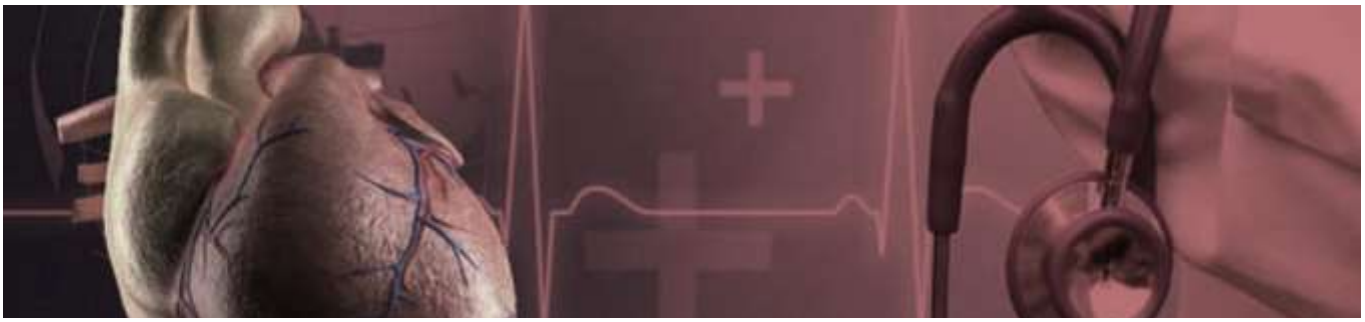
RIGHT-SIDED VALVE DYSFUNCTION REVEALING OVARIAN CARCINOID TUMOUR



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ABSTRACT

Neuro-endocrine tumours cause a paraneoplastic syndrome. Carcinoid cells synthesis and release a countless number of bioactive substances such as 5-Hydroxytryptamine, prostaglandins, bradykinins, and histamine. Thereby, carcinoid heart disease is due to a long exposure of the heart to vasoactive substances, especially serotonin. We report the case of a right valvular heart disease with patent foramen ovale revealing a carcinoid syndrome in a young woman of 54 year-old. She consults for asthenia, diarrhoea and repetitive episodes of flush syndrome in the lower limbs appearing during periods. The carcinoid heart disease was related to ovarian well-differentiated neuro-endocrine tumour confirmed by high level of serotonin, imaging (pelvic MRI, octreoscanner) and an anatomopathologic and immunohistochemical study of degenerated dermoid cyst after surgey. The clinical, paraclinical and therapeutic aspects are discussed in this work.

Keywords:

Carcinoid syndrome,
Carcinoid heart disease,
Complications, Fibrosis.

I. INTRODUCTION

Well-differentiated neuro-endocrine tumours (NET) occured in 5 per 100 000 per year in the US population [1]. However, this incidence still not well-known. The first case of NET was published many years ago by Lubrasch, two cases of gatrointestinal NET arising from small intestine have been diagnosed in autopsy [2]. In 1907 Oberndorf used the term ‘’carcinoid ‘’ to describe well-differentiated neuro-endocrine tumours [3], and in 1952, the first case of carcinoid heart disease was reported in a young man [4].

Patients with NET may develop carcinoid syndrome, it is estimated about 30%. Carcinoid syndrome, or paraneoplastic syndrome, is characterised by flush syndrome, abdominal pain, diarrhoea, and bronchospasms [5]. Carcinoid cells synthesis and release a myriad of bioactive substances such as 5-Hydroxytryptamine, histamine, and prostaglandins [6]. These substances act on various organs (skin, intestine, heart, lung, brain…). The most frequent NET is the gastrointestinal neuro-endocrine tumours emerging from the midgut in 74%. The pulmonary NET appears in 25% and the pancreas NET is rare [6]. The ovarian carcinoid cells are extremely rare, ranging from 0.31 to 1.36% [7]. The most important complication of carcinoid syndrome is carcinoid heart disease (CHD). The term CHD designates a fibrosis deposits in the heart endothelium. Surgical procedures of carcinoid tumour remain primary to decrease the progression of CHD. Medical and surgical management of CHD is still debated.

II. PRESENTATION OF CASE

A 54 year-old woman from Russian, living in Morocco. She has as risk factors, arterial hypertension under beta-blocker. She presented to our service with a 2 years history of asthenia, diarrhoea, palpitation and repetitive episodes of flush syndrome in the lower limbs appearing during periods, with progressive onset of dyspnoea which has worsened in stage II of NHYA classification.

