World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Case Report
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2025
Volume: 4; Issue: 2
Page: 957-963

KIKUCHI DISEASE IN ALPHA THALASSEMIA: CASE REPORT AND BRIEF REVIEW

Dr. Hamza Sümter*

Turkey.

Article Received: 11 March 2025 | | ***Article Revised: 1 April 2025*** | | ***Article Accepted: 22 April 2025***

***Corresponding Author: Dr. Hamza sümter**
Turkey.
DOI: https://doi.org/10.5281/zenodo.15303175

How to cite this Article: Dr. Hamza sümter (2025) KIKUCHİ DISEASE IN ALPHA THALASSEMIA: CASE REPORT AND BRIEF REVIEW. World Journal of Pharmaceutical Science and Research, 4(2), 957-963. https://doi.org/10.5281/zenodo.15303175

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ABSTRACT

Alpha thalassemia develops due to defects in the alpha gene. The clinical spectrum of alpha thalassemia ranges from asymptomatic cases to intrauterine demise. Kikuchi-Fujimoto Disease (KFD), also known as histiocytic necrotizing lymphadenitis, was first described in the 1970s. It presents with painful enlargement of the affected lymphoid tissue and fever. Its etiopathogenesis remains unclear, and diagnosis is based on morphology. KFD is a self-limiting benign disease. Although rare, its true prevalence is unknown. This study presents a case of Kikuchi disease in a patient with alpha thalassemia involving two alpha gene defects. The case was documented as no similar case was found in the literature, aiming to contribute to the knowledge of Kikuchi disease in alpha thalassemia patients.

KEYWORDS: Kikuchi- fujimoto, thalassemia alpha, histiocytic necrotizing lymphadenitis, fever, prognosis.

INTRODUCTİON

Kikuchi-Fujimoto Disease (KFD) commonly presents with painful cervical lymphadenopathy accompanied by fever, although it can occur at any site in the body. While men and women have an equal risk, it is more frequently observed in women. The disease typically occurs in individuals under the age of 40 but can be seen at any age.[1,2] Although rare worldwide, it is more common among Asian populations.[2] However, its true prevalence remains unknown. KFD's association with autoimmune diseases is noteworthy.[3] Despite various hypotheses, the pathogenesis is not fully understood. Histological evaluation is required for diagnosis. In biopsy samples, histiocytes are positive for CD68, CD163, CD11C, and myeloperoxidase, while negative for S100 and CD1a.[4-7] Differential diagnosis includes both malignant and benign conditions(frequent or rare causes that may form a palpable mass.[8]

Hemoglobin is composed of two alpha and two beta chains. While two gene loci are responsible for beta chain synthesis, four loci are involved in alpha chain synthesis. Depending on the severity of the defect in these loci, alpha thalassemia subtypes emerge. Defects in two alpha genes can present as (αα/--) or (α-/α-), forming the homozygous and heterozygous alpha thalassemia carrier groups.

4 Functional Alpha Genes (αα/αα): Normal

3 Functional Alpha Genes (αα/α-): Silent Alpha Carrier

2 Functional Alpha Genes (α-/α-): Heterozygous Carrier

2 Functional Alpha Genes (αα/--): Homozygous Carrier

1 Functional Alpha Gene (α-/--): Hemoglobin H Disease

Nonfunctional Alpha Genes (--/--): Hemoglobin Barts (Hydrops Fetalis).

