

# Novel Clinical and Pathologic Findings in a Heartland Virus-Associated Death

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## Abstract

**Background:** Heartland virus (HRTV) is an emerging tickborne phlebovirus. Clinical characteristics of infection include leukopenia, thrombocytopenia, and fever. In 2013, the first reported HRTV-associated death occurred in a man aged 80 years with multiple comorbidities. HRTV antigen has previously been detected in bone marrow and postmortem lymph node and splenic tissue. We describe an HRTV-associated death in Tennessee in 2015 with novel clinical and pathology findings.

**Methods:** We performed a chart review. Pathology specimens collected at autopsy were sent to the Centers for Disease Control and Prevention's Infectious Disease Pathology Branch for testing.

**Results:** A man aged 68 years with past medical history of small intracerebral hemorrhage (with no residual deficits), stage T2b melanoma (resected in 2013), remote peptic ulcer disease, and hypertension was hospitalized with altered mental status, nausea, vomiting, and fever. He developed septic shock, acute respiratory distress syndrome requiring mechanical ventilation, disseminated intravascular coagulation, renal failure, and atrial fibrillation. Despite maximum medical therapy, the patient died on hospital day 6; an autopsy was performed. Notable laboratory findings included hyperferritinemia (46,789 ng/mL), leukocytosis ( $31.1 \times 10^3/\mu\text{L}$ ), increased creatine kinase (7,361 IU/L), and increased lactate dehydrogenase (5,093 U/L) (Figure 1). Despite extreme hyperferritinemia, the patient did not meet diagnostic criteria for hemophagocytic lymphohistiocytosis. Notable autopsy pathology findings included detection of HRTV antigen by immunohistochemistry in brain (thalamus, associated with remote infarct), liver, pancreas, heart, lung, large and small bowel, kidney, testes, and skin lesion, in addition to previously described bone marrow, lymph nodes, and spleen (Figure 2A-J).

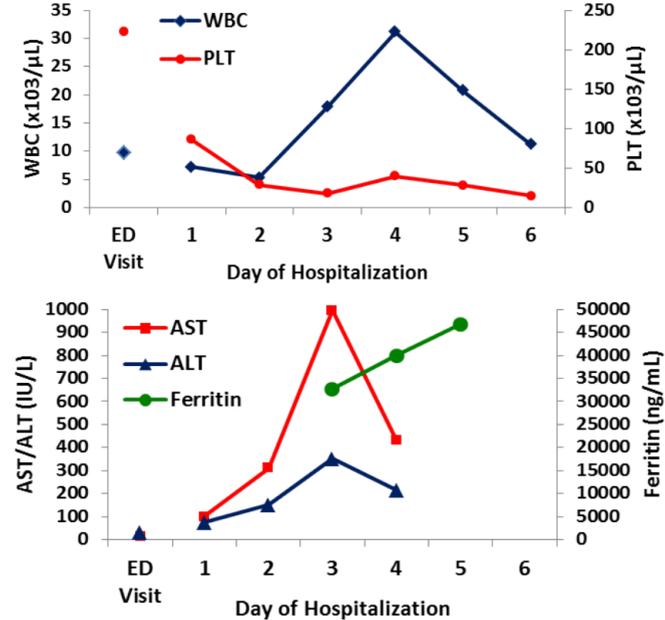
**Conclusion:** HRTV can cause rapidly fatal, widely disseminated infection with severe shock, and multisystem organ failure in a patient without notable preexisting comorbidities. We identified viral antigen in organ tissues where it had been undetected previously. Clinicians should consider this diagnosis, and pursue testing, in cases with compatible clinical and laboratory findings.

## Introduction

- HRTV is an emerging tickborne phlebovirus that was first isolated in Missouri in 2009
- Clinical symptoms: fever, fatigue, headache, anorexia, nausea, diarrhea, myalgia
- Laboratory features: leukopenia, thrombocytopenia, elevated liver enzyme studies
- Since 2009, 8 HRTV cases have been reported in the U.S.
  - All men aged  $\geq 50$  years; 75% required hospitalization
  - 1 death in 80 yoM with multiple comorbidities
  - HRTV has previously been detected in premortem bone marrow, whole blood and serum, and postmortem lymph node (mediastinal and mesenteric) and splenic tissue.
- HRTV has been isolated from *Amblyoma americanum* (Lone Star tick) nymphs, implicating this tick as the vector