Her background was an unheeded ovarian cyst for the past 20 years. Physical examination found asthenic patient, oedema of the lower limbs. Thrombophlebitis and erysipelas have been eliminated. Cardiac examination revealed the following results: BP: 120/80mmhg, pulse rate: 75 beats/mn, and temperature: 37°C. The heart sound showed a systolic murmur in the pulmonary region, without signs of right heart failure. The electrocardiogram showed a sinus rhythm, normal voltage without ST-T wave abnormalities (figure 1).

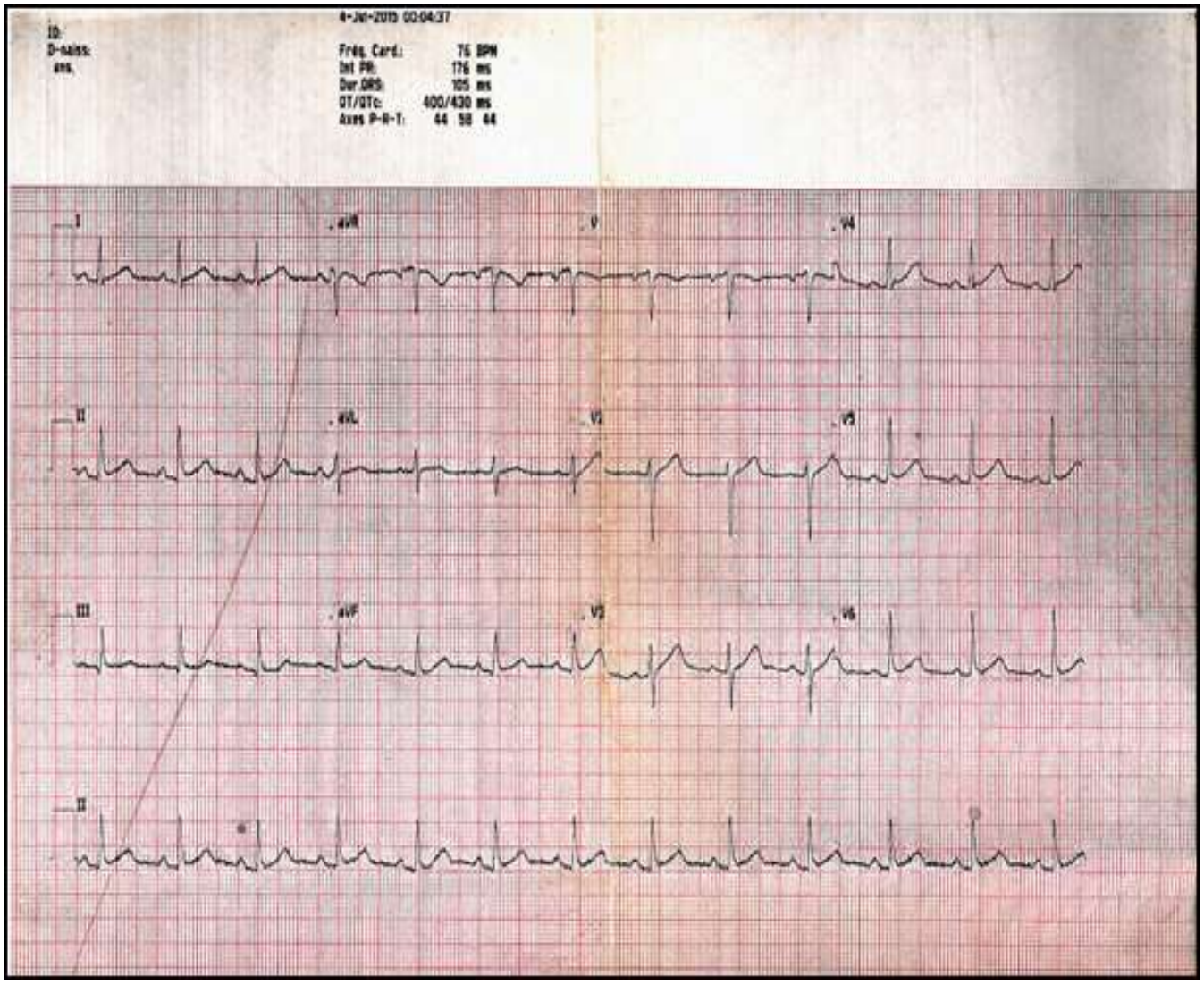


Figure1: electrocardiogram showed a sinus rhythm without ST-T wave abnormalities.

