Clinical Pathological Conference: a 51-year-old man with a history of stroke and red streaks in the legs

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In the following discussion, a diagnostically challenging case is presented by Jeffrey W. Olin, DO, and Thomas J. Masaryk, MD. Mark E. Mayer, MD, examines the clinical, laboratory, and radiologic features and works through the differential diagnosis. Kandice Kottke-Marchant, MD, PHD, provides a pathology-based diagnosis.

PRESENTATION OF CASE

DR. OLIN: A 51-year-old white man presented in June 1992 with two major complaints: red streaks running down his legs and left lower quadrant abdominal pain.

He has had at least five distinct episodes of red streaks running down his legs during the last 2 years. These have occurred in either leg and are warm, red, and extremely tender. Each episode usually has lasted approximately 2 weeks. Most episodes have involved the medial aspect of the leg or posterior calf. Fever or chills have not been associated with these red streaks.

He was initially treated with naproxen 500 mg twice a day and later switched to ticlopidine 250 mg twice a day. Neither of these therapies helped this condition.

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Since an automobile accident in July 1991, he has had pain in his left lower quadrant radiating down the posterior lateral aspect of his left leg. This has usually occurred when walking, but has also occurred occasionally at rest. His appetite has not changed, and food does not exacerbate the discomfort. There has been no weight loss, no change in bowel habits, and no melena or hematochezia. A recent proctosigmoidoscopic examination was normal.

His medical history included at least four previous strokes. He cannot adequately describe what symptoms he had during each of these strokes, but he does remember that one time his entire left side became numb and this persisted for days. He has a history of a seizure disorder that started after his first stroke. He usually "blacks out" at the onset of the seizure. He has had several typical tonic-clonic seizures, and several complex partial seizures that were witnessed. The results of electroencephalography (EEG) from another hospital were normal.

A lung carcinoma was removed in 1985 and reportedly was cured. He has a long history of recurrent chest pain, shortness of breath, or both; these symptoms may occur at any time and are not related to exertion. Because he has had several negative evaluations for cardiac disease, some of his physicians have diagnosed this as representing an anxiety disorder.

He was taking the following medications at the time of his initial visit to The Cleveland Clinic Foundation: doxepin 50 mg at bedtime, ticlopidine 250 mg twice a day, phenytoin 100 mg three times a day, clonazepam 0.5 mg in the morning and 1.0 mg

in the evening, and naproxen as needed. The physical examination revealed a blood pressure of 120/70 mm Hg. The temperature was 37°C. There was no lymphadenopathy. The thyroid gland was not enlarged. Examination of the heart demonstrated a rate of 72 beats per minute with a normal rhythm. There were no murmurs, rubs, or gallops. The lungs were clear to percussion and auscultation. The abdominal examination demonstrated normal bowel sounds. There were no masses or organomegaly. The aorta was palpable but not enlarged. There was mild tenderness to deep palpation in the left lower quadrant. No carotid bruits were detected. The peripheral pulses were normal. The legs were not swollen, and there was no red streaking. There were no changes that would have indicated chronic venous insufficiency. On neurologic examination, there was evidence of memory loss to recent events. He was able to follow simple commands. The cranial nerves were intact. The reflexes were 2+ and equal bilaterally. There were no Babinski's signs and no focal neurologic deficits.

The complete blood count showed a white blood cell count of 8500 per μL with a hemoglobin of 16.7 g/dL and a hematocrit of 49.1%. The platelet count was 108 000 per μL. The mean corpuscular volume was 92 μm^3, mean corpuscular hemoglobin 31 pg per red blood cell, and mean corpuscular hemoglobin concentration 34%. The differential showed 63.6% neutrophils, 25.1% lymphocytes, 4.8% monocytes, 5.1% eosinophils, and 1.5% basophils. The prothrombin time was 12.0 seconds, and the activated partial thromboplastin time (aPTT) was 41.7 seconds. The Westergren sedimentation rate was 6 mm/hour. The C-reactive protein was 1.2 mg/dL. The antinuclear antibody (ANA) was positive in a titer of 1:160 in a homogeneous pattern. The anti-DNA was 143 SIU/mL (normal 0 to 800 SIU/mL). The test for extractable nuclear antibody (ENA) was negative. The test for anticentromere antibody was negative. The C_3, C_4, and CH_{50} complement levels were normal.

