

Acute Sarcoidosis (Löfgren's Syndrome) in a Patient Treated with Etanercept for Psoriatic Arthritis-Case Report and Impacts of Biologic Agents Review

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Abstract

Patients treated with biologic drugs for various-not only dermatological-diseases are growing in number. Biologic drugs applied as a long-term therapy of psoriasis are safe, enable disease remission, and most importantly, help improve the patient's quality of life. It is also crucial to note, that biologic agents decrease patient mortality rate. Much research has shown the unquestionable efficiency of biologic therapies despite their also well-documented rare adverse effects. Due to the growing range of application of these agents, it is critical to keep an observant eye during the monitoring of the patient in case of new disease activity. This study aims to present the case of a female patient treated with etanercept for severe psoriasis arthritis (PsA) who subsequently developed acute sarcoidosis and to examine the risk of serious adverse events.

Keywords: Etanercept; Sarcoidosis; Löfgren's syndrome; Psoriatic arthritis; TNF- α inhibitors; Adalimumab

Introduction

Biologic drugs, TNF- α inhibitors in particular, are currently more commonly used in the long-term treatment of Psoriasis Vulgaris (PV) and Psoriatic Arthritis (PsV). A growing number of studies are documenting the course of these therapies. Noticeably, the drugs are characterized by high efficiency and may lead to disease remission, which relieved the patient of any stigma commonly associated with PV or PsV. Thus, the patient's quality of life may improve so significantly that any consideration of therapy modification, including biologic agent cessation, may induce great fear in the patient. With the increasing application of these drugs, it is imperative to continuously keep in mind the potential risks of any rare adverse effects these therapies may induce in an otherwise low-risk patient. This study aims to report the case of a female patient treated for severe psoriatic arthritis with etanercept-a biologic drug-who developed acute sarcoidosis, and to examine the risk of serious adverse events.

Case Report

A 51-year-old female patient was urgently admitted to the Poznan Provincial Hospital due to nodular inflammatory lesions on the skin of her crura (Figure 1). Based on the nature of the manifestations, a diagnosis of Erythema nodosum was made. In addition to the cutaneous changes, the patient presented with a high fever (40°C), swollen joints, emotional unease, fatigue, lack of appetite, continuing cough, and pain in the chest and shortness of breath. The symptoms were first noticed three weeks prior to hospital admission. The patient was treated with antibiotics by a general practitioner with the suspicion of an upper respiratory tract infection. The therapy did not bring the expected outcomes. In addition to the other findings, the patient presented with nodular lesions on the skin of the crus, which were

suspected to be caused by black fly bites. These flies are frequently observed in the period between May and June in the Wielkopolska Province where the patient lives.

At hospital, the patient had a chest x-ray performed. The scan test showed bilateral enlargement of the lymph nodes of pulmonary hila. Sarcoidosis was suspected and the patient was referred to a pulmonologist for further workup. The consulting pulmonologist confirmed that the patient developed sarcoidosis.

During admission, additional laboratory tests yielded the following deviations from normal ranges: ESR at 100 mm/h, anemia (HGB 10.5 g/dl, RBC 3.73 M/UL, HCT 32.7%, MCV 87 fl), and an elevated platelet level (PTL 429 K/UL). The calcium level was measured at Ca-M 1.9 mmol/d; an Old Tuberculin (OT) test was also performed (0 mm). Abdominal ultrasonography was unremarkable.

Chest CT scan

Chest CT scan was performed and the following results were observed:

Nodules (a nodule of 8 mm in diameter in the right upper lobe near the bronchus up to PS3, fairly numerous subpleural nodules of up to 7 mm-8 mm in both lower lobes),

Non-dense fibrous compaction and thickening of the interstitial framework in the basal segments of the right lower lobe above the diaphragm,

Enlarged lymph nodes (in the upper mediastinum, lower paratracheal nodes, subcarinal lymph nodes, lower area of the posterior mediastinum, in the right and left hila).

The CT imaging confirmed the clinical diagnosis of stage 1 or 2 of sarcoidosis.



Figure 1: Photograph of skin lesions on crura. Nodular inflammatory lesions were observed amidst psoriatic plaques.

Bronchoscopy

Bronchoscopy was performed and the whole bronchial tree was reported as thickened, slightly hyperemic with minor nodular lesions. Bronchoalveolar lavage yielded no acid-fast bacilli, however, *Candida sp.* (+) and *Blastomyces sp.* were reported. No tumorous cells were found. Fine needle aspiration biopsy was also performed. Cytology did not justify sarcoidosis to be confirmed (squamous epithelia, ciliated cells of the respiratory tract and lymph node cells were reported). The diagnosis of sarcoidosis was ultimately determined after a biopsy of a small non-caseating granuloma in the wall of the bronchium (under the mucosa) was performed.

