Housecalls

Underwriting Case Studies & Insights

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Our Casebook

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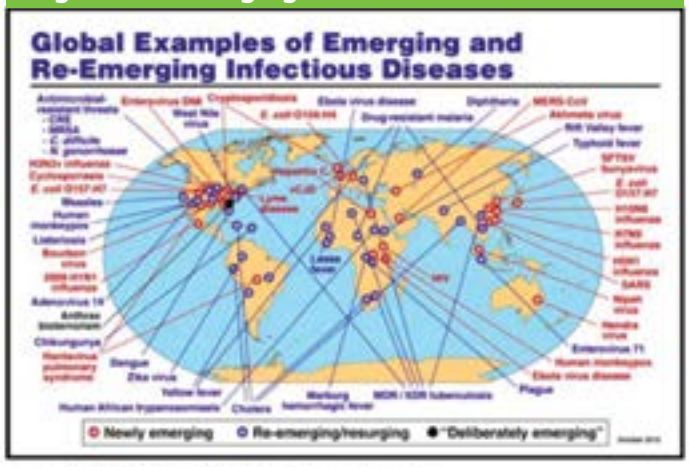
According to the Centers for Disease Control and Prevention (CDC) website, an emerging infectious disease (EID) is one whose incidence in humans has increased in the past 2 decades or threatens to increase in the near future. The CDC and the World Health Organization (WHO) are major players in the identification, verification, and responses to EID. And with today's 24/7 news cycle, each new EID is reported with gusto (Figure 1). The EIDs can arise from mutations or evolution in existing infectious organisms or spread from known organisms to new areas (e.g., Zika). They can arise when humans move into areas containing pathogens or animal vectors migrate, or they can develop through antimicrobial resistance. And they can be exacerbated by cultural practices that foster the spread. EID can be spread person to person, in the food or water supply, or from animals to humans (zoonosis).

Figure 1 – Emerging Disease Outbreaks



(Courtesy National Institute of Allergy and Infectious Diseases)

In this issue Dr. Buffet, from SCOR's Paris office, presents a case of possible Zika virus infection and discusses the probable ramifications for underwriting. SCOR will continue monitoring EID and report to markets when warranted.

In contrast to Dr. Buffet's Zika case, which involves evolving information practically daily, I present a case that, while unique, is more traditional to the types of cases that client underwriters refer to us. The case involves an applicant with hypercalcemia. We examine the disease, its mortality implications and advise on how best to approach such cases.

Emerging diseases raise curiosity and concern – the latter for good reason: the spread of the Zika virus has already reached pandemic proportions in certain areas of Latin America. And whether because of news cycles, greater awareness and monitoring or actual evolution, sometimes it seems that once we successfully contain an outbreak we must turn to face another, new contagion risk all over again. In the process we still confront diseases with which we have some greater familiarity. SCOR's medical team is committed to monitoring developments and keeping clients informed. ∞

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Case #1
A Case of Zika Virus, or Is It?

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Dr. Buffet joined SCOR Global Life in 2006 as Associate Medical Director, Research & Development. She earned her medical degree with a specialization in internal medicine from the Federal University of Rio Grande in Brazil, where she later served as a professor of Infectious Diseases. Gabriela has also received the certificate in Epidemiology, Statistics and Clinical Research (University "Paris-Sud") and a master's degree in Microbiology and Infectious Diseases (ESSSCAN, Spain). She is a Member of the Infectious Diseases Society of America.

A 35 year-old man applied for life insurance with waiver of premium for disability benefit. His medical records indicate that he was previously in good health when he presented to his doctor about one month prior to the application. He was complaining of a 103° F fever, a headache, and muscle aches. There was no evidence of a stiff neck, rash, gastrointestinal or respiratory complaints. He admitted that he started feeling bad 3 days earlier while on a return flight from Honduras, where he had been on a church mission in the rural countryside. His doctor recommended fluids, rest, antipyretics and analgesics. He also ordered a CBC and a sample for Zika virus testing to be sent to the state health department. The doctor suggested that the proposed insured isolate himself until the fever had resolved for 5 days and return for follow up if he worsened, or in one week for test results. This was the last entry in the medical record.