The total protein was 5.9 g/dL, albumin 3.3 g/dL (normal 3.5 to 5.0 g/dL), calcium 9.0 mEq/L, phosphate 3.0 mg/dL, uric acid 6.0 mg/dL, total bilirubin 0.5 mg/dL, glucose 98 mg/dL, sodium 138 mEq/L, potassium 3.9 mEq/L, chloride 104 mEq/L, CO_2 24 mEq/L, blood urea nitrogen 32 mg/dL, and creatinine 1.5 mg/dL. The lactic dehydrogenase was 160 IU/L, aspartate aminotransferase 30 IU/L, and alkaline phosphatase 81 IU/L.

The free phenytoin level was 0.9 μg/mL (therapeutic level 1 to 2 μg/mL).

EEG demonstrated nonspecific disturbances of cerebral activity over the temporal region. A computed tomographic (CT) scan of the brain demonstrated multiple remote small infarcts with involvement of the posterior limb of the right internal capsule. No enhancing lesions suggestive of metastatic disease were noted. A CT scan of the chest showed postthoracotomy changes and no evidence of recurrent tumor. A CT scan of the abdomen and pelvis was normal.

Left ventricular size and function were normal on two-dimensional echocardiography. There was no evidence of thrombus, vegetations, or masses. A duplex ultrasound examination of the veins in the lower extremities was negative bilaterally for acute iliofemoral or popliteal deep venous thrombosis. A duplex ultrasound study of the carotid arteries was normal.

Electromyography of the left lower extremity with a limited examination of the left upper and right lower extremities showed evidence of very subtle, chronic, and inactive L-5 and S-1 motor fiber loss on the left and L-5 motor fiber loss on the right. These changes likely represented the residuals of remote lumbosacral motor radiculopathy. There was no electromyographic evidence of active or ongoing motor fiber loss to indicate an active lumbosacral motor radiculopathy.

A diagnostic test was performed.

REVIEW OF RADIOLOGIC FINDINGS

DR. MASARYK: On the chest x-ray from July 1992, we saw borderline cardiomegaly and evidence of a previous thoracotomy, with surgical clips and suture material. Otherwise, the chest x-ray was unremarkable and relatively unchanged compared with a previous study from 1987.

As Dr. Olin mentioned, the CT scans of the abdomen, pelvis, and chest were performed because of the patient's complaint of left lower quadrant pain and the finding of the left lower quadrant tenderness on physical examination. The CT scans demonstrated punctate focal calcifications within the spleen, suggesting previous granulomatous disease. The retroperitoneum, including the pancreas and great vessels, was unremarkable. There was no organomegaly, and the kidneys were normal. Lower cuts demonstrated the retroperitoneum to be free of

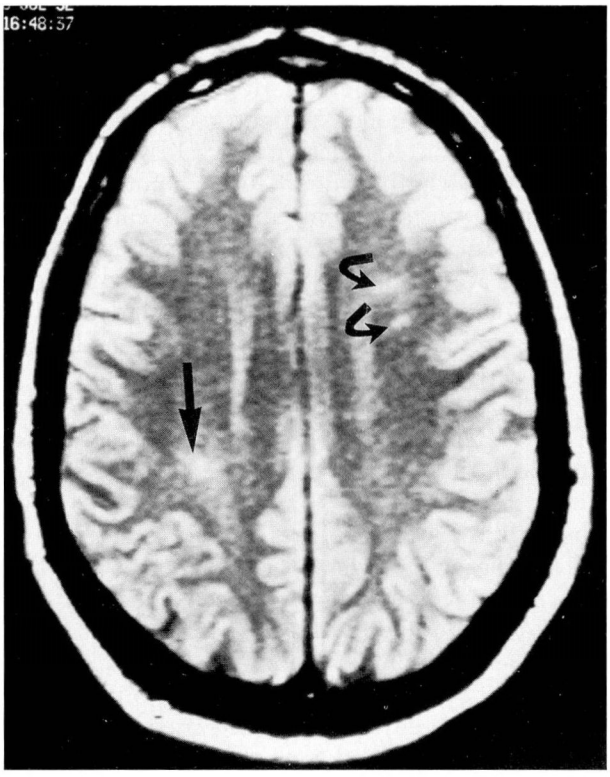

FIGURE 1. Magnetic resonance imaging study demonstrating several cerebral infarcts (arrows).

