

CLINICAL CASE OF THE MONTH

Gastrointestinal Stromal Tumors: A Case Report and Review of the Literature

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and Fred A. Lopez, MD (Section Editor)

TARGET AUDIENCE

The May/June Clinical Case of the Month is intended for family physicians, general internists, medicine subspecialists including oncologists, general practitioners, gastroenterologists, critical care specialists, emergency medicine physicians, radiologists, and pathologists.

EDUCATIONAL OBJECTIVES

The Clinical Case of the Month is a regular educational feature presented by the Louisiana State University Department of Medicine in New Orleans. Medical students, residents, postdoctoral fellows, and faculty collaborate in the preparation of these discussions. After reading this article, physicians should be able to better identify and understand the pathophysiology, clinical presentation diagnosis and treatment of gastrointestinal stromal tumors. Estimated time to complete this activity is one (1) hour.

CME INFORMATION

CREDIT

The LSMS Educational and Research Foundation designates this educational activity for a maximum of one (1) *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

DISCLOSURE

Drs. Laperouse, Raines, Diamond, Rivera, Newman, and Hew, Jr. have nothing to disclose.

Dr. Lopez discloses that he is a member of the *Journal* Board of Trustees. He is also on the *Journal* Editorial Board.

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CASE REPORT

A 75-year-old man presented with a three day history of dark, "tarry" stools associated with a one week history of increasing fatigue and dyspnea on exertion. He denied any abdominal pain, vomiting, or use of non-steroidal anti-inflammatory agents (NSAIDs), with the exception of a daily dose of 81 mg of aspirin. His past medical history was significant for hyperlipidemia and hypertension. He reported having a normal colonoscopy over 20 years ago. Social history was negative for alcohol, tobacco, or illicit drug use. His family history was unremarkable. On physical exam, the patient was orthostatic and tachycardic. His abdomen was soft and nontender, and auscultation revealed normal bowel sounds. Rectal exam revealed heme-positive, brown stool. The rest of his exam was unremarkable with the exception of pale conjunctiva.

Laboratory evaluation was significant for a hematocrit of 21.7% (38.4-51.7 gm/dL), mean corpuscular volume (MCV) of

86 (80-97 fl), concentration of nitrogen in the form of urea in the blood (BUN) of 17 (10-25 mg/dL), and creatinine of 1.1 (0.7-1.3 mg/dL). Cardiac markers and electrocardiographic (EKG) tracings were normal. Both upper and lower endoscopies were performed.

Colonoscopic examination was normal, but upper endoscopy revealed a 5-cm mass proximally in the body of the stomach. The mucosa overlying the mass lesion was ulcerated and had stigmata of recent bleeding (Figures 1-3).

After endoscopic evaluation was complete, a computed tomographic (CT) scan of the abdomen was performed which visualized the mass lesion in the stomach but did not reveal additional lesions in the abdomen or pelvis (Figure 4).

The patient underwent an uncomplicated partial gastrectomy. The abdominal cavity was free of metastatic lesions by gross inspection. The gross pathologic specimen was 50 x 35 x 35 mm. The margins were clear on resection. The spindle-cell tumor was confined to the wall of the stomach without involving the gastric mucosa or invading the serosa

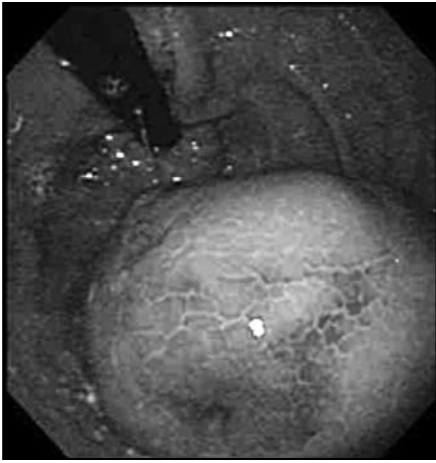


Figure 1. Mass lesion in the proximal stomach observed on retroflexion of the endoscope.

