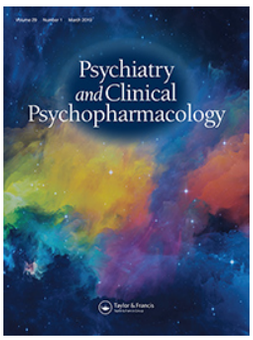

Psychiatry and Clinical Psychopharmacology

ISSN: 2475-0573 (Print) 2475-0581 (Online) Journal homepage: https://www.tandfonline.com/loi/tbcp21

# Improvement of an atypical Kikuchi-Fujimoto disease (KFD) with antidepressant treatment: the first psychiatric approach to a KFD case

Murat Eren Ozen, Mehmet Hamdi Orum, Aysun Kalenderoglu & Murad Atmaca

**To cite this article:** Murat Eren Ozen, Mehmet Hamdi Orum, Aysun Kalenderoglu & Murad Atmaca (2019) Improvement of an atypical Kikuchi-Fujimoto disease (KFD) with antidepressant treatment: the first psychiatric approach to a KFD case, Psychiatry and Clinical Psychopharmacology, 29:1, 107-109, DOI: 10.1080/24750573.2018.1431352

**To link to this article:** https://doi.org/10.1080/24750573.2018.1431352

© 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

Published online: 02 Feb 2018.

Submit your article to this journal

Article views: 471

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=tbcp21

PSYCHIATRY AND CLINICAL PSYCHOPHARMACOLOGY
2019, VOL. 29, NO. 1, 107–109
https://doi.org/10.1080/24750573.2018.1431352

Taylor & Francis
Taylor & Francis Group

CASE REPORT

OPEN ACCESS Check for updates

# Improvement of an atypical Kikuchi-Fujimoto disease (KFD) with antidepressant treatment: the first psychiatric approach to a KFD case

Murat Eren Ozen [a], Mehmet Hamdi Orum [b], Aysun Kalenderoglu [b] and Murad Atmaca [c]

[a]Private Adana Hospital, Psychiatry, Adana, Turkey; [b]Department of Psychiatry, Adiyaman University Faculty of Medicine, Adiyaman, Turkey; [c]Department of Psychiatry, Firat University Faculty of Medicine, Elazig, Turkey

**ABSTRACT**

Kikuchi-Fujimoto disease (KFD) is a sporadic and benign disorder of the lymph nodes of young individuals. A preceding fever, occasional skin rashes, and lymphopenia, suggest a viral aetiology and there have been reports of viral association. However, so far, no infectious agent has been proved to be aetiologically related. We herein report KFD in a 27-year-old female who presented with fevers, weight loss and tender cervical lymph nodes. The patient had depressive symptoms before the onset of KFD. During the disease process, depressive symptoms worsened with the KFD course. She had not relieved with the supportive treatment and major depressive disorder (MDD) became more severe gradually. After the treatment of MDD and with the improvement of mental health, clinical symptoms and the lymph node growth became reversed. The authors conclude that this clinical course of KFD with the treatment of MDD suggests an immune system response or immunological problem in these patients.

**ARTICLE HISTORY**
Received 25 December 2017
Accepted 18 January 2018

**KEYWORDS**
Kikuchi-Fujimoto disease; histiocytic necrotizing lymphadenitis; major depressive disorder; antidepressive agents

## Introduction

Kikuchi-Fujimoto disease (KFD), also known as subacute necrotizing histiocytic lymphadenitis, is a benign, sporadic, and self-limited disease with an uncertain aetiology. KFD usually presents with fever and cervical lymphadenopathy in healthy young women with most cases being under the age of 30 years. Fever is the most prominent symptoms and can persist for a week [1]. The main clinical feature is typically involvement of the unilateral cervical lymphadenopathy (56–98% of the cases) that is seen in all of the patients but there may be involvement of the axillary, mediastinal, iliac, intraparotid, celiac, retrocrural, and peripancreatic lymph nodes [2]. The onset of the disease could be acute or subacute and evolves over two to three weeks. Systemic symptoms and lymphadenopathy generally resolve within weeks or months (1–4 months) [3].

