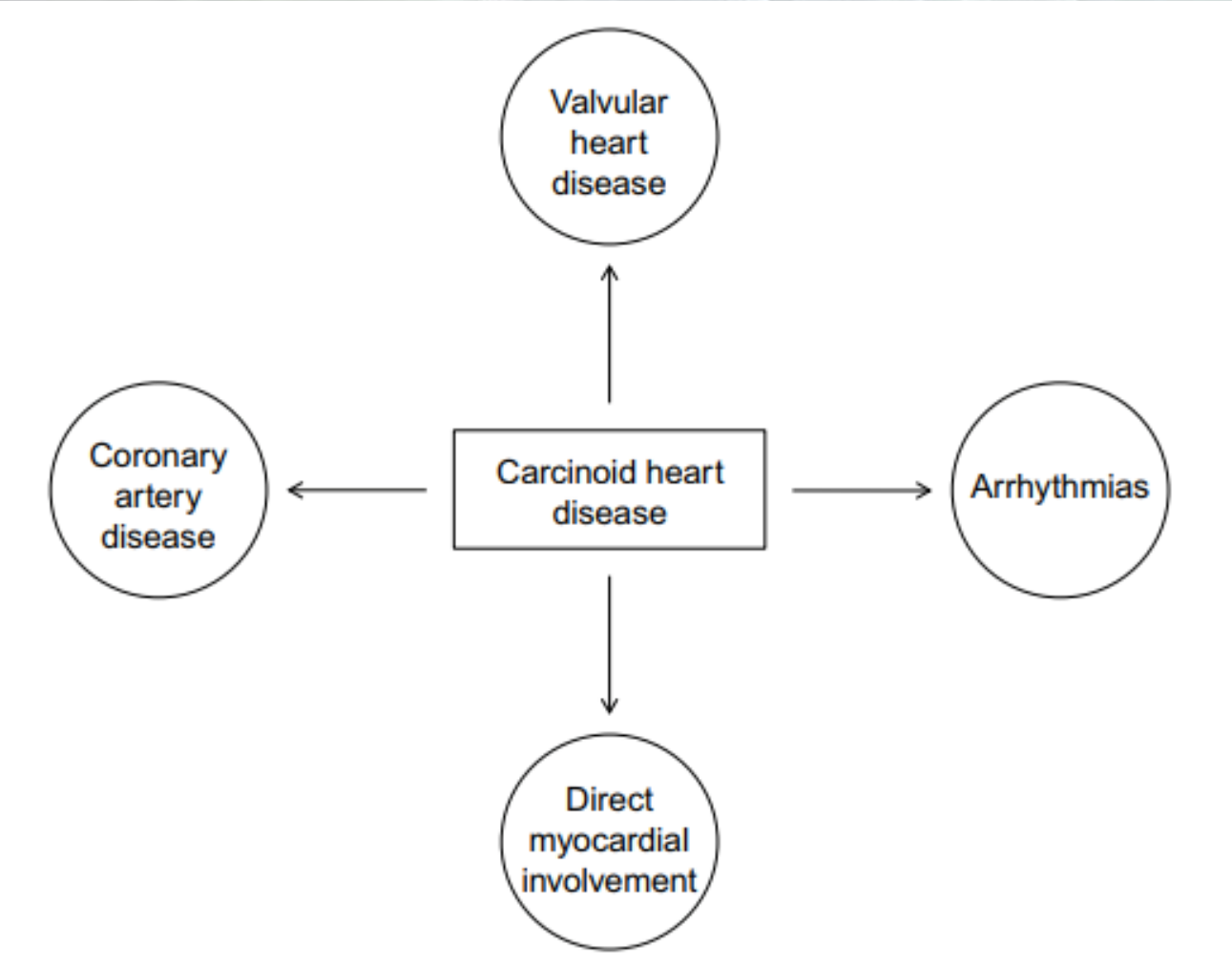
- Despite this intervention, her symptoms persisted and progressed to include nausea and diarrhea.
- Over time they worsened, and this time were attributed to infectious colitis and treated with antibiotics and ranitidine, again, without resolution of her symptoms.
- she developed cardiac symptoms with fatigue and exercise intolerance.

Over the years, she began experiencing more symptoms including headaches, shortness of breath (SOB), intermittent leg swelling, abdominal fullness, and abdominal pain.

Signs and symptoms of carcinoid syndrome and carcinoid heart disease

CARCINOID SYNDROME	CARCINOID HEART DISEASE
Bronchospasm	Ascites
Cyanosis	Dyspnea
Diarrhea and cramping	Fatigue
Flushing	Jugular venous pressure elevation
Hypotension	Peripheral edema
Pellagra	Pleural effusion
Teleangiectasia	Systolic murmur

Diagram shows clinical manifestations of carcinoid heart disease.



Arrhythmia

- In canine studies, serotonin was implicated in paroxysmal ventricular tachycardias and atrial arrhythmias.
- The underlying mechanism is thought to be increased sympathetic discharge induced by a vasoactive substance, leading to cardiac excitation and tachyarrhythmias.

Coronary Artery Disease

- Coronary artery vasospasm is also associated with carcinoid HD, usually in patients who have nonocclusive coronary artery disease
- Therapeutic decisions include whether to use vasodilators such as calcium channel blockers, serotonin antagonists, or somatostatin analogues.

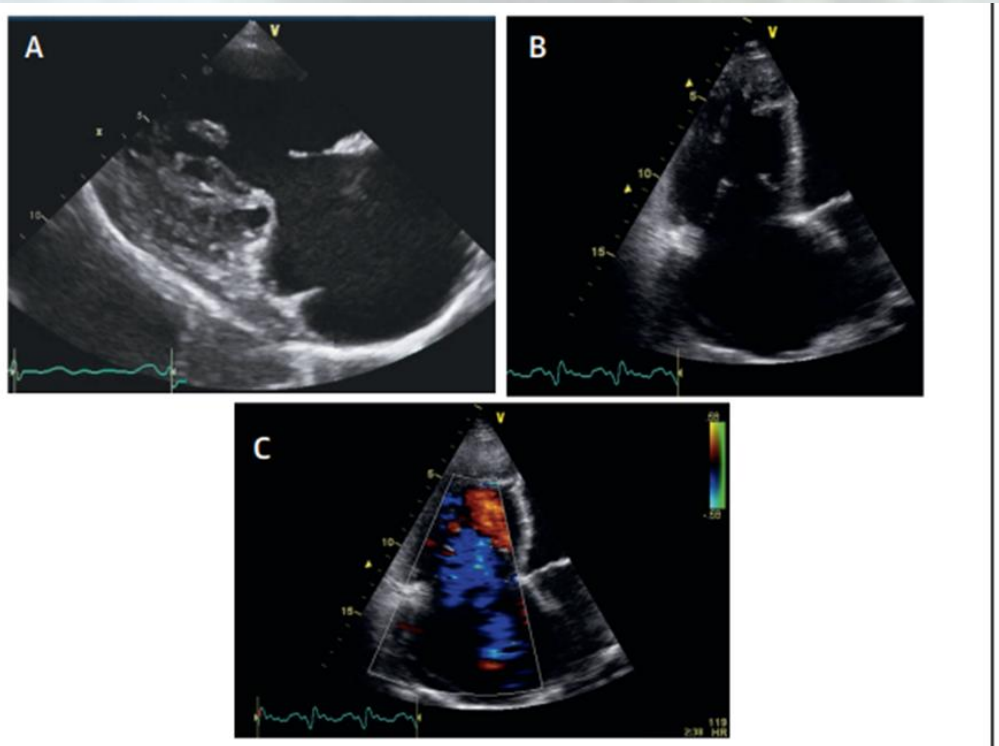
Imaging findings of our case

- CT abdominal imaging during the visit revealed a **mesenteric mass** and multiple lesions in her abdomen and liver.

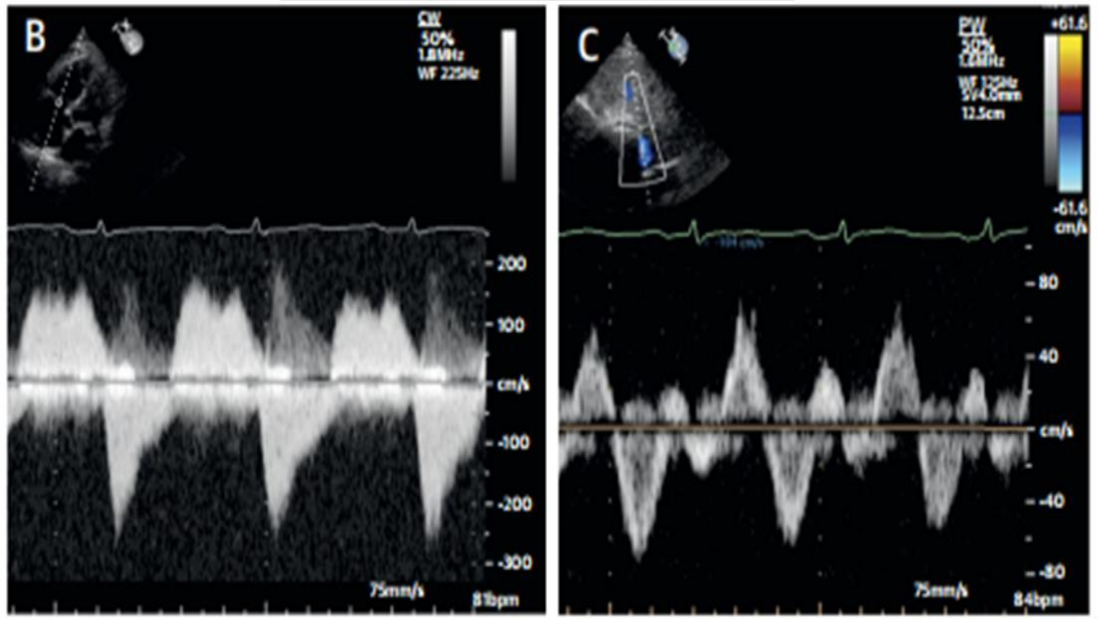
- MRI was recommended to better characterize the lesions. Unfortunately, due to her uninsured status, the MRI was delayed by another 3 months MRI showed an enhancing lobulated mesenteric mass measuring 2.4 × 2.7 cm and innumerable T2 hyperintense liver lesions which were concerning for liver metastasis .

- Two weeks later, she underwent biopsy of the liver lesions, which revealed a well differentiated neuroendocrine tumor.

TTE



(A) Parasternal right ventricular inflow view in systole. Note position of tricuspid leaflets with wide gap, increased echogenicity of leaflets, and increased size of the right atrium (Video 1). **(B)** Apical modified 4-chamber view, in systole, with the same tricuspid leaflet characteristics as in **(A)**. The RV and the right atrium are dilated, with the ventricular septum bulging to the left side (Video 2). **(C)** Color Doppler image of apical modified 4-chamber view with severe ("torrential") tricuspid regurgitation (Video 3). RV = right ventricle.



(A) Apical continuous-wave Doppler of low diastolic forward and systolic backward velocities across the tricuspid valve in extremely severe regurgitation and atrial fibrillation with severely depressed right ventricular function. Forward flow ceases before the end of diastole due to early diastolic pressure equalization. **(B)** Triangular regurgitant systolic flow velocity profile by apical continuous-wave Doppler. In this case, regurgitation is not as extreme as in **(A)**, and sinus rhythm is preserved. Note elevated diastolic forward velocities due to high regurgitant volume. **(C)** Pulsed-wave Doppler of hepatic vein flow shows substantial systolic backward flow as a sign of severe tricuspid regurgitation.

