Housecalls

July 2018

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INSIDE THIS ISSUE

MORTALITY IMPROVEMENT DRIVER?

FDA Bans Trans Fats

Drivers of mortality come in many forms, and a potentially significant one will come in June in the form of an FDA ban on trans fats in packaged foods. We are familiar with improvements in cardiovascular mortality in the population due to less smoking, improved diet/exercise and improved treatments and technology. We should see another reduction coming from wholesale reduction of trans fats in US pre-packaged foods.

Trans fats are partially hydrogenated oils that were developed for shelf life and the creamy texture. However, studies have shown that they raise LDL (bad) cholesterol and contribute to the development of cardiovascular disease. US companies have been moving away from using trans fats since 2006, when labelling requirements were initiated.

As of June 18, 2018 the FDA will no longer recognize partially hydrogenated oils as "generally recognized as safe" and will ban them from being added to manufactured foods. When Denmark instituted a ban on trans fats, one study showed a reduction of 14.2 deaths per 100,000 people due to cardiovascular disease over the next three years. And in a study comparing jurisdictions restricting trans fats with those without restrictions in New York, it was found that hospital admissions for myocardial infarction and stroke were reduced 6.2% in those areas with restrictions.

The World Health Organization on May 14 released a plan to eliminate industrially produced trans-fatty acids from the world food supply. Estimates are that, if fully implemented, the plan may eliminate 10 million cardiovascular deaths per year worldwide. Fortunately, trans fats can be replaced without an increase in cost or a loss of taste. Implementation of these preventative dietary measures should continue to improve mortality.

In this issue Dr. Kadouch presents a case of paraganglioma. This is an unusual tumor in that histology, histochemistry and biomarkers do not predict the risk of recurrence or metastases. The tumor is only determined to be malignant when metastases are found in tissues that do not normally contain the underlying cell type (chromaffin cells). For this reason, surveillance for recurrence is often maintained for years.

And Dr. Rooney presents a case of erythromelalgia. This disorder is diagnosed clinically as there is no definitive test that defines the disease.

And finally, a Puzzler is included for your perusal and interpretation.

SCOR
The Art & Science of Risk

CASE #1

Paraganglioma

By James Kadouch, MD
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A 37-year-old male applied for life insurance. He has a history of metastatic paraganglioma initially diagnosed in September 2009 after symptoms of left chest and left groin pain and fatigue, followed by a finding on CT scan, ultrasound and MRI of an 18x16x8.5 cm tumor in the left perirenal area.

A genetic test revealed a mutation in SDHB (succinate dehydrogenase unit B) gene. In 2010, he was found to have metastasis to the bones, ribs, sternum, left upper abdomen and lungs. He received treatment with 135 mCI of 131 Iodine MIBG. Seven years later he had a CT scan of the chest, abdomen and pelvis that did not show evidence of progressive disease. But a slight elevation of chromogranin A prompted an MRI of the cervical, thoracic and lumbosacral spine which showed two lesions at the level of T3 and T4 not seen previously. A PET scan was ordered, but the results are not provided.

What is a paraganglioma tumor and what are the mortality implications?

Definition

Paragangliomas (PGLs) are rare vascular, neuroendocrine tumors of paraganglia cell clusters originating from the neural crest that have co-migrated with the autonomic nervous system. PGLs are associated with either the sympathetic tissue in adrenal (pheochromocytomas (PCCs)) and extra-adrenal locations (sympathetic PGLs (sPGLs)) or the parasympathetic tissue of the head and neck paragangliomas (parasPGLs, formerly called glomus tumors).

PCCs and sPGLs are catecholamine-secreting tumors that arise from chromaffin cells, whereas parasPGLs are mostly chromaffin-negative tumors and usually non-functioning.

