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An unusual cause of bruising

A 61-year-old woman presented to our hematology clinic for evaluation of multiple episodes of bruising. The first episode occurred 8 months earlier, when she developed a large bruise after water skiing. Two months before coming to us, she went to her local emergency room because of new bruising and was found to have a prolonged activated partial thromboplastin time (aPTT) of 60 seconds (reference range 23.3–34.9), but she underwent no further testing at that time.

At presentation to our clinic, she reported having no fevers, night sweats, unintentional weight loss, swollen lymph nodes, joint pain, rashes, mouth sores, nosebleeds, or blood in the urine or stool. Her history was notable only for hypothyroidism, which was diagnosed in the previous year. Her medications included levothyroxine, vitamin D_3, and vitamin C. She had been taking a baby aspirin daily for the past 10 years but had stopped 1 month earlier because of the bruising.

On examination, she had a single small hematoma on her right thigh. She had no ecchymoses, petechiae, or adenopathy, and her spleen was nonpalpable.

Ten years earlier she had been evaluated for a possible transient ischemic attack; laboratory results at that time included a normal aPTT of 25.1 seconds and a normal factor VIII level of 153% (reference range 50%–173%).

Laboratory testing at our clinic showed a normal complete blood cell count (**Table 1**); the coagulation factor assay confirmed that her aPTT was elevated (prolonged), but other values were normal (**Table 2**).

Causes of an isolated prolonged aPTT include medications (eg, heparin), inherited factor deficiencies, acquired inhibitors of coagulation factors, and inherited or acquired von Willebrand disease. Lupus anticoagulant

can prolong the aPTT but is usually associated with thrombosis rather than bleeding.[1] The differential diagnoses for this and other patterns of coagulation assay abnormalities are listed in **Table 3**.

■ EVALUATION FOR AN ISOLATED PROLONGED aPTT

1 What is the appropriate next test to evaluate this patient's prolonged aPTT?

☐ Lupus anticoagulant panel
☐ Coagulation factor levels
☐ Mixing studies
☐ Bethesda assay

Mixing studies
Once a prolonged aPTT is confirmed, the appropriate next step is a mixing study. This involves mixing the patient's plasma with pooled normal plasma in a 1-to-1 ratio, then repeating the aPTT test immediately, and again after 1 hour of incubation at 37°C. If the patient does not have enough of one of the coagulation factors, the aPTT immediately returns to the normal range when plasma is mixed with the pooled plasma because the pooled plasma contains the factor that is lacking. If this happens, then factor assays should be performed to identify the deficient factor.[1]

Various antibodies that inhibit coagulation factors can also affect the aPTT. There are 2 general types: immediate-acting and delayed.

With an immediate-acting inhibitor, the aPTT does not correct into the normal range with initial mixing. Immediate-acting inhibitors are often seen together with lupus anticoagulants, which are nonspecific phospholipid antibodies. If an immediate-acting inhibitor is detected, further testing should focus on evaluation for lupus anticoagulant, including phospholipid-dependency studies.

Factor VIII inhibitor is the most common factor inhibitor

TABLE 1

Our patient's complete blood cell count results

Test	Value[a]	Reference range
White blood cell count	8.91×10^9/L	3.70–11.00
Red blood cell count	5.16×10^{12}/L	3.90–5.20
Hemoglobin	14.6 g/dL	11.5–15.5
Hematocrit	44.5%	36.0%–46.0%
Platelet count	251×10^9/L	150–400
Neutrophils	**60.6%**	40%–60%
Lymphocytes	34.1%	20%–40%
Monocytes	4.7%	2%–8%
Eosinophils	**0.4%**	1%–4%
Basophils	**0.2%**	0.5%–1%

[a] Abnormal results are shown in bold.

TABLE 2

Our patient's coagulation test results

Test	Value[a]	Reference range
Prothrombin time	11.0 seconds	8.4–13.0
International normalized ratio	1.0	0.8–1.2
Activated partial thrombo-plastin time	**46.7 seconds**	23.0–32.4

[a] Abnormal results are shown in bold.

With a delayed inhibitor, the aPTT initially comes down, but subsequently goes back up after incubation. Acquired factor VIII inhibitor is a classic delayed-type inhibitor and is also the most common factor inhibitor.[1] If a delayed-acting inhibitor is found, specific intrinsic factor levels should be measured (factors VIII, IX, XI, and XII),[2] and testing should also be done for lupus anticoagulant, as these inhibitors may occur together.

