Housecalls

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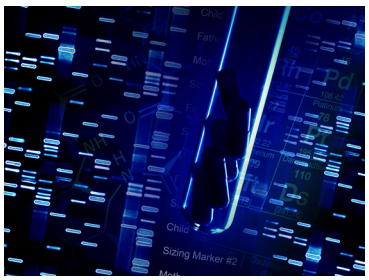
INSIDE THIS ISSUE

ADVANCES IN ONCOLOGY TREATMENT

Evaluating Genetic Markers

All of medicine is evolving rapidly. But one of the fastest changing areas is oncology. Traditionally cancers were evaluated and treated based on the extent (size and dispersion) of the cancer when it was discovered and/or treated. This is captured in the TNM (Tumor, Node, Metastases) classification system.

Tumors are also graded based on the histology (appearance of the cells under the microscope). The tumor cells may range from well-differentiated to anaplastic. An example of this is the Gleason grading system used in prostate cancer.



But more recently, the biggest change has occurred in the evaluation of genetic molecular markers or their cellular products. Tumor markers such as prostate specific antigen (PSA) or carcinoembryonic antigen (CEA) have been recognized for years as proteins produced in excess by some prostate or colon cancers.

Some molecular markers are found in cancers arising from differing organs. One example would be Microsatellite instability (MSI) by genetic sequencing which is associated with mismatch repair deficiency (MMR-D) by immunohistochemistry of the tumor. As these markers are studied and validated as contributing to treatment and outcomes, they are being added to the diagnostic evaluation of the tumor.

On a macro level prognosis is determined by the extent of the tumor (size and spread), the aggressiveness of the tumor cells and markers that may indicate a more treatable versus less treatable tumor. The addition of molecular markers introduces a challenge in crafting tumor guidelines since each of these factors must be considered in the proper proportion based on the contribution to prognosis. In addition guidance still must be available in cases where the tumor occurred prior to the addition of newer molecular markers.

SCOR Global Life in the Americas is in the process of updating the tumor guidelines in the SCOR Online Electronic Manual (SOLEM) to include recognized molecular markers. We expect this process to be ongoing as oncology continues to evolve.

SCOR
The Art & Science of Risk

CASE #1

Cardiac Effects of Doxorubicin

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A 53-year-old woman applied for life insurance. She had a 10-year history of hypertension. Her BMI was 32. She reported being diagnosed with stage II HER2-positive breast cancer four years prior, and she underwent a mastectomy followed by adjuvant chemotherapy.

This adjuvant therapy was doxorubicin (60 mg/m^2) given every three weeks for four cycles. Shortly after receiving her final planned dose of doxorubicin, she developed shortness of breath and marked fatigue. An echocardiogram was performed and revealed her left ventricular ejection fraction (LVEF) to be approximately 40%. This had significantly changed from a pre-treatment evaluation showing a normal LVEF of 55-60%.

A beta blocker and an angiotensin converting enzyme (ACE) inhibitor were begun. She had a rapid clinical response to treatment with all symptoms abating. Holter monitor testing revealed no arrhythmias. A follow-up echocardiogram a few weeks later showed the ejection fraction to have returned to the pre-treatment range of 55-60%.

She has had annual echocardiograms since then (including eight weeks ago), and the ejection fraction has remained normal. She remains on an ACE inhibitor for BP control. She has had no further cardiac symptoms. She completed her planned chemotherapy prior to the onset of symptoms so no change in therapy was needed. She has had good breast cancer follow up and has had no evidence of recurrence. Current electrocardiogram is within normal limits.

What are the cardiotoxicity concerns with use of anthracyclines?

Doxorubicin (trade name Adriamycin), the medication mentioned in the case above, is one of the anthracycline types of medications. Other common medication in this class include daunorubicin, mitoxantrone, epirubicin and idarubicin.

