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Case Report

Two Cases of an Enigmatic Entity: Kikuchi's Disease

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Background: Kikuchi's disease [KD] is a self-limited rare disorder characterized by necrotizing lymphadenopathy in especially women with a mean age of 27.4 years. It mostly arises in the posterior cervical triangle. Lympadenopathy may be accompanied by fever, chills, myalgias, arthralgias, splenomegaly, hepatomegaly and/or skin rashes. KD's etiology is unknown, and it is commonly misdiagnosed as lymphoma. Herein, we present two cases of KD consulted to our institute in two weeks period.

Case Presentations: The first case was a 41 year-old male presented with a posterior cervical lymphadenopathy of 2x1.7x1 cm in size. The second case was a 33 year-old female presented with a left axillary lymphadenopathy of 1.5x1x1 cm in size. The paraffin blocks of lymph node biopsies were evaluated. Similar findings were detected in both cases, and the diagnoses of KD were reached microscopically. There were multiple foci of patchy necrosis. Necrotic foci were composed of nuclear dusts phagocytosed by numerous histiocytes with crescentic nuclei that were positive for myeloperoxidase immunohistochemically. Numerous immunoblasts with atypical nuclei were detected.

Discussion: It should be noted that discriminating KD from systemic lupus erytematosus [SLE], cat-scratch disease, and particularly some lymphomas showing necrosis in the lymph nodes is usually difficult. A brief summary about the clinicopathological characteristics and clues about the differential diagnosis of KD are given in this report with two demonstrative cases in order to contribute a better understanding of this rare enigmatic entity.

Key Words: "Kikuchi's disease", "lymphadenopathy", "lymphadenitis", "necrosis".

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Introduction

Kikuchi's disease [KD] – [histiocytic necrotizing lymphadenitis, Kikuchi-Fujimoto lymphadenitis] was intially described in 1972 by Kikuchi and Fujimoto et al in Japan [1-4]. It is a self-limited rare disorder characterized by necrotizing lymphadenopathy in especially young Asian patients [mean age: 27.4 years], and much rarely in Western countries [1, 2]. Female-to-male ratio is 1.6/1 [1]. It mostly arises in the cervical lymph nodes, especially in posterior cervical triangle [1, 5]. It is usually unilateral [88.5%] [1, 5]. Less commonly it occurs in axillary and inguinal lymph nodes [1].

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Also, generalized lymphadenopathy have been reported [1]. KD is usually asymptomatic and lympadenopathy is usually painless. However lympadenopathy may be accompanied by leukopenia, fever, chills, myalgias, arthralgias, and/or skin rashes in 20% to 30% of cases [1, 3]. Involvement of extranodal sites, such as liver and spleen enlargement, is unusual but rarely reported in the literature [1]. Leukopenia below 4,000/mm3 may be detected in 56% of cases accompanied by mild lymphocytosis [1]. Atypical lymphocytes might be seen in 25% to 30% of cases [1,3,6]. There is no sign of bone marrow involvement [7]. Among laboratory tests, lactate dehydrogenase, interferon, and interleukin-6 levels may be elevated but they usually decrease to normal limits [1]. KD's etiology is still unclear although infections of Epstein-Barr virus [EBV], cytomegalovirus [CMV], parvovirus B19, Human Herpes Virus type 6 [HHV-6], and Human Herpes Virus type 8 [HHV-8], and autoimmunity have been

suggested in the literature [ioachmi]. In general, the disease tends to resolve spontaneously within several months [1 to 3 months] without any treatment [1]. About 3% show recurrences within several years [3]. Also, a few fatal cases have been documented that presented with fever and systemic necrotizing lymphadenitis were related to organ transplantation, necrotizing myocarditis, or fulminant hepatitis [1, 8-9]. It has still no specific therapy. Herein, we present two cases of KD consulted to our institute in two weeks period.