The echocardiography showed a normal left systolic function with a severe tricuspid regurgitation with a right-sided heart dilatation (figure 2). The tricuspid valve was virtually immobile frozen and partly open, resulting in the both stenosis and regurgitation. Tricuspid leaflets were thickened (figure. 3).

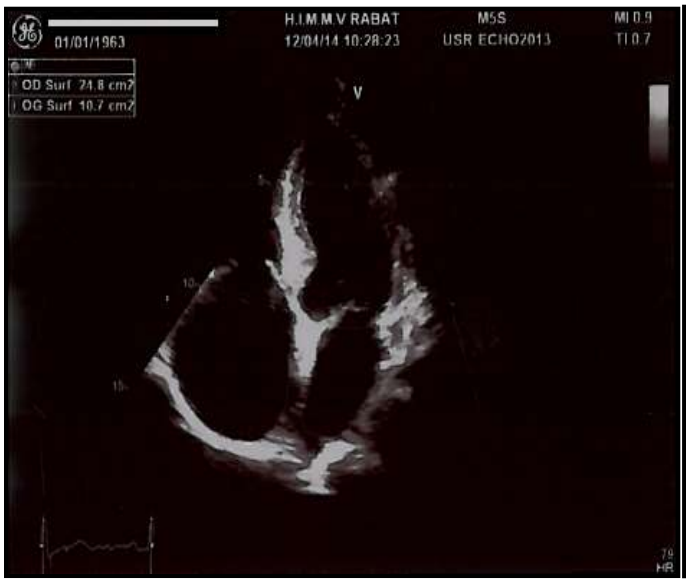


Fig- 2: dilated right-sided heart, with non-coaptation of tricuspid valve.

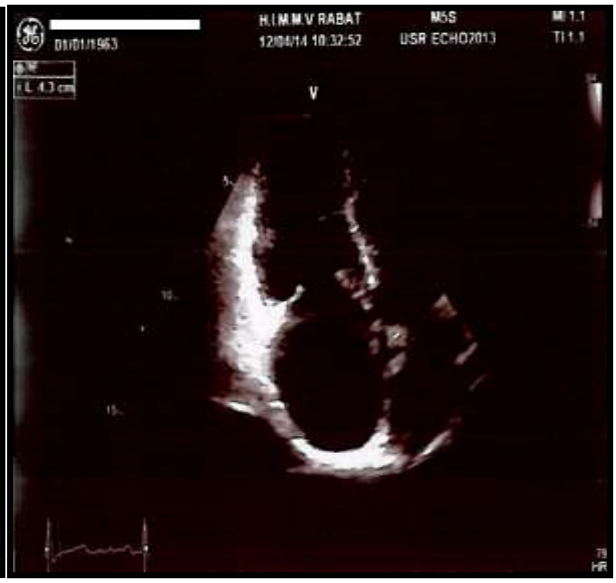
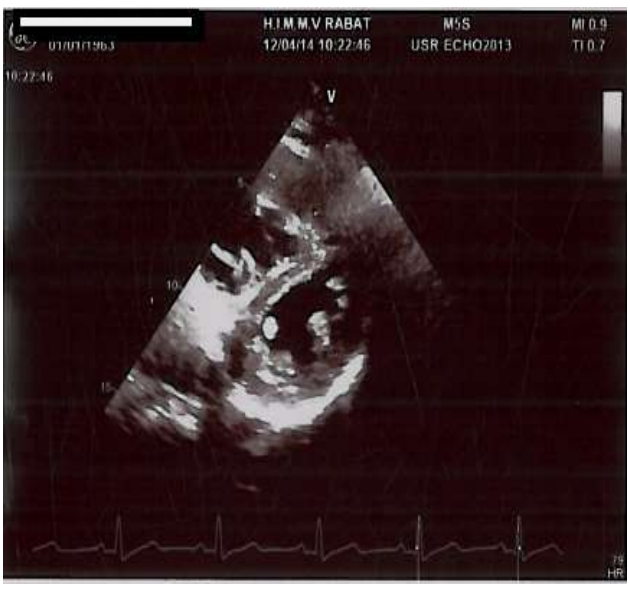


Fig- 3: thickened tricuspid valve in a semi open fixed position.

