The Missing Conduit...

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We presented clinical details to a discussant (physician) and he analyzed the data according to the available data. The details presented are in **BOLD**, whereas his discussion is in standard font.

PATIENT DESCRIPTION

A 23 year old peripartum female was admitted to the emergency department due to abdominal swelling and bilateral lower extremity edema. Ten days prior to presentation she delivered her first baby by an uneventful Cesarean section. The urgent operation was due to poor progression of labor. During her pregnancy she was diagnosed with gestational diabetes, which was treated by diet only. Two weeks prior to her admission she noticed swelling of her right leg. Duplex ultrasound was performed twice with no evidence of deep vein thrombosis (DVT). Nevertheless, because of the high suspicion for thrombosis in the deep pelvic veins, she was treated with therapeutic doses of enoxaparin until her admission. The patient was otherwise healthy. She denied dyspnea or chest pain.

It was important to determine whether the patient suffered from a generalized problem such as anasarca or from localized edema limited to the lower extremities. Localized edema can be caused by obstruction of venous drainage as can be seen in deep vein thrombosis, which is relatively common during the postpartum or post-surgery period. Obstruction of lymphatic drainage can also cause edema; however, these diagnostic possibilities did not explain the abdominal swelling. Therefore, it was important to search for stigmata of chronic liver or kidney disease or signs of congestive heart failure, as well as post-surgical or postpartum fluid shift, postpartum cardiomyopathy, or postpartum preeclampsia. Elevation of the jugular venous pressure (JVP) can help distinguish between volume overload conditions, such as right heart failure or local causes for edema in the extremities.

On physical examination, the patient's temperature was 36.1°C, her heart rate was 69 beats per minute, and her blood pressure was 108/59 mmHg. Oxygen saturation level was 94%. Cardiac examination disclosed an accentuated second heart sound, with mild (2/6) systolic murmur. The JVP was slightly elevated. Her lungs were clear. Abdominal examination disclosed shifting dullness. This was accompanied by severe bilateral pitting edema over the lower limbs. Homan's sign was negative. There was no finger or toe clubbing on the hands or feet.

The physical examination suggested the presence of anasarca. Several major causes may lead to anasarca, including congestive heart failure, liver failure, acute or chronic renal failure, or hypoalbuminemia caused by different mechanisms. The fact that these findings appeared in the early postpartum period narrowed the possible diagnosis, which included eclampsia, pulmonary embolism, or peripartum cardiomyopathy.

It is recognized that in the immediate postpartum period patients remain at risk for developing preeclampsia. Preeclampsia can cause dependent edema, although it is characterized by hand and facial edema, which were absent in the present patient. In addition, the patient's blood pressure did not meet the conventional criteria for preeclampsia. Nevertheless it was important to consider proteinuria. Although hypertension in the postpartum period is a relatively common phenomenon, this diagnosis was dismissed because the patient had normal blood pressure.

The leading cause of maternal death in the United States during the postpartum period is venous thromboembolism (VTE). This complication can cause direct peripheral edema due to local obstruction. The incidence of VTE during the postpartum period is five times higher than during pregnancy. Based on Wells' criteria, the patient had at least three points (post-surgery, swelling of the legs, pitting edema) rendering her at high risk for DVT. Right heart failure caused by massive pulmonary embolus is also another explanation for peripheral edema. Pulmonary embolism (PE) is significantly more common at the postpartum period. However, in massive or chronic PE the patient has shortness of breath. In the present case the patient denied shortness of breath. Nevertheless, it was important to search for blood gas abnormalities and to continue to consider VTE.

Another possible cause for anasarca in the postpartum period is peripartum cardiomyopathy. This condition is characterized mainly by the development of left ventricular failure during the last month of pregnancy or within the first 5 months after delivery, with no evidence of other cause of heart failure. The patient described here did not have pulmonary edema and the physical findings supported right rather than left heart failure.

