Catastrophic Thrombosis

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Disclosures

- Research support: NIH, PCORI, Stago, Siemens, Instrumentation Laboratory
- Consultant positions: None

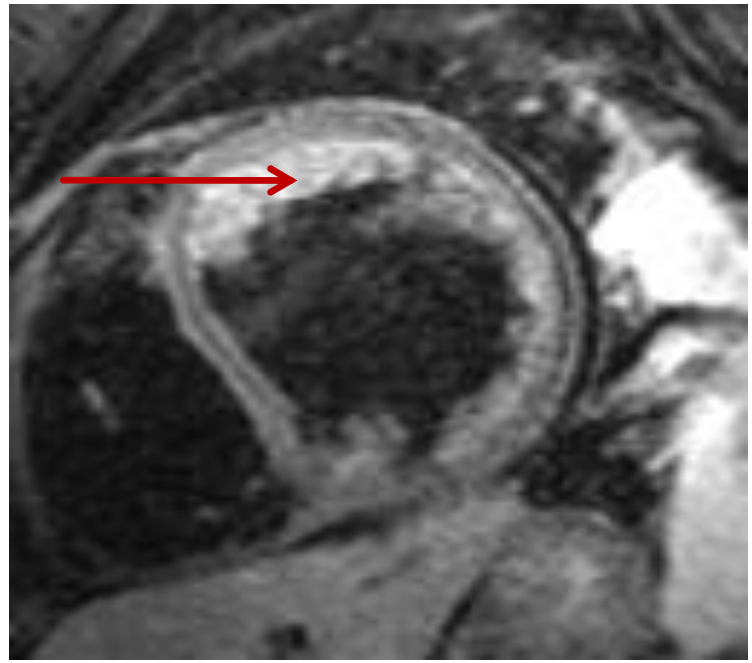
- Off-label medication use: non-heparin anticoagulants, plasma exchange, immunomodulatory therapies…

Patient 1 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

Patient 1 Presentation

- She is started on anticoagulant therapy, but develops labile blood pressure, decreased cardiac output
- TTE: biventricular thrombi
- Cardiac MRI confirms extensive intracardiac thrombi involving both ventricles



Patient 1 presentation

- She developed decreased alertness, and an evolving left MCA stroke was found by CT scan
- New leg swelling → RLE DVT identified by US
- Heparin continued and plasma exchange initiated for possible CAPS (clinical diagnosis only)
- Developed new thrombocytopenia → anti-heparin/PF4 antibodies were positive
- Heparin discontinued and started on bivalirudin

Laboratory Analyses & Follow-up

- No further thrombotic events

- 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

- Survived acute episode, currently doing well on chronic anticoagulant therapy without recurrence

Patient 1

- What was our final assessment?

1) Multiple thrombotic occlusions following an initial provocative event
2) Course complicated by heparin-induced thrombocytopenia (HIT)

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.**

REVIEW

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Thrombotic S… Criteria Sugg…

…gnostic …Study Group

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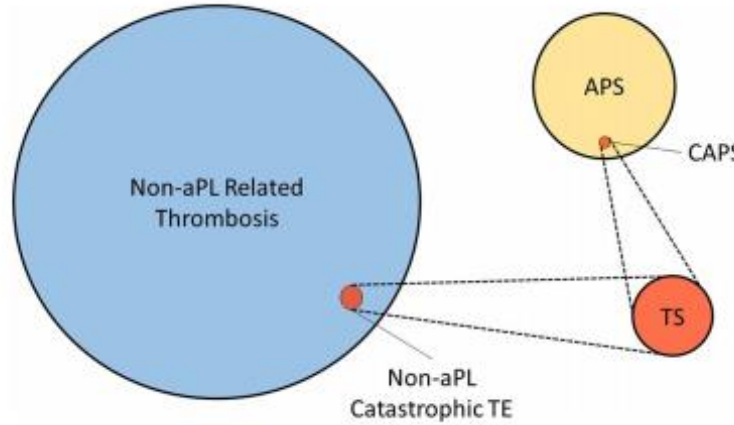
Table 2 Clinical Characteristics of Our Patients with Thrombotic Storm

