Development of interferon induced sarcoidosis in a patient with familial mediterranean fever

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ÖZET

Ailevi akdeniz ateşi olan bir hastada interferon tedavisine bağlı sarkoidoz gelişimi

Ailevi akdeniz ateşi tanısıyla kolşisin tedavisinde olan 42 yaşındaki erkek hasta, eforla nefes darlığı yakınmasıyla başvurdu. Hastanın daha önce interferon-alfa (IFN-α) kullanım öyküsü vardı. Göğüs radyografisinde her iki akciğerde difüz retikülonodüler opasiteler görüldü. Bilgisayarlı toraks tomografisinde mediastinal ve bilateral hiler lenfadenopatiler, translusent dansiteler, konsolidasyonlar, retiküler opasiteler ve subplevral milimetrik kistik alanlar mevcuttu. Solunum fonksiyon testlerinde difüzyon ve vital kapasite bozuklukları saptandı. Histopatolojik değerlendirme granülomatöz lenfadenitle uyumluydu. Hastaya pulmoner sarkoidoz tanısı kondu. Hasta, IFN'ye bağlı sarkoidozun özelliklerine sahip olmakla birlikte, IFN tedavisinin kesilmesiyle semptomların gelişimi arasında 42 ay vardır ve bu süre genel olarak beklenenden uzundur. Bu hastada IFN-α kullanım öyküsü, IFN tedavisi ve sarkoidoz gelişimi arasındaki olası birliktelik nedeniyle, sarkoidozdan şüphelenmemizi sağladı.

Anahtar Kelimeler: *Ailevi akdeniz ateşi, interferon-alfa (IFN-α), Th1 cevabı, granülom formasyonu, sarkoidoz.*

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SUMMARY

Development of interferon induced sarcoidosis in a patient with familial mediterranean fever

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A 42-year-old male patient, who had been on colchicine therapy for familial mediterranean fever admitted with dyspnea on exertion. He had a history of interferon-alpha (IFN-α) administration. The chest X-ray showed diffuse distribution of reticulonodular opacities in both lungs. A computerized tomography scan of the lungs revealed mediastinal and bilateral hilar lymphadenopathies, translucent densities, consolidations, reticular opacities and subpleural milimetric cystic spaces. Pulmonary-function studies demonstrated defects in diffusing and vital capacity. Histopathological evaluation was compatible with granulomatous lymphadenitis. The patient was diagnosed as having pulmonary sarcoidosis. He reflects the characteristics of IFN-induced sarcoidosis, but the duration between the cessation of IFN therapy and the development of symptoms is 42 months, which is longer than usually expected. In this case, history of IFN-α administration led us to suspect sarcoidosis because of a possible association between IFN therapy and the development of sarcoidosis.

Key Words: *Familial mediterranean fever, interferon-alpha (IFN-α), Th1 response, granuloma formation, sarcoidosis.*

Familial mediterranean fever (FMF) is the most common autoinflammatory disease clinically characterized by recurrent attacks of fever and polyserositis, and pathogenetically by autosomal recessive inheritance due to a mutation in the *MEFV* gene on the short arm of chromosome 16 (1). FMF primarily affects Turkish, Armenian, Arab and Jewish populations (2).

Sarcoidosis is characterized by noncaseating epithelioid granulomas that may affect any organ system. The disease most commonly involves granuloma formation in the lungs. The etiology of sarcoidosis is unknown, but several immune aberrations have been noted and are thought to play a role in its pathogenesis. Here, we report an unusual case of sarcoidosis who has been treated with the diagnosis of FMF for approximately 20 years.

CASE REPORT

A 42-year-old male patient admitted to rheumatology department with pain and swelling in his right ankle and increasing dyspnea on exertion. He had been on regular colchicine therapy (1.5 mg/day/PO) for 20 years with the diagnosis of FMF. He fulfilled the Tel-Hashomer criteria for FMF (3). Four years before admission, the patient became unresponsive to higher doses of colchicine administration (2 mg/day/PO); so, interferon-alpha (IFN-α) 3 million units, three times a week was added to this regimen. Six months later, his symptoms were resolved and acute phase response returned to normal levels. IFN administration was stopped and FMF treatment was continued with colchicine. He had been having rarely mild attacks of FMF. He had the last attack of fever and abdominal pain six months ago. The dyspnea of the patient was present for fifteen days. He denied any recent fevers, cough, or hemoptizia. He had a 5 pack-year history of tobacco use, and quit smoking one month before admission. There was no history of allergic rhinitis, asthma, nasal polyps, exposure to persons with tuberculosis or to irritant fumes, orthopnea, or paroxysmal nocturnal dyspnea. The pain and swelling in his right ankle started seven days before admission and responded to nonsteroidal anti-inflammatory drugs. Physical examination showed no abnormal findings except scattered bibasillar cracles. The chest X-ray showed a diffuse distribution of