Bethesda assay

If factor levels are decreased, a Bethesda assay should be performed to differentiate a specific factor inhibitor from a lupus anticoagulant. In the case of a factor VIII inhibitor, serial dilutions of patient plasma are incubated at 37°C with pooled normal plasma for 2 hours, then factor VIII activity is measured. The reciprocal dilution of patient plasma that results in 50% of factor VIII activity in the control plasma is 1 Bethesda unit (BU). The stronger the inhibitor in the patient's sample, the more dilutions are required to measure factor VIII activity, and thus the higher the Bethesda titer.[3]

Case continued:
Results of mixing and Bethesda studies

Results of the mixing study (**Table 4**) showed an initial correction of the aPTT in a 1-to-1 mix, but after 1 hour of incubation, the aPTT was again prolonged at 42 seconds (reference range < 37.3). Further testing revealed very low levels of factor VIII (< 1%), and the presence of a factor VIII inhibitor, quantified at 5.8 BU (reference range < 0.5) (**Table 5**). Additional coagulation tests, including von Willebrand factor testing and a lupus anticoagulation panel, were negative.

■ FACTOR VIII INHIBITOR EVALUATION

2 What is the most likely underlying condition associated with this patient's factor VIII inhibitor?

☐ Autoimmune disease
☐ Malignancy
☐ A medication
☐ Unknown (idiopathic)

Acquired hemophilia A (AHA) is a rare disorder caused by autoantibodies against factor VIII. Its estimated incidence is about 1 person per million per year.[4] It usually presents as unexplained bruising or bleeding and is only rarely diagnosed by an incidentally noted prolonged aPTT. The severity of bleeding is variable and can include subcutaneous, soft-tissue, retroperitoneal, gastrointestinal, and intracranial hemorrhage.[5]

AHA is considered idiopathic in more than half of cases. A study based on a European registry[5] of 501 patients with AHA and a UK study[6] of 172 patients found no underlying disease in 52% and 65% of patients, respectively. For patients with an identified cause, the most common causes were malignancy (12%[5] and 15%[6]) and autoimmune disease (12%[5] and 17%[6]).

Drugs have rarely been associated with factor VIII inhibitors. Such occurrences have been reported with interferon, blood thinners, antibiotics, and psychiatric medications, but no study yet has indicated causation. However, patients with congenital hemophilia A treated with factor VIII preparations have about a 15% chance of developing factor VIII inhibitors. In this setting, inhibitors develop in response to recombinant factor VIII exposure, unlike the autoimmune phenomena seen in AHA.

■ TREATMENT OF ACQUIRED HEMOPHILIA A

3 What is the most appropriate treatment for AHA?

☐ Desmopressin and prednisone
☐ Recombinant porcine factor VIII and prednisone plus cyclophosphamide
☐ Recombinant factor VIIa and rituximab
☐ Any of the above

Any of the above regimens can be used. In general, treatment of AHA has two purposes: to stop acute hemorrhage, and to reduce the level of factor VIII inhibitor. No standard treatment guidelines are available; evidence of the effectiveness of different drugs is based largely on data on congenital hemophilia A.[3]

Acute treatment to stop bleeding

Initial treatment of AHA often focuses on stopping an acute hemorrhage by either raising circulating levels of factor VIII or bypassing it in the coagulation cascade.

Desmopressin can temporarily raise factor VIII levels, but it is often ineffective in AHA unless the patient has very low inhibitor titers.[3]

Factor VIII concentrate (human or recombinant porcine factor VIII) may be effective in patients with low inhibitor titers (< 5 BU). Higher doses are often required than those used in congenital hemophilia A. Factor VIII concentrate is usually combined with immunosuppressive treatment to lower the factor VIII inhibitor level (described below).[3]

If these methods are ineffective or the patient has high inhibitor titers (> 5 BU), activated prothrombin complex concentrates, known as FEIBA (factor eight inhibitor by-

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TABLE 3

Differential diagnoses associated with coagulation assay results

Prolonged prothrombin time (PT), normal activated partial thromboplastin time (aPTT)

Factor VII deficiency or factor VII inhibitor

Liver disease

Vitamin K deficiency

Warfarin use

Disseminated intravascular coagulation

Normal PT, prolonged aPTT

Deficiency of intrinsic pathway factors (VIII, IX, XI, XII) or inhibitors of these clotting factors

von Willebrand disease (if factor VIII is very low)