CASE REPORT

A 43-year-old female patient was evaluated in the hematology outpatient clinic due to painful cervical swelling and a fever of 38.3 °C. Upon questioning, no history of medical or herbal drug use was found concerning the fever, which had been present for two days. Physical examination revealed cervical lymphadenopathy, but no other lymphadenopathy was detected. Laboratory tests showed normal biochemical parameters (transaminases and renal function tests). The complete blood count results were as follows: leukocytes: 3440/µL, neutrophils: 1620/µL (normal: 1600–2000/µL), hemoglobin (Hgb): 10.3 g/dL (normal: 12–16 g/dL), platelets (Plt): 203 K/µL (normal: 150–400 K/µL), red blood cells (RBC): 4.93 million/µL (normal: 3.5–5 million/µL), mean corpuscular volume (MCV): 68.5 fL (normal: 80–100 fL), and C-reactive protein (CRP): 13.6 mg/dL (normal: 0–5 mg/dL). No atypical cells were observed in the peripheral blood smear (Figures 1–2). Given the low MCV and elevated RBC in the complete blood count, a review of the hospital's medical records revealed hemoglobin electrophoresis results (Figure 3). Genetic testing for a suspected thalassemia variant identified a deletion in two alpha genes (Figure 4). Viral markers (HBV, HCV, HIV) showed no pathology. Ultrasonography of the palpable neck swelling revealed a 11 x 19 mm lymphadenopathy (LAP) in the left submandibular region, a 13 x 24 mm LAP in the right submandibular region, and bilateral axillary LAPs measuring 6.5 x 13 mm. Due to suspicion of malignancy based on the ultrasonographic findings, an excisional biopsy was performed. Histopathological examination showed paracortical thickening and macrophages, some with crescentic morphology, that had phagocytosed apoptotic cellular debris. The findings were interpreted as Kikuchi-Fujimoto disease (KFD). In contrast to the expected elevated sedimentation rate reported in the literature for KFD [8], this case had a sedimentation rate of only 1 mm/h. During follow-up, no treatment other than nonsteroidal anti-inflammatory drugs (NSAIDs) was administered. At the three-month follow-up, spontaneous regression was observed.

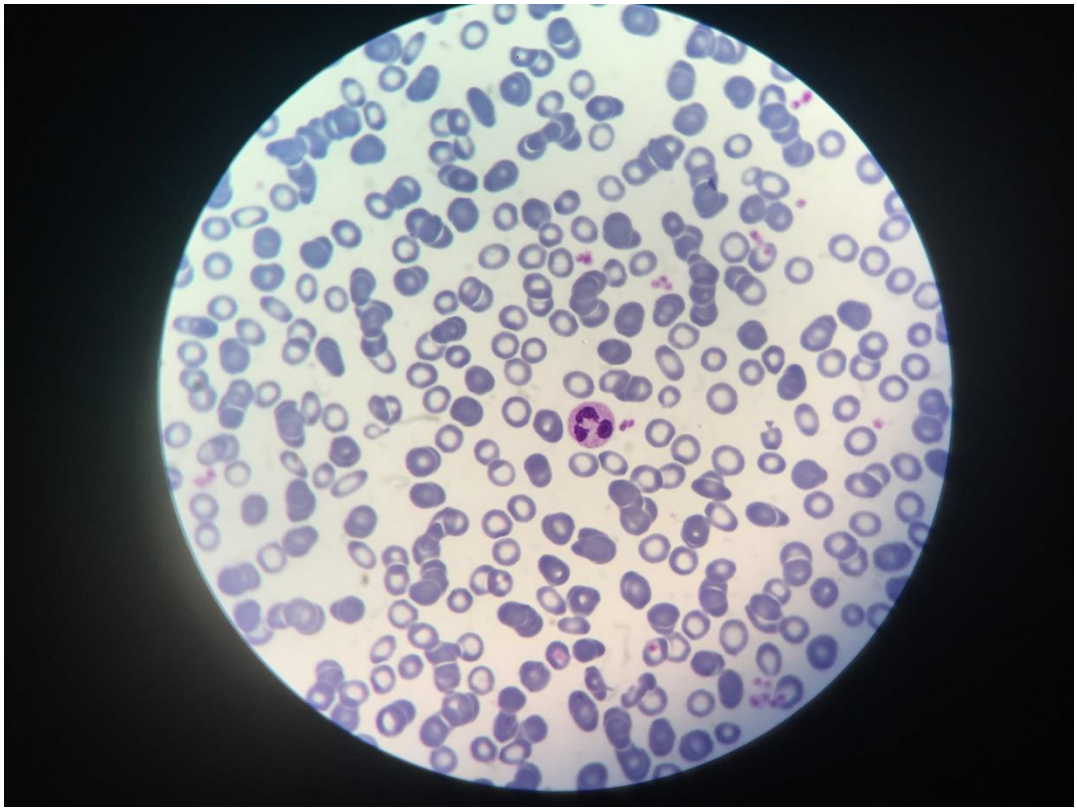


Figure 1.

