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Educational Case: Differentiating Thrombotic Thrombocytopenic Purpura From Other Thrombotic Microangiopathies and Potential Role of the Spleen

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see http://journals.sagepub.com/doi/10.1177/2374289517715040.[1]

Keywords
pathology competencies, organ system pathology, hematopathology, platelets, coagulation disorders, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, spleen

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Primary Learning Objective

Objective HPCD1.4: Thrombocytopenic Purpura: Compare and contrast thrombotic thrombocytopenic purpura with hemolytic uremic syndrome.[1]

Competency 2: Organ System Pathology; Topic HPCD: Hematopathology—Platelets and Coagulation Disorders; Learning Goal 1: Platelets

Secondary Learning Objective

Objective HWC7.1: Splenic Function: Explain the contribution of normal splenic function to nonneoplastic diseases.

Competency 2: Organ System Pathology; Topic HWC: Hematopathology—White Cell Disorders, Lymph Nodes, Spleen, and Thymus; Learning Goal 7: Spleen

Patient Presentation

A 32-year-old female with a history of well-controlled asthma and bipolar disorder presents to the emergency department with confusion and fever. She is accompanied by her husband who states that the patient had been in her normal state of health prior to that morning. She is prescribed lithium and albuterol with no recent changes in dose. She has no history of illicit drug use. Physical examination is notable for a temperature of 38.9 °C and a pulse of 115 beats per minute. She is able to have a somewhat coherent conversation and can be redirected when confused.

Diagnostic Findings, Part 1

Selected laboratory studies are presented in Table 1. The patient had blood work performed 6 months prior due to her lithium therapy, and these results are shown for comparison. Additional studies are ordered in the emergency department.

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Table 1. Laboratory Studies From the Patient at Presentation Compared to 6 Months Prior.

Lab test	Time of presentation	6 months prior	Normal range
Hemoglobin	9.2	13.7	13.0-17.0 g/dL
Hematocrit	27.6	39.1	39.0%-51.0%
White blood cell count	12.05	7.68	3.70-11.00 k/μL
MCV	82.8	91.3	80.0-100.0 fL
RDW	16.4	12.0	11.5%-15.0%
Platelets	77	256	150-400 k/μL
Reticulocyte count	5.1	1.5	0.4%-2.0%
Lactate dehydrogenase	690	Not performed	135-225 U/L
Haptoglobin	10	Not performed	31-238 mg/dL
Creatinine	1.5	0.7	0.73-1.22 mg/dL

Abbreviations: MCV, mean corpuscular volume; RDW, red cell distribution width.

Chest x-ray is unremarkable. A lumbar puncture is negative for signs of acute meningitis. Because of the findings in the complete blood count, a peripheral blood smear review is requested. Her peripheral smear findings are presented in Figure 1.

