

Case Report

J Korean Soc Pediatr Nephrol 2012;16:138-141
DOI: <http://dx.doi.org/10.3339/jkspn.2012.16.2.138>

ISSN 1226-5292 (print)
ISSN 2234-4209 (online)

신증후군 환자에서 Rituximab 사용 후 발생한 기쿠치병 1례

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Received: 31 August 2012
Revised: 7 September 2012
Accepted: 19 September 2012

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Kikuchi-Fujimoto Disease, A Possible Complication of Rituximab Treatment

Rituximab, a chimeric anti-CD20 IgG1 monoclonal antibody, has been used as a rescue therapy for steroid-dependent or refractory nephrotic syndrome. However, the adverse effects of rituximab are yet to be investigated. We report a case of a 9-year-old boy with steroid-dependent nephrotic syndrome who developed Kikuchi-Fujimoto disease after several cycles of rituximab therapy. Kikuchi-Fujimoto disease is a benign, self-limited necrotizing histiocytic lymphadenitis of unknown etiology. In the present case, Kikuchi-Fujimoto disease developed when the peripheral blood B-cell count of the patient was at nadir, and the lesion regressed slowly but spontaneously after recovery of the B-cell count. To our knowledge, although the pathologic diagnosis of Kikuchi-Fujimoto disease was unavailable, this is the first report of Kikuchi-Fujimoto disease with clinical diagnosis as a possible adverse effect of rituximab.

Key words: B-cell, Kikuchi-Fujimoto disease, Nephrotic syndrome, Rituximab

Introduction

Rituximab is a chimeric anti-CD20 IgG1 monoclonal antibody which inhibit CD20-mediated B-cell proliferation and differentiation by binding to CD20+ B-cells [1, 2]. Rituximab has been proposed as a rescue therapy for refractory nephrotic syndrome (NS) on the basis of favorable clinical observations [3]. However the long-term effects on maintaining remission and the information on the safety profile of rituximab are limited. Several published data reported on the unpredictable adverse effects of rituximab, such as interstitial pneumonia, severe ulcerative colitis and

acute fatal thrombocytopenia have been reported [4-6].

We report a case, the first to our knowledge, of Kikuchi-Fujimoto disease (KFD), a benign, self-limited necrotizing histiocytic lymphadenitis of unknown etiology [7, 8], which developed after several cycles of rituximab in a child with steroid-dependent minimal change NS. Although the pathologic diagnosis of KFD was unavailable in this case, the characteristic image findings supported the highly confirmative clinical diagnosis.

Case Report

An 8-year-old male developed NS in 2004, which was refractory over an 8-week course of daily oral prednisolone. He achieved first remission after seven high dose cycles of intravenous methylprednisolone, and a renal biopsy reported minimal change lesion. He was switched to oral steroid, but proteinuria relapsed in two days. He was treated with cyclosporine A (CyA) and oral steroid since March 2005, and remission was achieved. However, he remained steroid- and CyA-dependent with nine full-blown relapses for three years.

In May 2008, he was given rituximab intravenously at a dose of 375 mg/m² of body surface area weekly for two weeks, and his proteinuria remitted. He received additional doses according to the increase in peripheral CD19+ cell counts with or without relapse of NS, at approximately six-month-interval. In July 2010, he achieved a sustained complete remission and his steroid and CsA were tapered off.

The last rituximab infusion, the 7th cycle, was given in March 2011. His CD19+ cell count remained at nadir (0/uL, 0%), indicating persistent B-cell depletion, until August 29th.

On the 5th of September 2011, the patient developed a right infra-auricular mass with tenderness and an intermittent low grade fever. Laboratory tests for tuberculosis (Tb) and Mycobacterium other than tuberculosis (MOTT), including PCR of the mass aspiration samples as well as the interferon gamma assay from his peripheral blood, were all negative. His leucocytes count was $9.96 \times 10^3/\mu\text{L}$ (reference range: 4.0-10.0) which fall was within normal limit, while the erythrocyte sedimentation rate and the C-reactive protein were increased to 44 mm/hr (0-9) and 2.14 mg/dL (0-0.5), respectively. Computerized tomography (CT) revealed