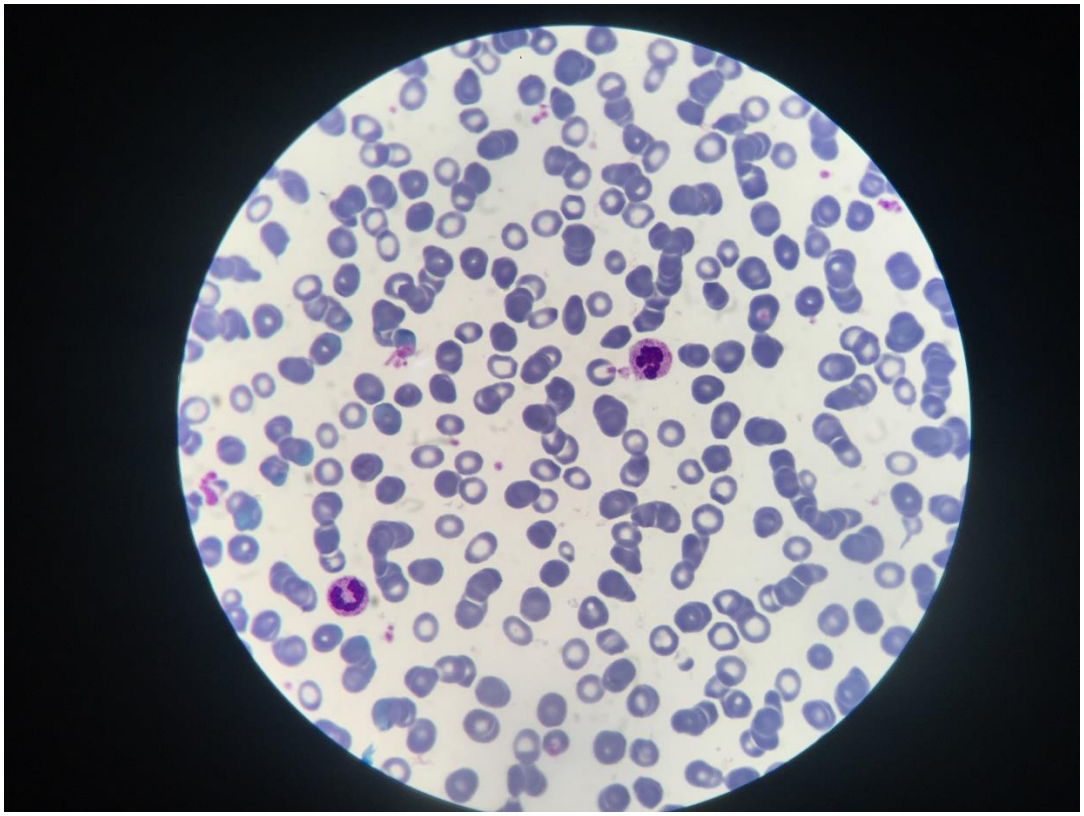
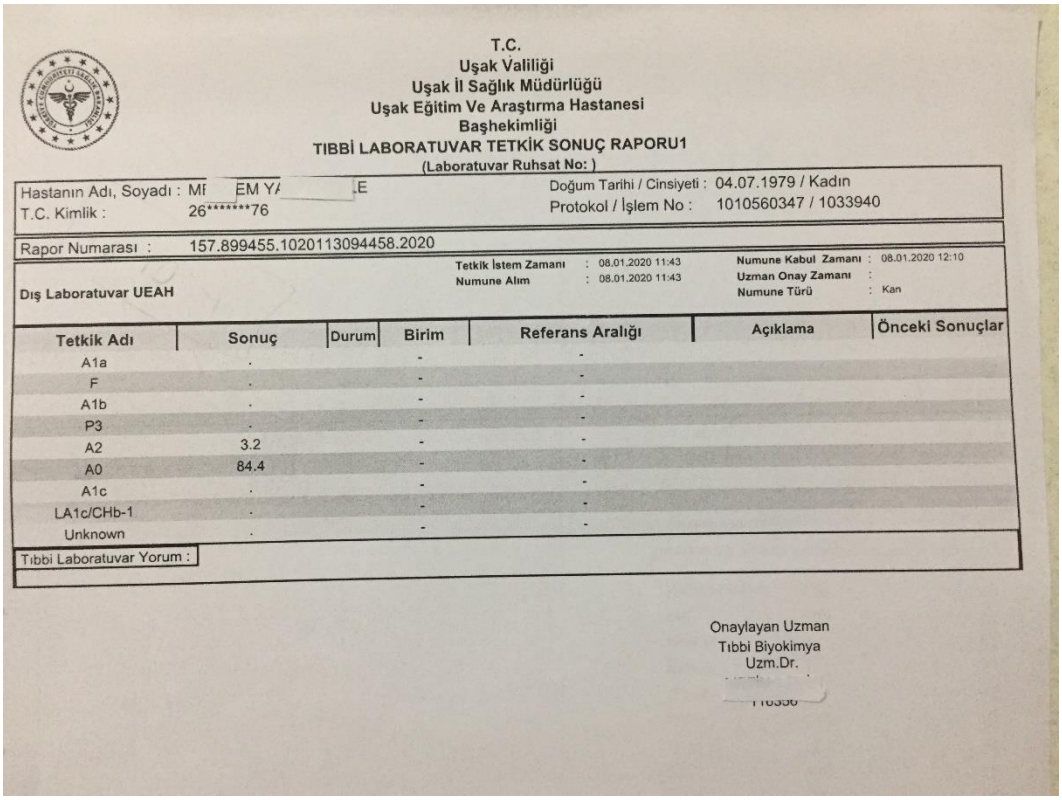


