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Blood Disorders Day 2021

FOR Health Professionals

Zebras on the Prairies:
Acquired Hemophilia A and TTP

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University of Manitoba

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Presenter Disclosure

- **Faculty / Speaker's name: Emily Rimmer**

- **Relationships with commercial interests:**
  - **Grants/Research Support: none**
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  - **Other: none**

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Mitigating Potential Bias

- Not Applicable

Learning Objectives

At the end of this session, the participant will:

1. Understand the presentation and initial work-up for rare but serious hematologic conditions that require urgent hematology referral including acquired hemophilia, and thrombotic thrombocytopenic purpura

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Referral to Hematology

- Indication: Easy bruising.
- Relevant Clinical History: Seen in the ER July 25 for belly pain with a normal CT and workup. Since then she had extensive bruising around her left anteecubital venipuncture site as well as unexplained bruising to her lateral left ankle, ulnar aspect of her right forearm and her anterior right shoulder. The venipuncture was swollen up at that time the intravenous was discontinued and she reports no history of trauma to the ankle or the shoulder which appeared to have an injury pattern or bruising. She has microscopic hematuria in her urine and a past hysterectomy. She reports no history of bleeding issues and her CBC creatinine INR and platelets are all normal. Could you assess her for more functional because of acquired easy bruising.

Bleeding history

- Personal history of bleeding
  - Epistaxis, cutaneous, bleeding from minor wounds, oral cavity, GI bleeding, hematuria, tooth extractions, surgery, menorrhagia, post-partum hemorrhage, muscle hematoma, hemarthrosis, CNS bleeding, other
  - Severity, requirement of medical intervention, transfusions
- Family history
- Medications: ASA, NSAIDS, warfarin, DOAC

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Value of BAT

- ISTH-BAT cut off scores
  - Women ≥ 6
  - Men ≥ 4
  - Children ≥ 3
- Utility of BAT
  - Sensitivity 97%
  - Specificity 50%
  - NPV 99%

http://letstalkperiod.ca/self-bat/
https://c.ymcdn.com/sites/www.isth.org/resource/resmgr/ssc/isth-ssc_bleeding_assessment.pdf

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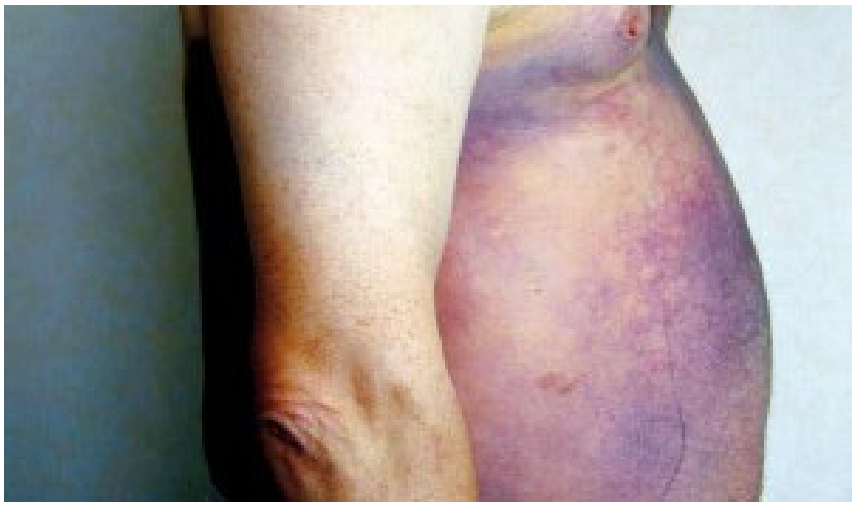
Further information

- 2-month history of bruising
- Ecchymosis covering torso and both arms
- Denies previous bleeding history
- Tonsillectomy as child, no bleeding
- Several tooth extractions without incident
- No medical history
- No medications
- No family history



Google images

Further information

- WBC 8.9 x 10e9/L, Hgb 100g/L, Plt 350 x 10e9/L
- INR 0.9, PT 13 seconds (N 9-15 sec)
- *aPTT 127 seconds (N 25-35 sec)*

