Thrombotic Storm

HIT, TTP, APS and Other Hypercoagulable States

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Disclosures

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- Consultant positions: None

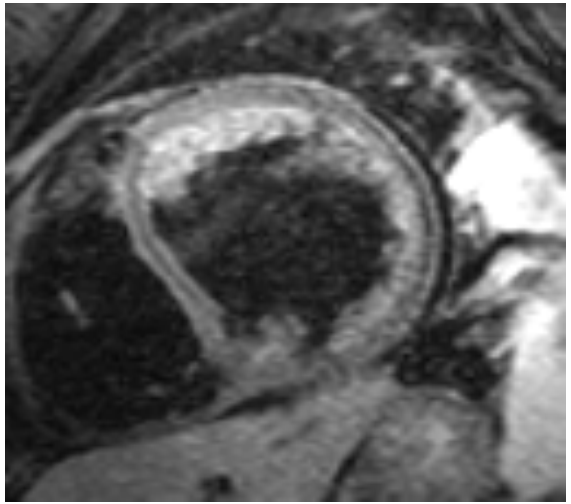
- Off-label medication use: alternative antithrombotic strategies in severe thrombotic disorders

Patient Presentation

- 32 year old female with no past medical history, presents to the ED with dyspnea, fatigue, AMS
- Relevant history includes use of oral contraceptives, and recent transcontinental flight with several connections
- CTA revealed filling defects in the right main pulmonary artery and several segmental pulmonary arteries
- US reveals extensive LLE DVT

Patient Presentation

- Anticoagulation is initiated, but she develops labile blood pressure and decreased cardiac output
- TTE reveals extensive thrombus in both ventricles
- Because of decreasing alertness, a CT scan is obtained, which reveals an evolving left MCA CVA



REVIEW

Thrombotic Storm: When Thrombosis Begets Thrombosis

Craig S. Kitchens, MD

Patients with hypercoagulability may present with a single thrombosis and subsequently develop progressive thromboses at other sites. With inadequate therapy, the thrombotic process may self-perpetuate, leading to multiple thromboses and even death. Six cases are presented demonstrating key features of what may be termed thrombotic storm: (1) an underlying hypercoagulable disorder; (2) a provocation to initiate thrombosis; (3) rapid development of new thromboses; (4) response to prompt use of thrombolytic agent or anticoagulant therapy; and (5) remarkable good long-term prognosis if the cycle of thrombosis is interrupted. Continued activation of coagulation by fresh thrombosis is hypothesized as the cause of the syndrome, which may explain its control by anticoagulants. Whereas these unusual patients' courses most likely represent only an extreme of hypercoagulability and not a new disorder, their characteristic behavior warrants attention. **Am J Med. 1998;104:381–385.**

Disorders presenting as Thrombotic Storm

- Catastrophic APS
- Cancer/Trousseau's syndrome
- Heparin-induced thrombocytopenia/thrombosis
  - "Spontaneous HIT"
  - "Delayed HIT"
- Atypical presentations of thrombotic microangiopathies (*i.e.*, macrovascular TE)
- Hypercoagulable state, with or without a specific 'trigger'

Catastrophic APS

- Affects ~1% of patients with APS, characterized by the following criteria:
  1) Evidence of vascular occlusions affecting ≥3 organs, systems and/or tissues;
  2) Development of manifestations simultaneously, or in less than a week;
  3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue; and
  4) Confirmation of antiphospholipid antibodies on two separate occasions.

Asherson RA, *et al*. Lupus 2003;12:530

Brief Report

THROMBOSIS AND HEMOSTASIS

Spontaneous heparin-induced thrombocytopenia syndrome: 2 new cases and a proposal for defining this disorder