The thickening was diffused from the tips to the base. Chordae and papillary muscle were affected too. The pulmonary valve was visualised and displayed the same abnormalities. The leaflets were shortened, thickened and decreased systolic motion resulting in both moderate regurgitation and stenosis. Bulging of the interventricular septum into the left ventricular cavity, especially in diastole, suggested right ventricular pressure overload (figure 4-5). The inferior vena cava was not dilated. Saline contrast maneuver showed a foramen ovale patency.



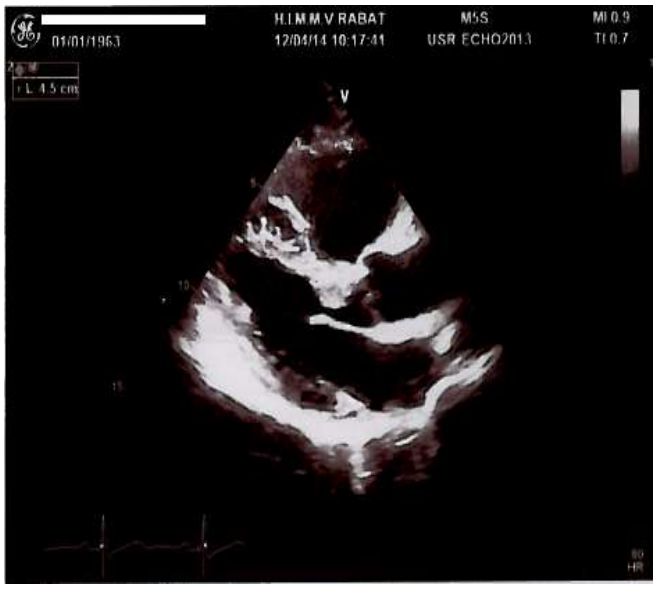


Figure 4,5: Bulging of the interventricular septum into the left ventricular cavity.

Due to the combination of flushing syndrome and echocardiography aspect of thickened and fixed tricuspid valve, a carcinoid syndrome was suspected. Additional investigations confirmed the diagnosis of carcinoid tumour as we found an elevation of urinary 5-hydroxyindoleacetic acid (5-HIAA) at 500mg/24h and serum chromogranin A at 2969ng/ml with a right ovarian heterogeneous process (fatty, fleshy and cystic component, figure 6). Octreotide scanning and FDG-PET didn't localise any other region of fixation expect of the tumour. The patient was prepared for a hysterectomy with bilateral annexectomy. There were no perioperative complications. The anatomopathologic study confirmed the presence of well-differentiated carcinoid cells with intensive expression of chormagranin. The treatment with lanreotide, a synthetic analogue of somatostatin, wasn't indicated in our patient.