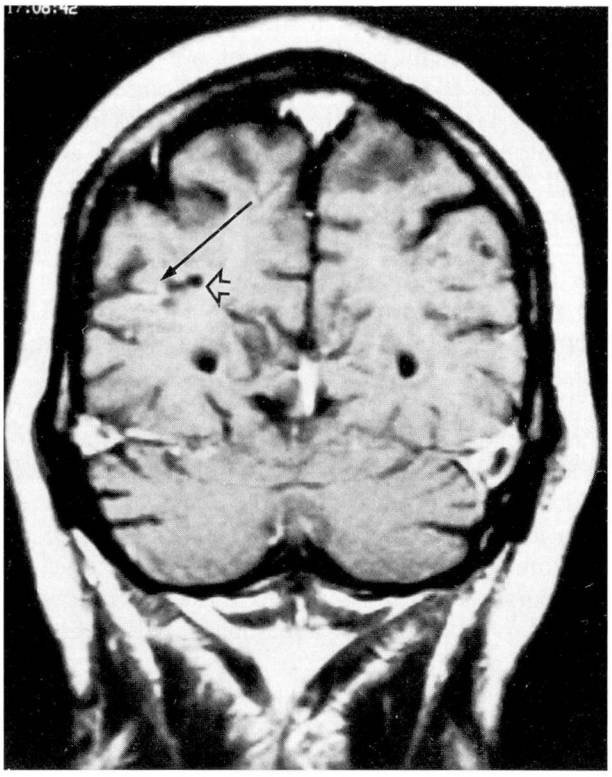

FIGURE 2. Magnetic resonance imaging study (coronal view) showing right parietal infarct.

any mass lesions or lymphadenopathy. The left lower quadrant was also benign in appearance. The CT scan of the chest was unremarkable except for the postthoracotomy changes, as described above.

I do not have the CT scan of the brain, but a magnetic resonance imaging (MRI) study was performed and is available. On the lower cuts, one can appreciate flow void indicative of patent large vessels, ie, both carotid siphons as well as the basilar artery. On some of the high cuts, particularly through the right parietal lobe, one can appreciate a cortical defect indicating a small cortical infarct. Again, on some of the higher cuts on the left side, we also observed small punctate foci of high signal intensity suggestive of lacunar infarcts (*Figure 1*). T1-weighted sagittal MRI scans through the right parietal lobe again indicated a small infarct; coronal views in the same region verify this (*Figure 2*). Following gadolinium injection, there was a faint suggestion of enhancement. No new infarcts or evidence of recent or remote hemorrhage was observed. Some of the specialized T1-weighted MRI studies showed multiple small focal defects in the region of the posterior limb of the right internal capsule and thalamus, likewise suggesting small lacunar infarcts. This is an unusual combination, in that we have both cortical disease, suggesting a thromboembolic event, and small-vessel disease, as indicated by the small lacunar infarcts. The patient had a previous MRI study in 1987; these areas of multiple infarcts were not visualized on that previous study.

DIFFERENTIAL DIAGNOSIS

DR. MAYER: The patient is a 51-year-old man who has had at least four strokes, seizures, and recurrent warm tender red streaks in the legs for at least 2 years. He has had left lower quadrant abdominal pain for 11 months since an auto accident. He underwent lung cancer resection 7 years ago, and has experienced recurrent chest pain and shortness of breath. We have no information on the cell type of his prior lung cancer, the smoking history, or family history. Physical examination was largely negative, except for mild left lower quadrant abdominal tenderness to deep palpation, and poor short-term memory.

His hemoglobin was at the upper end of normal at 16.7 g/dL. The platelet count was decreased at 108 000 per µL. The aPTT was prolonged at 41.7 seconds, but the prothrombin time was normal. The albumin level was slightly decreased at 3.3 mg/dL; the blood urea nitrogen and creatinine were slightly elevated at 32 mg/dL and 1.5 mg/dL, respectively. The urinalysis was not given. The ANA was 1:160 in a homogeneous pattern; however, the anti-DNA was normal, and the ENA negative. The sedimentation rate and C-reactive protein were normal.

