

## Severe Hypertriglyceridemia as a Cause of Aortic Thrombus with Peripheral Embolic Complications

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### INTRODUCTION

Hypertriglyceridemia is known to increase blood viscosity thus creating a hypercoagulable state. However, this predominantly has been associated with venous thrombosis.<sup>1,2</sup> Pro-thrombotic mechanisms mediated by triglycerides include: 1) increased platelet aggregation, decreased antithrombin III activity, interaction with coagulation factors, 2) increase in proinflammatory markers, and 3) endothelial dysfunction. However, while hypertriglyceridemia has been associated with an increased risk of venous thrombosis, its association with arterial thrombosis has not been described previously. We present a case of elevated triglycerides and isolated aortic atherothrombosis causing renal and splenic infarcts.

### CASE REPORT

A 51-year-old white female with history of hypertension and type 2 diabetes presented with nausea, vomiting, and acute left-sided flank pain. A computed tomographic angiogram (CTA) demonstrated the presence of splenic and bilateral renal infarcts. No obvious risks for thrombosis were evident on history except for the use of combination oral contraceptives to control menorrhagia. There was also a family history of hypertriglyceridemia. Her physical exam was unremarkable with body mass index of 33 kg/m<sup>2</sup>. A test for COVID-19 infection was negative. Her basic chemistries and complete blood count were normal. Fasting lipid profile revealed elevated triglycerides at 1,274 mg/dL (replicated on two separate occasions), directly measured low-density lipoprotein cholesterol was 39 mg/dL, lipoprotein(a) was 6 mg/dL, very low-density lipoprotein-cholesterol (VLDL) was 255 mg/dL, and non-high-density lipoprotein-cholesterol level was 214 mg/dL. Her fasting blood glucose and hemoglobin A1c were 170 mg/dL and 7.6%, respectively.

An extensive hypercoagulable and autoimmune work-up was unremarkable (Table 1). A CTA of the chest, abdomen, and pelvis revealed a focal protruding noncalcified atherothrombotic lesion in the mid to distal segment of the descending thoracic aorta (Figure 1A). No significant atherosclerotic lesions were visualized in the other segments of the aorta or vascular beds. No vascular calcification was seen. The lesion in the distal thoracic aorta was determined as a culprit for the visceral infarctions via embolic mechanisms. Treatment with low dose aspirin and therapeutic dose of low-molecular weight heparin was initiated followed by apixaban and aspirin on discharge. Over the course of the hospital stay, her abdominal pain gradually resolved. She was started on atorvastatin 40 mg, fenofibrate 145 mg, icosapent ethyl 4 g,

resulting in a 70% reduction in the triglyceride levels on the follow-up testing (Table 2).

In three months, a repeat CTA showed almost complete resolution of the aortic lesion with a mild residual plaque on the adjacent aortic wall (Figure 1B). Further supporting that the etiology of the lesion was a bulky thrombus developing on a mild plaque. At the six month follow-up visit, she was switched to dual antiplatelet therapy and remained asymptomatic.

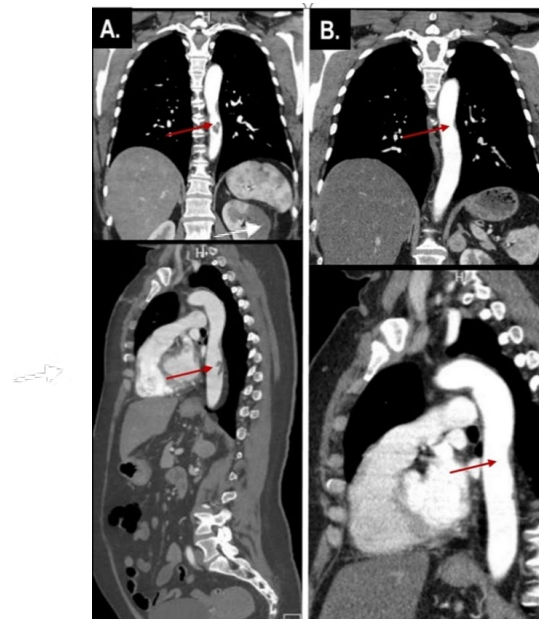


Figure 1. A) Admission CTA images show 8.3 x 2.7 cm left renal hypoattenuation consistent with infarction (white arrow). Normal caliber thoracic aorta with mural thickening in the mid thoracic aorta with associated mild atherosclerotic plaque and 10x6 mm posterior eccentric thrombus within caudal thoracic aorta (red arrow). Tiny right lower pole renal infarct. B) At three month follow-up: A significant improvement in irregular eccentric thrombus in the posterior descending thoracic aorta with nearly resolved endophytic portion extending into the aortic lumen.

