

## CONTINUING MEDICAL EDUCATION ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

### Hematology Quiz – Case 59

A 24-year-old man presented to the outpatient clinic because of pain in the lumbar spine of three months duration. The X-ray examination of the spine was unremarkable. Laboratory tests revealed mild normochromic and normocytic anemia (Ht 36%, Hb 12.0 g/dL), leukocytosis (WBC  $13 \times 10^9/L$ , differential count: neutrophils 80%, lymphocytes 6%, monocytes 8%, metamyelocytes 3%, and myelocytes 3%), and normal platelet count ( $340 \times 10^9/L$ ) (fig. 1). Serum biochemistry was as follows: BUN 0.4 g/dL, creatinine 0.8 mg/L, SGOT 20 IU/L, SGPT 25 IU/L, bilirubin 0.9 mg/dL, LDH 1.000 IU/L, alkaline phosphatase 38 IU/L and  $\gamma$ GT 32 IU/L. The ESR was 90 mm/h. Serum protein electrophoresis was normal. He was put on non-steroid antiinflammatory medication; the pain resolved.

Four months after the first symptom, the pain deteriorated, localized now only in the lumbar, but also along the left iliac crest. The patient also complained of fatigue, weakness and malaise, as well as petechiae in the extremities and abdominal area. On examination, skin and mucosal paleness, ecchymoses and hemorrhagic lesions in the whole body, were noted. There was tenderness to percussion on the lumbar spinous process and a left paraspinal mass was palpable with difficulty. On fundoscopy, retinal hemorrhages in the right eye were found. Hematological profile was as follows: Ht 24% (reticulocytes 10%), WBC  $16 \times 10^9/L$  (N=75%, L=10%, M=2%, metamyelocytes 5%, myelocytes 6%, and promyelocytes 2%; 6% of the nucleated cells were erythroblasts), platelet count  $20 \times 10^9/L$  (fig. 2) and three days later (fig. 3). Biochemistry was as follows: BUN 0.6 g/dL, creatinine 1.2 mg/

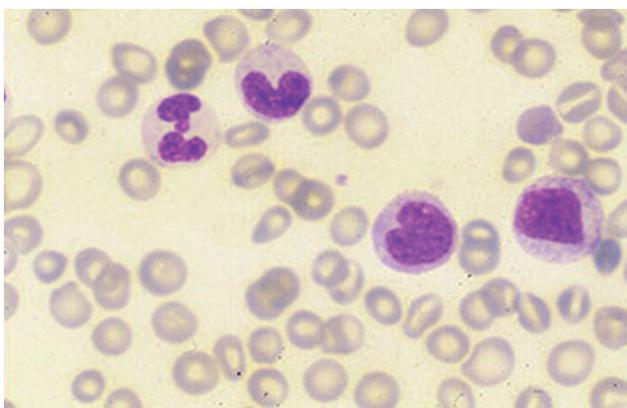


Figure 1

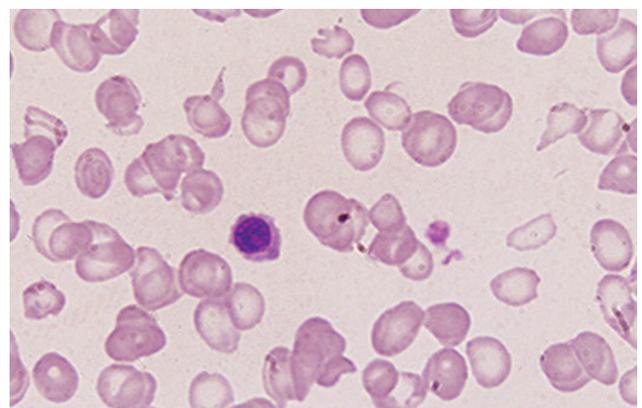


Figure 2

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2018, 35(3):428–431

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dL, SGOT 70 IU/L, SGPT 80 IU/L, bilirubin 1.3 mg/dL (direct 0.4 mg/dL), LDH 1.200 IU/L, alkaline phosphatase 380 IU/L,  $\gamma$ GT 38 IU/L, and serum electrophoresis was normal. The coagulation tests showed: PT 20 sec, APTT 52 sec, TT 40 sec. Fibrinogen was 80 mg/dL, protamine test and fibrinogen degranulation