Anthracyclines are a potent class of cancer chemotherapeutic medications and have been available since the 1960s. They are used effectively to treat many types of cancers, including carcinomas (bladder, breast, esophagus, liver, lung, stomach and thyroid), sarcomas (Ewing, osteogenic bone and soft tissue) and lymphomas (Hodgkin's and non-Hodgkin's). They are used in both pediatric and adult patients.

While being extremely effective in treating malignancy there are several potential serious adverse complications associated with anthracycline use. One of these complications is cardiotoxicity. Anthracyclines can cause direct damage to cardiomyocytes.

Research continues to shed light on the mechanism of injury, but currently the evidence points to a variety of contributing factors including DNA damage from interaction of the medication with an enzyme named topoisomerase-II, induction of apoptosis (programmed cell death), mitochondrial iron accumulation, oxidative stress and decreased protein synthesis.

Although other complications of anthracycline toxicity (e.g. arrhythmias) are described, cardiac toxicity is frequently identified as a decreased left ventricular ejection fraction, with or without symptoms or signs of heart failure. The incidence of this myocardial dysfunction appears to vary based upon the cumulative dose and the presence of various risk factors in the individual.

Below are risk factors for cardiotoxicity with anthracycline use.

- Cumulative dose
- Obesity
- Concomitant radiation exposure
- Female sex
- Pre-existing low LVH ejection fraction
- Concomitant exposure to trastuzamab
- Age (<4 or >65)
- Hypertension
- Valvular disease
- Diabetes
- Renal failure
- Smoking

The cumulative dose risk factor is especially important. The incidence of cardiotoxicity has been estimated to vary from 5% for cumulative doses of 400 mg/m^2 to 48% in those exposed to 700 mg/m^2.

The dosage of doxorubicin, for example, varies based upon the type of cancer being treated. Dosage can depend upon whether doxorubicin is used as a single agent versus part of a combination therapy with other chemotherapeutic medications. Breast cancer frequently has a lower cumulative dose than other cancers.

Considerations prior to anthracycline use

When clinicians are evaluating a cancer patient for potential anthracycline chemotherapy they typically consider the cardiac condition and cardiac risk factors of the individual patient. Frequently this evaluation includes obtaining an echocardiogram for evaluation of the LVEF and detection of valvular issues or other structural and functional issues.

Once evaluated, they weigh the risk of therapy versus the potential benefit. Prevention of toxicity is sometimes best done by identifying the risk and avoiding anthracyclines altogether when there is a readily acceptable alternative chemotherapy. When anthracyclines are considered the best alternative, modifiable risk factors are aggressively treated.

At times initiation of an ACE inhibitor, an angiotensin II receptor blocker (ARB) and/or a beta blocker prior to anthracycline therapy is helpful. Cessation of smoking, ideal weight maintenance, adequate BP control and excellent diabetic sugar control are all strongly encouraged. Using a different delivery formulation of anthracycline (liposomal formulation) and a modified delivery infusion rate (infusional rather than bolus) also has been shown to have a favorable impact. These maneuvers are considered important in mitigating the cardiotoxicity impact of the anthracyclines.

In addition, there is one FDA-approved medication (dexrazoxane) that is sometimes used for cardio-protection. Currently the FDA recommends using this medication only for those with metastatic breast cancer when >300 mg/m^2 of doxorubicin is required for cancer control. However, it is occasionally used in an off-label way for other malignancies.

Continued

CASE #1

Cardiac Effects of Doxorubicin

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Cardiotoxicity timing

Anthracyclines can induce cardiac damage very early in treatment or at times can have a delayed effect. Myocardial dysfunction can develop years or even decades later in some individuals. For instance, adult survivors of cancer who were exposed to anthracyclines as children have been identified years later with markedly reduced ejection fractions.

In 2015 one group of investigators (Cardinale, D. et al) prospectively evaluated the timing and outcome of anthracycline induced cardiotoxicity in 2,625 patients and reported the results in the journal *Circulation*. In this study cardiotoxicity was defined as having both a LVEF decrease >10 absolute points from the baseline and the absolute value being <50%.

