Letter to the Editor

Sarcoidosis with Granulomatous Hepatitis and Autoimmune Endocrine Involvement

Dear Editor,

Sarcoidosis is a systemic granulomatous disease of unknown aetiology. It emerges in the form of hiler adenopathy and interstitial pulmonary disease in most cases. The lungs, eyes, skin, abdominal organs, central nerve system and bones are among the organs involved.[1,2]

Although non-caseous granulomas are detected histopathologically in the involvement of the liver in sarcoidosis, the values obtained from liver function test are generally normal. Hepatomegaly and retroperitoneal adenopathy are most frequently seen even though radiological evidence in sarcoidosis-related granulomatous hepatitis is rare.[2,3]

Sarcoidosis may also be related to endocrine autoimmune diseases. Autoimmune thyroiditis accompanying sarcoidosis has been reported in the literature; however, the combination of sarcoidosis with other autoimmune diseases is not frequent.[4,5]

Autoimmune diseases such as type 1 diabetes mellitus (DM) and Hashimoto's thyroiditis, elevation of the liver function test values and granulomatous hepatitis with hepatomegaly were observed to accompany sarcoidosis in our case. To our knowledge, no other sample cases with all these components have been reported in the literature.

A 50-year-old female patient complaining of backache and fatigue was admitted to our clinic due to elevation of liver function test values. The patient had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy 6 years prior to this presentation. She was diagnosed with type 1 diabetes mellitus 25 years ago and has had Hashimoto's thyroiditis, osteoporosis and fibromyalgia for 3 years. A high-resolution computed tomographic (CT) scan, obtained in February 2004 due to dyspnoea, revealed a ground-glass appearance in the lungs. Open lung biopsy was performed and the diagnosis of sarcoidosis was made. One-year methlyprednisolone therapy was started.

She weighed 74 kg and her height was 1.7 m. Her blood pressure was 100/80 mmHg. The thyroid gland palpated heterogeneously. Incision scars of approximately 10 cm extending from the left anterior axillary line to the posterior axillary line and a median infra-umbilical incision of approximately 15 cm were noted. The liver was palpable approximately 5 cm below the costal margin. There were numerous subdermal nodules, and the biggest of which was 1 x 1 cm in the right upper and lower extremities.

Laboratory investigations revealed the following – fasting glucose level: 228 mg/dL, total cholesterol: 279 mg/dL, triglyceride: 299 mg/dL, ALT: 37 U/L (2-40), AST: 32 U/L (2-40), ALP: 857 U/L (65-300), GGT: 232 U/L (2-50), LDH: 342 U/L (220-450), total bilirubin: 0.4 mg/dL, direct bilirubin: 0.1 mg/dL, free T3: 2.8 pg/mL (1.57-4.71), free T4: 1.5 ng/dL (0.85-1.78), TSH: 1.41 uIU/mL, anti-TG >3000 IU/mL and anti-TPO >1000 IU/mL. The complete blood count, chest x-ray and electrocardiography were within normal limits.

The patient was taking 11 units (U) insulin aspart (NovoRapid®) every morning and every afternoon, 12 U every evening and 25 U detemir (Levemir®) every night for DM and thyroxine (Levotiron®) tb 1 x 0.15 mg, etodolac (Etol Fort®) 400 mg 2 x 1, strontium ranelate (Protelos®) 2 g every day for the other diagnoses. As results of the liver function tests were elevated, the treatment of strontium ranelate (Protelos®) and etodolac (Etol Fort®) were discontinued. The hypoechoic areas and heterogenous parenchymal echo, the border of which could not be clearly distinguished in the thyroid tissues in a form to be congruent with the thyroiditis, were monitored on the thyroid ultrasonography of the patient whose thyroid auto-antibodies were positive. The thyroid biopsy of the patient performed 3 years ago was reported with a diagnosis of Hashimoto's thyroiditis. In the examination of the rise in ALP and GGT values, the viral hepatitis markers Anti-HBs, Anti-HBe and Anti-HBcIgG were positive, whereas the others were negative. Of the autoimmune hepatitis markers, ANA, AMA, LKM-1, Anti ds DNA and SMA antibodies were negative. 5' nucleotidase (19.40 U/L, N: 0-9) and ALP L_2 liver isoenzyme (% 18, N: % 1-14) values were detected as high. The craniocaudal dimension of the liver measured 19 cm. A 15-cm hyperechoic solid mass lesion, congruent with haemangioma, was detected in the lateral segment of left lobe of the liver on abdominal ultrasonography.

