65-Year-Old Woman With Swelling of the Right Lower Limb

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A 65-year-old woman presented to the emergency department for evaluation of pain and swelling of her right lower extremity, which was associated with warmth and tenderness. She denied experiencing any recent long-distance travel, trauma, estrogen use, fever, chest pain, dyspnea, hemoptysis, syncope, or previous deep venous thrombosis. She had a 2-month history of increasing dysuria, urinary frequency, nocturia, urge incontinence, and intermittent vaginal bleeding. In addition, she had excreted no urine for 24 hours. The patient denied having any flank pain, hematuria, or passage of gravel in her urine. She had taken no analgesics nor been exposed to any radiologic contrast media.

The patient’s history was notable for several episodes of pyelonephritis during pregnancy, pelvic inflammatory disease, vulval papillomas (one of which demonstrated in situ carcinoma on excision 40 years previously), and gastroesophageal reflux disease. She was a long-term smoker but consumed no alcohol. There was no family history of renal disease, thromboembolism, or cancer.

On examination, the patient appeared ill and pale. Her temperature was 37.2°C, pulse rate was 80/min, blood pressure was 100/60 mm Hg with no orthostatic drop, and respirations were 20/min. She had no adenopathy, goiter, or rash. Findings on a breast examination were normal. The apex beat was not displaced, the heart sounds were normal with a soft systolic murmur at the base, and there was no pericardial friction rub. Diffuse expiratory rhonchi were detected in the chest. Her abdomen was soft, nondistended, and without tenderness or bruits. The bladder was not palpable. Her right lower limb was swollen, warm, and tender up to the mid thigh with no cords palpable.

Initial laboratory results (reference ranges shown parenthetically) were as follows: hemoglobin, 5.9 g/dl (12.0-15.5 g/dL); mean corpuscular volume, 80 fL (81.6-98.3 fL); leukocytes, 11.5 × 10⁹/L (3.5-10.5 × 10⁹/L); platelet count, 224 × 10⁹/L (150-450 × 10⁹/L); activated partial thromboplastin time, 29 seconds (21-33 seconds); sodium, 130 mEq/L (135-145 mEq/L); potassium, 5.1 mEq/L (3.6-4.8 mEq/L); calcium, 8.9 mg/dL (8.9-10.1 mg/dL); phosphorus, 7.7 mg/dL (2.5-4.5 mg/dL); urea, 193 mg/dL (6-21 mg/dL); creatinine, 14.2 mg/dL (0.6-0.9 mg/dL); bicarbonate, 14 mEq/L (22-29 mEq/L); chloride, 100 mEq/L (100-108 mEq/L); anion gap, 16 (7-15); albumin, 3.4 g/dL (3.5-5.0 g/dL); total protein, 152 g/dL (70-100 mg/dL); glucose, 152 mg/dL (70-100 mg/dL); and uric acid, 7.7 mg/dL (2.3-6.0 mg/dL).

Insertion of a catheter yielded a small amount of urine that had an osmolality of 330 mOsm/kg and protein of 82 mg/24 h, with 4 to 10 erythrocytes per high-power field with no casts. The 24-hour urinary protein level was 1.5 g. Urine culture was negative.

1. Which one of the following is the most likely cause of renal failure in this patient?
   a. Sepsis
   b. Vasculitis
   c. Chronic pyelonephritis
   d. Acute tubular necrosis
   e. Obstructive uropathy

Sepsis can result in renal failure due to hypotension, immune complex deposition, or direct kidney involvement. Often the treatment of sepsis itself can result in worsening renal function. Because our patient had no evidence of infection, sepsis is an unlikely cause of her renal failure.

One of the most worrisome complications of any vasculitic process is renal involvement due to immune complex deposition. Diseases such as systemic lupus erythematosus, Wegener granulomatosis, polyarteritis nodosa, and Goodpasture syndrome can cause acute renal failure due to a crescentic glomerulopathy. This is often associated with extrarenal manifestations such as palpable purpura and nailfold hemorrhages. Our patient had no history or signs to suggest such a process. Of importance, urinalysis showed no erythrocyte casts, the hallmark of glomerulonephritis.

