Hemodynamic rounds and clinical pathology correlation: Evaluation of a polycythemic patient guided by imaging, hemodynamics, and endomyocardial biopsy

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ABSTRACT

A 32-year-old male with symptomatic polycythemia was investigated by hematologist for myeloproliferative malignancies and underwent five therapeutic phlebotomies. The identification of hypoxia on pulse oximetry later led to pulmonology evaluation that showed normal lung function tests as well as normal lung parenchyma and airways on advanced imaging. The absence of murmurs and significant precordial findings, normal chest X-ray, and unremarkable findings in electrocardiogram apart from first-degree heart block delayed the cardiac referral. Cardiac imaging showed a significant right to left shunt through a large oval fossa defect, mild hypoplasia of the right ventricle, normal right ventricular function and mild fibrosis within the myocardium. Hemodynamic assessment with test balloon occlusion led finally to a complete closure of the defect, which normalized the hypoxia. A step-by-step clinical approach finally leading to the management is presented in this clinicopathology correlation and hemodynamic rounds.

Keywords: Adult congenital heart disease, cardiovascular physical examination, central cyanosis, endomyocardial biopsy, hypoxia, redington wave

INTRODUCTION

Cardiac illnesses that cause minimal abnormalities on clinical examination are likely to be undetected for many years.[1] These patients may present to different clinicians in later age and get investigated for diverse ailments. A detailed clinical examination, imaging and diagnostic work-up will finally clinch the diagnosis and aid in an appropriate management.[2] The schematic flow of the thought processes in the diagnosis and decision-making will aid the clinician to pay more attention to finer clinical details and improve their diagnostic acumen. We present an adult male who presented with symptomatic polycythemia who was referred after a detailed hematological and pulmonology work-up to a cardiology unit. All details of clinical findings, imaging, biopsy, and hemodynamics were explained in a step-wise manner, ultimately culminating in the correct diagnosis and management.

CASE REPORT

A 32-year-old software engineer with effort intolerance for few years was diagnosed to have polycythemia with hemoglobin levels of 23 g/dl and hematocrit of 70%. Apart from ruddy complexion and plethoric conjunctiva, mildly elevated jugular venous pressure that was not

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recognized on earlier evaluations, clinical examination did not show any abnormality. He used to avoid physical exercises in his childhood and was later treated with lithium and aripiprazole for bipolar disorder. Initial evaluation by a hematologist showed erythroid precursor hyperplasia in the bone-marrow, normal positron emission tomography and absence of JAK-2 gene mutations. Therapeutic phlebotomies were periodically performed five times to reduce the hematocrit levels. Oxygen saturations of 82% in pulse oximetry during a routine nCOVID-19 screen warranted a high-resolution computed tomography that showed normal lungs and airways as well as normal-sized cardiovascular structures.

Other than uniform cyanosis and clubbing, cardiovascular examination showed normal pulses, blood pressures and jugular venous pulsations, mildly elevated jugular venous pressure, absence of cardiomegaly, no precordial abnormalities, normal first and second heart sounds, no additional sounds or murmurs. Chest X-ray showed normal cardiothoracic ratio, cardiac contour, and pulmonary vasculature [Figure 1a]. Electrocardiogram was unremarkable and showed no chamber enlargement except for a markedly prolonged PR interval [Figure 1b].

Echocardiography showed mild inferior caval vein dilatation with normal inspiratory collapse, mild right atrial enlargement, 20 mm oval fossa defect with right-to-left flows, mild tricuspid regurgitation, nondilated right ventricle with normal systolic pressures, [Video 1] normal outflow tracts, nondilated pulmonary arteries, and normal venous drainage. Prominent atrial systolic flow reversals in hepatic veins and atrial systolic antegrade diastolic flows through pulmonary valve (Redington wave) were indicative of the right ventricular diastolic abnormality [Figure 2]. Lack of a definite reason for a right-to-left atrial shunt prompted a cardiac magnetic resonance imaging that showed a small indexed right ventricular end diastolic volume of 55 ml (5th centile) with an ejection fraction of 50% [Figure 3]. The ventricular myocardium and moderator band showed altered texture and subendocardial late gadolinium enhancement indicative of fibrosis.