Liver biopsy was performed with the present findings. Granulomatous hepatitis was suspected. The biopsy revealed that granulomatous hepatitis was accompanied by light degree lobular activity without duct damage.

There are numerous pathologies that may cause granulomatous hepatitis. Hepatitis B, alcohol or chronic liver disease due to haemochromatosis, sarcoidosis, tuberculosis, neoplasms, agents of infection and medicines are among these pathologies.[6] Anderson et al[7] established sarcoidosis in 12% of patients with hepatic granuloma.

Non-caseous granulomas may cause biochemical variations in the cholestatic pattern by locating at the periportal area in the granulomatous hepatitis due to sarcoidosis.[8] Likewise, the elevation of the ALP and GGT levels, suggesting cholestatic pathology with non-caseous

granulomas, was also established in our case.

Clinical features are usually not distinct in cases of granulomatous hepatitis due to sarcoidosis. While the elevation of the liver function test values are established in 40% of the cases, it presented in only 20% of cases of hepatomegalia.[9] Likewise, an elevation of the liver function test values together with hepatomegalia was detected on abdominal ultrasonography.

Granulomas may be lost spontaneously, but they may also cause progressive fibrosis. Fibrosis was detected in 21% of the biopsies in a recent study.[10] Portal hypertension or cirrhosis which shows the involvement of only the liver and not the lung or any other organs may develop due to fibrosis. This may result in sarcoidosis and can be dangerous and life-threatening

Only patients with non-caseous granulomas in the liver involvement due to sarcoidosis are recommended to take up follow-up sessions, as in our case. Improvement in clinical picture and biochemical values established by glucocorticoid therapy were found only in a few patients with sclerosant cholangitis and primary biliary cirrhosis.[1]

There are immunoglobulins developing against numerous antigens, including the self-antigens in the circulation, together with the local cellular immune response in patients with pulmonary sarcoidosis. This also suggests that sarcoidosis may accompany autoimmune diseases.[11,12] It has been shown that it is difficult for immunoglobulins to inhibit TPO activity, and to bind to their own antigens in the healthy tissue. However, it has also been thought that TPO and TG antibodies may cause inflammation by binding to their own antigens in the target tissue on the condition of impairment of the thyroid tissue due to sarcoidosis. Consequently, the patients with positive anti-TPO and anti-TG at low titration have been supported to have a long-term follow-up due to the development of Hashimoto's thyroiditis.[13]

Papadopoulos et al[4] detected autoimmune thyroiditis in 13 (16.7%) and type 1 DM in 2 (2.6%) of 78 cases with sarcoidosis. The frequency of autoimmune thyroiditis was found to be significantly high when compared with the control group; however, no difference could be acquired when type 1 DM was compared with the control group. In another study, autoimmune thyroiditis was reported in only 2 (3.1%) of 64 Japanese cases.[12] Nakamura et al[14] reported both positive anti-TPO and anti-TG in 17 (27.4%) of 62 cases with pulmonary sarcoidosis. Hashimoto's thyroiditis was established in only 7 (11.3%) of the cases. Besides that, the positivity of anti-TPO and anti-TG was established in cases over 40 years old.