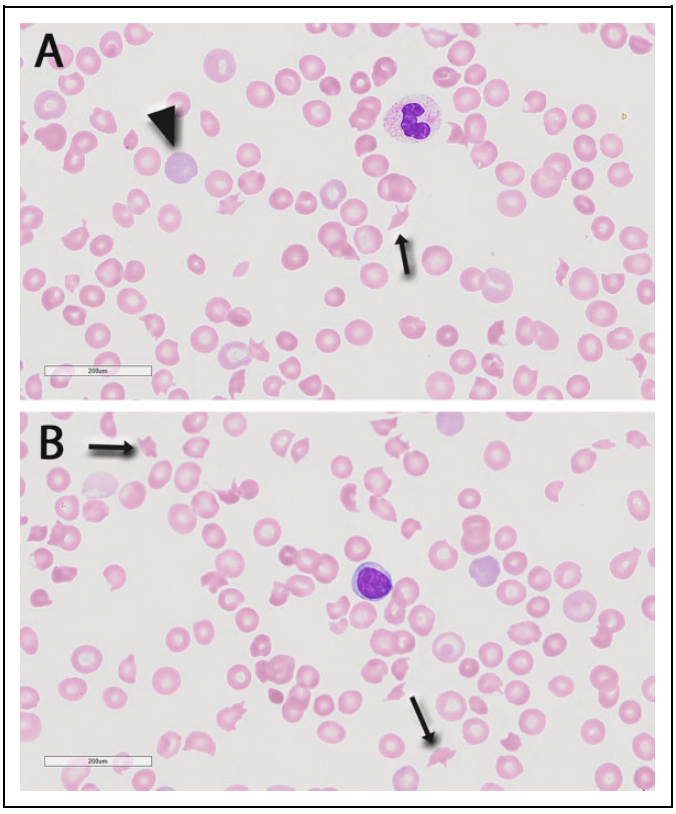

Figure 1. The patient's peripheral blood smear. Image (A) shows schistocytes (arrow) as well as reticulocytes (arrowhead). Image (B) shows additional examples of schistocytes (arrow). Note that platelets are not well seen in either image.

Question/Discussion Points, Part 1

What Is the Initial Differential Diagnosis for This Patient?

At the time of initial presentation, the differential diagnosis is broad and includes meningitis, drug intoxication, and panic attack, among other processes. For example, accidental or intentional drug overdose (such as anticholinergic agents) can cause hyperthermia and confusion. Lithium may cause pancytopenia, neurologic symptoms, and kidney disease in some cases.[2]

Interpret the Patient's Laboratory Studies

The patient has anemia and thrombocytopenia. Her white blood cell count is essentially normal. Her creatinine is elevated from baseline, concerning for acute kidney injury. A negative cerebrospinal fluid analysis argues against meningitis.

Do the Results in Table 1 Provide Any Other Clues About the Cause of the Patient's Anemia?

The serum lactate dehydrogenase is elevated and serum haptoglobin is low. Serum lactate dehydrogenase is an enzyme involved in anaerobic glycolysis and can be a measure of hemolysis.[3] Although all cells contain lactate dehydrogenase, red blood cells lack mitochondria to perform oxidative metabolism and must derive energy from anaerobic metabolism. Lactate dehydrogenase catalyzes the final step of this process with production of lactate from pyruvate and reducing nicotinamide adenine dinucleotide from its oxizided form (NAD+ to NADH) such that glycolysis can continue. However, serum lactate dehydrogenase is a nonspecific marker of increased tissue turnover and can be elevated in cancers, cardiac arrest, trauma, or other processes. To aid in interpretation, serum haptoglobin is measured in conjunction. Haptoglobin binds free hemoglobin released from damaged red cells to prevent it from causing vascular damage.[4] Serum haptoglobin is depleted in the setting of significant intravascular hemolysis. The combination of these markers in this patient is characteristic intravascular hemolysis.

What Are Some Potential Causes of Intravascular Hemolysis?

The potential causes of intravascular hemolysis are diverse and may include autoimmune hemolytic anemia, increased complement-mediated destruction in paroxysmal nocturnal hemoglobinuria, hemoglobinopathies such as sickle cell disease, or abnormalities within the vasculature resulting in red cell destruction. A peripheral smear review can be helpful in differentiating some of these causes.

Interpret the Patient's Peripheral Blood Smear in Figure 1. What Are the Arrows and Arrowhead Indicating?

The peripheral blood smear is notable for thrombocytopenia as well as anemia. The arrowhead points to a reticulocyte

Table 2. Differentiating Potential Causes of Microangiopathic Hemolytic Anemia.

