

Sarcoidosis with systemic hypertension: Case report

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SUMMARY

Sarcoidosis, which occurs often with the lung involvement and causes significant morbidity, is a multisystem granulomatous disease. This disease manifests itself with signs, and symptoms of neurological disease such as uveitis, blindness or end-stage pulmonary fibrosis, pulmonary hypertension, dysrhythmias, cardiomyopathy, hypercalcemia and renal insufficiency. However, systemic hypertension secondary to hypercalcemia is very rare.

We present a 29-year old male patient admitted to the emergency service with complaints of headache and nausea. His arterial blood pressure and calcium level were 220/110 mmHg, and 17.4 mg/dl, respectively, and histopathological evaluation after splenectomy confirmed the diagnosis of sarcoidosis.

Key words: Sarcoidosis, systemic hypertension

ÖZET

Sistemik hipertansiyon ile başvuran sarkoidoz olgusu: Olgu takdimi

Sarkoidoz, sıklıkla akciğerleri tutan ve önemli morbiditeye neden olan multisistem granülatöz bir hastalıktır. Bu hastalık nörolojik bir hastalık olarak kendini gösterebileceği gibi uveitis, körlük, son dönem pulmoner fibrosis, pulmoner hipertansiyon, disritmiler, kardiyomyopati, hiperkalsemi ve renal yetmezlik bulguları ile de karşımıza çıkabilir. Bununla birlikte, hiperkalsemiye sekonder sistemik hipertansiyon çok nadirdir.

Biz de baş ağrısı ve bulantı şikayetleriyle hastanemiz acil servisine başvuran 29 yaşındaki erkek hastanın yapılan değerlendirmelerinde arteriyel kan basıncı 220/110 mmHg ve kalsiyum 17.4 mg/dl ile splenektomi sonrası patoloji raporunda sarkoidoz saptanan olguyu sunacağız.

Anahtar kelimeler: Sarkoidoz, sistemik hipertansiyon

Diagnosis of sarcoidosis often takes time and requires detailed investigations. The time between the onset of the pulmonary symptoms and the diagnosis is at least 6 months. Thoracic involvement is detected in more than 90 % of the cases. Symmetrical hilar lymphadenopathy is the most common finding. Pulmonary hypertension is detected in 6-23 % of the patients at rest and 40 % of them during exercise. Pulmonary hypertension can be found more frequently in advanced parenchymal involvement and it worsens the prognosis.

Sarcoidosis is a multisystem inflammatory disease characterized by T-lymphocyte infiltration, granuloma formation and distortion of normal tissue

structure. Sarcoidosis which manifests well-formed non-caseous epithelioid granulomas which are induced by uncontrolled cell-mediated immune reactions (1). Immunological findings such as limited T cell receptor repertoire and expansion of oligoclonal T-cells suggest the selective activation of the immune system and acquired and innate immune responses as stereotypical factors. Serum amyloid A may play an important role in innate immune response in patients with chronic sarcoidosis (2). According to currently accepted theory, sarcoidosis is caused by the cell-mediated immune response against antigens which cannot be identified on a genetic background (3). *Mycobacteria* and *Propionibacteria* were identified as possible causal

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bacteria. In a study, mycobacterial tuberculosis catalase peroxidase protein has been identified in approximately 50 % of sarcoid tissue samples (4). Immune granulomas are comprised of a central follicle containing epithelioid histiocytes and CD4 type 1 helper T cells surrounded by fibroblasts, B cells, and CD8 T lymphocytes. Activated tissue macrophages which are the primary source of angiotensin-converting enzyme, are similar to the epithelial cells. Development of granuloma includes four phases namely initiation, accumulation, effector phase and resolution (5). Initiation phase includes macrophages and monocytes. Antigens are internalized by macrophages and presented to CD4 T cells through the MHC class II molecules (6). The interaction between macrophages and T lymphocytes is essential for the development of T cell activation and the initiation of granuloma development. In this case, CD80, CD83, CD86 and HLA-DR have an important role as co-stimulatory molecules. After that, the release of mediators by macrophages and T lymphocytes amplifies TH1 response inducing proliferation. At the final phase, cytokine produced by macrophages (such as transforming growth factor β) increases causing fibrosis (7). T cells may be activated by various mechanisms such as T cell receptor complexes, toll-like receptors and cytokine receptors. Toll-like receptors binding to bacterial and viral products produce intracellular signals by mitogen-activated protein kinases and nuclear factor-kB (NF-kB). As a result, transcription factors such as NF-kB activating protein 1 and nuclear factor of activated T lymphocytes are translocated to the nucleus and genes which encoded transcription are induced.

In sarcoidosis, TH1 lymphocytes spontaneously produce interleukin 2 (IL-2) and interferon- α (IFN- α) (8,9). While IL-2 plays a role as a growth factor for T cells, IFN- α increases helper and cytotoxic functions of T lymphocytes. IL-12 and IL-18 increase the cytotoxicity of T lymphocytes (10). In sarcoidosis granulomas, the activation and secretion of normal T lymphocytes can be increased by many cytokines (11). As a result, sarcoidosis as a

multisystem inflammatory disease caused by cellular immune response develops.

