Copyright © Athens Medical Society
www.mednet.gr/archives
ARCHIVES OF HELLENIC MEDICINE: ISSN 11-05-3992

CONTINUING MEDICAL EDUCATION
ΣΥΝΕΧΙΖΟΜΕΝΗ ΙΑΤΡΙΚΗ ΕΚΠΑΙΔΕΥΣΗ

Hematology Quiz – Case 77

ARCHIVES OF HELLENIC MEDICINE 2027, 44(1):141–144
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2027, 44(1):141–144

I. Stamatiou,
I. Liapis,
C. Misidou,
S. Papadakis,
V. Sakka,
L. Inglezou,
B. Malkots,
E. Panagiotopoulos,
D. Grigoriou,
H. Suleiman,
C. Pattas,
P. Kolovos,
E. Charitaki,
V. Lampropoulou,
C. Roubakis,
M. Papoutselis,
E. Spanoudakis,
Z. Bezirgiannidou,
G. Vrachiolias,
I. Kotsianidis,
K. Liapis

Department of Hematology,
University Hospital of Alexandroupolis,
Alexandroupolis, Greece

As a part of annual screening, a 40-year-old man with a history of chronic kidney disease was found to have anemia with a hemoglobin level of 10.4 g/dL, a white-cell count of 4.2×10^9/L, a platelet count of 286×10^9/L, MCV 90 fL, reticulocyte count 1.64%, serum creatinine 3.5 mg/dL and glomerular filtration rate (GFR) 22 mL/min/1.73 m^2. He was referred to us for evaluation of anemia. One year previously, he had a serum creatinine of 1.8 mg/dL, GFR 48 mL/min/1.73m^2, and hemoglobin 12.6 g/dL, while on erythropoietin 10,000 units once-weekly. He was also noted to have high blood pressure (161/90 mmHg), mild hepatosplenomegaly without lymphadenopathy, lactate dehydrogenase 200 U/L (125–220), hyperuricemia (9.0 mg/dL), hypercalcemia (11.6 mg/dL), normal phosphorus and alkaline phosphatase, parathyroid hormone 11 pg/mL (8.7–79.6), proteinuria (2.23 g/24 hours) (<0.1 g/24hours), serum ferritin 233 ng/mL (17–204), vitamin B_{12} 900 pg/mL (170–590), and folate 3.12 ng/mL (1.5–5.5). A chest radiograph was unremarkable, but a skeletal survey revealed a small lytic lesion along the right inferior pubic ramus as well as a small lytic lesion in the right femur.

Images of the bone-marrow aspirate (figures 1–5 are stained with May-Grünwald-Giemsa stain and figures 6–8 are stained for iron with Prussian blue stain) and the bone-marrow biopsy (figures 9–11 are stained with hematoxylin and eosin) are shown.

Comment

The Prussian blue (Perl's) iron stain of the aspirate revealed plentiful storage iron (reticuloendothelial iron stores) (fig. 6), but no iron granules within the cytoplasm of red cell precursors (figures 7 and 8). This pattern is typical for anemia of chronic disorder (also referred to as anemia of inflammation and previously as anemia of defective

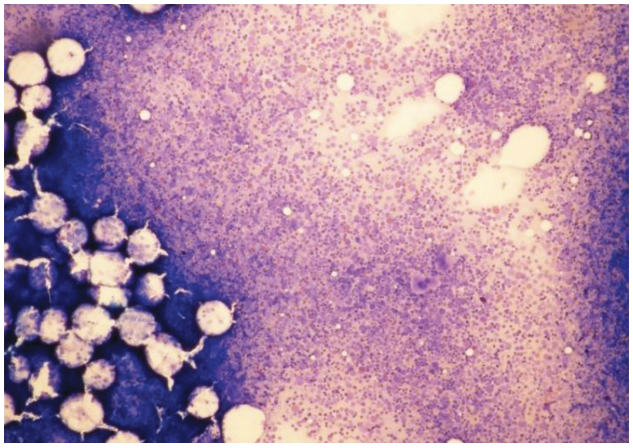


Figure 1.