The CT scan of the head and the MRI showed remote infarcts; the faint enhancement on the postgadolinium MRI is of unclear significance. The CT of the chest was negative, with no evidence of metastatic or recurrent cancer, and the CT of the abdomen and pelvis was also unremarkable. The echocardiogram and carotid duplex ultrasonogram were normal. Venous duplex ultrasound of the legs was negative, although this test is less sensitive for distal than for proximal thrombosis. The electromyogram was negative except for the remote lumbar radiculopathy. EEG showed nonspecific changes.

Hypercoagulable states

Tying together four or more strokes (presumably starting in the patient's 40s) and recurrent warm tender red streaks in the legs is best done by evoking a hypercoagulable state, preferably one that can cause both arterial and venous thrombosis. We do not have evidence of an atrial septal defect with a shunt, so we cannot interpret the arterial episodes as paradoxical emboli.

Factors predisposing to thrombosis and thromboembolism include obesity, varicose veins, trauma, general anesthesia, malignancy, congestive heart failure, blood protein defects, oral contraceptives, infection, surgery, pregnancy, immobility, and nephrotic syndrome.[1]

The patient was not obese. He had no venous abnormalities. We were not told of infection, surgery, anesthesia, congestive heart failure, or immobility. He was in an auto accident, but this occurred 11 months before he presented and postdated many of the thrombotic events. There is no evidence of nephrotic syndrome but it will be discussed briefly, as we do not have a urinalysis. Blood protein defects are a strong possibility and will be explored.

Several congenital blood protein defects are associated with hypercoagulability, including antithrombin-III (AT-III) deficiency, protein C deficiency, protein S deficiency, heparin cofactor II deficiency, plasminogen deficiency, dysfibrinogenemia, plasminogen activator deficiency, and Hageman factor (coagulation factor XII) deficiency. The first three of these are the most common.[1]

Many of the same protein defects can also be acquired. In addition, antiphospholipid antibodies including anticardiolipin antibodies and the lupus anticoagulant may be seen. Plasminogen deficiency and the presence of fibrolytic inhibitors and fibrinolytic activator inhibitors can also be acquired.[1]

The most common acquired defects appear to be AT-III deficiency and the presence of antiphospholipid antibodies.

Congenital protein defects

To begin an overview of congenital protein defects, protein C is a vitamin K-dependent factor synthesized in the liver. Deficiency is inherited in an autosomal-dominant fashion. The primary anticoagulating effect of protein C is inactivation of factors V and VIII. Protein C must be activated by a thrombin-thrombomodulin complex on the endothelial surface. The activity of protein C is markedly enhanced by protein S. Hereditary defects of protein C lead to three distinct syndromes. The first is recurrent deep venous thrombosis and pulmonary embolus, typically starting in the second decade of life, though the range is from age 10 to age 60. The second syndrome is warfarin-induced skin necrosis. The half-life of protein C is shorter than factor X or prothrombin, so before anticoagulation by warfarin is established, a state of hypercoagulability resulting from a lack of protein C can occur; if protein C is already deficient, this may be quite severe. The third syndrome is neonatal purpura fulminans, seen in homozygous protein C-deficient patients, in whom rampant disseminated intravascular coagulopathy occurs.

Protein C assays can be functional or immunologic. Functional assays are generally preferred, because they can assess for dysfunctional protein C, as well as for an absolute lack.

Protein S is another vitamin K-dependent factor. It is made in hepatocytes and megakaryocytes, and its production is inherited in an autosomal-dominant fashion. It is a cofactor of protein C. About half exists in a free state, with the other half attached to C4-binding protein. The free protein S is the active moiety. Therefore, both quantitative and

qualitative deficiencies of protein S occur. Heterozygous patients have a strong tendency to develop deep venous thrombosis, although arterial thrombosis can occasionally be seen.