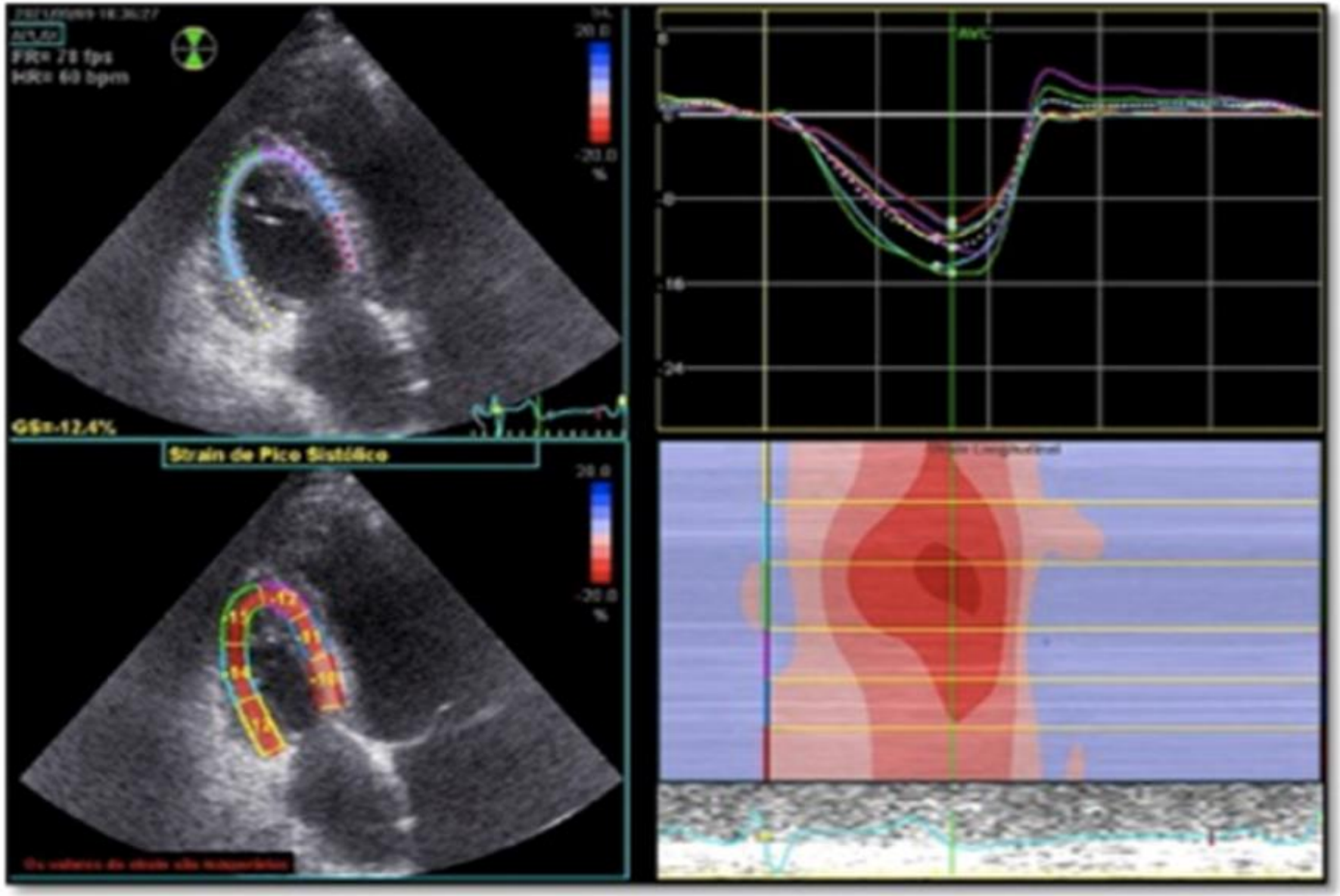
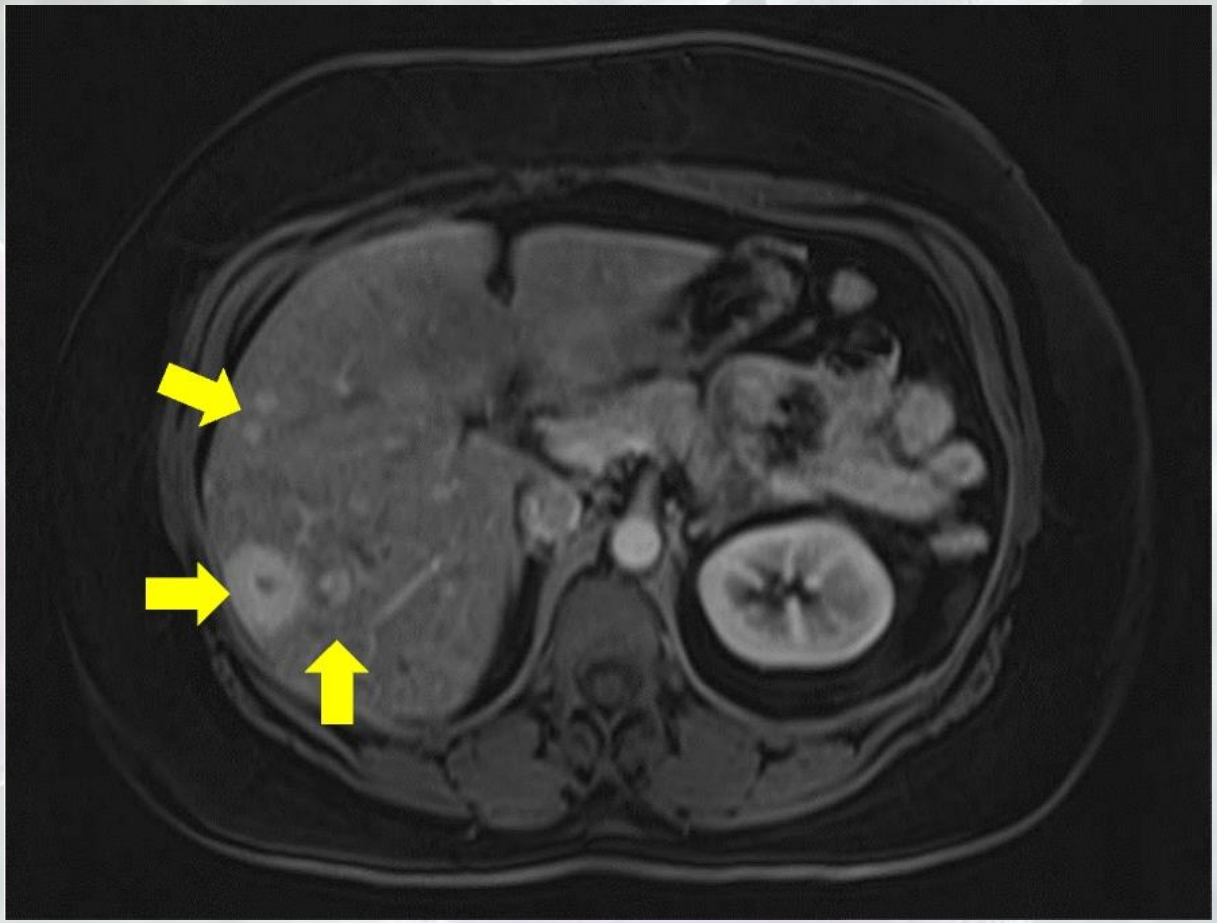
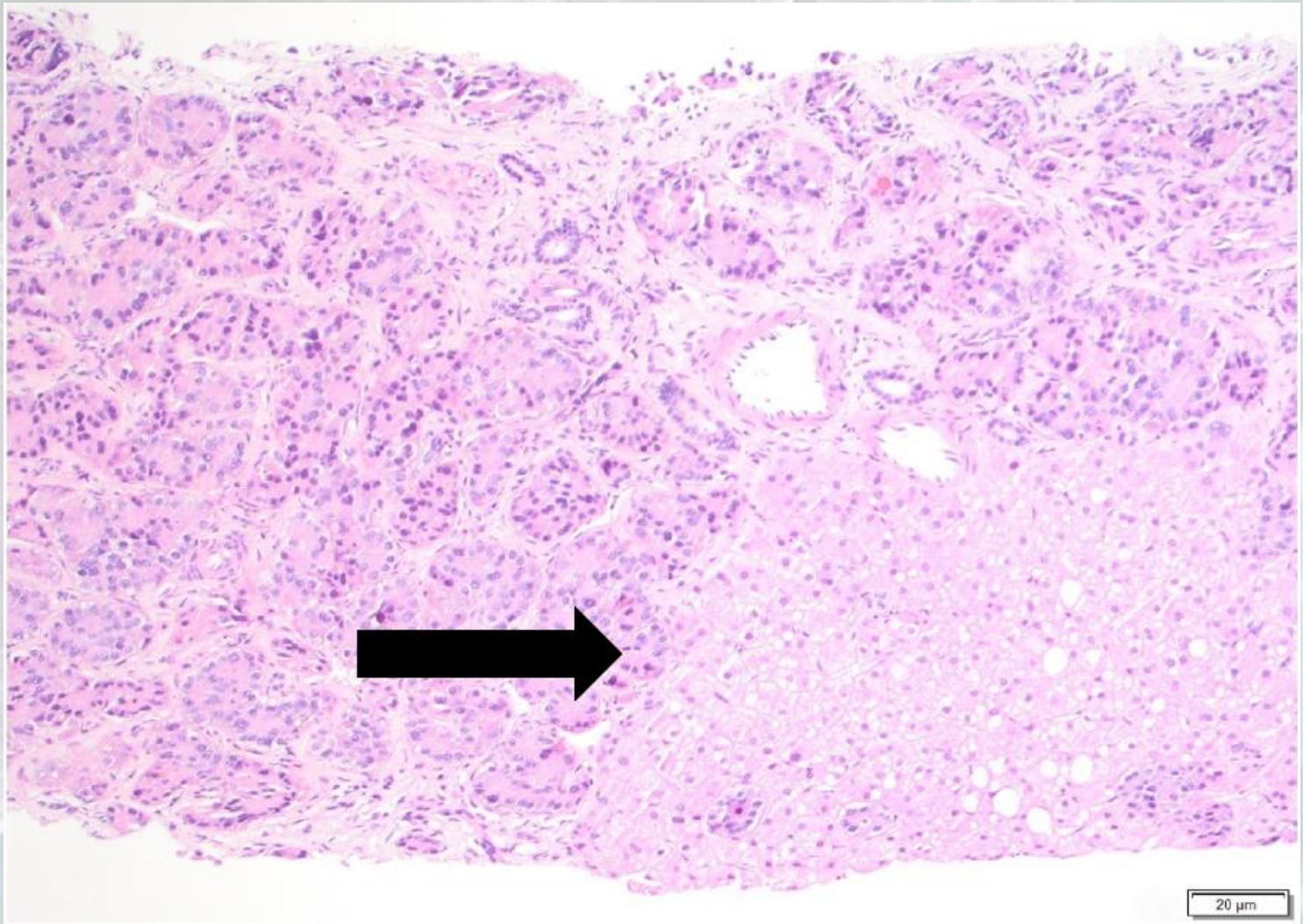


Figure 2 – *Apical four-chamber view (focused on the right ventricle); quantification of right ventricular strain by speckle-tracking echocardiography showing abnormal global and free wall strain values (12.4% and 13.6%, respectively).*

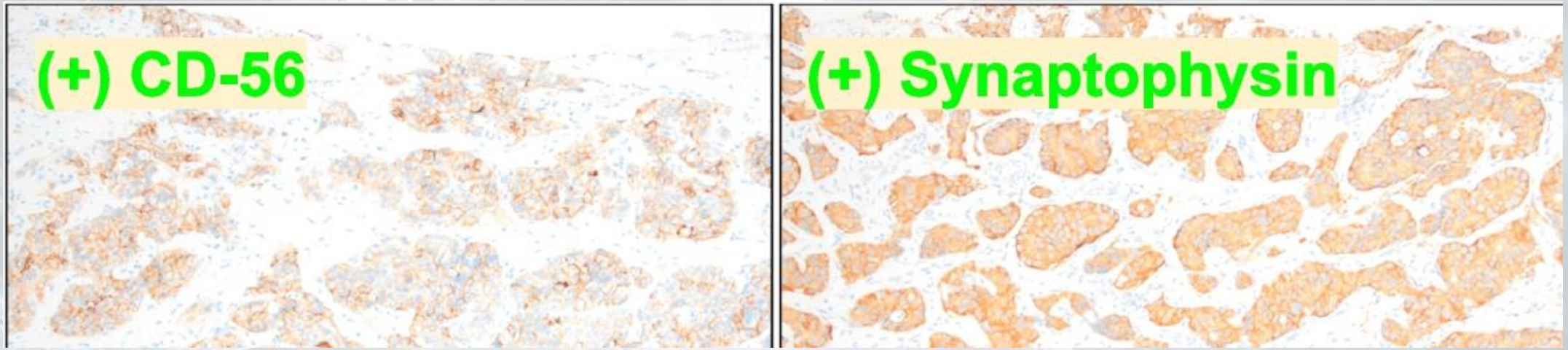
Contrast-Enhanced MRI of abdomen and pelvis. Note the innumerable mild T2 hyperintensities (see the arrows), which correlate to the arterial enhancing, rounded masses throughout the liver



Liver core biopsy showing nested architecture of neoplastic cells composed of small to medium-sized cells with ample eosinophilic cytoplasm (see the arrow) in a background of hepatic parenchyma (hematoxylin and eosin stain, 100 × magnification)



Immunohistochemical stains demonstrated neuroendocrine origin. Positive membranous staining with CD56 (top left, see the text label), membranous and cytoplasmic staining with synaptophysin (top right, see the text label) and chromogranin (bottom left, see the text label) were seen. A low ki67 proliferation index of 2% was present in the tumor cells (bottom right, see the text label) consistent with a diagnosis of well-differentiated neuroendocrine tumor (100 × magnification



Diagnosis & treatment

- After the diagnosis of neuroendocrine carcinoid tumor was made, the patient established care with oncology and gastroenterology for further workup and treatment.
- Her oncologist started monthly octreotide infusions, which significantly improved her carcinoid symptoms.
- Seven months after her diagnosis of a carcinoid tumor, her oncologist obtained a TTE after a new murmur was noted on the patient's physical exam.
- The TTE revealed CHD with evidence of right heart failure (enlarged RV and RA), severe TR, possible pulmonary valve stenosis, and pulmonary hypertension.

Other findings

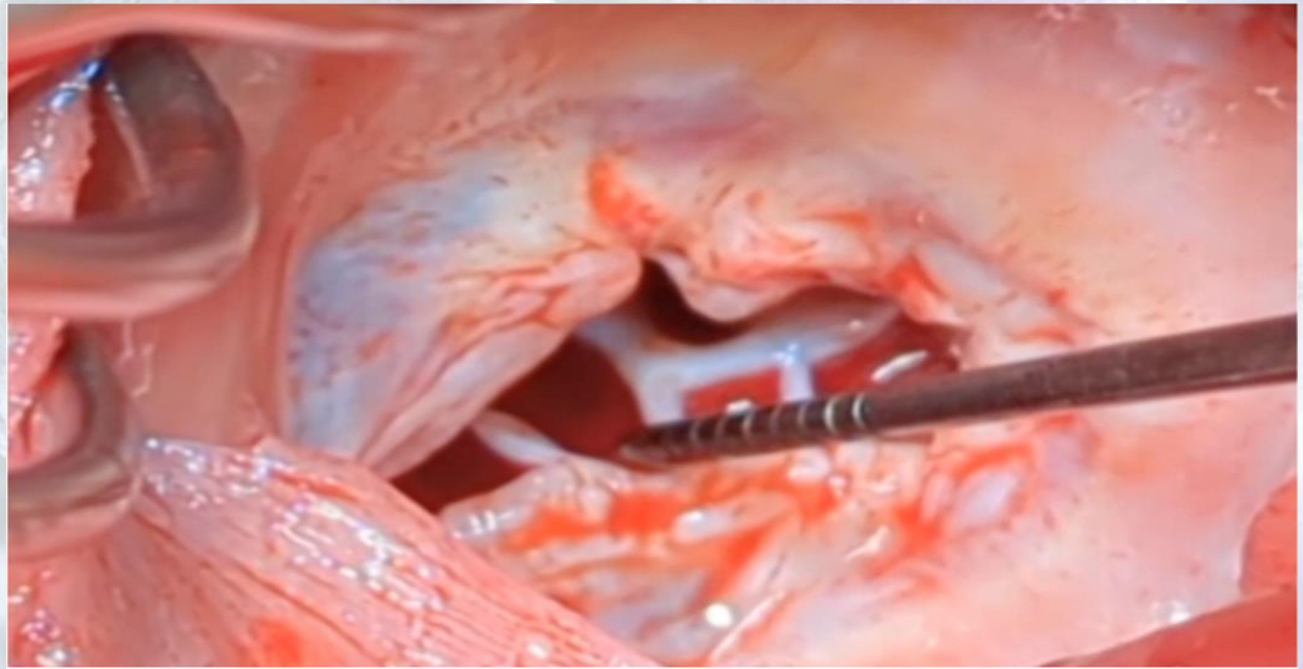
Physical exam was notable for JVP at 12 cm H2O, giant V waves, 1 + bilateral lower extremity edema, and auscultation of a murmur at the 4th sternal border.