CASE REPORT

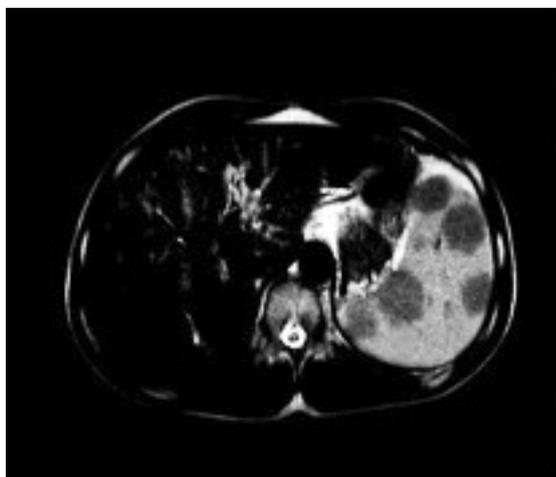
In the examination of 29-year-old male patient admitted to the emergency department with complaints of headache and nausea, arterial blood pressure was found as 220/110 mmHg. Biochemical examination was normal except creatinine level (1.68 mg/dl). Blood pressure of the patient without a known history of disease or drug use was controlled and he was admitted to internal medicine service to investigate the cause of secondary hypertension. In physical examination Traube space was closed, and he had a 10 cm palpable spleen on midclavicular line and other systems were normal. Complete blood count, biochemical parameters, thyroid function tests, parathyroid hormone, aldosterone, angiotensin converting enzyme (ACE), serum and urine metanephrin, normetanephrin, valine mandelic acid were measured. Abdominal ultrasonography showed splenomegaly (163 mm) with homogeneous parenchyma. Biochemical examination revealed hypercalcemia (calcium 17.4 mg/dL) and intravenous hydration and furosemide were initiated as an emergency treatment. Because



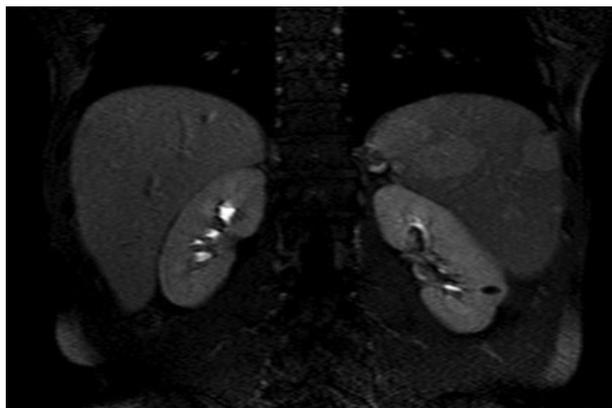
Figure 1. Chest CT in lung window demonstrated multiple paranchimal nodules. Hilar and paratracheal adenopathy is not seen, consistent with stage III sarcoidosis.



A



B



C

Figure 2.A,B,C. Magnetic Resonance Imaging (MRI) scan revealing splenomegaly, measuring 185 mm. On coronal T2 weighted and axial T2 weighted MRI numerous splenic nodules are seen hypointense on both sequences. After gadolinium injection Nodules enhances homogenously on coronal postcontrast images.

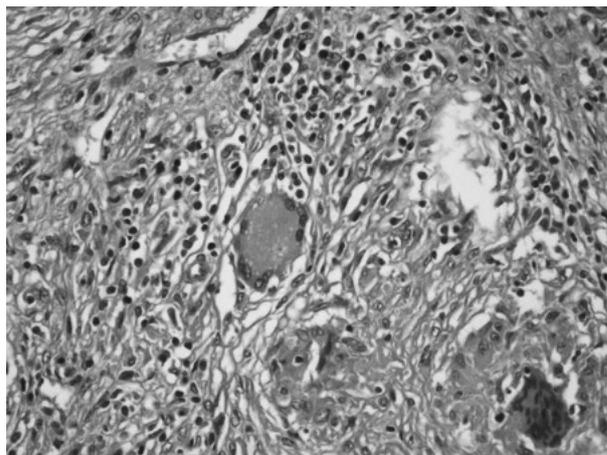


Figure 3. Asteroid body in the cytoplasm of a multinucleated giant cell in sarcoidosis (H&E x200).