Laboratory tests showed albumin levels of 34 g/L (normal is 35–40) and creatinine

of 75 micromol/L (normal is 60–106). Alkaline phosphatase was 216 U/L (normal is 40–130), and gamma-glutamyl transferase (GGT) was 102 U/L (normal is 10–80). Liver transaminase levels were within normal range. Blood gases were normal. C-reactive protein (CRP) was 3.5 mg% (normal is 0–1), and D-dimer was 4.64 microgrfeu/ml (normal is 0–0.5). Urinalysis revealed traces of protein and protein secretion in 24 hours of urine collection was 1.04 gr/24h (normal is 0–0.25).

The lab results did not show significant hypoalbuminemia that could have explained anasarca, and the urine protein, although pathological was not in the nephrotic range. The abnormal serum level of alkaline phosphatase did not necessarily imply liver disease. Serum levels of this enzyme increase gradually as pregnancy proceeds, reaching maximal values in the third trimester, and return back to normal levels by 20–24 weeks postpartum. The serum alkaline phosphatase activity averaged 2.1-fold higher in the late third trimester than in the first trimester due to its production by the placenta. Typically GGT is not elevated in these cases. Alternative possible explanations might be that liver enzymes reflect the cholestasis of liver congestion due to heart failure. The elevated GGT may support this notion.

During pregnancy, D-dimer increases progressively, and its levels have a poor value in excluding VTE after 20 weeks of gestation. During labor, D-dimer is usually very high. Levels return to normal only several weeks postpartum; therefore, D-dimer levels can only rule out VTE after 4 weeks postpartum. Thus, the high serum levels of D-dimer did not support or oppose the possibility of DVT or PE, and further inquiry was needed.

Computed tomography (CT) pulmonary angiogram demonstrated moderate right sided pleural effusion and an edematous liver with periportal edema, which is consistent with vascular congestion. Ascites and edema of the abdominal wall were also seen, as well as reflux of contrast media to the inferior vena cava. The pericardium was normal with no thickening or calcifications. There was no evidence of PE or DVT. Doppler ultrasound of the pelvic veins demonstrated no evidence of venous occlusion.

These investigations ruled out a diagnosis of PE. However, the findings were consistent with right heart failure, which was reflected by the reflux of contrast media to the inferior vena cava (IVC). Possible causes in this setting could be congenital or acquired heart diseases, left-to-right shunt, or pulmonary hypertension. The option of pericarditis is most unlikely since the patient did not suffer from chest pain, fever, or recent viral disease, which would have supported that diagnosis. Theoretically an abnormality of the right ventricular wall may be caused by a silent myocardial infarction during a Cesarean section. An echocardiogram should be conducted to evaluate the structure and function of the right heart and its valves as well as the right heart pressures.

An echocardiogram was performed and demonstrated a moderately dilated right ventricle with normal global systolic function. Diastolic flattening of the interventricular septum (IVS) suggested right ventricle volume overload. The left ventricle size and function were normal. The mitral and aortic valves appeared to be normal but the leaflets of the tricuspid valve were thickened with mild calcification and moderate regurgitation with a gradient across the tricuspid valve of 31 mmHg.

In the absence of left heart failure or PE, the entity of idiopathic pulmonary arterial hypertension should be considered as a cause of pulmonary hypertension. It is an uncommon condition with strong female predominance, which may affect patients from infancy into the seventh decade. It is defined by a mean pulmonary artery pressure greater than 25 mmHg at rest or greater than 30 mmHg during exercise, with normal pulmonary capillary wedge pressure and the absence of associated causes of pulmonary hypertension. The predominant symptoms are dyspnea and fatigue, and right heart failure is the main cause of death. Tricuspid regurgitation is a common secondary feature of this condition. The gradient measured across the tricuspid valve in this patient was within the high values of the normal range.

The patient denied suffering from dyspnea or fatigue, or of having a family history of pulmonary hypertension. Following a consultation with a cardiologist, it was decided that the patient would undergo another echocardiogram after proper diuresis. The rational was to verify whether the thickened tricuspid valve was transient and would disappear with forced diuresis. The patient was treated with furosemide in doses of 40–60 mg daily for 7 days. This resulted in disappearance of the peripheral edema and the abdominal swelling. The patient also lost 8 kg of her weight during this period.

An echocardiogram was repeated after diuresis and demonstrated a mildly dilated right ventricle with normal global systolic function. The tricuspid valve leaflets were mildly thickened and only moderate regurgitation was seen. The estimated gradient on the tricuspid valve remained 30 mmHg. There was no evidence of right-to-left shunt by bubble contrast.