Patient characteristics	Acquired TTP	HUS	Atypical HUS	DIC
Patient age	Adults	Children	Adults	Any
Related infection	None	*Escherichia coli* O157: H7	None	Sepsis
Renal dysfunction	Yes	Yes	Yes	No
Neurologic symptoms	Yes	Subset	No	No
Bloody diarrhea	No	Yes	No	No
Platelets	Decreased	Decreased	Decreased	Decreased
Hemoglobin	Decreased	Decreased	Decreased	Decreased to normal
Schistocytes	Yes	Yes	Yes	Yes
Platelet count	Decreased	Decreased	Decreased	Decreased
Coagulation factor levels	Normal	Normal	Normal	Decreased
PT/INR and PTT	Normal	Normal	Normal	Prolonged
ADAMTS13 activity level	Low to undetectable	Normal	Normal	Normal

Abbreviations: DIC, disseminated intravascular coagulation; HUS; hemolytic uremic syndrome; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; TTP, thrombotic thrombocytopenic purpura.

(Figure 1A), which is an immature red blood cell. Her reticulocyte count is elevated consistent with a response to the anemia with increased production/release of immature red blood cells from the bone marrow. The black arrows point to schistocytes, or fragmented red blood cells. The finding of fragmented red cells is consistent with a microangiopathic cause of hemolytic anemia. This can result from systemic disorders, such as disseminated intravascular coagulation (DIC) resulting clots in microvasculature that shear red cells as they pass through. Other systemic causes include thrombotic microangiopathies such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS), which are characterized by the presence of schistocytes, elevated lactate dehydrogenase, low haptoglobin, anemia, and thrombocytopenia in the setting of organ dysfunction.[5] Exogenous mechanical forces such as a prosthetic heart valve can also damage red cells but are less associated with thrombocytopenia or other end-organ dysfunction.[6]

Given the patient's laboratory values and evidence of end-organ damage with confusion and acute kidney injury, the peripheral smear findings are helpful in further narrowing the differential diagnosis to a microangiopathic hemolytic anemia.

Microangiopathic hemolytic anemias may show overlapping features at presentation (Table 2). However, identifying the correct underlying cause is critical for effective treatment. In order to further narrow the differential, one should know the distinctive features of DIC, forms of HUS and TTP.

What Are the Key Clinical, Laboratory, and Pathologic Features of Disseminated Intravascular Coagulation?

Disseminated intravascular coagulation can occur in a variety of clinical settings and is characterized by intravascular activation of the coagulation cascade with consumption of clotting factors. This process may be triggered by malignancy, trauma, obstetric complications, or infection. In a subset of cases, DIC may originate from damage to the microvasculature or otherwise cause features of a thrombotic microangiopathy. Only a subset of patients with DIC will show features of a microangiopathic hemolytic anemia.[7] This may lead to platelet consumption, thrombotic occlusion of small- to medium-sized vessels, and end-organ damage.[8]

The clotting cascade involves a series of plasma proteins that ultimately convert soluble fibrinogen into insoluble fibrin which is cross-linked to stabilize a platelet plug into a clot. There are different but interconnected ways in which the clotting cascade may be activated. Aspects of the clotting cascade can be assessed in vitro by measuring the prothrombin time (PT, standardized as the international normalized ratio or INR) and activated partial thromboplastin time (PTT). These measure the activity of different subsets of clotting factors and are typically prolonged due to the widespread consumption of clotting factors but may yield normal or even shortened results in some cases.[9] However, in DIC, there is also secondary activation of fibrinolysis following production of the polymerized fibrin clots. This process is characterized by the production of fibrin-related markers, such as D-dimer, which is evidence that polymerized fibrin was broken down. These markers can be detected at elevated levels in the serum of patients with DIC. Overall, there is not a single specific laboratory marker of DIC, but diagnosis can be aided by evaluation of coagulation tests and markers of fibrinolysis in the context of the clinical presentation.[9] Treatment focuses on addressing the underlying cause and providing supportive care.

What Are the Key Clinical, Laboratory, and Pathologic Features of Various Forms of Hemolytic Uremic Syndrome?

Hemolytic uremic syndrome is classically caused by the Shiga toxin produced by *Escherichia coli* O157: H7. Patients will present with renal dysfunction, microangiopathic hemolytic anemia, and a subset may have neurologic symptoms.[10] Hemolytic uremic syndrome will often also be associated with bloody diarrhea, abdominal pain, vomiting, and fever.