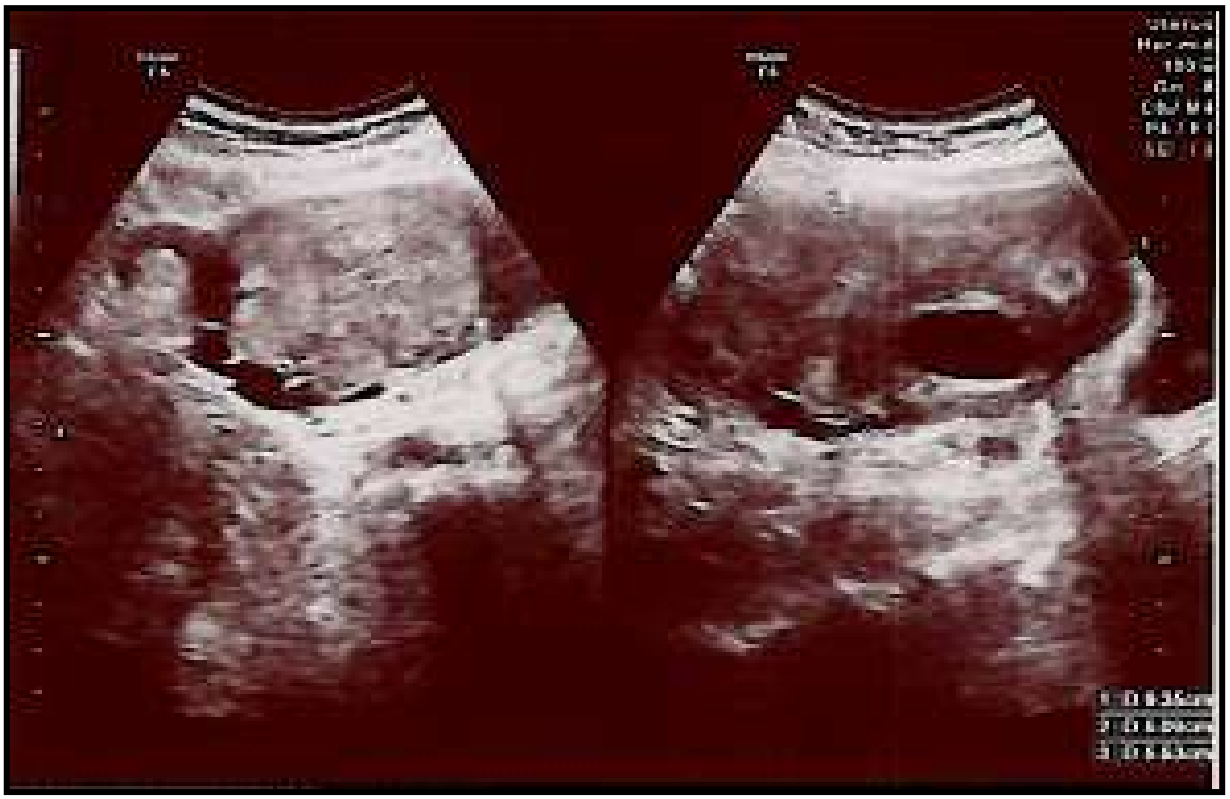


Figure 6 : Right ovarian heterogeneous process with fatty, fleshy and cystic component

Follow-up of 18 months was favourable. Clinical improvement was observed few weeks after the operation with a normalisation in the first month of urinary 5-HIAA (6.2ng/24h) and chormagranin. The echocardiography showed a moderate regression of pulmonary abnormalities. The leaflets were more mobile. The other findings were similar.

We decided to be conservative towards valve surgery because of asymptomatic tricuspid regurgitation with good right ventricle function. The patient is reviewed every 6 months for clinical and echocardiography examination.

III. DISCUSSION

The term carcinoid heart disease "CHD" is a rare form of typical thickened and restrictive valvular heart disease [8]. A series of 132 patients with NET and flushing syndrome, CHD was present in 56% [9]. Other series mention incidence rates ranging from 35 – 59% [10, 11-12]. However, this incidence will change because of the new available imaging techniques, such as the PET-CT gallium 68. Despite the fact that the pathogenesis remains unknown, it was suggested that the vasoactive substances lead to proliferation of myofibroblast and developing of extracellular matrix [13, 14]. This structural transformation is responsible for a thickening of the endothelium with an increase in its rigidity, which explains the fixed appearance of the valves. This pathophysiological concept is first explain by the high level of 24-hour urinary 5-HIAA in the case of CHD [15, 16], second by the fact that serotoninergic drug such as cabergoline, Ectasy and fenfluramine induce right-sided valvular fibrosis deposits [17], and finally by the studies that show the impact of exogenous serotonin administration in the genesis of endothelial proliferation and fibrotic plaque deposition in the subendothelial [18]. Serotonin seems to be the important vasoactive substance, but it is believed that CHD is a multifactorial phenomen, and other mediators are involved in the CHD, such as TGF-β protein [19], tachykinins [20] and connective tissue grow factor [21]. Lung and hepatic tumour metastatic spread circumvent the hepatic metabolism of these vasoactive substances and induces endothelial lesions of the right-sided heart [22]. The left-sided heart is protected from CHD except in case of a patent foramen ovale such as in our case, and in patients with bronchial carcinoids or very poor-controlled carcinoid syndrome "CS" [23]. The importance of fibrosis leads to a retraction and fixation of the valve and subvalvular apparatus with restrictive motion, which are clinically transduced by a variable combination of stenosis and regurgitation of right-sided valve.

