Willie Sutton Strikes Again

Eli Ben-Chetrit MD[1], Ayman Abu Rmeileh MD[2], Karine Atlan MD[3] and Eldad Ben-Chetrit MD[2]

[1]Unit of Infectious Diseases, Shaare Zedek Medical Center, Jerusalem, Israel
Departments of [2]Medicine and [3]Pathology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

KEY WORDS: epithelioid granuloma, sarcoidosis, lymphoma, hypercalcemia

IMAJ 2016; 18: 756–760

A 68 year old woman presented to our Department of Medicine because of weakness and low grade fever (37.6–38°C) lasting 3 weeks. A few days previously she had noticed the appearance of ecchymosis on her right arm. Physical examination revealed normal blood pressure, clear lungs, and normal heart sound with regular rhythm. Abdominal examination disclosed splenomegaly of four fingers below the costal margin, with no hepatomegaly or peripheral lymphadenopathy. Preliminary results of complete blood count showed pancytopenia with hemoglobin 8.1 g/dl, white blood cells (WBC) 3000 mm^3 with 65% neutrophils and 95,000 platelets/mm^3.

This patient's presentation of weakness and ecchymosis is easily explained by the anemia and the relative thrombocytopenia respectively. Splenomegaly irrespective of the cause can produce neutropenia frequently in association with mild thrombocytopenia and anemia. Splenic sequestration and increased peripheral destruction are the conventional proposed mechanism. The low grade fever with the neutropenia and splenomegaly can result from an inter-current viral infection. At this point it is necessary to investigate the etiology of the splenomegaly and the associated pancytopenia and to determine whether they are linked in any way.

Further laboratory results during hospitalization showed erythrocyte sedimentation rate (ESR) 22 mm at 1 hour (normal 10–20 Westergren) and total serum protein 63 g/L with 39 g/L albumin. Kidney and liver function tests were normal. The uric acid, however, was 417 µMol/L (normal 180–380) and lactate dehydrogenase (LDH) 800 units (normal 240–480). Total bilirubin was normal as were serum electrolytes and glucose. Urine analysis was normal and Coombs' test was negative. Blood and urinary cultures were sterile. Chest radiogram was normal and abdominal ultrasound disclosed splenomegaly only. Bone marrow biopsy revealed a normocellular pattern with normal granulocytic and megakaryocytic cell series. A single epithelioid granuloma without caseation was seen among the normal hematopoietic cells [Figures 1A & B].

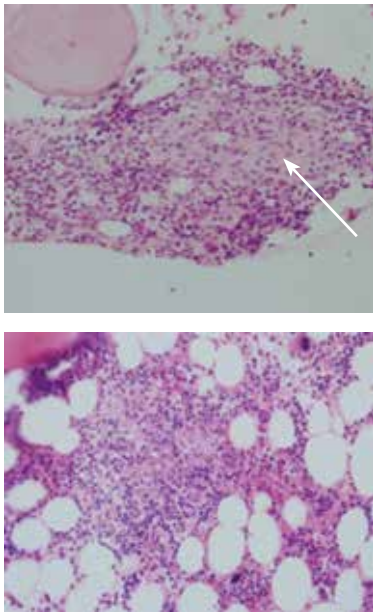

Figure 1. Bone marrow, trephine biopsy (hematoxylin&eosin x400) showing: **[A]** core of bone with normocellular trilineage hematopoiesis, and non-necrotizing sarcoid-like epithelioid granuloma (arrow), with narrow rim of small lymphocyte. **[B]** core of bone with normocellular trilineage hematopoiesis, and non-necrotizing sarcoid-like epithelioid granuloma. No malignancy is seen

The abdominal ultrasound confirmed the presence of an enlarged spleen. Splenomegaly may be the result of several primary disorders such as cirrhosis of the liver, acute or chronic infections (bacterial endocarditis, infectious mononucleosis, etc.) inflammatory diseases (sarcoidosis), connective tissue diseases (lupus, Felty's syndrome), lympho- or myeloproliferative disorders, congenital or acquired hemolytic anemias, or congenital storage diseases. Although the findings are non-diagnostic they may restrict the differential diagnosis slightly. The mildly elevated LDH and uric acid should raise the possibility of hemolysis or, alternatively, neoplastic disorders such as lymphoma. However, the presence of epithelioid granuloma seen in the bone marrow biopsy may suggest a wide range of differential diagnoses, which include viral infection (Epstein-Barr virus and cytomegalovirus), bacterial infection (tuberculosis, brucellosis or Q fever), fungal infections (histoplasmosis) following drug exposure, autoimmune diseases, or sarcoidosis.