Case Presentations

The first case [Case 1] was a 41 year-old male presented with a posterior cervical lymphadenopathy of 2x1.7x1 cm in size that was present for a few days. The second case [Case 2] was a 33 year-old female presented with a left axillary lymphadenopathy of 1.5x1x1 cm in size. Their medical histories were unremarkable. Routine hematology and biochemical tests were in normal limits. Lymph node biopsies of those cases were performed at another institute and diagnosed as "necrotizing lymphadenitis". The cases were consulted to our department in the same two weeks period to differentiate particularly Kikuchi's disease from cat-scratch disease, SLE, and lymphomas showing necrosis. Hematoxylin & Eosin sections were prepared, and immunohistochemical and histochemical studies were performed from the paraffin blocks of each cases. Under light microscope, similar histopathological and immunohistochemical findings were detected in both cases. Paracortical hyperplasia and some reactive follicles were present. There were multiple foci of patchy necrosis dispersed in the subcortical and paracortical areas. Necrotic foci were composed of apoptotic nuclear dusts phagocytosed by numerous histiocytes with crescentric nuclei that were positive for CD68 and myeloperoxidase immunohistochemically. Necrotic foci were devoid of neutrophil and eosinophil leukocytes, and multinuclear giant cells. Numerous immunoblasts with atypical nuclei positive for CD30 were detected around the necrotic foci. There were CD3, CD4 and CD8 positive T cells more than CD20 positive B cells in the interfolllicular areas. Scattered plasma cells around the necrotic areas were detected. Both of the cases were negative for EBV immunohistochemically. Histochemically, no specific microorganism was observed by PAS [for fungi], Ehrlich-Ziehl-Neelsen [for acid resistant bacilli], and Warthin Starry [for Bartonella henselae]. The demonstrative microscopic photos of Case 1 are illustrated as Figure 1, and the microscopic photos of Case 2 are illustrated as Figure 2. The patients did not attend for follow-up in our institute, thus no laboratory or radiologic findings or prognostic information could be achieved.

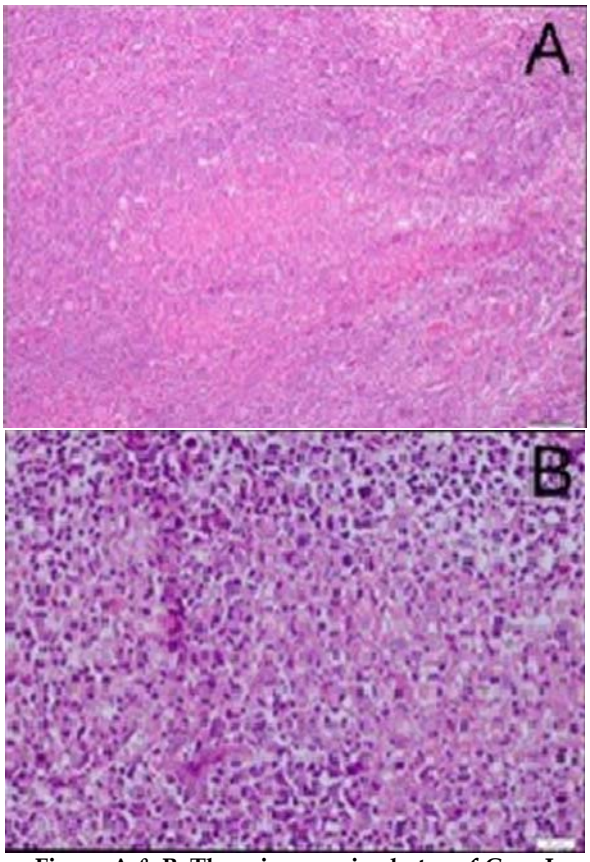


Figure A & B: The microscopic photos of Case-I
Necrotic foci in the lymph node containing necrotic and apoptotic nuclear debris, and crescent like histiocytes, [Hematoxylin &Eosin stain, x100, x400]

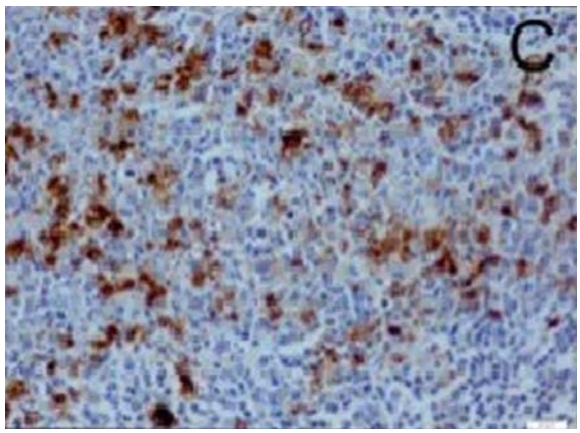


Figure C: The microscopic photos of Case-I
CD68 positivity of the histiocytes in the necrotic focus [Avidin-biotin-peroxidase method, x400]

