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Histiocytic Necrotizing Lymphadenitis without Granulocytic Infiltration (the so called Kikuchi-Fujimoto Disease)

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The report describes five cases of a rare disorder – necrotizing lymphadenitis – diagnosed in Polish patients in the Department of Pathomorphology, Collegium Medicum, Jagiellonian University, Krakow, in the years 1993–2006. The disease was firstly described by Kikuchi and Fujimoto in the Oriental population of Japan in 1972 and for this reason it is called Kikuchi-Fujimoto disease (or Kikuchi lymphadenitis). Its characteristic histological picture includes necrosis without granulocytic infiltrate surrounded by plasmocytoid monocytes, histiocytes (CD68+, lysozyme+, myeloperoxidase+) and immunoblasts, sometimes with atypia, with concomitant lymphocytes, predominantly cytotoxic T CD8+. The histology together with the rare occurrence of the disease in Poland may be a considerable diagnostic challenge for a pathologist, leading to misdiagnosing the lesion as a neoplastic process (malignant lymphoma).

Introduction

The disease was for the first time described in Japan in 1972 [10, 16], and subsequently in Oriental populations in the east - Taiwan [19] and Hong Kong [4, 30]. Publications have also appeared recently reporting the incidence of Kikuchi-Fujimoto disease in America and Europe [1, 3, 8, 20, 24, 25, 32]. The first Polish case was presented during a diagnostic-consultative meeting held in Warsaw in 1997 (No. 1, Papla). A single case occurring in Poland was also reported by Hrycek et al. [12].

Kikuchi disease commonly presents with lymphadenopathy, mainly involving the cervical nodes, accompanied by fever and peripheral leucopenia. Cutaneous lesions (rash) are a more rare phenomenon, similarly as weakness, nocturnight sweats, body weight loss, arthralgia, anorexia, diarrhea, nausea, vomiting and abdominal pain [10, 12, 15, 16]. Usually the disease has a benign course and resolves spontaneously. Its characteristic feature is adenopathy persisting for several months and involving one or several cervical or axillary lymph nodes – lymphadenopathy involving other sites is rare – which results in a suspicion of a lymphoma and a lymphadenectomy performed to allow for a histological evaluation of the lymph node. The lymph nodes may be tender on palpation or be generally painful. Histology findings allow experienced pathologists for a relatively easy determination of the diagnosis. A question emerges whether the disease has appeared only recently, was formerly undiagnosed due to its benign and self-limiting course and lack of histopathological verification, or else used to be diagnosed as malignant lymphoma.

A Case Descriptions

In the archives of the Krakow Chair of Pathomorphology, five cases of Kikuchi disease occurring in Polish nationals were found within the period spanning the years 1993–2006. The group included five young Caucasian individuals, four females and one male, with the mean age of 32.6 years. Detailed data on the patients are included in Table 1.

The predominant clinical presentation was persistent adenopathy of a peripheral lymph node, followed by a lymphadenectomy performed to provide material for histopathology. Usually the patients were treated with antibiotics, but regardless of therapy, they all gradually improved and normalized.

The lymph nodes for histopathology were formalin-fixed, routinely passaged and paraffin-embedded. Subsequently HE-stained. Another paraffin sections were prepared to be employed in immunohistochemical tests (CD3, CD4, CD8, CD68, myeloperoxidase, CD20). Antibodies

TABLE 1

No.	No. of examination	Sex	Age	Location of enlarged lymph nodes	Preliminary clinical diagnosis	Clinical presentation
1	1262105	F	44	Cervical, nuchal, axillary, inguinal	Hodgkin's disease	Fever, leucopenia, high lymphocyte count, sweats, low IgG level
2	1346806	F	42	Cervical	Systemic proliferation	Fever, leucopenia, skin rush
3	1491515	F	29	Cervical	Lymphadenopathy	No data available
4	1589887-8	M	22	Cervical	Cystis colli lateralis	No data available
5	1591399	F	26	Axillary	Still's disease	Fever, arthralgia, rash, leukocytosis

provided by DAKO were used in the tests; the test and control reactions were carried out in agreement with the routine protocol.