In this study, LVEF was measured at baseline every three months during chemotherapy, every three months during the following year, every six months over the next four years and then yearly afterwards. The median follow-up was 5.2 years.

The overall incidence of cardiotoxicity was 9% (9.7% in breast cancer patients, 6.2% in non-Hodgkin disease). The median time for cardiotoxicity discovery was 3.5 months.

In 98% of cases cardiotoxicity occurred within one year. Of patients with cardiotoxicity, 11% had complete recovery, 71% had partial recovery. In their conclusions they mentioned that in their study "early detection and prompt therapy of cardiotoxicity appear crucial for substantial recovery of cardiac function."

The finding that 98% of all the cases of cardiotoxicity occurred within the first year is especially interesting. Late reductions in LVEF did occur >5 years after treatment, but the degree of anthracycline causation of this LVEF decline is difficult to ascertain. A "double hit" phenomenon is speculated to possibly occur after the original insult by anthracycline chemotherapy.

Monitoring for cardiotoxicity

While on the anthracycline therapy and following the completion of therapy, patients are frequently monitored for signs of cardiotoxicity. Clinicians have keen clinical interest in obtaining baseline measurements and monitoring patients who are undergoing chemotherapy, because early detection of cardiotoxicity can result in a change in treatment which can favorably impact long-term (including mortality) outcomes.

Several clinical guidelines have been developed expressing general agreement of the importance of monitoring asymptomatic patients who are undergoing anthracycline chemotherapy for cardiotoxicity. However, there is no consensus regarding the specifics of how to do this.

Monitoring therefore is frequently individualized and depends on the presence of risk factors as well as the development of any cardiac signs. Clinical assessment includes evaluation for symptoms and signs of congestive heart failure such as dyspnea, edema, orthopnea and extreme fatigue.

Transthoracic echocardiography is typically used for imaging. It is not uncommon for clinicians to obtain a baseline echocardiogram followed by additional echocardiograms during and/or immediately following therapy. Repeat imaging is then considered 6-12 months later even if there are no cardiac symptoms.

Significant drop in LVEF with or without cardiac symptoms is a sign of cardiotoxicity. Cardiac MRI and/or nuclear imaging are sometimes performed in place of or in addition to echocardiograms. They are frequently ordered when the echocardiogram is equivocal.

Some investigators are evaluating other forms of cardiac damage detection such as measuring troponin or natriuretic peptides (brain natriuretic peptide; N-terminal pro-brain natriuretic peptide) levels. A rise in the troponin levels or natriuretic peptide levels can be seen with cardiotoxicity and is an early marker of cardiac damage.

Electrocardiograms (EKG) are frequently performed but are not very sensitive in detecting early cardiac problems. However, supraventricular or ventricular arrhythmias, atrioventricular block and pericarditis findings on an EKG can be indicative of early cardiotoxicity.

Figure 1 – Treatment alternatives for Anthracycline

- Stop the anthacycline
- ACE inhibiter?
- ARB
- B-blocker?
- Dexrazoxane
- Statin?

When cardiotoxicity is discovered

If anthracycline induced cardiotoxicity is discovered during therapy, clinicians evaluate the need for additional anthracycline and frequently discontinue the treatment and rely on other treatment choices, if possible. For instance, in breast cancer there are several other options such as docetaxel and cyclophosphamide which have comparable results.

If ongoing doxorubicin is needed, then dexrazoxane can be given prior to each future dose. Treatment of cardiotoxicity includes beta blockers, ACE inhibitors, ARBs and statins alone or in combinations. Some but not all patients respond nicely to these treatments.

Cardiac function returns to normal in many individuals. However, some impacted individuals have persistent cardiotoxicity concerns. Long-term cardiac dysfunction and chronic congestive heart failure can occur.