In view of the magnetic resonance findings, additional echocardiographic parameters observed later showed borderline abnormalities that included a reduced right ventricular tissue Doppler S' wave (9 cm/s), normal fractional area change (45%), reduced free wall strain (–8%), reduced tricuspid annular plane systolic excursion (16 mm), normal tricuspid E/A ratio (1.57), reduced E/E' (3.7), normal E deceleration time (165 ms), and normal right ventricular myocardial performance index (0.44). The left ventricle was normal in size, ejection fraction was 67% and global longitudinal strain was –18.9%. The working diagnosis was secondary polycythemia caused by a right to left shunt through an oval fossa defect in the setting of borderline right ventricular hypoplasia with diastolic dysfunction.

Catheter hemodynamics in awake resting state showed elevated mean right and left atrial pressures (12 mmHg) with similar wave forms, normal right ventricular systolic, and pulmonary arterial pressures. The right ventricle and pulmonary arterial traces showed a strikingly prominent atrial systolic wave during ventricular diastole akin to an atriopulmonary Fontan physiology, well separated from the systolic wave due to the coexistent first-degree heart block [Figure 4]. The right and left ventricular end-diastolic pressures were elevated. Oximetry showed a pulmonary to systemic shunt ratio of 1:1 with a matching 12%–13% step-up in pulmonary artery and step-down in aorta [Table 1]. The right ventriculogram showed normal trabeculations, normal systolic contractility, and diastolic tricuspid regurgitation during atrial systole [Figure 5 and Video 2].

Endomyocardial biopsy samples taken from right and left ventricle (through the atrial communication) showed

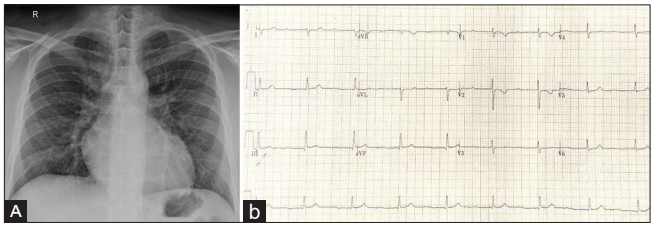

Figure 1: Chest X-ray (a) shows normal cardiothoracic ratio, contour and pulmonary vasculature. Electrocardiogram (b) is unremarkable except for prolonged PR interval of 400 msonds. There were no pointers to an atrial septal communication in these tests

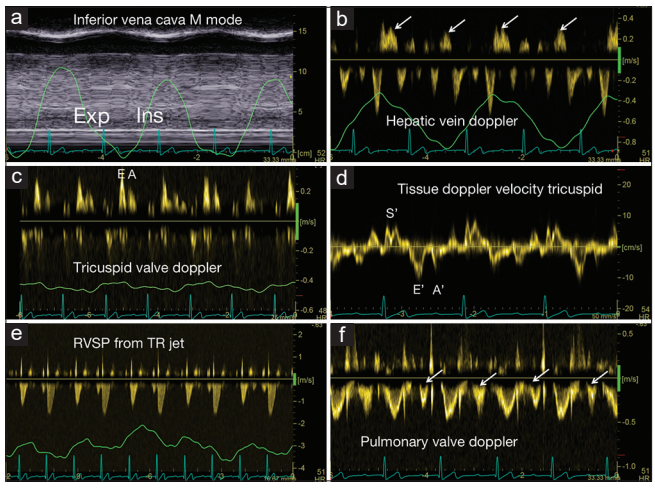

Figure 2: Respiration and electrocardiogram gated echocardiogram shows minimal inferior caval congestion (a), prominent atrial systolic flow reversals (arrow) in hepatic vein Doppler with normal inspiratory augmentation of forward flows and normal expiratory augmentation of reversals (b), tricuspid E and A too close to each other due to prolonged PR interval (c), mildly reduced s' velocity in tricuspid annular tissue Doppler image (d), normal right ventricular systolic pressures from tricuspid regurgitation jet (e) and antegrade pulmonary flows in ventricular diastole due to effect of atrial systole (arrow) directly transmitting atrial blood towards the pulmonary artery (f)

