

## CLINICAL VISTAS

## An elderly man with fever and hypodense lesions in the spleen and liver

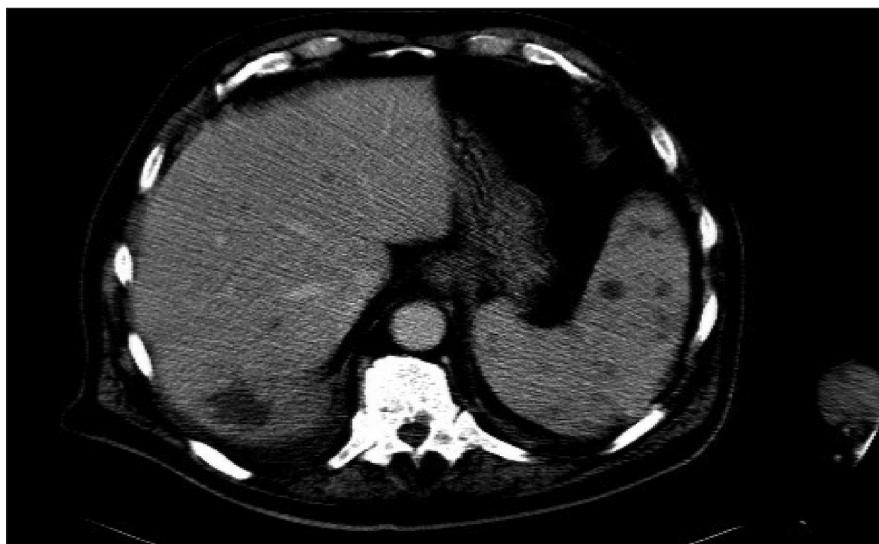


Fig. 1: CT scan showing hypodense lesions in spleen and liver.

An 82-year-old man with a history of hypertension and prostatectomy for benign hypertrophy was admitted with left flank pain of sudden onset. He had no bowel or bladder symptoms, and findings on physical examination were normal. Results of laboratory tests revealed the following elevated values: erythrocyte sedimentation rate 32 (normal < 20) mm/h, C-reactive protein level 124 (normal < 6) mg/dL, leukocyte count  $18.8$  (normal  $5-10$ )  $\times 10^9/L$ , serum calcium level 2.72 (normal < 2.58) mmol/L, and  $\gamma$ -glutamyl transferase (GGT) level 77 (normal < 50) U/L. His serum albumin level, renal function, other liver function test results and chest radiograph were normal.

Prolonged fever ( $> 38.3^\circ C$ ), lassitude, anorexia and weight loss ( $> 10\%$  of body weight) developed over the following 4 weeks, with neither localizing symptoms nor abnormal findings on examination. A leukemoid reaction developed: the patient's leukocyte count was  $64.3 \times 10^9/L$ , with a marked left shift and mild monocytosis (neutrophils 67%, bands 18%, lymphocytes 2%, monocytes 13%), but otherwise the

blood smear was normal. His alkaline phosphatase level rose to 525 (normal < 126) IU/L and GGT level to 620 U/L, with normal bilirubin and aminotransferase levels. His serum calcium level increased to 3.29 mmol/L, with normal levels of serum parathyroid hormone, angiotensin-converting enzyme and vitamin D; the hypercalcemia responded to hydration and 60 mg of pamidronate.

Blood and urine cultures and lumbar puncture results were negative. Echocardiography, to rule out endocarditis, revealed normal findings. A tuberculin skin test was positive at 20 mm. Abdominal ultrasonography and CT scanning revealed multiple hypodense lesions up to 1.5 cm in size in the spleen and liver (Fig. 1). Osteolytic lesions in a few thoracic vertebrae were consistent with bone metastases or granulomatous disease, but bone marrow biopsy was inconclusive. A chest CT scan showed emphysema but no acute disease or enlarged lymph nodes. Liver biopsy showed fatty liver and non-specific granulomas and stained negative for acid-fast bacteria. With a differential diagnosis of splenic lymphoma or disseminated tuberculosis, 4 anti-

tuberculous drugs were prescribed, but with no effect. Thrombocytopenia developed, which prevented guided splenic biopsy or splenectomy.<sup>1</sup> The patient died 5 weeks after admission.