Heparin use

Lupus anticoagulant (usually associated with thrombosis instead of bleeding)

Prolonged PT and aPTT

Deficiency of common pathway factors (II, V, X, or fibrinogen)

Severe liver disease

Vitamin K deficiency

Warfarin use

Disseminated intravascular coagulation

Heparin overdose

Normal PT and aPTT with bleeding

Platelet dysfunction (acquired or congenital)

von Willebrand disease (if factor VIII is mildly decreased)

Scurvy

Ehlers-Danlos syndrome

Hereditary hemorrhagic telangiectasia

Factor XIII deficiency

Hyperfibrinolysis

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passing activity), or recombinant factor VIIa is available. These agents bypass factor VIII in the clotting cascade.

Immunosuppression to reduce factor VIII inhibitor

Immunosuppressive agents are the mainstay of AHA treatment to lower the inhibitor level.

TABLE 4

Our patient's mixing study results

Test	Value[a]	Reference range
Activated partial thromboplastin time (aPTT) screen	**61.2 seconds**	24.4–33.4
Immediate aPTT 1:1 mix	33.1 seconds	< 33.5
Incubated aPTT 1:1 mix	**42.2 seconds**	< 37.3

[a] Abnormal results are shown in bold.

TABLE 5

Further studies

Test	Value[a]	Reference range
Factor VIII:C assay	**1%**	50%–173%
Bethesada assay	**5.8 Bethesda units**	< 0.5

[a] Abnormal results are shown in bold.

The stronger the inhibitor in the patient's sample, the higher the Bethesda titer

Regimens vary. A 2003 meta-analysis[4] including 249 patients found that prednisone alone resulted in complete response in about 30% of patients, and the addition of cyclophosphamide increased the response rate to 60% to 100%. High-dose intravenous immunoglobulin led to conflicting results. Conclusions were limited by the variability of dosing and duration in treatment regimens among the 20 different studies included.

An analysis of 331 patients in the European Acquired Hemophilia Registry (EACH2)[7] found that steroids alone produced remission in 48% of patients, while steroids combined with cyclophosphamide raised the rate to 70%. Rituximab-based regimens were successful in 59% but required twice as long to achieve remission as steroid or cyclophosphamide-based regimens. No benefit was noted from intravenous immunoglobulin.

Risks of disease and treatment

AHA is associated with significant risk of morbidity and death related to bleeding, complications of treatment, and underlying disease.

In EACH2, 16 of the 331 patients died of bleeding, 16 died of causes related to immunosuppression, and 45 died of causes related to the underlying condition.[5] In the UK registry of 172 patients, 13 patients died of bleeding, and 12 died of sepsis related to immunosuppression.[6]

The factor VIII level and inhibitor titer are not necessarily useful in stratifying bleeding risk, as severe and fatal bleeding can occur at variable levels and patients remain at risk of bleeding as long as the inhibitor persists.[6,7]

■ CASE CONTINUED: TREATMENT, LYMPHOCYTOSIS

The patient was started on 60 mg daily of prednisone, resulting in a decrease in her aPTT, increase in factor VIII level, and lower Bethesda titer. On a return visit, her absolute lymphocyte count was 7.04×10^9/L (reference range 1.0–4.0). She reported no fevers, chills, or recent infections.

■ EVALUATING LYMPHOCYTOSIS

Lymphocytosis is defined in most laboratories as an absolute lymphocyte count greater than 4.0×10^9/L for adults. Normally, T cells (CD3+) make up 60% to 80% of lymphocytes, B cells (CD20+) 10% to 20%, and natural killer (NK) cells (CD3–, CD56+) 5% to 10%. Lymphocytosis is usually caused by infection, but it can have other causes, including malignancy.

Peripheral blood smear. If there is no clear cause of lymphocytosis, a peripheral blood smear can be used to assess lymphocyte morphology, providing clues to the underlying etiology. For example, atypical lymphocytes are often seen in infectious mononucleosis, while "smudge" lymphocytes are characteristic of chronic lymphocytic leukemia. If a peripheral smear shows abnormal morphology, further workup should include establishing whether the lymphocytes are polyclonal or clonal.[8]

■ CASE CONTINUED: LARGE GRANULAR LYMPHOCYTES

On the patient's peripheral smear, 54% of lymphocytes were large lymphocytes with moderate amounts of pale cytoplasm filled with azurophilic granules, consistent with large granular lymphocytes (LGLs) (**Figure 1**).