Patient history and hospital course

The patient's history was positive for diffuse psoriasis vulgaris and psoriatic arthritis from which she suffered for 30 years. The disease was severe and aggressive, and the patient was repeatedly hospitalized at the Department of Skin Diseases at the Poznan Provincial Hospital. She was prescribed both systemic (methotrexate, cyclosporine A, phototherapy) and topical (Cignolin [Dithranol], glucocorticosteroids, prodemin, vitamin D3 derivatives) treatments. Despite the prescribed standard therapy methods, remission was unsuccessful. In 2009, the patient was qualified for biologic therapy with etanercept. The biologic treatment had a beneficial impact on the skin lesions and the disease's

arthralgia symptoms. The patient experienced a significant clinical improvement, which also led to improving the patient's quality of life. The treatment was well tolerated. No adverse events of the therapy were observed until later, when the patient experienced sarcoidosis symptoms.

Once the diagnosis of sarcoidosis was made, etanercept was discontinued. The patient was not switched to another form of biologic therapy. She was maintained on a combination of general and topical medications. Pulmonologic symptoms and blood work results significantly improved 1.5 months after discontinuing etanercept. These results were compared to her hospital admission initial laboratory findings.

Discussion

Biologic drugs, and TNF- α inhibitors in particular, are increasingly common among dermatologists as treatment agents. With a growing number of patients on biologic treatment, attention is drawn to potential adverse events, which have been considered as rare. This study elaborates on a female patient who developed acute sarcoidosis during etanercept therapy. References worldwide quote over 30 cases of sarcoidosis developed during treatment with TNF- α inhibitors. The majority of the cases involve patients treated for rheumatologic disorders, with lungs and adjoining lymph nodes being most often affected as a result. Most frequently, the development of symptoms was observed 22 months following the start of biologic therapy, as is the case with the patient in question. Once the therapy was discontinued in the cases involved, the symptoms slowly remitted to completely disappear after 5 to 6 months [1].

Sarcoidosis, also known as Boeck's, Besnier's or Schaumann's disease, is a multisystemic disorder of unknown cause. The original description of sarcoidosis was in 1877 but the etiology of the disease is still a diagnostic enigma [2,3]. The active stage of the disease is characterized by reduced type IV hypersensitivity, which results in anergia to tuberculin, etc. [4]. Undoubtedly, immunological reactions to stimulate the formation of granulomas are of crucial importance. In the case of exposure to an antigen, cell reaction is initiated and effector cells stimulate various inflammatory responses. Interestingly, the same cells to stimulate the formation of granulomas may also stimulate fibrosis. Atypical mutated mycobacteria tuberculosis is also considered to play a crucial role in the development of the disease. Notably, the analysis of blood in patients shows the prevalence of Ts (suppressive) lymphocytes, also found on the perimeter of the granulation tissue, while Th (auxiliary) lymphocytes prevail in the granulation tissue itself. T lymphocytes with gamma-delta receptors are numerous in infiltrations, which indicate a patent antigen stimulation and immunotolerance. Fibrosis observed in the course of the disease is caused by the fibroblast growth factor (FGF) from macrophages, IL-1 and fibronectins. Increased immunoglobulin production is also observed in the course of the disease. Sarcoidosis may be a result of an immunological response to a constant stimulation with antigens, which are most often unidentifiable in patients with genetic predispositions. These numerous causative agents that are yet to be fully explained indicate that immunological factors are responsible for the presence and development of lesions [2-4].

Sarcoidosis is most common in persons between 20 and 40 years, but is increasingly observed in older individuals [2]. The extent of manifestations is wide and related to the age of a person under treatment, in particular where the manifestations occur as adverse

events of biologic treatment. Some 10 incidents per 100,000 persons are registered annually in Poland [2], as an example.

Sarcoidosis is more and more described as a complication after treatment with TNF- α inhibitors. With over 30 case reports on patients experiencing the above symptoms during biologic therapy, attention is drawn to the role of the drugs in the induction of granulomatous disorders, including sarcoidosis [1,5]. The development of granulomatous lesions in patients prescribed etanercept for various causes has been recently noticeable. According to a study by Daien et al. in ten cases described, in addition to pulmonary symptoms, skin symptoms were the most frequent manifestation of the disease during treatment with TNF- α inhibitors [6].