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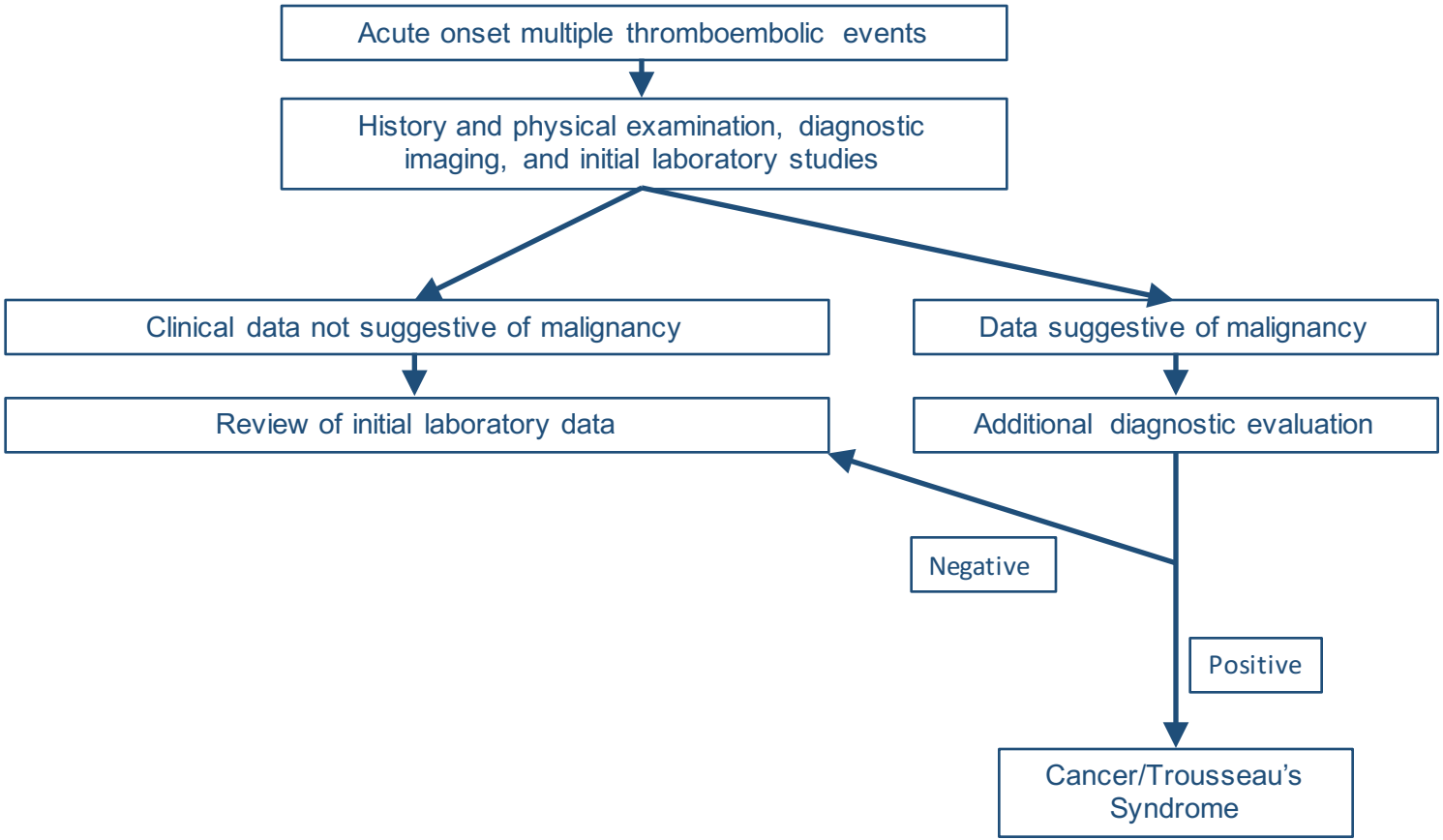
Key Points

- Two well-documented cases of a HIT-mimicking disorder without proximate heparin exposure (spontaneous HIT syndrome) are reported.
- The definition of spontaneous HIT syndrome should include strong serum-induced platelet activation at 0 IU/mL heparin (inhibited at 100 IU/mL).

