Life-Threatening Presentation of Kikuchi-Fujimoto Disease in a 5-month-old infant

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ABSTRACT :

Kikuchi-Fujimoto disease, also known as histiocytic necrotizing lymphadenitis, is a rare inflammatory disorder affecting both children and adults all over the world with a higher prevalence among Asiatic populations. It is characterized by cervical lymphadenopathy, often associated with fever and night sweats. Its etiopathogenesis is not fully understood, although it may include predisposing genetic background and a possible infectious triggering event. The diagnosis is provided by anatomopathological and immunohistochemical study. The clinical course is generally favorable within few months. Herein, we report a case of a Tunisian infant presented with fever and multiple cervical lymphadenopathies complicated with subcutaneous infiltration and edema. The biological tests showed pancytopenia. Within 48 hours, the patient showed signs of respiratory distress due to tracheal compression. He was admitted in a pediatric intensive care unit and required assisted ventilation. He was also treated with antibiotics and intravenous corticosteroids. Histopathological examination of a lymph node biopsy showed necrotizing lymphadenitis with histiocyte infiltrate and multiple apoptotic cells and allowed the diagnosis of Kikuchi-Fujimoto disease. Clinical remission was achieved within two weeks. In conclusion, this uncommon disease has a wide clinical spectrum that sometimes includes severe symptoms. Thus, clinicians and pathologists should be aware of it in order to differentiate it from infectious diseases, lymphoma and other inflammatory disorders.

Key words: Kikuchi-Fujimoto disease; histiocytic necrotizing lymphadenitis; lymphadenopathy; infant

RÉSUMÉ :

La maladie de Kikuchi-Fujimoto, également connue sous le nom de lymphadénite nécrosante histiocytaire, est une maladie inflammatoire rare qui touche les enfants et les adultes dans le monde entier, avec une prévalence plus élevée dans les populations asiatiques. Elle se caractérise par des adénopathies cervicales, souvent associées à une fièvre et à des sueurs nocturnes. Son étiopathogénie n'est pas entièrement comprise, bien qu'elle puisse inclure un contexte génétique prédisposant et un éventuel événement infectieux déclencheur. Le diagnostic est établi par une étude anatomopathologique et immunohistochimique. L'évolution clinique est généralement favorable en quelques mois. Nous rapportons ici le cas d'un nourrisson tunisien présentant une fièvre et des adénopathies cervicales multiples compliquées d'une infiltration et d'un œdème sous-cutanés. Les examens biologiques ont montré une pancytopénie. Dans les 48 heures, le patient a présenté des signes de détresse respiratoire dus à une compression trachéale. Il a été admis dans une unité de soins intensifs pédiatriques et a nécessité une ventilation assistée. Il a également été traité avec des antibiotiques et des corticostéroïdes par voie intraveineuse. L'examen histopathologique d'une biopsie des ganglions lymphatiques a montré une lymphadénite nécrosante avec un infiltrat d'histiocytes et de multiples cellules apoptotiques, ce qui a permis de diagnostiquer la maladie de Kikuchi-Fujimoto. Une rémission clinique a été obtenue en deux semaines. En conclusion, cette maladie, peu commune, présente une présentation clinique variable qui inclut parfois des symptômes graves. Les cliniciens et les pathologistes doivent donc la connaître afin de la différencier des maladies infectieuses, des lymphomes et d'autres maladies inflammatoires.