Antithrombin-III (AT-III) is an alpha-2-globulin. Autosomal dominant inheritance of AT-III deficiency is the rule, though other modes have occasionally been described. AT-III inactivates thrombin, factors X, IX, XI, and XII, protein C, and kallikrein. The most important step may be inactivation of factor X. The presence of heparin accelerates inactivation of thrombin and factor Xa by AT-III. The incidence of congenital AT-III deficiency is about 1 in 2000. A markedly increased risk of venous thrombotic events and pulmonary embolus is seen in individuals with AT-III deficiency.

Heparin cofactor II deficiency is less common. The normal effect of heparin cofactor II is inhibition of thrombin; the effect is accelerated in the presence of heparin (and dextran sulfate). Clinical manifestations can include both venous and arterial thrombosis.[2-4]

The predominant manifestations of deficiencies of protein C, protein S, AT-III, and heparin cofactor II are venous thrombosis.

There are many types of congenital dysfibrinogenemia. About 90% of these cause a bleeding diathesis, but about 10% exhibit enhanced coagulation, mostly manifested as venous thrombosis.

Congenital plasminogen deficiency is inherited as an autosomal recessive disorder. Thrombotic events usually begin in the teens, and are primarily deep venous thrombosis and pulmonary embolus.

Acquired protein defects

Among acquired protein disorders, AT-III deficiency and the presence of antiphospholipid antibodies are the most common. AT-III deficiency is seen especially in severe nephrotic syndrome. Antiphospholipid antibodies can be seen with a variety of illnesses, in which rearrangement of phospholipid surfaces probably induces antibody production, rendering patients hypercoagulable.

Inhibitors of fibrinolytic activity occur in several states. These include inflammatory disorders, the postoperative state, thrombotic thrombocytopenic purpura, and scleroderma.

Atherosclerosis

After this brief overview of blood protein defects and disorders, let me step back to see if we have any evidence of fixed atherosclerosis in this patient. We are not given the smoking history, but with a history of lung cancer, smoking, at least remotely, is a reasonable surmise. His lipid status was not given. He has no history of atherosclerotic heart disease. On physical examination, pulses were normal and the aorta was not enlarged. Carotid duplex ultrasound and echocardiography were normal. Except for possible small-vessel disease in the brain, which could have occurred from blood protein disorders, we have no evidence of atherosclerosis.

Cancer

The possibility of hypercoagulability associated with cancer should also be explored. Hypercoagulability is seen especially in adenocarcinoma and in certain leukemias. This patient had a cancer resected 7 years previously, with no evidence of recurrence. The possible faint enhancement on MRI of the brain after gadolinium injection is of unclear significance.

Several recent papers have evaluated coagulation in cancer. As mentioned before, and as demonstrated recently by Prandoni and colleagues,[5] adenocarcinoma predominates among patients presenting with thrombosis. Whether to search for cancer in the face of thrombosis is still controversial. In Prandoni's series, 17% of patients with recurrent deep venous thrombosis were found to have cancer.

In this patient, the chest pain or shortness of breath could represent recurrent emboli or thrombosis in the pulmonary circulation. If so, venous thrombosis associated with cancer could be a proximate cause.

Several etiologies of hypercoagulability in cancer have been proposed; different causes may be operant in various cases. Platelet activation, release of tissue factor, hyperfibrinogenemia and dysfibrinogenemia, tumor necrosis factor, and antiphospholipid antibodies are potential causes.[6]

Most cancer patients have a normal platelet count and aPTT. However, tumor necrosis factor infusions have been shown to decrease the platelet count.[7] Antiphospholipid antibodies are known to depress the platelet count and elevate the aPTT.[8]

Three other entities seem possible, at least briefly, when considering the differential diagnosis. One is hyperviscosity. The patient's hemoglobin was not quite high enough in and of itself, and we have no definite evidence of a paraprotein. The low serum globulin makes heavy-chain disease unlik ly; urine protein by sulfosalicylic acid would have been help-

ful to exclude excess light chains. Thrombotic thrombocytopenic purpura is another fleeting possibility. Neurologic and renal findings and thrombocytopenia were tantalizing; however, lack of anemia or fever eliminate this entity. Low-grade disseminated intravascular coagulopathy can be a difficult diagnosis to make. Coagulation tests and platelets can be normal. Increased fibrin split products may be the only abnormal laboratory finding. Clinical and laboratory features of this case make disseminated intravascular coagulopathy unlikely.