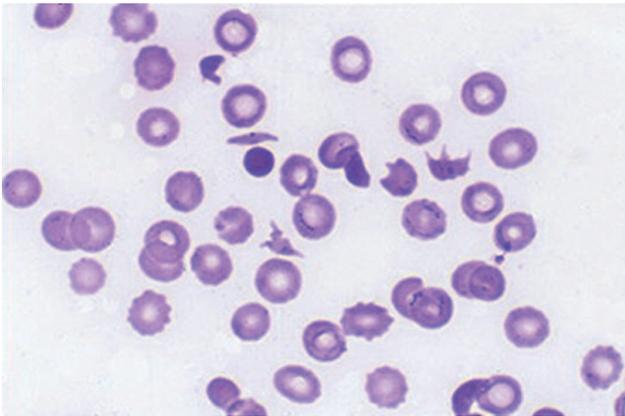


Figure 3

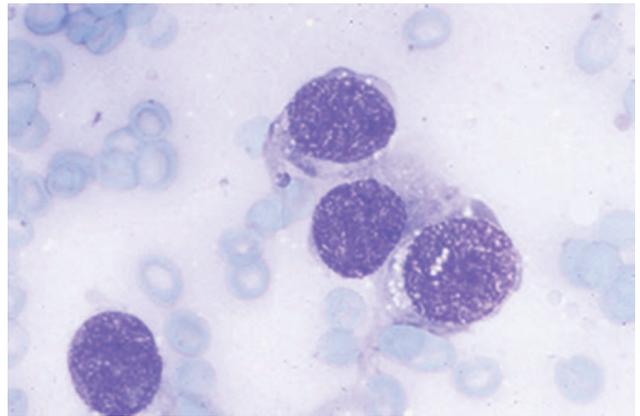


Figure 6

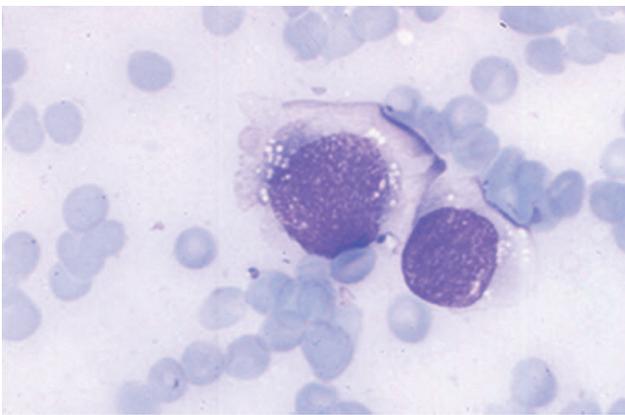


Figure 4

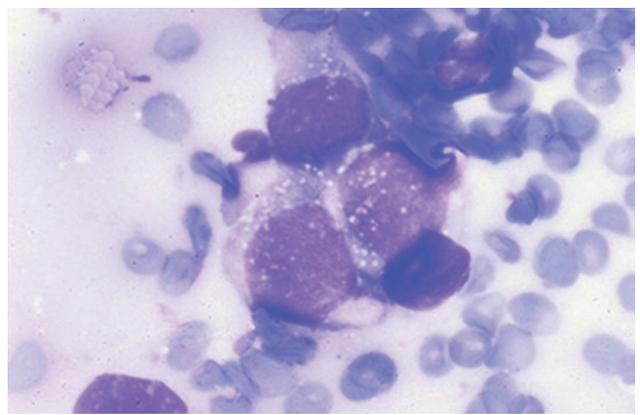


Figure 7

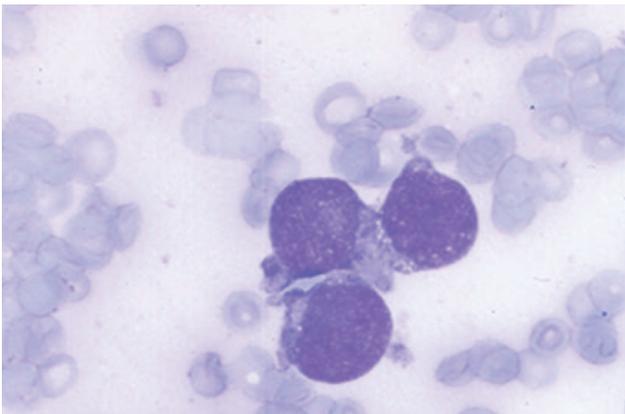


Figure 5

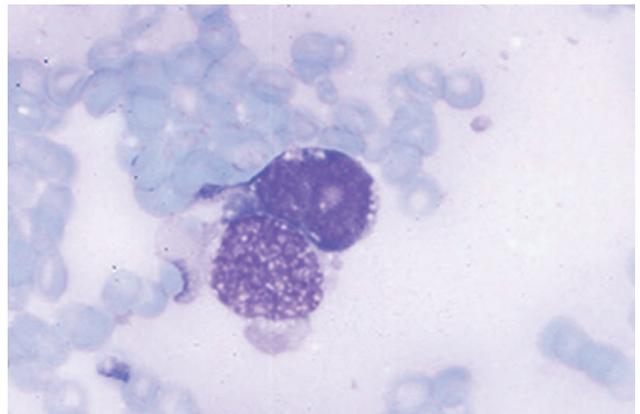


Figure 8

products (FDPs) were positive. Radiology revealed osteolytic lesion in the left iliac crest. A bone  $^{99m}\text{Tc}$  scanning showed an increased uptake by the left iliac crest. Bone marrow aspiration from the lytic lesion region revealed a marrow hyperplasia with

focal infiltration with non-hematopoietic cells (figures 4 to 8). Platelets, plasma and heparin were administered to the patient together with induction therapy for the underlying disease characterized by bone marrow trephine biopsy.

## Comment

The most frequent bone marrow metastases are derived from the lung, breast, prostate and thyroid neoplasms, while more rarely from stomach, pancreas, colon neoplasms and hypernephroma. In the bone marrow metastasis by malignant melanoma, neuroblastoma, medulloblastoma, fibrosarcoma and other rare tumors may be present. Although the majority of primary bone and muscle neoplasms are not disseminated in the long run, bone marrow metastasis can present in cases of Ewing sarcoma and rhabdomyosarcoma. In cases of spread of metastases, the presence of leukoerythroblastic reaction of the peripheral blood is characteristic. Bone marrow metastasis may be present as large or small clusters of cells often assuming a syngitral formation. Malignant epithelial cells may be of small size and of relatively unvariable morphology (lung neoplasm) or may be as large sized undifferentiated cells (breast neoplasm), containing many vacuoles (neoplasms from cells producing mucus) or containing deep colored granulation (malignant melanoma). Some neoplastic cells (microcytic lung cancer, neuroblastoma) do not appear as clusters and are not usually present as blast-like cells of different size (larger cells with fine chromatin appearance, well visible nucleoli in comparison with the blastic cells) or may be arranged as a rosette formation (neuroblastoma). The best diagnostic approach of malignant cell nature is made by using appropriate monoclonal antibodies with indirect immunofluorescence techniques or by the alkaline-anti-alkaline phosphatase technique (AP-AAP).