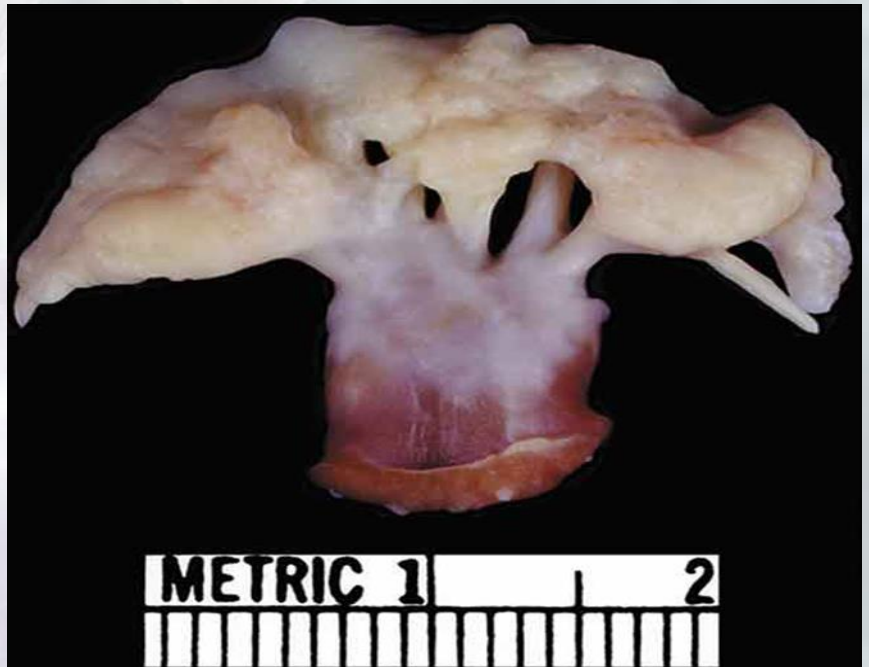
- A follow up TEE confirmed the diagnosis with visualization of a thickened tricuspid valve with limited motion and torrential tricuspid regurgitation .

- She was started on diuretic therapy and referred to cardiothoracic surgery for tricuspid valve replacement.

Cardiac surgery

- She underwent tricuspid valve replacement with a 31 mm Hancock valve and placement of permanent epicardial atrial and ventricular bipolar leads. She tolerated the intervention well and had no issues with the carcinoid crisis during her hospital course.



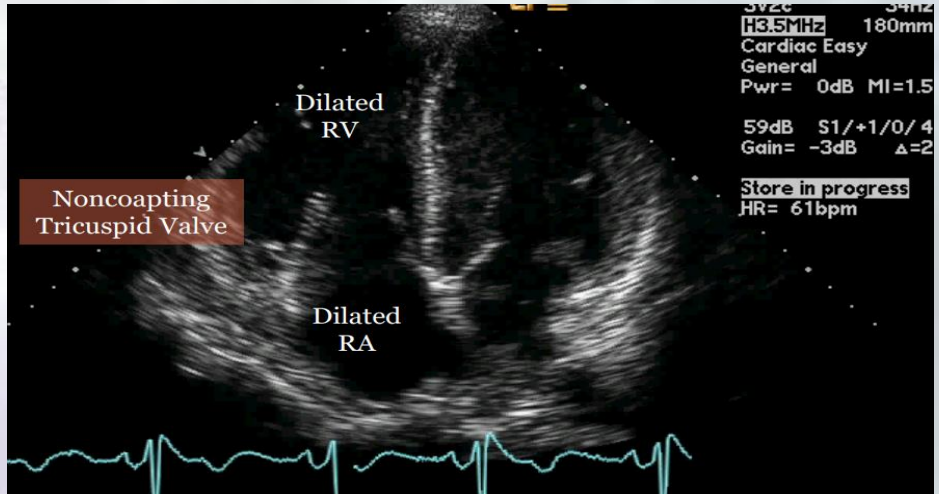


Discussion

- Most cases of CS are difficult to diagnose because of the rarity of the condition and the non-specific symptoms it presents with.
- Unfortunately, in our patient's case, her diagnosis was even further delayed, potentially by up to 12 years.
- Though timely diagnosis of CS is challenging, this patient's delayed diagnosis was likely exacerbated by poor access to the healthcare system due to her uninsured status.

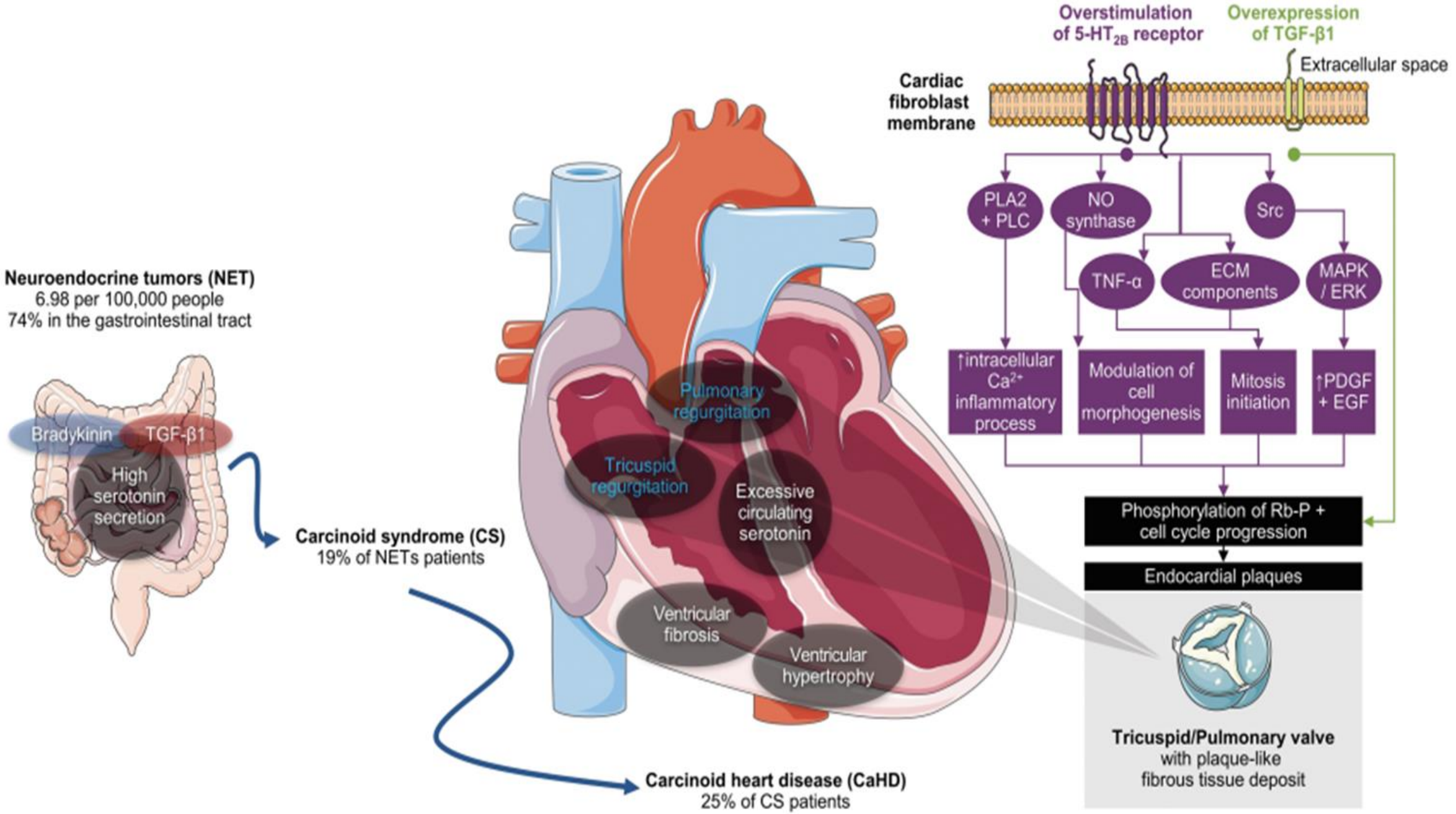
Discussion

- Delayed diagnosis of CS is thought to increase chances of developing CHD because it results in prolonged myocardial exposure to vasoactive substances, specifically serotonin, that induce cardiac valvular fibrosis .
- While serotonin is likely not the sole culprit for development of CHD, there are clinical studies that show that serotonin and 24-h urinary 5-HIAA were significantly higher (2-4 times higher) in pts who developed CHD in comparison to those who did not



The threshold for elevated urinary 5-HIAA levels has been set at >300 μmol/24 h (57 mg/24 h)

- 2.7-fold higher risk for CaHD with 5-HIAA levels 300-599 μmol/24 h (57-113 mg/24 h)
- 3.2-fold higher risk for CaHD with 5-HIAA levels 600-899 μmol/24 h (114-170 mg/24 h)
- 3.4-fold higher risk for CaHD with 5-HIAA levels ≥900 μmol/24 h (≥171 mg/24 h).
- High 5-HIAA levels with a median range of >150 mg/24 h) have been reported for disease progression and worsening of CaHD


Neuroendocrine tumors (NET)
6.98 per 100,000 people
74% in the gastrointestinal tract
Bradykinin
TGF-β1
High serotonin secretion
Carcinoid syndrome (CS)
19% of NETs patients
Carcinoid heart disease (CaHD)
25% of CS patients
Pulmonary regurgitation
Tricuspid regurgitation
Excessive circulating serotonin
Ventricular fibrosis
Ventricular hypertrophy
Overstimulation of 5-HT2B receptor
Overexpression of TGF-β1
Extracellular space
Cardiac fibroblast membrane
PLA2 + PLC
NO synthase
Src
TNF-α
ECM components
MAPK / ERK
↑intracellular Ca2+ inflammatory process
Modulation of cell morphogenesis
Mitosis initiation
↑PDGF + EGF
Phosphorylation of Rb-P + cell cycle progression
Endocardial plaques
Tricuspid/Pulmonary valve
with plaque-like
fibrous tissue deposit

- TTE is also the gold standard for diagnosis of CHD .
- Development of CHD has been associated with increased morbidity and mortality due to risk of death from progressive heart failure .
- Higher levels of serotonin are associated with CHD, lowering serotonin levels with somatostatin analogues has not been shown to prevent development or progression of CHD .
- Therapy with somatostatin analogues should still be initiated for theoretical CHD prevention, reduction of carcinoid symptoms, and for prevention of carcinoid crisis in the perioperative setting.

Conclusion and Follow up

- Once CHD is diagnosed, patients should be evaluated every 3–6 months for progression with TTE, NT-pro-BNP, chromogranin A, and urinary 5-HIAA levels to assess for valvular disease, heart failure, and recurrence or worsening of carcinoid malignancy .

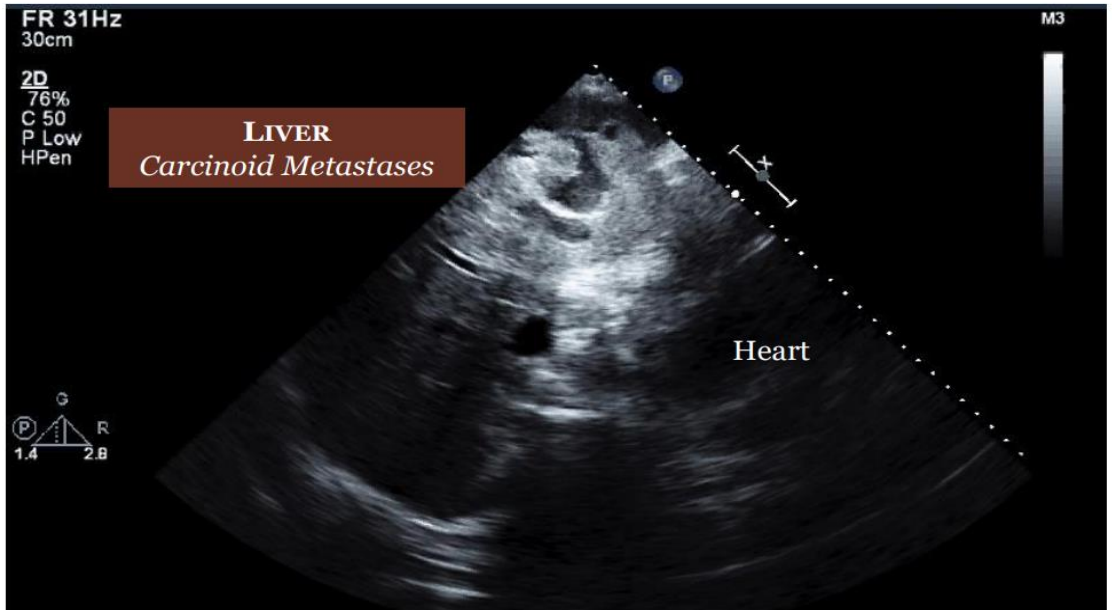
- Once CS is identified, prompt treatment with a somatostatin analogue or new ICI drugs and regular screening for CHD with TTE should occur.