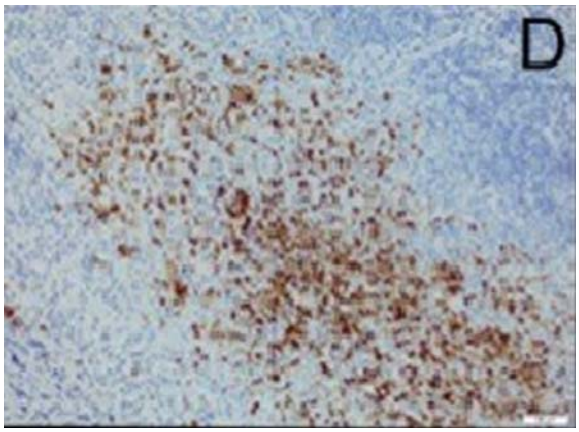


Figure D: The microscopic photos of Case-I Myeloperoxidase positivity of the histiocytes in the necrotic focus [Avidin-biotin-peroxidase method, x200]

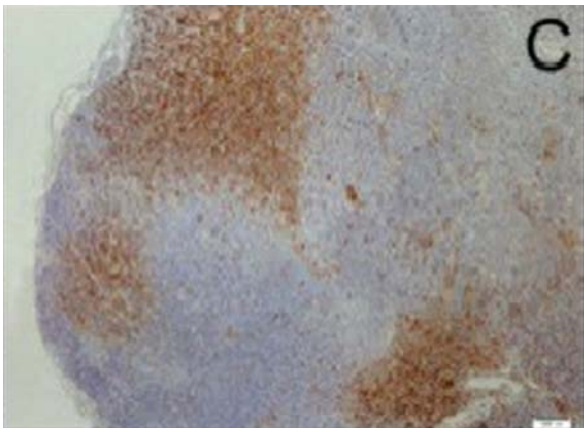
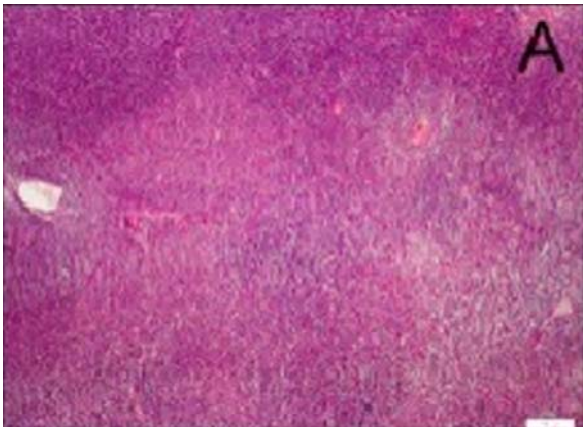


Figure C: The microscopic photos of Case 2 CD68 positivity of the histiocytes in the necrotic foci [Avidin-biotin-peroxidase method, x40]



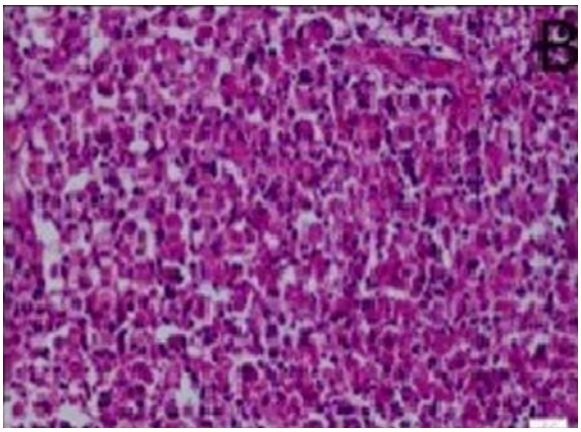


Figure 2 A&B: The microscopic photos of Case 2 Necrotic foci in the lymph node containing necrotic and apoptotic nuclear debris, and crescent like histiocytes, [Hematoxylin&Eosin stain, x40, x400]

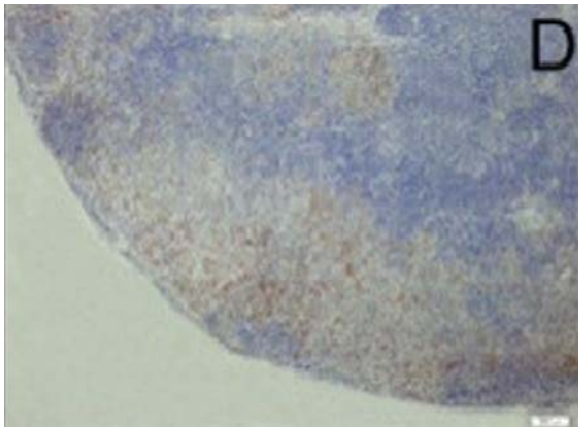


Figure D: The microscopic photos of Case 2 Myeloperoxidase positivity of the histiocytes in the necrotic foci [Avidin-biotin-peroxidase method, x40].