Etiology

Most PGLs occur as sporadic tumors, however at least one-third of PGLs/PCCs are hereditary. Four hereditary syndromes can be associated with development of PGLs:

- Von Hippel-Lindau Syndrome: patients with VHL gene (found on chromosome 3) can develop pheochromocytomas (often bilateral), paragangliomas, retinal angiomas, central nervous system hemangioblastomas, renal cell carcinoma, renal and pancreatic cysts, pancreatic endocrine tumors, and epididymal cystadenoma.
- Multiple Endocrine Neoplasia Syndrome type 2A and 2B: are due to mutations in the RET gene and usually associated with bilateral pheochromocytomas.
- Neurofibromatosis type 1, also known as Von Recklinghausen's disease, is the result of mutation in chromosome 17: pheochromocytomas can occur in up to 5% of cases, both inside and outside the adrenal gland.
- Familial Paraganglioma Syndrome: is caused by mutations in the succinate dehydrogenase (SDH) gene, and can be associated, albeit rarely, with pheochromocytomas.

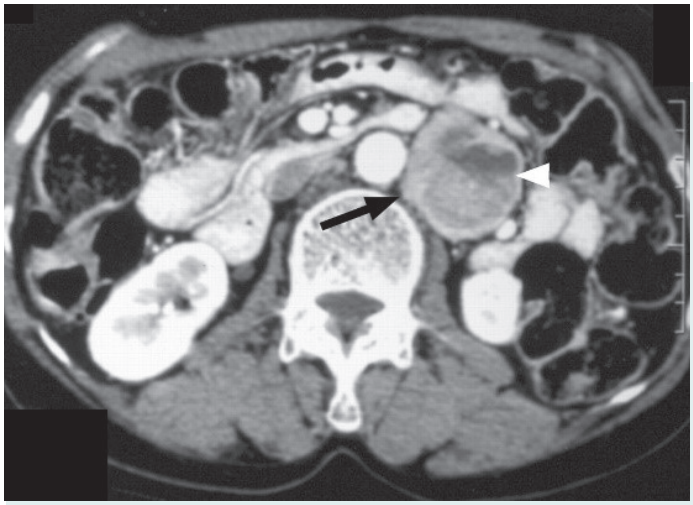


Figure 1 — CT scan showing tumor

Enhanced CT scan show 4.5-cm retroperitoneal PGL (arrow) with heterogeneous enhancement in left paraaortic area. Note large cystic component with fluid level (arrowhead) within tumor mass. High attenuation of dependent fluid in cystic portion is suggestive of intratumoral hemorrhage.

American Journal of Roentgenology.2006;187:492-504

Epidemiology

The prevalence of PGLs is unknown, but has been estimated to be between 1:6500 and 1:2500 in the USA. The annual incidence has been reported to be two to ten cases per million.

PGLs may occur at all ages, with the highest incidence between 40 and 50 years, and with an approximately equal sex distribution.

Most PGLs/PCCs are benign, but 10–15% are malignant, defined by the presence of metastatic spread in sites where chromaffin tissue is normally absent, such as lymph nodes, liver, bone and lungs.

Malignant pheochromocytoma and sympathetic paraganglioma affect only about 100–200 people per year in the United States.

Diagnosis

The diagnosis of paragangliomas is based on physical examination, biochemical testing, and imaging studies.

Pheochromocytomas in the adrenal gland may produce both adrenaline and noradrenaline. However, only paragangliomas that occur in the organ of Zuckerkandl, which is found along the lower part of the aorta, can make adrenaline. The remainder of paragangliomas are either non-functioning or produce noradrenaline only.