reticulonodular opacities throughout both lungs (Figure 1). Routine laboratory tests demonstrated slight increases in C-reactive protein (CRP, 1.75 mg/dL, normal < 0.8 mg/dL), and erythrocyte sedimentation rate (ESR, 23 mm/hour, normal < 20 mm/hour). Biochemical evaluation revealed normal liver and renal function tests. Serum calcium and 24-hour urine calcium levels were also normal. A complete blood count revealed monocytosis and basophilia. The value for angiotensin-converting enzyme was 103 U per liter (normal range, 8.0 to 52.0). A computerized tomography (CT) scan of the chest revealed mediastinal and bilateral hilar lymphadenopathies. A parenchimal nodular opacity was present in the right upper lobe medially. Translucent densities, consolidations, reticular opacities and subpleural milimetric cystic spaces involved both lungs, particularly the right lung (Figure 2).

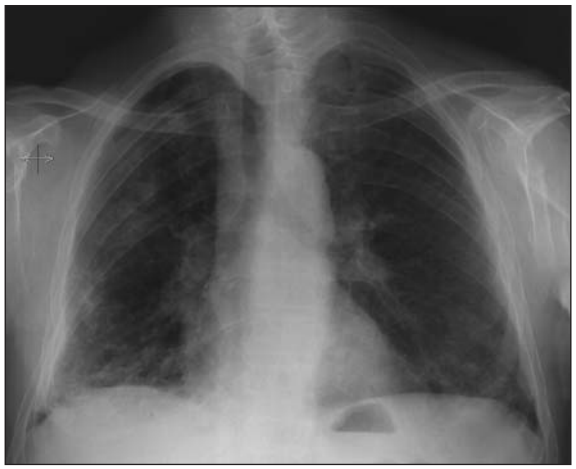

Figure 1. Posteroanterior radiograph of the chest showing bilateral diffuse distribution of reticulonodular opacities and bilateral hilar lymphadenopathy.