## Results: Clinical/Laboratory

Figure 1

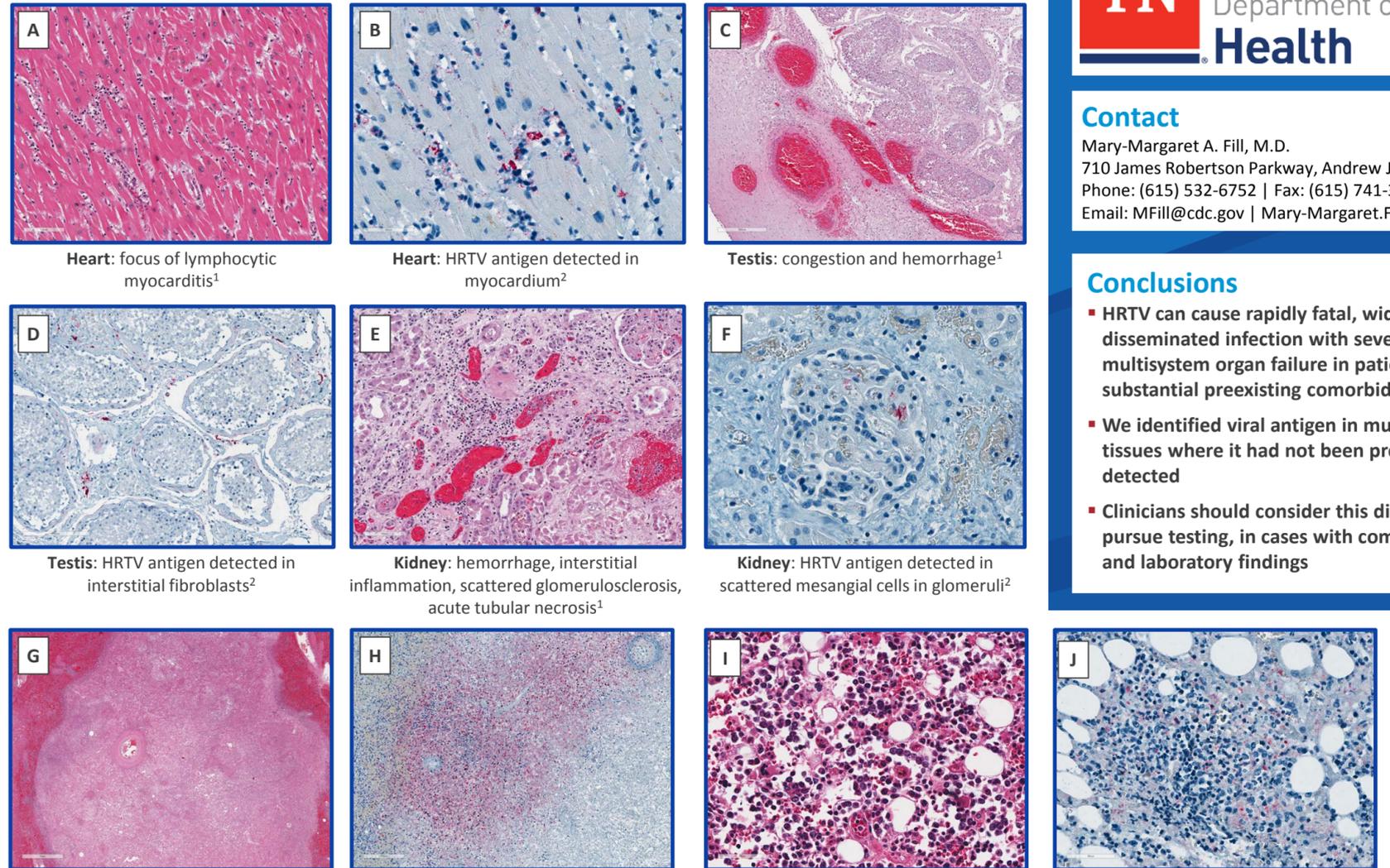


Complete blood count, liver function test and ferritin data.

Abbreviations: WBC, white blood cell count; PLT, platelet count; AST aspartate aminotransferase; ALT, alanine aminotransferase.

## Results: Pathologic

Figure 2



Heart: focus of lymphocytic myocarditis<sup>1</sup>

Heart: HRTV antigen detected in myocardium<sup>2</sup>

Testis: congestion and hemorrhage<sup>1</sup>

Testis: HRTV antigen detected in interstitial fibroblasts<sup>2</sup>

Kidney: hemorrhage, interstitial inflammation, scattered glomerulosclerosis, acute tubular necrosis<sup>1</sup>

Kidney: HRTV antigen detected in scattered mesangial cells in glomeruli<sup>2</sup>

Spleen: Infarction and hemorrhage<sup>1</sup>

Spleen: HRTV antigen detected in areas of infarction and necrosis<sup>2</sup>

Bone marrow: apoptosis and occasional hemophagocytosis<sup>1</sup>

Bone marrow: HRTV antigen detected in mononuclear cells in bone marrow<sup>2</sup>

<sup>1</sup> Routine hematoxylin and eosin stain

<sup>2</sup> Immunoalkaline phosphate staining, naphthol fast red substrate with light hematoxylin counterstain



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## Conclusions

- HRTV can cause rapidly fatal, widely disseminated infection with severe shock, and multisystem organ failure in patients without substantial preexisting comorbidities
- We identified viral antigen in multiple organ tissues where it had not been previously detected
- Clinicians should consider this diagnosis, and pursue testing, in cases with compatible clinical and laboratory findings