4 What is the next step to evaluate the patient's lymphocytosis?

☐ Bone marrow biopsy
☐ Karyotype analysis
☐ Flow cytometry
☐ Fluorescence in situ hybridization

Flow cytometry with V-beta analysis is the best first test to determine the cause of lymphocytosis after review of the peripheral smear. For persistent lymphocytosis, flow cytometry should be done even if a peripheral smear shows normal lymphocyte morphology.

Most T cells possess receptors composed of alpha and beta chains, each encoded by variable (V), diversity (D), joining (J), and constant (C) gene segments. The V, D, and J segments undergo rearrangement during T-cell development in the thymus based on antigen exposure, producing a diverse T-cell receptor population.

In a polyclonal population of lymphocytes, the T-cell receptors have a variety of gene segment arrangements, indicating normal T-cell development. But in a clonal population of lymphocytes, the T-cell receptors have a single identical gene segment arrangement, indicating they all originated from a single clone.[9] Lymphocytosis in response to an infection is typically polyclonal, while malignant lymphocytosis is clonal.

Monoclonal antibodies against many of the variable regions of the beta chain (V-beta) of T-cell receptors have been developed, enabling flow cytometry to establish clonality.

T-cell receptor gene rearrangement studies can also be performed using polymerase chain reaction and Southern blot techniques.[9]

Karyotype analysis is usually not performed for the finding of LGLs, because most leukemias (eg, T-cell and NK-cell leukemias) have cells with a normal karyotype.

Bone marrow biopsy is invasive and usually not required to evaluate LGLs. It can be especially risky for a patient with a bleeding disorder such as a factor VIII inhibitor.[10]

Case continued:
Flow cytometry confirms clonality
Subsequent flow cytometry found that more than 50% of the patient's lymphocytes were LGLs that co-expressed CD3+, CD8+, CD56+, and CD57+, with aberrantly de-
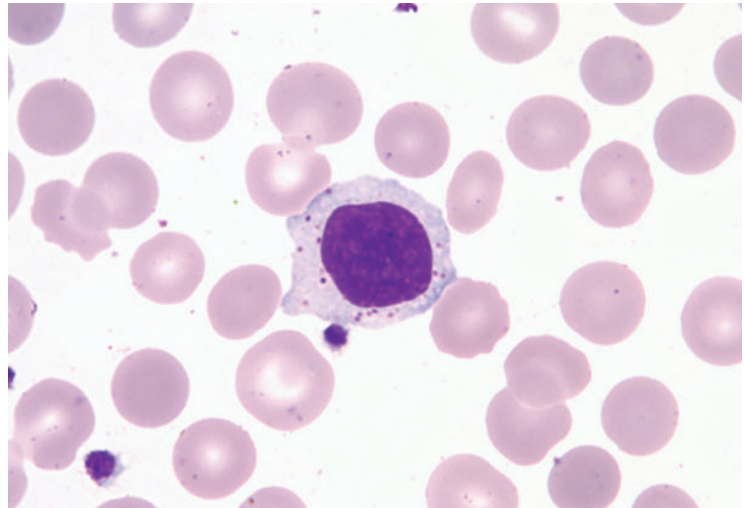

Figure 1. A large granular lymphocyte.

Image provided by Karl Theil, MD, Clinical Pathology, Cleveland Clinic.

creased CD7 expression. T-cell V-beta analysis demonstrated an expansion of the V-beta 17 family, and T-cell receptor gene analysis with polymerase chain reaction confirmed the presence of a clonal rearrangement.

■ LGL LEUKEMIA:
CLASSIFICATION AND MANAGEMENT

LGLs normally account for 10% to 15% of peripheral mononuclear cells.[11] LGL leukemia is caused by a clonal population of cytotoxic T cells or NK cells and involves an increased number of LGLs (usually $> 2 \times 10^9$/L).[10]

LGL leukemia is divided into 3 categories according to the most recent World Health Organization classification[10,12]:

T-cell LGL leukemia (about 85% of cases) is considered indolent but can cause significant cytopenias and is often associated with autoimmune disease.[13] Cells usually express a CD3+, CD8+, CD16+, and CD57+ phenotype. Survival is about 70% at 10 years.

Chronic NK-cell lymphocytosis (about 10%) also tends to have an indolent course with cytopenia and an autoimmune association, and with a similar prognosis to T-cell LGL leukemia. Cells express a CD3–, CD16+, and CD56+ phenotype.