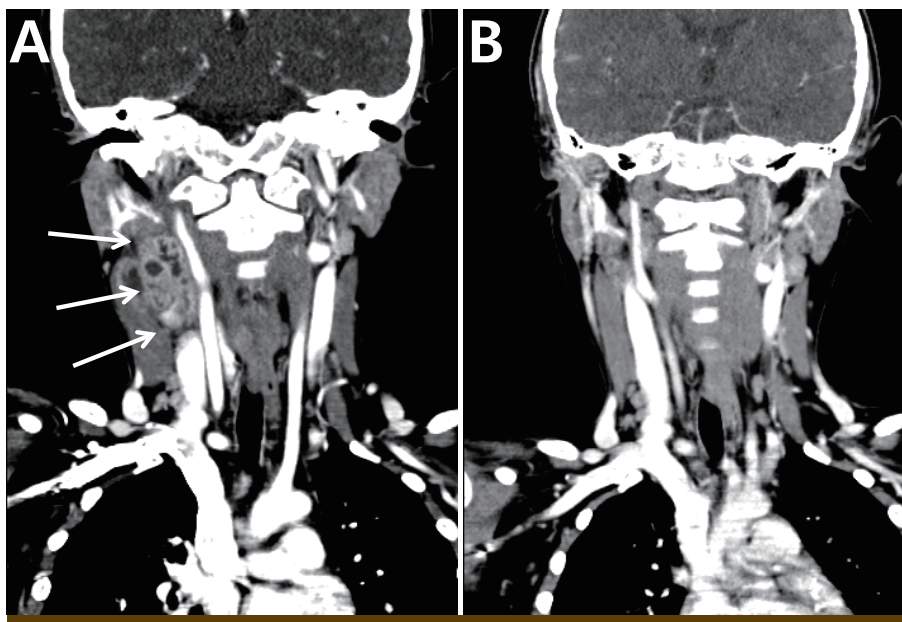


Fig. 1. Serial computerized tomography findings. (A) Multiple conglomerated necrotic lymph nodes in the right infra-auricular area (arrows, September 2011). (B) near total regression of the mass (December 2011).

multiple conglomerated necrotic lymph nodes, with the radiologic report suggesting tuberculosis-associated or necrotizing histiocytic lymphadenitis (Fig. 1). After two weeks of empirical antibiotics which had no effect, an excisional biopsy was planned. Meanwhile, his CD19+ cell count rose up to 9% (266/uL) on September 19th, followed by 10% on October 26th. While waiting for a few weeks for the procedure, however, the lymph nodes had been markedly diminishing in size, since mid-November. A follow-up CT scan on December 5th, 2011 stated a marked decrease in number and size of the lymph nodes with remnant central necrosis, and these findings suggested the resolving stage of KFD above other infectious lymphadenopathy or malignancy. By late December, the lesion had nearly disappeared and was not detectable in next January, 2012. Throughout the period of development and regression of KFD, his NS remained in quiescence.

Discussion

The golden standard of diagnosis of KFD is tissue biopsy followed by laboratory results and imaging studies to facilitate the diagnosis [9]. However, since a biopsy is an invasive procedure considering the self-limited course of the disease, imaging studies have gained diagnostic value increasingly in regions where KFD is relatively prevalent, mainly in the Northeast Asia including Korea. Recently published studies on radiologic findings for KFD have made the radiologic diagnosis highly more confirmative [9, 10]. The present case revealed clusters of multiple lymph nodes with internal necrosis and perinodal infiltrates which are described as the radiologic findings of KFD [9, 10]. Moreover, Kwon et al [9] also reported on the additional common features of KFD as: unilateral (right more common than left) and homogeneous enlargement of lymph nodes affecting levels II-V (II, most common). The present case affected the right level II lymph nodes displaying all the listed radiologic characteristics. Although we lost the optimal timing for biopsy in this case, the CT findings, negative laboratory results for infections such as tuberculosis,

unresponsiveness to 2 weeks of antibiotics and the self-limited course could provide evidences to support the diagnosis of KFD over other conditions.

The pathogenesis of KFD is not yet fully determined. Infectious etiologies, such as Epstein-Barr virus and parvovirus B19 have been claimed responsible. Unidentified viral or bacterial infection complicated by rituximab treatment may have led to acquiring KFD. In terms of limitations, the present case has not fully performed studies for viral infectious agents of KFD [7, 8]. In the histopathologic view, KFD generally shows CD8+ T-cell predominance in lymphocytes with a rare B-cell profile [7]. In the present case, the B-cell count was not recovered until the week before developing lymphadenopathy and the lesion diminished as (or after) the B-cell count increased. We hypothesize that alterations in the T-cell pool by B-cell depletion may have induced cytotoxic response [1-3, 7, 11] against associated antigens, to develop the supposed KFD. We hope this paper would be of a clinical help with reference to another possible unpredictable complication from rituximab use in NS. Further studies and reports are warranted to strengthen the association.

Acknowledgements

This study was supported by a grant (A080588) from the Korea Healthcare technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea.

한글요약

리툽시맵(Rituximab)은 CD20에 대한 키메라형 IgG1 단클론 항체로 스테로이드 의존성 또는 난치성 신증후군에 대한 새로운 치료약제로 이용되고 있다. 그러나 리툽시맵의 약제 부작용에 대해서는 아직까지 더 많은 연구가 필요하다. 저자들은 스테로이드 의존성 신증후군을 앓고 있던 9세 남아에서 수차례의 리툽시맵 사용 후 기쿠치병(Kikuchi-Fujimoto disease)이 병발한 증례를 보고하는 바이다. 기쿠치병은 자연 회복의 양성 경과를 보이는 조직구 과사성 림프절염으로 아직 원인은 알려져 있지 않다. 이 증례에서는 환

자의 말초 혈액 B 면역세포 수치가 매우 감소되었을 때 발병하였으며, 이후 환자의 B 면역세포가 회복되면서 서서히 자연 소실되었다. 이 증례는 비록 병리 조직학적 진단은 뒷받침되지 못하였지만 임상적으로 진단된 기쿠치병이 리툽시맙 사용의 부작용으로 발생할 수 있다는 연관성을 시사하는 첫 번째 보고로써, 소아 신증후군에서 리툽시맙 사용의 안전성에 대한 이해의 폭을 넓히고자 하였다.

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