The patient received a single blood transfusion and was discharged with a recommendation to remain under close observation through our outpatient clinic. Two months later she was rehospitalized in the Department of Medicine because of dry cough, mild dyspnea and weight loss of about 2 kg during this period. Laboratory tests revealed serum calcium 3.5 mmol/L (normal 2.15–2.55), serum creatinine 240 µMol/L (normal 58–110), and urea 14.6 mmol/L (normal 0–8.3). This time, serum LDH and uric acid were within normal limits. A second bone marrow biopsy was performed, again showing non-caseating epithelioid granulomas with no signs of malignancy.

The patient's past medical history was remarkable for ischemic heart disease with stable angina pectoris, essential hypertension, and osteoporosis, for which she had been taking aspirin, atenolol, and vitamin D, calcium and alendronate respectively.

During the second admission her main complaints were dry cough and shortness of breath – symptoms that can be related to the respiratory system. In addition, laboratory tests revealed that she also had hypercalcemia. The combination of the latter finding together with the finding of epithelioid granulomas in the bone marrow points to sarcoidosis as the diagnosis. On the other hand, the late age of disease onset is unusual for sarcoidosis (occurring mostly before age 40). The absence of any findings on chest radiograph as well as the lack of involvement of any other organs – such as liver, eyes, joints, skin or central nervous system – casts some doubt on this diagnosis but does not exclude it. Furthermore, obviously splenomegaly with hypersplenism is quite rare in sarcoidosis. Other possible causes of hypercalcemia in the present case should include hyperparathyroidism, hyperthyroidism, calcium and vitamin D excess, or malignancy. The disturbed kidney function may be attributed to hypercalcemia alone or to interstitial nephritis which characterizes renal sarcoidosis.

Splenomegaly with weight loss and respiratory complaints may point to a diagnosis of lymphoma with lung involvement. The disturbed kidney function may also be related to direct or paraneoplastic effects of the lymphoma. However, the absence of peripheral lymphadenopathy together with normal ESR and LDH may perhaps make lymphoma a less likely possibility but certainly does not exclude it as a diagnosis. Furthermore, hypercalcemia is also relatively uncommon in lymphoma. Serum electrophoresis, serum levels of alkaline phosphatase, vitamin D and parathyroid hormone will now be of considerable interest.

On physical examination the patient looked very well; she was not in stress and continued to work as a lawyer from her bedside in the hospital. The fever ranged intermittently between 37.5 and 38°C. Blood pressure was 125/70 mmHg and heart rate 84/minute. Apart from the enlarged spleen no other remarkable findings were noted. Laboratory investigation revealed ESR of 34 mm in the first hour (Westergren). Hemoglobin was 8.5 g/L, WBC 5100 with 57% neutrophils and 27% lymphocytes and platelets were 105,000/mm^3. Total protein was 62 g/L and albumin 36 g/L. Liver enzymes were also within normal limits. The calcium level was 2.91 mmol/L and phosphorous was normal, while creatinine was 219 µMol/L and serum urea 12 mmol/L. Electrophoresis of plasma and urine proteins did not show any paraprotein. Partial thrombin and prothrombin times were normal. Antinuclear antibodies (ANA) and rheumatoid factor (RF) were not detected and serum levels of C3 and C4 were normal. Antibodies against Sm, RNP, smooth muscle, mitochondria or parietal cells were not found. Urinary calcium was 12.99 mEq/24 hr (normal < 7.5 on normal calcium diet). Serum thyroid and parathyroid hormones were within normal limits. Serology for hepatitis B and C viruses, parvovirus, Epstein-Barr virus (EBV), cytomegalovirus, brucellosis and Q-fever were negative. Tuberculin test (Mantoux test) was negative as well.

The above investigations probably exclude the presence of hyperparathyroidism, hyperthyroidism or multiple myeloma. Furthermore, the probability of an infectious disease as well as the possibility of a common systemic connective tissue disorder also becomes unlikely. We now remain with symptoms of low grade fever, and findings of splenomegaly, hypersplenism and hypercalcemia in a patient who otherwise looks quite well. These data combined with the mildly elevated ESR and the above-described laboratory results do not exclude a diagnosis of a benign disease. Nevertheless, we still need more imaging data in order to exclude a malignancy, particularly lymphoma. It seems that the dry cough and shortness of breath were due to inter-current viral infection.