Figure 1 – American/Caribbean Countries with Confirmed ZKV Cases

Cases of the Zika virus have been reported throughout Latin America and the Caribbean. Many cases in the US involve foreign travelers.

Question

What are the implications of Zika virus infection for mortality and morbidity risks?

Answer

Zika virus (ZKV) is an emerging mosquito-borne virus (Flavivirus) that was first identified in Uganda in 1947. It was subsequently identified in humans in 1952 in Uganda and the United Republic of Tanzania. Outbreaks of Zika virus disease have been recorded in Africa, the Americas, Asia and the Pacific.

The most recent outbreak reported in Latin America and the Caribbean is an immediate health concern for the region, and news continues to develop on this topic rapidly. We present what is known at the time of publication and encourage our colleagues in client companies to contact us for further discussion.

Outbreak and Transmission

ZKV in the Americas was first identified in Brazil in April 2015. Since then, the number of infections and complications have increased and the infection has been reported by almost all American countries. Incubation for Zika virus is likely to be a few days to a week.

The ZKV natural transmission cycle involves mosquitoes, especially *A.aegypti* and *A.albopictus*. However, ZKV transmission by sexual intercourse has been reported and transfusion-transmitted ZKV infections have also been demonstrated.

Signs and Symptoms

About 80% of people infected with ZKV are asymptomatic. When people are symptomatic, the

illness is usually mild with symptoms lasting for several days to a week. The main symptoms are headache, low-grade fever, mild joint pain, skin rash (exanthema) and conjunctivitis. Other less common symptoms are sore throat, cough and vomiting. Joint pain may persist for approximately one month. Deaths are rare.

Diagnosis and Treatment

Zika virus is diagnosed through PCR (polymerase chain reaction) and virus isolation from blood samples.

Zika virus disease is usually relatively mild and requires no specific treatment. No medications or vaccines currently are available to prevent or treat Zika infections, though several labs are testing interventions.

Complications

Increased incidence of neurological syndromes and microcephaly were reported in Brazil since the beginning of the outbreak.

This increase in the incidence of rare pathologies during Zika virus outbreak is consistent with a temporal and spatial link with the Zika virus outbreak. However, the etiopathogenesis and associated risk factors have not yet been well established.

Pathological complications include neurological syndromes, increased risk of microcephaly and other birth defects and ophthalmological anomalies.

Neurological syndromes – The rate of neurological syndromes in adults increased during the last Zika virus outbreak. Observed incidence of Gullain Barré syndrome and other neurological anomalies is about 10-20 times expected.

Microcephaly – The association between Zika virus infection and the increased number of reports of congenital microcephaly and other birth defects is a serious issue. The average of annual incidence of microcephaly in the 4 last years in Brazil was 163 (SD 16.9) cases. Since the beginning of the outbreak the incidence of microcephaly has increased dramatically. Since the epidemiological 1st week of 2016, 3530 cases of microcephaly in Brazil have been reported.

Ophthalmological anomalies – Ophthalmological lesions have been reported in newborns. Ocular findings commonly involve the macular region, such as macular neuroretinal atrophy.

Prevention

The first line of prevention is effective mosquito control, including reducing the risk of mosquito bites:

Figure 3 – Comparison of Zika, Chikungunya and Dengue Viruses

	Zika Virus	Chikungunya Virus	Dengue Virus
Transmission	*Aedes* mosquitoes, blood transfusion, sex	*Aedes* mosquitoes	*Aedes* mosquitoes
From infection to disease in...	1 in 5 people	3 in 4 people	1 in 4 people
Incubation (range)	2-12 days	2-12 days	3-14 days
Symptoms	Low grade fever, maculopapular rash, arthritis (smaller joints of the hands and feet), and conjunctivitis	Fever, joint pain in multiple joints, headache, muscle pain, rash and joint swelling	Fever, headache, retro-orbital pain, joint pain, muscle and/or bone pain, rash, mild bleeding (nose or gums, easy bruising), nausea, vomiting, diarrhea
Typically resolves	2-7 days	7-10 days	Febrile phase: 2-7 days Critical phase: 1-2 days Recovery phase: 2-3 days
Complications (associations)	Perinatal infection: fetal loss; microcephaly Guillian-Barré syndrome	Joint swelling and pain may recur for several months	Bleeding, neutropenia, thrombocytopenia, liver enlargement, shock can occur
Mortality	Very rare	Rare, mostly in adults	Severe Dengue – 2.5% CFR*

The Zika, chikungunya and dengue viruses present common symptoms. It is advisable that physicians test for the presence of all three when infection is suspected. (* CFR = Case fatality rate. Severe defined as requiring hospitalization.)