Take home message of case 2

- This case highlights the importance of adequate access to healthcare for timely diagnosis and treatment of CS, appropriate screening for CHD once CS is diagnosed, and appropriate monitoring and and prompt therapy when CHD develops.

TRANSTHORACIC ECHOCARDIOGRAM

TTE showed **severe tricuspid** and **pulmonic regurgitation**... and something else in subcostal view



CASE 3

Left-sided heart valve involvement before right-sided heart valve involvement in carcinoid heart disease

- A 76-year-old woman with no prior exposure to anorexigens who had an established diagnosis of carcinoid disease with liver metastasis.
- She originally sought treatment for diarrhea and flushing and was found to have a **cecal mass** that ultimately resulted in a diagnosis of carcinoid disease.
- Subsequently, she underwent partial resection of the distal small bowel and the proximal large bowel.
- One year later , she had a total hysterectomy and bilateral salpingo-oophorectomy.

Findings

- Over the next 10 years, her health was relatively good; then she began losing weight and had increasing symptoms of diarrhea and fatigue.

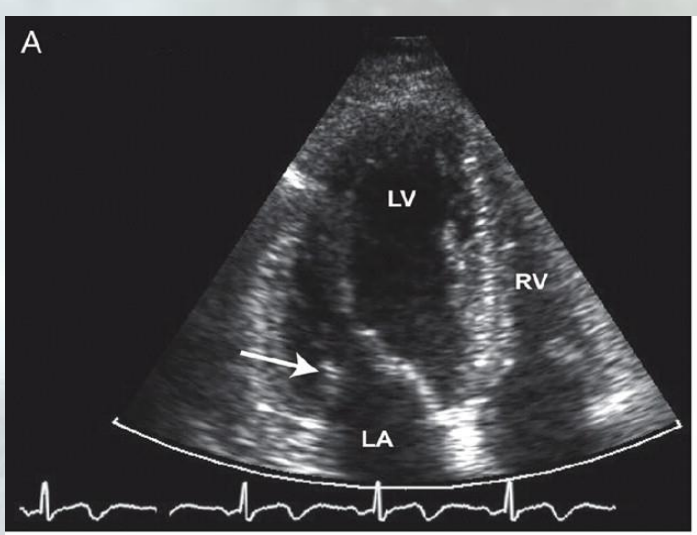
- Further evaluation by abdomen and pelvis CT scans and an octreotide nuclear scan of the patient revealed metastatic carcinoid tumors not only in the liver but also in the pelvis and the head of the pancreas;

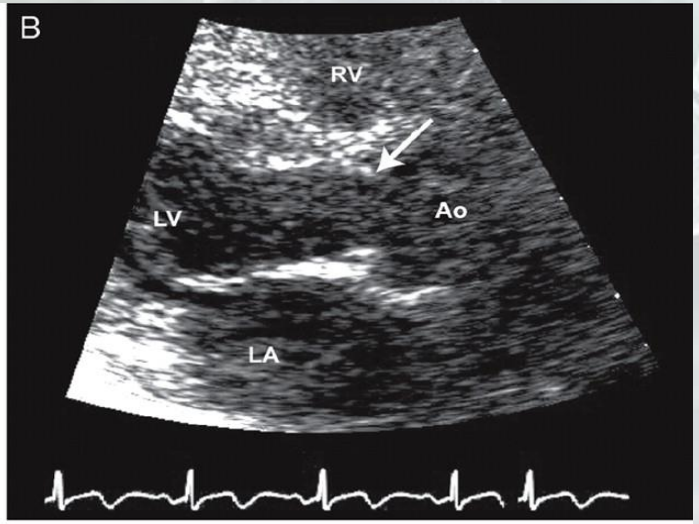
- The concentration of urinary 5-hydroxyindoleacetic acid (5-HIAA) was38 mg/24 h.

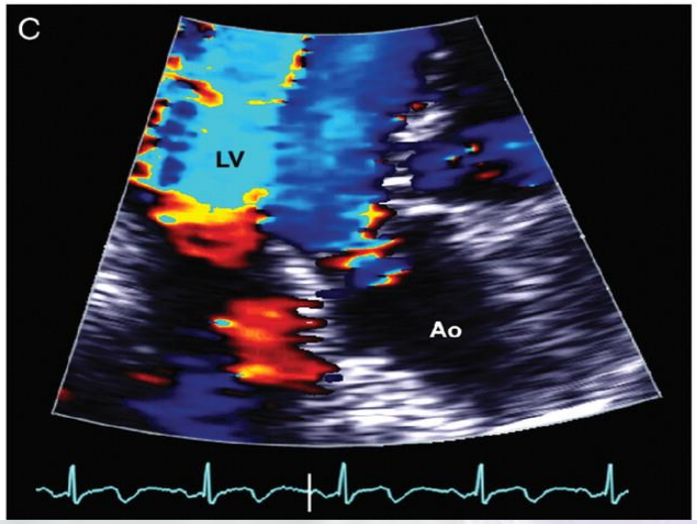
TTE

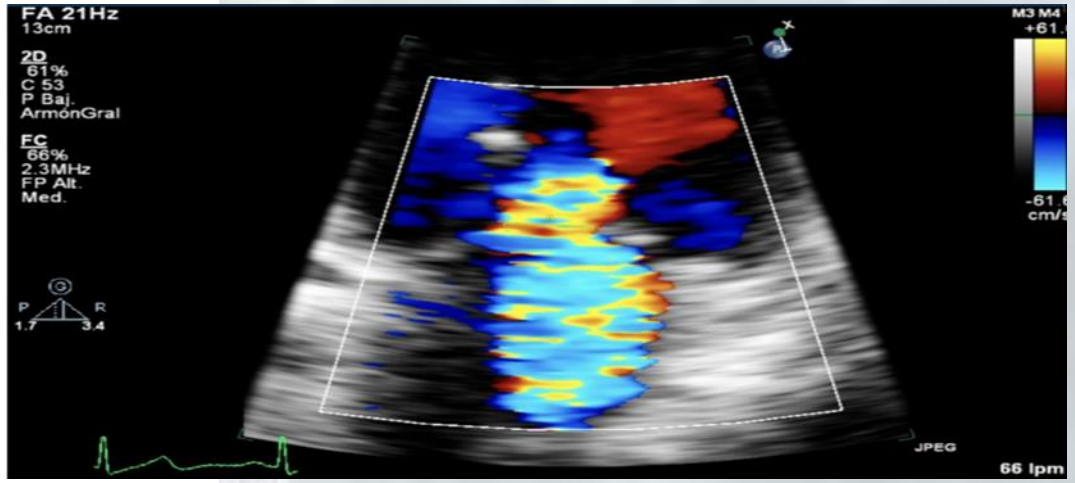
- An echocardiogram showed preserved left and right ventricular systolic function.
- The mitral valve was thickened, with restriction of the posterior mitral valve leaflet and **moderate regurgitation** but no stenosis.
- The aortic valve was also thickened, with slight doming of the right coronary cusp during systole with **mild to moderate regurgitation.**
- Although the pulmonary valve was not well visualized, Doppler imaging did not show any pulmonary valve stenosis or regurgitation .
- The tricuspid valve had minimal thickening without regurgitation.
- Echocardiographic imaging during agitated saline contrast injection confirmed the existence of a PFO

(A) Initial echocardiogram shows thickened mitral valve leaflets as seen from the apical four-chamber view. Image also shows posterior leaflet (arrow) motion being restricted in diastole. (B) Parasternal long-axis view showing thickened aortic valve leaflets (arrow). (C) Doppler colour flow imaging from apical long-axis view showing aortic regurgitation.

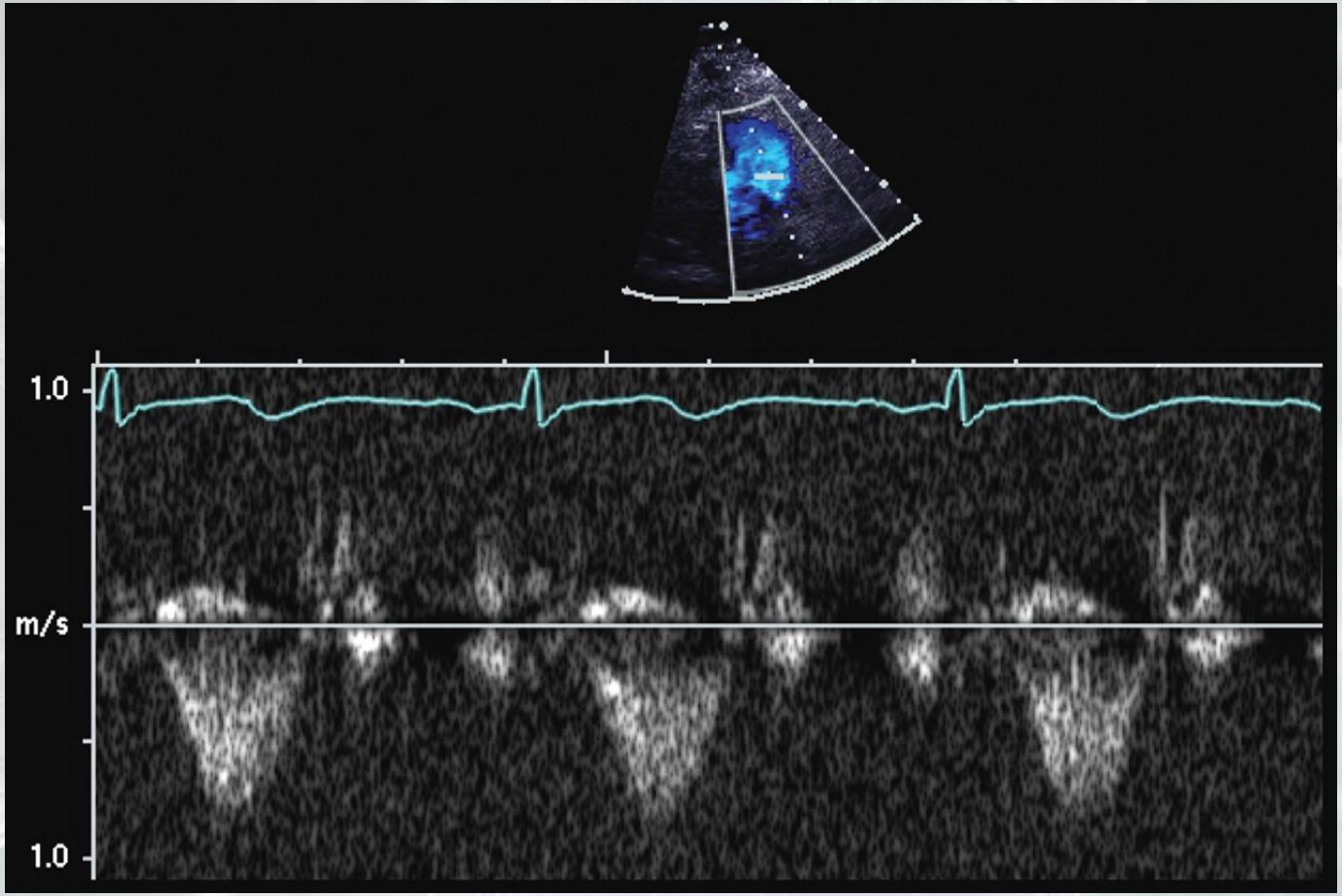




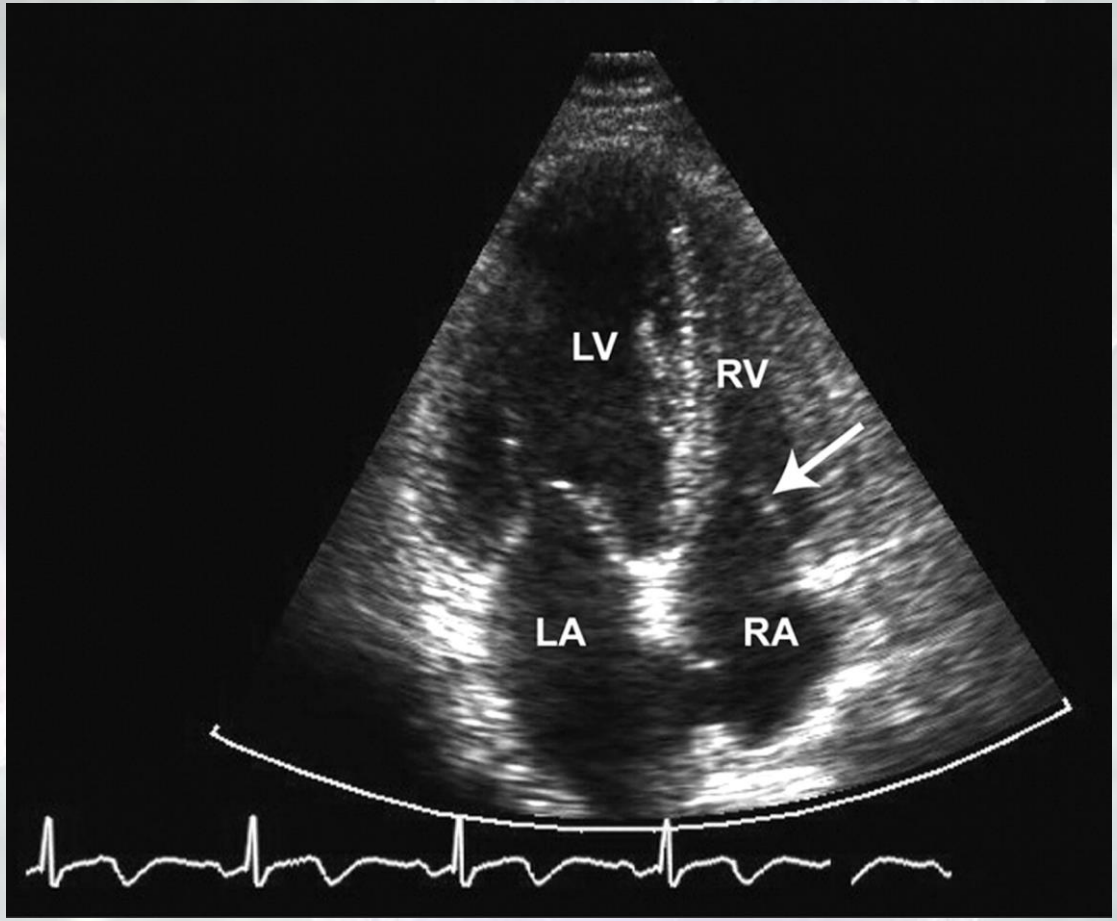




Initial echocardiogram shows Doppler velocity profile from the pulmonary valve and the absence of significant stenosis or regurgitation (peak velocity of only 1 m/s).