Histologically, the lymph nodes demonstrated the presence of diffuse or blended complete or incomplete necrosis of the lymphatic tissue, with nuclear debris (karyorrhexis) resembling apoptotic bodies; the necrosis involved extensive, usually large central regions of the nodes (Fig. 1). Frequently, necrosis was associated with lymph node fragmentation. Regions situated in the immediate vicinity of necrosis and the necrosis itself were devoid of granulocytic infiltration and accompanied only by a situated on the periphery varied abundance of histiocytes with crescentic nuclei (Fig. 2, 3 and 4). On the periphery of the lesions involving the lymph node there were also seen numerous plasmacytoid monocytes with eccentrically situated round nuclei and amphophilic cytoplasm, as well as a diversified number of immunoblasts, at times showing signs of nuclear atypia, such as irregular contours and granular chromatin and mitotic figures (Fig. 5). Remnants of the preserved lymph node structure were observed on the lymph node periphery; at times, follicular hyperplasia was also noted. Cases 1, 2 and 4 were mainly characterized by proliferation with a small amount of necrosis; in Case 3, extensive necrosis was the predominant feature accompanied by the vessel walls being stained by the nuclear material (the Azzopardi phenomenon).

Immunohistochemical tests demonstrated that the lymphocytes situated on the periphery of the necrotic regions were predominantly T lymphocytes, mostly CD8+ (Fig. 6); the number of lymphocytes reacting with CD4 was much lower and single lymphocytes were CD15+. No positive CD30 reactivity was noted in the investigated cases. Some T lymphocytes were in the proliferative phase, what was manifested by their positive reaction for Ki67. On the other hand, abundant histiocytes were positive for CD68 (Fig. 7), lysozyme and – what is characteristic of the disease – myeloperoxidase (Fig. 8); in addition, some histiocytes were also positive for CD4.

Discussion

Kikuchi-Fujimoto disease mostly affects young people, showing a preponderance for females, although isolated cases have been reported that involved children and elderly individuals [4,14,19, 20, 22, 25, 30, 32, 33]. There are also single reports describing a higher incidence of the disease in males (five men per nine cases in the series presented by Chan and Saw) [4]. In rare instances, the disease recurs after a period of remission [2, 19, 20, 30].

Familial cases have been also observed [2]. Kikuchi disease usually presents with concomitant leucopenia, although several exceptional, isolated cases with leukocytosis have been reported [19]. Some patients also demonstrate elevated erythrocyte sedimentation reaction.

Menasce et al. [20] observed in Great Britain a seasonal character of the disease, with the peak incidence in

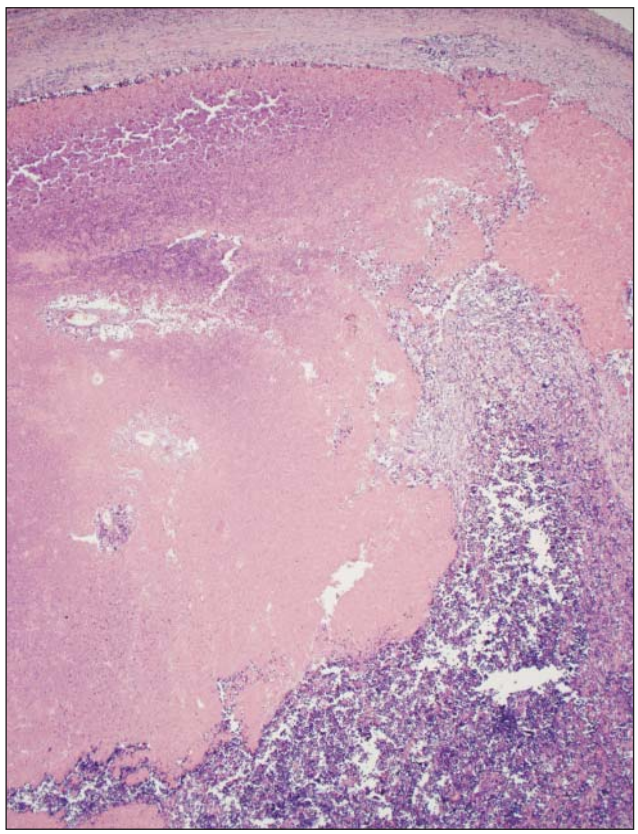

Fig. 1. Extensive areas of coagulative necrosis without granulocytic infiltration in a lymph node.