subendocardial and intramyocardial fibrosis [Figure 6]. A normal probrain natriuretic peptide ruled out a recent and ongoing variation in the myocardial function. As a test balloon occlusion of the oval fossa defect normalized the pulse oximetry without causing any further elevation of the right atrial pressures or fall of aortic pressures even after 15 min, [Figure 5] the defect was completely closed with a 22 mm atrial septal occluder. On a 2-month follow-up, there were no features of systemic venous congestion without any diuretics and his effort tolerance, hematocrit (45%), and oxygen saturations (100%) returned to normal.

DISCUSSION

Cyanosis with normal cardiovascular findings

After excluding hematological causes such as methemoglobin, sulfhemoglobin and abnormal hemoglobin variants, cardiopulmonary causes for central cyanosis with normal findings on cardiovascular examination suggest possibilities of pulmonary arteriovenous fistula, abnormal right superior caval drainage to left atrium, completely unroofed coronary sinus, right pulmonary artery to left atrial communication and large abnormal connections between pulmonary arteries and pulmonary veins.[3-5] Even though an unfavorable streaming of superior caval blood through a superior sinus venosus defect, a similar streaming of inferior caval blood through a posteroinferior oval fossa defect (additionally facilitated by prominent Eustachian valve) or unroofed coronary sinus in the setting of Raghib's defect lead to cyanosis, they will often show features of a left to right shunt with a wide fixed split of second sound with pulmonary flow murmurs.[6] Our patient had normal second sound and lacked pulmonary flow murmurs.

Split of second heart sound

Pulmonary component of second sound is delayed in atrial septal defect due to higher right ventricular stroke volume facilitated by improved right ventricular compliance and long hang-out interval due to high pulmonary arterial capacitance.[7,8] Hypoplastic noncompliant right ventricle

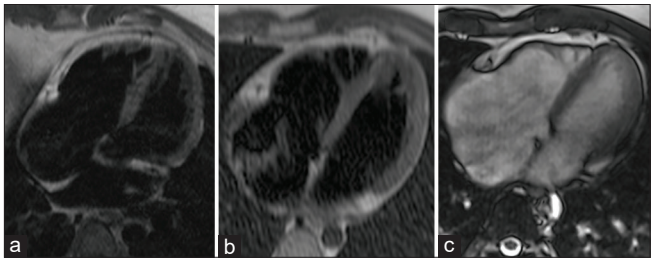

Figure 3: Black blood (a and b) images on magnetic resonance imaging demonstrate mild hypoplasia of right ventricle, altered texture of myocardium and moderator band. A white blood image shows oval fossa defect and mild hypoplasia of apical part of right ventricle. A white blood image (c) shows oval fossa defect and mild hypopasia of apical part of right ventricle

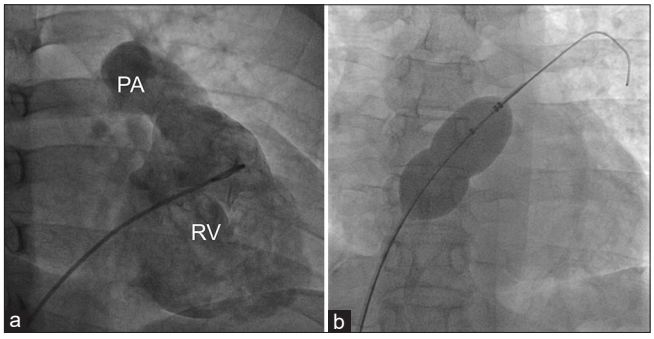

Figure 5: Right ventriculogram (a) showed tripartite mild hypoplastic right ventricle, normal apical trabaculations, no out pouchings, no calcifications. Balloon occlusion for 15 min (b) did not result in elevation of right atrial pressures or fall of aortic pressures