- No correction with mixing study
- Factor VIII <1%, Bethesda titre 130 BU

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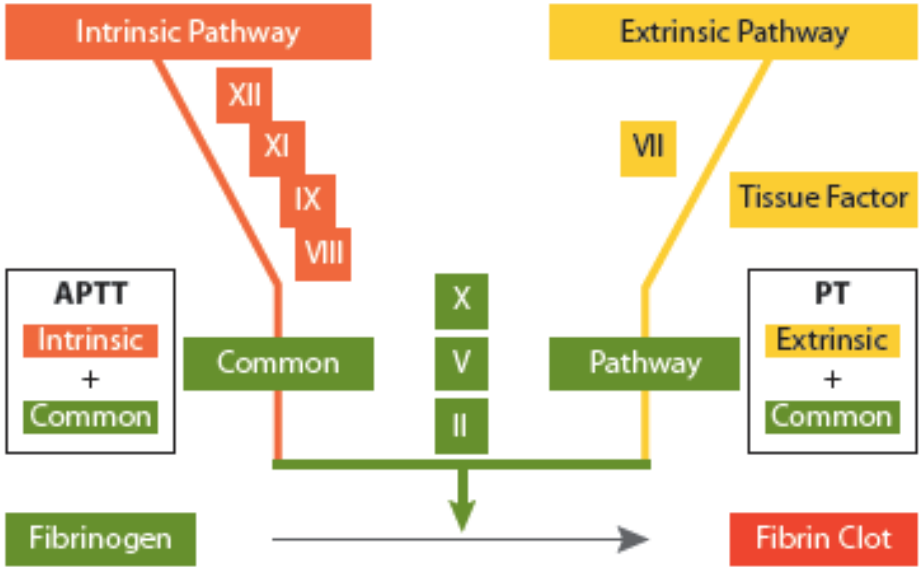
Basics of clotting tests

Activated partial thromboplastin time (aPTT)



Prothrombin time (PT)

International normalized ratio (INR)

<u>THESE REPRESENT THE SAME THING</u>

Modified from Lin et al. Bloody Easy Coagulation Simplified…

Prolonged PTT

- Should not be ordered as a routine test in unselected patients

FVIII or FIX deficiency – acquired or congenital
FXI deficiency
Heparin therapy
*Lupus inhibitor***
FXII, HMWK, PK deficiency

Acquired FVIII inhibitors

- Age standardized incidence in Manitoba is 1.98 per million per year
- Majority of cases occur in patients older than 60 years
  - 2 peaks: pregnancy and older age
- In approx. 50% of cases an underlying cause is not identified
  - Autoimmune disorder (14%)
  - Malignancy (11%)
  - Pregnancy (9%)

Baudo, F., et al. 2012. *Blood* 120:39-46.
Perija et al. ASH 2017

Clinical Manifestations

- Pattern of bleeding is different than congenital hemophilia
  - Spontaneous hemarthroses rare
- **Severe bruising and subcutaneous hematomas are characteristic**
- Hemorrhage
  - Skin (80%)
  - Muscles (45%)
  - Mucous membranes (GI 21%, GU 9%, retroperitoneal 9%)
- Because many occur in elderly population, concomitant medications are often suspected

Treatment

- 2 considerations:
  - Treatment of acute bleeding episode using an agent that will bypass the inhibitor
  - Long-term eradication of the autoantibody with immunosuppression

- High likelihood of cure with treatment

Back to case

- Treated with bypassing agent to treat bleeding
- 3 month course of prednisone and cyclophosphamide with complete remission of acquired hemophilia
- No evidence of recurrence 3 years later

Barriers to Practice Change

- Recognize that bleeding disorders cannot be ruled out by INR/PT alone
- Requires a PTT test
  - Please contact hematology on call or hematopathology on call