Figure 2.



T.C.
Uşak Valiliği
Uşak İl Sağlık Müdürlüğü
Uşak Eğitim Ve Araştırma Hastanesi
Başhekimliği
TIBBİ LABORATUVAR TETKİK SONUÇ RAPORU1
(Laboratuvar Ruhsat No:)

Hastanın Adı, Soyadı : MI EM YA LE
T.C. Kimlik : 26*******76
Doğum Tarihi / Cinsiyeti : 04.07.1979 / Kadın
Protokol / İşlem No : 1010560347 / 1033940

Rapor Numarası : 157.899455.1020113094458.2020

Dış Laboratuvar UEAH

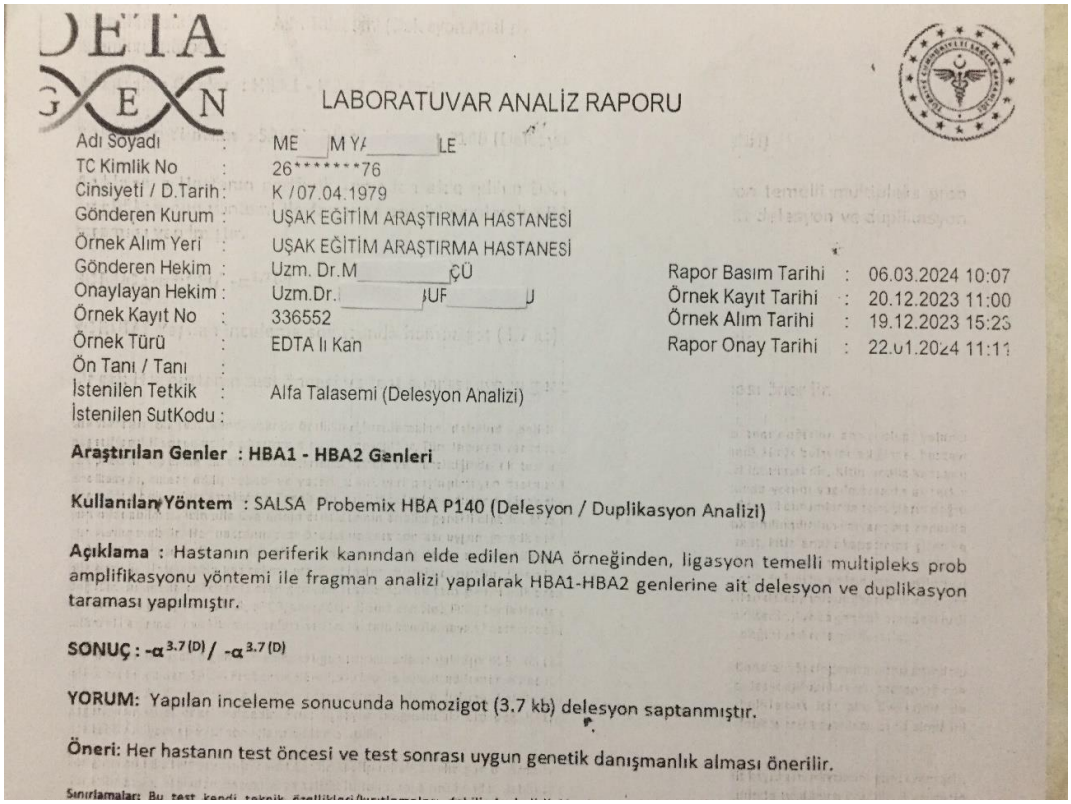
Tetkik İstem Zamanı : 08.01.2020 11:43
Numune Alım : 08.01.2020 11:43
Numune Kabul Zamanı : 08.01.2020 12:10
Uzman Onay Zamanı :
Numune Türü : Kan