Mots clés: maladie de Kikuchi-Fujimoto; lymphadénite nécrosante histiocytique; nourrisson

Introduction

Kikuchi-Fujimoto disease (KFD), also called histiocytic necrotizing lymphadenitis, is an uncommon cause of lymphadenitis. It was first reported in Japan in 1972. Since then, this disease has been described worldwide, but more frequently in Asian population. It is known to be affecting adult, mostly young women, aged from 20 to 35 years [1,2]. However, there

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are numerous recent studies reporting the disease among pediatric patients [3,4]. Despite many recent studies and case reports, the exact etiology and pathogenesis remain unclear. Typically, KFD manifests with fever and cervical lymphadenopathy, with the posterior lymph nodes being the most commonly affected [5, 6]. Other systemic symptoms including skin rash, hepatomegaly, splenomegaly, arthralgia and myalgia are rare. Laboratory evaluation usually shows a slight increase of inflammatory biomarkers rate and leukopenia [5, 6]. As the biological and clinical findings are non-specific, patients can easily be mistaken for having viral infections, tuberculosis, lymphoma, autoimmune conditions such as systemic lupus erythematosus (SLE), or other inflammatory pathologies. Therefore, a lymph node biopsy is necessary for histopathological diagnosis. Although most patients have a benign course, a fatal issue and severe complications such as hemophagocytic lymphohistiocytosis have been reported in some cases [3]. In this article, we report a case of a Tunisian infant having a severe, life-threatening presentation of KFD.

Case presentation

A 5-month-old boy without any past medical history presented with persistent fever for 3 days, reaching 39.5°C, irritability, vomiting and diarrhea. Initial physical examination showed bilateral enlarged lymph nodes in the posterior cervical region, measuring approximately 1 cm, along with tenderness. Biological tests revealed anemia (hemoglobin rate at 10.6 g/dl), leukopenia at 1990/mm3, neutropenia at 960/mm3, lymphopenia at 520/mm3, thrombocytopenia at 84000/mm3, and mild elevated C-reactive protein (CRP: 58 mg/l). Blood smear showed the presence of activated lymphocytes, and the absence of malignant cells. Ultrasound showed conglomerated enlarged lymph nodes, with increased perinodal and central fat echogenicity, with a short diameter of the largest lymph node measuring 8 mm and no evidence of colliquative phenomena (figure1).

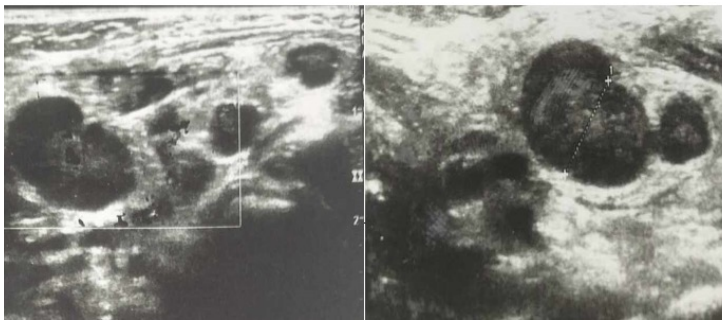

Figure 1: Cervical ultrasound showing a mass of adenopathies with a fatty centre

Given the suspicion for an infectious etiology, the infant received broad-spectrum intravenous antibiotics (ceftazidime 200 mg/kg/day; and amikacin 15 mg/kg/day). Within the next 48 hours, a progressive enlargement of the lymph nodes and an infiltrative subcutaneous cervical edema were noted (Figure 2).

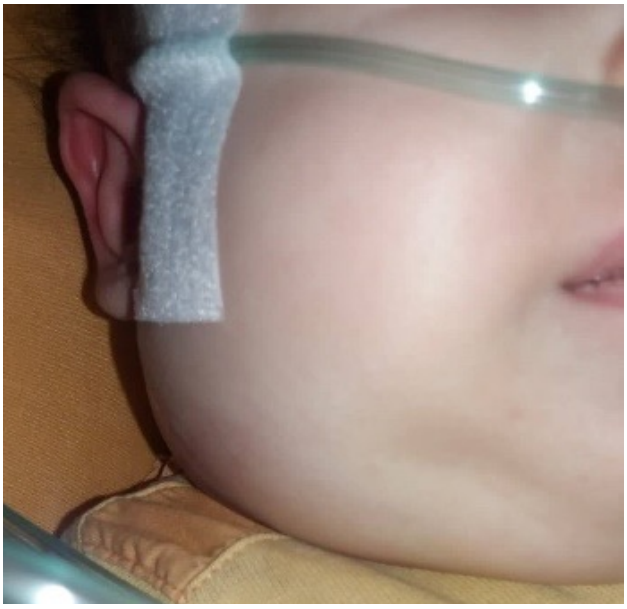

Figure 2: Cervical lymphadenopathy and subcutaneous infiltration in an infant with KFD