Aggressive NK-cell LGL leukemia (about 5%) is associated with Epstein-Barr virus infection and occurs in younger patients. It is characterized by severe cytopenias, "B symptoms"

AHA usually presents as unexplained bruising or bleeding

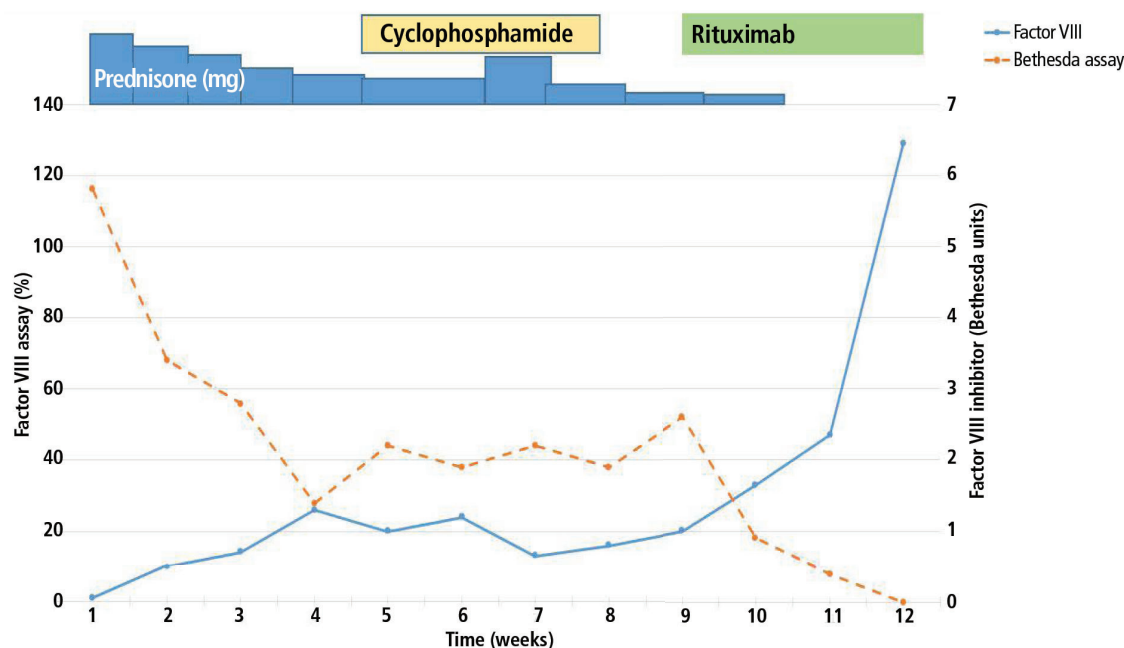### Factor VIII inhibitor response to treatment

Figure 2. The patient's clinical course: factor VIII inhibitor response to treatment.

(ie, fever, night sweats, weight loss), and has a very poor prognosis. Like chronic NK-cell lymphocytosis, cells express a CD3–, CD16+, and CD56+ phenotype. Fas (CD95) and Fas-ligand (CD178) are strongly expressed.[10,13]

Most cases of LGL leukemia can be diagnosed on the basis of classic morphology on peripheral blood smear and evidence of clonality on flow cytometry or gene rearrangement studies. T-cell receptor gene studies cannot be used to establish clonality in the NK subtypes, as NK cells do not express T-cell receptors.[11]

Case continued:
Diagnosis, continued course

In our patient, T-cell LGL leukemia was diagnosed on the basis of the peripheral smear, flow cytometry results, and positive T-cell receptor gene studies for clonal rearrangement in the T-cell receptor beta region.

While her corticosteroid therapy was being tapered, her factor III inhibitor level increased, and she had a small episode of bleeding, prompting the start of cyclophosphamide 50 mg daily with lower doses of prednisone. She then developed elevated liver enzymes, prompting discontinuation of cyclophosphamide. Rituximab was started and continued

for 4 weekly doses, resulting in normalization of aPTT and factor VIII level with undetectable Bethesda titers (**Figure 2**).

