ANKILOZAN SPONDİLİT NEDENİYLE ETANERCEPT KULLANIMINA BAĞLI SARKOİDOZ OLGUSU

A SARCOIDOSIS CASE ASSOCIATED WITH THE USE OF ETANERCEPT BECAUSE OF ANKYLOSING SPONDYLITIS

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ÖZET

TNF-alfa blokerlerinden olan etanercept tedavisi altında ortaya çıkan ve mediastinoskopi ile tanı koyduğumuz sarkoidoz olgumuzu literatür bilgileri ışığında irdelemeyi amaçladık. Ankilozan spondilit tanısı ile etanercept tedavisi alan 31 yaşındaki erkek hasta tedavinin beşinci yılında başlayan ses kısıklığı ve yutma güçlüğü yakınması ile kliniğimizde başvurdu. Toraksın bilgisayarlı tomografisinde bilateral multipl mediastinal ve hiler lenfadenopati saptanan bu olguda mediastinoskopik biyopsi materyalinin histopatolojik incelemesinde kazeifikasyon göstermeyen granüloma formasyonunun görülmesi ve tüberküloz gibi diğer granülomatöz hastalıkların ekarte edilmesi ile sarkoidoz tanısı konuldu. Sistemik steroid tedavisi başlanan olguda klinik ve radyolojik iyileşme sağlandı. Steroide direçli sarkoidoz olgularının tedavisinde de kullanılan TNF-alfa blokerlerinin yol açtığı sarkoidoz son yıllarda bildirilen yeni bir yan etkidir ve sarkoidoz ile TNF-alfa blokerleri arasındaki bu ilişki paradoksal bir durum olarak tanımlanmaktadır.

SUMMARY

We aimed to discuss under the light of literature, the sarcoidosis case diagnosed by mediastinoscopy under the treatment of etanercept which is one of the TNF-alpha blockers. A 31 year-old male patient, taking etanercept treatment because of ankylosing spondylitis admitted to our clinic with the complaints of cough, hoarseness and dysphagia at the fifth year of etanercept treatment. Bilateral, multiple mediastinal-hilar lymphadenopathy were detected in thoracic computerized tomography, diagnosis of sarcoidosis was established by seeing non-caseating granuloma formation in histopathological examination of mediastinoscopic biopsy and ruling out the other granulomatous diseases such as tuberculosis. Clinical and radiological improvement was provided by systemic steroid treatment. Sarcoidosis caused by TNF-alpha blockers that are also used in treatment of sarcoidosis resistant to steroid is a new side effect and this relationship between the sarcoidosis and TNF-alpha blockers are defined as paradoxal situation.

INTRODUCTION

Sarcoidosis is a chronic inflammatory disease characterized with non-caseating granuloma and can involve all tissues and organs. Primarily lungs and mediastinal lymph nodes are involved. TNF-α, synthesized by macrophages, is one of the primary cytokines that play role in the immunopathogenesis of the sarcoidosis. TNF-α leads to the migration of the lymphocytes to the inflammation site and the proliferation of them by increasing the release of many cytokines and chemokines and it causes the formation of granuloma (1,2). It is known that TNF-α has important biological and physiopathological effects in the natural or acquired immunity, cachexia, endotoxic shock, inflammation, remodeling of the tissue, infection and immunity, cytotoxicity and apoptosis. Anti TNF-α drugs can be classified as monoclonal antibodies such as infliximab and adalimumab and soluble TNF-α receptor antagonists such as etanercept. These drugs are utilized in the connective tissue diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS), juvenile rheumatoid arthritis (JRA), psoriatic arthritis. Furthermore, TNF-α blockers are also effective in diseases such as Crohn Disease, Wegener Granulomatous Disease and sarcoidosis (3). Infections are the most common side effects of the TNF-α blocker drugs. Demyelinating disease, lupus-like clinical manifestation, congestive heart failure and malignancies particularly lymphoma constitute other side effects (1). In the recent years, some manuscripts on the TNF-α blockers as a cause of sarcoidosis has been reported. On the other hand, when the effectiveness of infilixmab and adlimumab in steroid refractory chronic sarcoidosis cases is considered, this newly defined side effect of the TNF-α blockers are specified as a paradoxal situation (1,4,5). In this article, we aimed to report a case receiving etanercept treatment due to ankylosing spondylitis who were diagnosed as sarcoidosis in the fifth year of this treatment.