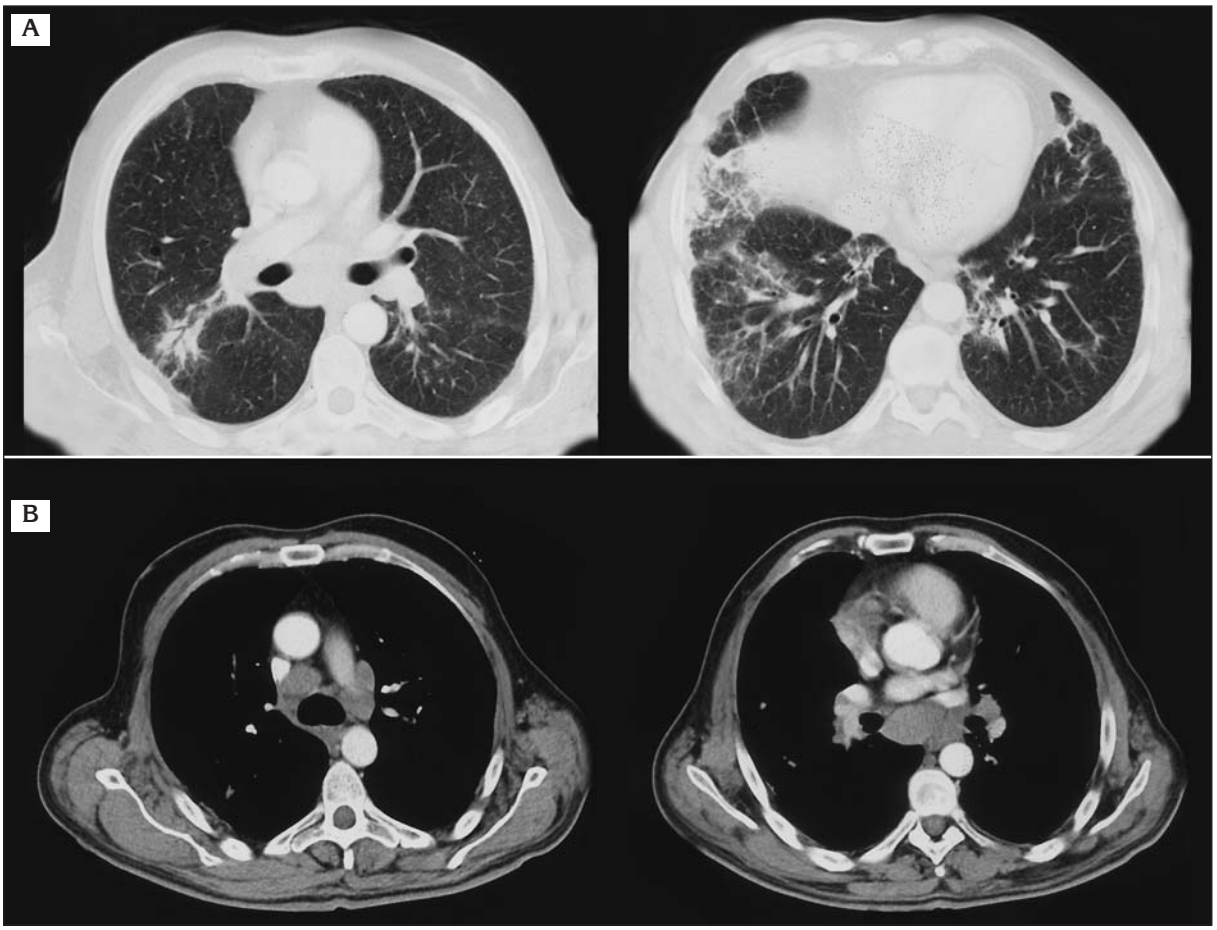

Figure 2. CT scan of the lungs demonstrating (A) translucent densities, consolidations, reticular opacities and subpleural milimetric cystic spaces in both lungs, particularly in the right and (B) mediastinal hilar and subcarinal lymphadenopathy.

Pulmonary function studies demonstrated defects both in diffusing capacity and in vital capacity. A bronchoscopy was performed; granulated appearance of the respiratory tract mucosa (cobble stone) and bulgy, small and pale lesions in some areas were determined. Histopathological evaluation of tissue fragments was compatible with granulomatous lymphadenitis. The lymphocyte subset analysis of bronchoalveolar lavage fluid revealed a CD4/CD8 ratio of 6.1 (CD4/CD8, 31/5). Ziehl-Neelsen staining, cultures for bacteria and *Mycobacterium tuberculosis* from bronchial fluid was negative.

The patient was diagnosed as having stage II pulmonary sarcoidosis according to his clinical, laboratory and transbronchial biopsy findings. Thereupon, we started with prednisolone 30 mg/day and continued with colchicine 1 mg/day.

DISCUSSION

To date, only a few cases of sarcoidosis in association with FMF have been reported. Sarcoidosis is a systemic, idiopathic, granulomatous disease with a wide range of manifestations. The lungs are almost always involved, the pulmonary inflammation is located especially in the upper lobes, and hilar lymphadenopathy is generally present at some time during the course of the disease (4). The blood level of angiotensin-converting enzyme is elevated in approximately 60% of patients with active sarcoidosis (5). Reduced delayed-type hypersensitivity responses and cutaneous anergy to tuberculin intradermal testing occurs in many patients (6). The etiology of sarcoidosis is unknown, but genetic and immunological factors are thought to play an important role in the development of the disease through increased susceptibility to antigenic stimulation. Immune dysregulation has been theorized to be due to a persistent antigen of low virulence that is poorly cleared by the immune system, leading to a chronic T cell of the Th1 subtype response with accumulation of $CD4^+$ Th1 lymphocytes and mononuclear phagocytes in affected organs which results in non-caseating granuloma formation (6, 7). Proposed antigens fall into 3 categories that include infectious, environmental, and autoantigens (8). The administration of medications, such as IFN-α is thought to skew CD4 T cells toward a Th1 immune response, resulting in clinical disease in susceptible individuals (9-11).