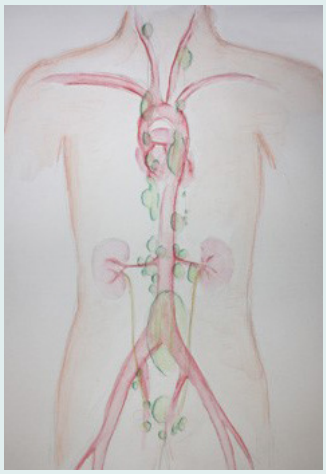
Continued

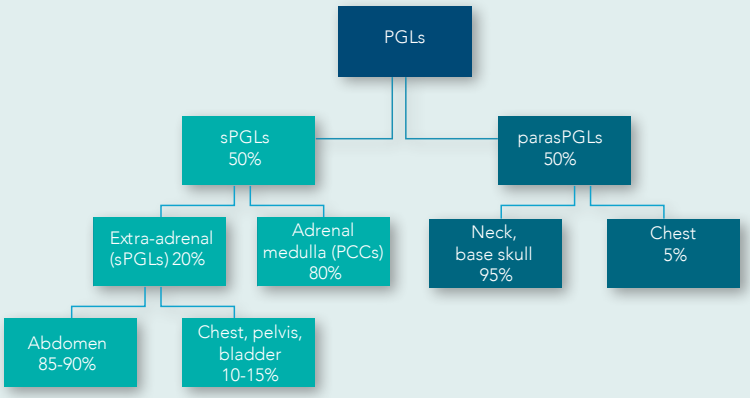
CASE #1

Paraganglioma

FIGURE 2 — PARAGANGLIOMAS (PGL) AND INCIDENCE OF MALIGNANCY BY PGL TYPE

Paragangliomas (PGLs) are rare vascular, neuroendocrine tumors of paraganglia cell clusters originating from the neural crest that have co-migrated with the autonomic nervous system. The chart at right shows the incidence of malignancy of various types of PGLs.





Clinical presentation

The majority of sPGLs and PCCs produces catecholamines in advanced cases causing symptoms of catecholamine excess.

Highly variable symptomatology in patients with PGLs may reflect variations in the nature and types of catecholamines secreted, as well as co-secretion of neuropeptides.

Hypertension, continuous or paroxysmal, is the most common feature of advanced PCCs and sPGLs. Typical symptoms are paroxysms of severe headache, palpitations, and diaphoresis, 'the classic triad'. Other symptoms may include anxiety, nausea, vomiting, and weakness. In addition, hyperglycemia, resulting from metabolic actions of catecholamines, may be the presenting symptom.

ParasPGLs are usually benign and only a minority (4%) produces catecholamines. They can remain clinically silent for years. But their usual location in the head and neck in the proximity of nerves and vascular structures often results in considerable morbidity due to compression or infiltration of the adjacent structures. They may cause symptoms such as hearing loss, tinnitus, dysphagia, and cranial nerve palsy. Carotid body tumors are the most common parasympathetic PGL, usually presenting as a painless neck mass.

Biochemical tests

Studies have found the rate of elevated catecholamine metabolites to be 88% in abdominal/pelvic PGL. Compared to PCC the levels of urinary metanephrines, while elevated, were much lower. The level of normetanephrines in PGL were much higher than in PCC.

Levels of catecholamines (adrenaline, noradrenaline, dopamine) and metanephrines may be measured in either the plasma or in a 24hour urine collection. Levels that are 2 or more times the upper limit of normal levels confirm the diagnosis of paraganglioma.

Imaging studies

When the diagnosis is confirmed with plasma or urine studies, the patient should have a CT scan or MRI to identify the location of the PGL.

Nuclear medicine tests like a MIBG (metaiodobenzylguanidine) scan or PET (positron emission tomography) scan can be helpful in locating tumors. The MIBG scan is specific for adrenaline-producing tumors while the PET scan identifies any very metabolically active tumors.

There is no definite histological finding that can be used for the diagnosis of malignant PGL. Therefore, malignancy is defined by the presence of metastases: tumor spread to sites where chromaffin tissue is normally absent.