Table 3. The Patient's Coagulation Studies and ADAMTS13 Level at Presentation Are Shown.

Test name	Patient result	Normal range
Prothrombin time (PT)	11	9.7-13 seconds
International normalized ratio (INR)	1.2	0.9-1.3
Partial thromboplastin time (PTT)	26	23.0-32.4 seconds
D-dimer	<500	< or = 500 ng/mL Fibrinogen Equivalent Units
ADAMTS13 enzyme level	10	>10%

Secondary causes of HUS due to a coexisting disease should also be considered.[11,12] Causes of secondary HUS include *Streptococcus pneumoniae*, influenza, HIV, autoimmune disease, cancer, and pregnancy.[12] All of these conditions may cause cellular injury that can result in complement system activation and in turn cause signs and symptoms consistent with a microangiopathic hemolytic anemia.

There is also a form of atypical HUS, which is a rare, chronic disorder most often caused by a genetic deficiency in a complement regulatory protein. These patients had episodes of uncontrolled amplification of the alternative complement pathway, platelet aggregation, and endothelial injury resulting in hemolysis and tissue damage including renal injury.[5] Atypical HUS is often associated with a relapsing, chronic clinical course.[12]

What Are the Key Clinical, Laboratory, and Pathologic Features of Thrombotic Thrombocytopenic Purpura?

Thrombotic thrombocytopenic purpura can be congenital or acquired. Both forms relate to decreased function/availability of the ADAMTS13 metalloproteinase, which is responsible for cleaving von Willebrand factor multimers into smaller multimers. Von Willebrand factor is produced by endothelial and other cells and secreted into the serum. Endothelial cells show increased secretion in response to certain stimuli. One function of von Willebrand factor is to act as a bridging molecule that enables platelets to adhere to areas of vacscular injury and to each other. In the setting of TTP, extremely large multimers can be detected, which would normally be partially broken down by ADAMTS13. The extremely large multimers are more likely to entrap platelets, adhere to vascular walls, and result in development of microthrombi.[15] They cannot be physiologically broken down without ADAMTS13. Platelet consumption during thrombi formation results in thrombocytopenia. These microthrombi also shear red blood cells, causing hemolytic anemia. Potential end-organ damage can occur, similar to other forms of thrombotic microangiopathic hemolytic anemia. In the case of TTP, a pentad of symptoms and laboratory findings has been described including microangiopathic hemolytic anemia, neurologic symptoms, thrombocytopenia, renal dysfunction, and fever. Importantly, the majority of patients with TTP may not show the full pentad of symptoms, particularly early in the course of their disease. Microangiopathic hemolytic anemia and thrombocytopenia are the most frequent, and fever is the least common of the 5 symptoms.[13,14] Congenital TTP occurs when a mutated form of ADAMTS13 is inhertited,[16] while acquired TTP is caused by autoantibodies to ADAMTS13 resulting in a reduction of enzyme levels.

Diagnostic Findings, Part 2

Given the differential diagnosis has been narrowed to include potential causes of microangiopathic hemolytic anemia, additional studies for coagulation factors, markers of fibrinolysis and ADAMTS13 enzyme levels are performed as shown in Table 3.

Question/Discussion Points, Part 2

What Is the Importance of Measuring Coagulation Studies in This Setting?

As above, DIC can be distinguished from other potential causes of thrombotic microangiopathies by the consumption of coagulation factors, prolongation of measures of the clotting cascade (PT, INR, and PTT), and production of markers of fibrinolysis. The patient's coagulation studies are normal, and D-dimer, a fibrin split product, is not elevated. A diagnosis of DIC can be excluded.

How Can Other Forms of Thrombotic Microangiopathy Be Distinguished in This Setting? What Is the Diagnosis for This Patient?