Further investigations yielded the following results: angiotensin-converting enzyme (ACE) activity was normal. Computerized tomography (CT) of the chest revealed non-significant fibrotic markings in the left lingular lobe. Abdominal CT confirmed the presence of a large spleen with a hyperdense upper part compared with its lower portion. Mammography disclosed a small calcified lesion in the left breast. Blood and urine cultures were once again sterile. Stomach aspirate was negative for tuberculosis on Ziehl-Neelsen staining and culture. A third bone marrow biopsy showed a normocellular picture with three normal hematopoietic cell lines. There was slight megaloblastic change in the erythroid cell series. A few epithelial granulomas with minor increase in plasma cells and moderate lymphocytosis were evident. Periodic-acid Schiff and Ziehl-Neelsen staining of the bone marrow were negative. No clear-cut histology of lymphoma was evident

despite the presence of moderate lymphocytosis together with granulomas and plasma cells.

The presence of a calcified lesion in the breast and the associated hypercalcemia may raise the need to exclude metastatic breast carcinoma. Formation of epithelioid granulomas in the bone marrow has been reported in response to micrometastases of lobular breast carcinoma, though rarely.

Still, the main differential diagnosis between sarcoidosis and lymphoma that could be isolated to the spleen remained unchanged. The absence of pulmonary involvement in the chest CT together with the normal liver function tests leads to some hesitation in making an unequivocal diagnosis of sarcoidosis. On the other hand, the patient's good general condition, the presence of hypercalcemia and the bone marrow epithelioid granulomas all support this diagnosis. For the diagnosis of lymphoma, the patient was apparently too well, had no peripheral lymphadenopathy, while three successive bone marrow biopsies failed to establish the diagnosis with confidence. In order to progress further a liver biopsy is recommended. If there are many granulomas the diagnosis of sarcoidosis will be further strengthened. If no granulomas are found a diagnostic splenectomy should be considered.

The patient firmly refused liver biopsy and requested a second opinion, which recommended splenectomy as the next step. This suggestion was readily accepted by the patient. At laparotomy, a large spleen with a small spleniculus was resected and a wedge biopsy from the liver was also taken. Pathological examination revealed that the spleen was replaced by a nodular process composed of non-caseating epithelioid granulomata with extensive infiltration of small lymphocytes [Figures 2 & 3]. In addition there was also some microscopic evidence of extramedullary hematopoiesis. The spleniculus showed the same histological picture. The liver biopsy showed only a small number of small lymphocytes in the sinusoids. The histopathological picture was clearly that of small lymphocytic lymphoma of the spleen with associated non-specific granulomata. Immunocytochemistry using anti-CD20 staining confirmed the diagnosis of a small B cell lymphocytic lymphoma [Figure 4].

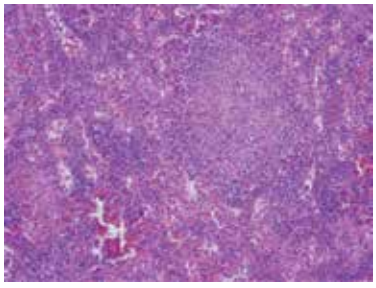

Figure 2. Biopsy of spleen (H&E x100) showing non-necrotizing sarcoid-like granuloma surrounded by a rim of small lymphocytes. Extramedullary hematopoiesis is also noted

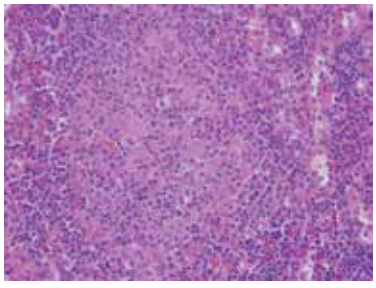

Figure 2. Biopsy of spleen (H&E x400) showing an extensive infiltration of small round lymphocytes which surround the granulomas and infiltrate the red pulp. Extramedullary hematopoiesis is seen

COMMENTARY

The patient described here illustrates the difficulties in establishing a precise diagnosis when faced with two relatively common diseases that present clinically with their uncommon manifestations. This case also poses a dilemma regarding the best approach to take in order to reach the correct diagnosis.