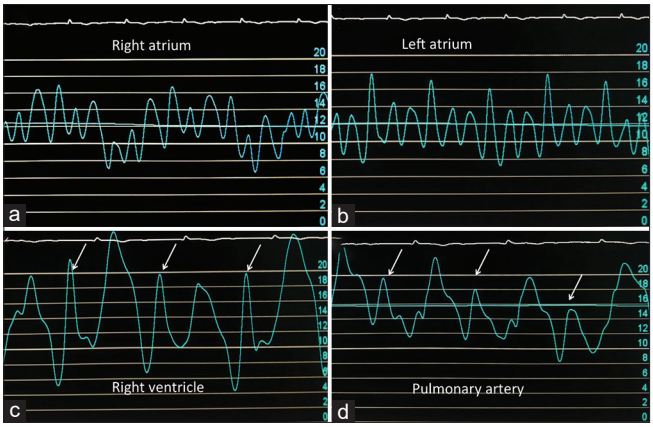

Figure 4: Right (a) and left (b) atrial pressures show equal a and v waves and elevated mean pressures. Right ventricular (c) and pulmonary artery (d) pressures show prominent atrial systolic impulses (arrow) during early diastole

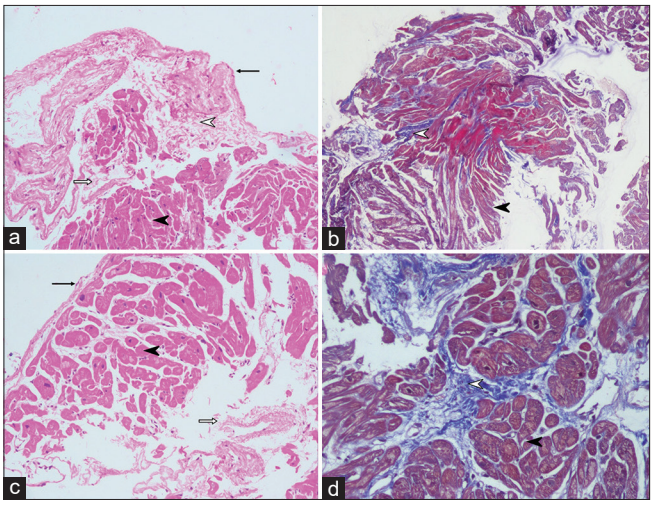

Figure 6: Right ventricular endomyocardial biopsy in H and E (a) and Mason trichrome stain (b) show normal myocardium (black arrow) interspersed with fibrosis (white arrow) as well as subendocardial fibrosis (straight arrow). Similar findings (c and d) are seen in left ventricular biopsy also

Table 1: Hemodynamic recordings

Sampling site	PCO_2	PO_2	SO_2	Basal pressures	On balloon occlusion
Superior vena cava	38	34	61		
Inferior vena cava	35	33	62		
Right atrium				a-16, v-15, m-12	a-16, v-15, m-12
Right ventricle				Sys-24, ED- 14	
Pulmonary artery	30	40	75	24/10/16	
Right pulmonary vein	28	118	98		
Left pulmonary vein	29	90	96	a-18, v-14, m-12	
Left ventricle				Sys-130, ED-18	Sys-130, ED-14
Aorta	30	51.4	86	126/70/98	132/76/98
QP (L/min)	4.41			QEP (L/min)	2.71
QS (L/min)	3.91			L-R shunt (L/min)	1.7
QP/QS	1.13			R-L shunt (L/min)	1.2
PVRI (wood units)	1.73			SVRI (wood units)	43.12

PO_2: Partial pressure of dissolved oxygen (mmHg), PCO_2: Partial pressure of dissolved carbon di oxide (mmHg), SO_2; Percentage oxygen saturation of hemoglobin on cooximetry, ED: End diastolic, QP: Pulmonary blood flow (L/min), QS: Systemic blood flow (L/min), QEP: Effective pulmonary blood flow (L/min), L-R: Left to right, R-L: Right to left, PVRI: Pulmonary vascular resistance index, SVRI: Systemic vascular resistance index

in our patient prevented establishment of a significant left to right shunt resulting in normal-sized pulmonary arteries. The pulmonary component of the second heart sound was not delayed in the absence of increase of the right ventricular ejection time. The hang-out interval was not prolonged as the pulmonary arteries never increased their capacitance beyond normal.