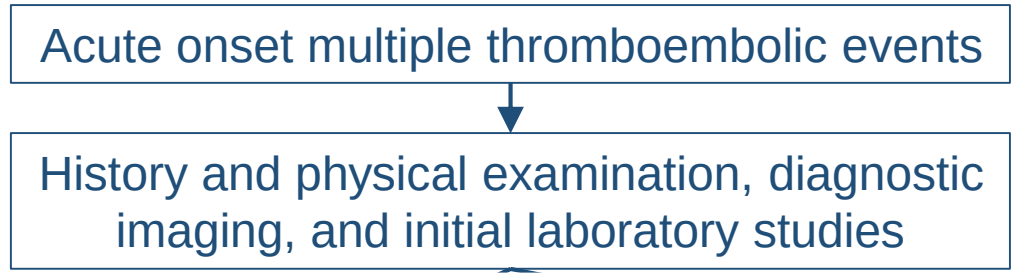
Typically encountered characteristics
Younger age *plus* 2 or more of the following criteria:
Acute, 2 or more arterial or venous thromboemboli, with or without thrombotic microangiopathy,* typically in a compressed period of time (1-2 weeks) yet may recur from time to time over years.
Unusual location†
Progressive/recent unexplained recurrence
Refractory to acute therapy or atypical response to therapy
Exacerbated by inadequate or interrupted treatment (eg, subtherapeutic anticoagulation)
Frequently preceded by an initiating event ("trigger")‡
Characteristics usually not encountered
Cancer (excluding minor skin cancers)
Myocardial infarction in the setting of advanced coronary artery disease
Cocaine use associated with symptom onset
Expected thrombotic complications associated with intravascular devices
Known paroxysmal nocturnal hemoglobinuria or myeloproliferative disorder
Multi-trauma/severe trauma (eg, multiple limb injury)
Premorbid clinical status before development of thrombotic complications

Catastrophic Thrombotic Syndromes

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



Diagnostic Strategy



Patient 2 Presentation

- 61 yr old woman presents with bilateral, painless, bluish discoloration of multiple toes
- She was on no anticoagulants and had no history of thromboembolic complications

Patient 2 Presentation

- New T-wave inversions noted on EKG with elevated cardiac enzymes
- No arterial occlusions on US of the legs, but she did have bilateral peroneal vein occlusions
- CTA of the chest revealed bilateral pulmonary emboli…
- and multiple, hypodense liver lesions with a pancreatic mass