A Case of Zika Virus, or Is It? (cont.)

using an insect repellent; wearing clothing (preferably light colored) that covers most of the body; using physical barriers such as screens, closed doors and windows; and sleeping under mosquito nets. It is very important to identify and eliminate potential mosquito breeding sites. This is especially true for travelers. Some agencies recommend pregnant women against travelling to epidemic countries.

Vaccines

No vaccines are available currently. However, a vaccine for the Zika virus is in development by US and Canadian scientists with Inovio Pharmaceuticals Inc (INO.O) and South Korea's GeneOne Life Science Inc. The first approved vaccination could be available for emergency use before the end of the year, with clinical trials scheduled to start by September 2016.

Returning to the Case

It is not clear that this case is a Zika virus infection. The Center for Disease Control (CDC) recommends that all samples tested for Zika virus also be tested for dengue virus and chikungunya virus as all three are present in Latin America, they share the same mosquito vector (*aedes aegypti, aedes albopictus*), and the initial presentations are all very similar (Figure 3).

Given the mortality implications of dengue infection and the possible post-infection morbidity with any of the infections it would be prudent to postpone issuing any policy for at least 6 months, and then reconsider with results of testing and an up-to-date evaluation for complications. ∞

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Case #2
Hypercalcemia

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A 28 year-old male applied for life insurance. Medical history revealed that he had a general physical about 9 months prior to the application. His BMI was 33.9.

On the screening blood work he had an elevated serum calcium of 10.7 mg/dl (8.7-10.2 mg/dl) or 2.67 mmol/L (2.17- 2.54 mmol/L). His albumin was 5.0 g/dl (3.6-5 g/dl) or 50 g/L (36-50 g/L) and the total protein was 7.6 g/dl (6.1-8.2 g/dl) or 76 g/L (61-82 g/L).

A repeat blood test showed his serum calcium remained elevated at 11 mg/dl or 2.74 mmol/L, his serum albumin was 4.7 g/dl, and his ALT was slightly elevated at 61 (0-45 UL). He was feeling well, was on no medication, and taking no supplements or vitamin D. There was no history of endocrine tumors, fracture or kidney stones in him or his family. Other than obesity, his physical examination was normal.

He was referred to an endocrinologist. These records showed that his corrected calcium was 10.1 mg/dl, 24-hour calcium in the urine was 218 mg (100-300 mg). Other values included Parathyroid hormone related protein (PTHrP) < .74 pmol/L, Vitamin D 25 Hydroxy 19.9 ng/ml (30-100 ng/ml), PTH 30 pg/ml (15-65 pg/ml). The tentative diagnosis was familial hypocalciuric hypercalcemia. He was placed on a diet with adequate hydration and moderate calcium restriction and prescribed 800 IU of vitamin D daily. Follow-up was scheduled for 1 month, but records were not included.

Question

Is the work-up sufficient to diagnose familial hypocalciuric hypercalcemia (FHH)? And what are the mortality implications of hypercalcemia?

Answer

Hypercalcemia is a serious finding as over 90% of individuals will have either hyperparathyroidism or malignancy as the cause. Calcium is absorbed in the intestine, deposited in bone, and excreted by the kidneys. Excessive absorption from the gut, resorption from bone, decreased excretion by the kidneys or any combination of the three can result in hypercalcemia.

One caveat should be noted when considering serum calcium: 40%-45% is bound to serum proteins, mostly to albumin. The free or ionized calcium is considered to be physiologically important. For the most part, normal laboratory ranges account for this. However, an adjustment sometimes is made when the serum albumin levels are exceptionally high or low. One common formula (US units) for this correction is:

Corrected calcium = Serum calcium + 0.8 * (normal albumin – patient albumin)

[Note: normal albumin is often 4.0 for women and 4.4 g/dl for men].