Natural history

These tumors are derived either from sympathetic tissue in adrenal or extra-adrenal abdominal locations (sPGLs) or from parasympathetic tissue in the thorax or head and neck (parasPGLs); the two types occur with similar frequency.

sPGLs may develop anywhere there are sympathetic nerve cells, and this usually means along any of the major arteries in the body. They frequently produce considerable amounts of catecholamines, and in approximately 80% of patients, they are found in the adrenal medulla. The remaining 20% of these tumors are located outside of the adrenal glands, in the prevertebral and paravertebral sympathetic ganglia of the chest, abdomen, pelvis and bladder. Far and away, the most common site is within the abdomen where approximately 85-90% are located. Most abdominal sPGLs arise from a collection of chromaffin tissue around the origin of the inferior mesenteric artery (the organ of Zuckerkandl) or aortic bifurcation.

In contrast, the most common location for a parasPGL is the carotid body in the neck. Carotid body paragangliomas arise at the bifurcation of the internal and external carotid arteries and have classic radiographic features.

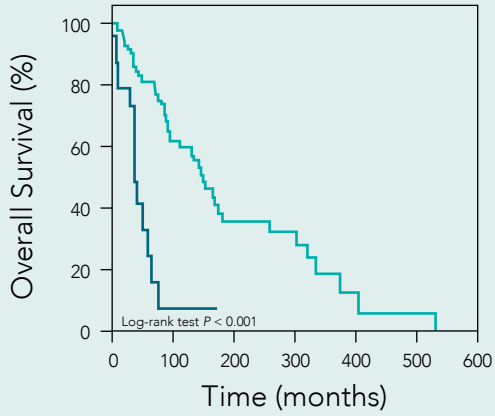
While most PPGLs are benign, about 10% of PCCs, 20-25% of extra-adrenal abdominal and mediastinal secretory PGLs are malignant. In the skull base and neck, malignancy is least common for jugulo-tympanic tumors (2-4%), slightly higher for carotid body tumors (4-6%), and highest for vagal tumors (10-19%).

There is no definite histological finding that can be used for the diagnosis of malignant PGL.

CASE #1

Paraganglioma

FIGURE 3— RETROSPECTIVE STUDY RESULTS



In a retrospective study, patients with metastatic pheochromocytoma or paraganglioma who underwent palliative resection of the primary tumor (green line, n = 28) had longer median overall survival than those who did not (blue line, n = 24).

Roman-Gonzalez A, et al. Ann Surg. 2017

Compared to adrenal PCCs, PGLs have a higher risk of being malignant or cancerous, as high as 40-50% in some studies. Larger tumor size (over 5 cm), invasion of the tumor into adjacent structures, and metastases to other organs are characteristics of malignant paragangliomas.

PGLs typically metastasize to lungs, liver, bones, and lymph nodes.

Paraganglioma syndrome 4 (PGL4) is associated with mutations in SDHB at gene locus 1 and is the second most common type of familial paraganglioma. SDHB mutations are associated with a higher malignancy rate (21% to 79%) than other types of SDHx-associated familial paraganglioma syndromes, and with renal cell carcinoma.

Treatment

The definitive treatment of PGLs is surgical excision of the tumor. Laparoscopic surgery is commonly the technique of first choice for resection adrenal and extra-adrenal PGLs when oncologic principles can be followed. Surgery can also be used as a curative treatment for recurrent or limited metastatic tumors.

Traditional chemo-therapy with cyclophosphamide, vincristine, and dacarbazine (CVD) has been used most extensively with progressive and widely metastatic PGLs. Molecular targeted therapies such as sunitinib (tyrosine kinase inhibitor) and everolimus (mTOR inhibitor) have been tried with mixed results.

Prognosis

The long-term prognosis of patients after operation for non-malignant PGLs is excellent, although nearly 50% may remain hypertensive after surgery. On long-term follow-up, about 17% of tumors recur, with about half of these showing signs of malignancy. Although follow-up is especially important for patients identified with mutations of disease-causing genes, there is currently no method based on pathological examination of a resected tumor to rule out potential for malignancy or recurrence. The prognosis of metastatic PCC/PGLs is variable. Long-term survival is possible even in the presence of distant metastatic disease, but five-year survival rates are ≤ 60%.