Majumder S, et al. J Pancreas, 2012; 13: 231-4

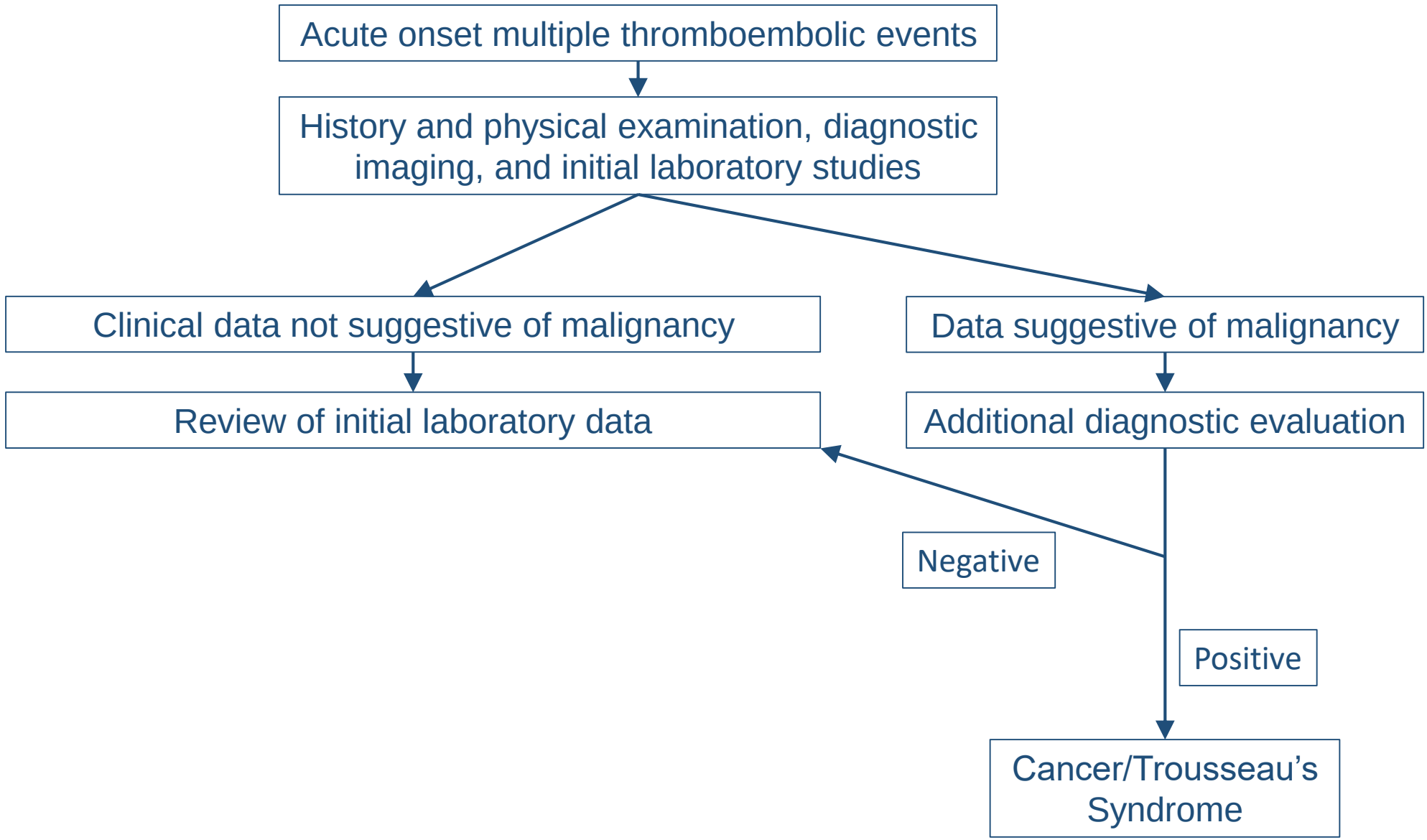
Cancer with atypical thrombotic complications

- Overall risk for VTE in patients with cancer is ~7-fold greater (OR, 6.7; 95% CI, 5.2-8.6) compared to patients without cancer…

- Trousseau's syndrome, however, is more aggressive and may present with migratory superficial thrombophlebitis, arterial emboli in various organs, and hemorrhagic complications