For SI units the formula is:

Corrected calcium = Serum Calcium+0.02 * (normal albumin – patient albumin)

[Normal albumin is often 40 for women and 44 g/L for men].

Laboratory evaluation of hypercalcemia typically begins with the measurement of parathyroid hormone (PTH). Produced in the parathyroid gland, PTH increases bone resorption and intestinal absorption of calcium. A common cause of elevated PTH and consequent hypercalcemia is parathyroid adenoma. This is the most common cause of primary hyperparathyroidism. Typically, primary hyperparathyroidism will elevate serum calcium minimally, less than 11 mg/dl (2.75 mmol/L). And in some cases the hypercalcemia of primary hyperparathyroidism will cause intermittent hypercalcemia or high normal serum calcium, requiring repeated measurements.

If the PTH measures low (<20 pg/ml), measurement of Vitamin D metabolites (1,25-dihydroxyvitamin D) and parathyroid hormone related protein (PTHrP) is recommended. If PTHrP is elevated, then malignancy should be strongly considered and sought. In that setting, vitamin D is usually normal or low. PTHrP increases bone resorption and reduces renal excretion of calcium, resulting in relatively higher levels of hypercalcemia.

Hypercalcemia is relatively common in cancer, occurring in 20%-30% of cases. Cancer can elevate serum calcium by several mechanisms. The most common (~80%) is humoral hypercalcemia of malignancy (HHM) mediated by secretion of PTHrP. The more common tumors associated with HHM are squamous cell carcinomas of the lung, head, or neck, and breast, bladder, renal or ovarian carcinomas.

A second mechanism, accounting for most of the remainder of the cases of hypercalcemia in malignancy, is osteolytic metastasis. The tumor stimulates osteoclast production and activity, releasing calcium into the blood. Breast cancer and multiple myeloma often cause hypercalcemia by this method.

Figure 1 - Medications that Can Cause Hypercalcemia

Medication	Mechanism of hypercalcemia
Lithium	Raises the calcium "setpoint" to suppress PTH release
Thiazide Diuretics	Reduces urinary calcium excretion (rare cause)
Theophylline (toxicity)	Mild elevations, subsides
Hypervitamininosis D or Calcitriol or Calcidiol Rx	Increases gut absorption and bone resorption
Hypervitaminosis A	Increased bone resorption

Certain drugs unrelated to typical mechanisms of hypercalcemia can nevertheless cause the condition to manifest.

Hypercalcemia (cont.)

A less common mechanism is an increased production of 1,25-dihydroxyvitamin D (calcitriol) which can be seen with Hodgkin's and non-Hodgkin's lymphomas. This elevation can also be seen in non-malignant granulomatous disease like tuberculosis or sarcoidosis.

Rarely, tumors such as small cell lung cancer, ovarian cancer, papillary cancer of the thyroid, and pancreatic cancer can independently produce excess PTH.

Quite often, hypercalcemia is a late finding in malignancy, and it often portends a poor prognosis.

If the PTHrP is not elevated, physicians turn to the Vitamin D levels in the evaluation of hypercalcemia. An elevated blood level of vitamin D leads one to consider vitamin or supplement intake, lymphoma, or chronic granulomatous disease (TB or Sarcoid), and order a chest x-ray.

In the setting of hypercalcemia and low PTH with low/normal PTHrP and Vitamin D levels, other causes including medications (Figure 1), hyperthyroidism, acromegaly, adrenal insufficiency, immobilization, parenteral nutrition, or milk alkali syndrome should be investigated.

For completeness, secondary hyperparathyroidism should be considered, although serum calcium levels are typically normal. This disorder is characterized by elevated PTH to maintain serum calcium levels in response to another disorder. Renal failure and intestinal malabsorption (e.g., bariatric surgery, Celiac disease) are among the more common causes.

The most common cause of asymptomatic hypercalcemia is primary hyperparathyroidism (PHPT), and after malignancy has been excluded attention can be focused on this. Symptomatic PHPT is characterized by the mnemonic:

- Bones (bone pain from calcium resorption)
- Stones (nephrolithiasis)
- Abdominal Moans (anorexia, nausea, constipation)
- Psychic Groans (anxiety, depression, cognitive changes)

However, symptomatic PHPT is much rarer than the asymptomatic variant. Subclinical muscle weakness may also be detected with appropriate testing.