Prognosis is impacted by tumor burden, location of metastases, and rate of progression; patients with brain, liver, and lung metastases tend to have a worse prognosis than do those with isolated bone lesions.

Returning to the case

Unfortunately, and despite the resection of the primary PGL tumor with the nephrectomy, this case has unfavorable features such as the onset of a malignant PGL at a relatively-young age, the very large dimensions of the tumor, and the presence of metastases. Moreover, the two lesions recently found on the MRI of his spine are quite possibly a recurrence. Finally, the mortality rate associated with metastases would raise very significant long-term mortality concerns.

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CASE #2

Erythromelalgia

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A 49-year-old female is applying for life insurance. She was diagnosed with erythromelalgia three years ago. She experiences frequent episodes of severe pain and redness of her feet and hands. These episodes seem to be precipitated by mild changes in temperature or vigorous exercise.

Diagnostic testing included normal lower extremity doppler vascular studies. An electromyogram (EMG) was abnormal with the impression stating the criteria for axonal neuropathy were fulfilled. A complete blood count (CBC) done initially was normal. Repeat CBCs have been performed annually, and the most recent was abnormal with the WBC elevated at 18,000 per µL, platelets were slightly elevated, and the hemoglobin slightly reduced. A referral to a hematologist was made, but this evaluation hadn't been completed at the time of the application.

There is a recent note mentioning the severity of the painful episodes has been mitigated satisfactorily with a combination of pharmacological use of gabapentin along with nonpharmacological use of icy water applied to the skin with onset of an exacerbation. The recent addition of daily aspirin has made a significant favorable impact.

What are the mortality considerations of a diagnosis of erythromelalgia?

Erythromelalgia is a rare disorder characterized by intermittent episodes of severe burning pain and marked erythema of the extremities. The condition was initially described in 1878 and named erythromelalgia, as it was very descriptive of the clinical findings.

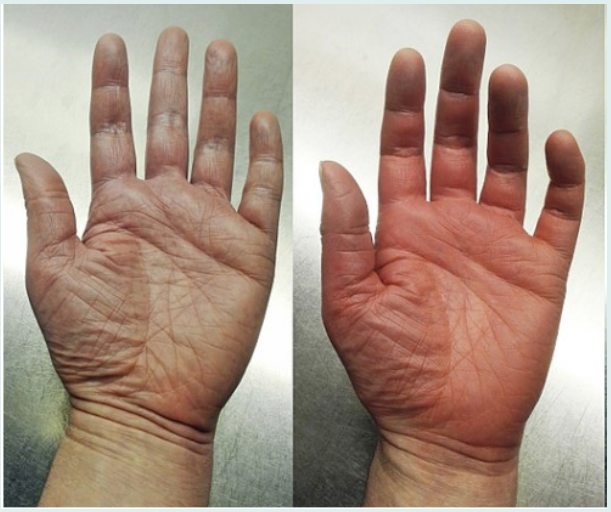
The term was derived from the words: Erythros (red), melos (extremity) and algos (pain). The disorder typically involves the lower extremities (most commonly the feet); however, it can occasionally also involve the upper extremities and/or the face.

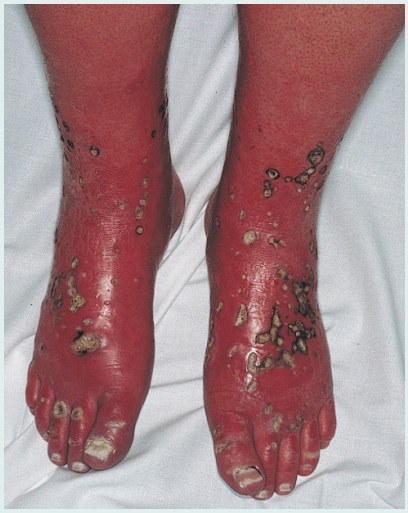
Precipitating factors for the intermittent symptomatic episodes include a mild increase in ambient heat or exercise. Unfortunately, there is no cure for the condition. There are however multiple treatment options, both pharmacological and nonpharmacological.