CASE REPORT

A thirty one year-old male patient admitted to our clinic with the complaints of cough, hoarseness and dysphagia. In his history, the patient had diagnosis of ankylosing spondylitis six years ago and did not have benefit from the nonsteroidal anti-inflammatory and immunosuppressive treatment. Since his complaints became increasingly violent, subcutaneous 0.25 mg etanercept treatment in two days per week was initiated five years ago. During the last year, the dose was reduced to 0.25 mg in one day per week. The complaints associated with ankylosing spondylitis were improved significantly during the etanercept treatment. But he had complaints becoming increasingly severe for the last six months such as hoarseness and dysphagia that impairs his nutrition and he was refered to the outpatient clinic of pulmonary diseases.

No pathology related to the respiratory system was detected in his physical examination, acido-resistant bacillus in the sputum was negative two times with direct method. Tuberculin skin test was also found as negative (non-reactive). In the postero-anterior chest x-ray of the patient, bilateral hilar adenopathy was detected. His hemogram and routine biochemical examinations were within the normal limits. In the thoracic computerized tomography examination, several bilateral parenchymal nodules in millimetric dimensions were observed in addition to the bilateral paratracheal, subcarinal, aortopulmonary, paraesophageal and hilar lymphadenopathies. The biggest lymphadenopathy was 4 cm in size (Figure 1, 2).

There was no characteristic except the slight restrictive pattern in the respiratory function tests. Electrocardiyographic examination was in normal limits. When the file of the patient was investigated, it was detected that tuberculin skin test was negative and there was no pathology in the chest x-ray in series

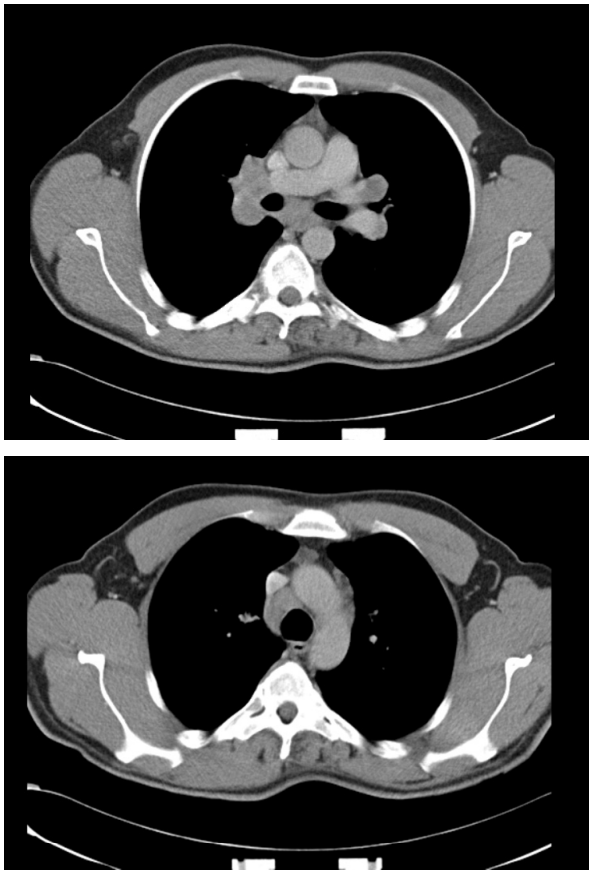

Figure 1. Bilateral mediastinal and hilar lymph nodes are seen in thoracic computed tomography

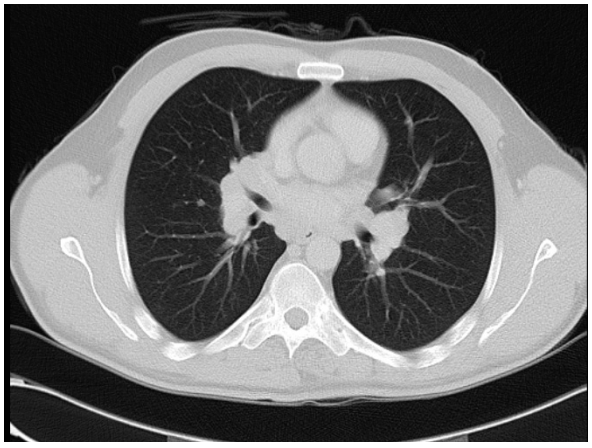

Figure 3. The paranchymal nodule seen at the right lung in the thoracic computed tomography