The spleen and liver showed multiple well-demarcated nodules at autopsy consisting of grey hemorrhagic tissue with areas of necrosis. Histologic examination revealed irregular vascular spaces lined by atypical pleomorphic endothelial cells showing a focal papillary pattern of proliferation as well as widespread necrotic areas and hemorrhages (Fig. 2). These findings were consistent with primary angiosarcoma of the spleen.

Primary angiosarcoma of the spleen is a highly aggressive malignant disease with a median survival of 5 months irrespective of treatment. It arises from the endothelial lining of the splenic blood vessels, and hence the malignant cells express both endothelial (e.g., CD34 and CD31) and histiocytic (e.g., CD68 and lysozyme) markers.<sup>2</sup> Men and women are affected equally, and the disease usually occurs in people over age 60 years. Common presenting symptoms include upper abdominal pain (in 66% of cases), fever, anorexia and weight loss. Splenomegaly is the most common finding (in 75%), and splenic rupture can occur. As in the case we describe, imaging is characteristic, showing masses in an enlarged spleen.<sup>3</sup> Metastatic spread is common to the liver (in 60%), causing cholestatic disease, and to the spine (in 20%),

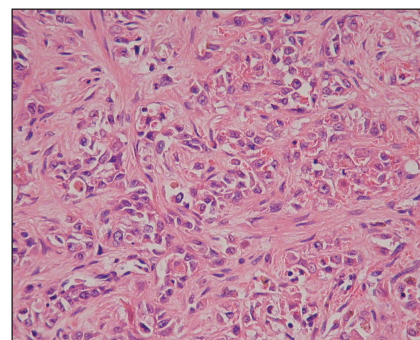


Fig. 2: Spleen tissue, showing irregular vascular spaces lined by atypical pleomorphic endothelial cells and widespread areas of necrosis and hemorrhage.

causing hypercalcemia.<sup>2,3</sup> Other laboratory abnormalities include a leukemoid reaction, possibly related to the production of granulocyte colony-stimulating factor by the tumour cells. Diagnosis can be confirmed by liver biopsy, but a “sampling error” may occur, as happened in our case. There are no current therapies of benefit, and treatment remains palliative.

**Ami Schattner**  
**Alon Bassevitch**  
 Department of Medicine  
**Judith Diment**  
 Department of Pathology  
 Kaplan Medical Centre  
 Rehovot, Israel  
 Hebrew University Hadassah  
 Medical School  
 Jerusalem, Israel

## REFERENCES

1. Kraus MD, Fleming MD, Vonderheide RH. The spleen as a diagnostic specimen: a review of 10 years' experience at two tertiary care institutions. *Cancer* 2001;91:2001-9.
2. Neuhauser TS, Derringer GA, Lester DR, et al. Splenic angiosarcoma: a clinicopathologic and immunophenotypic study of 28 cases. *Mod Pathol* 2000;13:978-87.
3. Thompson WM, Levy AD, Aguilera NS, et al. Angiosarcoma of the spleen: imaging characteristics in 12 patients. *Radiology* 2005;235:106-15.

## HEALTH AND DRUG ALERTS

## The Evra (ethinyl estradiol/norelgestromin)

## contraceptive patch: estrogen exposure concerns

**Reason for posting:** The Evra contraceptive transdermal patch is appreciated by many women for its once-a-week convenience. Recently, however, the US Food and Drug Administration (FDA) warned that women using the US version of the patch, which contains 0.75 mg of ethinyl estradiol (the patch sold in Canada contains 0.60 mg), are exposed to 60% more estrogen in a monthly cycle than women taking a typical 35- $\mu$ g oral contraceptive (www.fda.gov/cder/drug/infopage/orthoevra [accessed 2005 Dec 7]). The potential for excess estrogen exposure raises concerns about the risks of adverse effects, which include nausea, breast tenderness and venous thromboembolism.