Other potential causes of thrombotic microangiopathy (TTP, HUS, secondary HUS, atypical HUS) may show multiple overlapping features at clinical presentation (Table 2 and discussion above).[17] The patient does not have a history of bloody diarrhea or abdominal pain to point to a potential HUS diagnosis. Hemolytic uremic syndrome patients are significantly less likely to present with neurologic symptoms as compared to patients with TTP. Additionally, patients with HUS tend to be younger than patients with TTP, but exceptions often occur.[7,18,19] Secondary causes of HUS are more challenging to exclude. In terms of laboratory testing, measuring ADAMTS13 activity levels can be informative. In HUS, the ADAMTS13 activity will be normal. In this patient, the ADAMTS13 activity level is undetectable, and so a diagnosis of TTP can be made.

What Organs Can Be Involved in Thrombotic Thrombocytopenic Purpura? What Would You Expect to See Histologically?

Any organ can be affected in TTP and may vary between patients. Platelet microthrombi accumulate in vessels, causing ischemic damage to organs.[17] This damage accounts for many

of the clinical features of TTP, including neurologic symptoms (manifested by confusion in this patient) and renal dysfunction. Patients can also have elevated troponins, indicating cardiac ischemia, as well as elevated liver function testing.

Histologically, one would expect to see microthrombi in the vessels of affected organs. In cases of severe TTP or in autopsy cases in which the patient died of TTP, there may be extensive involvement by arterial thrombi along with ischemic foci.[17]

What Are Potential Treatments for Thrombotic Thrombocytopenic Purpura?

Thrombotic thrombocytopenic purpura is potentially fatal and requires urgent treatment. Patients are treated with emergent plasmapheresis and immunosuppression, initially with steroids.[20] In plasmapheresis, the patient's plasma is exchanged with donor plasma. In TTP, this procedure plays 2 roles. First, removing the patient's plasma removes inhibitory autoantibodies to ADAMTS13. Second, the donor plasma contains functional ADAMTS13, which will cleave von Willebrand multimers in the patient. Because the patient will continue to produce autoantibodies after the plasmapheresis procedure is over, patients with TTP often require multiple plasmapheresis sessions.

A subset of patients will be refractory (10%-40%) or show progressive symptoms and require additional therapy.[20] In this scenario, it is critical to make sure that potential causes of microangiopathic hemolytic anemia have been adequately evaluated. Refractory TTP may be treated with increased immune suppression such as higher doses of steroids or rituximab. Rituximab is a monoclonal antibody against CD20, a surface protein on B cells. Terminally differentiated B-cells can produce autoantibodies. Using an anti-CD20 drug helps suppress the patient's B cell population and will decrease ADAMTS13 autoantibody production. Stronger immunosuppressive agents such as cyclosporine or cyclophosphamide may also be considered.

Caplacizumab is a relatively new drug that can be used to treat TTP.[21] It targets the A1 domain of von Willebrand factor and prevents platelets from binding at this site. Therefore, platelet consumption and microthrombi production decreases. Caplacizumab can used as an initial treatment in very severe cases of TTP.

Due to thrombocytopenia, these patients are at risk of bleeding. In one study, approximately 10% of patients hospitalized for TTP received platelet transfusion, often in the setting of bleeding.[22] However, such transfusions appear to be relatively contraindicated as transfused platelets may be consumed to generate further microthrombi and end-organ damage. In this study, platelet transfusion was associated with increased risk of arterial thrombi and mortality among TTP patients.[22]

Diagnostic Findings, Part 3

Emergent plasmapheresis is initiated. After multiple rounds are performed, the patient's disease remains refractory to treatment. Thus, a splenectomy is performed. The spleen is mildly enlarged, weighing 204 g. The capsule and parenchyma are grossly unremarkable. Microscopic findings are shown in Figure 2.