before the initiation of the treatment until he was admitted to us. It was detected that the patient received INH 300 mg/day for six months at the beginning of the etanercept treatment as a prophylaxis for tuberculosis. The pre-diagnosis of sarcoidosis, tuberculosis and lymphoma were established with these findings, and it was suggested that the disease was developed under the treatment of etanercept. Bronchoscopy was performed and no endobronchial lesions were detected, bronchial mucosa biopsies and bronchial lavage were done. During the bronchoscopy, transbroncheal needle aspiration was performed at lymph nodes 7 and 4R. The bronchial mucosa biopsy were reported as normal bronchial mucosa. No acido-resistant bacillus was detected in the bronchial lavage fluid. Although lymphoid tissue cells were seen in the transbronchial needle aspiration material, no diagnostic characteristic was detected. There were no pathologies in the ophthalmic examination. Since bronchoscopic examination was non-diagnostic, lymph nodes at the stations 7 and 4R were sampled via mediastinoscopy under the general anesthesia. In the pathological examination of the samples, non-caseating granuloma formation was seen. When it was assessed with clinical, radiological and pathological findings, diagnosis of sarcoidosis was established and systemic steroid treatment was initiated as per oral 40-mg-prednol by ceasing anti TNF-α (etanercept) treatment. After one-month steroid treatment in the control chest x-ray, regression was detected in the bilateral hilar lymph adenopathies and in addition, dysphagia was regressed and hoarseness was continued. The proliferation was not detected in the BACTEC culture of sputum and bronchial lavage fluid acquired in the beginning. When the medication history was asked again at the second month of steroid treatment, the pains of the patient were aggravated too much after ceasing the etanercept treatment and, his quality of life was impaired thus he began to use etanercept again fifty days ago. Since he refused to cease the etanercept treatment, he was recommended to continue 40-mg prednol

treatment and to maintain the follow-up. It was detected that complaints of the patient were completely recovered at the fourth month of steroid treatment. It was detected that mediastinal, hilar lymph nodes and parenchymal nodules were totally regressed at thoracic computerized tomography. The dose of the systemic steroid was decreased gradually and ceased at the sixth month. It was recomended to the patient to stay in the follow-up.

DISCUSSION

Sarcoidosis is a chronic granulomatous disease which can involve all tissues and organs and its cause is unknown. Diagnosis is established by the detection of non-caseating epithelioid granulomas histopathologically beside the clinical and radiological findings. There is evidence on the fact that granuloma and inflammation are Th1-type immune responses characterized by the activated macrophage and $CD4^+$ T lymphocytes on the genetic background in sarcoidosis. In this immune response, TNF-α and IFN-γ play the main role in the formation and maintenance of the granuloma. Therefore, TNF-α blockers are used in the treatment of the steroid-resistant cases. None the less, the case reports in increasing number are being reported on TNF-α blockers as a cause of sarcoidosis (3,5,6). Etanercept is a synthetic fusion protein being used in the treatment of AS, JRA and other connective tissue diseases and playing role as a soluble TNF-α receptor (6,7). In the treatment with soluble TNF-α receptors, it has been reported that sarcoidosis is seen more frequently, on the other hand that tuberculosis reactivation is seen less frequently compared to the treatment with monoclonal anti-TNF antibodies (infiliximab, adlimumab). Dhaille et al. were reported that of the 19 cutaneous or visceral sarcoidosis cases being related with the TNF-α published until 2002, 12 were associated to etanercept, 6 were associated to the infliximab and one was associated to adalimumab (8). Our case was also receiving etanercept and he was in the more risky group in terms of sarcoidosis compared to other anti-TNF-α drugs according to the literature. When assessed in terms of drug efficiency, etanercept is not as successful as adalimumab and infiliximab in the treatment of the granulomatous diseases such as Wegener, Crohn disease and uveitis. So, it seems that there is a differential efficacy and important distinction in the safety profile of etanercept and monoclonal antibodies in the development and treatment of different inflamatory process and etanercept appears to stabilize granuloma formation (2,9). Etanercept is a soluble recombinant p75 TNF receptor protein different from monoclonal anti-TNF antibodies, it cannot inhibit neither p55 nor p75 receptors. In the use of etanercept, p55 receptors are intact. When etanercept is compared with infliximab, while infliximab blocks irreversibly TNF, etanercept forms more unstable complex with TNF (2,4,9). Furthermore, etanercept does not inhibit γ-interferon whereas infiliximab achieves γ-IFN inhibition. Gamma-IFN is the other important cytokine in the granuloma formation. These discrepancies constitute some differences between the effect and side effect spectrum of two groups of TNF-α blockers (2,10,11). When the sarcoidosis cases related to the TNF-α treatment are assessed, although intrathoracic sarcoidosis cases constitute the majority of these cases, hepatic, neuro-ocular and cutaneous sarcoidosis cases were also reported (1,6,7). In our case, there were no other organ involvment.