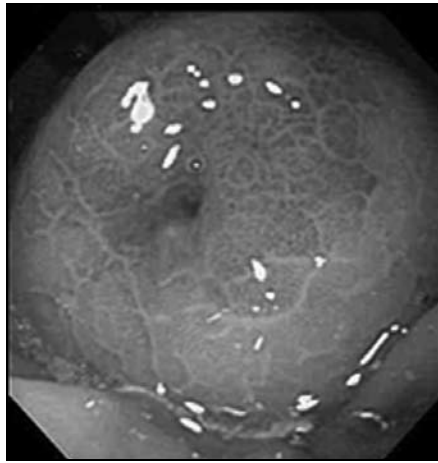


Figure 2. Close-up view of the mass lesion reveals ulceration.

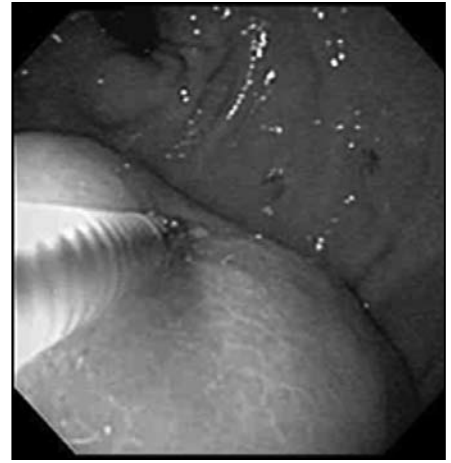


Figure 3. Probing of the mass reveals a soft texture.

(Figure 5). The mitotic activity was found to be less than 5 mitoses per 50 high-powered fields. Antibody tests were positive for CD117, CD34, and desmin (few positive cells). There was no immunologic support for neural differentiation (negative S100) or leiomyoma (negative SMA/smooth muscle actin). The results of the antibody tests were consistent with a spindle-cell type gastrointestinal stromal tumor (GIST). Based on the pathology and size of the tumor, our patient was considered to be at intermediate risk for recurrence and was advised to consider adjuvant chemotherapy with imatinib, a drug which was begun shortly afterwards.

DISCUSSION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract.

These tumors are believed to originate from the intestinal pacemaker cell, ie, the interstitial cell of Cajal. In the past, these tumors may have been classified as leiomyomas, leiomyosarcomas, and leiomyoblastomas, but it has become increasingly clear that GIST is a separate tumor entity. In the past, it was difficult to differentiate GIST from other non-epithelial mesenchymal tumors of the GI tract. The term GIST was first used in 1983 by Mazur and Clark to include gastrointestinal non-epithelial neoplasms that lacked the immunohistochemical features of Schwann cells and did not have the ultra-structural characteristics of smooth muscle.¹ With the advent of immunohistochemical studies and electron microscopy, it appeared that GISTs had both myogenic and neurogenic components.² In 1998, Hirota et al reported the gain of functional mutations in the KIT (c-kit) proto-oncogene which are present in about 95% of GIST.³ This CD 117 antigen

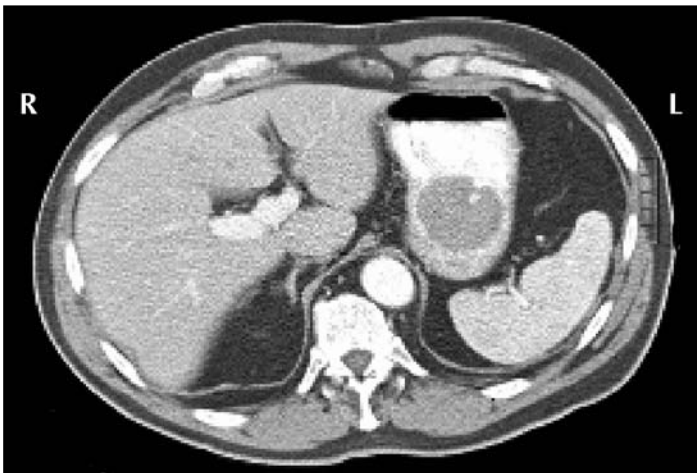


Figure 4. Computed tomographic scan of the abdomen with oral contrast revealing the lesion in the stomach.