The impressive response to diuretics with the significant weight loss supports the notion of fluid overload probably due to right heart failure. The reduction in the tricuspid valve thickness following this treatment may suggest previous partial edema of the valve leaflets, which was also improved. Yet the reason for the right heart failure with the fluid overload remained unclear. A concern was that the patient had a congenital cardiac malformation.

At this point a revision of the CT pulmonary angiogram was made by a chest expert radiologist who raised a suspicion of partial anomalous pulmonary venous return (PAPVR). Pulmonary magnetic resonance angiography (MRA) demonstrated aberrant drainage of the left upper pulmonary vein, partially to the brachiocephalic vein through a large vessel and the other part to the left atrium [Figure 1].

The surprising finding in the MRA for PAPVR clearly explained the right heart failure due to the left-to-right shunt aggravated during pregnancy and the

Figure 1. Three-dimensional reconstruction of a magnetic resonance angiography demonstrating abnormal drainage of the left upper pulmonary vein (LUPV) to left subclavian vein (LSV) and through it into the superior vena cava (SVC)

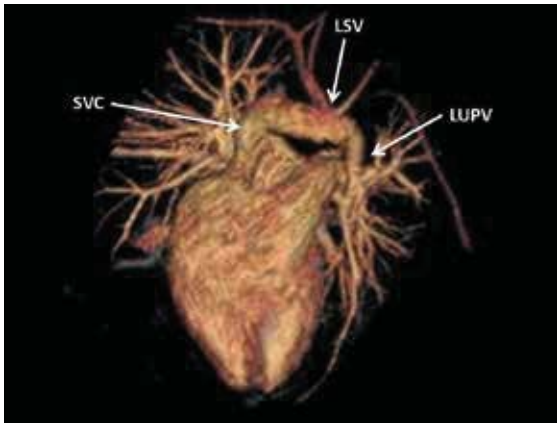

Figure 2. Magnetic resonance angiography showing aberrant left pulmonary vein (arrow) drainage to the left subclavian vein

postpartum period. However, the structural defect in the tricuspid valve could not be explained by this defect. Diseases that may affect the tricuspid valve include infective endocarditis, rheumatic fever, myxomatous degeneration of the valve, or enlarged right ventricle. Therefore, it is important to investigate again the possible history of these diseases in her childhood. One more remote possibility to rule out was a carcinoid tumor, which may lead to valvular disease of the right heart, although this patient did not have any symptoms to support this diagnosis.

Tricuspid regurgitation may not have any symptom or the symptoms may be vague. They include weakness and fatigue, which results from heart failure. In more severe cases the liver may be congested and enlarged and the abdomen swollen with edema and the lower extremities. It may well be that in this case the tricuspid regurgitation and the PAPVR became symptomatic following hemodynamic changes due to pregnancy and the peripartum period.

The patient did not recall any medical history suggesting congenital heart disease or rheumatic fever. She denied any symptom or limitation due to any previous heart problem. A 24 hour urine collection for 5-hydroxyindoleacetic acid was normal. Serum antistreptolysin O (ASLO) titer was normal as well.

After discussion with adult and pediatric cardiologists as well as chest surgeons, it was decided that due to the patient's functional clinical condition, no corrective surgery was needed at this point. The patient was discharged with no medications. At her 4 year follow-up the patient was asymptomatic.

COMMENT

Congenital heart diseases (CHD) are the most common congenital malformation [1]. The evolution of the pediatric cardiology and cardiac surgery have led to an increase in the number of children with CHD surviving into adulthood. Therefore, a marked increase in the number of adults with CHD has been seen in the past few decades with prevalence of 4.09 per 1000 in the year 2000, representing an increase of 85% compared to 1985 [2]. An estimated 0.5–4% of pregnant patients have cardiac disease such as rheumatic disease, uncorrected congenital heart disease, and cardiomyopathy [3]. As a consequence of the growing number of adults with CHD, the number of women with congenital heart disease who reach childbearing age is increasing, and many of them contemplate pregnancy. Although some women with CHD cannot tolerate the hemodynamic changes associated with pregnancy, many have sufficient cardiac reserve to carry a pregnancy to term.