Treatment

These treatments have been successful in partial mitigation of the significant amount of pain and suffering that is associated with the condition. There is increased mortality from the condition centering mostly on the associated comorbid conditions, which includes myeloproliferative disorders. In addition, however, the symptoms of erythromelalgia can be so severe as to cause significant despair and depression leading to suicide.

FIGURE 1 — EXAMPLES OF ERYTHROMELALGIA





Hands image obtained 5/3/2018 using Google's search engine "labeled for reuse with modification"

https://commons.wikimedia.org/wiki/

Feet image obtained 5/3/18 using Bing's "Free to share and use commercially" search engine

https://jamanetwork.com/data/Journals/DERM/11693/dce9005f1.png

Incidence

The incidence rate is one to two cases per 100,000 people per year. It is a condition which is more common in women. It is much more common in adults, but rarely children can be impacted.

The pathogenesis of the disorder is incompletely understood. The condition is most commonly sporadic; however, in approximately 6% of cases it is thought to be inherited. Most of the inherited cases impact children.

A gene located on chromosome 2q24 has been identified in the inherited cases. This gene produces a protein involved in a voltage-gated sodium channel which is important in normal nerve function. Thus far, at least 10 mutations have been identified, and hereditary erythromelalgia is inherited as an autosomal dominant condition.

When functioning properly, the voltage-gated sodium channels closely control the depolarizations in nerves including dorsal root ganglions and sympathetic ganglions. Abnormally functioning channels are associated with nociceptor hyperexcitability, which is associated with the pain in patients with erythromelalgia.

While erythromelalgia is most commonly seen as a stand-alone diagnosis, the disorder has been, at times, associated with a variety of other comorbid conditions. These comorbid conditions include myeloproliferative disorders (e.g., chronic myelogenous leukemia, polycythemia vera), pregnancy, drug exposures, neoplasms, autoimmune diseases and infections. Erythromelalgia is associated with an underlying myeloproliferative disease in approximately 8% - 10% of cases. Erythromelalgia can precede the myeloproliferative disorder, occur simultaneously, or occasionally occur afterward.

Continued

CASE #2

Erthromelalgia

Diagnosis

Typically the diagnosis of erythromelalgia is made through the characteristic clinical history and supported by abnormal findings on physical examination. Presenting symptoms include burning, numbness and increased heat.

In one study[1] feet were involved in 88% of cases, hands in 25.6%, legs in 13.7%, and face in 3.5% of cases. Physical exam findings during an exacerbation include both a raised skin temperature as well as significant erythema.

Precipitating factors involved in exacerbations include exposure to increased ambient heat (52%)[1] and exercise (28.6%)[1]. There are no pathognomonic diagnostic tests available. However, there are abnormal tests frequently associated with the condition.

EMG and nerve conduction studies are frequently abnormal. Erythrocyte sedimentation rate testing is occasionally abnormally increased. Skin biopsies are frequently performed to eliminate other diseases which can present similarly, but the skin biopsy results in erythromelalgia, while abnormal, are typically variable and nonspecific.

Sometimes the diagnosis of this condition can be challenging given the intermittent nature of the symptoms. A cooperative partnership with the physician is sometimes needed so that a timely office visit evaluation occurs with the onset of the symptoms and signs.

Disorders in the differential diagnosis of erythromelalgia would include peripheral vascular disease, Raynaud phenomenon, cellulitis, acrocyanosis and various neuropathies.

The treatment of erythromelalgia is directed at reducing the frequency and the severity of the symptoms. As is true for other conditions in medicine where there is no one consistently effective treatment available, multiple treatment modalities have been tried with varied success.