Discussion

Three histologic subtypes have been described for KD as "proliferative type", "necrotizing type" and "xanthomatous type", probably representing various stages in the evolution of the disease [2]. "Proliferative type" is considered as the earlier stage of KD composed of numerous immunoblasts with prominent nucleoli and basophilic cytoplasm in the paracortex, mimicking large cell lymphoma [2]. The immunoblasts are accompanied with large mononuclear cells, some histiocytes with curved nuclei called "crescentic histiocytes" and some with twisted nuclei, and aggregates of plasmacytoid dendritic cells [2]. Plasmacytoid dendritic cells seem like plasma cells however they are devoid of a clear Golgi area [2]. Karyorrhectic bodies are often dispersed among the plasmacytoid dendritic cells. The necrosis is often detected among the nests of these cells. The

"necrotizing type" is the most common type of KD. It is characterized by patchy areas of necrosis within the paracortex. The necrosis lacks neutrophils, has exytensive karyorrhectic nuclear debris, and is covered by a mixture of mononuclear cells as in the proliferative type [2]. Both of our cases were compatible with "necrotizing type" of KD. The "xanthomatous type" is the rarest type and considered to be the healing phase of KD [2]. It includes many foamy histiocytes and lesser immunoblasts than the other types. Necrosis may not be encountered in the xanthomatous type [2]. The diagnosis of KD should be established when paracortical clusters of plasmacytoid dendritic cells admixed with karyorrhectic bodies and crescentic histiocytes are seen that are the minimal criteria for KD diagnosis.

Immunohistochemically, the infiltrate is consisted of T lymphocytes, with CD8-positive cells more than CD4-positive cells; CD68, lysozyme, Mac 387, Ki-M1p and myeloperoxidase positive histiocytes; and CD68, CD4, CD43, and CD123 positive plasmacytoid dendritic cells [1-2, 6]. CD20 positive B cells are rare [1-2]. The plasmacytoid monocytes are positive for the antibody LN2 for the marker CD74 [1]. Although, most of the studies documented that they represent activated monocytes rather than T cells, the origin of those cells is still debated [1].

The electron microscope reveals the histiocytes as large cells with phagolysosomes including phagocytosed nuclear debris and myelin-like inclusions [10]. The plasmacytoid monocytes contain a well-developed endoplasmic reticulum with numerous parallel cisternae, which is in contrast to their lack of immunoglobulins or any other secretory products [11]. Tubuloreticular structures, described as intertwined, membrane-bound tubules present in viral lymphadenitides such as those caused by human immunodeficiency virus and in autoimmune diseases such as SLE have been also found in KD [12-13].

KD should be discriminated from the other conditions comprising necrotizing lymphadenopathies. The entities that should be considered in the differential diagnosis are given as follows: SLE, tuberculosis, histoplasmosis, leprosy, cat-scratch disease, syphilis, Yersinia infection, acute EBV infection, herpes simplex lymphadenitis, allergic lymphadenitis, non-Hodgkin lymphoma, lymph node infarction, and metastatic adenocarcinoma [1]. In systemic lupus lymphadenitis, the foci of fibrinoid necrosis with nuclear debris may be similar; however, the presence of extensive necrosis, hematoxylin bodies, and plasma cells or neutrophils favor SLE [1-2]. Our cases did not exhibit these features. Kikuchi's lymphadenitis might sometimes not be differed histopathologically from lupus lymphadenitis [1]. In addition, some studies have stated that there might be a relationship between those two entities [1]. However, the cases reported as Kikuchi's lymphadenitis in association with SLE are almost believed to be lupus lymphadenitis misinterpreted as KD [2]. Serologically antinuclear antibodies are negative in most of the cases with Kikuchi's lymphadenitis in contrast to those with SLE [2]. Serologic testing for SLE is advised; if test is positive, it should be diagnosed as lupus lymphadenitis.