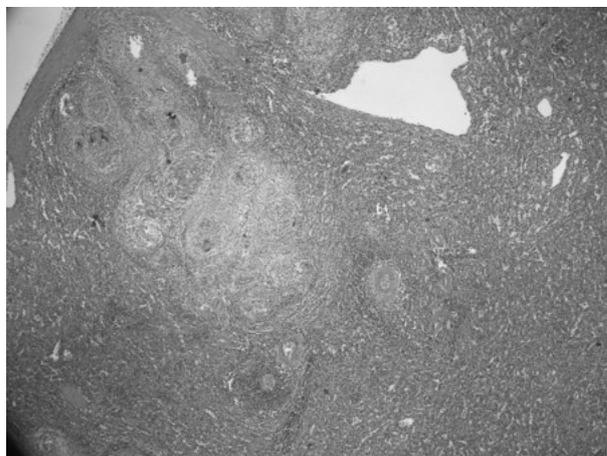


Figure 4. Numerous confluent non-necrotizing granulomas mainly composed of epithelioid cells in a splenectomy affected by sarcoidosis. (H&E x40).

no significant decrease was observed in calcium levels despite hydration and furosemide therapy, patient underwent hemodialysis with the indication of severe hypercalcemia. Then treatment of calcitonin was initiated. Calcium level and blood pressure decreased. Considering that the cause of hypertension was hypercalcemia, it was decided to investigate the etiology of hypercalcemia. Since parathyroid hormone level was low (0.1 pg/ml), primary hyperparathyroidism was excluded. After 72 hours of treatment with calcitonin, considering resistance development, zoledronic acid was administered. Thoracic CT reported small-sized lymph nodes in the anterior mediastinal fat tissue, pretracheal lymph nodes not exceeding 7 mm

short-axis, small areas of increased parenchymal density not exceeding 1 cm in diameter in the both lung fields and lymph nodes of both axillary regions the largest ones being in 10-11 mm (Figure 1). According to abdominal MRI: 1) the long axis of spleen was measured as 185 mm (splenomegaly), 2) large number of mass lesions of 2x5 cm were present sporadically in all parts of the spleen which were isodense with the spleen at T1-weighted sequences and hypointense at T2-weighted sequences, and these mass lesions showed higher contrast than the spleen in post-contrast sections, and 3) cysts in a diameter of 10 mm and 9 mm were detected, respectively in the parenchyma of the lower pole of the right kidney and in the middle-lower part of the left kidney, while a focus in a diameter of 13 mm which is clearly hyperintense compared to parenchyma at T1-weighted sequences and isodense at T2-weighted sequences, was observed in the pelvicalyceal system of the left kidney adjacent to these defined cystic structures (Figure 2). Other tests for secondary hypertension were normal except slightly higher ACE level. Diagnostic splenectomy was considered and the patient referred to general surgery clinic. Post-splenectomy histopathological diagnosis was sarcoidosis (Figure 3.4).

DISCUSSION

Sarcoidosis is a multisystem disease with a wide variety of clinical manifestations and sometimes the diagnosis takes long time. Despite the many theories are available, the etiology is not fully known. Thus, different treatment modalities and a variety of therapeutic agents have been tested. Corticosteroids remain a standard therapy despite lack of data on their long-term effects and various side effects. However, there is a need for much more effective treatment. Agents modulating CD4 TH1 lymphocytes may have positive effects. On the other hand, there is no evidence on inhibition of B cells in sarcoidosis treatment.

Methotrexate is an antimetabolite inhibiting cell-mediated immune response and it is used for the treatment of other granulomatous diseases. Although its mechanism of action is unknown, it is considered that methotrexate has both cytotoxic and anti-inflammatory by suppressing tumor necrosis factor (TNF) and increasing extracellular adenosine⁽¹²⁾. TNF which is an important cytokine in granulomatous diseases, has an impact on many cellular and subcellular levels. Therefore, selective inhibition of TNF is seen as a therapeutic strategy in this disease. For this purpose, TNF binding etanercept prevents interaction between TNF and cell surface. On the other hand, a study with etanercept showed no decrease in TNF level in serum and bronchoalveolar lavage, and lack of clinical benefit⁽¹⁸⁾. Similarly, another study demonstrated that infliximab inhibiting TNF had not any significantly different effect comparing with placebo⁽¹³⁾.

Cyclosporine is a calcineurin inhibitor, which prevents the activation of T cells, reversibly prevents IL-2 transcription, and decreases IL-6 and IFN- α synthesis. No benefit has been shown in the studies conducted with cyclosporine so far. Pentoxifylline which inhibits TNF and has an anti-inflammatory effect showed benefit in the treatment of pulmonary sarcoidosis^(14,15), and pentoxifylline also makes possible to reduce corticosteroids⁽¹⁶⁾.

Studies were initiated with statins which have immunomodulatory, and also cholesterol lowering effects⁽¹⁷⁾. Studies are being planned with phosphodiesterase 4 inhibitors which may inhibit the activation of T lymphocytes and this drug class will be tested in the treatment of sarcoidosis.

There are the reports of pulmonary hypertension caused by sarcoidosis with lung involvement. However, no report of systemic hypertension in patients with sarcoidosis was encountered in the literature. For this reason, this case was considered as worthy to report.

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