Tetkik Adı	Sonuç	Durum	Birim	Referans Aralığı	Açıklama	Önceki Sonuçlar
A1a	.		-	-		
F	.		-	-		
A1b	.		-	-		
P3	.		-	-		
A2	3.2		-	-		
A0	84.4		-	-		
A1c	.		-	-		
LA1c/CHb-1	.		-	-		
Unknown	.		-	-		

Tıbbi Laboratuvar Yorum :

Onaylayan Uzman
Tıbbi Biyokimya
Uzm.Dr.

Figure 3.



DETA GEN

LABORATUVAR ANALİZ RAPORU

Adı Soyadı : ME M YA LE
TC Kimlik No : 26*******76
Cinsiyeti / D.Tarih : K / 07.04.1979
Gönderen Kurum : UŞAK EĞİTİM ARAŞTIRMA HASTANESİ
Örnek Alım Yeri : UŞAK EĞİTİM ARAŞTIRMA HASTANESİ
Gönderen Hekim : Uzm. Dr.M ÇÜ
Onaylayan Hekim : Uzm.Dr. UF U
Örnek Kayıt No : 336552
Örnek Türü : EDTA li Kan
Ön Tanı / Tanı :
İstenilen Tetkik : Alfa Talasemi (Delesyon Analizi)
İstenilen SutKodu :

Rapor Basım Tarihi : 06.03.2024 10:07
Örnek Kayıt Tarihi : 20.12.2023 11:00
Örnek Alım Tarihi : 19.12.2023 15:23
Rapor Onay Tarihi : 22.01.2024 11:11

Araştırılan Genler : HBA1 - HBA2 Genleri

Kullanılan Yöntem : SALSA Probemix HBA P140 (Delesyon / Duplikasyon Analizi)

Açıklama : Hastanın periferik kanından elde edilen DNA örneğinden, ligasyon temelli multipleks prob amplifikasyonu yöntemi ile fragman analizi yapılarak HBA1-HBA2 genlerine ait delesyon ve duplikasyon taraması yapılmıştır.

SONUÇ : $-\alpha^{3.7\,(D)}$ / $-\alpha^{3.7\,(D)}$

YORUM: Yapılan inceleme sonucunda homozigot (3.7 kb) delesyon saptanmıştır.

Öneri: Her hastanın test öncesi ve test sonrası uygun genetik danışmanlık alması önerilir.

Sınırlamaları: Bu test kendi teknik özellikleri/uygulamaları dahilinde analiz edilmiştir.

Figure 4.