Chronic pyelonephritis is a possible cause of the renal failure because of her history of recurrent pyelonephritis, suggesting at least some reflux and thus the potential for scarring. The proteinuria and dilute urine are compatible...
with this diagnosis. However, this diagnosis would not explain the anuria.

Acute tubular necrosis is the result of episodes of prolonged hypotension with decreased renal perfusion (ischemic) or exposure to substances that are toxic to the renal tubules, such as aminoglycosides, contrast media, urate, oxalate, hemoglobin, and myoglobin. Our patient had no evidence of hypotension or exposure to nephrotoxic substances.

The most likely cause of our patient’s renal failure is obstructive uropathy. Her history is suggestive of progressive outflow tract obstruction. Anuria is almost always due to obstruction, although rarely, acute cortical necrosis or necrotizing glomerulopathy can present in this manner. Oligoanuria alternating with polyuria suggests the presence of intermittent urinary tract obstruction.

At the time of admission, pelvic examination revealed a hard, irregular mass arising from the cervix and fixed to the anterior wall of the vagina. Doppler ultrasonography of the lower limbs showed extensive deep venous thrombosis of the right superficial femoral vein. Anticoagulation with intravenous unfractionated heparin was initiated.

2. Which one of the following is the least likely cause of the deep venous thrombosis in this patient?
   a. Prolonged inactivity
   b. Neoplastic syndrome
   c. Paraneoplastic hypercoagulable state
   d. Pressure on pelvic veins by lymph nodes or tumor extension
   e. Antiphospholipid antibodies

Prolonged inactivity with vascular stasis predisposes to deep venous thrombosis, although this is usually accompanied by other risk factors. Our patient had not been well and had had limited activity for several days; thus, her risk for venous thrombosis was increased.

The nephrotic syndrome is associated with a thrombophilic state because of urinary losses of antithrombin III, altered levels and activity of proteins C and S, reactive hyperfibrinogenemia, impaired fibrinolysis, and increased platelet aggregation. The syndrome can slowly progress to end-stage renal failure. Renal venous thrombosis can result in acute deterioration of renal function in patients with this syndrome. This is usually associated with hematuria. However, the 24-hour urinary protein value was only 1.5 g in our patient. Thus, the nephrotic syndrome is excluded as the cause of the clot.

Malignancy results in a prothrombotic state by several mechanisms, including elevated levels of factor VIIa and fibrinogen and expression of tissue thromboplastin by numerous cancer cells. The latter is usually associated with mucin-secreting adenocarcinomas, but there are a few reports of undifferentiated squamous cell carcinoma producing this syndrome. In addition, malignant cells produce and express the so-called cancer procoagulant, recently identified as a cysteine protease, that can directly activate factor X.

Cervical carcinoma can spread to pelvic lymph nodes along the internal iliac vessels. Enlargement of these nodes or direct tumor extension can obstruct venous return and increase the risk of thrombosis.

Antiphospholipid antibodies cause a prothrombotic state. They may or may not be associated with systemic lupus erythematosus. Thus, antiphospholipid antibodies are a possible cause of deep venous thrombosis in our patient.

During her first night in the hospital, our patient developed anterior chest pain extending to the interscapular region. This was associated with nausea, vomiting, dyspnea, and sweating. Her pulse rate was 90/min, respirations were 22/min, and oxygen saturation was 95% by pulse oximetry. The blood pressure in her right arm was 130/60 mm Hg and in her left arm was 96/60 mm Hg with a distinct delay between radial pulses. The jugular venous pressure was not elevated. Her heart sounds were unchanged with no diastolic murmur or pericardial friction rub. Expiratory rhonchi were detected in the chest, and the abdomen was unchanged. There was no tenderness on chest wall or abdominal palpation or spinal tenderness. All pulses in the lower limb were equal. There were no bruits in the axillae. A 12-lead electrocardiogram was unchanged, and findings on a portable chest radiogram were normal. Antacids provided no relief of her pain. Her activated partial thromboplastin time was 70 seconds.

3. Based on the physical findings and symptoms described, which one of the following is the most likely cause of the chest pain in this patient?
   a. Gastroesophageal reflux
   b. Pericarditis
   c. Myocardial infarction
   d. Aortic dissection
   e. Pulmonary embolism

The patient had documented gastroesophageal reflux. Usually, patients describe the pain as "burning," and it may radiate to the lateral chest wall, jaws, and arms but not usually to the back. The pain is typically relieved rapidly with antacids. Because antacids resulted in no relief, reflux is an unlikely cause of her pain.