**The drug:** The Evra patch is applied a week at a time for 3 weeks, followed by a fourth week with no patch. This delivery system is intended to avoid gastrointestinal and hepatic first-pass metabolism of the contraceptive hormones. Patch users may experience more dysmenorrhea (13.3% v. 9.6%) and breast discomfort (18.7% v. 5.8%) than users of oral contraceptives. The patch may also be less effective for women weighing more than 90 kg.<sup>1</sup>

The patch was designed to administer 20  $\mu$ g of ethinyl estradiol and 150  $\mu$ g of norelgestromin (the primary active metabolite of norgestimate, the progestin component of the oral contraceptives Cyclen and Tricyclen) daily. When a patch is first applied, the rate of drug absorption plateaus by 48 hours; a steady state is reached within 2 weeks. Absorption rates through the buttock, upper outer arm, abdomen and upper torso are considered equivalent, and absorption appears unaffected by exercise or exposure to hot or cold water.

The FDA alert focused on recent unpublished studies comparing the mean pharmacokinetic profiles of the 0.75-mg transdermal patch with a “typical” oral contraceptive containing 250  $\mu$ g of norgestimate and 35  $\mu$ g of ethinyl estradiol. The systemic exposure to ethinyl estradiol is about 60% more for users of patches than of oral contraceptives, as measured by the area under the

**Table 2:** Mean systemic exposure to ethinyl estradiol with contraceptive patch use for up to 3 consecutive cycles\*

Parameter	Cycle 3, week			
	Cycle 1, week 1	1	2	3
$C_{ss}$ , pg/mL	46.4	47.6	59.0	49.6
$AUC_{0-168}$ , pg·h/mL	6796	7160	10 054	8840

Note:  $C_{ss}$  = steady-state concentration,  $AUC_{0-168}$  = area under the curve.

\*This table is adapted from the product monograph for the Evra 0.60-mg norelgestromin-ethinyl estradiol hormonal contraceptive patch.<sup>2</sup>

curve ( $AUC_{0-168}$  57%) and steady-state concentration ( $C_{ss}$  62%; Table 1). The peak concentration of ethinyl estradiol is about 35% higher with the oral contraceptive than with the 0.75-mg patch.

The pharmacokinetics of the 0.60-mg patch are less clear (Health Canada promises a more thorough review of the matter), but in the Canadian product monograph<sup>2</sup> the week-to-week variability in the mean parameters presented appears to be considerable. For the third week of cycle 3, the exposure values (Table 2) look very similar to those for cycle 2 with the 35- $\mu$ g oral contraceptive (Table 1).

**What to do:** Users of the 0.75-mg patch may be exposed to higher doses of estrogen than users of most oral contra-

**Table 1:** Mean systemic exposure to ethinyl estradiol with a typical 35- $\mu$ g oral contraceptive v. the Evra 0.75-mg transdermal contraceptive patch

Parameter	Oral (cycle 2, day 21)	Patch (cycle 2, week 3)
$C_{ss}$ , pg/mL	49.3	80
$AUC_{0-168}$ , pg·h/mL	8281	12 971

Note:  $C_{ss}$  = steady-state concentration,  $AUC_{0-168}$  = area under the curve.

Source: US Food and Drug Administration. Proposed text of the labeling for Ortho Evra (norelgestromin/ethinyl estradiol transdermal system) [product monograph]. Available: www.fda.gov/cder/drug/infopage/orthoevra (accessed 2005 Dec 7).

## Early release

All Health and Drug Alerts are posted online ahead of print and are available at www.cmaj.ca. This article was posted on Dec. 19, 2005.