Fixed split of second sound

A noncompliant right ventricle in our patient failed to accommodate beat-to-beat differences in the right ventricular inflow, despite a postnatal fall in pulmonary artery pressures. An inspiratory reduction in the intrathoracic pressures with a corresponding fall in the pulmonary artery pressures resulted in improved delivery of the increased systemic venous return to the pulmonary artery causing normal inspiratory prolongation of the split. The split was more dependent on the beat-to-beat variation in the systemic venous return during phases of respiration rather than the contribution from the oval fossa defect, as the right ventricle remained noncompliant to accommodate any additional volume.[9] Lack of pulmonary flow murmurs was evident from the hemodynamics that showed a step-up in the right heart equally matched by a step-down in the left heart. This also explained lack of plethora in chest X-ray and chamber enlargement in electrocardiogram.

Partial versus complete closure

Some of the pointers that showed a tolerance to complete closure of the atrial septal defect included normal lung pulmonary vascularity and normal pulmonary blood flow on catheterization study that indicated that the right ventricle was capable of pumping the normal systemic venous return to the pulmonary arteries without further rise of the right atrial pressures. Partial closure of the atrial communication is sometimes advocated in patients with borderline hemodynamics. Older hypertensive, diabetic patients with coronary artery disease and restrictive left ventricle may develop acute pulmonary edema on a complete closure. Partial closure is also advocated in hypoplastic right ventricle in Ebstein's anomaly, reinterventions after neonatal valvotomy in pulmonary atresia and intact ventricular septum and in patients with severe pulmonary stenosis and right ventricular hypertrophy.[10] Our patient who did not have any cardiac chamber enlargement needed improvement of effort tolerance by reduction in hypoxia and polycythemia. The additional aims were to prevent venous thrombosis from worsening polycythemia and paradoxical embolism. Leaving a fenestration would result in persistent hypoxia, right to left shunt, and secondary polycythemia. Lack of elevation of right atrial pressures on test occlusion for 15 min enabled a complete closure.

Is it an early restrictive cardiomyopathy?

Closure of interatrial communications may worsen the atrial pressures in a progressive disease like restrictive cardiomyopathy. Evidence of fibrosis in magnetic resonance imaging associated with the elevation of ventricular end-diastolic pressures might point to a restrictive ventricular physiology or rare clinical forms of forme-fruste of Uhl's anomaly and arrhythmogenic right ventricular dysplasia. Limitations of physical activity dating from childhood pointed to a restrictive right ventricle with hypoplasia from his early days, rather than a progressive pathology like restrictive cardiomyopathy. A normal probrain natriuretic peptide also possibly suggested a nonprogressive cardiac illness. Advanced genetic testing and high-resolution electron microscopic analysis of the biopsy though advisable, remained a theoretic possibility due to restricted resources.

CONCLUSIONS

Cyanosis with significant arterial desaturation and minimal precordial and auscultatory cardiovascular findings often leads to a set of investigations directing

the diagnosis to a few specific well-defined rare entities. However, a common condition like oval fossa defect with mildly hypoplastic and noncompliant right ventricle can also lead to a lack of significant shunt and fail to show the classical clinical, radiographic and electrocardiographic abnormalities characteristic of an atrial communication. Clinical presentation of such a patient with hypoxia and polycythemia may lead the clinician away from the primary diagnosis leading to inappropriate treatment. Utilization of simple tools like pulse oximetry, a clear understanding of the hemodynamics, reasons for the clinical examination findings, appropriate interpretation of imaging and pathology will aid in correct management.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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