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EDİTÖRE MEKTUP / LETTER TO EDITOR

Highlighting steroid indications for Kikuchi Fujimoto disease: a case report

Kikuchi Fujimoto hastalığında steroid kullanım endikasyonları: bir olgu sunumu

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To the Editor,

Kikuchi Fujimoto Disease (KFD), also known as histiocytic necrotizing lymphadenitis, was first described in 1972 simultaneously by Kikuchi and Fujimoto in Japan[1-3]. It is a rare but increasingly recognized disease; our knowledge about this disease is mostly based on case reports. The disease onset is typically at age 20-35, it is best characterized among young Asian women, although may occur in men[3-5]. Tender posterior cervical lymphadenopathy and fever is the common presentation. Since it has no distinguishable features, diagnosis of KFD is largely based on clinical suspicion and histopathological confirmation. Disease is generally self limiting and often resolves within 1 to 8 months[6,8]. There is no specific treatment available; goal of management mainly is relief of symptoms. Even though severe and recurrent disease is rare, when occurs, high dose glucocorticoids and iv immunglobulin may be the treatment options, but, in literature, there are no clear declared indications for steroid treatment[1,2]. Therefore, herein, we present a 17 year old Turkish man with KFD that benefited significantly from systemic steroid treatment and aim to highlight the use of steroids.

A 17 year old Turkish male was referred to our hematology clinic from ear throat nose department with a history of painful lumps on his neck and fever for over 3 weeks. He had no associated constitutional symptoms. His past medical history and family history was non decisive, he had no medications recently.

His physical examination revealed tender right supraclavicular, post-auricular and cervical lymph nodes and non specific cutaneous lesions (rash). He had bicytopenia; leukocyte and thrombocyte counts were low (2.99 x 10^3/μL, 126x10^3/μL respectively), and had neutropenia (0.81 x 10^3/μL); no atypical cells or myeloid progenitors were observed on his blood smear. C-reactive protein and the erythrocyte sedimentation rate were normal; transaminases alanine aminotransferase (ALT) 331 U/L; aspartate aminotransferase (AST) 406 U/L and lactate dehydrogenases (LDH): 463 U/L were elevated.

Ultrasonography of the neck showed enlarged right parajugulary, retroauricular and clavicular lymph nodes, there was no evidence of abscess formation. Excisional biopsy was performed from the enlarged right supraclavicular lymph node and histopathological features were consistent with KFD.

Screenings for tuberculosis, autoimmune diseases and viral serologies, as well as collagenous markers were all completed. All except antinuclear antibody (ANA) came out negative. ANA was strongly positive (1/1000), anti ds DNA was as well negative. ANA positivity was not thought to be related to the systemic lupus erythematosis after consultation from rheumatology specialist. Despite symptomatic and broad spectrum antibiotic treatment there was no clinical improvement, therefore 1 mg/kg

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metilprednisolone was started straightly on the third week. The fever responded favorably just after the steroid initiation and on the 3rd day of the treatment transaminases began to decrease. His steroid dose started with 1mg/kg dose for 2 weeks and tapered by 25% dose decrement in every 3 days; trimetoprim sulphametoxazol and calcium was added to the treatment. After 2 months of treatment he was clinically good and all his laboratory tests were normal, since then he has been following up without recurrence.

Rash, increased ALT, AST and LDH levels; and the cytopenias should be considered as for steroid treatment. Our patient had all of these findings and did not have improvement in the first weeks of his symptomatic treatment and well responded to the steroid treatment afterwards.

The etiology of KFD is unclear. Infections and autoimmunity are the two main theories for the etiology of the disease. KFD is assumed to occur when one or more unidentified agents trigger an autoimmune process which is self-limited. Nevertheless autoimmune serologic markers are generally negative and positive serologic markers bring into the question of the disease alone[8,10]. KFD is a rare disease and differential diagnosis is wide, there are a numerous causes of infection related lymphadenopathy and it is also important to exclude malignancies and autoimmune conditions. There isn't a set of diagnostic criteria for KFD, therefore extensive investigations need to be performed and this may be a challenge to start an appropriate treatment for severe disease on time. Its diagnose is largely based on clinical suspicion and histopathological confirmation is obligatory. There is also no specific clinical feature for the disease. Inflammatory markers may be slightly increased, increased transaminases and serum LDH, leukopenia or leukocytosis are possible initial laboratory findings. On peripheral blood smear atypical lymphocytes can be observed however there is no specific or pathognomonic laboratory finding for KFD**.** Some histological features resemble to lymphoma that may lead to misdiagnosis. Negative laboratory results help to exclude other disorders[2,4,6,8]. Our patient had lymphadenopathy and fevers with no distinguishing clinical course as general, his inflammatory markers were normal. He had neutropenia with thrombocytopenia and his LDH, ALT/AST levels were elevated. In our case an early excisional biopsy provided a correct diagnosis without a delay.