DISCUSSION

Kikuchi–Fujimoto Disease, a rare disorder, was first described in 1972.[7] It is also known as histiocytic necrotizing lymphadenitis. Although it can occur at any age, most patients are under 40 years old.[9] Enlargement of the lymph node due to reactive lymphoid hyperplasia is observed.[7] The primary reasons for patient presentation are typically fever and swelling due to lymph node enlargement. The affected lymph nodes are tender and painful.[2] Although it can affect any part of the body, it primarily involves the cervical region.[7] Symptoms typically develop over a few weeks.[5] The size of the lymph node is typically 1-2 cm, though lymph nodes as large as 7 cm have been reported in the literature.[10] In 1-22% of cases, lymphadenopathy (LAP) is generalized.[5] Rare presentations, such as retroperitoneal lymphadenopathy (LAP), can also occur.[4] In clinical practice, maculopapular rashes, pruritus (in 40% of cases with skin involvement), upper respiratory tract symptoms, nausea, vomiting, headache, joint pain, night sweats, and weight loss may be observed.[2,5] Rashes are more common in children.[11] Mild hepatosplenomegaly has been reported in 5% of cases.[5,7,12] Presentations can vary. Although the etiology is unknown, viral and autoimmune causes are suspected.[13] These include Epstein-Barr virus (EBV), herpes simplex virus (HSV), cytomegalovirus (CMV), varicella-zoster virus (VZV), human herpesvirus (HHV6-7-8), parvovirus B-19, human papillomavirus (HPV), hepatitis B virus (HBV), human T-lymphotropic virus (HTLV-1), rubella, paramyxovirus, parainfluenza, brucella, Bartonella henselae, Toxoplasma gondii, Yersinia enterocolitica, Entamoeba histolytica, and species of Mycobacteria.[5] Additionally, the relationship between the HLA-DPA1 and HLA-DPB1 genes has been highlighted in the Asian population.[5,12] While it is said that the male-to-female ratio is equal for this disease in Asia, most studies report a female predominance.[2] Due to its nonspecific manifestations, misdiagnosis is possible. Differential diagnoses include infectious diseases such as tuberculosis and cat scratch disease, non-Hodgkin lymphoma, systemic lupus erythematosus (SLE), blastic plasmacytoid dendritic cell neoplasm (BPDCN), Kawasaki disease, sarcoidosis, herpes simplex virus (HSV), Epstein-Barr virus (EBV), and metastatic adenocarcinoma.[6,7] According to one study, 12% of patients have a history of SLE.[7] There is no diagnostic test in the laboratory to confirm the diagnosis. Inflammatory markers (CRP, sedimentation rate, ferritin, LDH, transaminases) may be mildly elevated.[5] Leukopenia has been described in 20-58% of cases. Leukocytosis is rare (2-5%)[5]. Atypical lymphocytes were seen in 25% of cases in peripheral blood smear.[5]

Histopathology is essential in the diagnosis. Three different patterns have been described as proliferative, necrotizing and xanthomatous.[2,12] In lymph node pathology, histiocytosis and coagulative necrosis are observed in the cortical and paracortical areas. Cell destruction is mediated by cytotoxic CD8+ T lymphocytes.[14] Interferon gamma and interleukin-6 may play a role in pathogenesis[15]. In immunohistochemistry, lysozyme+, myeloperoxidase (MPO)+, CD4+, CD11C+, CD11C+, CD68+ , CD163+, S100-, CD1a- are expected.[2,5,6] Histiocytes in the lesion are lysozyme+, MPO+, CD4+, CD68+, CD163+, while lymphocytes are more CD8+ than CD4.[2,16] CD123+ is seen in plasmacytoid dentritic cells around the necrotic area.[2,16] A small number of B cells may also be present.[2]

The disease is self-limiting. The disease regresses spontaneously within 1-6 months.[5,16] A recurrence risk of approximately 3% has been reported.[7]

There is no specific drug in treatment. NSAIDs, corticosteroids, hydroxychloroquine have been tried.[12] It has been reported that anakinran, an interleukin-1 receptor inhibitor, can be used in case of multiple recurrence.[12]

Complications such as encephalitis, meningoencephalitis and cerebellar ataxia, which are rarely CNS lesions, may be observed.[12] Kikuchi associated asymptic meningitis has also been described.[17] Very rarely, kikuchi disease may

cause hemophagocytic lymphohistiocytosis (HLH). Mortality rates up to 20-42% have been reported in case of HLH. Intravenous immunoglobulin, methylprednisolone can be used in HLH. Results are better in children.[18,19] It has been reported that the risk of SLE development slightly increased in long-term follow-up after Kikuchi disease.[20]

In the literature, a case of KFD in hemoglobin H disease (a form of thalassemia due to a pathological condition in the 3 alpha gene) was described and persistent high fever was emphasized in that case.[21] In another case, KFD was described in sickle cell anemia and its relation with autoimmune disease was emphasized[3] Steroid treatment was given in both cases. In this case, which presented with two alpha gene mutations, the absence of elevated sedimentation was noteworthy. It regressed spontaneously without steroid treatment.

In conclusion, kikuchi disease should be considered in the presence of high fever and lymphadenopathy which may mimic malignancy. Adequate biopsy is the main diagnostic parameter. Spontaneous regression is expected. According to our current knowledge, the role of hemoblobin chain changes in the course of the disease is unknown.

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