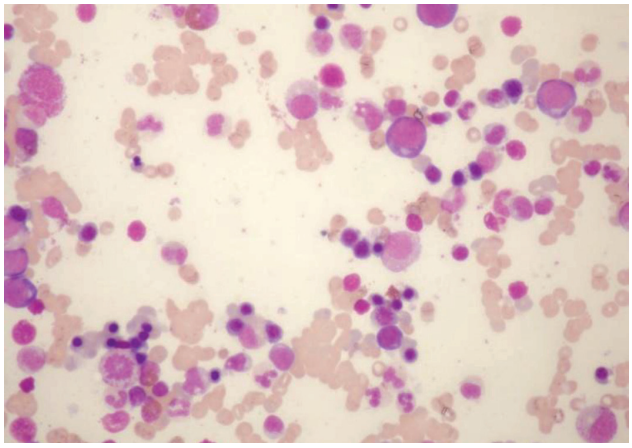


Figure 2

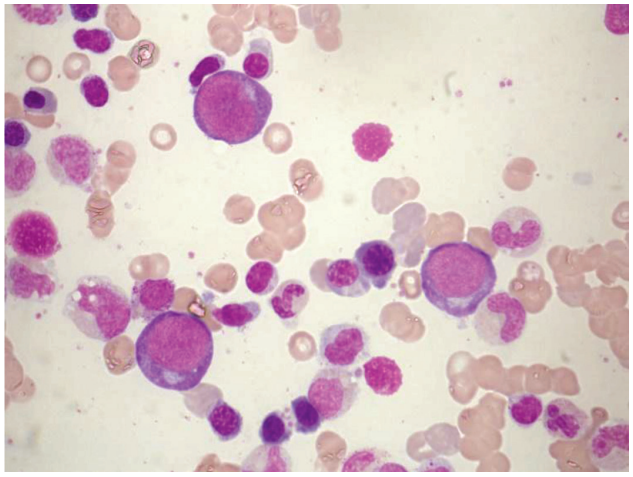


Figure 3

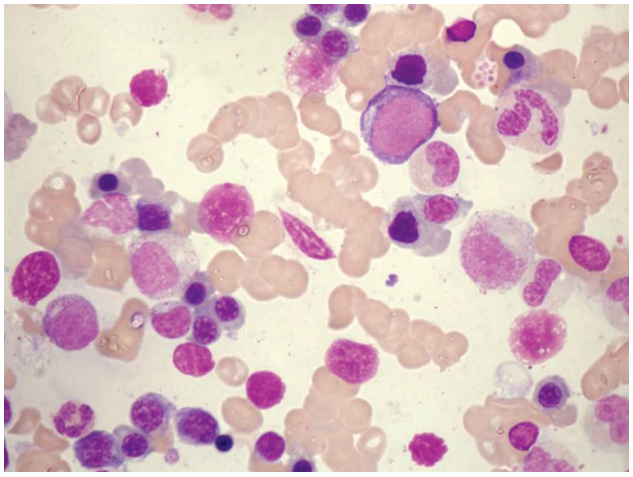


Figure 4

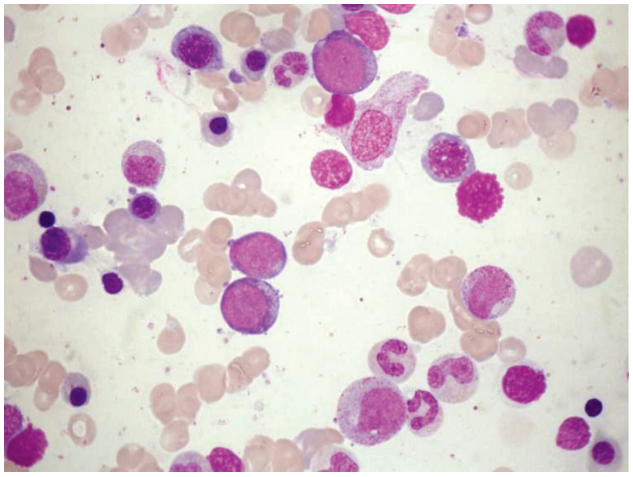


Figure 5

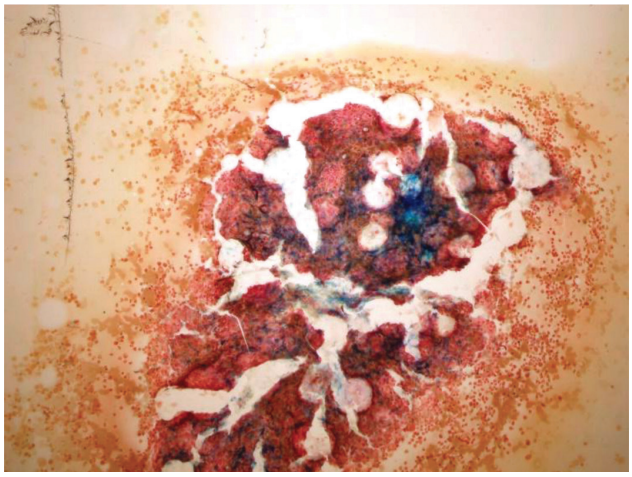


Figure 6

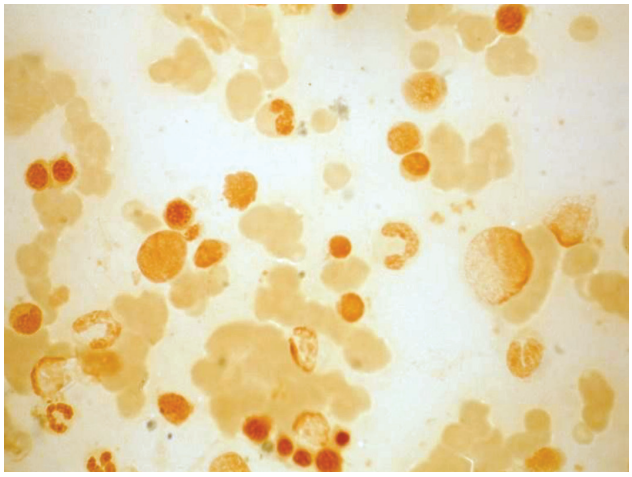


Figure 7

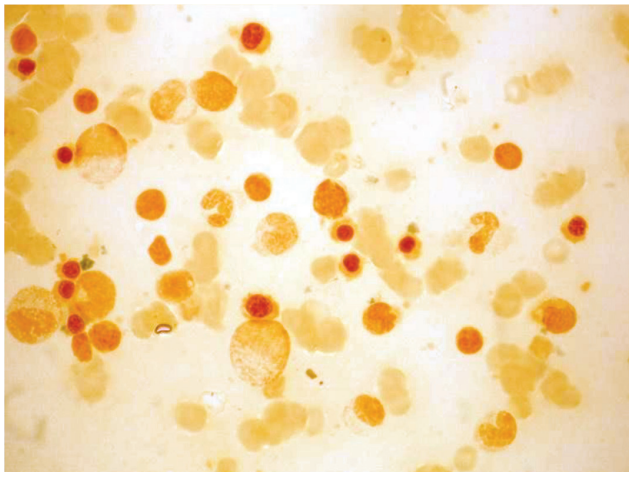


Figure 8

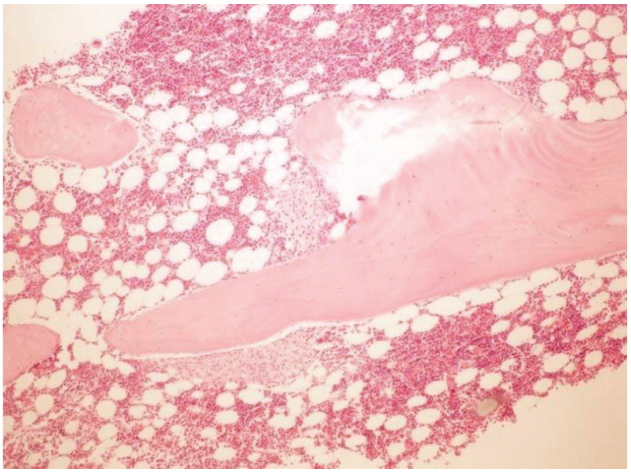


Figure 9