Pericarditis is common in renal failure. The pain is retrosternal and dull and may extend to the back. It is usually increased by swallowing, deep inspiration, or recumbency. Patients feel most comfortable stooping forward. The absence of a pericardial rub and the normal
electrocardiogram make this diagnosis unlikely. The patient has risk factors for coronary artery disease, and the pain pattern is compatible with a cardiac origin. However, the electrocardiogram during pain was normal, making the diagnosis of a myocardial infarction unlikely.

In any patient with chest or back pain in conjunction with asymmetrical pulses or blood pressure, aortic dissection must be specifically excluded. The pain is usually described as crushing or tearing and tends to migrate down the back as the dissection progresses. Physical signs can also include an early diastolic murmur of aortic regurgitation, pleural effusions, pulmonary edema, and neurologic signs. Patients at risk of coronary artery disease are also at risk for dissection. Based on physical findings, aortic dissection is the most likely cause of our patient’s pain.

Although pulmonary embolism is always a consideration in a patient with deep venous thrombosis, this would not explain our patient’s unequal pulses. In addition, her oxygen saturation had not changed since admission, and anticoagulation was adequate; thus, an initial diagnosis of pulmonary embolism is less likely.

Urgent transesophageal echocardiography showed no evidence of dissection. Serial electrocardiograms and cardiac enzymes ruled out myocardial infarction. Subsequently, a left subclavian artery stenosis found by ultrasonography explained the unequal blood pressure readings. Pulmonary angiography was not performed because of her renal failure, and a ventilation-perfusion scan was considered inappropriate in view of her smoking history. In light of the circumstances, the chest pain was most likely due to a pulmonary embolus, and an inferior vena caval filter was placed.

4. Which one of the following investigations is least likely to help in assessing this patient’s obstructive uropathy?
   a. Intravenous pyelography
   b. Cystoscopy
   c. Ultrasonography
   d. Computed tomography of the abdomen and pelvis
   e. Cancer antigen 125

Intravenous pyelography can demonstrate cortical scarring, which could suggest chronic pyelonephritis, hydronephrosis, and filling defects that could be due to blood clots, tumor, or stones. However, it cannot define the nature of any mass causing extrinsic compression on the ureters or bladder.

Cystoscopy is a procedure with both diagnostic and therapeutic potential. It allows direct visualization of the lower urinary tract and retrograde cannulation of the ureters. Biopsy of mucosal abnormalities is possible, and stents can be placed to relieve obstruction.

Ultrasonography is noninvasive and can quickly confirm the presence of obstruction. It can also give a good estimate of renal cortical size and detect major scarring. Depending on user expertise, ultrasonography can demonstrate the cause of any obstruction. In addition, if hydronephrosis is found, percutaneous nephrostomy tubes can be placed to decompress the kidneys and salvage function. It may give false-negative results if the patient is dehydrated or if there has been insufficient time for dilatation to occur.

Computed tomography of the abdomen and pelvis provides good visualization of the renal cortex, supplies evidence for analgesic nephropathy, and demonstrates stones. The soft tissue resolution allows tracing down the ureters to the point of obstruction and can usually define the cause of it. If a tumor is present, computed tomography provides valuable staging information.

An elevated cancer antigen 125 level is often found with ovarian tumors. However, it is not sufficiently specific to aid in diagnosis.

Computed tomography of the abdomen and pelvis showed a soft tissue mass in the region of the cervix, invading the urinary bladder at the trigone and possibly also the ureteral orifices. There was also pronounced dilatation of the pelvicaliceal system and ureters bilaterally, with some scarring in the right renal cortex. No pelvic lymph nodes were seen. Further images of the thorax showed multiple uncalcified pulmonary nodules compatible with metastatic disease.

A biopsy of the cervical mass showed invasive squamous cell carcinoma. The patient had advanced metastatic cervical carcinoma, with a poor prognosis.