Tuberculosis, histoplasmosis, leprosy and cat-scratch disease have characteristic necrotizing granuloma formations composed of epithelioid cells and multinucleated giant cells, and the responsible specific microorganisms can be determined by special stains [1]. Necrotizing lymphadenitis in syphilis usually includes perivascular plasma cell infiltrates. Yersinia infection often contains eosinophils and neutrophils [1]. Necrotizing lymphadenitis in acute EBV infection is characterized by reduced lymphocyte and by histiocytic hemophagocytosis [1]. In addition, serological tests for EBV-specific antigens are positive. Herpes simplex lymphadenitis might contain histiocytic infiltrate and focal necrosis, besides neutrophils and viral inclusions are also encountered. Moreover, the histocytes in herpes lymphadenitis or granulomatous lymphadenopathies are negative for myeloperoxidase, unlike KD as in our cases. Necrotic areas in allergic reactions are usually covered by eosinophils and plasmocytes. Non-Hodgkin lymphoma may sometimes be indistiguishable from KD, due to the obliterated sinuses and the accumulation of plasmacytoid monocytes and immunoblasts [1]. However, in KD, the reactive follicles, and the mixture of lymphocytes and histiocytes show benign morphologic findings [1]. Necrosis in lymphomas may usually be widespread, and they contain lymphoma cells in the peripheral part of the lymph nodes [1]. Lymph node infarction shows coagulation necrosis without unclear debris comprising the whole lymph node except a narrow subcapsular rim. The crescentic histiocytes, called "signet-ring histiocytes," might be misinterpreted as metastatic signet-ring adenocarcinoma, however differential diagnosis is straightforward by using immunohistochemical antibody of cytokeratin.

Conclusion

To conclude, KD is a rare enigmatic entity that should be considered in the differential diagnosis of necrotizing lympadenopaties. Partial involvement of the lymph node, excessive karyorrhectic debris, a mixture of cells that contains the crescentic histiocytes, lack of B-cell markers on immunoblasts, and absence of a B- or T-cell receptor gene rearrangement indicate KD. KD may be distinguished from its mimickers by the clinicopathological features and using the clues about the differential diagnosis that are given in the current report of two demonstrative cases.

References

1. Ioachim HL, Medeiros LJ. Lympadenopathies. In: Ioachim's lymph node pathology. 4th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009. p.200-202.
2. Hsi ED. The reactive lymphadenopathies. In: Hematopathology. 2nd ed. Elsevier Saunders, 2007. p.132-139.
3. Kikuchi, M. (1972) Lymphadenitis showing focal reticulum cell hyperplasia with nuclear debris and phagocytosis [in Japanese]. *Nippon Ketsueki Gakkai Zasshi,* **35**:379–380.
4. Fujimoto, Y., Kojima, Y., Yamaguchi, K. (1972) Cervical subacute necrotizing lymphadenitis. A new clinicopathological entity [in Japanese]. *Naika,* **20**, 920–927.
5. Bosch, X., Guilabert, A., Miquel, R., et al. (2004) Enigmatic Kikuchi-Fujimoto disease. A comprehensive review. *Am J Clin Pathol*, **122**, 141–152.
6. Kuo, T.T. (1995) Kikuchi's disease (histiocytic necrotizing lymphadenitis). A clinicopathologic study of 79 cases with an analysis of histologic subtypes, immunohistology and DNA ploidy. *Am J Surg Pathol*, **19**, 798–809.
7. Turner, R.R., Martin, J., Dorfman, R.F. (1993) Necrotizing lymphadenitis. A study of 30 cases. *Am J Surg Pathol*, **7**, 115–123.
8. Kikuchi, M., Ohshima, K. (2004) Cervical lymphadenopathy, fever and leukopenia (histiocytic-necrotizing lymphadenitis or Kikuchi disease). *Pathol Case Rev,* **9**, 199–205.
9. Chan, J.K.C., Wong, K.C., Ng, C.S. (1963) A fatal case of multicentric Kikuchi's histiocytic necrotizing lymphadenitis. *Cancer,* **63**, 1856–1862.
10. Imamura, M., Ueno, H., Matsuura, A., et al. (1982) An ultrastructural study of subacute necrotizing lymphadenitis. *Am J Pathol,* **107**, 292–299.
11. De Vos, R., De Wolf-Peeters, C., Facchetti, F., et al. (1990) Plasmacytoid monocytes in epithelioid cell granulomas: Ultrastructural and immunoelectron microscopic study. *Ultrastructural Pathol*, **14**, 291–302.
12. Sidhu, G.S., Stahl, R.E., El Sadr, W., et al. (1985) The acquired immunodeficiency syndrome: an ultrastructural study. *Hum Pathol*, **16**, 377–386.
13. Grimley, P.M., Barry, D.W., Schaff, Z., et al. (1973) Lupus-type tubular structures in human lymphoid cell cultures. *Arthritis Rheum*, **16**, 550..