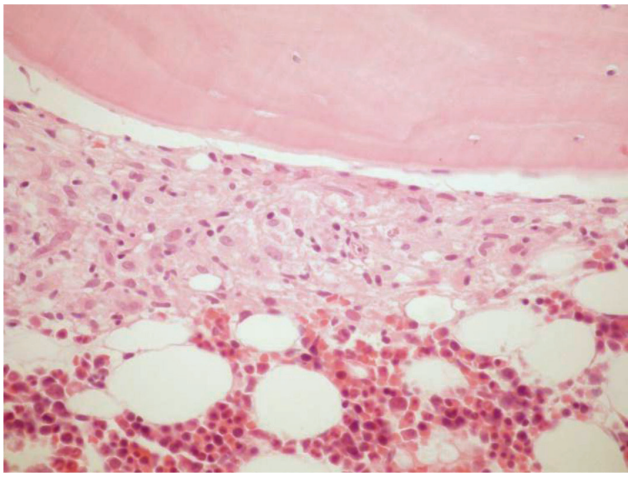


Figure 10

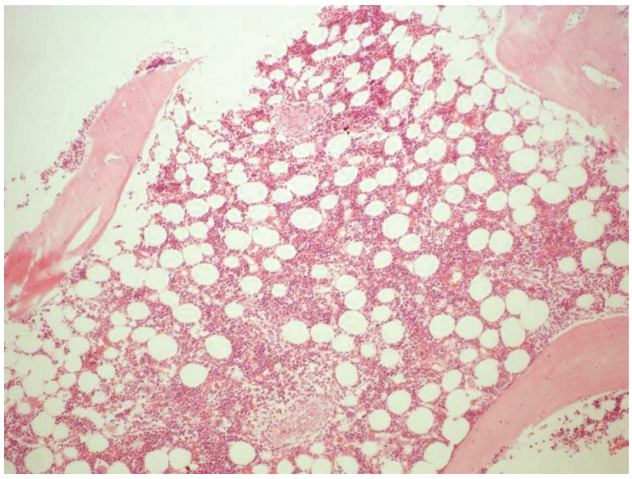
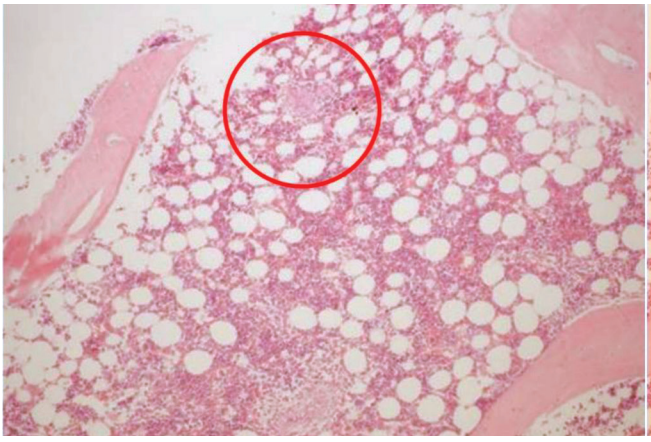


Figure 11

iron reutilization). It develops in the context of systemic inflammation because of decreased production of erythrocytes, accompanied by a modest reduction in erythrocyte survival. It is seen in patients with chronic infections, malignant disorders, and autoimmune conditions. It is the second most prevalent cause of anemia after anemia caused by iron deficiency. Anemia with chronic kidney disease shares some of the characteristics of anemia of chronic disease, but the decrease in the production of erythropoietin and the antiproliferative effects of accumulating uremic toxins are the most important causative factors. In this patent, the worsening renal function may be contributing.