Chronic congestive heart failure has serious long-term mortality concerns. Typically, those with a chronically decreased ejection fraction have the worst mortality outcomes, and the degree of LVEF loss correlates directly with the mortality concern. Other cardiac toxicity complications, such as recurrent arrhythmias, are also associated with adverse long-term results.

Returning to the case

The proposed insured had several risk factors for anthracycline-induced cardiotoxicity and indeed had evidence of a significant adverse event with treatment. However, it is very encouraging that she had a nice response to treatment with a quick return of her left ventricular ejection fraction back to normal. Her current echocardiogram shows no significant abnormalities with a normal ejection fraction. Her clinicians have documented that the breast cancer is in remission, and no further treatment is planned.

Late term cardiotoxicity could still occur. Recall that in the large prospective study by Cardinale et al approximately two percent of individuals that ever experienced cardiotoxicity had a delayed toxicity that developed after one year.

In this unique case, where early toxicity occurred but with a prompt and effective response by the clinical team, it is difficult to know what the long-term outcome will be. However, it is encouraging that this individual has had close follow up and has been asymptomatic without arrythmia, and with a normal ejection fraction for several years. There appears to be minimal cardiac risk in this case.

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CASE #2

Cardiac Hemangioma

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A 33-year-old male applied for life insurance. He had no cardiovascular risk factors. His build, blood pressure and insurance labs were within normal limits. Five years prior, he had a TIA-like event and palpitations while driving. Holter monitoring revealed a brief run of non-sustained ventricular tachycardia. A cardiac MRI found an approximately 1-cm mass in the left ventricle (LV). A transesophageal echocardiography confirmed the position of the mass on the apical anterior interventricular septum but was otherwise normal.

Because of patient's age and symptomatology, he underwent a surgical resection of this mass which was found to be a hemangioma. No postoperative complications were noted.During a recent cardiac follow up he denied any cardiac-related complaints, and his physical exam and ECG were normal. A recent echocardiogram is essentially normal as well.

What is a cardiac hemangioma, and what are the mortality implications?

Cardiac hemangiomas (CH) are very rare, benign, vascular, primary cardiac tumors that can occur in any heart chamber, the pericardium, endocardium or the myocardium.

They are classified as capillary, cavernous or arteriovenous. Endocardial hemangiomas are usually capillary or mixed cavernous-capillary. Intramural hemangiomas might be capillary, cavernous or arteriovenous.

CH are usually solitary, but they have also been associated with extracardiac hemangiomas, including cutaneous sites (port-wine stain of the face) or visceral sites (hemangiomas of the gastrointestinal tract).

Etiology

The pathogenesis of hemangioma is still not understood. Growth factors and hormonal and mechanical influences have been postulated to affect the abnormal proliferation of endothelial cells in hemangioma. However, the primary, causative defect in hemangiogenesis remains unknown, and no genetic alteration has been implicated.

Epidemiology

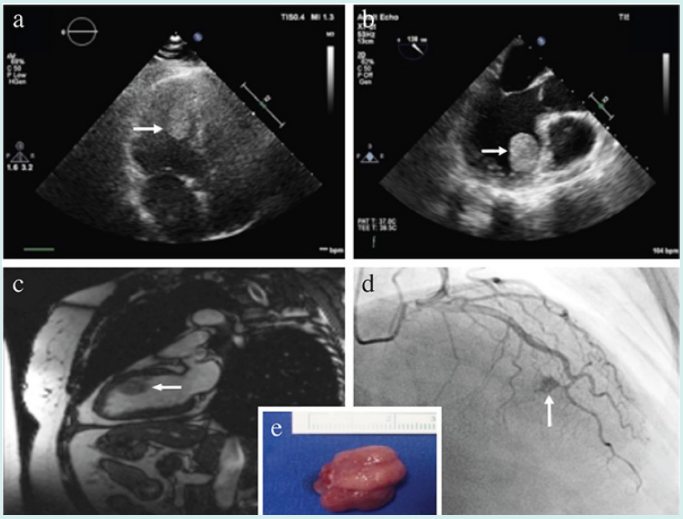
Primary tumors of the heart are rare and often diagnosed postmortem because of a mostly asymptomatic clinical course. The frequency of primary cardiac tumors seen at autopsy is 0.02%.