Sarcoidosis is a systemic disorder of unknown origin characterized by a pathological hallmark – non-caseating granuloma [1,2]. Disease manifestations can be non-specific and about 20% of patients are asymptomatic. Laboratory abnormalities are non-specific and include increased ESR, hyperglobulinemia, increased ACE activity, and occasional hypercalcemia and hypercalciuria. Histopathologically, the typical granuloma in sarcoidosis is usually compact and discrete, occasionally containing epithelioid and/or multinucleated histiocytes and separated by sclerotic collagen. Although any involved organ may be biopsied for pathological changes, transbronchial lung biopsy is positive in almost 90% of the cases with lung involvement. The bone marrow, spleen and liver are frequently involved but most have no clinical expression.

In this case the patient had no lung involvement and the ESR, globulins and ACE activity were all within normal limits. However, splenomegaly, hypercalcemia, hypercalciuria and epithilioid granulomata were found in three successive bone marrow biopsies. Therefore, the discussant was correct in raising the possible diagnosis of sarcoidosis. However, splenomegaly with hypersplenism is uncommon in sarcoidosis although it has been described in a few case reports [3,4]. A

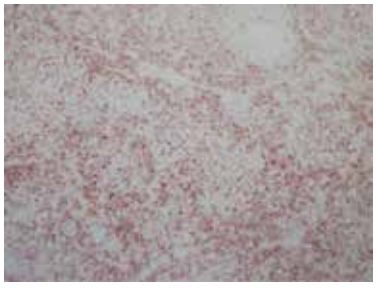

Figure 4. Biopsy of spleen (CD20 x100). Immunohistochemical staining for the B cell marker CD20 shows a moderate increase of small B lymphoid cells around and between the granulomas

basic question remains: was the suggestion to perform liver biopsy the best approach to establish the correct diagnosis?

Liver biopsy is positive in about 70% of patients with sarcoidosis. However, the finding of hepatic granulomata is not necessarily diagnostic of sarcoidosis [5]. In a study evaluating 163 patients with liver granulomas, a definite diagnosis was established in 145 cases [6]. The most common clinical diagnosis was primary biliary cirrhosis (55%, followed by sarcoidosis (18%). In addition, Crohn's disease, chronic active hepatitis, drug hypersensitivity, schistosomiasis, lymphoma and even adenocarcinoma were also found. Nonetheless, 11% of the cases (18 cases) remained idiopathic and undiagnosed. A remote diagnosis of carcinoma based on the presence of calcification in the breast in association with hypercalcemia cannot be excluded because granulomata of this type may indeed be found as a paraneoplastic phenomenon [7,8]. Thus, the mere presence of non-caseating granulomas in liver biopsy should not be interpreted as diagnostic for sarcoidosis.

It seems that the discussant was wrong in suggesting liver biopsy to reach the correct diagnosis in the present case. Indeed, it is very probable that he was biased, being so convinced that the patient had sarcoidosis. He may in fact have been looking for more granulomata in another organ (in addition to bone marrow) to confirm the diagnostic hypothesis of sarcoidosis.

Regarding the finding of hypercalcemia, although it is a rare manifestation of lymphoma it has already been described [9,10]. Increased renal calcium reabsorption is one of the mechanisms through which parathyroid hormone-related protein (PTHrP) leads to hypercalcemia. Squamous cell cancers, renal cancer, bladder cancer, breast cancer, ovarian cancer and non-Hodgkin's lymphoma account for the majority of malignancies leading to hypercalcemia via PTHrP. Thus, hypercalcemia was not necessarily a finding related only to sarcoidosis as the discussant originally thought. Nevertheless, it is of interest to mention that in the present case the true reason for the hypercalcemia was in fact an excessive intake of vitamin D and calcium to prevent osteoporosis. After stopping vitamin D ingestion and following a low calcium diet, the serum calcium normalized.