In 1986, Abdi et al. reported the first pathologically proven case of IFN-induced sarcoidosis (12). Since that time there has been other published reports that support a possible association between IFN therapy and the development or recurrence of sarcoidosis (10). Induction of autoimmune diseases during IFN-α therapy is well known. Diabetes mellitus, hypo/hyperthyroidism, rheumatoid arthritis, lupus-like syndrome, idiopathic thrombocytopenic purpura, haemolytic anemia and polyarthropathy have all been reported in correlation with IFN-α therapy (9). Hoffmann et al. reported a 5% incidence of sarcoidosis in a cohort of 60 patients who participated in a randomised trial of IFN-α for chronic hepatitis C infection (13). However, the true prevalence of IFN-induced sarcoidosis is probably underestimated, because its insidious presentation is similar to the constitutional IFN-related adverse effects. The mean age of onset of IFN-induced sarcoidosis is 50.0 ± 9.1 years, while that of natural sarcoidosis is around 20-29 years, which reflects the older age group that requires IFN therapy and indirectly adds evidence to its causality (14). Ninety-five percent of the IFN-induced sarcoidosis cases have been reported in patients receiving IFN-α therapy and the remainder have been in patients receiving IFN-β. The mean time to onset of symptoms was 11.4 months (range 1-60 months). In some instances, symptoms developed from as early as one week to as late as three years after discontinuation of the drug (15). Approximately 40-50% of affected individuals present with constitutional and/or respiratory symptoms. The lungs are the most frequent organ affected in IFN-induced sarcoidosis (70%), similar but not as high as the incidence reported in natural sarcoidosis (90%). The most frequent symptoms are dry cough and dyspnea. The most common radiological findings are enlargement of mediastinal lymph nodes and pulmonary interstitial infiltrates (66 and 41%, respectively). Reports of pulmonary function are scarce, with the most com-

mon reported abnormality being a mild reduction in the diffusing capacity of carbon monoxide (45%) (10).

Daily colchicine is the mainstay of the therapy for FMF, resulting in complete remission or marked reduction in the frequency, duration, and severity of attacks in most patients, but in patients whose conditions do not respond to colchicine, the use of IFN-α may be effective. Tunca et al. achieved to relieve the symptoms with IFN-α during the typical FMF attacks in colchicine-unresponsive patients (16). Calguneri et al. demonstrated that continuous IFN-α treatment in addition to colchicine might be effective for controlling colchicine-resistant FMF attacks (17). In our case, since the patient became completely unresponsive to higher doses of colchicine, IFN-α was added to this regimen. He had no past medical history of sarcoidosis or signs of sarcoidosis before IFN therapy and it is unclear whether sarcoidosis was precipitated by IFN-α, or existed coincidentally. Our case reflects the characteristics of sarcoidosis that seem to be typical in association with IFN-α therapy, except the duration between the cessation of IFN therapy and the development of symptoms. It is fourty-two months in our case and this period is longer than usually expected. Nevertheless, there are some reported cases in the literature in which symptoms developed as late as five years after the withdrawal of the drug (18,19). Sarcoidosis may become clinically apparent during, or after withdrawal of therapy and cellular immunological reactions activated by exogenous IFN can take a long time to form sarcoid granulomas.

Clinicians should suspect sarcoidosis in all symptomatic patients with current or recent exposure to IFN therapy. Criteria to diagnose IFN-induced sarcoidosis should follow that of naturally occurring sarcoidosis: a compatible clinical presentation, histologic demonstration of non-caseating granulomas and exclusion of other diseases capable of producing a similar picture. Any suspicious skin lesion should be biopsied, and the presence of dry cough or dyspnea warrants further evaluation with chest X-ray and pulmonary function testing. In most cases, transbronchial lung biopsy is the recommended procedure for histological confirmation. It has been reported that some patients responded to a dose reduction of IFN therapy and in others, sarcoidosis regressed after discontinuation of the IFN with or without the addition of steroid therapy (20,21). Adjuvant therapy with systemic steroids was reported in 24 patients, all with a favourable response, and a therapeutic trial might be warranted for patients with progressive disease or serious extrapulmonary manifestations (10).

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