The laboratory findings for the most common causes of hypercalcemia are listed in Figure 2.

Figure 2 – Typical Hypercalcemia Lab Test Results and Likely Diagnosis

Diagnosis	PTH	24 hour urinary calcium	25OH Vitamin D
PHPT	^^ or high normal	Elevated (40%) or normal	Normal or elevated
Cancer	Low (< 20 pg/ml)	High	Depends on intake and type of malignancy
Familial hypocalcuric hypocalcemia (FHH)	Normal in majority, slightly elevated in 15%	Low (<100 mg/24 hours)	Normal

Each diagnosis has a unique, distinguishing series of values.

PHPT diagnosis is related to routine measurement of serum calcium on multichannel screening blood tests. The majority of diagnoses are made between ages 50 and 65. Women are affected twice as often as men. PHPT is usually (80%-85%) caused by a solitary benign adenoma, although double adenomas or diffuse hyperplasia does occur. Parathyroid carcinoma is the cause in < 1% of cases.

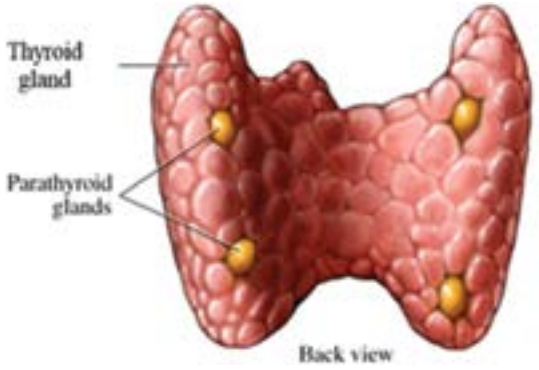
Research indicates that PHPT may be associated with other disorders like multiple endocrine neoplasia, obesity, type 2 diabetes, anemia, and monoclonal gammopathy, although some studies are conflicting for some disorders.

Treatment

Treatment of PHPT consists of observation or surgical removal of parathyroid tissue. Surgery for symptomatic patients is recommended, while some asymptomatic patients may be observed. In asymptomatic PHPT patients followed for 10 years, 27% had progression of serum calcium and PTH, while 37% progressed over 15 years of follow-up. It was noted that younger patients were more likely to progress.

Criteria to be considered that make asymptomatic patients candidates for surgery include: serum calcium 1 mg/dl or more above the upper limit of normal; eGFR < 60 ml/min; nephrolithiasis or nephrocalcinosis, elevated 24-hour urinary calcium excretion (>400 mg/day); severely reduced bone density or frailty fractures; and age < 50 years. In patients in which surgery is

Figure 3 – the Thyroid and Parathyroid Glands



Four parathyroid glands located on the posterior aspect of the thyroid gland.

recommended, but who cannot or will no undergo surgery, medications are available that can mimic calcium's effect on parathyroid tissue while others will reduce bone resorption. A detailed discussion is beyond the scope of this case study.

PHPT-related mortality in some reports is related to the severity of the hypercalcemia, with higher levels having higher mortality. In various Scandinavian studies the range of relative risk of all-cause mortality in PHPT was 1.2-2.0. However, these studies were done before the availability of PTHrP testing. US studies have not shown an increase in mortality above the general population in association with mild PHPT, even among those who did not undergo surgery, although these patients generally had lower levels of serum calcium. One more recent study from the UK compared populations having elevated calcium and elevated PTH to an age and gender-matched cohort from the area, who had either normal or no calcium measurements. The study group did not fit the NIH criteria for surgical referral. They found hazard ratios (HR) of 2.24 for all-cause mortality in the PHPT group. They further adjusted for higher rates of underlying morbidity and propensity for calcium testing and obtained a HR of 1.64 (1.43-1.87) for all-cause mortality.

Familial hypocalciuric hypocalcemia (FHH) is a rare condition due to at least partial inactivation of the calcium-sensing receptors (CaSR). The familial form is due to a genetic mutation. CaSR are present on cells of the parathyroid and kidneys, and allow those cells to adjust PTH levels and urinary calcium secretion and calcitriol levels to maintain serum calcium in a tight range. Approximately 200 mutations to the CaSR have been identified. The severity of the hypercalcemia is related to the particular mutation, penetrance and hetero versus homozygosity. If the clinical picture is unclear, mutational analysis tests for the more common mutations are available commercially.