The patient's left lower quadrant pain is a problem. It is of shorter duration than the strokes or red streaks in the legs, but it could have a similar cause. Let us consider entities involving thrombosis which could yield such a picture.

Mesenteric venous thrombosis

Mesenteric venous thrombosis is the first such entity.[9] In mesenteric venous thrombosis, abdominal pain is out of proportion to physical findings. The onset of complications can be quite delayed; however, the duration of symptoms is usually weeks before catastrophe or intervention, rather than months, as in our case. Imaging with CT or MRI of the abdomen may reveal the diagnosis.

Predisposing factors include deficiencies of AT-III, protein C, or protein S. Since these primarily cause venous thrombosis, we are still confronted with how to explain the strokes.

Renal vein thrombosis

Another possibility is renal vein thrombosis (RVT). It often causes smoldering abdominal pain. RVT can be caused by nephrotic syndrome, especially nephrotic syndrome with AT-III deficiency in the setting of membranous glomerulopathy. The absence of edema makes this somewhat unlikely, but the absent urinalysis necessitates a brief discussion of RVT. If the patient's chest pain and shortness of breath represented pulmonary emboli, RVT becomes more likely, as pulmonary emboli are seen in about half of patients with RVT. Still, AT-III deficiency does not explain strokes well.

Nephrotic syndrome

Nephrotic syndrome without RVT can cause hypercoagulability.[10] Mild renal insufficiency does not preclude nephrotic syndrome. Decreased AT-III levels occur, especially if albumin is under 2.0 g/dL or if proteinuria exceeds 5 g/day. Decreased plasminogen and increased fibrinogen may also be seen in nephrotic syndrome, counterbalanced to an extent by urinary losses of factors IX, XI, and XII. Deficiencies of factors IX or XII can prolong the aPTT. Hyperaggregability of platelets can occur in nephrotic syndrome as well. The hypercoagulability in nephrotic syndrome usually causes venous thrombosis. Of all arterial thromboses reported, only a small fraction have occurred in the cerebral circulation.[11]

Lupus antibody

The explanation that ties the clinical presentation together best is an antiphospholipid antibody, particularly the lupus anticoagulant. Cerebral arteries are the most common site of arterial thrombosis with the lupus anticoagulant. Venous thrombosis can occur, with the arterial-to-venous clot ratio about 1:1. Superficial thrombophlebitis is seen in about a third of cases.[12] Seizures can result from cerebral ischemia even without a large stroke.

Recent reviews of antiphospholipid antibodies demonstrate that there are overlapping populations with the lupus anticoagulant and anticardiolipin antibodies.[8,13] Decreased platelet counts are often seen with both; however, the prolonged aPTT is a cardinal feature of the lupus anticoagulant.

"Lupus anticoagulant" is a misnomer. Association with conditions other than lupus is very common. Hypercoagulability is typical; the "anticoagulant" tag derived from the ability to inhibit phospholipid-dependent clotting, especially in the activated partial thromboplastin system.

Alterations in phospholipid create neonantigens, thought to stimulate production of antibodies. It is not entirely clear whether the lupus anticoagulant is an epiphenomenon or is in fact responsible for hypercoagulability. Mechanisms of action that have been proposed include decreases in prostacyclin production by endothelium, increased platelet activation, increased platelet consumption through various means, and inhibition of protein C function. The latter does not explain the frequent association with arterial thrombosis.

The antigen that provokes lupus anticoagulant production is thought to be phospholipid in a hexagonal configuration, seen in membrane remodeling. (Membrane phospholipid is usually in a lamellar arrangement.) The antigen may in fact be platelet phospholipid.

As mentioned before, the prolonged aPTT and the decreased platelet count are characteristic of the

lupus anticoagulant. They are usually not both seen with other causes of hypercoagulability.

The diagnostic test in our case was probably a circulating anticoagulant test to look for a lupus anticoagulant. If the aPTT is prolonged, a dilute Russell's viper venom test can be done. If prolonged, as seen in most lupus anticoagulants, platelet neutralization can be done; addition of platelets corrects the prolonged aPTT. Platelet-poor plasma does not correct the aPTT, as this does not represent a factor deficiency.