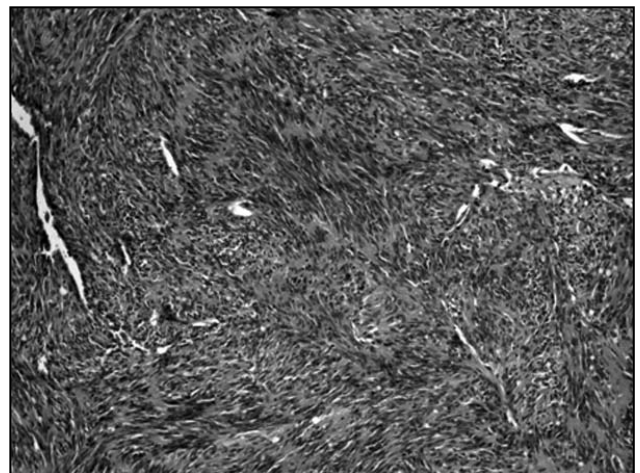


Figure 5. High power microscopic picture of the spindle-cell tumor.

allowed further immunohistochemical characterization and differentiation from other spindle-cell neoplasms of the gastrointestinal tract.⁴

In multi-cellular organisms, a fundamental mechanism for communication among cells is the binding of polypeptide ligands to cell surface receptors possessing tyrosine kinase activity. These receptor-associated tyrosine kinases play a crucial role in cell proliferation, differentiation, migration, and metabolic changes through different signaling pathways.⁵ The intra-cytoplasmic portion of KIT functions as tyrosine kinase. This is significant because GISTs were generally resistant to modern chemotherapy with an extremely poor outcome. Ifosfamide and doxorubicin-based chemotherapies have a response rate of only 0%-27%.⁶ Regimens including paclitaxel have response rates of 5%-7%.⁷ In 2001, imatinib mesylate (Gleevec®), a highly selective inhibitor of tyrosine kinase, was found to be highly active against chemotherapy-resistant GIST. Imatinib was found to be effective in inhibition of certain tyrosine kinases including KIT, PDGFRs, BCR-ABL, ABL, ARG and c-FMS mutations.⁸

The prognosis for patients who have been diagnosed with GIST has changed with the identification of the KIT mutation's association with tumor growth. In embryologic development KIT has been shown to be vital for hematopoiesis, melanogenesis, gametogenesis, and mast cell growth/differentiation. Although most GIST express KIT (95%), a minority will be negative for KIT or express wild-type KIT. Wild-type or KIT-negative tumors have been shown to contain Platelet Derived Growth Factor Receptor- α (PDGFR) mutations which also result in continued tumor growth and cell division.⁷ In 1998, Hirota first described mutations in the KIT proto-oncogenes, and GIST tumors subsequently began gaining widespread interest.⁹ The use of specific tyrosine kinase inhibitors against these tumors has resulted in dramatic improvements in the management of patients with metastatic and unresectable tumors. Imatinib's role in the management of these tumors is still being defined with clinical trials, and several newer agents for imatinib-resistant tumors are being evaluated.

EPIDEMIOLOGY

The epidemiologic information on GIST is still evolving. Because of recent breakthroughs in immunohistologic markers in diagnosing GIST, it is obvious that previous estimates about its annual incidence were low. GIST has been shown to affect men (55%) slightly more than women.⁹ Most patients are diagnosed between the ages of 40 and 80 years with a median age of 60 years, and only 3% of GISTs are diagnosed before the age of 21 years.¹⁰⁻¹² Using the most recent criteria for diagnosing GIST, three studies found the annual incidence of GIST to be 14.5 per million in Sweden, 11 per million in Iceland, and 12.7 per million in the Netherlands. In the United States from 1992-2000, the incidence was estimated at 6.8 cases per million. From these figures and data from the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute

(NCI), it can be estimated that there are roughly 3500 to 4500 new cases of GISTs in the United States per year.¹³

PRESENTING SIGNS AND SYMPTOMS

GISTs that cause symptoms tend to be larger in size, usually 6 cm or greater. The most common symptom at presentation is GI bleeding, which may manifest as melena, hematemesis, or anemia. Sometimes these tumors bleed into the abdominal cavity resulting in an acute abdomen requiring surgery. GISTs that are large can also cause symptoms related to mass effect, including early satiety, bloating, and abdominal pain. There have been reported cases of GIST growing around the duodenum and causing compression of the bile duct resulting in obstructive jaundice.⁸ Approximately 10%-25% of patients present with metastatic disease. Only 70% of patients present with symptoms; the remaining 30% of these tumors are diagnosed incidentally or at autopsy.¹⁴