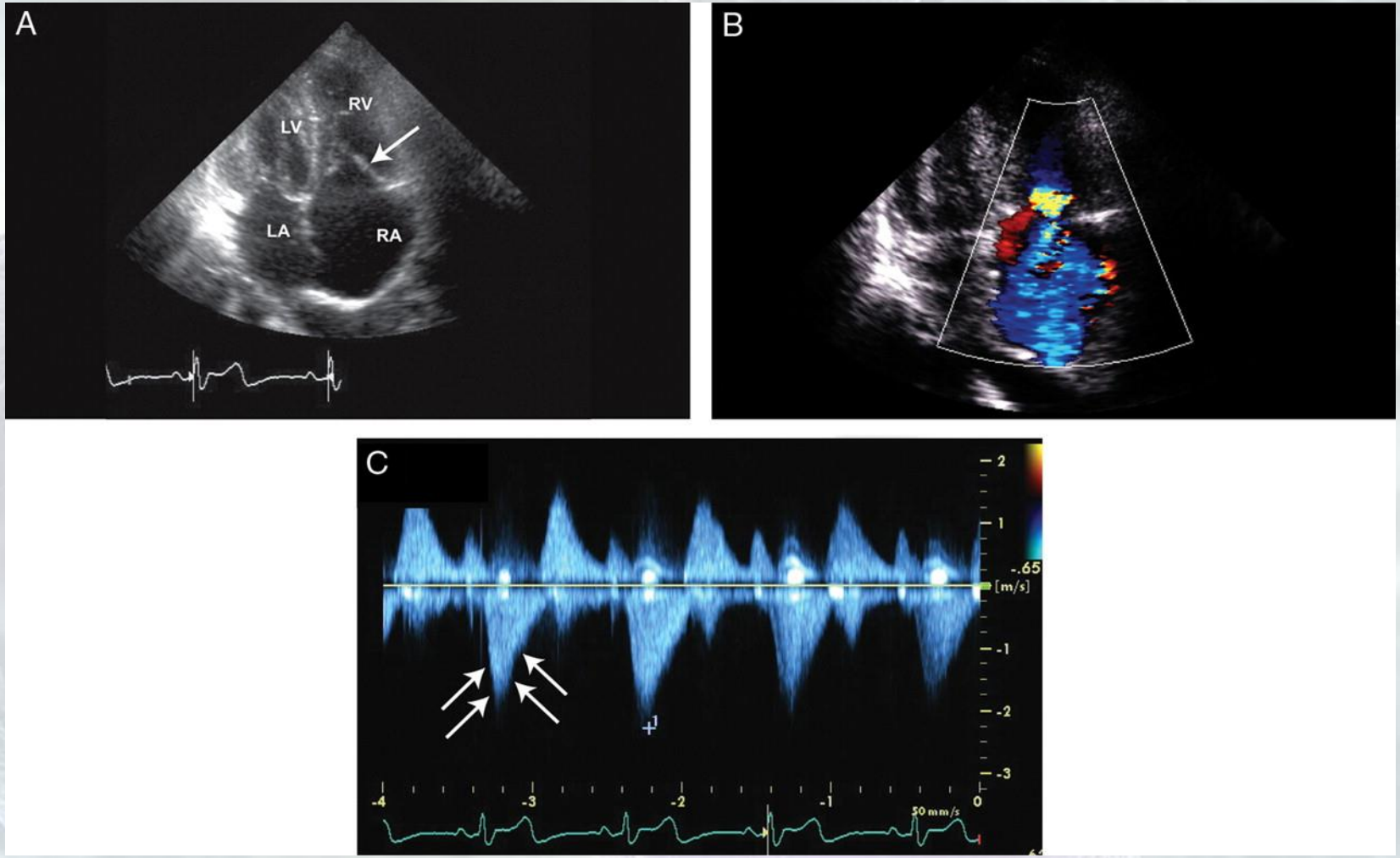
Initial echocardiogram showing apical four-chamber view of minimally thickened tricuspid valve (arrow) without dilation of right atrium (RA) or right ventricle (RV).

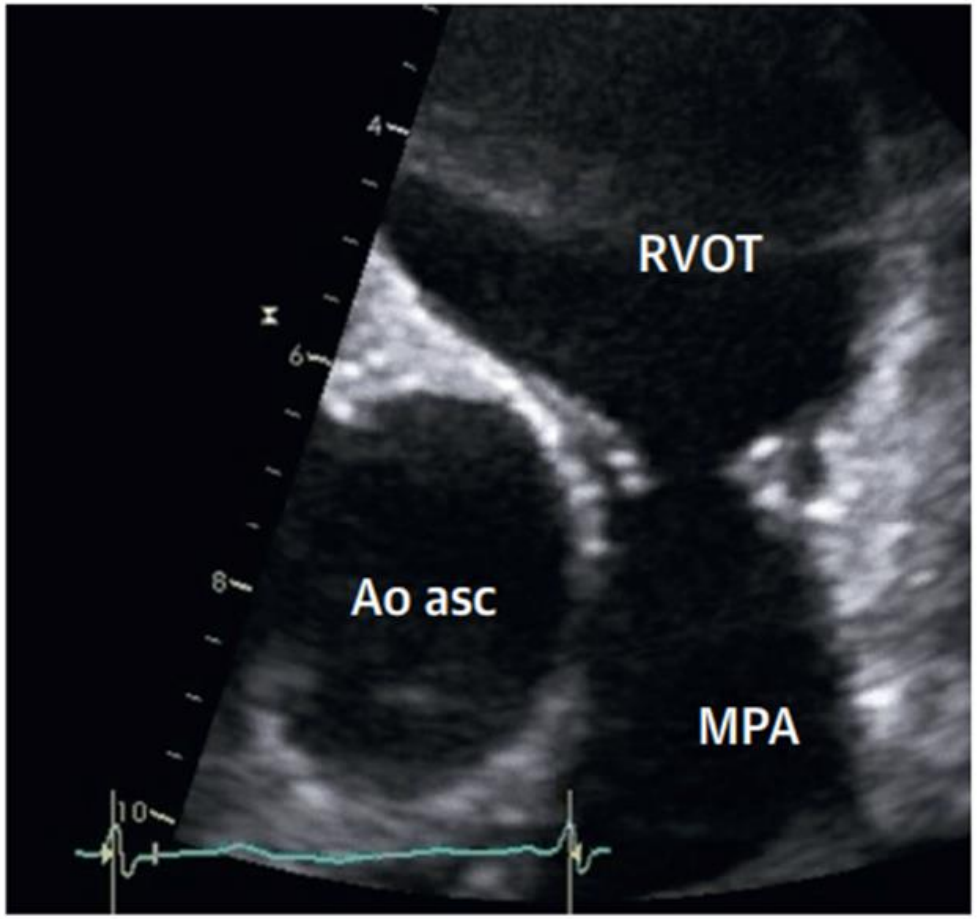


Follow up TTE

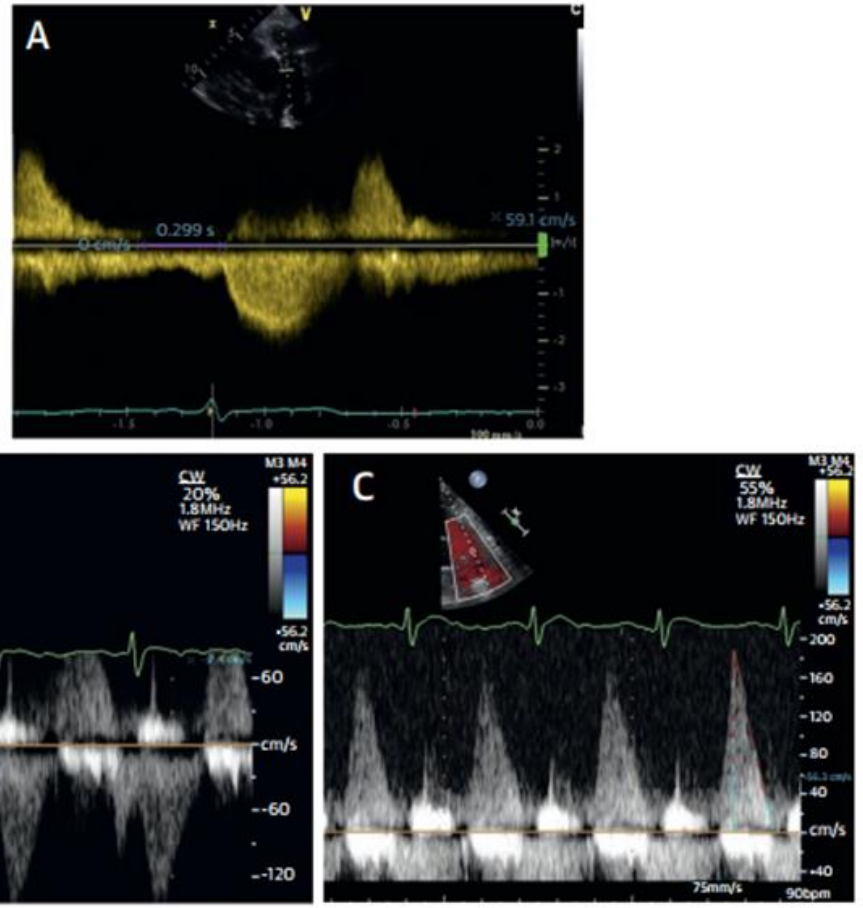
- Over the next 2 years, the patient experienced progressive short-ness of breath, ascites, and marked deterioration in functional capacity.
- Both the aortic valve and the mitral valve appeared to show progressive thickening since they had been last examined 2 years ago.
- Unlike its appearance on the previous echocardiogram, the TV was markedly thickened, with nearly immobile TV leaflets and severe TR .
- The dagger-shaped TR signal was consistent with severely elevated right atrial pressure indicated by a large V-wave . The pulmonary valve was thickened, with significant regurgitation , and the Doppler signal showed minimal stenosis of the pulmonary valve.

(*A*) Subsequent echocardiogram 2 years later shows markedly thickened and retracted tricuspid valve leaflets (arrow) with dilated right atrium (RA) and right ventricle (RV). LA indicates left atrium; LV, left ventricle. (*B*) Doppler colour flow imaging from apical four-chamber view showing severe tricuspid regurgitation. (*C*) Doppler imaging of tricuspid regurgitation showing dagger-shaped signal (arrows) due to severe tricuspid regurgitation with elevated right atrial pressure.



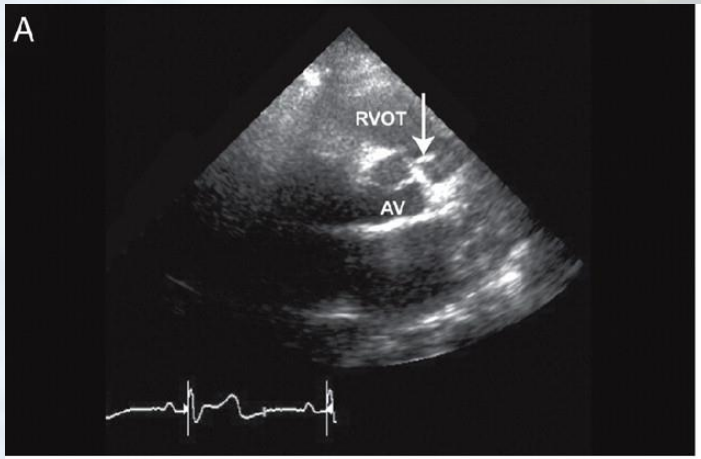


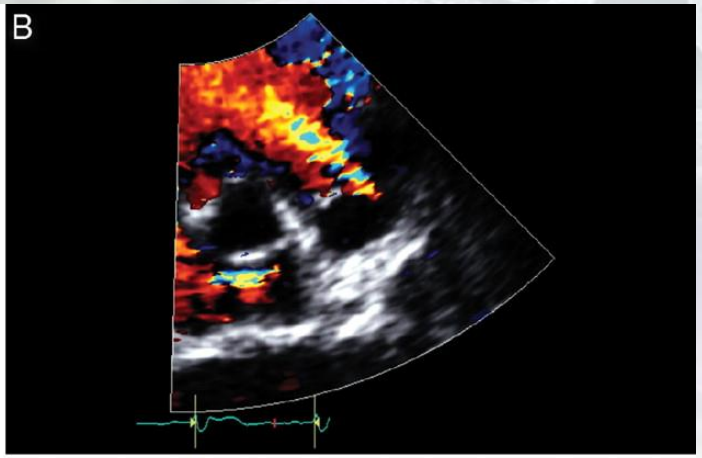
Modified parasternal short-axis view of the ascending aorta in systole. The pulmonary valve leaflets have an increased echo-density. The RVOT is dilated. Accompanying 2-dimensional Video 4 shows that the leaflets do not close in diastole and color Doppler video (Video 5). Ao asc = ascending aorta; MPA = main pulmonary artery; RVOT = right ventricle outflow tract.