The significance of the moderately elevated ANA is unclear. The lupus anticoagulant is seen in many non-lupus situations, including cancer, infections, drugs, and the acquired immune deficiency syndrome. One drug known to induce lupus anticoagulants is phenytoin, which the patient was taking, but presumably since the first stroke and seizure.

In conclusion, given the facts of the case as presented to me, it is my opinion that this patient has a hypercoagulable state, which is responsible for multiple arterial and venous thromboses. The derangement was probably a lupus anticoagulant.

DR. MAYER'S DIAGNOSIS

Hypercoagulability due to a lupus anticoagulant, with resultant strokes and episodes of superficial thrombophlebitis.

PATHOLOGICAL DISCUSSION

DR. KOTTKE-MARCHANT: As Dr. Mayer surmised in his consideration of the differential diagnosis, the findings in this patient—arterial and venous thrombosis, an elevated aPTT, and a low platelet count—are indeed consistent with an antiphospholipid antibody. His mention of low-grade disseminated intravascular coagulopathy is also a worthy consideration, given the patient's history of lung cancer.

Determining the cause of hypercoagulability

As Dr. Mayer suspected, a hypercoagulable profile was done. There have been many studies of how to predict what, if any, acquired or congenital abnormalities of coagulation proteins might occur in patients with hypercoagulable states. It has been shown that there is no single good screening test or no specific information in patients' histories that would point to one type of protein deficiency or other. The aPTT in this case helps point to a lupus anticoagulant, but a panel of assays must be performed to exclude other causes of the hypercoagulable state. Even the family history will not necessarily point to a congenital AT-III, protein C, or protein S deficiency. Studies have shown that even a familial history of thrombosis does not make finding a congenital protein deficiency more likely.[14]

The patient's prothrombin time is 12 seconds. In our laboratory's hypercoagulable profile, the aPTT was 46.4 seconds, which is elevated. In patients with high aPTT, one must make sure they are not taking heparin. One of the most confounding factors seen in the laboratory evaluation of hypercoagulable states is that many of these patients are on anticoagulants. There is a reagent called polybrene which neutralizes heparin. If you add this reagent to a patient's plasma and the aPTT returns to normal, the sample is certainly heparinized. The presence of heparin in a sample makes it very difficult to diagnose a lupus anticoagulant. Heparin interferes with every laboratory test for antiphospholipid antibodies with the exception of anticardiolipin antibodies done by an ELISA method.

From the initial laboratory testing, we see that this patient has a high aPTT and that it is not a heparin effect, since the aPTT with polybrene is still abnormal. His fibrinogen is normal. The reptilase time is normal. The reptilase time is performed using a snake venom that can help detect dysfibrinogenemias or dysfunctional fibrinogens. The next test is a circulating anticoagulant test, a timed mixing study, to look for an immediate-acting inhibitor or a delayed-acting inhibitor. In this case, this test was positive for an immediate-acting inhibitor.

The next test is the dilute Russell's viper venom time. In this test, another snake venom is used which activates factor X followed by activation of the common pathway. The lupus anticoagulant is thought to be an antiphospholipid antibody; phospholipid is a major factor in some of the later steps in the common pathway. With a lupus anticoagulant, this test will usually be prolonged beyond 24 seconds. In this case, we did not see that. The immunoglobulin G was greater than 80 g/L for an anticardiolipin antibody, which is elevated.[15]

The other tests for the congenital anticoagulant proteins, AT-III, heparin cofactor II, protein C, protein S, and plasminogen were all normal. We also tested for homocysteine, which was elevated in this patient.

Deficiency or inhibition?

The aPTT measures abnormalities of both the intrinsic and common pathways. Mixing studies are performed to determine if there is a deficiency of a factor or an inhibitor such as a lupus anticoagulant. The patient's plasma is mixed with a normal plasma; if the aPTT is still prolonged, it suggests the presence of an inhibitor. If the aPTT returns to normal, there is probably a factor deficiency.

Inhibitors are usually endogenously produced substances or immunoglobulins. They can arise secondary to transfusions or replacement therapy in patients with hereditary bleeding disorders such as hemophilia A. They may arise de novo in patients with a previously normal hemostatic system.

