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DIAGNOSIS AND TREATMENT, EPIDIMIOLOGY OF KIKUCHI-FUJIMOTO'S DISE

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Annotation: Kikuchi-Fujimoto's disease is a benign hyperplasia of the lymph nodes, presumably of immunological or infectious origin. It is manifested by unilateral cervical (rarely generalized) lymphadenopathy, soreness of the lymph nodes, fever, malaise, weight loss, night sweats, hepatosplenomegaly. The diagnosis is established using ultrasonography, results of a lymph node biopsy. For the treatment of pathology, NSAIDs, glucocorticoids, intravenous immunoglobulin, and immunosuppressants are prescribed.

Key words: Kikuchi-Fujimoto's disease , immunomodulatory,biopsy, fever, malaise, weight loss, night sweats.

Kikuchi-Fujimoto's disease (BCF, necrotizing histiocytic lymphadenitis) a rare self-limiting inflammatory process that develops in the cervical lymph nodes. The disease owes its eponymic name to the Japanese pathologists M. Kikuchi and E. Fujimoto, who first described it in 1972. BKF occurs in different ethnic groups, but the highest prevalence is observed in residents of the Asian region. Most often, young patients under 30 years of age are ill, among them women predominate (W:M – 4: 1). Pathology is often misdiagnosed, which leads to unjustified use of antibiotics and irrational management of patients.

Reasons

The etiology of Kikuchi-Fujimoto's disease is not fully defined. Based on clinical observations and pathohistological conclusions, two leading theories regarding the causes of histiocytic lymphadenitis were formulated: infectious and autoimmune:

- Infection. Both viral and bacterial agents are considered as possible triggers. The list of viruses includes EBV, chickenpox virus, rubella, hepatitis B, parainfluenza, cytomegalovirus, and herpes viruses 1, 2, 6, 7, 8, parvovirus B19, HPV, human T-lymphotropic virus, paramyxovirus, SARS CoV2. Among the bacterial microorganisms called brucella, bartonella, Yersenia, toxoplasma, mycobacteria. However, neither viruses nor bacteria were isolated from lymph node biopsies.
- Immunopathology. BCF is associated with a wide range of autoimmune diseases, including SLE, Wegener's granulomatosis, Sjogren's syndrome, rheumatoid arthritis, including Still's disease, Hashimoto's thyroiditis. In Asian populations, a more widespread distribution of Kikuchi-Fujimoto's disease was observed in carriers of the DPB1 and DPA1 HLA alleles.
- Other factors. There are also cases of CDF in the literature in patients with malignant neoplasms, renal failure, neuroinfections, interstitial lung diseases, as well as those who

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have undergone implant placement, bariatric interventions, and hematopoietic stem cell transplantation.

Currently, the prevailing view is that an unknown infectious trigger causes a self-limiting immune-inflammatory process in the lymph nodes of a susceptible population. Hereditary transmission of Kikuchi-Fujimoto's disease has not been recorded.

Pathomorphology

Clinical and pathological features of Kikuchi-Fujimoto's disease reflect the immune response mediated by T-cells and histiocytes to an infectious or non-infectious antigen. In necrotizing histiocytic lymphadenitis, the main changes affect the paracortical zone of the lymph nodes. There are three pathohistological stages in the course of BCF:

1. Proliferative. It is detected in 30% of cases. It is characterized by follicular hyperplasia of lymphoid tissue with infiltrates consisting of histiocytes and lymphocytes.
2. Necrotizing. It is observed most often – in 50% of studies. Extensive destruction of cell nuclei (karyorexis) and multiple foci of necrosis are typical, while the architectonics of the lymph nodes remain unchanged.
3. Xanthomatous. It is found in less than 20% of histologies. Microscopy reveals foamy histiocytes with regression of necrosis.

Immunohistochemical analysis shows histiocytes positive for myeloperoxidase, CD68-lysozyme, CD163 and CD4; CD8 - + T cells, plasmacytoid dendritic cells, rare B cells.

The onset of the disease is usually acute or subacute (in the latter case, clinical manifestations develop within 2-3 weeks). The main sign of Kikuchi-Fujimoto syndrome is cervical lymphadenopathy mainly in the lateral region. The lymph nodes are painful, their size varies from 0.5 to 4 cm, less often reaches or exceeds 5-6 cm.

In most cases, the lesion is limited to unilateral cervical lymphadenitis, in rare cases, bilateral lymphadenopathy may occur. Generalized lymphadenopathy develops in 1-22% of patients, occurs with an increase in axillary, supraclavicular, intraparotid, mediastinal, inguinal, mesenteric, iliac, celiac, retroperitoneal and other groups of lymph nodes.