Referral to Hematology

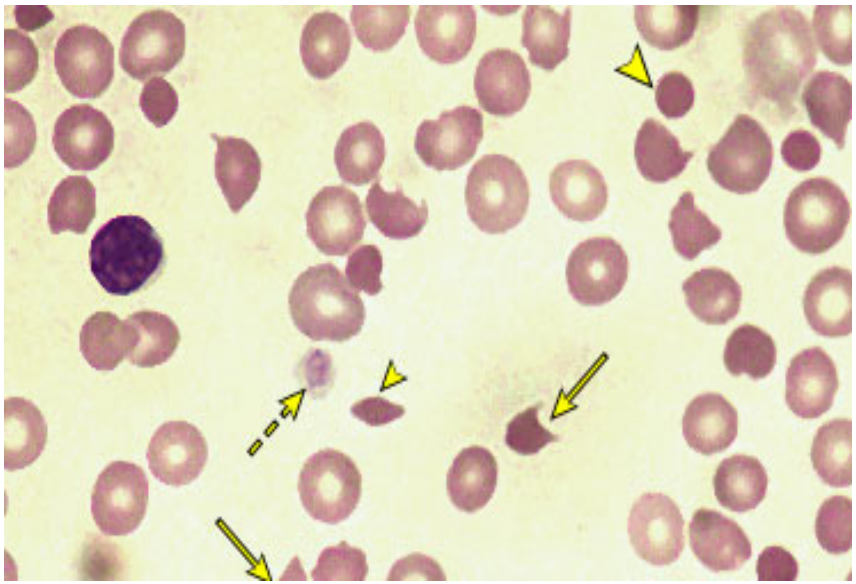
- 45yo F, previously well, presents to rural hospital with 3-day history of petechiae
- On exam alert and oriented, afebrile, BP 159/90, petechiae noted
- CBC show Hb 113 g/L, **plt 13 x 10^9/L**, WBC 6.3 x 10^9/L with normal differential
- Creatinine 54, T bilirubin 22

Further information

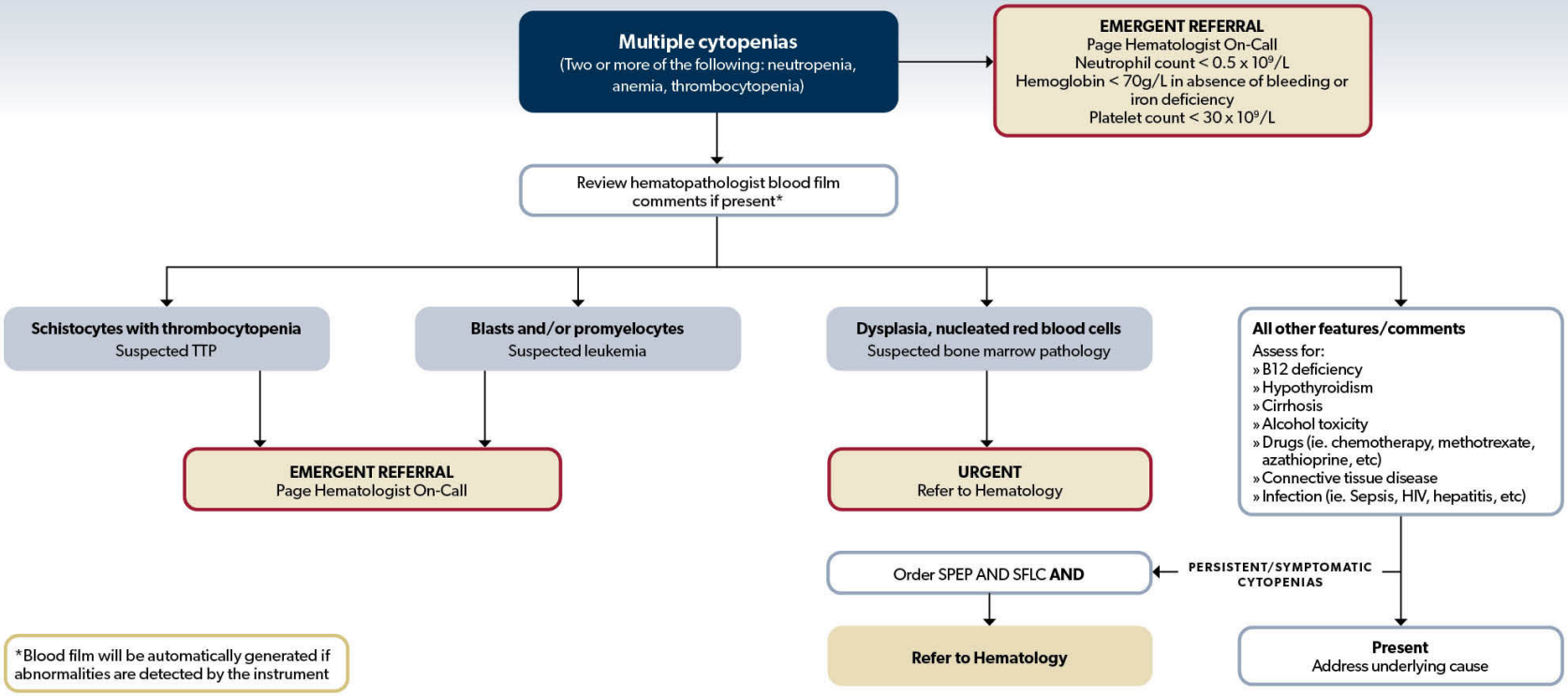
- CBC 3 months prior: WBC 4.5, hemoglobin 143, plt 173
- Advice from hematology on call:
  - Repeat CBC with retic, request blood film
  - LDH, total and direct bilirubin, haptoglobin
  - DAT, HIV, Hep serologies
  - Start dex 40mg for 4 days for presumed ITP