Blom JW, et al. JAMA, 2005; 293: 715-22
Sack GH, et al. Medicine, 1977; 56: 1-37

Diagnostic Strategy



Screening laboratory tests

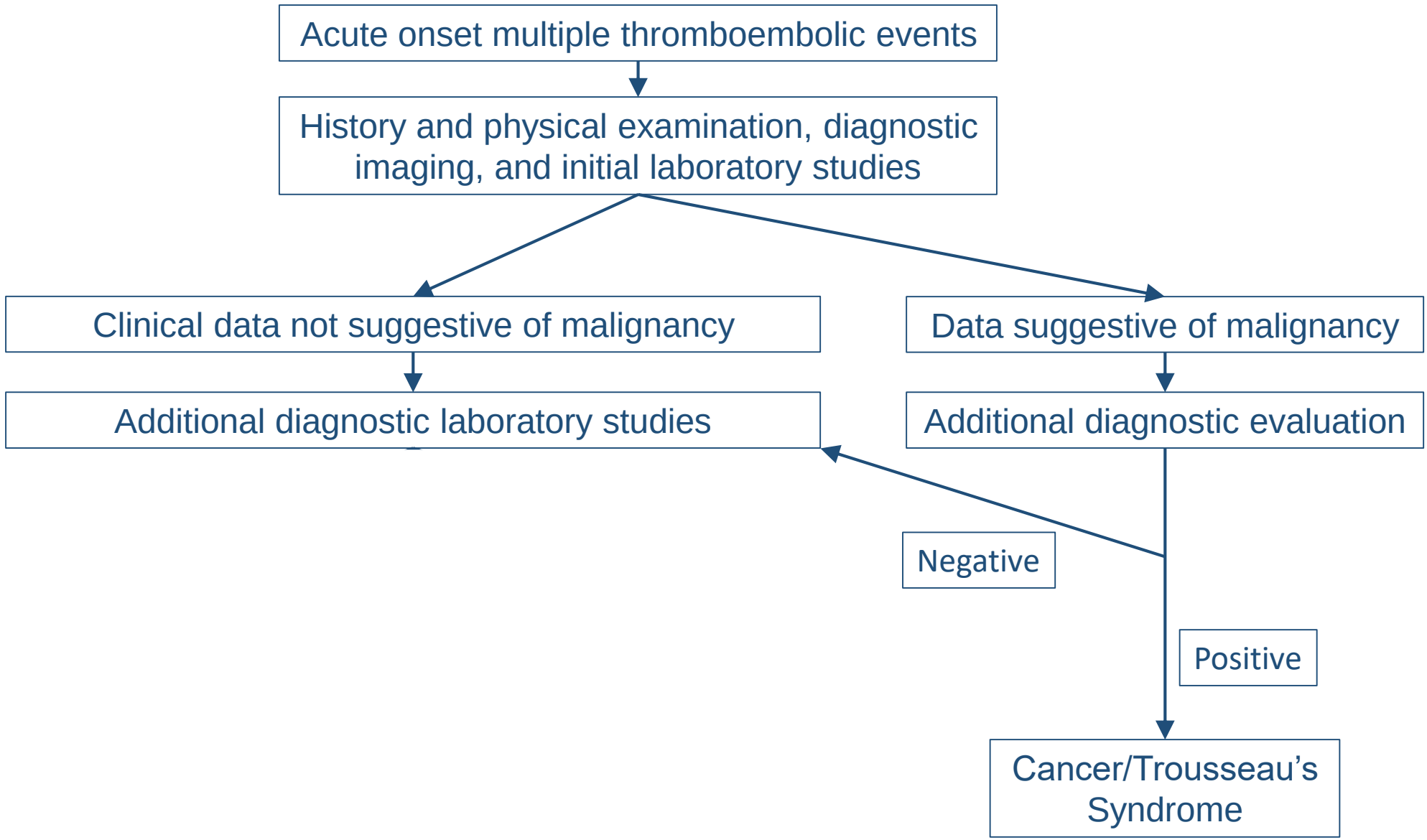
- Initial studies: CBC, blood film, PT, aPTT, fibrinogen

↓ platelets, normal PT/aPTT, MAHA	→	Consider atypical TTP, catastrophic APS
↓ platelets, normal PT/aPTT, no MAHA	→	Consider spontaneous HITT
↑ aPTT, +/- ↓ platelets	→	Consider catastrophic APS
↓ platelets, ↑PT/aPTT ↓ fibrinogen	→	Rule out DIC

Additional laboratory studies

- Additional laboratory studies that should be sent early in the patient's course (before starting anticoagulation, plasma exchange):
  - 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

Diagnostic Strategy



Catastrophic APS

- Affects ~1% of all patients with APS
- Approximately half of the patients with catastrophic APS do not have a prior diagnosis of APS
- Presents with rapidly progressive thromboses resulting in multiple organ dysfunction syndrome, systemic inflammatory response syndrome, and thrombotic microangiopathy
- Frequently fatal if not rapidly treated

Catastrophic APS: Diagnostic 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) Laboratory confirmation of antiphospholipid antibodies.