The Computed Tomography (CT) scan showed widespread perinodal infiltration and extensive cervical cellulitis, without obvious collection, exerting a mass effect on the aero-digestive tract associated with a slight edematous infiltration of the submandibular and parotid glands and multiple necrotic enlarged cervical lymph nodes. Afterwards, the infant showed signs of respiratory distress and hemodynamic instability. Therefore, he was transferred to a pediatric intensive care unit. He required emergent endotracheal intubation, assisted ventilation and fluid resuscitation. He was also treated with intravenous corticosteroids (methylprednisolone 2 mg/kg/day) for 5 days. Bacterial serum tests were all negative. Viral serologies including HIV, CMV, and EBV serologies were negative. Complement fractions (C3, C4) levels were normal. Quantitative and qualitative measurements of C1 inhibitors were performed, ruling out an angioneurotic edema.The histopathological examination of a lymph node biopsy showed the presence of punctuate necrotic foci, numerous histiocytes and small lymphocytes, with multiple nuclear debris and apoptotic cells. Moreover, no foci of suppuration, no caseous granulomas and no malignant cells were observed. These findings were consistent with Kikuchi-Fujimoto lymphadenitis. The assisted ventilation was maintained 5 days, then the patient's general condition improved, with progressive regression of the cervical cellulitis and lymphadenopathy. Defervescence was obtained within 48 hours after corticosteroids administration. After two weeks of hospitalization, biological assessment showed a complete normalization of inflammatory markers, blood white cells and platelets rate. Then, the boy was discharged with iron supplementation. Three months later,

at the follow-up visit, he was still in a good general condition, and the complete blood count was normal.