Disseminated intravascular coagulation (DIC) or the disorder of coagulation because of consumption it represents an abnormal manifestation of the normal coagulation mechanism. Under normal conditions the continuation of the coagulation mechanism is avoided by different mechanisms: (a) Dilution of the activated factors circulating in the blood, (b) clearance by the reticuloendothelial system (RES) of the liver of the activated coagulation factors as well as tissue thromboplastin, (c) local fibrinolysis and (d) action of the normal coagulation inhibitors: Antithrombin III, protein C and protein S. The action of these confined factors is perturbed in different abnormal situations resulting in the presence of the disseminated intravascular coagulation syndrome, the clinical presentation of which is promoted by shock (retardation of circulation and acidosis) and liver insufficiency.

In DIC the mechanism of coagulation may be activated by (a) vascular endothelium damage (e.g. toxins of gram negative microorganisms): the connective tissue of subendothelium activates the intrinsic coagulation pathway and (b) by tissue destruction (neoplasm metastasis) tissue thromboplastin is released, which activates the extrinsic coagulation pathway.

Schematically: (a) By coagulation mechanism activation, large quantities of thrombin are produced: a decrease of factors which is sensitive to thrombin action is present (factors V, VIII and I) and small fibrin thrombi are present into the vessels which enclose the platelets (thrombocytopenia) resulting in disseminated microthromboses, (b) there is a consumption of coagulation factors as well as of platelets resulting in a bleeding syndrome, and (c) this hemorrhagic syndrome is aggravated by the presence of a reactional fibrinolysis (local or generalized) and by the presence of fibrin degradation

products (PDF) presenting an anticoagulant action. The soluble fibrin complexes are an association of fibrin monomers and of its degradation or with fibrinogen. These products have an inhibitory action to fibrin formation, a fact enhancing the already existing hemorrhagic syndrome.