Definite catastrophic APS: All 4 criteria

Asherson RA, et al. Lupus 2003;12:530-4

Catastrophic APS and malignancy

- Catastrophic APS Registry
  - 23 of 262 patients with CAPS had cancer (9%)
  - Most common malignancies were lung (4), colon (2), and hematologic (6)
- Treatment → anticoagulation, steroids, plasma exchange, chemotherapy

Miesbach W, et al. Autoimmunity Rev, 2006; 6: 94-7;
Ideguchi H, et al. Lupus, 2007; 16: 59-64

Patient 3 Presentation

- 54 yr old woman presents with R leg swelling, L arm weakness/paresthesias, and a new thrombocytopenia, two weeks after a shoulder hemiarthroplasty (no heparin exposure)
- Brain MRI revealed an acute ischemic stroke, and US revealed a proximal DVT in the right leg
- Echocardiogram negative for PFO or ASD
- Started on IV heparin → platelet count dropped from 69,000 to 34,000/mcL

Patient 3 Presentation

- No schistocytes on blood film
- Heparin is discontinued and she is switched to argatroban
- Anti-PF4/heparin antibody testing is positive, confirmed by serotonin-release assay
- Platelet count gradually normalizes, with no further thrombotic events

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)

Autoimmune HIT syndromes

- Defined by the presence of anti-platelet factor 4/heparin antibodies that activate platelets in the absence of added heparin, but are blocked by the addition of excess heparin

Table 1 Autoimmune heparin-induced thrombocytopenia (aHIT) syndromes

Clinical entity	Description
Delayed-onset HIT	HIT that begins or worsens after stopping of heparin
Persisting HIT	HIT that persists for > 1 week despite stopping of heparin
Spontaneous HIT syndrome	HIT without proximate heparin exposure
Flush heparin HIT	HIT induced by exposure to heparin flushes
Fondaparinux-associated HIT	HIT that is believed to be triggered by exposure to fondaparinux
Severe HIT (e.g. platelet count of $< 20 \times 10^9$ L^{-1}) with overt DIC	Overt HIT-associated DIC defined as proven HIT with one or more of the following: relative/absolute hypofibrinogenemia, elevated INR (without another explanation), and normoblastemia (circulating nucleated red blood cells)

DIC, disseminated intravascular coagulation; INR, International Normalized Ratio.

Greinacher A, et al. J Thromb Haemost, 2017; 15: 2099-14

“Atypical” Presentations of TTP

- Clinical presentation with acute stroke and/or acute coronary syndromes
- Venous thromboembolism is uncommon
- Clinical manifestations may precede hematologic findings by days to weeks, or longer
- These patients may, or may not, have a prior diagnosis of TTP
- ADAMTS13 level is typically decreased

Sarode R. J Clin Apheresis, 2009; 24: 47-52

“Idiopathic” thrombotic storm

- 14 year old boy, sustains knee injury playing football, develops HA, N/V, and seizures 2 days later
- MRI demonstrates thrombosis of the sagittal, right transverse, and sigmoid venous sinuses
- Florid DIC interferes with attempts to initiate anticoagulant therapy
- Progressive deterioration on anticoagulation including development of bilateral PE, pelvic vein thromboses, and, ultimately, death
- All hypercoagulable testing negative

Therapeutic Approach

- Multiple thrombotic events, involving multiple vascular beds (arterial, venous, microvascular)
  - Differential diagnosis includes rare disorders that can be rapidly fatal if incorrectly treated
  - Diagnostic laboratory testing is essential but is frequently complex and may take days to turn around

→ How do I approach treatment in this clinical setting?