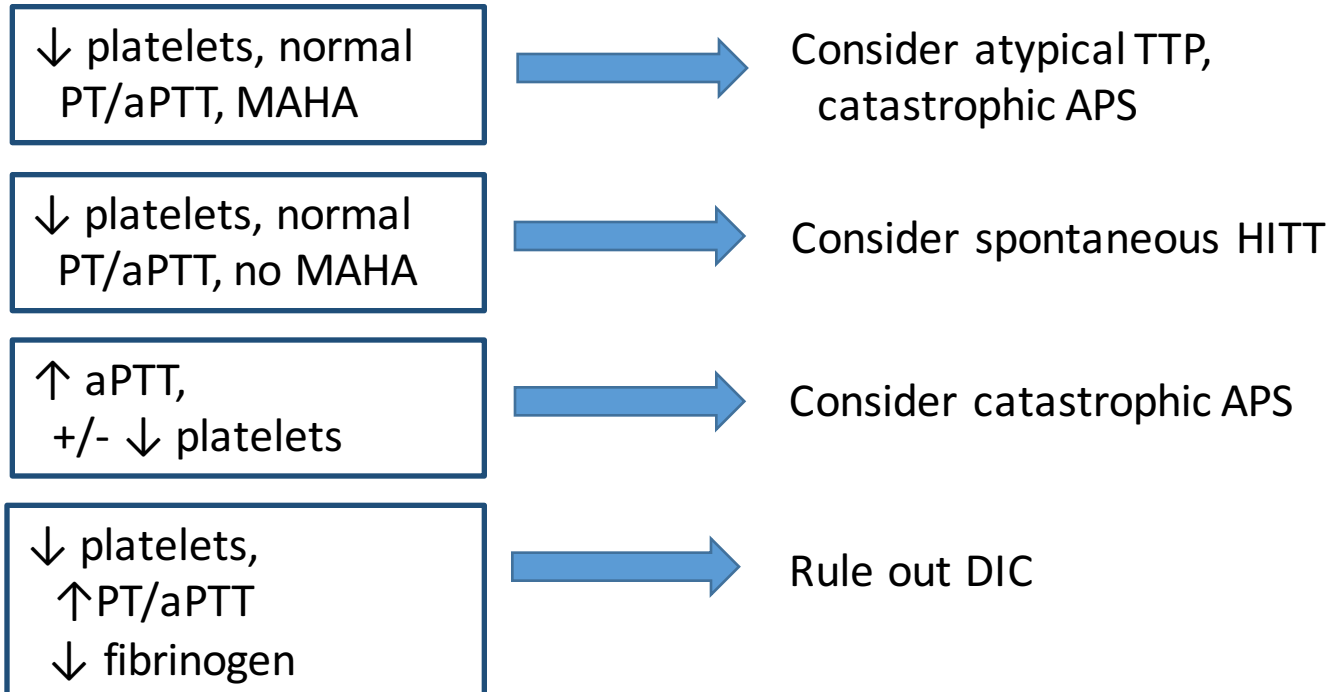
The existence of spontaneous heparin-induced thrombocytopenia (HIT) syndrome (or autoimmune HIT), defined as a transient prothrombotic thrombocytopenic disorder without proximate heparin exposure serologically indistinguishable from HIT, is controversial. We describe 2 new cases presenting with thrombotic stroke/thrombocytopenia: one following shoulder hemi-arthroplasty (performed without heparin) and the other presenting to the emergency room without prior hospitalization, heparin exposure, or preceding infection. Both patients tested strongly positive for anti-platelet factor 4 (PF4)/heparin immunoglobulin (Ig)G in 2 different immunoassays and in the platelet serotonin-release assay. Crucially, both patients' sera also caused strong (>80%) serotonin release in the absence of heparin, a serologic feature characteristic of delayed-onset HIT (ie, where heparin use precedes HIT but is not required for subsequent development or worsening of thrombocytopenia). We propose that a rigorous definition of spontaneous HIT syndrome should include otherwise unexplained thrombocytopenia/thrombosis without proximate heparin exposure and with anti-PF4/heparin IgG antibodies that cause strong in vitro platelet activation even in the absence of heparin. (*Blood*. 2014;123(23):3651-3654)

Diagnostic Strategy



Diagnostic Strategy

- Initial studies: CBC, blood film, PT, aPTT, fibrinogen



Therapeutic Interventions

- Management driven by initial findings

Catastrophic APS	→	Anticoagulation, apheresis, steroids
Atypical TTP	→	Apheresis, steroids/rituximab
Spontaneous HITT	→	Anticoagulation with a DTI or fondaparinux
“Idiopathic” TS	→	Anticoagulation, may consider apheresis, lytics

Additional diagnostic evaluation

- The following laboratory tests should be sent early in the patient's course (preferably before apheresis, anticoagulation):
  - Antiphospholipid antibody testing (lupus anticoagulant, anticardiolipin and anti-β2GPI antibodies)
  - ADAMTS13 activity
  - Anti-platelet factor 4/heparin immunoassay (if thrombocytopenic)
- However, therapeutic decisions cannot wait on the results from these studies

Back to our patient

- Plasma exchange initiated for possible catastrophic APS
- Developed new thrombocytopenia within first 24 hours and an elevated anti-PF4/heparin antibody level was detected
- Heparin discontinued and started on bivalirudin

- No further thrombotic events

Follow-up

- All testing for antiphospholipid antibodies (anticardiolipin, anti-β_2-glycoprotein I, and lupus anticoagulant) proved negative on multiple occasions (during and after event)
- All other hypercoagulable testing negative

- After surviving the acute episode, she is currently doing well on chronic anticoagulant therapy without recurrence

Thrombotic Storm Study Group

- 2009 Study Group Meeting, Miami, FL

Thrombotic Storm Study

- Affected probands and available family members are recruited to participate in a study investigating genetic mechanisms underlying thrombotic storm.
- Current enrollment includes:
  - One multiplex family with 2 affecteds and one possible
  - Sixteen “trios” (affected proband and both parents)
  - 26 additional unrelated patients with parents and/or siblings where available
- Samples collected include: genomic DNA; whole blood RNA in PAXgene tubes; samples for iPSC’s; plasma & serum

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  - University of Colorado; Dr. Manco-Johnson
  - Hospital for Sick Children; Dr. Brandao
  - Michigan State University; Dr. Kulkarni

- Information on TS study
  - www.thromboticstorm.com
  - Email: thomas.ortel@duke.edu; HIHGTS@med.miami.edu

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