30-50% of patients have subfebrile or febrile fever, chills. Also, systemic manifestations are characterized by dyspeptic syndrome, weight loss, and hepatosplenomegaly. Less frequent complaints include sore throat, night sweats, malaise, arthralgia, and myalgia.

Of the extranodal manifestations of Kikuchi-Fujimoto's disease, skin rashes are the most frequently reported (30%). They can be represented by facial erythema, lupus-like rash, papulomacular elements, individual plaques, nodules, and local ulcerative defects. Sometimes there is itching of the skin, alopecia occurs. Possible damage to the mucous membranes in the form of ulceration of the oral cavity, oropharyngeal hyperemia, papillary conjunctivitis.

Complications

In most patients, Kikuchi-Fujimoto's disease is uncomplicated. In typical cases, after 1-4 months, spontaneous regression of all manifestations occurs, but approximately 3-4% of patients may have relapses of lymphadenitis.

There is an increased risk of autoimmune complications (2.7%).: systemic lupus erythematosus, other collagenoses, and thrombocytopenia, but the causal relationship between these conditions is not fully understood. Extremely rare consequences of CDF include hemophagocytic lymphohistiocytosis (3%), myocarditis, and CNS damage

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(meningoencephalitis, aseptic meningitis, cerebellar syndrome, and optic neuritis). Deaths are extremely rare.

Diagnostics

Due to the rarity of the disease and the non-specific clinical symptoms, the diagnosis of Kikuchi-Fujimoto's disease is largely difficult. To exclude other immunological, infectious and oncohematological diseases, the patient often needs to consult a number of specialists: an immunologist, an infectious disease specialist, a hematologist. For the purpose of diagnostics, the following is performed::

- Ultrasound of the lymph nodes. Sonography reveals enlarged cervical lymph nodes with a hypoechoic nucleus and a hyperechoic rim along the periphery. Sometimes hypertrophy of the lymph nodes of other groups (supraclavicular, axillary, inguinal), etc. is detected.
- Lymph node biopsy. More often, it is performed by the excisional method, since a fine-needle biopsy often turns out to be uninformative. Pathomorphological and immunohistochemical examination of the material corresponds to the picture of necrotizing histiocytic lymphadenitis.
- Blood tests. Peripheral blood in Kikuchi-Fujimoto's disease is characterized by anemia, leukopenia, the presence of atypical lymphocytes, an increase in ESR, and thrombocytopenia. Also, non-specific laboratory signs include elevated levels of CRP, liver enzymes, and serum lactate dehydrogenase. Autoimmune serological markers are usually negative.
- Additional instrumental diagnostics. To confirm/exclude generalized lymphadenopathy, an X-ray or CT scan of the chest, abdominal ultrasound, PET /CT is performed.

Differential diagnosis

Histology and immunohistochemistry make it possible to exclude alternative differential diagnoses of infectious and lymphoproliferative diseases:

- lymphadenitis in infectious mononucleosis, cat scratch disease, HSV, tuberculosis, HIV;
- Kawasaki disease;
- sarcoidosis;
- dermatopathic lymphadenopathy;
- parotid salivary gland tumors;
- autoimmune diseases: Wegener's granulomatosis, lupus;
- hemoblastoses: acute leukemia, myeloid sarcoma, non-Hodgkin's and Hodgkin's lymphoma;
- metastases of adenocarcinoma to the lymph nodes.

Treatment of Kikuchi-Fujimoto's disease

Clinical manifestations of BCF are usually stopped independently. In some cases, symptomatic treatment is used to relieve local and general complaints. To reduce the soreness of the lymph nodes and reduce the temperature, analgesics and NSAIDs can be

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used. Studies indicate that fever usually subsides after removal of the affected lymph node, which indicates a possible therapeutic benefit of an excisional biopsy.

In severe generalized Kikuchi-Fujimoto's disease with extranodal symptoms, short courses of glucocorticosteroids are given. Less often, cytostatics, antimalarials, an IL-10 inhibitor are used, and intravenous administration of immunoglobulin is resorted to. In some cases, the effectiveness of antibacterial drugs (fluoroquinolones, tetracyclines) in the remitting nature of Kikuchi-Fujimoto's disease was noted.

Prognosis and prevention

The course of BCF is usually benign, and the symptoms regress spontaneously or under the influence of short-term treatment without serious consequences. Complicated and refractory forms of pathology are rare. At the same time, patients who have had Kikuchi-Fujimoto's disease need regular observation by a rheumatologist and systematic examination for several years to exclude the development of SLE and other collagenoses.

Since the etiopathogenesis of Kikuchi-Fujimoto's disease has not been sufficiently studied, primary prevention measures have not been developed. It is recommended to avoid contact with infectious triggers that can trigger the development of the disease.

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