### DISCUSSION

Insights from biology, epidemiology, and genetics strongly suggested that elevated triglyceride-rich lipoproteins (TRL) represent causal risk factors for atherosclerosis, inflammation, and all-cause mortality.<sup>3-7</sup> However, there were limited clinical data on association of hypertriglyceridemia with arterial thrombosis. We reported a clinical case of a woman who developed embolic complications from an aortic wall atherothrombotic lesion in the setting of familial hypertriglyceridemia. Contributing risk factors included type 2 diabetes, hypertension, and contraceptive use. Almost complete resolution of the thrombus was observed with conservative management including an antiplatelet agent, anticoagulant, and aggressive triglyceride-lowering regimen. Oral contraceptive use has been linked to an increased risk of stroke, myocardial infarction, and deep venous thrombosis.<sup>8-10</sup> However, arterial thrombosis was less likely to occur with the use of oral contraceptive pills in the absence of cardiovascular risk factors. This clinical observation highlighted importance of optimization of lipid control in patients taking contraceptives.

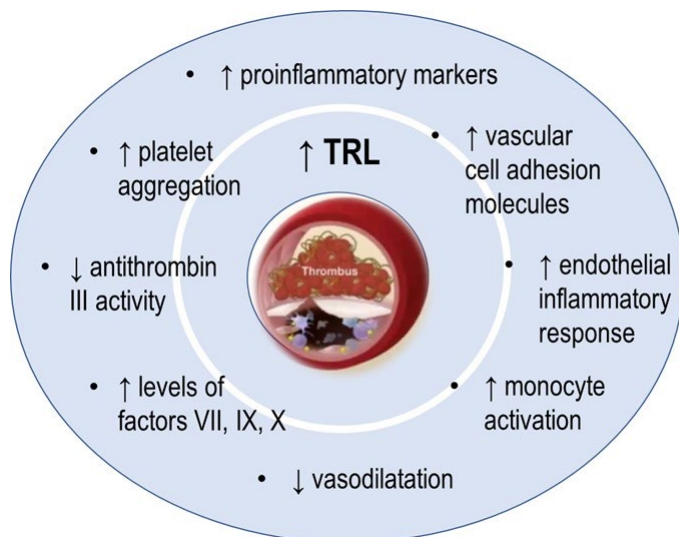
**Table 1. Results of the autoimmune, coagulation, and systemic work-up prior to initiation of anticoagulation.**

Autoimmune Work-Up		Coagulation Work-Up		Systemic/Infectious Work-Up	
ANA	< 80 titer/ Negative	<b>Prothrombin F2 G20210A PCR</b>	Negative	<b>Tuberculosis testing</b>	Negative
Myeloperoxidase antibodies	< 0.2/ Negative	<b>INR</b>	1.1	<b>Hepatitis panel</b>	Negative
Serine Protease3 antibodies	< 0.2/ Negative	<b>aPTT</b>	29	<b>Syphilis antibodies (rapid plasma reagin)</b>	Negative
Immunoglobulin G with normal subclasses	915 mg/dL	<b>F5 Leiden Screen (activated protein C resistance)</b>	3.2 (> 2.5)/Negative	<b>1,25-dihydroxyvitamin D</b>	78 pg/mL
Beta-2 glycoprotein 1 antibodies for IgG	< 1.4 U/mL/ Negative	<b>Homocysteine</b>	7.9 Umol/L (5-15)	<b>Serum electrophoresis</b>	No paraprotein
Beta-2 glycoprotein 1 antibodies for IgM	0.8 U/mL/ Negative	<b>Protein S</b>	108% (55-124%)	<b>Angiotensin Converting Enzyme</b>	6 U/L (16-85)
Cardiolipin antibodies for IgM	0.8 gpl/mL/ Negative	<b>Protein C activity</b>	150% (70-130)		
Cardiolipin antibodies for IgG	< 1.6 gpl/mL/ Negative	<b>Serum cryoglobulin</b>	Trace cryoprecipitate		
Hexagonal phase phospholipid test (confirmatory test for lupus anticoagulant)	0 sec/Negative	<b>Dilute Russell's viper venom time (dRVVT)</b>	1.4		