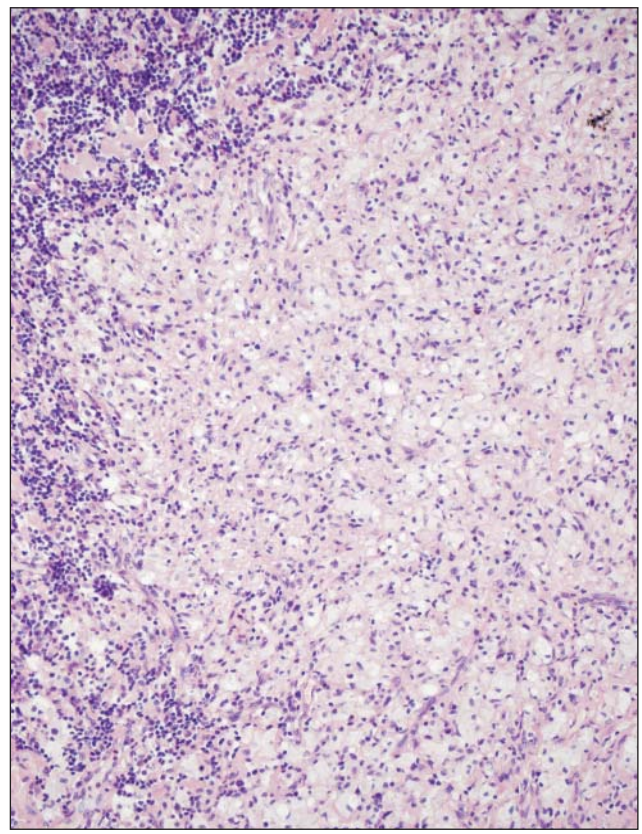

Fig. 2. Numerous histiocytes with clear, abundant cytoplasm on the periphery of necrosis (the xanthomatous form).

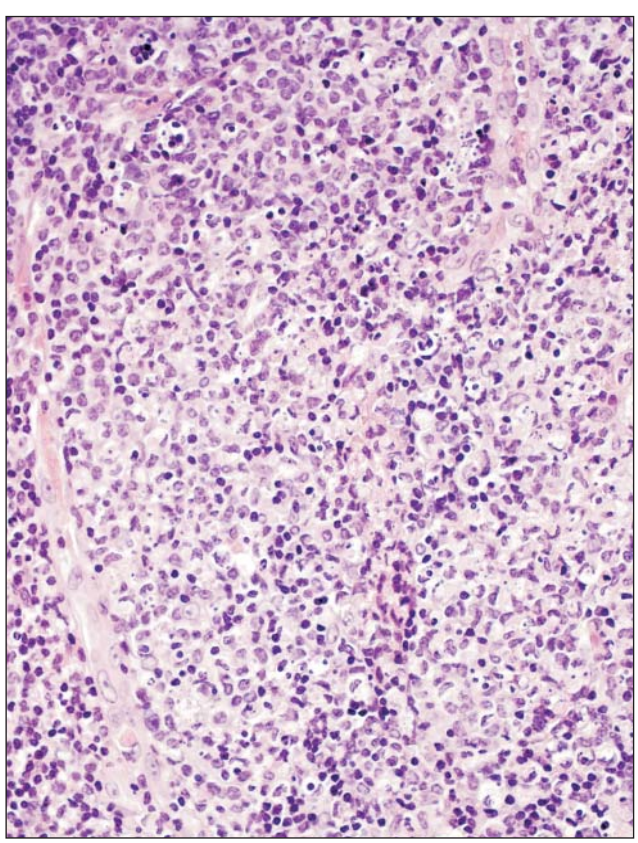

Fig. 3. Histiocytes with crescentic nuclei, characteristic of Kikuchi disease.