In the literature search, there has not been any defined or reported psychiatric symptoms or disorders that comorbid KFD. In this case, we present a patient suffering from KFD with an atypical onset, course, poorly responsive to supportive treatments and its improvement with antidepressant medication.

## Case presentation

A 27-year-old female from Adana (The Mediterranean region, Turkey) came to our psychiatric outpatient clinic with the complaints of decreased interest in activities, fatigue, and guilt. A year and a half ago, the patient had managed by sertraline 50 mg/day but not used more than one week. After 3 months, she had started to have an ongoing intermittent fever (daily spikes reaching up to 39.2°C), weight loss, and decreased appetite. There had been no history of chronic cough, diarrhoea, or other significant symptoms. A referred pain from the neck to jaw and teeth had started and fever was prominent. Evaluations by a dentist and internal medicine specialist had revealed normal signs. The treatment for this case had been managed by corticosteroids and antipyretics. But, this approach had not reversed the disease progression or relieve the patient's complaints enough, so she had admitted to emergency services for many times.

In her background, there were stressful psychosocial events related to interpersonal relations. Her sister and brother had been diagnosed with generalized anxiety disorder in her family history. There was no history of use of alcohol, cigarette and cannabis. She had no a diagnosis of systemic lupus erythematosus or infections and especially tuberculosis. There was no family history of autoimmune diseases and tuberculosis. The patient was married, having two children, unemployed and had left school after the fifth grade to live with her family. In the psychiatric assessment, she gave relevant answers to questions but she had a slowed speech. Her mood was depressed with elevated negative affect. Her judgement and insight were complete. She had no suicidal

CONTACT Mehmet Hamdi Orum mhorum@hotmail.com Private Adana Hospital, Psychiatry, Adana, Turkey

© 2018 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

thoughts. Physical examination (e.g. spleen, liver, and thyroid), laboratory results (e.g. complete blood count, thyroid hormones, liver and kidney functions, electrolytes, peripheral smear test, anti-nuclear antibody, anti-double-stranded deoxyribonucleic acid, and rheumatoid factor), and chest X-ray were within the normal range. There was no evidence of doubts for any disease other than lymph nodes. Magnetic resonance imaging showed 5 (3 of mobile, 2 fixed) lymph nodes on the left side and 4 (all of them mobile) in the right axillary region (totally 9), and 4 (all mobile) lymph nodes on the left side and 4 (3 mobile, 1 fixed) on the right side of the cervical region (totally 8). There was no pain associated with each node or due to their enlargement. There was no increase in endurance and temperature on the mass. No abnormal findings were found in the endoscopic examinations of oropharynx, larynx, and nasopharynx. An excisional biopsy of affected lymph nodes showed irregular paracortical areas of coagulative necrosis with abundant karyorrhectic debris. After the consultation of ear–nose–throat specialist, the patient diagnosed with KFD, with atypical signs.

Based on his clinical presentation, according to the 'Diagnostic and statistical manual of mental disorders', 5th edition, a diagnosis of major depressive disorder (MDD) was postulated the patient who had depressive symptoms before the onset of disease related to fever and lymphadenopathy. She was treated by fluoxetine 20 mg/day (in the morning) and mirtazapine 30 mg/day (nightly). By the end of the first month, she was in partial remission. Fluoxetine 20 mg/day was added to the treatment in the afternoon. Evaluation in the eighth week revealed a full remission and free of depressive symptoms. It was decided to continue on this daily dosage (fluoxetine 40 mg and mirtazapine 30 mg). On the follow-ups (12 and 16 weeks), her mood changes went in a positive way with accompanying relief of KFD course, which showed a decrease in lymph node growth and without the need to excise any of them. On the sixth evaluation, her KFD symptoms relieved well and there has been no need to supportive medications (especially corticosteroids) for fever. She has not admitted to emergency services again while the present treatment was continued. The Hamilton Rating Scale for depression applied to the patient initially (score was 43) and at 12th week (score was 20) has demonstrated the recovery in numerical terms.