## Etiology

*Infections (infections releasing endotoxins: Gram positive and negative microorganisms, acute meningococcal purpura etc., and fungal infections (aspergillosis, histoplasmosis), Rickettsiae, protozoal (malaria, visceral leishmaniasis, trypanosomiasis) or viral (herpes, rubella, acute hepatitis, CMV etc.).*

*Gynecological complications: Premature placenta detachment, amniotic fluid embolism, endometrial fetal death; more rarely the leiomyomas degeneration, mole pregnancy, uremic hemolytic syndrome post-delivery, eclampsia, passage of fetal blood in maternal circulation etc. Neonatal period: ABO blood group incompatibility of mother and child, hyaloid membrane, infections.*

*Operations: Pelvis, thorax, portal-inferior vena cava anastomosis. Multiple wounds, extended burns, crush syndrome, congestive cardiac failure with pneumonic embolism, myocardial infarction, cardiac arrest, hypothermia, extracorporeal circulation, large venous thrombosis with residence of stable catheters, lipid embolism etc.*

*Giant hemangiomas, aneurysms, Takayasu arteritis, valve stenosis, large arterial grafts, cyanotic heart diseases.*

*Collagen diseases (vasculitis, glomerulonephritis, polyarteritis nodosa, rarely systemic lupus erythematosus [SLE]).*

*Acute promyelocytic leukemia (also other AML types), histiocytosis.*

*Neoplasms (lung, uterus, prostate, pancreas, ovaries etc.), metastases (carcinoid, rhabdomyosarcoma, neuroblastoma etc.).*

*Acute and chronic liver failure, acute pancreatitis.*

*Acute intravascular hemolysis (incompatible blood transfusion, drug-induced hemolysis, paroxysmal nocturnal hemoglobinuria, sickle cell anemia, snake and scorpion venoms etc.).*

*Other disorders: Amyloidosis, anaphylaxis, drug reactions, graft versus host (GVH) reaction, graft rejection, fulminant purpura, diabetic acidosis, galactic acidosis, status epilepticus, acute respiratory distress syndrome (ARDS) etc.*

**Differential diagnosis** (acute fibrinolysis, acute liver failure, sometimes the combination is possible).

## Disseminated intravascular coagulation

- Platelet numbers: Decreased
- Fibrinogen: May be decreased in all three cases
- Quick time (study of VII, X, V, II and I factors): Prolonged (decrease of II, V, VII and I factors)
- Cephalin time (study of the intrinsic pathway): Prolonged
- Thrombin time: Prolonged (decrease of factor I, PDF action)
- Prothrombin complex: (V ↓↓↓, VII+X ↓, II ↓↓, VIII ↓↓↓)
- Serum PDF: Often increased (about 40 µg)
- Soluble complexes (ethanol test): PRESENT
- Plasma euglobulins lysis time (also coagulation factors of

fibrinolytic system, less, fibrinolysis inhibitors) which shows serum fibrinolytic activity (a thrombus lysis less than 2 hours is abnormal). In DIC this is normal or slightly decreased.

#### Acute liver failure

- Platelet numbers: More or less decreased (hypersplenism)
- Fibrinogen: May be decreased
- Quick time: Prolonged
- Cephalin time: Prolonged if fibrinogen is decreased
- Thrombin time: Prolonged
- Prothrombin complex: (V not always ↓, VII+X ↓↓, II ↓↓, VIII ↓)
- Serum PDF: Often increased
- Soluble complexes: Absent
- Plasma euglobulins lysis time: Normal or shortly decreased.

#### Primary fibrinolysis

- Platelet numbers: Initially normal
- Fibrinogen: May be very decreased
- Quick time: Prolonged
- Cephalin time: Prolonged
- Thrombin time: Prolonged
- Prothrombin complex: (V ↓, VII+X normal or ↓, II normal or ↓, VIII ↓)
- Serum PDF: Very increased (more than 120 μg)
- Soluble complexes: Absent
- Plasma euglobulins lysis time (von Kaulla test): Very decreased.

#### Clinical types of disseminated intravascular coagulation

- Chronic DIC (latency, only laboratory). It is present mainly in disseminated cancer (Ca) (e.g. Ca prostate) or in liver cirrhosis which is complicated by an infection. There is not any bleeding syndrome and its detection is only in the laboratory. There is danger of progression in the acute type.

- “Covert” DIC because of fibrinogen reactional overproduction or other factors, chronic infections where the disseminated coagulation decreases but preserves the fibrinogen within normal levels or convert decrease of platelet numbers because of preexistence of a thrombocythemia
- DIC accompanied by liver failure
- DIC accompanied by acute fibrinolysis.

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