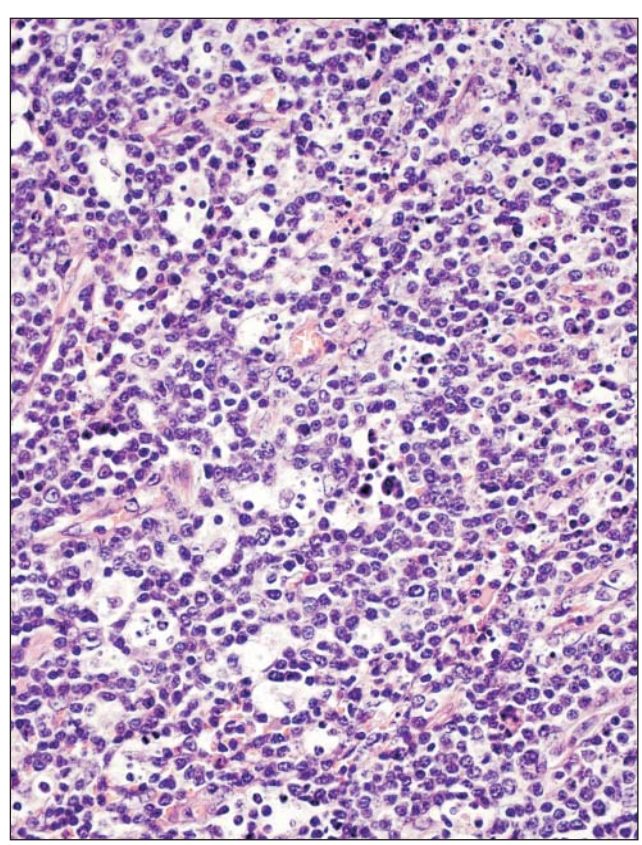

Fig. 4. Numerous histiocytes with apoptotic bodies in the cytoplasm – the "starry sky" appearance.

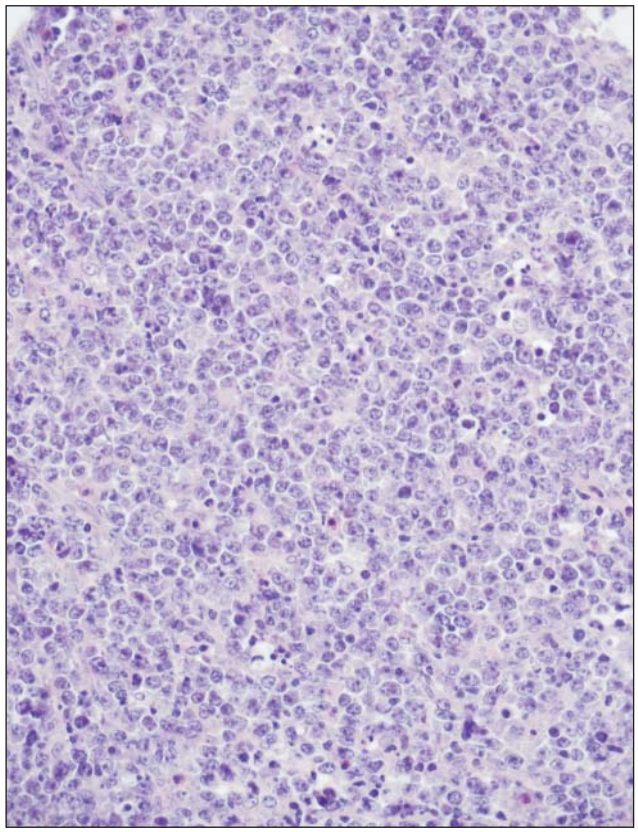

Fig. 5. The proliferative form with clearly visible mitotic figures – the picture suggestive of a lymphoma.