During the course of pregnancy, hormonally mediated changes result in about 18% increase in blood volume, red blood cell mass, and 50% increase in cardiac output from the sixth week of gestation, peaking at the third trimester with a concurrent decrease in systemic vascular resistance (SVR) [4]. These changes are achieved by systemic vasodilatation, increased contractility, and myocardial hypertrophy.

The immediate postpartum period is characterized by an additional increase in cardiac output up to 60% within 10 to 15 minutes after vaginal delivery [5] and up to 35% after Cesarean section with epidural anesthesia [6]. The increased cardiac output following delivery is the result of multiple factors including increase in preload due to removal of venocaval obstruction by the gravid uterus, transfusion of blood from the uterus to the intravascular space, and shift of fluid from the extravascular to the intravascular space. Therefore, cardiac decompensation can be experienced in patients with CHD during pregnancy and the postpartum period, which can cause maternal and fetal complications. Although maternal deaths in pregnant women with congenital heart disease are rarely reported [7-8], maternal cardiac and neonatal complications are often described [9].

The risk for maternal cardiovascular events during pregnancy in patients with CHD varies from 18 to 23% in several cohort studies [9,10]. This risk depends on the underlying cardiac disease, history of previous repair, current hemodynamic status, and functional status according to the New York Heart Association functional classification. Increased risk for cardiac events during pregnancy or the peripartum period is seen in several conditions such as pulmonary arterial hypertension, severe left heart obstruction, right ventricle dilatation, or severe pulmonary regurgitation [10,11].

The most common maternal cardiac event during pregnancy is pulmonary edema with congestive heart failure, followed by symptomatic tachyarrhythmia. Other potential complications include aortic dissection (for patients with coarctation, bicuspid aortic valve, and Marfan's

syndrome), endocarditis, and even death [10,12].

PAPVR is an uncommon congenital anomaly that was first described by Winslow in 1739 [13]. The estimated overall incidence is about 0.5–0.7% of the general population at the time of autopsy [14]. However the actual incidence may be higher as many case reports describe incidental diagnosis in asymptomatic cases of this condition [15,16]. PAPVR is defined as left-to-right shunt where one or more, but not all, of the pulmonary veins drain into a systemic vein. It is often associated with congenital heart defects, most commonly an atrial septal defect [17]. The presence and severity of symptoms depends on the degree of shunting and the severity of the associated cardiac defect. Isolated PAPVR (without any other cardiac abnormalities) usually becomes symptomatic when 50% of the pulmonary veins or more are involved. The most common manifestations are exertional dyspnea, atrial arrhythmia, and ultimately right heart failure with pulmonary hypertension. Most cases of PAPVR are located in the right lung, and the anomalous veins are frequently connected to the superior vena cava or right atrium [18]. In only 3% of the patients the drainage is from the left lung to the innominate vein [19].

The diagnosis of PAPVR is best made using CT and MRA [20]. Surgical correction is recommended for symptomatic patients or asymptomatic patients with a pulmonary-to-systemic blood flow ratio exceeding 1.5 because of the higher likelihood of progression to pulmonary hypertension and right ventricular failure [21].

Several case reports describe asymptomatic PAPVR in adult patients, in whom it was an incidental finding. In a Medline search we found only two reports of patients with uncorrected total anomalous pulmonary venous return who completed pregnancy, although intrauterine growth retardation was seen [22].

Our patient posed a diagnostic and therapeutic problem. Since she did not have any history of congenital heart disease her physicians looked for an acquired problem, which may have led to cardiac decomposition during pregnancy. The finding of tricuspid insufficiency could not explain the presence of pulmonary hypertension. However, the presence of pulmonary hypertension could not explain the thickening and calcifications of the tricuspid valve. It seems that the patient had mild congenital or rheumatic deformation of the tricuspid valve, which contributed to the heart failure mainly caused by the PAPVR. The patient completed an uneventful pregnancy but developed cardiac decompensation a few days before delivery and during the postpartum period. It should be emphasized that the patient did not have fluid overload during her Cesarean section.