5. Which one of the following is most appropriate in the further management of the patient’s renal failure?
   a. Percutaneous nephrostomy
   b. Pelvic irradiation
   c. Ureteral diversion
   d. No intervention, provide supportive care only
   e. Cystoscopy with ureteral stent placement

Percutaneous nephrostomy is a reliable way of decompressing the upper urinary tract and can be done under local anesthesia with ultrasound guidance. It provides useful renal salvage. However, long term this is inconvenient, and infection can be a problem.

Pelvic irradiation can shrink the tumor and possibly relieve the obstruction, but it can take days. Radiation also helps to control the bleeding. Ureteral diversion requires major surgery in which the ureters are dissected from the retroperitoneum and implanted into an isolated segment of ileum, draining via a cutaneous stoma. It is not indicated in a patient with metastatic cancer and a limited life expectancy.
Some experts may advocate that, in the face of metastatic carcinoma, only supportive care should be provided, and uremia should be allowed to take over slowly. This approach may be reasonable, but it is a major decision and the patient must be intimately involved after a clear discussion of all the options with the expected outcomes.

Cystoscopy with retrograde ureteral stent placement is the ideal procedure. It is minor surgery and allows internal decompression of the upper renal tract. After discussion with the patient, cystoscopy was performed. The posterior wall of the bladder was found to be completely infiltrated by tumor, and the ureteral orifices could not be seen; thus, retrograde ureteral stents could not be inserted. As a second best option, a percutaneous nephrostomy tube was inserted into the left kidney, and the creatinine level decreased to 1.7 mg/dL. Radiation, 30 Gy, was given to the pelvis with good control of the bleeding. Since then, the patient’s hemoglobin concentration has normalized with no transfusion. She was dismissed with the nephrostomy tube in place and was to be followed up as an outpatient.

DISCUSSION

Despite the introduction of effective screening techniques, invasive cervical cancer is still common, with an estimated 13,700 new cases leading to 4900 deaths in 1998. Risk factors include intercourse at a young age, multiple sexual partners, multiparity, low socioeconomic status, and cigarette smoking. The human papillomavirus is intimately involved in pathogenesis, with types 16, 18, 31, and 33 being found often in preinvasive and invasive cervical lesions. Expression of ras and c-myc oncogenes increases the risk of nodal and metastatic spread.

Initially, the tumor invades locally into the upper vagina and cardinal and ureterosacral ligaments. Extension into the parametrium can result in obstruction of 1 or both ureters. Anterior spread invades the bladder with a risk of vesicovaginal fistula formation (especially after surgery or irradiation). Posterior extension results in rectal invasion. Hydronephrosis and uremia are common end-stage features. Intrapерitoneal spread can also occur. Lymphatic spread initially involves the pelvic lymph nodes with later extension into the para-aortic group. With advanced disease, supraclavicular adenopathy can be found. Pelvic lymph node obstruction can result in lymphedema and metastatic spread to the groin and the external genitalia.

Most women with cervical cancer present with vaginal bleeding, including menorrhagia or intermenstrual or post-coital bleeding, or vaginal discharge. Pelvic pain, urinary frequency, and hematuria are unusual, and it is rare for a patient to present with uremia, leg swelling, or evidence of disseminated disease. Computed tomography may be used to define spread of disease, although it may not detect lymph nodes smaller than 2 cm in diameter. Clinical staging is best done with the patient under anesthesia, usually at the time of cystoscopy or sigmoidoscopy.

Management depends on the stage. Our patient has stage IV disease. For stage IB to IIA (local disease without parametrial invasion), radical hysterectomy can result in a 5-year survival rate of 90%. If the local lesion is more than 4 cm in diameter, there is microscopic infiltration of the parametrium, or there is lymph node involvement, adjuvant radiotherapy or chemotherapy may be given. Stages IIB to IV (locally advanced to metastatic disease) are treated by a combination of surgery, radiation, and chemotherapy. Induction chemotherapy can result in tumor bulk reduction before radiation therapy or radical hysterectomy. Response rates to chemotherapy vary from 35% to 85%. For stage IIB and III, radiotherapy can result in a 5-year survival rate of 65% and 45%, respectively. Cure of disseminated disease is rare.

REFERENCES


Correct answers: 1. e, 2. b, 3. d, 4. e, 5. e