Clinically, FHH is usually a benign, asymptomatic condition, without complications. Hypercalcemia remains mild and stable and surgical removal of parathyroid tissue is not helpful or indicated.

Returning to the case

As this discussion illustrates, the evaluation of hypercalcemia can be challenging. In this particular case the normal PTH levels combined with the normal 24-hour urinary calcium secretion would make FHH a strong possibility. But FHH is much less common than PHPT, and the low Vitamin D levels confuse the picture somewhat. Once Vitamin D is replenished, the clinical picture may shift to one of PHPT with normal levels of PTH and increased urinary calcium excretion. One could not be faulted for awaiting completion of the work-up and stability of the serum calcium to be established prior to consideration. However, it would also be reasonable to offer at a minimal to mildly elevated mortality rating with reconsideration possible upon further clinical diagnosis. ∞

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Underwriting Puzzler...

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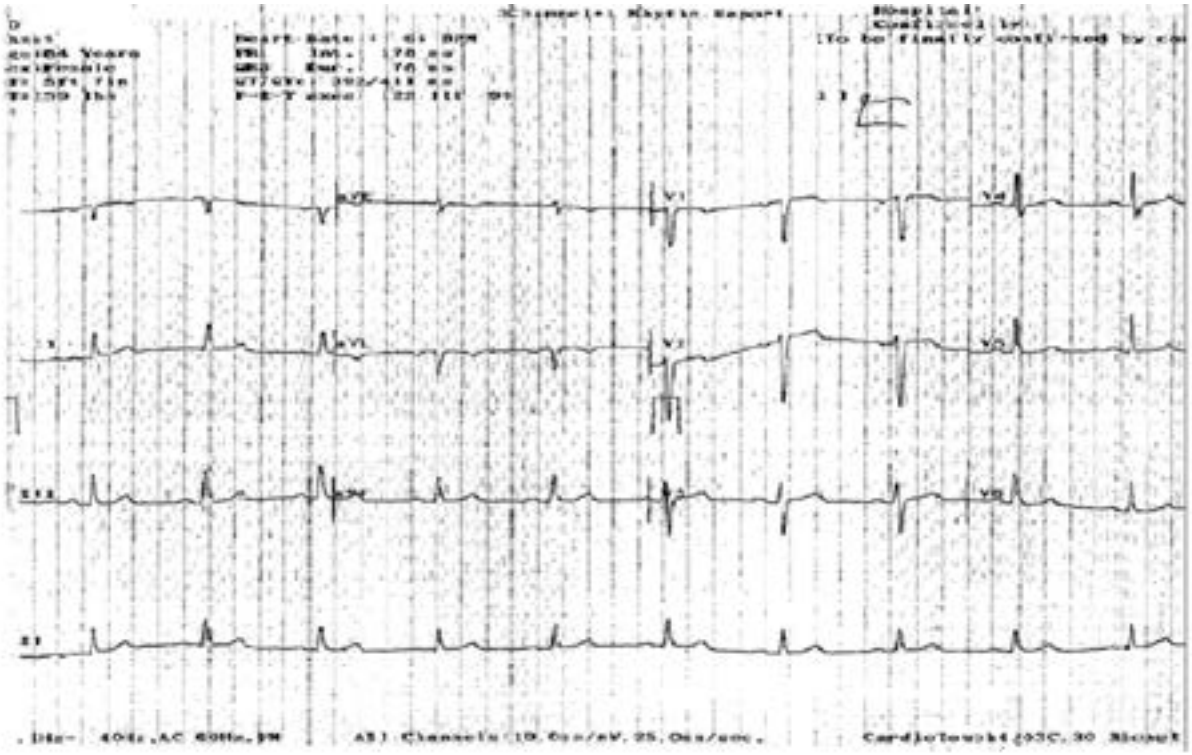
In this issue of the Puzzler Dr. Rooney presents another EKG. What is the major abnormality presented in this EKG? To find the answer, be sure to visit the *Housecalls* page on www.scorgloballifeamericas.com. Click on the "March Puzzler" Powerpoint presentation to confirm your findings. ∞



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