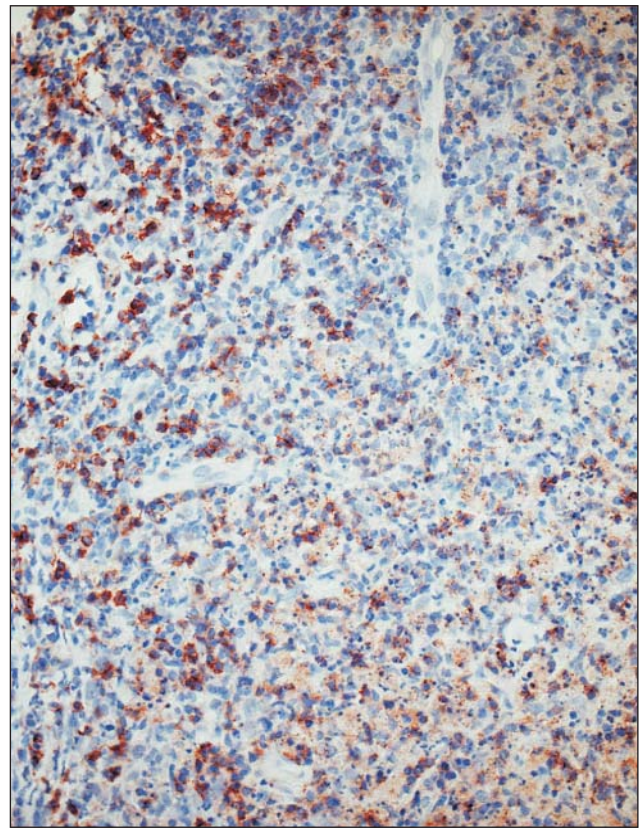

Fig. 6. Positivity for CD8 antigen in cells situated on the periphery of necrosis.

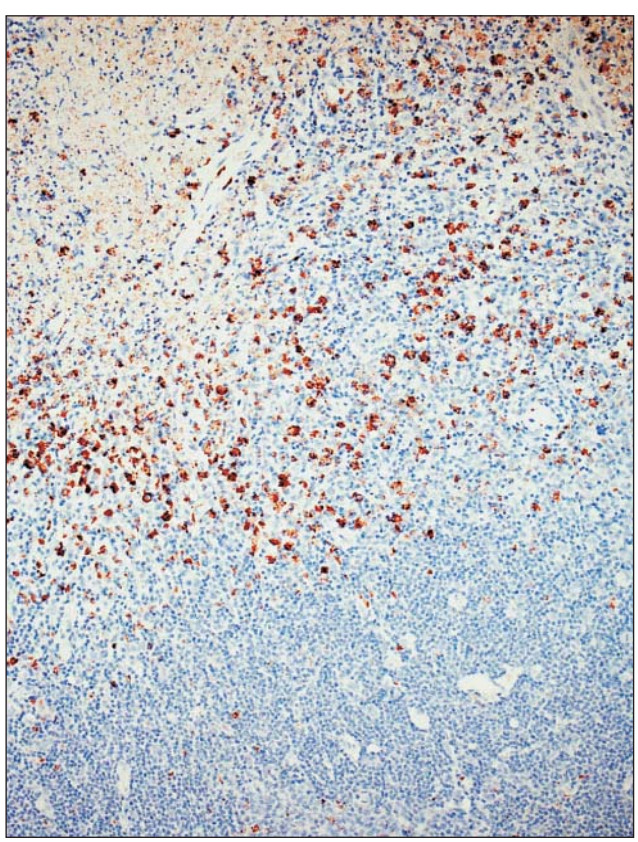

Fig. 7. Immunohistochemical reactions for CD68 antigen in numerous scattered histiocytes. Vessel walls on the periphery stained by residual DNA.