NET can be silent or (non-functioning) or clinically symptomatic (functioning). Paraneoplastic syndrome is clinically characterised by flushing attacks, diarrhoea, and hypotension. The cardiac symptoms usually appear late after a period of 2 years [10]. This possibly explains by well-tolerated of gradual and progressive aggravation of right side valvular dysfunction. Asthenia and progressive dyspnea are often the first symptoms. Right heart failure is expressed by Oedema, hepatomegaly, abdominal pain and by ascites in the advance stage. Physical examination tries to find external jugular venous distension [24] murmurs of tricuspid or pulmonary valvular disease in asymptomatic patients [25]. Electrocardiogram is often normal or with no specific abnormalities, chest-x ray is also inaccurate for the diagnosis [25]. Echocardiography is the important method to detect CHD. Tricuspid valve is the most affected and occurs in up to 90% [26]. Tricuspid leaflets are thickened and in non co-optation

fixed position leading to both tricuspid regurgitation and stenosis. Pulmonary abnormalities are less often detected (49-69%) [25, 26]. Severe tricuspid regurgitation leads to right ventricular and atrial dilatation [26]. The development of foramen ovale patency marks CHD progression with risk of left-sided valvular disease [27]. Cardiac magnetic resonance imaging (MRI) can add further accurate information, such as right ventricular ejection fraction and severity of tricuspid regurgitation [28, 29].

The European Neuroendocrine Tumour Society (ENETS) guidelines recommend an annually transthoracic echocardiography or IRM in patients with CHD and more often if it's required [30].

Once diagnosed, Carcinoid valvular disease is most often not reversible. The treatment is divided into two parts, treatment of NET and treatment of cardiac disease. For the first part, the correlation between high levels of 5-HIAA urinary CHD progression has been suggested. That is why some authors suggest medical therapy, such as somatostatine [31] or octreotide [32], to control the 5-HIAA urinary level. A recent study of 273 patients with NET receiving Lanreotide, demonstrate the efficiency of Lanreotide to improve symptoms related to carcinoid syndrome such as diarrhoea and flush [33]. PROMID and RADIANT-2 studies also showed the efficiency of octreotide to reduce the time progression of tumour [32-34]. However, neither showed a favourable effect in regressing cardiac lesions. The surgical resection of the tumour is necessary to end the progression of the CHD. However surgical and anesthetic risks are not low. A prior preparation is essential to avoid the risk of carcinoid crisis. Carcinoid crisis is a life-threatening complication mimicking an anaphylactoid reaction.

On the other hand, the treatment of cardiac lesions remains debated. At an early stage of cardiac disease, the treatment targets the control of tumour progression. The carcinoid syndrome treatment inhibits the progression of CHD which is fixed. A retrospective analysis of 77 patients with CHD shows that the resection of metastatic liver cells stops the progression of heart endothelium lesions [36]. The medical therapy CHD is above all palliative with loop diuretics, fluid and salt restriction to reduce oedema. Recently, novel strategies have been tested such as bosentan with promising results [35].

The definitive therapy of advanced CHD is valve replacement surgery or valvuplasty. A retrospective analysis of the Mayo Clinic shows significant reduced ten-year mortality after cardiac surgery [37] but perioperative mortality remains worrying. Early postoperative 30-day mortality reached 63% [38]. The operative timing for valve replacement is still debated. The surgical option is discussed case by case, depending on the severity of the valve pathology and the prognostic of the tumour. No studies have shown the best valve prosthesis type to use. The decision must to be made after a large discussion with a multidisciplinary team of cardiologists, cardiac surgeons, and with family to take into patient's preferences. Mechanical prosthesis require permanent anticoagulation and biological valves are prone to premature degeneration [39,40]. Additionally, some reports indicated that percutaneous closure procedure of a patent foramen ovale improves length and quality of life [41].

IV. LEARNING POINTS/TAKE HOME MESSAGES

- The carcinoid heart disease is rare form of carcinoid valvular heart disease, especially due to serotonin.
- CHD presents a diagnostic challenge for clinicians.
- Pathogenesis still unknown but is likely secondary to high level of serotonin. Thereby, we suggested that the control of serotonin level may delay the progression of CHD.
- All patients with carcinoid syndrome must be screened for CHD through an echocardiographic study.
- A multidisciplinary therapeutic strategy combining medical care and surgery as far as possible reduces the symptoms considerably and improves length and quality of life of these patients.

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