Avoiding precipitating factors is helpful. Nonpharmacologic treatment consists of intermittent fan use, limb elevation and timely application of cool water to the involved skin. Topical pharmacologic therapy includes anesthetics, capsaicin and gabapentin ointment. Systemic pharmacologic therapy includes aspirin (which is reported to be especially helpful in those with a comorbid myeloproliferative disease), gabapentin, amitriptyline, beta blockers and calcium antagonists, among others. The multidisciplinary approach usually experienced at pain rehabilitation programs has been shown to be especially helpful.

Those with erythromelalgia are monitored frequently for response to treatment. Despair and depression are monitored closely and treated aggressively in those who don't otherwise get good relief from the preventative and therapeutic maneuvers. Complete blood counts are regularly performed to monitor for the relatively rare, increased risk of myeloproliferative disorders.

Sometimes the diagnosis of this condition can be challenging given the intermittent nature of the symptoms.

Returning to the case

Erythromelalgia is associated with increased mortality risk. Most of the mortality risk centers around an increased risk for suicide in those who struggle obtaining adequate pain relief and the increased risk of comorbid conditions such as myeloproliferative disorders.

In this case documentation suggests the pain is under adequate control. However, the recent leukocytosis and thrombocytosis findings raise some concern about the possibility of a developing myeloproliferative disorder. It would be prudent to postpone until a full hematological evaluation has been completed.

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Images as per the documentation beside each.

SOLVE

ECG Puzzler...

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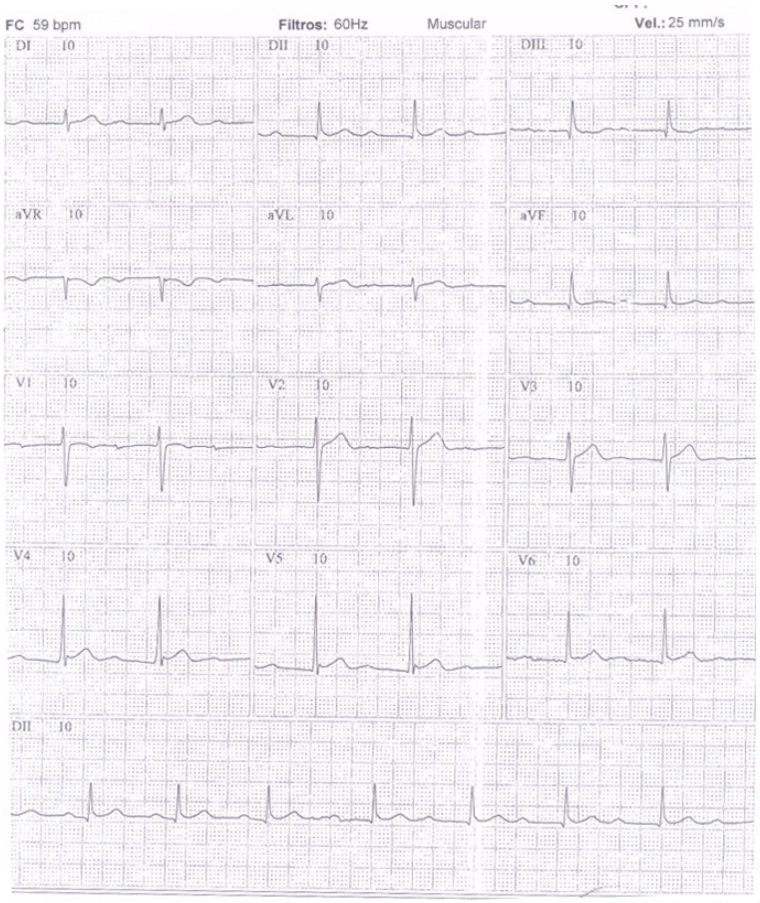

Here is the latest ECG Puzzler to solve.

A 23-year-old male applied for life insurance with no cardiac history. What is the major abnormality in this ECG?

To find the answer, visit the Housecalls page at www.scorgloballifeamericas.com. Click on June 2018 Puzzler to confirm your findings.

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