Conclusion

Sarcoidosis is likely to be as a result of an interplay of environmental and genetic factors as well as an external agent triggering a characteristic immune response in genetically susceptible individuals. Despite a recent large multicentre study, A Case-Control Etiologic Study of Sarcoidosis (ACCESS), no single causative environmental agent has been identified. It affects mostly young people, targeting primarily the lung and hilar lymph nodes. In some cases, the liver is also involved. Although the clinical features of the granulomatous hepatitis are making good progresses, it should keep in mind that in the treatment of patients with sarcoidosis, fibrosis, portal hypertension and cirrhosis may develop over time.[15] Besides that, it should not be forgotten that endocrine organs may be damaged because of the systemic involvement of sarcoidosis due to autoimmune causes. Healthcare providers should be aware of the diverse range of multi-systemic presentations. Our case is unique as there has been no article on such a combination of involvement in the literature.

REFERENCES

1. Blich M, Yeouda E. Clinical manifestations of sarcoid liver disease. J Gastroenterol Hepatol 2004;19:732-7.
2. Farman J, Ramirez G, Brunetti J, Tuvia J, Ng C, Rotterham H. Abdominal manifestations of sarcoidosis, CT appearances. Clin Imaging 1995;19:30-3.
3. Maddrey WC, Johns CJ, Boitnott JK, Iber FL Sarcoidosis and chronic hepatic disease: a clinical and pathologic study of 20 patients. Medicine (Baltimore) 1970;49:375-95.
4. Papadopoulos KI, Hörnblad Y, Lilijebladh H, Hallengren B. High frequency of endocrine autoimmunity in patients with sarcoidosis. Eur J Endocrinol 1996;134: 331-6.
5. Hancock BW, Millard LG. Sarcoidosis and thyrotoxicosis: a study of five patients. Br J Dis Chest 1976;70:129-33.
6. Cable GG. Granulomatous hepatitis due to sarcoidosis: a case report. Aviat Space Environ Med 2001;72:1141-4.
7. Anderson CS, Nicholls J, Rowland R, LaBrooy JT. Hepatic granulomas: a 15-year experience in the Royal Adelaide Hospital. Med J Aust 1988;148:71-4.
8. Ishak KG. Sarcoidosis of the liver and bile ducts. Mayo Clin Proc 1988;73:467-72.
9. Takada K, Ina Y, Noda M, Sato T, Yamamoto M, Morishita M. The clinical course and prognosis of patients with severe, moderate or mild sarcoidosis. J Clin Epidemiol 1993;46:359-66.
10. Devaney K, Goodman ZD, Epstein MS, Zimmerman HJ, Ishak KG. Hepatic sarcoidosis. Clinicopathologic features in 100 patients. Am J Surg Pathol 1993;17:1272-80.
11. Hunninghake GW, Crystal RG. Mechanisms of hypergammaglobulinemia in pulmonary sarcoidosis. Site of increased antibody production and role of T lymphocytes. J Clin Invest 1981;67:86-92.
12. Wiesenhutter CW, Sharma OP. Is sarcoidosis an autoimmune disorder?: Report of four cases and review of literature. Semin Arthritis Rheum 1979;9:124-44.
13. Chida K, Sato A, Yasuda L, Shichi I, Iwata M, Gemma H, et al. Clinical aspects of sarcoidosis with autoantibodies. Nihon Kyoshu Shikka Gakkai Zasshi 1989;27: 194-9
14. Nakamura H, Genma R, Mikami T, Kitahara A, Natsume H, Andoh S, et al. High incidence of positive autoantibodies against thyroid peroxidase and thyroglobulin in patients with sarcoidosis. Clinl Endocrinol (Oxf) 1997;46:467-72.
15. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeager H Jr, Bresnitz EA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med 2001;164:1885-9.

Ismail Hakki Kalkan,[1]*MD*, Ilkay Koca Kalkan,[2]*MD*, Dilek Tüzün,[1]*MD*, Murat Suher,[1]*MD*

[1] Internal Medicine Department, Ankara Ataturk Education and Research Hospital, Turkey

[2] Pulmonology Department, Ankara Ataturk Chest Disease and Surgery Education and Research Hospital, Turkey

Address for Correspondence: Dr Ismail Hakki Kalkan, 65 Sokak 19/8, Emek 06510, Ankara, Turkey. Email: drismailster@gmail.com