Secondary malignancies (metastatic) are the most frequent, with a 20-40 times higher incidence than primary tumors.

Three-quarters of primary cardiac tumors can be classified histologically as benign, with myxoma being the most frequent entity. Hemangiomas account for only 2% to 3% of all benign primary cardiac tumors, which means they are extremely rare. Hemangiomas can present at all ages, from individuals of seven months to 80 years old. The diagnosis is most frequently made during the fifth decade of life.

The right atrium and left ventricle are predominant locations for CH. In half of the cases CHs are pedunculated and mobile. The average size is four to five centimeters, but varies from 0.5cm to 15 cm.

Figure 1 — Diagnosing Cardiac Hemangioma



(a) Preoperative transthoracic echocardiography; apical four-chamber view showing a hyperechoic, round, mobile mass (arrow). (b) Transesophageal echocardiography revealed a homogenous, round, pedunculated mass (arrow) originating in the anteroseptal wall of the left ventricle. (c) A round, hyperintense mass (arrow) originating in the anteroseptal wall of the left ventricle is seen on the two-chamber white blood cardiac magnetic resonance imaging. (d) Preoperative coronary angiography demonstrated the characteristic finding of cardiac hemangioma "tumor blush" (arrow), which highlights the vascular nature of the tumor. (e) Image of the excised cardiac mass measuring 2.3×1.5×1.0 cm.

Source: A Rare Cause of Left Ventricular Mass, Cardiac Hemangioma: Altin C et al Balkan Medical Journal 35; March 2018. Available via license CC BY 2.5

Diagnosis

Clinical presentation depends on the location, size and growth rate of the tumor.

In most cases, they do not cause any symptoms and are diagnosed incidentally. Symptoms can arise from tumor evolution causing compression, infiltration, rupture, embolization and/or growth. Life-threatening complications include outflow tract obstruction, coronary insufficiency, heart failure, pericardial tamponade, thromboembolism, dysrhythmia and even sudden cardiac death.

Although CHs are often asymptomatic, the most frequent symptoms include dyspnea, palpitations, atypical chest pain and arrhythmia. Physical examination may reveal a heart murmur, usually systolic, in one-third of all cases.

Electrocardiogram is normal or nonspecific in more than three-quarters of cases but can show an atrioventricular block when CH is located in the area of the atrioventricular node.

Echocardiography has become the most important screening and diagnostic tool because of its relatively high accuracy and noninvasiveness. Hemangiomas appear on echocardiography as hyperechoic lesions.

Enhanced magnetic resonance imaging and *computed tomography* are used to evaluate the size, location and extracardiac involvement of CH. Magnetic resonance imaging is good at describing the high vascularity of CH. Typically, CH shows intermediate and high signal intensity in T1- and T2-weighted images, respectively, when compared with normal myocardium. Rapid homogeneous enhancement after contrast infusion is another typical manifestation of CH. The high vascularity of CH is of great diagnostic value clinically.

Coronary angiography is indicated in patients with CH to evaluate the location of feeding vessels or tumor blushes. Tumor blush is a typical sign of hemangioma.

Histopathologic examination is necessary to confirm the diagnosis.

Continued

CASE #2

Cardiac Hemangioma

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Differential diagnosis

Differential diagnosis of CH includes other cardiac tumors, thrombi and vegetations. Myxoma is the most common primary cardiac tumor, and they usually originate in the interatrial septum. In contrast, CHs most commonly arise in the right atrium and left ventricle.

Cardiac hemangiosarcoma is a malignant tumor with presenting symptoms and imaging manifestations much like CH. Consequently, histopathologic examination is essential for a final diagnosis.