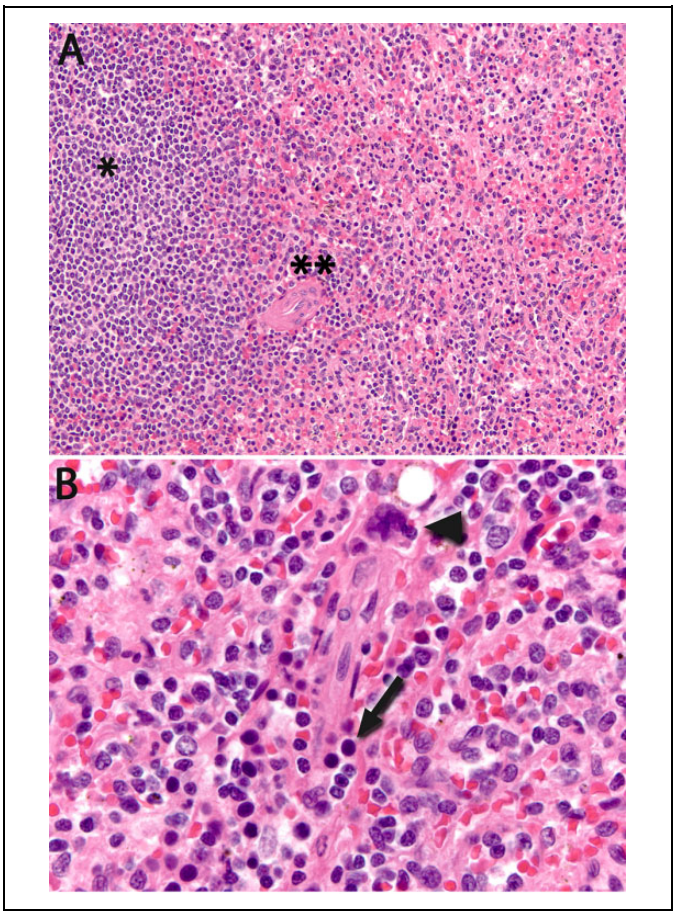

Figure 2. Histologic sections of the patient's spleen. Image (A) shows retained splenic architecture with a lymphoid follicle (left, "*") adjacent to an arteriole ("**"). The splenic red pulp (right side of image) includes splenic cords and sinusoids. At higher power within the red pulp (B), focal extramedullary hematopoiesis is appreciated with scattered megakaryocytes (arrowhead) and small erythroid islands. An immature erythroid element as identified by its condensed chromatin and very round nucleus is identified by an arrow. Scattered hemosiderin-laden macrophages were also present but are not as well appreciated in these images.

Question/Discussion Points, Part 3

What Is the Potential Role of the Spleen in the Pathogenesis of Thrombotic Thrombocytopenic Purpura and Refractory Thrombotic Thrombocytopenic Purpura?

The role of the spleen in TTP is controversial, but it may contain memory B cells specific to ADAMTS13.[23] Splenectomy was historically used as one of the early treatments for TTP.[24] Outcomes were generally dismal, but in the absence of treatment, TTP is also almost invariably fatal. In some cases, the combination of splenectomy and steroids was reported to result in sustained remissions.[25] Dramatically improved results were ultimately obtained with plasmapheresis, following its

introduction as a potential therapy in the 1970s.[26] Although approximately 80% of patients with acquired TTP will respond to plasmapheresis and immune suppression, the potential role of the spleen has again been considered for refractory or relapsed disease with mixed results.[24,26]

What Is the Normal Physiologic Role of the Spleen?

The spleen plays a key role in red blood cell turnover, removing aged or abnormal cells, and in innate and adaptive immune function.[27] It may also sequester blood elements and serve as a secondary site of normal or abnormal hematopoiesis in various disease states. Phagocytosis is performed by splenic macrophages and involves the consumption of aged or abnormal red blood cells. This is in part aided by the unique structure of the venous sinusoids, which may also aid in removal of blood-borne pathogens.[28]