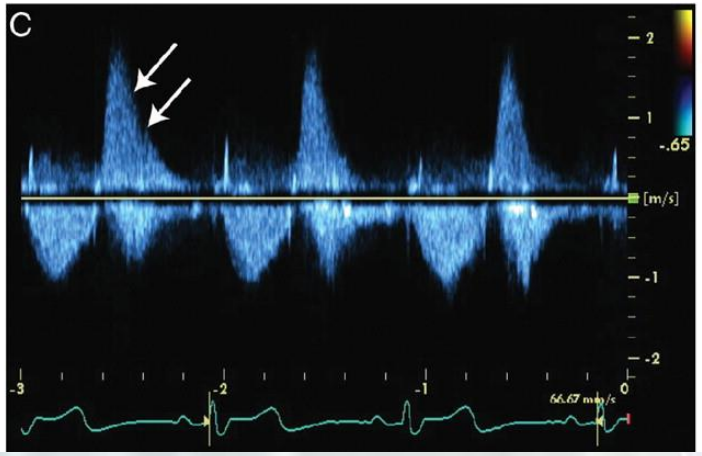


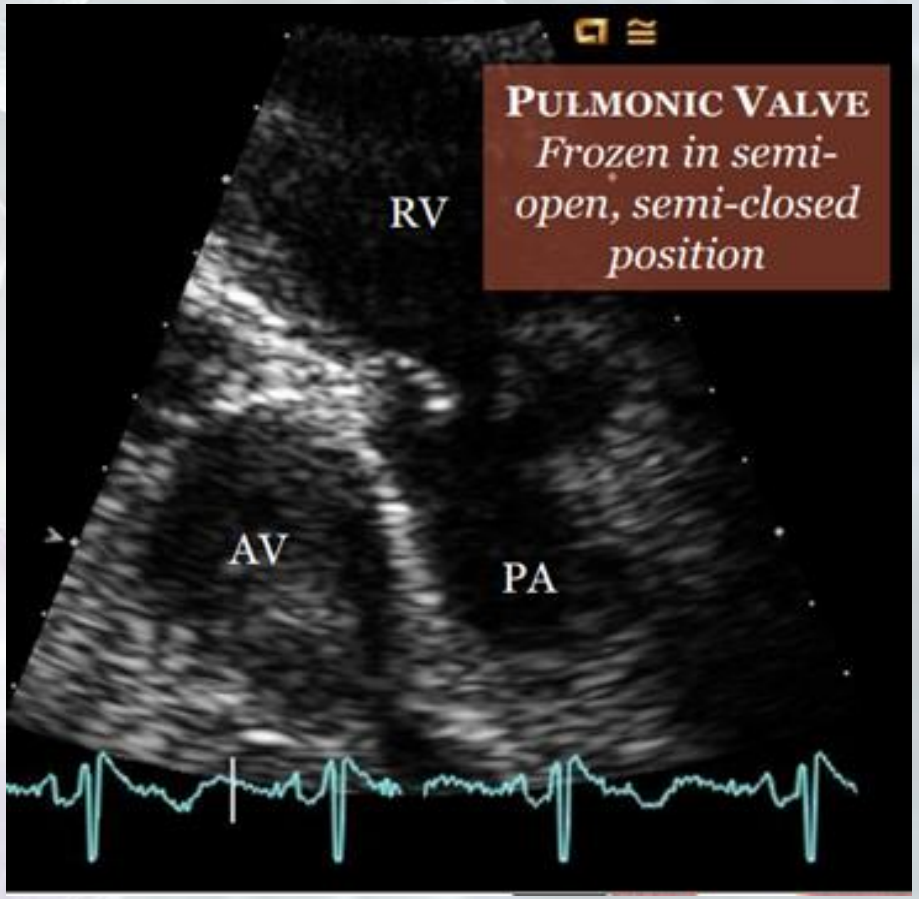
(A) Continuous-wave Doppler of pulmonary valve (same patient as in Figure 3). a short pulmonary regurgitant flow is seen which ends 299 ms before the next ejection (heart rate was 48 beats/min). See Video 3 to appreciate the visual impression of mild regurgitation due to its brief duration. With a pressure half-time of 53 ms and a pulmonary regurgitation index of 61%, this represents severe pulmonary regurgitation. Systolic forward flow velocities are mildly increased (V_{max}, 1.8 m/s). **(B)** Carcinoid pulmonary valve disease. Continuous-wave Doppler signals of moderate-to-severe pulmonary regurgitation show diastolic pulmonary regurgitant flow ending 100 ms before the onset of systolic forward flow **(blue arrows)**. Note also prominent antegrade a wave, suggesting "restrictive physiology" of the right ventricle. **(C)** Short pressure half time of pulmonary regurgitant flow (63 ms).

Subsequent echocardiogram 2 years later. (*A*) Parasternal short-axis view shows thickened pulmonary valve leaflets (arrow). AV indicates aortic valve; RVOT, right ventricular outflow tract. (*B*) Doppler colour flow imaging shows clinically significant pulmonary regurgitation. (*C*) Doppler velocity profile demonstrates minimal pulmonary valve stenosis (peak velocity of only 1 m/s) and rapid deceleration due to significant pulmonary regurgitation (arrows).



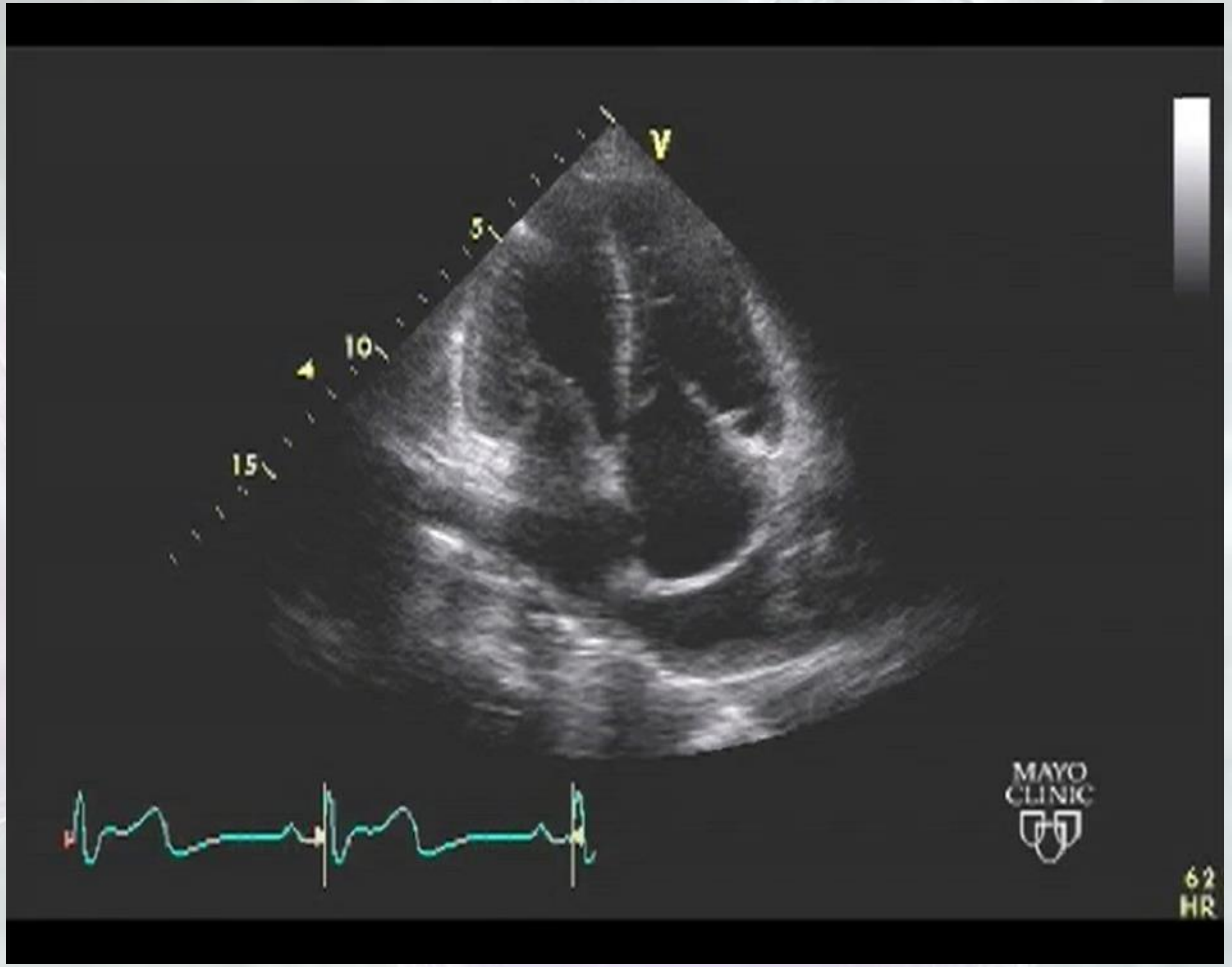






Urinary 5-HIAA increased to 49 mg/24 h, compared with 38 mg/24 h noted 2 years earlier.

Carcinoid plaques on 4 valves.

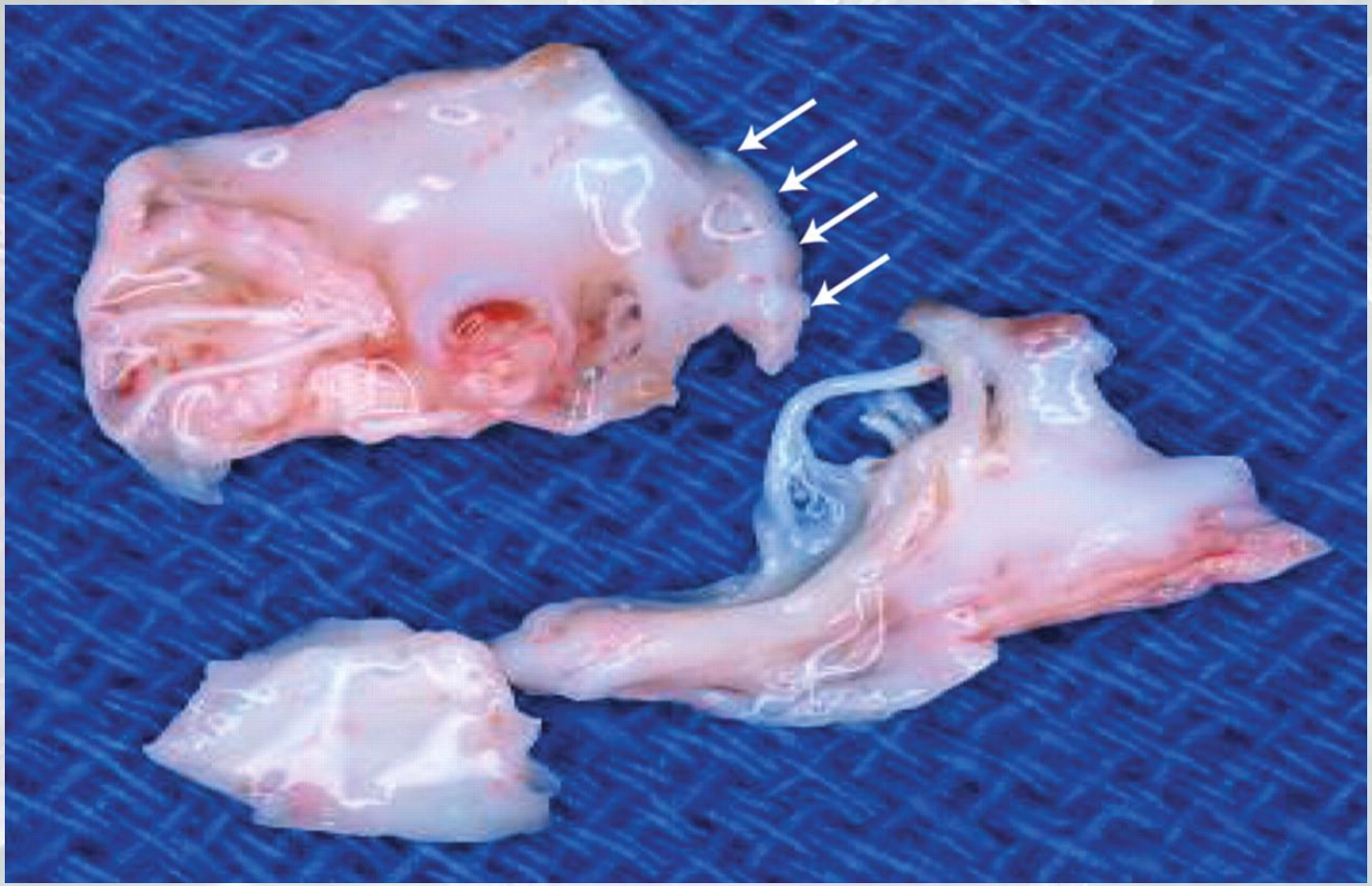


Cardiac surgery

- The patient subsequently underwent cardiac surgery that consisted of closure of the PFO and replacement of both the tricuspid valve and the pulmonary valve with tissue valves with MV repair.

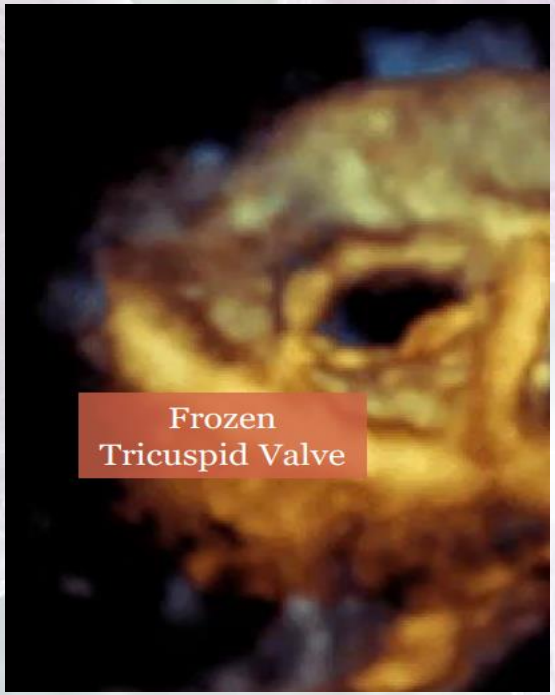
- The explanted tricuspid valve was observed to be markedly thickened and fibrotic , as was the pulmonary valve.