Sarcoidosis can be revealed in any period of the treatment in cases using etanercept or other TNF-α blockers. It is detected in the literature that the cases were diagnosed as sarcoidosis from the first month until the sixtieth month of the TNF-α treatment (6,12). Daien et al have reported that median delay duration for the etanercept treatment is 18 months (2-26 months) (12). In our case,

diagnosis of sarcoidosis was established in the sixtieth month of the treatment. When the published cases were studied, it was seen that most common radiological finding was mediastinal and hilar lymph nodes and in some cases parenchymal infiltrations were also detected (1,6,12). In our case, there were several millimetric parenchymal nodules besides the hilar and mediastinal lymphadenopathies. The lymph nodes were extremely large and the patient had hoarseness and severe dyspahgia related to the compression of these lymph nodes. We couldn't find another case developing hoarsness and dysphagia in the literature. In sarcoidosis cases revealed under the etanercept treatment, although symptomatic and radiological improvements are usually seen with the cessation of TNF-α blockers, it has been reported that systemic steroid treatment in some cases is required (12,13). It is not known yet that whether a complete response takes place or not in the sarcoidosis with the cessation of TNF-α blocker. However Cuchacovich detected granulomatous hepatitis at the beginning in the liver biopsy of a sarcoidosis case associated with etanercept and reported that granulomatous lesions were lost ten months later following the cessation of the etanercept (5,14). We also ceased the etanercept treatment and in addition since the patient had hoarseness and severe dysphagia that impair his nutrition, we decided to initiate the systemic steroid treatment.

Skoie et al. have reported that in one of their three cases sarcoidosis series, adenopathies were regressed completely fifteen days after cessation of etanercept and that adalimumab treatment was initiated after five months. Also they reported that etanercept treatment was initiated three years after the recovery of sarcoidosis in another case and no recurrence associated with sarcoidosis was seen in these case in the long-term follow-ups (4).

In our case, since the pain associated with the ankylosing spondylitis began after the cessation of the etanercept treatment, the patient started again to use etanercept, despite this, partial radiological and clinical response was obtained in the first-month control and complete radiological and clinical response was obtained in the fourth-month control. Daien et al. reported in one of their 10 cases series, although etanercept treatment was not ceased, clinical improvement was seen with the treatment of prednisone 15mg/day but uveitis revealed again with the reduction of the steroid dose (12).

Although the reason of sarcoidosis development during the treatment of TNF-α is not known, primarily two hypotheses have been suggested. According to the first hypotheses, microorganisms such as mycobacterium tuberculosis and corynebacterium acnes trigger the clinical symptoms of an occult sarcoidosis. According to the second hypothesis, TNF- α and the ratio of T lymphocytes expressing IFN-γ being the second important cytokine of the granuloma formation especially in the patient using etanercept increase and the granuloma develops on this background (3,6).

In conclusion, sarcoidosis is defined as a new and paradoxal side effect of the TNF-α blockers primarily etanercept. Although the cases treated with TNF-α blockers are followed primarily by the rheumatologists, these patients are oriented to the pulmonary diseases outpatient clinics for first assessment in the beginning of the treatment and for the assessment of the side effects with certain intervals during the treatment process. In the assessment of the pulmonary diseases, although the basic goal is tuberculosis, sarcoidosis resembling to the tuberculosis in terms of clinical, radiological and histopathological aspects should be taken into the account.

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