In assessing bone-marrow iron stain, one should always look both at iron stores in fragments (with low or medium power objective lens i.e., ×10 or ×40) and intracellular iron (×100). Iron stores are graded according to the method by Ranch and Finch on a scale 0–6+. In practical terms, however, marrow iron stores can be classified as being: Absent, decreased, normal, or increased. Intracellular iron utilization is an important indicator of the adequacy of iron utilization within cells. Normally, 20–60% of nucleated red cells contain iron, the so-called "sideroblasts". Normal sideroblasts contain 1–4 fine iron granules randomly distributed in the cytoplasm. The iron granules ("siderotic granules") consist of ferritin aggregates.The proportion of sideroblasts usually parallels the percentage saturation of transferrin



Labelled figure 9



Labelled figure 10

(T_{SAT}). A reduced proportion of sideroblasts is seen in iron deficiency and anemia of chronic disorders; an increased proportion is seen in hemolytic anemia, megaloblastic anemia, iron overload, and thalassemia disorders.

Results of iron smear assessment may be interpreted as: (a) Normal status (normal iron stores and normal erythroblast iron); (b) functional iron deficiency (normal iron stores and deficient erythroblast iron); (c) iron stores deficiency (depleted iron stores and normal erythroblast iron); (d) both functional iron and iron stores deficiency (depleted iron stores and deficient erythroblast iron).

The bone-marrow aspirates were normocellular, with no abnormal cells seen. However, multiple small non-caseating epithelioid cell granulomas ("sarcoid-type") were identified in the bone-marrow biopsy (labelled figures 9 and 10). Ziehl-Neelsen staining was negative, and staining with periodic acid-Schiff (PAS) and Gomori's methenamine silver stain did not show fungal elements.

Additional work-up included a renal biopsy which showed non-caseating epithelioid-cell granulomas and tubulointerstitial nephritis. Serum angiotensin-converting enzyme (ACE) was 110 U/L (8–53). QuantiFERON-TB and Wright's agglutination test were negative. The patient received a diagnosis of extrapulmonary sarcoidosis in view of the bone-marrow and renal tissue granulomas, bone lytic lesions, hypercalcemia, and high levels of ACE. Bone-marrow and renal sarcoidosis is an uncommon manifestation of extrapulmonary sarcoidosis. Bone-marrow sarcoidosis may manifest as unexplained anemia due to infiltration with granulomas or anemia of chronic disorder caused by granulomatous inflammation, as in our patient. Osseous lesions may also occur in a minority of patients with sarcoidosis. When these lesions do occur, they are most frequently limited to the bones of the hands and feet, but long-bone (as in our patient), skull, and vertebral involvement have also been reported. The patient was treated with corticosteroids with normalization of serum calcium and improvement of his renal function and hemoglobin level.

Epitheliod cell granulomas are composed mainly of epithelioid cells (derived from blood monocytes), macrophages/histiocytes, and few multinucleated giant cells fuse to form giant cells. Other cells admixed in granulomas include lymphocytes, plasma cells, mast cells, and eosinophils. Histologic sections are required for diagnosis but, sometimes, it may be possible to identify granulomatous inflammation on aspirates by finding epitheliod cells. There are two main types of giant epitheliod cells: Langhans' giant cells and foreign-body giant cells. In Langhans' type of giant cell there is a horse-shoe shaped arrangement of nuclei; in the foreign type of giant cell there are many nuclei spread all over the cytoplasm.