Discussion

KFD is an enigmatic disease that has been frequently reported in individuals of Asian descent [5,6]. Nowadays, a worldwide distribution has been noted, although the specific incidence remains unknown. In north Africa and more precisely in Tunisia, it is considered an uncommon cause of lymphadenopathy, and only few cases have been reported yet [7]. It affects both adult and pediatric population. The onset of KFD can either be acute or subacute, evolving over a period of 10 to 20 days [5, 6]. In our case, the onset was acute, at an early age of 5 months. The exact etiopathology of KFD remains unclear. It has been suggested that KFD may be the result of a reaction to a viral infection, or an autoimmune condition mainly SLE [5, 6]. Our patient didn't have any medical history of severe infections, nor autoimmune diseases. Besides, HIV, CMV, and EBV serologies were negative. However, other viral serologies including parvovirus B19, HHV6 and HHV8 were not performed. Therefore, the post-infectious theory is not fully excluded, and further studies has yet to be conducted in order to demonstrate the presumable role of these viruses in the etiopathology of KFD. Cervical lymphadenopathy is the most common manifestation (60-100%), and it is usually localized in the posterior cervical triangle and along the jugular carotid chain [1,3, 4]. In 72-88% of cases, it is unilateral [1,3, 4], yet it can be bilateral as in our observation. In some cases, supraclavicular, axillary, mediastinal, mesenteric, and inguinal lymph nodes may also be involved [1,2,3, 4]. The affected lymph nodes are usually solid, tender, and painful but not suppurative. Their size commonly ranges from 0.5 to 4 cm, but it can reach 6 to 7 cm in some rare cases [5]. Fever is frequently observed in KFD (35-77%) [3, 4]. According to Kang et al [3], the median duration of fever was 9 days, 37% of cases had prolonged fever (> 2 weeks), and 8% had fever for more than 4 weeks. In our case, the patient developed fever for 3 days, which was persistent 4 days after hospitalization. So, the total duration of fever was 9 days, which was similar to the literature's published data. In addition to fever and cervical lymphadenopathy, our patient presented with irritability, vomiting and diarrhea. In fact, other manifestations are less frequently reported in KFD, including skin rash (30-40%), nausea, vomiting, weakness, weight loss, headache, arthralgia, myalgia, night sweats, upper respiratory symptoms, hepatomegaly, splenomegaly, myocarditis and neurologic involvement mimicking meningitis [5,6]. Regarding the laboratory assessment, it usually shows leukopenia (20-74%) specifically neutropenia, anemia (20-40%), and/or thrombocytopenia (20-30%), mild elevated CRP, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), as well as abnormal liver enzymes [1,2,3,4]. In the literature, additional findings may include weakly positive antinuclear antibody (ANA) titers (4-15%) [4]. In our case, biological findings included pancytopenia and mild elevated CRP. Nevertheless, AAN were not tested.Imaging studies are not specific. Besides enlarged lymph nodes, CT-scan may show homogeneous contrast enhancement, perinodal infiltration, and in some cases an involvement of the parotid [8]. These radiological findings were similar to those described in our observation. Moreover, bacterial investigations and serologic testing can be useful to rule out the diagnosis of infectious diseases such as mononucleosis, toxoplasmosis, and tuberculosis. However, the diagnosis of KFD is confirmed by histological analysis of samples from an affected lymph nodes' biopsy. Characteristic features include focal necrosis predominantly in the paracortical region with abundant karyorrhectic debris and apoptic cells, and an extensive histiocytic infiltrate with numerous lymphocytes [9]. These histological features were observed in our patient, leading to the diagnosis of KFD. It is classically known that KFD is a benign condition that typically resolves within 1 to 6 months, with a low rate of recurrence. However, life-threatening associated conditions and severe complications may occur, including hemophagocytic lymphohistiocytosis, disseminated intravascular coagulopathy, pulmonary hemorrhage, pleural and pericardial effusion, myocarditis and acute heart failure [1]. Likewise, in our observation, a nearly fatal issue due to respiratory failure was noted. It was related to tracheal compression caused by the widespread cervical infiltration which was a remarkable feature in our case. In fact, perinodal infiltration has been frequently reported in other studies and KFD cases. Histologically, structures surrounding the lymph nodes are infiltrated by an attenuating perivascular and interstitial inflammatory cell population. However, the extension of this perinodal infiltration widely differs from case to case [8]. It may appear as a mere obliteration of the adjacent fat plane in some cases, or as a widespread infiltration involving nearly the entire cervical space as shown in our observation. Up to day, there are no specific guidelines regarding the management of KFD. Symptomatic measures using analgesics and antipyretics aim to alleviate lymph node tenderness and fever. In case of severe symptoms or prolonged fever lasting more than 2 weeks, glucocorticoids, mainly oral prednisolone, are recommended [3,4], but there is not a clear consensus on dosing or duration of the treatment. Given the severe course of the disease in our observation, the patient was treated with intravenous methylprednisolone (2 mg/kg/day) for 5 days, with a spectacular response. Other therapeutic options include intravenous immunoglobulin and hydroxychloroquine [2,10]. Our patient was unique as he had an early onset with an acute aggressive course of KFD. A major limitation to our case report was the incomplete medical records as some serologic testing were not per-

formed. Another constraint was the limited period of follow-up which was not sufficient to detect a possible recurrence, or the development of other conditions such as SLE.

Conclusion

It is important for clinicians and pathologists to recognize KFD as a separate entity in order to avoid a misdiagnosis of lymphoma, infectious diseases or other inflammatory disorders. Considering the possibility of recurrence and severe complications, a close and regular monitoring is required. Since no guidelines on the management of KFD are available, further studies are needed in order to assess the therapeutic options and long-term outcome, specifically in children.

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