## Discussion

KFD is a self-limiting disease of unknown aetiology involving the lymph nodes that diagnosed on the basis of histopathological evaluation showing necrotising lymphadenitis characteristically. The patients are young and seek care because of fever, cervical lymphadenopathy, and acute tender [4]. The main aim of the treatment in KFD is controlling the autoimmune reactions with different choices (corticosteroids, antipyretic drugs, non-steroidal anti-inflammatory drugs, hydroxychloroquine, and intravenous immunoglobulin) and supportive therapy [5]. While the lymph nodes in a typical KFD patient are unilateral and cervical [2], it was bilateral, also axillary and cervical in our case. There was no a self-limitation and symptoms persisted for months, over one year. Pain is another common feature of KFD reported recently [2] which is not seen in this case.

From the psychiatric view, our patient had depressive symptoms before the onset of KFD. She did not relieve the supportive care (corticosteroids and antipyretics) and MDD became more severe gradually. Subsequent to antidepressant treatment, the lymph node growth and related symptoms became reversed. The supportive treatment was stopped by the amelioration of MDD. This clinical course and improvement of KFD with the treatment of MDD suggests an immune system response or immunological problem in these patients.

There is now evidence to suggest that MDD is accompanied by signs of an immune response. Chronic stress and depression are widely known to downregulate the immune system. An imbalanced immune system has long been to influence a variety of mood disorders including anxiety, obsessive-compulsive disorders and MDD. Although there is not a direct correlation, cytotoxic T cells ($CD8^+$ T lymphocyte) is shown to be a useful indicator in assessing the potential relationship between MDD and immunity [6]. Ko et al. [7] reported that depression and anxiety may be associated with increased levels of CD8 in T-lymphocyte subsets, suggesting that an imbalance of T-lymphocyte subsets may be a factor facilitating MDD in some immune-depressed patients. The studies showed that the immune response may be altered or enhanced by the help of some other drugs, including antidepressants. Several antidepressants can reverse this impairment, with or without effects in normal subjects. Although the central nervous system is undoubtedly involved in these events, some psychotropic drugs can also exert direct effects on lymphoid cells (i.e. natural killer cells and B lymphocytes) [8]. Thornton et al. [9] demonstrated that the psychological treatment directly reduces depressive symptoms and indirectly reduces inflammation. According to the study of Guilbaud et al. [10], women with alexithymia exhibit decreased CD4 (T helper cell)/CD8, as well as reduced CD4 percentages. It is demonstrated that alexithymic women have altered immune function with a predominance of depressed cell-mediated immunity and a skewed Th1 (Type 1 T helper)/Th2 (Type 2 T helper) towards Th2 response.

The treatment process of KFD could be enriched by selecting antidepressants with anti-inflammatory properties as well. The TCA nortriptyline had antidepressant effects compared to the SSRI escitalopram among patients with a CRP > 3 mg/L [11]. Hence, future antidepressant treatment algorithms may target the

inflammatory cascade. Besides antidepressants, the inclusion of specific symptoms, inflammatory biomarkers such as C-reactive protein or interleukin 6, and anti-inflammatory agents may help in the development of more personalized antidepressant treatment procedures. Animal studies revealed that tumour growth inhibition by mirtazapine is thought to be due to the alteration of the tumour microenvironment, which includes the activation of the immune response and the recovery of serotonin level [12]. Fluoxetine is found to able to reverse T cell reactivity impairment in vitro by a direct action at clinically relevant doses [8]. These results highlight the relevance of pharmacological treatment of stress and depression, and may help to begin elucidating the complex events triggered (directly and/or indirectly) by antidepressants in non-neuronal cell types [9].

## Conclusion

In summary, studies investigating the interaction of inflammation and depression have three main findings: (1) inflammation markers have been found at increased levels among the patients with MDD; (2) inflammation increases the risk of depression; and (3) inflammatory agents induce depressive symptoms, which can be treated with antidepressants [11].