Positron emission computed tomography is helpful in the differential diagnosis by detecting metastatic cardiac tumors. Atrial thrombi are typically located in the atrial appendage and are usually associated with atrial fibrillation, atrial dilation and mitral valve disease. Ventricular thrombi typically occur in the region of a ventricular aneurysm or akinesis. In general, both thrombi are associated with myocardial infarction or cardiomyopathy.

Valvular hemangioma should be differentiated from valvular vegetation, which is usually secondary to infectious endocarditis and valvular destruction.

Natural history

The natural history of CH is unpredictable with the options including continuous growth, stable size or even spontaneous shrinkage. Most CHs are stable during clinical follow-up. However, a few CHs show rapid growth.

Hemangiomas can cause sudden death, most often from a conduction disturbance in the heart. Often these CHs are in the region of the AV node or in the ventricles. A rare mechanism of sudden death in individuals with cardiac hemangioma is rupture of the tumor and pericardial tamponade.

Of the 120 cases of primary cardiac tumors causing sudden death reported by Cina et al six were due to hemangiomas.

According to Li et al in a retrospective study of 200 cases of CHs, tumor location in the interatrial or interventricular septum is an independent predictor of CH-related death.

Treatment

The surgical indication for CH remains controversial. Most scholars think that patients with CH should undergo surgical excision because of the potential risk of embolism, rupture and sudden death. Despite the consensus for surgical removal in symptomatic patients, a few experts favor conservative therapy as CH is histopathologically benign. Radiotherapy, corticosteroid and b-receptor blocker were reported as effective conservative treatments and are indicated, especially in patients with unresectable CH.

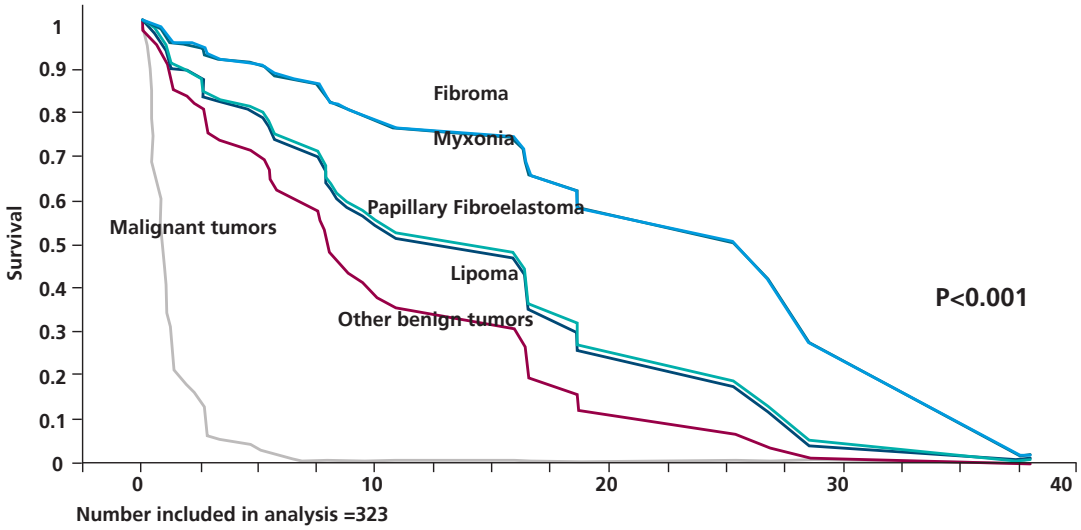
Nonetheless, since the natural course of these tumors is quite variable and unpredictable and there is low incidence of postoperative long-term adverse events and recurrence, surgical resection is the treatment of choice. However, excessive tumor removal is not necessary, because partial tumor resection is equally as effective as complete removal. Biopsy alone is not suggested owing to its high incidence of long-term adverse events.