So, what would be the best procedure to establish the diagnosis in this particular case? Here perhaps we need to remind ourselves of 'Sutton's Law'. The patient's clinical presentation included low grade fever, enlarged spleen, pancytopenia and cutaneous ecchymoses. Although these symptoms and clinical signs are indeed not specific, they do suggest that the main pathology is probably in the spleen. Therefore, it follows that the next step would be to obtain a tissue sample from the spleen because "that's where the money is"! The remaining question is whether to perform a needle biopsy or a splenectomy? In a reported series, 64 fine needle aspiration biopsies (FNAB) from the spleen were performed in 58 patients with diffusely enlarged spleens [11]. Lymphoproliferative diseases were found in 6 cases (9.4%), while metastatic adenocarcinoma, sarcoidosis, *Candida albicans* and enterococcal infection were found in 4 additional single cases. The remaining 48 biopsies (82.7%) showed either normal splenic tissue or were non-diagnostic. The procedure was safe and well tolerated. In another study FNAB of the spleen was performed in 50 patients of whom 40 had had a previous diagnosis of malignancy [12]. In this study, only six specimens were non-diagnostic. Thus, it seems that FNAB of the spleen may be of value in investigating splenomegaly in patients with an established hemato-oncology disorder. In a recent study a better yield was obtained using core needle biopsy (CNB) (18–20 gauges) [13]. The biopsies were diagnostic in 93% of the cases. However, of the 97 core needle biopsies, there were 7 minor complications (pains) (7.2%) and a single major complication (hemothorax) (1.0%). The overall complication rate was 8.2% (n=8).

Another approach, laparoscopic splenic biopsy, has similar diagnostic accuracy as CNB but is more invasive, time consuming and expensive. Its main advantage over CNB is the ability to detect and treat any post-biopsy bleeding. However, laparoscopic splenic biopsy is limited with regard to the visualization of intrasplenic lesions [14].

The patient described here had thrombocytopenia, a situation that harbors a high risk of bleeding in close splenic biopsy. Therefore, in this case, splenectomy is relatively safer, has a better diagnostic yield, and can also play a therapeutic role in improving the peripheral blood count. Thus, the approach of the physician who gave a "second" opinion recommending splenectomy seems to be the correct one.

In summary, the present case illustrates the need once again to adopt Willie Sutton's law. According to this notorious bank robber, when a robber needs money he will probably "rob a bank because that's where the money is." The main findings of the patient were splenomegaly and hypersplenism. When attempting to reach a diagnosis, the physician should first consider the obvious and take a biopsy or sample from the site of the major findings.

Correspondence
Dr. E. Ben-Chetrit
Head, Rheumatology Unit, Hadassah-Hebrew University Medical Center, Jerusalem 91120, Israel
Fax: (972-2) 677-7394
email: eldad@hadassah.org.il

References

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med* 2007; 357: 2153-65.
2. Judson MA. The clinical features of sarcoidosis: a comprehensive review. *Clin Rev Allergy Immunol* 2015; 49: 63-78.
3. Ali Y, Popescu NA, Woodlock TJ. Extrapulmonary sarcoidosis: rapid spontaneous

remission of marked splenomegaly. *J Natl Med Assoc* 1996; 88: 714-16.

4. Bader-Meunier B, Fabre M, Gauthier F, et al. Sarcoidosis with hematologic involvement and hypogammaglobulinemia. *Arch Pediatr* 1996; **3**: 576-9.
5. Lagana, SM, Moreira RK, Lefkowitch JH. Hepatic granulomas: pathogenesis and differential diagnosis *Clin Liver Dis* 2010; 14: 605-17.
6. McCluggage, WG, Sloan JM. Hepatic granulomas in Northern Ireland: a thirteen year review. *Histopathology* 1994; 25: 219-28.
7. Eid A, Carion W, Nystrom JS. Differential diagnoses of bone marrow granuloma. *West J Med* 1996. 164: 510-15.
8. Kettle P, Allen DC. Bone marrow granulomas in infiltrating lobular breast cancer. *J Clin Pathol* 1997; 50: 166-8.
9. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med* 2005; 352: 373-9.
10. Akhtari M, Mansuri J, Newman KA, Guise TM, Seth P. Biology of breast cancer bone metastasis. *Cancer Biol Ther* 2008; 7: 3-9.
11. Lishner M, Lang R, Hamlet Y, et al. Fine needle aspiration biopsy in patients with diffusely enlarged spleens. *Acta Cytol* 1996; 40: 196-8.
12. Caraway NP, Fanning CV. Use of fine-needle aspiration biopsy in the evaluation of splenic lesions in a cancer center. *Diagn Cytopathol* 1997; 16: 312-16.
13. Olson MC, Atwell TD, Harmsen WS, et al. Safety and accuracy of percutaneous image-guided core biopsy of the spleen. *Am J Roentgenol* 2016; 206: 655-9.
14. McInnes MD, Kielar AZ, Macdonald DB. Percutaneous image-guided biopsy of the spleen: systematic review and meta-analysis of the complication rate and diagnostic accuracy. *Radiology* 2011; 260: 699-708.