Bone-marrow granulomas are classified into the following categories: (a) Tubercularcaseating epithelioid granulomas (well-formed or ill-formed caseating epithelioid granulomas with Langhans' giant cells and inflammatory cells are the usual features of bone marrow involvement in disseminated tuberculosis). (b) Non-caseating non-necrotic (sarcoid-type) epithelioid granulomas (they are often small in size and pratrabecular, as shown in fig. 11). (c) Lipid granulomas or lipogranulomas (they are a relatively common, nonspecific and frequently non-clinically significant finding in bone marrow sections), usually found in close proximity to sinusoids or lymphoid nodules. They contain a central lipid vacuole admixed with variable number of lymphocytes, plasma cells, and eosinophils). (d) "Doughnut" or fibrin-ring granuloma (it is a subtype of epithelioid granuloma characterized by a central fat vacuole and annular peripheral fibrinoid material. It occurs in association with infections particularly Q fever, brucellosis, and viral infections such as Epstein-Barr virus [EBV], cytomegalovirus [CMV], and hepatitis A and more rarely in patients with Hodgkin's lymphoma, peripheral T-cell lymphoma, and allopurinol-induced hepatitis). (e) Epithelioid granulomas seen in Hodgkin's lymphoma (variably-sized histiocytic and/or epithelioid granulomas with or without reticulin fibrosis may be the initial manifestation of bone-marrow involvement with Hodgkin's lymphoma; the presence of atypical Hodgkin cells or Reed-Sternberg cells in a polymorphous background leads to the correct diagnosis). (f) Histiocytic/epithelioid granulomas with erythrophagocytosis (they are seen in typhoid fever).

References

1. HUGHES DA, STUART-SMITH SE, BAIN BJ. How should stainable iron in bone marrow films be assessed? *J Clin Pathol* 2004, 57:1038–1040
2. PEÑA-GARCIA JI, SHAIKH S, BARAKOTI B, PAPAGEORGIOU C, LACASSE A. Bone marrow involvement in sarcoidosis: An elusive extrapulmonary manifestation. *J Community Hosp Intern Med Perspect* 2019, 9:150–154
3. SUGAI M, MURATA O, OIKAWA H, KATAGIRI H, MATSUMOTO A, NAGASHIMA H ET AL. A case of bone marrow involvement in sarcoidosis with crescentic glomerular lesions. *Respir Med Case Rep* 2020, 31:101202
4. BAIN BJ, CLARK DM, WILKINS BS. *Bone marrow pathology*. 4th ed. Wiley-Blackwell, London, c2011
5. ZUMLA A, JAMES DG. Granulomatous infections: Etiology and classification. *Clin Infect Dis* 1996, 23:146–158
6. BRODBECK WG, ANDERSON JM. Giant cell formation and function. *Curr Opin Hematol* 2009, 16:53–57
7. BLANCO P, VIALLARD JF, PARRENS M, MERCIÉ P, PELLEGRIN JL. Bone-marrow fibrin-ring granuloma. *Lancet* 2003, 362:1224
8. EID A, CARION W, NYSTROM JS. Differential diagnoses of bone marrow granuloma. *West J Med* 1996, 164:510–515
9. RAO DA, DELLARIPA PF. Extrapulmonary manifestations of sarcoidosis. *Rheum Dis Clin North Am* 2013, 39:277–297
10. BHARGAVA V, FARHI DC. Bone marrow granulomas: Clinicopathologic findings in 72 cases and review of the literature. *Hematol Pathol* 1988, 2:43–50
11. BRACKERS DE HUGO L, FFRENCH M, BROUSSOLLE C, SÈVE P. Granulomatous lesions in bone marrow: Clinicopathologic findings and significance in a study of 48 cases. *Eur J Intern Med* 2013, 24:468–473

Corresponding author:

C. Misidou, Department of Hematology, University Hospital of Alexandroupolis, Dragana, 681 00 Alexandroupolis, Greece
e-mail: xmisidou@yahoo.gr