■ LGL LEUKEMIA AND AUTOIMMUNE DISEASE

Patients with LGL leukemia commonly have or develop autoimmune conditions. Immune-mediated cytopenias including pure red cell aplasia, aplastic anemia, and autoimmune hemolytic anemias can occur. Neutropenia, the most common cytopenia in LGL leukemia, is thought to be at least partly autoimmune, as the degree of neutropenia is often worse than would be expected solely from bone-marrow infiltration of LGL cells.[10,14,15]

Rheumatoid arthritis is the most common autoimmune condition associated with LGL leukemia, with a reported incidence between 11% and 36%.[13–15]

Felty syndrome (rheumatoid arthritis, splenomegaly, and neutropenia) is often associated with LGL leukemia and is thought by some to be part of the same disease process.[15]

Treat with immunosuppressives if needed

Indications for treating LGL leukemia include the development of cytopenias and associ-

ated autoimmune diseases. Immunosuppressive agents, such as methotrexate, cyclophosphamide, and cyclosporine, are commonly used.[10,11,14] Most evidence of treatment efficacy is from retrospective studies and case reports, with widely variable response rates that overall are around 50%.[10]

ACQUIRED HEMOPHILIA A AND HEMATOLOGIC MALIGNANCY

A systematic review found 30 cases of AHA associated with hematologic malignancies.[16] The largest case series[17] in this analysis had 8 patients, and included diagnoses of chronic lymphocytic leukemia, erythroleukemia, myelofibrosis, multiple myeloma, and myelodysplastic syndrome. In 3 of these patients, the appearance of the inhibitor preceded the diagnosis of the underlying malignancy by an average of 3.5 months. In 1 patient with erythroleukemia and another with multiple myeloma, the activity of the inhibitor could be clearly correlated with the underlying malignancy. In the other 6 patients, no association between the two could be made.

In the same series, complete resolution of the inhibitor was related only to the level of Bethesda titer present at diagnosis, with those who achieved resolution having lower mean Bethesda titers.[17] Similarly, in EACH2, lower inhibitor Bethesda titers and higher factor VIII levels at presentation were associated with faster inhibitor eradication and normalization of factor VIII levels.[7]

Murphy et al[18] described a 62-year-old woman with Felty syndrome who developed a factor VIII inhibitor and was subsequently given a diagnosis of LGL leukemia. Treatment with immunosuppressive agents, including cyclophosphamide, azathioprine, and rituximab, successfully eradicated her factor VIII inhibitor, although the LGL leukemia persisted.

Case conclusion: Eradication of factor VIII inhibitor

Our patient, similar to the patient described by Murphy et al[18] above, had eradication of the factor VIII inhibitor despite persistence of LGL leukemia. Between the time of diagnosis at our clinic, when she had 54% LGLs, and eradication of the inhibitor 3 months later, the LGL percentage ranged from 45% to 89%. No clear direct correlation between LGL and factor VIII inhibitor levels could be detected.

Given the strong association of LGL leukemia with autoimmune disease, it is tempting to believe that her factor VIII inhibitor was somehow related to her malignancy, although the exact mechanism remained unclear. The average age at diagnosis is 60 for LGL leukemia[11] and over 70 for AHA,[5,6] so advanced age may be the common denominator. Whether or not our patient will have recurrence of her factor VIII inhibitor or the development of other autoimmune diseases with the persistence of her LGL leukemia remains to be seen.

At last follow-up, our patient was off all therapy and continued to have normal aPTT and factor VIII levels. Repeat flow cytometry after treatment of her factor VIII inhibitor showed persistence of a clonal T-cell population, although reduced from 72% to 60%. It may be that the 2 entities were unrelated, and the clonal T-cell population was simply fluctuating over time. This can be determined only with further observation. As the patient had no symptoms from her LGL leukemia, she continued to be observed without treatment.

TAKE-HOME POINTS

- The coagulation assay is key to initially assessing a bleeding abnormality; whether the prothrombin time and aPTT are normal or prolonged narrows the differential diagnosis and determines next steps in evaluation.
- Mixing studies can help pinpoint the responsible deficient factor.
- Acquired factor VIII deficiency, also known as AHA, may be caused by autoimmune disease, malignancy, or medications, but it is usually idiopathic.
- AHA treatment is focused on achieving hemostasis and reducing factor VIII inhibitor.
- Lymphocytosis should be evaluated with a peripheral blood smear and flow cytometry to determine if the population is polyclonal (associated with infection) or clonal (associated with malignancy).
- LGL leukemia is usually a chronic, indolent disease, although an uncommon subtype has an aggressive course.
- The association between AHA and LGL leukemia is unclear, and both conditions must be monitored and managed. ■

AHA causes significant morbidity and mortality from bleeding, complications of treatment, and underlying disease

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