Reported course of the KFD is mostly benign and is typically limited within 1 to 8 months[6,8]. There is no guideline for treatment of KFD; recommendations are based on case reports, expert opinions and experience. Treatment is generally supportive, mainstay of the management is treating symptoms with analgesics, antipyretics, non-steroidal anti-inflammatory drugs and letting the disease run its course once the diagnosis has been established by biopsy[1-3,8,9]. But the clinical manifestations can be very distressing for some patients. 3-7 % of the patients experience recurrence and even fatalities have been reported during the acute phase of the disease, hence more aggressive treatment may be required for particular patients who suffer from severe and persisting symptoms and recurrence. Glucocorticoids have been widely used in various inflammatory conditions due to their anti-inflammatory and immune modulating effects[3]**.** In management of Kikuchi disease, use of glucocorticoids and immune suppressants was rarely reported and was limited only to complicated cases. In general, extra nodal KFD, neurologic involvement (aseptic meningitis, cerebellar ataxia), hepatic involvement, elevated levels of LDH and in severe lupus like syndrome (positive ANA titres) are accepted indications for corticosteroid use in KFD. In these groups of patients' responses to glucocorticoids were good. Reliable prognostic markers are missing, although not commonly recommended without extra cervical or extra nodal disease; corticosteroid treatment can have beneficial outcomes. If the disease is resistant to steroids and recurrent disease is on the nail, use of hydroxychloroquine, minocycline and iv immunoglobulin have been described as succesfull treatment as well[1,4,8].

One of the first reported uses of glucocorticoids without complications or accompanying SLE was in the cases of Jang et al. They administered prednisone to one of their patients with Kikuchi disease with prolonged fever and annoying symptoms lasting more than 2 weeks despite aspirin and NSAIDs, to one having recurrent disease and another who strongly desired a faster return to work and responses were satisfactory. In the light of their experience Jang and colleagues recommended to widen the indications for corticosteroid use in KFD to less severe forms of the disease[1]. However, short course and reduced dosages of corticosteroids might be responsible for recurrences even though they were manageable as outpatient base. There isn't a

consensus for when to start, the dosage and duration of steroid treatment; earlier and longer course of treatment may provide a better outcome.

Most common affected organ was reported to be skin after lymph nodes. Clinical and histopathological cutaneous findings in KFD are heterogeneous and no specific skin changes in KFD lesions have been described. It has been reported by Sumiyoshi et al. that patients with skin lesions had more severe clinical signs such as fever and liver disfunction[7]. In our case, we started 1 mg/kg metilprednisolone to our patient on the 3rd week of his symptoms, considering the increased LDH, high AST/ALT levels, bicytopenia and cutaneous involvement as indicators to a complicated and more severe course of the disease and tapered the dosage slowly and continued longer than most of the reported cases. He significantly benefited from systemic administration of corticosteroid and there is no recurrence since then.

In conclusion, KFD is a rare condition generally with a benign self limited course. Management of KFD is typically supportive; corticosteroids and immune suppressive treatment are reserved for severe cases. Despite this general benign nature of the disease symptoms maybe troubling and more ominous course may be experienced. Proper evaluation and diagnosis may help to start appropriate treatment for patients in time. There is no reported pathognomonic pattern of the disease, becoming more familiar with this condition can help to improve patient outcomes. For patients who are diagnosed by biopsy and do not respond to initial symptomatic treatment and having rash, cytopenias, increased ALT, AST and LDH levels; earlier initiation of corticosteroids with adequate dose and duration may be an effective option. This can provide an early and sustained recovery.

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