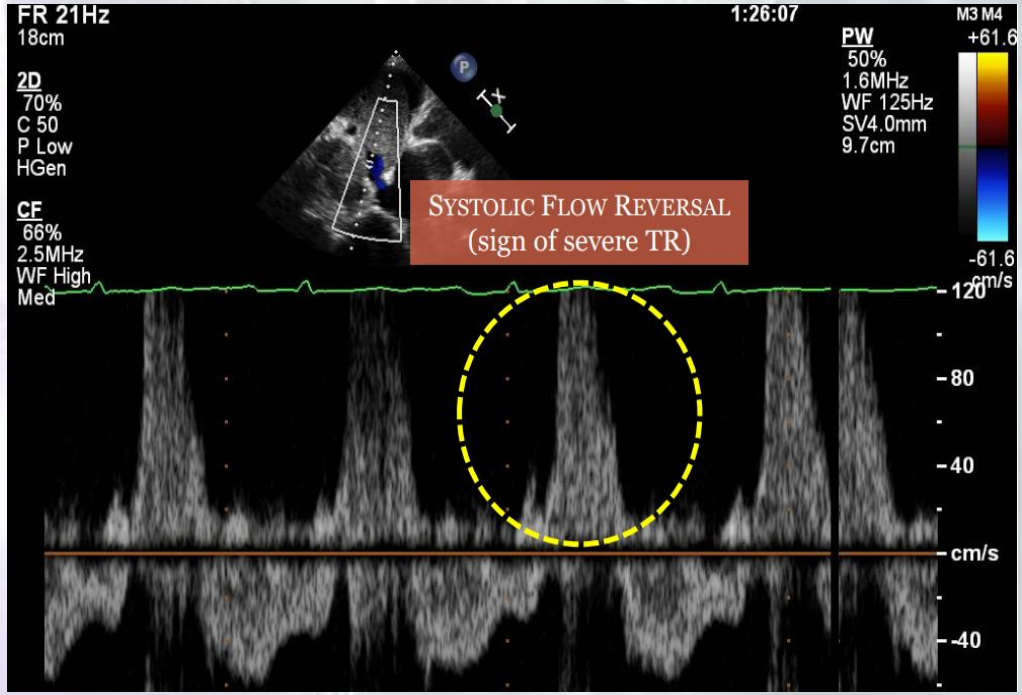
Gross pathology of the tricuspid valve shows thickened leaflets (arrows denote the edges of the leaflets).
Carcinoid heart disease is characterized by plaque-like deposits of fibrous tissue that commonly occur on the endocardial surfaces of the valve cusps, leaflets, and cardiac chambers.



Discussion

- Similar echocardiographic findings are also found in patients with drug-induced valvular heart disease, radiation-induced valve disease, and even rheumatic heart disease.





Discussion

- In carcinoid heart disease, the presence of hepatic metastases plays a permissive role in allowing high quantities of tumor products, such as serotonin and other vasoactive amines, to be available and carried directly to the right heart.

- However, the left heart is less involved due to the protective mechanism of the lung.

- As blood passes through the lungs, serotonin is degraded to 5-HIAA, which substantially reduces serotonin levels capable of inducing left heart fibrosis.

- Nonetheless, the presence of primary bronchial carcinoid, high-circulating vasoactive substances, and an atrial right-to-left shunt such as a PFO may facilitate involvement of the left heart.

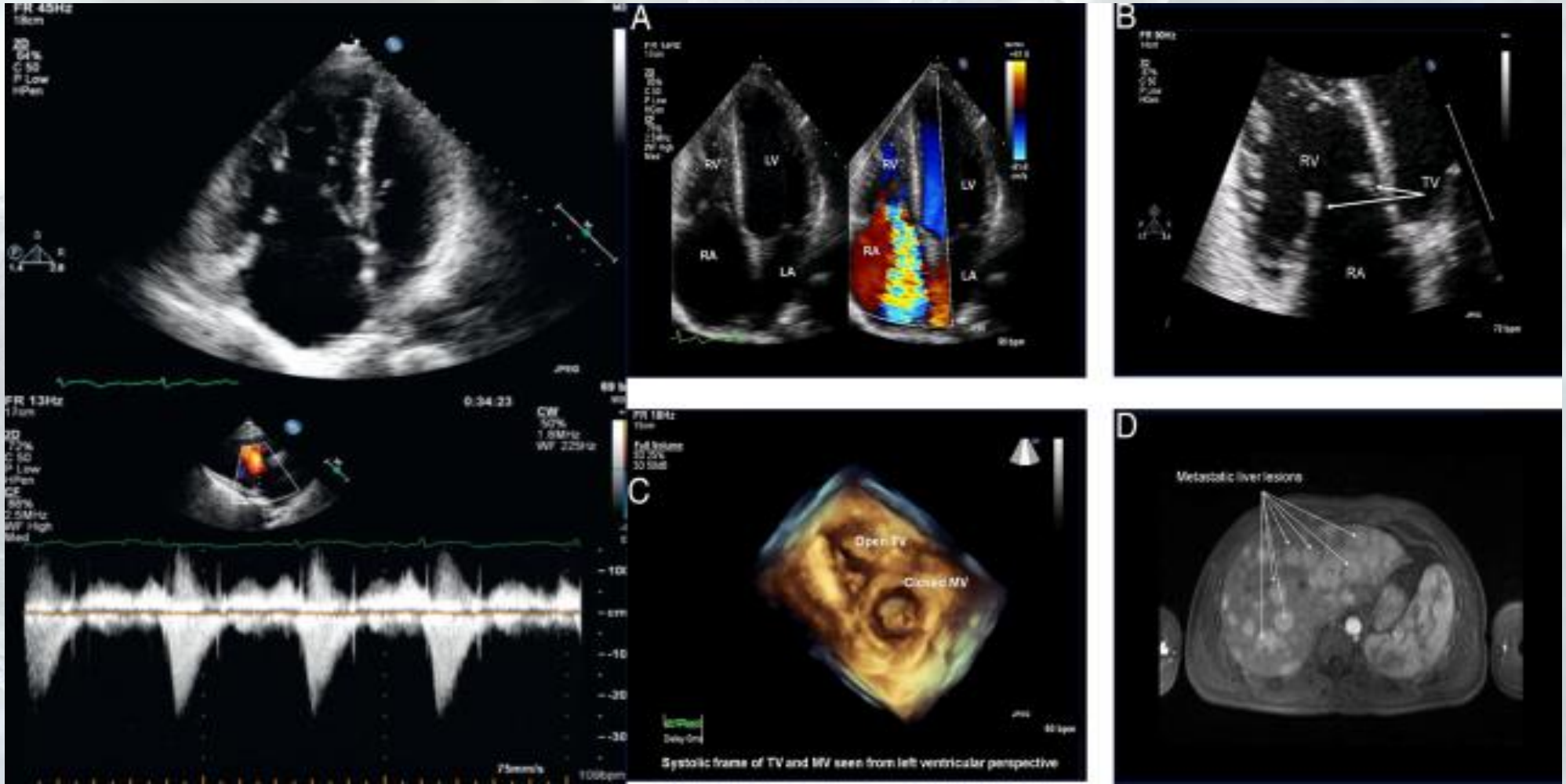
Take home message of case 3

- In our patient, the presence of elevated vasoactive peptides and a PFO paved the way for earlier involvement of the left-sided valves before the clinically significant right-sided valvular involvement.

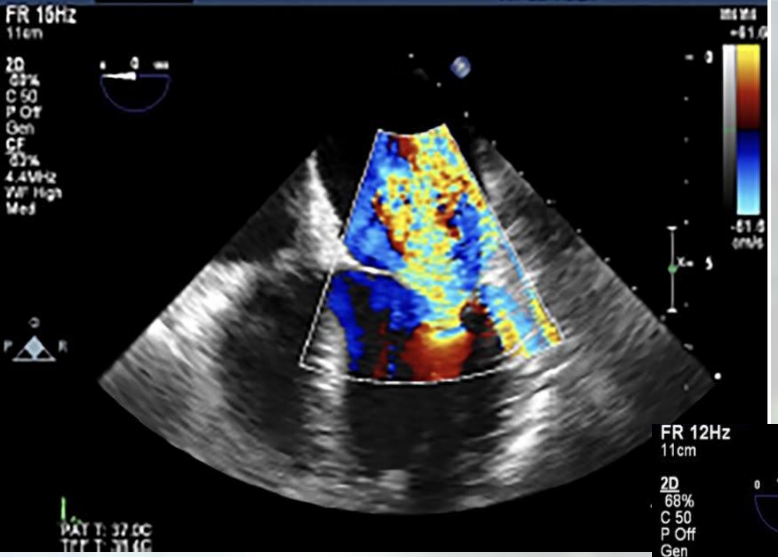
- Relatively less common manifestation of carcinoid heart disease in that aortic and mitral valve abnormalities due to carcinoid heart disease preceded the development of more common right-sided valvular heart disease.

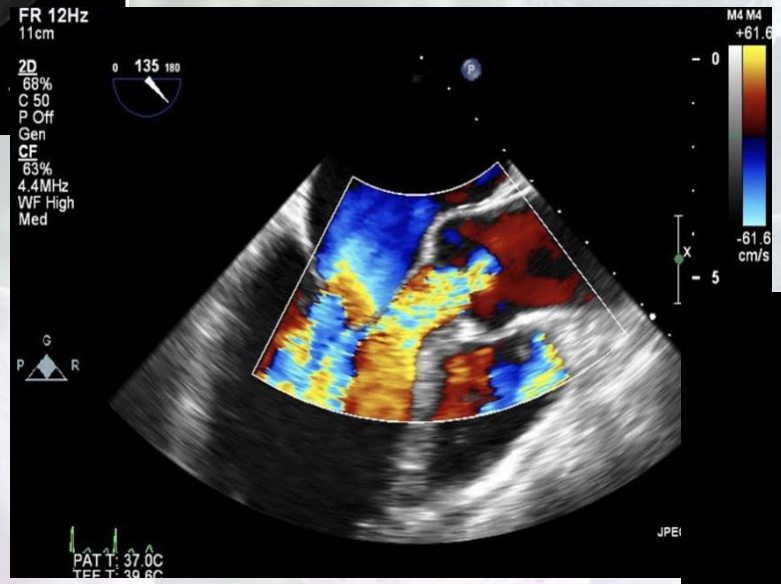
- This finding underscores the need for close surveillance of pts with carcinoid tumors.

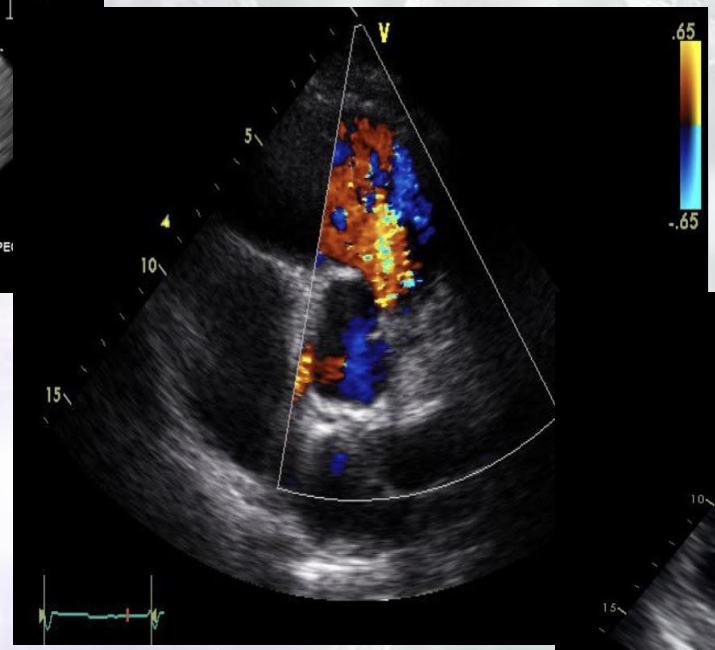
OUR PUBLISHED ANOTHER CASE: 75 year – old nice woman who presented with complaint of dyspnea ,fatigue ,edema and palpitation. CARCINOID Syndrome since 4 years ago (Neuroendocrine tumor with liver metastasis)