Inhibitors may be an incidental finding or may be associated with hemorrhage or thrombosis; in this case, it is the inhibitor-associated thrombosis that we are interested in. We attempted to differentiate lupus anticoagulant associated with thrombosis from other types of inhibitor. Lupus anticoagulants are immediate-acting inhibitors, because of the effect on phospholipid. Specific factor inhibitors often take time to demonstrate an in vitro inhibitory effect, because of equilibrium of the inhibitor with its target factor protein.[16] A circulating anticoagulant test was performed, which is an incubated mixing study test. In this case, the test results revealed an immediate-acting inhibitor, which is consistent with a lupus anticoagulant.

As Dr. Mayer mentioned, the lupus anticoagulant interferes with phospholipid-dependent coagulation tests like the aPTT, the Russell's viper venom time, and the recalcified clotting time. It usually does not affect the prothrombin time. Lupus anticoagulants are thought to primarily interfere with the prothrombinase complex by binding to the phospholipids.

Many conditions have been associated with the lupus anticoagulant. Phenytoin, one of the drugs that the patient was taking, could be responsible.

Testing for lupus anticoagulants

Laboratory testing for lupus anticoagulants is one of the most difficult areas of coagulation testing. Experts in lupus anticoagulants recommend that testing should occur at several levels.[17,18] One level is screening, such as with the aPTT, with a reagent sensitive to the lupus anticoagulant. Another step is a specific test for an inhibitor, such as a mixing study. The final level is a lupus anticoagulant-specific test, in which the lipid is the rate-determining or deciding factor. Such lipid-sensitive tests include the dilute Russell's viper venom time and platelet neutralization test.

The dilute Russell's viper venom test, which sensitively measures the prothrombinase complex in a lipid-poor system, is used so that the lupus anticoagulant binds to the lipid and yields an abnormal, prolonged result. The platelet neutralization test works another way: platelets (with lipid membranes) are added to the patient's plasma (containing the lupus anticoagulant), and this added lipid binds the lupus anticoagulant and corrects the clotting time (aPTT).

An anticardiolipin antibody test can also be done. Not every patient who has a lupus anticoagulant will also have a positive anticardiolipin antibody. Some will demonstrate both antiphospholipid antibodies (as our patient did), but some will just have an anticardiolipin antibody, or a lupus anticoagulant.

Homocysteine

Homocysteine, which is newly studied, may be a risk factor for hypercoagulability. Homocysteine is metabolized to methionine via methionine synthase, which is vitamin B12- and folate-dependent. High homocysteine levels are seen in vitamin B12 and folate deficiency; in this patient, who had a hemoglobin of 16.7 g/dL, that is unlikely. Homocysteine can also be metabolized via transsulfuration to cystathionine by a pyridoxine-dependent pathway.

Hyperhomocystinemia due to a homozygous deficiency of the cystathionine-beta-synthase enzyme does result in thrombosis and premature vascular disease. These patients are homocystinuric and also have multiple neurologic defects and developmental anomalies. The main cause of premature death is thrombosis and vascular disease. The vascular disease and thrombosis can be both arterial and venous.

Recently, interest has increased in patients with mildly elevated homocysteine levels. These have been found to be an independent risk factor in premature coronary artery disease, (which this patient did not have), stroke, and peripheral vascular disease.[19] We have evaluated patients with high homocysteine levels but otherwise normal hypercoagulable profiles. Elevated homocysteine levels not related to vitamin B12 or folate deficiencies were observed in a substantial proportion of patients in which no other causes of increased thrombosis could

be found.[20] High homocysteine levels may lead to endothelial injury and down-regulation of thrombomodulin on endothelial cell surfaces. We do not yet know enough about mildly elevated homocysteine to tell if it caused hypercoagulability in this patient. A potential hypothesis is that the elevated homocysteine could have resulted in a hypercoagulable state, and the patient may have subsequently developed a lupus anticoagulant secondary to phenytoin therapy. He may have had two causes of hypercoagulability. I believe he had a lupus anticoagulant and that this was the most likely reason for his hypercoagulable state.

PATHOLOGICAL DIAGNOSES

Lupus anticoagulant; mild elevation of homocysteine level.

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