The burden of pregnancy and the postpartum period led to the expression of these malformations, otherwise they would not have been detected.

In this patient, the diagnosis of PAPVR was suspected by CT pulmonary angiogram while looking for PE. Indeed, MRA confirmed this diagnosis. The involvement of the left upper pulmonary vein was an additional and unique finding in this patient.

The growing numbers of adults presenting with congenital heart disease will make similar cases more common. A high level of suspicion and awareness are needed for the diagnosis of this malformation. Early diagnosis will enable us to give these patients the appropriate treatment and avoid unnecessary investigations.

TEACHING POINTS

- Due to the growing number of adults with congenital heart diseases (CHD), an increasing proportion of pregnant women may present with complications.
- During the course of pregnancy, hormonally mediated changes result in an increase in red blood cell mass of about 20%, and cardiac output increases by 50% from the sixth week of gestation, peaking at the third trimester.
- Hormonally mediated changes during pregnancy trigger the clinical expression of, a priori, asymptomatic congenital heart diseases (CHD).
- Partial anomalous pulmonary venous return (PAPVR) is an uncommon congenital anomaly in which one or more, but not all, of the pulmonary veins drain into a systemic vein such as the inferior vena cava (IVC) and subclavian.
- Overall estimated incidence of partial anomalous pulmonary venous return (PAPVR) is about 0.5–0.7% of the general population at the time of autopsy.

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Capsule

DNA damage linked to fitness loss in aging

Loss of metabolic function is associated with physical decline and diseases associated with aging. Park et al. provided evidence for a link between accumulated DNA damage and such metabolic dysfunction. Activity of the DNA-dependent protein kinase (DNA-PK), which is activated in response to DNA damage, was increased in skeletal muscle of older mice. DNA-PK phosphorylates HSP90α, a chaperone protein that protects the activity of a key metabolic regulator, called adenosine monophosphate, activated protein kinase. A small-molecule inhibitor of DNA-PK improved the physical fitness of young obese mice and older mice. Whether such benefits can be provided without the deleterious effects of inhibited DNA repair, such as cancer, remains to be explored.

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Eitan Israeli

Capsule

Vaccine priming is restricted to draining lymph nodes and controlled by adjuvant-mediated antigen uptake

The innate immune mechanisms by which adjuvants enhance the potency and protection of vaccine-induced adaptive immunity are largely unknown. Liang and co-authors introduced a model to delineate the steps of how adjuvant-driven innate immune activation leads to priming of vaccine responses using rhesus macaques. Fluorescently labeled human immunodeficiency virus (HIV)-1 envelope glycoprotein (Env) was administered together with the conventional aluminum salt (alum) adjuvant. This combination was compared to Env given with alum with preabsorbed Toll-like receptor 7 (TLR7) ligand (alum-TLR7) or the emulsion MF59 because they show superiority over alum for qualitatively and quantitatively improved vaccine responses. All adjuvants induced rapid and robust immune cell infiltration to the injection site in the muscle. This resulted in substantial uptake of Env by neutrophils, monocytes, and myeloid and plasmacytoid dendritic cells (DCs) and migration exclusively to the vaccine-draining lymph nodes. Although less proficient than monocytes and DCs, neutrophils were capable of presenting Env to memory $CD4^+$ T-cells. MF59 and alum-TLR7 showed more pronounced cell activation and overall higher numbers of Env^+ cells compared to alum. This resulted in priming of higher numbers of Env-specific $CD4^+$ T-cells in the vaccine-draining lymph nodes, which directly correlated with increased T-follicular helper cell differentiation and germinal center formation. Thus, strong innate immune activation promoting efficient vaccine antigen delivery to infiltrating antigen-presenting cells in draining lymph nodes is an important mechanism by which superior adjuvants enhance vaccine responses.

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Eitan Israeli

"As societies grow decadent, the language grows decadent, too. Words are used to disguise, not to illuminate, action: you liberate a city by destroying it. Words are to confuse, so that at election time people will solemnly vote against their own interests"

Gore Vidal, (1925–2012), (born Eugene Louis Vidal) American writer and public intellectual known for his patrician manner, epigrammatic wit, and polished style of writing