How I treat catastrophic thrombotic syndromes

Thomas L. Ortel,[1] Doruk Erkan,[2] and Craig S. Kitchens[3]

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Catastrophic thrombotic syndromes are characterized by rapid onset of multiple thromboembolic occlusions affecting diverse vascular beds. Patients may have multiple events on presentation, or develop them rapidly over days to weeks. Several disorders can present with this extreme clinical phenotype, including catastrophic antiphospholipid syndrome (APS), atypical presentations of thrombotic thrombocytopenic purpura (TTP) or heparin-induced thrombocytopenia (HIT), and Trousseau syndrome, but some patients present with multiple thrombotic events in the absence of associated prothrombotic disorders. Diagnostic workup must rapidly determine which, if any, of these syndromes are present because therapeutic management is driven by the underlying disorder. With the exception of atypical presentations of TTP, which are treated with plasma exchange, anticoagulation is the most important therapeutic intervention in these patients. Effective anticoagulation may require laboratory confirmation with anti–factor Xa levels in patients treated with heparin, especially if the baseline (pretreatment) activated partial thromboplastin time is prolonged. Patients with catastrophic APS also benefit from immunosuppressive therapy and/or plasma exchange, whereas patients with HIT need an alternative anticoagulant to replace heparin. Progressive thrombotic events despite therapeutic anticoagulation may necessitate an alternative therapeutic strategy. If the thrombotic process can be controlled, these patients can recover, but indefinite anticoagulant therapy may be appropriate to prevent recurrent events. (*Blood*. 2015;126(11):1285-1293)

Anticoagulation

- Start with unfractionated heparin with a target aPTT in the high therapeutic range (unless an atypical manifestation of HIT is suspected)
- If baseline aPTT is prolonged, or doesn't respond appropriately to heparin therapy, need to confirm heparin is therapeutic with an anti-factor Xa assay
- If aPTT is subtherapeutic with a therapeutic anti-factor Xa assay, would check an antithrombin level and consider supplementing if low
- Don't stop anticoagulation unless actively bleeding

Additional antithrombotic interventions

- If atypical HIT is suspected → bivalirudin, argatroban
- Fibrinolytic therapy may be indicated in patients with massive thrombus burden (e.g., acute stroke, massive PE with right heart failure)
- Antiplatelet therapy may be useful in patients with arterial thrombotic events, but would use in addition to anticoagulant therapy
- Generally prefer to avoid IVC filters in this highly prothrombotic setting

Plasma exchange

- Presence of microangiopathic hemolytic anemia with thrombocytopenia raises concern for catastrophic APS, atypical TTP
- Prior history of systemic lupus erythematosus or known APS raises concern for catastrophic APS

→ Would consider initiation of plasma exchange

Immunomodulatory agents

- Prednisone, intravenous immunoglobulin, rituximab, and recently eculizumab have been used in the treatment of patients with catastrophic APS
- Prednisone and rituximab are also used in the treatment of acquired TTP
- IVIG has been used for autoimmune HIT

- “Idiopathic” thrombotic storm may respond to any of these therapies

Daily management

- Follow anticoagulant therapy with aPTT and/or anti-factor Xa levels
- Follow platelet count daily
- Re-assess areas with known thrombotic occlusions and investigate any new areas of concern
- Decisions concerning plasma exchange based on platelet count response, review of peripheral blood film, and clinical response

Subsequent Management

- Initially, I use heparin/LMWH until clinically stable, and then convert to warfarin
- For patients with atypical HIT and/or recurrent events on heparin/LMWH → bivalirudin or argatroban
- For patients with malignancy-related catastrophic thrombotic events, I use long-term LMWH
- If the data are consistent with an atypical presentation of TTP → discontinue anticoagulation

Long-term Management

- If thromboembolic events were venous only, and no recurrent events within six (or more) months, I would consider switching to a direct oral anticoagulant for long-term maintenance
- If thromboembolic events were arterial, I would continue long-term on warfarin (or LMWH), with or without aspirin
- I typically recheck antiphospholipid antibody tests if negative (or positive) in the acute setting

Thrombotic Storm Study Group

2-3 March 2009

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journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Variants in chondroitin sulfate metabolism genes in thrombotic storm

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  - Hospital for Sick Children; Dr. Brandao
  - Michigan State University; Dr. Kulkarni

- Information on TS study
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Questions?