GISTs most commonly originate in the stomach (40%-60%) or small intestine (30%-40%), but can occur anywhere in the GI tract. It is not uncommon to have numerous intra-abdominal metastasis located on the peritoneal, mesenteric, and liver surfaces. These lesions are thought to arise from seeding by the primary tumor, perhaps explaining why some tumors are found in surgical scars and biopsy tracts. Liver lesions are thought to be from hematogenous spread, but the majority of metastasis from these tumors are thought to be directly related to seeding.^{15,16} Extra-abdominal and lymph node metastasis of GIST are rare.¹⁷ Staging is accomplished through CT and magnetic resonance imaging (MRI) to evaluate the primary tumor and rule out metastases. Lesions typically appear hyperintense and enhance on CT, but sometimes appear to be of soft tissue density with no enhancing characteristics (Figure 4). During treatment, fluorodeoxyglucose positron emission tomographic (FDG-PET) imaging can be used to assess metabolic activity, assisting in determining response to chemotherapy when coupled with a CT scan. Percutaneous biopsies should not be used for potentially resectable tumors due to the low diagnostic yield and the risk for seeding malignant cells. A biopsy is only recommended in cases where the diagnosis will change clinical management, and ideally should be done endoscopically to decrease chances of seeding other surfaces. In some cases, a tumor that is not resectable may be treated with neoadjuvant imatinib in an effort to shrink the tumor and enhance its potential for surgical resectability. The management of each case should be individualized and tailored with a multidisciplinary approach using a patient care team which includes a pathologist, gastroenterologist, surgeon, radiologist, and oncologist.

PATHOLOGY

GISTs usually are between 0.5 and 8 cm with a range of a few millimeters to larger than 30 cm. They are usually circumscribed and have some type of pseudocapsule. Histologically the most commonly characterized GIST is a

spindle-cell type (70%), appearing as uniform fusiform cells in intersecting whorls. There is also an epithelioid type (20%) appearing as rounded cells in a nested pattern. Rarely, GIST tumors can be mixed with features of both.¹⁸

The characteristic immunohistochemical profile of GISTs has been very helpful in diagnosis. GISTs are commonly positive for CD 117 antigen/KIT protein (95%), CD 34 (70%), and smooth muscle actin (30%-40%), while testing negative for the neural cell marker S-100 and the muscle protein desmin. Five percent of tumors are positive for the PDGFR mutation.¹⁹

Risk of recurrence is determined by the size of the tumor and its mitotic count (Table).¹⁹ Tumors that ruptured during surgery are at an extremely high risk for recurrence. Historically, tumors from small bowel, colon, rectum or mesentery have had a poorer prognosis than those originating from the stomach. Data from patients diagnosed from 1992-2000 in the United States showed a 5-year survival rate of 45%. Five-year survival after complete resection was approximately 50%-65%. Complete resection can be accomplished in 40%-

is roughly 50% with complete resection and only 8%-9% with incomplete resection.¹¹ Laparoscopic resection is not recommended unless the tumor is small (< 3 cm), in an ideal location, or characterized as benign or of low-grade malignancy by pathology. These tumors are extremely soft and friable, so extreme caution must be taken to avoid seeding the surgical field. With such a high post-operative rate of recurrence (40%-90%), this is a critical determinant in patient outcome.

With the advent of imatinib therapy, recurrence and survival rates are expected to improve significantly. Currently, imatinib is approved by the FDA for use in unresectable and/or metastatic KIT-positive GIST in the United States and Europe. Preoperative management with imatinib in patients with inoperable or malignant GIST may enable these patients to undergo subsequent curative resection. There have been various case reports with good results in such cases, but patient selection has been highly specialized.²⁰ Another role for imatinib is adjuvant chemotherapy combined with surgical resection for patients at high risk for recurrence based on tumor characteristics (Table). However, this treatment is not benign, and there is a risk of developing secondary resistance through mutations and other mechanisms that are not yet completely elucidated.⁵