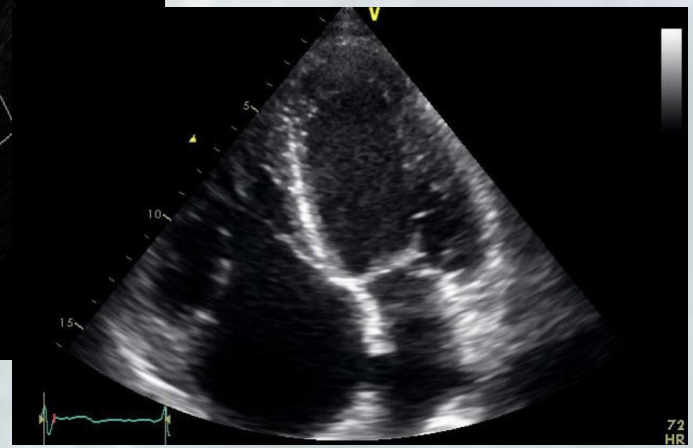


Another patient from our center with 4 valves involvement



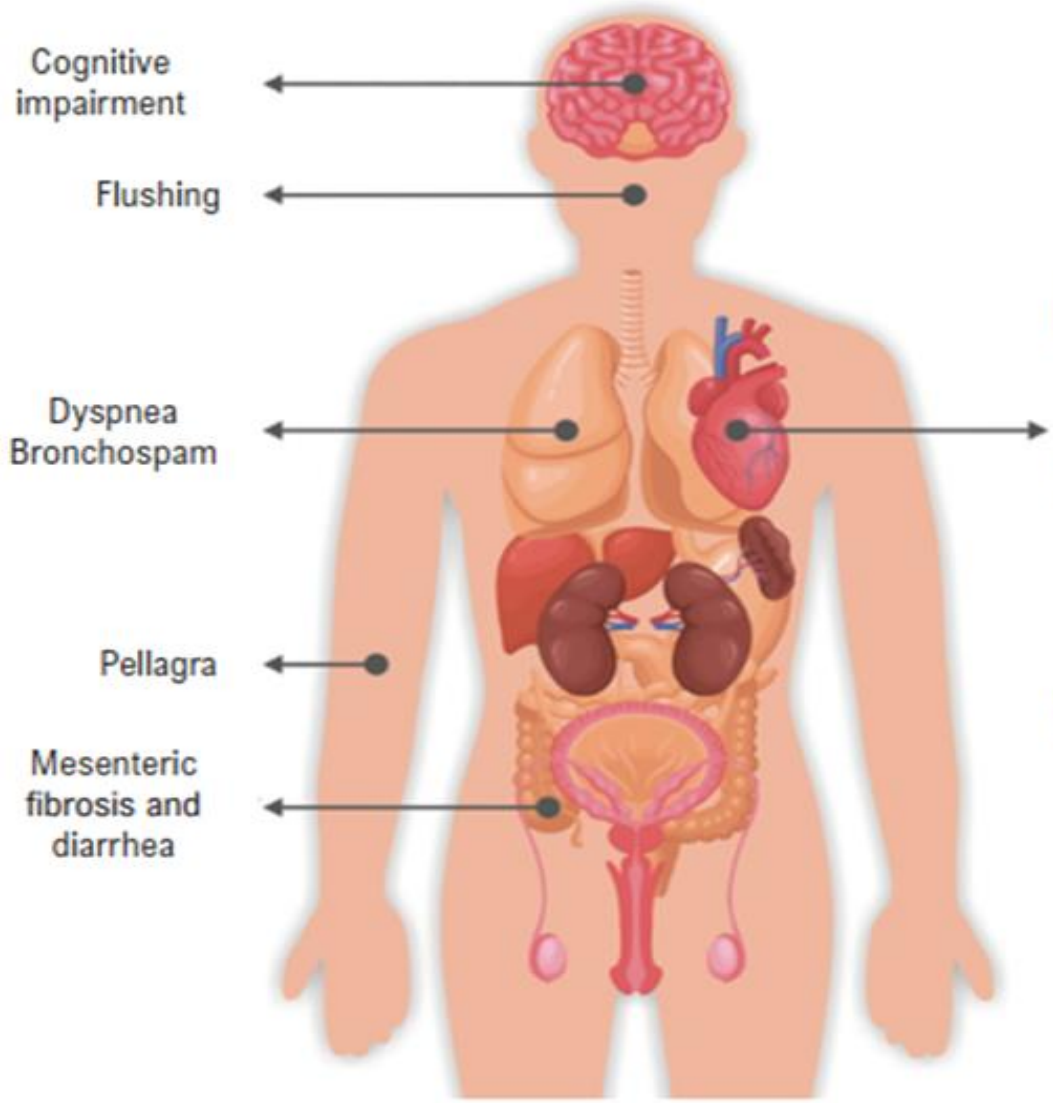







Conclusion & Treatment

Carcinoid Syndrome



Carcinoid Heart Disease

Dyspnea, palpitation, peripheral edema, ascites, hepatomegaly, jugular turgescence, hepatojugular reflux, pulmonary and tricuspid murmur

Biomarkers: NT-proBNP, 5HT, cromogranin, 5HIAA
ECG, echocardiography and CMR: RV dysfunction and right-sided valve disease (regurgitation and stenosis), RV subendocardial fibrosis

Main option: Somatostatin analogues (SSAs) - Sadostatin LAR or Lanreotide autogel.
Alternative: Octreotide, Interferon alpha.
Telotristat, Lutetium peptide receptor targeted radionuclide therapy

Interventions: Trans-arterial embolization and Surgical Reduction of Tumour Burden in NETs
Cardiac Surgery: valve replacement

LAB DATA

- There exists a high concordance between plasma and urinary 5-HIAA, with precision varying only 3%-5% for within-day and day-to-day analyses of plasma and urinary 5-HIAA.
- Plasma 5-HIAA offers the convenience and reproducibility of a single blood sample rather than a 24-h urine collection that requires prolonged dietary restriction to avoid serotonin-rich food.
- High 5-HIAA levels also correlate with risk of Cardiac involvement, disease progression and also death due to CaHD.

NT-proBNP has been suggested as a reasonable early diagnostic marker of CaHD, as it appears to be produced by cardiomyocytes when under mild or moderate strain even before an echocardiographic finding of CaHD can be detected.

- NT-proBNP is an inactive neurohormone released in response to high ventricular wall stress due to cardiac volume and pressure overload.
- Baseline NT-proBNP assessment is recommended at the time of CS diagnosis.
- Across multiple studies, the median NT-proBNP levels were higher among patients with CaHD compared to those without CaHD

- Chromogranin A (CgA), a glycoprotein produced by NET cells, is a non-specific biomarker for severe CaHD.

- CgA is not routinely used clinically by most NET and CaHD specialists to guide NET therapy.

- Its metabolite, pancreastatin, may be of more utility in predicting survival since it is unaffected by proton pump inhibitor use and pernicious anemia

Comparison of select CaHD/CS evaluation recommendations from major guidance papers.

	NCCN[22]	NANETS[20]
5-HIAA	Urinary or plasma 5-HIAA	Threshold of >5× ULN urinary or plasma 5-HIAA to undergo annual echocardiogram
NT-proBNP	—	Negative predictive value
Echocardiogram	TTE every 1-3 years or as clinically indicated for morphologic evaluation of the valves (especially tricuspid and pulmonic valves) and right heart	Annual echocardiogram in patients with ↑ serotonin or 5-HIAA
Other imaging	^{68}Ga DOTATATE or ^{68}Ga DOTATOC or ^{64}Cu DOTATATE PET scan to assess somatostatin receptor status	^{68}Ga DOTATATE PET scan for overall tumor assessment

Comparison of select CaHD/CS evaluation recommendations from major guidance papers

	ACC[6]	ENETS[21]
5-HIAA	>300 μmoL/24 h urinary or plasma levels; screen all patients with small intestinal NETs	≥300 μmol/24 h urinary or plasma
NT-proBNP	>260 pg/mL or 31 pmol/L; screen every 6 months for CaHD in patients with CS	>260 pg/mL or 31 pmol/L; screen patients with ↑ 5-HIAA or symptoms at baseline and follow-up
Echocardiogram	TTE every 3-6 months for patients with CS and high suspicion of CaHD; 3D TTE preferred over 2D TTE to assess valve pathology	TTE every 6-12 months to screen patients with ↑ NT-proBNP
Other imaging	CMR scans valuable as adjuncts; CCT accurate for left/right ventricular volume calculations	CMR scans and CCT useful as alternatives

Comparison of select CaHD/CS management recommendations from major guidance papers

	NCCN[22]
Anti-tumor therapies/control of CS syndrome	1st line: SSA[a] 2nd line: depending on site of disease, disease stage, line of therapy, and other factors, treatment options may include PRRT[b], systemic therapy, surgical cytoreduction, hepatic arterial embolization
Diarrhea volume control[d]	Telotristat ethyl
HF symptom control	—
Embolization therapy	—
Valve replacement surgery	Valve replacement (typically tricuspid and pulmonary) indicated for patients with symptomatic disease

Comparison of select CaHD/CS management recommendations from major guidance papers

	NANETS[20]	ACC[6]	ENETS[21]
Anti-tumor therapies/control of CS syndrome	1st line: SSA[a] 2nd line: PRRT[b], everolimus, liver embolization Last: IFN-α	1st line: SSA[a] 2nd line: IFN-α, PRRT[c] Use with caution: everolimus, TAE, surgical hepatic debulking	1st line: SSA[a] 2nd line: PRRT[b], everolimus, IFN-α Use with caution: surgical hepatic resection, TAE, TACE, TARE/SIRT
Diarrhea volume control[d]	Telotristat ethyl	Telotristat ethyl	Telotristat ethyl
HF symptom control	—	Loop and thiazide diuretics, aldosterone	Loop and thiazide diuretics, aldosterone
Embolization therapy	Bland embolization, chemoembolization, and radioembolization can be appropriate		
Valve replacement surgery	Bioprosthetic preferred over mechanical tricuspid and pulmonary valves for moderate-severe CaHD with life expectancy >1 year	Bioprosthetic preferred over mechanical valve; percutaneous catheter-based interventions for high-risk patients	Bioprosthetic preferred over mechanical valve; percutaneous valve-in-valve in degenerated surgical bioprosthesis

Medical Therapy of CS and CHD

- The overriding goal of therapy for a patient with CaHD is the aggressive reduction of NET hormone secretion while managing complications arising from right heart failure

- Across the 4 major guidance papers for CaHD/CS, all recommend the use of SSAs as first-line anti-tumor therapy and as means of controlling carcinoid syndrome

- Loop and thiazide diuretic & Spirinolactone → control fluid status

- Somatostatin analogues (long-acting) → Octreotide and Lanreotide → control CS signs and symptoms + counteract the development or progression of CaHD ???

these medications neither

reverse the progression of the carcinoid cardiac involvement

nor improve survival prospects

- Telotristat etiprate → peripheral 5-HT synthesis inhibitor → diarrhea control

- Pasireotide (new somatostatin analogue) → symptomatic patients + refractory to octreotide therapy

- **Interferon-alpha** → uncontrolled carcinoid syndrome resistant to somatostatin

- **Paclitaxel and trastuzumab** + **interleukin-12** → therapy for human epidermal growth factor receptor 2/neuexpressing malignancies, including carcinoid tumors

- **Temozolomide and capecitabine (CAPTEM)** → potent debulking option in pancreatic and lung NETs, and in well-differentiated small bowel NETs with higher Ki-67 indexes

Main drugs used in carcinoid syndrome treatment and key clinical trials

DRUG	REFERENCES
Octreotide	Rubin et al[35]
Lanreotide	Ruszniewski et al[36] Ruszniewski et al[37] Vinik et al (ELECT trial)[38]
Telotristat ethyl	Kulke et al[39] Pavel et al[40] Kulke et al[41] Pavel et al (TELECAST trial)[42]
Peptide receptor radionuclide therapy: ^{90}Y-edotreotide ^{177}Lu-Dotatate	Bushnell et al[43] Strosberg et al (NETTER-1 trial)[44]
Interferon alfa	Pavel et al[45]
Everolimus	Pavel et al (RADIANT-2 trial)[46]
Pasireotide	Kvols et al[47] Wolin et al[48]
Capecitabine/ temozolomide	Papaxoinis et al[49] de Mestier et al[50]

Non-cardiac intervention

- Transcatheter arterial embolization → decreasing tumor burden and hormone levels in subjects with substantial metastases in the liver.
- Nonetheless, it must be applied cautiously in subjects with advanced CaHD and right ventricle dysfunction or substantial liver involvement since adverse events (bleeding or liver failure)

Total portal vein occlusion, poor overall performance status, and liver failure are perceived as relative contraindications to such therapy

- **Cytoreduction, interventional treatment with resection, radiofrequency ablation, bland embolization, chemoembolization or radioembolization is possible.**
- **Partial hepatic resection** → decreases tumor burden and improves the quality of life and overall survival.
- Nonetheless, such procedures might be challenging as well as life-threatening. **They should be performed after heart valve repair.**

Cardiac surgery

- **Cardiac surgery → mainly valve replacemen**

in advanced CaHD → relieve persistent

symptoms and improve prognosis

- **Tricuspid valve insufficiency** (the most common abnormality) → **severe** tricuspid valve insufficiency + without contradictions → should be qualified for **valve replacement**
- **RVOT obstruction** and **pulmonary valve insufficiency** → subjects are eligible for pulmonary valve replacement and RVOT enlargement with a patch.
- **Mitral or Aortic valve disease → valve replacement or repair** (depending on the severity of the disease)

- PFO closure as well as the excision of carcinoid metastasis

- Also, in sporadic cases, quadruple valve replacement/repair might be required

- Tricuspid with or without pulmonic bioprosthetic valve replacement is preferred over mechanical valve replacement for patients with severe CaHD and ≥12 months of anticipated post-operative survival to avoid long term anticoagulation in these patients who may patients with CaHD and CS who may have a propensity for bleeding

- Percutaneous interventions are reserved for selected patients

- **Carcinoid crisis** is a potentially life-threatening complication in subjects with CS undergoing surgery as well as when catecholamine release due to stress, tumor manipulation and exposed to anesthetic drugs or other medicines (eg, vasopressors or opioids).
- In this scenario, cardiogenic shock due to RV dysfunction might occur, resulting in high rates of mortality
- In prevention in the perioperative period, subjects with CaHD should receive **octreotide venous infusion** with a flow rate of 50 to 100 mg/h for 12 hours before surgery.
- The infusion should be maintained throughout the operation and then thereafter until the patient's state stabilization.

- In CaHD patients, cardiac output monitors are suggested to assess the fluid status, to optimize the cardiac index and to prevent tissue hypoxia.

- In vasoplegic shock, hydrocortisone (100 mg every 8 hours) and intravenous vasopressin (0.04 U – 0.06 U/h) might be considered

After valve surgery for carcinoid heart disease :

- Immediate post-operative echocardiography
- An echocardiographic examination **3–6 months** postoperatively and thereafter yearly are recommended in the absence of new symptoms.
- A focus of post-operative surveillance should be on the evolution of trans-prosthetic valves gradients, as an increase may indicate thrombosis or structural degeneration of the prosthesis and also other parameters of echocardiography should be evaluated comprehensively.


Thank for your attention