Prognosis

In view of the benign nature of the tumor, the long-term prognosis is favorable after adequate surgical resection. Even incomplete resection or only tumor debulking seems associated with medium-term survival benefits. Nevertheless, due to the rarity of these tumors, long term survival studies are lacking.

Interestingly, ElBardissi AW et al found in a retrospective study of survival after resection of primary cardiac tumors over 48 years that five exceptionally rare benign tumors (calcified amorphous tumors, hemangiomas, teratomas, unilocular developmental cysts and rhabdomyomas) grouped together to gain statistical power had an unexpectedly poor survival; a finding that may be attributable to the complexity of these tumors and the population in which they occur.

FIGURE 2 - LONG-TERM SURVIVAL OF PRIMARY CARDIAC TUMORS



Source: ElBardissi AW et al Survival After Resection of Primary Cardiac Tumors A 48-Year Experience Circulation. 2008;118[suppl 1]:S7–S15

Continued

CASE #2

Cardiac Hemangioma

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Returning to the case

In this case, there was a small hemangioma totally resected with five years of follow-up without any symptoms or recurrence. There was also a recent normal echocardiogram.

The location of the tumor was in the interventricular septum, but it was at the apex and not in the atrioventricular node region (which is associated with a higher risk of sudden death because of possible complete AVB). Therefore, the potential for future mortality risk appears low to moderate.

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SOLVE

ECG Puzzler...

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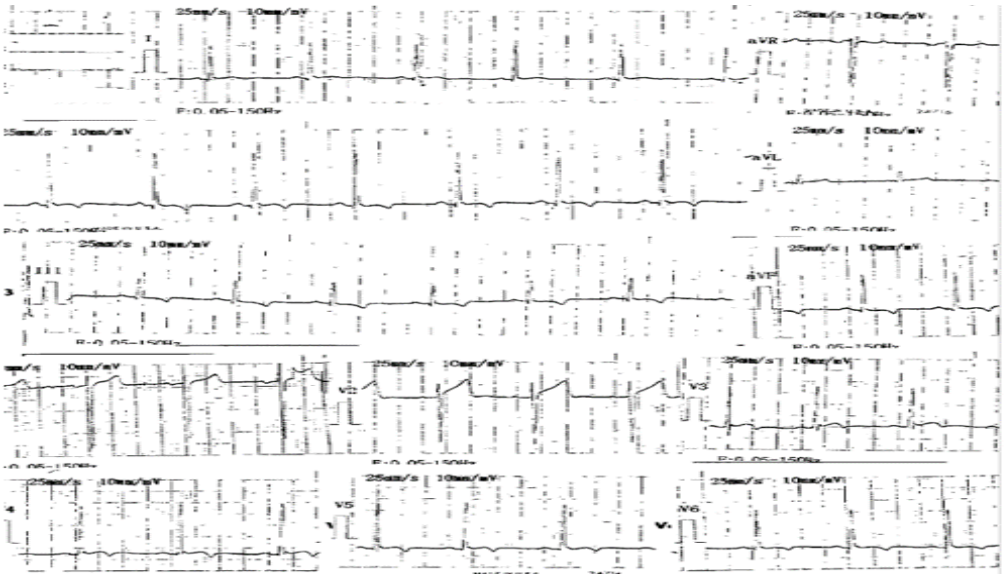
Editor's note: Congratulations to Dr. Rosace who recently became Board Certified in Insurance Medicine. Board certification requires significant time and dedication to the field of Insurance Medicine. We applaud Dr. Rosace in her accomplishment.



Here is the latest ECG Puzzler to solve.

A 23-year-old professional athlete applies for $3 million of life insurance. BMI 38, BP, lipids and LFTs are all normal. No declared family history. What does the ECG reveal?

Visit the Housecalls page on our website to find the answer at www.scorgloballifeamericas.com. Click on Winter 2018 Puzzler to confirm your findings.

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