Currently, roughly two-thirds of patients with GIST will have metastasis or recurrence. Median time to recurrence after surgery is 19-25 months.⁸ Imatinib is the treatment of choice for metastatic GIST. Treatment should be started immediately when a metastatic lesion is diagnosed and continued until the development of intolerance or tumor progression.²¹ Studies using FDG-PET scans show response by some tumors as quickly as 24 hours after the initiation of imatinib.²² Other tumors can take up to one year to manifest a change in tumor volume.²³ Approximately 65%-70% of patients achieve a partial response, another 15%-20% have stable disease, and only 5% or less achieve a complete response.¹⁷ There are no consensus guidelines for follow-up imaging after resection, but CT imaging at baseline, 1 month, and 3 months after surgery is a commonly pursued protocol. FDG-PET imaging can also be used to evaluate for tumor metabolic activity while monitoring progression or response after treatment. Typically, changes in lesions may be more difficult to characterize by CT alone, and the utilization of multiple imaging modalities can give a more accurate idea of patient response.²⁴ Evaluation for patient response to therapy includes monitoring for a reduction in tumor size or disease stabilization. Treatment response may also be suggested by a reduction in tumor density (Hounsfield Units) on CT scan and/or a decrease in metabolic activity on PET scan.²¹

Follow-up for recurrence is long term because metastases have been reported to occur as late as 30 years after removal of the primary tumor.²⁵ Surgery is usually not recommended with peritoneal involvement because complete resection is accomplished in less than 50% of cases. However, if a patient becomes symptomatic from a necrotic, bleeding, or infected tumor, surgery is recommended for palliation.¹⁵

Table. Risk of recurrence in resectable gastrointestinal stromal tumor.

Risk	Tumor size	Mitotic count/ (HPF)
Very low risk	< 2 cm	< 5/50
Low risk	2 - 5 cm	< 5/50
Intermediate risk	< 5 cm	6 - 10/50
	5 - 10 cm	< 5/50
High risk	> 10 cm	any mitotic rate
	Any size	> 10/50
	> 5 cm	> 5/50

Modified from Fletcher et al.¹⁹

60% of all patients who have GIST and in more than 70% of those with primary or non-metastatic disease. These data also demonstrated a 40%-90% risk in surgical patients of post-operative recurrence or metastasis.¹⁰ For patients with metastatic GIST or recurrent tumor after resection, median survival was 10-20 months before the advent of imatinib.

MANAGEMENT

Once a diagnosis of GIST is made, CT or MR imaging should be performed to rule out metastatic disease. If the disease appears to be localized, management is primarily surgical. Surgical resection should include en-bloc removal with the pseudocapsule intact. There have been no data to support lymph node resection because nodal metastases are rare. Rupture of the tumor, residual tumor after resection, and perforation are significant factors that directly affect the outcome in patients with tumor resection. The 5-year survival

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UTILIZATION OF IMATINIB

KIT and PDGFRA mutation status predict the likelihood of response to imatinib. It has been shown that patients with an exon 11 KIT mutation have a predicted response of up to 85%-90%, while those with an exon 9 mutation have a predicted response of 50%. The majority of patients treated with imatinib should be started on a daily dose of 400 mg.

Imatinib was evaluated in two large trials at daily doses of 400 mg and 800 mg, respectively. The higher dose was associated with a longer time to disease progression but did not improve overall survival and was associated with increased toxicity.²⁶ Side effects of imatinib therapy include edema, muscle cramps, nausea, vomiting, fatigue, and rash. Hematologic effects include anemia, neutropenia, and elevated liver function tests.²⁷ Increasing the dose to 800 mg per day is recommended in patients who do not respond to 400 mg per day. Roughly 5% of patients who progress on 400 mg will achieve a response with dose escalation, and 30% will have stabilization of their disease.²⁸ Preliminary estimates after treatment with imatinib predict that 44%-52% of patients will be progression free at 2 years.^{26,27} The estimated overall survival rates in patients receiving imatinib 400-800 mg per day were 85%-88% at 1 year and 69%-76% at 2 years.¹⁷ Most patients obtain subjective benefit within a few days. The median time to onset of a complete response in these trials was 30 weeks. In patients that responded, the median time to best response was 12-15 weeks but, occasionally, best responses were seen after 2 years of treatment.²⁶ One study (BFR14) evaluated whether imatinib therapy could be discontinued in responding patients after 12 months of treatment. Discontinuation of this drug showed disease progression in 66% of patients compared with 15% of those who continued taking the medication.²⁹ In

patients with advanced disease, it is currently recommended that they be treated indefinitely.