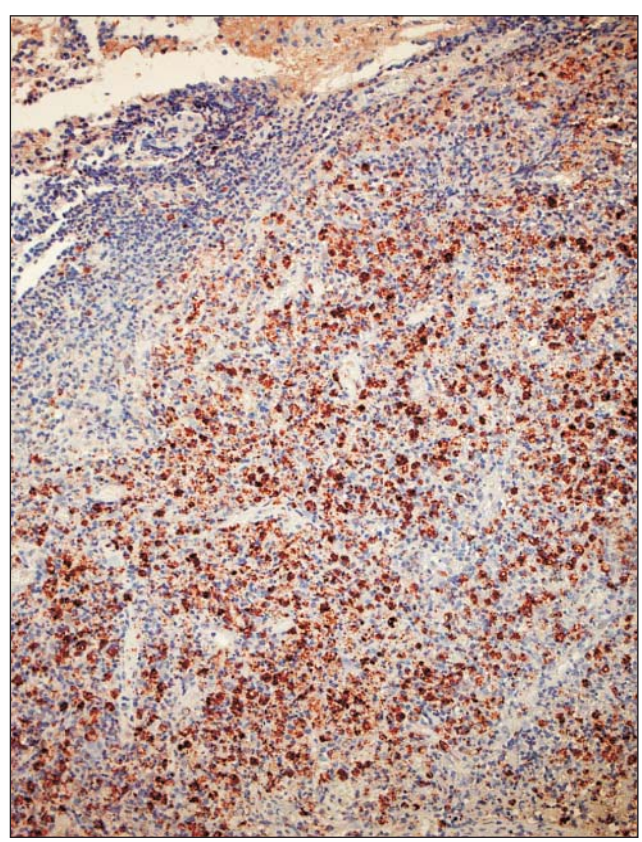

Fig. 8. Strong positivity for myeloperoxidase in monocytoid mononuclear cells with concomitant absence of granulocytes on the periphery of necrosis.

spring and early summer (between March and July), what has not been reported by other authors. The patients from the present series also manifested signs of the disease in the above mentioned period, with the exception of Case 1. Peripheral blood of some patients demonstrated the presence of atypical lymphocytes [20].

Kuo proposed a classification of Kikuchi disease into three histopathological forms: proliferative, necrotic and xanthomatous [19]. The most common form, accounting for more than 50% of cases, would be the necrotic form, the least frequent – the xanthomatous form. Necrotic disease would be accompanied by tenderness of the lymph nodes. According to Kuo, Kikuchi disease is characterized by sequentiality: the condition starts with proliferative changes, progresses to necrotic lesions and ends with xanthomatous changes. There is, however, no evidence in the form of serial lymph node examinations that would indicate that it is so, and data on the duration of the disease do not correlate with the histological picture seen in the above sequences. Kikuchi et al. [17] proposed a different classification based on morphological findings. The investigators distinguished four forms: lymphohistiocytic, phagocytic, necrotic and with foam cells. Various forms of the disease may possibly have different etiology or pathogenesis [19].

The cause of necrosis developing within a lymph node is believed to be an immunological hyperreaction induced by various antigens or an immunological process, with apoptosis playing the major role [9, 18]. Isolated ultrastructural studies in Kikuchi disease have been also carried out, yet they have not made any significant contribution [1, 2, 6, 18].

Immunohistochemically studied lymphocytes situated within the lesions are mostly CD8-positive T lymphocytes. Their number is particularly high in the proliferative picture and gradually increases in comparison to the number of CD4+ lymphocytes as the disease develops [21]. It should be, however, borne in mind that some CD4+ cells are plasmacytoid monocytes rather than lymphocytes [28, 29]. The presence of the Ki67+ antigen indicates their intensified proliferation. Isolated lymphocytes demonstrate positivity for CD15 [13, 17, 22, 29]. Histiocytes, found in particular abundance in the necrotic region, demonstrate the presence of lysozyme, alpha-1-antichymotrypsin and myeloperoxidase [13, 18, 23]. According to Pileri et al. [23], myeloperoxidase is found in 25 to 75% of histiocytes in Kikuchi disease and in Kikuchi-like SLE, therefore, it is a very reliable marker in these diseases, differentiating them from neoplastic diseases. Histiocytes originating from MPO+/CD68+ monocytes that are transferred from blood to tissues require myeloperoxidase in oxidative processes in absence of granulocytes.