Further information

- Repeat Hemoglobin 109**, plt 11**, retic 151
- T Bilirubin 39 umol/L, Direct 10 umol/L
- LDH **1746** U/L (ULN 490 U/L)
- Haptoglobin undetectable
- DAT negative
- PT, INR normal



Pancytopenia



SPEP = Serum protein electrophoresis
SFLC = Serum free light chain

TTP = Thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP)

- Incidence of 2 per million per year
- Median age 41
- Females preferentially affected (2-3F:1M)
- Median platelet count 10-30 x 10^9/L, hemoglobin 80-100
- Due to antibodies against ADAMTS13

Hematology 2018;2018:530-538

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TTP Manifestations

- Hallmark symptoms: Severe thrombocytopenia (typically <30), and hemolytic anemia characterized by the presence of schistocytes, often with a markedly elevated LDH

- Symptoms related to organ involvement
  - 60% have neurologic symptoms (headache, confusion, stroke, coma)
  - 25% have cardiac ischemia
  - Renal impairment (usually mild)

- Long term consequences include cognitive impairment, depression, hypertension, shortened life expectancy

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Diagnosis

- Presumptive diagnosis in the setting of MAHA and moderate – severe thrombocytopenia
- Confirm diagnosis with ADAMTS13 level (usually less than 10%) with or without the presence of an inhibitor

Table 2. Clinical and laboratory findings in TTP[2-7,12]

	Frequency (%)
Clinical presentation, %	
MAHA with thrombocytopenia	100
Neurological abnormalities	39-80
Major	18-53
Minor	27-42
Fever	10-72
Gastrointestinal symptoms	35-39
Renal involvement	10-75
Classic pentad*	7
Laboratory findings	
Median platelet count, $\times 10^9$/L	10-17
Median creatinine, μmol/L	0.96-1.42
Median LDH, U/L	1107-1750
Median hematocrit, %	20-27

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TTP treatment

- Case fatality rate >90% prior to effective therapy
- Initiate treatment as soon as TTP suspected, don't wait for confirmatory testing
- Treatment of choice is plasma exchange
- Addition of steroids improves responses
- Rituximab also helpful, evidence suggests decreased risk of relapse

Back to case

- Treated with plasma exchange daily x 7 days
- Prednisone and rituximab
- Complete remission without recurrence 4 years later

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Take home messages

- Unexplained bleeding requires basic clotting tests including a CBC, INR and PTT
- Acquired hemophilia has characteristic bleeding; requires emergent hematology involvement due to high risk of bleeding
- Severe thrombocytopenia with red cell fragmentation (schistocytes) requires emergent hematology involvement to initiate treatment for suspected TTP

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Thank you

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