In two cases described, Verschuern et al. emphasize the unquestionable relation between sarcoidosis and biologic therapy-a fact confirmed by a complete remission of the disease after etanercept was discontinued. Nevertheless, how the lesions are formed is still not quite unclear [7]. Paradoxically, recent research has shown the effectiveness of TNF- α blocker therapy in sarcoidosis treatment [8]. According to Tong et al. in recent years sarcoidosis has been increasingly diagnosed in patients treated with TNF- α inhibitors, which may be due to the fact that the disease was less identifiable and not directly relatable to biologic treatment earlier. All the three drugs of anti-TNF blockers are under observation in terms of sarcoidosis induction for adverse events caused by a group of drugs and not by a specific drug [9]. Nonetheless, based on the cases observed the symptoms were more often found during etanercept treatment as compared to adalimumab or infliximab [10]. Skoie et al. also emphasize patients treated with etanercept tend to develop granulomatous reactions more frequently. They highlight a startling fact that attempts to use infliximab and adalimumab in sarcoidosis treatment have been successful [11]. Burns, Green and Pasternak report an interesting case of a 59-year-old female patient who developed rheumatoid arthritis. Her etanercept-induced sarcoidosis remitted after adalimumab was introduced to her treatment. The patient has taken the drug for 2 years with good clinical results and without relapse of sarcoidosis symptoms, which shows how difficult it is to interpret the pathogenesis of the disease manifestations [12]. However, according to data from March 2012, which analyzed the safety and efficiency of TNF- α inhibitors in sarcoidosis, there is no unequivocal evidence to prove the absolute efficiency of the drugs. Nonetheless, infliximab seems to be effective in certain manifestations of the disease. Before a decision on infliximab treatment is made, however, the risk to benefit ratio must be weighed on an individual basis [13]. Some authors ponder whether the development of sarcoidosis is indeed induced by biologic therapy, or whether it is a coincidental co-existence of the disease in a specific patient. Haron, Raya and Harney reported the case of a patient who developed sarcoidosis 6 months after etanercept treatment was discontinued. The patient experienced spontaneous regression of the symptoms without any therapy. The authors put forward a question whether the patient developed sarcoidosis unexpectedly or whether the disease was due to the deregulation of his immunological system as a result of him taking TNF- α blockers [14]. In a study by Sawahata et al., with the 226 patients (65 men and 161 women) newly diagnosed with sarcoidosis between the years, 2003 and 2012, at Jichi Medical University Hospital in Japan, there were three cases of sarcoidosis, which developed during etanercept treatment for RA. All 3 cases were women who had undergone bilateral oophorectomy more than 20 years earlier [15]. Miyagi et al. observed the development of pulmonary and cardiac sarcoidosis during etanercept therapy in their examined patients [16].

While, Viera et al. reported a case of a patient with rheumatoid arthritis who, after 2 months of treatment with etanercept, developed disseminated violaceous papules. Biopsy of the skin lesion showed chronic granulomatous dermatitis with negative staining for fungi and acid-fast bacilli (AFB). The lesions improved once etanercept was discontinued [17]. Over the years, similar observations are being reported in literature with significance.

However, new research is examining the role of biologic agents in the treatment of various stages of sarcoidosis, especially in individuals who fail cytotoxic agents. Literature is demonstrating certain biologic agents, such as infliximab (chimeric monoclonal antibody against TNF- α) and adalimumab (recombinant human monoclonal antibody against TNF), to be successful in the treatment of refractory organ-threatening sarcoidosis [18] and even argued to be considered third-line therapy when other options have failed [19]. One randomized control trial conducted by Baughman RP et al. showed a beneficial response for pulmonary sarcoidosis when treated with infliximab, especially in chronic patients. While another study by Sodhi M et al. observed a significant response to infliximab in cutaneous and neurologic sarcoidosis patients, even claiming, "infliximab therapy rescues cyclophosphamide failure in severe central nervous system sarcoidosis" [20]. In a small-randomized controlled trial including 16 patients with cutaneous sarcoidosis, Pariser RJ et al. observed a significant improvement compared to the placebo. Such findings show great promise in the future of biologic agents in the treatment of sarcoidosis.

Conclusion

Sarcoidosis has been and continues to be a disease of ambiguous etiopathogenesis involving a modified immunological response to a non-diagnosed antigen. Numerous factors are taken into account as far as the disease's induction is concerned, not to exclude drugs, including biologic agents, such as TNF- α inhibitors. By impacting individual elements of a cascade of inflammatory disorders responsible for the development of numerous diseases, including psoriasis, these drugs may cause adverse events, which have previously been rarely observed when using other, less novel medications. This requires that any symptoms reported by patients who are on biologic treatment be scrupulously analyzed to prevent symptoms of often-serious diseases from being overlooked. However, this does not mean that biologic agents should be excluded in such patients, but rather considered on an individual basis. More research is needed on the effects of different biologic drugs in the course of sarcoidosis pathophysiology.

Declaration of Interest

The authors declare no conflict of interests.

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