The psycho-immune associations of the final model are physiologically consistent and suggest that distress-related alterations in killer lymphocyte immunity may play a role in the biobehavioral mechanisms linked with immunologically deficient patients' pathogenesis. On the other hand, which is still a question, data suggest that inflammation can contribute to depressive symptoms, although the converse remains untested. Immunocellular mechanisms that account for the association between psychosocial risk factors and increased susceptibility to faster progression of immunodeficient patients are largely unknown [13]. Validation of these findings might provide new clues on the mechanism by which early life immune modulation might impact mood response in adults and provide a further link between immune and emotional well-being. Corticosteroids may have worsened the clinical course indirectly or directly by depressing the immune system, and, antidepressants or a good mental health may have been a factor in the relief of the disease by immune system enhancers and/or modulators [11].

The unresponsive and atypical forms of KFD could be a starting point for further psychiatric evaluations and investigations which may alter the course and the treatment.

## Acknowledgements

Concept – M.E.O.; Design – M.H.O., A.K.; Supervision – M.A., M.E.O.; Resource – M.E.O., M.H.O.; Materials – M.E.O., M.H.O.; Data Collection and/or Processing – M.E.O., M.H.O.; Analysis and/or Interpretation – M.A., A.K.; Literature Search – M.E.O.; Writing – M.E.O., M.H.O.; Critical Reviews – M.A.

## Disclosure statement

No potential conflict of interest was reported by the authors.

## ORCID

*Murat Eren Ozen* http://orcid.org/0000-0003-2981-8036
*Mehmet Hamdi Orum* http://orcid.org/0000-0002-4154-0738
*Aysun Kalenderoglu* http://orcid.org/0000-0002-8216-8610
*Murad Atmaca* http://orcid.org/0000-0003-2772-4124

## References

[1] Duskin-Bitan H, Kivity S, Olchovsky D, et al. Kikuchi-Fujimoto disease. Isr Med Assoc J. 2010;12(10):617–621.
[2] Bosch X, Guilabert A, Miquel R, et al. Enigmatic Kikuchi-Fujimoto disease: a comprehensive review. Am J Clin Pathol. 2004;122(1):141–152.
[3] Sousa AA, Soares JMA, Santos MHS, et al. Kikuchi-Fujimoto disease: three case reports. Sao Paulo Med J. 2010;128(4):232–235.
[4] Kucukardali Y, Solmazgul E, Kunter E, et al. Kikuchi-Fujimoto disease: analysis of 244 cases. Clin Rheumatol. 2007;26(1):50–54.
[5] Deaver D, Horna P, Cualing H, et al. Pathogenesis, diagnosis, and management of Kikuchi- Fujimoto disease. Cancer Control. 2014;21(4):313–321.
[6] Rattazzi L, Piras G, Ono M, et al. $CD4^+$ but not $CD8^+$ T cells revert the impaired emotional behavior of immunocompromised RAG-1-deficient mice. Transl Psychiatry. 2013;3:e280.
[7] Ko FY, Tsai SJ, Yang AC, et al. Association of CD8T cells with depression and anxiety in patients with liver cirrhosis. Int J Psychiatry Med. 2013;45(1):15–29.
[8] Frick LR, Rapanelli M, Cremaschi GA, et al. Fluoxetine directly counteracts the adverse effects of chronic stress on T cell immunity by compensatory and specific mechanisms. Brain Behav Immun. 2009;23(1):36–40.
[9] Thornton LM, Andersen BL, Schuler TA, et al. A psychological intervention reduces inflammatory markers by alleviating depressive symptoms: secondary analysis of a randomized controlled trial. Psychosom Med. 2009;71(7):715–724.
[10] Guilbaud O, Curt F, Perrin C, et al. Decreased immune response in alexithymic women: a cross-sectional study. Biomed Pharmacother. 2009;63(4):297–304.
[11] Kohler O, Krogh J, Mors O, et al. Inflammation in depression and the potential for anti-inflammatory treatment. Curr Neuropharmacol. 2016;14(7):732–742.
[12] Fang CK, Chen HW, Chiang IT, et al. Mirtazapine inhibits tumor growth via immune response and serotonergic system. PLoS One. 2012;7(7):e38886.
[13] Greeson JM, Hurwitz BE, Llabre MM, et al. Psychological distress, killer lymphocytes and disease severity in HIV/AIDS. Brain Behav Immun. 2008;22(6):901–911.