**Table 2. Fasting lipid profile on admission and following three months of lipid-modifying therapy (all in mg/dL).**

	Admission	Three Month Follow-Up
<b>Total cholesterol</b>	253	227
<b>Triglycerides</b>	1,274	306
<b>LDL-C</b>	39	55
<b>VLDL-C</b>	255	-
<b>HDL-C</b>	90	111
<b>Non-HDL-C</b>	214	-
<b>Lp(a)</b>	6	-

LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); VLDL = very low-density lipoprotein; HDL-C = high-density lipoprotein cholesterol



**Figure 2. Summary of reported pro-thrombotic mechanisms mediated by triglyceride-rich lipoproteins and remnants.**

As a hypothesis-generating finding, we speculated that the driving force in the formation of the arterial thrombosis was aggregation of TRL in the subintimal space leading to accumulation of lipid-laden macrophages, inflammation, platelet aggregation and activation of the coagulation cascade in the setting of high shear stress (Figure 2). TRL comprise chylomicrons and VLDL and serve as transporters of triglycerides and cholesterol in circulation. Alteration of the rheological properties, including redistribution of the wall shear stress, endothelial lining damage, disorganization of the fibroelastic microstructure, platelet activation, intima-media remodeling, are implicated in thrombogenesis.

TRL enter the arterial intima at a slower speed than the LDL particles due to a larger particle size; however, once trapped, reentry into arterial lumen against blood pressure gradient is more difficult.<sup>11,12</sup> TRL can be taken up by peripheral macrophages via the VLDL and apolipoprotein B48 receptors without modification or downregulation by intracellular lipoproteins, along with lipoprotein lipase.<sup>13-17</sup> TRL have shown to cause low grade inflammation at a whole-body level, including arterial intimal inflammation.<sup>18,19</sup> TRL retain in the subendothelial space and contribute to the atherosclerotic lesion initiation and progression. Through apolipoprotein E-mediated uptake of TRL,<sup>20</sup> activation of metalloprotease expression prompted by atherogenic macrophage modification was shown to result in a vulnerable, thin fibrous cap atheroma phenotype.

Meta-analyses including 57,277 individuals demonstrated that an 89 mg/dL elevation in triglycerides was associated with a 14% to 37% higher incidence of cardiovascular disease independent of other risk factors in men and women, respectively.<sup>21,22</sup> Although multivariable Mendelian randomization analyses have suggested a deleterious causal effect of increased triglycerides on coronary heart disease risk,<sup>23,24</sup> there was heterogeneity amongst different TRL. In 29,039 individuals with no history of myocardial infarction from the Copenhagen General Population Study, during a mean follow-up of 10 years, the hazard ratio for myocardial infarction was 3.5-fold for VLDL and 1.3-fold for intermediate-density lipoproteins and LDL combined for the same number of apoB-containing particles measured using nuclear magnetic resonance spectroscopy.<sup>25</sup>

Prothrombotic properties of TRL are thought to be driven by direct and indirect mechanisms. A redox-sensitive mechanism has been implicated in upregulation of endothelial expression intercellular adhesion molecule-1, vascular cell adhesion molecule-1, tissue factor in cultured human endothelial cells by TRL remnants.<sup>26</sup> Platelet activation was shown to be increased in patients with hypertriglyceridemia.<sup>27</sup> Low antithrombin III activity and increased platelet aggregation have been observed in individuals with triglyceride levels above 200 mg/dL.<sup>28</sup> Heparin has been shown to activate lipoprotein and hepatic lipases; therefore, heparin-containing therapies might be considered as a preferred initial strategy in individuals with hypertriglyceridemia.

In animal models, intravenous infusion of long chain saturated

fatty acids caused thrombosis and resulted in significant reduction of cardiac output.<sup>29</sup> Properties of triglyceride-containing particles affect the activity of vitamin K dependent coagulation factors. For instance, coagulation factors VII and X are transported by TRL and show a strong fixation to chylomicrons and VLDL fractions.<sup>30</sup> Increased levels of factor VII were observed in individuals with elevated triglyceride levels.<sup>31</sup>

## CONCLUSIONS

The atherothrombotic potential of TRL composition is an area of active investigation. This case suggested that elevated triglycerides can be considered as a risk factor for arterial thrombosis, supporting further research of the role of targeted triglyceride-lowering therapies on atherothrombotic outcomes. Further studies on impact of genetic architecture of hypertriglyceridemia on clinical outcomes in cohorts with diverse ethnic/racial backgrounds are warranted.

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