In descriptions of Kikuchi disease, the term "plasmocytoid monocyte" has been repeatedly employed. The name refers to a medium-sized cell, with a round, eccentrically situated nucleus and a small amount of cytoplasm. The literature on the subject became a forum for a discussion on the role and origin of plasmacytoid monocytes. Initially, they were classified as special forms of T lymphocytes [3, 8, 14] in view of their positivity for CD4. The reaction is also seen in cells of the monocyte origin [11]. Further investigations have demonstrated that they belong to the monocyte line and show positivity for the Ki-M1P antibody [7, 11, 29]. They may constitute precursors of epithelioid cells. Cells of this type are not, however, characteristic of Kikuchi disease and are also seen in other lymph node inflammatory reactions. Myeloperoxidase-negative plasmacytoid monocytes are involved in immunological cytotoxic reaction and may play a role in type I interferon secretion, but their role in Kikuchi disease is not as significant as the importance of MPO+/CD68+ histiocytes.

In some cases from his series, Kuo [19] investigated cell ploidy, finding it normal, what supports the non-neoplastic character of the disease, although it should be borne in mind that cases of lymphomas with maintained correct ploidy do occur.

In differential diagnosis of Kikuchi disease one should consider malignant lymphoma of T-lymphocyte origin [3, 13, 20, 26] and lymph node lesions accompanying systemic lupus erythematosus. Many pathologists have erroneously misdiagnosed patients with Kikuchi disease, who do not require any special treatment, as suffering from malignant lymphoma [20]. The presence of numerous nuclear fragments among blast cells should alert a diagnostician to the impropriety of diagnosing a lymphoma. A positive reaction to myeloperoxidase in histiocytes is also highly helpful in differentiating between Kikuchi disease and lymphomas.

Another problem is posed by the high similarity of lymph node changes to lesions observed in some autoimmune diseases, mainly in systemic lupus erythematosus (SLE) [1, 5, 12, 14, 19, 20]. Several cases have been encountered where Kikuchi disease was concomitant with SLE; instances have been also noted where systemic lupus erythematosus developed several years after resolution of primarily diagnosed Kikuchi disease [5,19] or where SLE preceded Kikuchi-Fujimoto disease [31]. Dorfman et al. [5] have proposed the thesis that necrotizing lymphadenitis is a self-limiting form of SLE, and thus also an autoimmune disease. Facchetti et al. [7] suggest an immunological reaction mediated by T lymphocytes, which leads to necrosis of plasmacytoid monocyte aggregates. In numerous cases of SLE, only the large extent of necrosis may indicate Kikuchi disease. In other patients, establishing the diagnosis of SLE

is facilitated by the presence of hematoxylin bodies and numerous plasma cells, which are usually absent in Kikuchi disease. Any doubts should, however, be interpreted in favor of systemic lupus erythematosus and lead to conducing further tests to confirm or exclude SLE. If we acknowledge Kikuchi disease to be an autoimmune process [9], the similarities between these entitles should not be surprising. In rare doubtful cases, testing for tuberculosis is also indicated [26].

No etiological factor involved in Kikuchi disease has been elucidated to date [21]. Apart from an autoimmune disease, infectious etiology has been also considered. The suggestion proposed by Feller et al. [9], who implicated Yersinia enterocolitia, has not been confirmed by other investigators [25]. The majority of authors are in favor of a viral background of Kikuchi disease. According to Kuo [19], the presence of atypical lymphocytes in blood is supposed to also follow from viral etiology of the disease. A similar opinion on its etiology is shared by Asano et al. [2] and Dorfman et al. [5]. Also the presence of alpha-interferon in lymph nodes may support this hypothesis [28]. Pilleri et al. [23] draw attention to the fact that to date, not a single case of the disease being transmitted from the affected patients to other individuals has been described, what might undermine the thesis of its viral character.

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