The role of adjuvant imatinib treatment in GIST is unclear but currently being investigated in ongoing clinical trials. Clinical trials involving patients that have undergone radical surgery are being conducted with various inclusion criteria and malignant potential as dictated by the grading system established by Fletcher et al in 2002.¹⁸ ACOSOG-Z9000 involves treatment with imatinib (400 mg/day) for 1 year in patients with high risk GIST (with no control arm). ACOSOG-Z9001 compares imatinib treatment with placebo in patients with tumors > 3 cm (low, intermediate and high risk tumors). EORTC-62624 involves treating patients with intermediate and high risk GIST treated with imatinib (400 mg/day) versus placebo for 2 years. Also, SSG-XVIII is evaluating high risk GIST treated with imatinib (400 mg/day) for 1 or 3 years.¹⁵

In one study of 23 patients with high risk GIST, patients were treated with imatinib 400 mg/day for 12 months after resection with a follow-up of 40 months.⁶ Mean tumor size was 9.4 cm. There were 48 matched historical controls of high risk GIST with radical surgery. Mean tumor size was 12.3 cm. Only 1 out of 23 (4%) patients developed recurrent disease in treatment group in contrast to 32 out of 48 (67%) in the control group. The vast majority of recurrences in patients with high-risk GIST are within 2 years of diagnosis. Notably, in this study, there was no recurrent disease in the treatment group during the first 2 years after diagnosis. The one patient that developed metastasis after treatment was found 22 months after imatinib was discontinued.⁶

It is apparent that a large number of patients with metastatic disease will eventually develop imatinib resistance. Resistance to imatinib is thought to be due to mutations at the ATP/Imatinib binding pocket.^{27,30} There may be many other

mechanisms of resistance but further investigations are needed to determine these. The option for people who have disease progression despite treatment and dose escalation on imatinib includes sunitinib, a multi-targeted tyrosine-kinase inhibitor with activity against KIT, PDGFR, and VEGFR 1 and 2.⁷ Other options include clinical trials investigating other potential tyrosine kinase inhibitors or other targets.

CONCLUSION

The development of imatinib heralds the era of targeted cancer therapy. As we try to understand further imatinib resistant tumors, their molecular markers and mutations, further advances will follow. As clinical trials continue, our understanding of imatinib's role in the management of these tumors will improve. Future and current protocols will help define the most effective approaches to managing patients with these tumors.

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CME QUESTIONS

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Choose the answer that is most correct for each question.

1. True/False:
The risk of recurrence in resectable Gastrointestinal Stromal Tumors (GISTs) is determined by the tumor size and its mitotic count.
2. GIST is most commonly found in which area of the GI tract?
 - a. small intestine
 - b. stomach
 - c. colon
 - d. rectum
3. True/False:
GIST is the most common mesenchymal tumor of the gastrointestinal tract and is believed to originate from the interstitial cell(s) of Cajal.
4. What is the most common GIST-associated symptom at presentation?
 - a. pain
 - b. bleeding
 - c. early satiety
 - d. bloating

West Nile Update by Raoult Ratard, LA State Epidemiologist

A second case of West Nile infection was reported in a blood donor. The person lives in Jefferson Parish and was diagnosed on April 11. He was asymptomatic. No further cases were reported from this area. We have now only two cases of West Nile for this year, both among blood donors. The transmission season for West Nile usually starts mid July to last until early December, depending on the temperature. As we are approaching West Nile season it is important to remind people of the major precautions against West Nile:



1. Make sure your house is mosquito proofed.
2. Wear long pants and shirts, or use mosquito repellent when going out at a time of mosquito activity.
3. Do not breed mosquitoes by keeping standing water around your residence.

*State Epidemiologist Raoult Ratard, MD, MPH,
Louisiana Office of Public Health*