The spleen is thought to be the major site of production of autoantibodies as well as immunoglobulin M antibodies to bacterial polysaccharides. The spleen can be a major site of extramedullary hematopoiesis in patients with myeloproliferative disorders and other hematologic aberrations. Normally, the spleen contains approximately 40% of the body's platelets, but this can dramatically increase in the setting of splenomegaly with sequestration up to 90% of the peripheral platelet mass, resulting in thrombocytopenia.[29] A massive spleen can also result in sequestration of red blood cells and granuolcytes, resulting in pancytopenia.[29]

Describe Normal Spleen Histology in Light of Its Function

The spleen can be divided into red pulp, which includes the cords and sinusoids involved in blood filtration, and white pulp, the lymphoid compartment of the spleen. The majority of splenic parenchyma is composed of the red pulp,[27] which includes cordal macrophages and a reticular framework that is rich in capillaries. A fraction of the blood that enters the spleen will pass through the splenic sinusoids during each pass. This aids in the red pulp's main function of blood filtration and red cell culling for aged, abnormal, or damaged red cells.[27]

In the white pulp, T lymphocytes are found predominantly around arterioles and form the periarteriolar lymphoid sheaths. The B lymphocytes form reactive follicles with expanded marginal zones and are located primarily at arteriolar branch points. The arrangement of the lymphoid tissue is such that the blood as it is filtered through the spleen is directed to prioritize passage over the B-cell follicles and maximize opportunity for antigen exposure.

What Might Be Expected Findings in a Splenectomy Specimen From a Patient With Refractory Thrombotic Thrombocytopenic Purpura?

Are there any histologic findings in this patient? Splenic findings in TTP are variable and may include hemosiderosis, periarteriolar concentric fibrosis, arteriolar thrombi, and hemophagocytosis. Rarer findings include extramedullary hematopoiesis, endothelial cell proliferation, blood lakes, and infarcts. However, in the setting of splenectomy for refractory/relapsed TTP, the majority of spleens showed no significant pathology.[24] In this patient, there is evidence of extramedullary hematopoiesis, but the histopathologic findings are largely unremarkable.

What Are the Future Clinical Ramifications of Splenectomy for This Patient?

Patients who are post-splenectomy are at an increased risk of sepsis caused by encapsulated bacteria. The spleen is the main source of antibodies to polysaccharide antigens and is also a site of antigen presentation, particularly for blood-borne pathogens. If a patient is expected to undergo splenectomy, it is recommended that they receive vaccinations for encapsulated organisms, including *Neisseria meningitidis*, *Haemophilis influenzae* type b, and *Streptococcus*.

What Change Would Be Expected on the Peripheral Blood Smear of a Patient Who Has Undergone a Splenectomy?

Post-splenectomy patients will often have Howell-Jolly bodies in their red blood cells as these nuclear remnants are typically removed during passage through the splenic sinusoids.

Teaching Points

- Thrombotic thrombocytopenic purpura classically presents with a pentad of clinical findings (microangiopathic hemolytic anemia, thrombocytopenia, neurologic symptoms, renal dysfunction, and fever), but patients will typically present with only a subset of these symptoms.
- Thrombotic thrombocytopenic purpura can be congenital or acquired and affects ADAMTS13 function, which cleaves von Willebrand factor. When not cleaved, von Willebrand multimers secreted by endothelial cells may result in platelet aggregation and microthrombi, consuming platelets and shearing red cells.
- Hemolytic uremic syndrome and atypical HUS may show overlapping clinical features with TTP. HUS is often associated with bloody diarrhea and more often occurs in younger patients. Thrombotic thrombocytopenic purpura can be distinguished from HUS and atypical HUS by low activity levels of ADAMTS13. Disseminated intravascular coagulation can be distinguished by consumption of clotting factors (resulting in prolonged PT/PTT) and production of fibrin degradation products (such as D-dimer).
- Acquired TTP is treated by plasmapheresis and immune suppression.
- The spleen may play a role in inhibitory autoantibody production against ADAMTS13 with splenectomy considered in refractory cases. The spleen also helps remove damaged red cells, may sequester platelets, and serve as a site of extramedullary hematopoiesis in times of hematopoietic stress.

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