DIAGNOSTIC CHALLENGES IN ROSAI-DORFMAN-DESTOMBES DISEASE. CASE DESCRIPTION AND LITERATURE REVIEW

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ABSTRACT

The described clinical case presents 39-year-old patient with no clinically significant accompanying diseases. Since the beginning of October 2015, the patient has complained of fever, abdominal pain and generalized enlarged lymph nodes. Biopsy of axillary lymph node evidences Rosai-Dorfman-Destombes (RDD) disease. Treatment with corticosteroids has been started but with no clear influence on paraclinical activity and lymphadenomegaly. From the additionally made examinations, clinical laboratory data for malignant histiocytosis are found. According to literary data, in 27% of patients suffering from RDD, it transforms into malignant histiocytosis. The presented clinical case is interesting not only because of the registered clinical laboratory data of malignant histiocytosis but for the unclear diagnostic and prognostic importance of this phenomenon, as well.

Keywords: *Rosai-Dorfman-Destombes disease, sinus histiocytosis with massive lymphadenomegaly, malignant histiocytosis*

INTRODUCTION

Rosai-Dorfman–Destombes (RDD) disease, known as sinus histiocytosis with massive lymphadenomegaly, was described for the first time by Destombes in 1969 (1). In the same year, Juan Rosai and Ronald Dorfman found another 4 cases of the disease, and later – in 1972, they analyzed another 30 reports and defined it as a nosological entity (2). RDD is a benign, systematic, histioproliferative disease with unknown etiology. It most often presents with massive lymphadenomegaly, fever, and extranodal manifestations. The size of the affected lymph nodes varies – from massive and compressing to discreet lymphadenomegaly. In 87% of the cases, nodal involvement was found, and in 20 to 40% – extranodal localization (skin, soft tissues, central nervous system, etc.) (3-9).

Emperipolesis and positive immunohistochemical markers for histiocytes (S100 and CD68) in combination with negative CD1 are typical and sufficient for accurate diagnosis to be made (2,8,10).

RDD occurs extremely rarely. The calculated frequency in USA is about 100 cases a year (11).

The etiology of the disease is unknown and histiocytosis is still considered idiopathic. Some re-

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Received: March 7, 2017
Accepted: June 14, 2018

searchers of the disease connect it to an infectious agent. However, the current results are contradictory. Some publications show that viral infections such as Human Herpesvirus 6 (HHV-6), Parvovirus B19, Epstein-Barr virus can be a trigger factor in the etiopathogenesis (9, 12-14). An expression of the HHV-6 antigen is identified in histiocytes in patients with RDD, while parvovirus B19 is found in lymphocytes, phagocytized by histiocytes (14,15). The disease is most often found in children and adolescents, with morbidity peak about the age of 20. There is no convincing evidence of racial, ethnic or socio-economic predisposition.

In the literature, there is no consent with respect to the treatment protocol. With most patients, watch-and-wait approach is applied. Progressive disease or cases with symptoms are treated with high-dose steroids, surgically, radiotherapy treatment and/or chemotherapy in refractory cases (16). Data from applying high-dose interferon alfa show achieving long-lasting remission (17). Disease development can be feeble, last for years and conclude with spontaneous regression (18).If there is progression, the prognosis is bad. A few cases of progressive development are described, including 17 cases with lethal outcome.

Differential diagnosis in RDD is difficult and includes tuberculosis, sarcoidosis, Wegener's granulomatosis, Gaucher disease, hemophagocytic lymphohistiocytosis, juvenile xanthogranuloma. From the group of malignant diseases, in terms of differential diagnosis, the following should be taken into account: acute lymphoblastic leukaemia, Hodgkin disease and Non-Hodgkin lymphoma, metastases from melanoma, carcinoma and histiocytic sarcoma (18-20).

CLINICAL CASE

We present a 39-year-old male, with no clinically significant pre-existing conditions. At the beginning of October 2015 he presented with fever up to 39 °C, significant abdominal pain and generalized enlarged unpainful lymph nodes. Long-term, outpatient, antibiotic treatment was performed with no significant effect. Physical examination of the patient revealed fever and generalized enlarged lymph nodes (cervical, axillary and inguinal lymphadenopathy) with size 3/3 cm, moderate hepatomegaly and splenomegaly.

Hematological investigations showed mild-grade anemia (Hb 116 g/L), leukocytosis (Leu-11.53x10^9/L) and normal platelet count. The chemistry panel had no deviations. Tuberculin test and serological tests for viral infections including HbsAg /-/, Anti-HCV /-/, Anti-HIV/-/, Anti HSV IgM /-/, Anti HSV IgMG /-/, Anti HSV2 IgM /-/, Anti HSV2 /-/, Anti CMV IgG /-/, Anti CMV IgM /-/, Anti EBV IgM /-/ were negative.

From the computed tomography of the thorax and abdomen, cervical, axillary, abdominal lymphadenopathy and hepatosplenomegaly were established.

Biopsy performed on axillary lymph node with subsequent histological and immunohistochemical examination evidenced a morphological image of sinus histiocytosis. Fig.1 presents a histological preparation from a lymph node with damaged architectonics, massive sinusoidal dilation with presence of histiocytes, lymphocytes and plasma cells (10). Emperipolesis in the cytoplasm of histiocytes is a classical and pathognomonic finding (2,9,12).

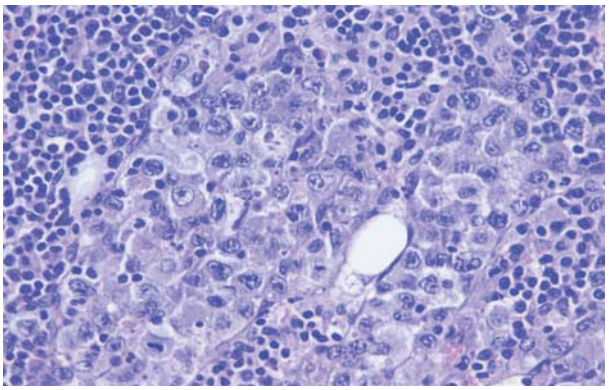

Fig. 1. Histological preparation from lymph node with damaged architectonics, massive sinusoidal dilation with presence of histiocytes, lymphocytes and plasma cells -lymphophagocytosis and emperipolesis

Immunohistochemical examination of histiocytes in sinus histiocytosis with massive lymphadenomegaly /SHML/ shows positive marking for CD68, S100, CD163, Ki67 and usually negative for CD1a (Fig. 2).

Approximately 2 weeks after diagnosis was made, with a treatment with corticosteroids performed, clinical laboratory examinations showed ex-

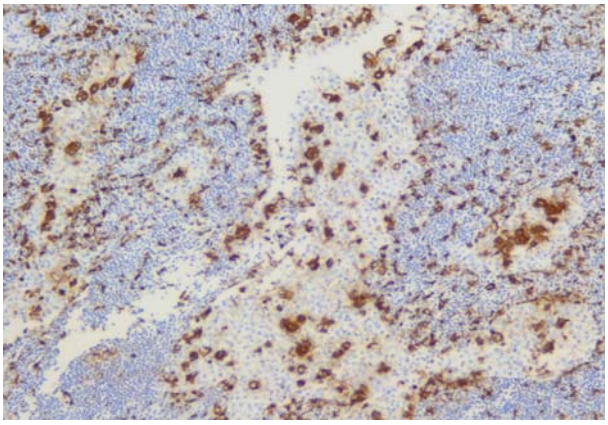
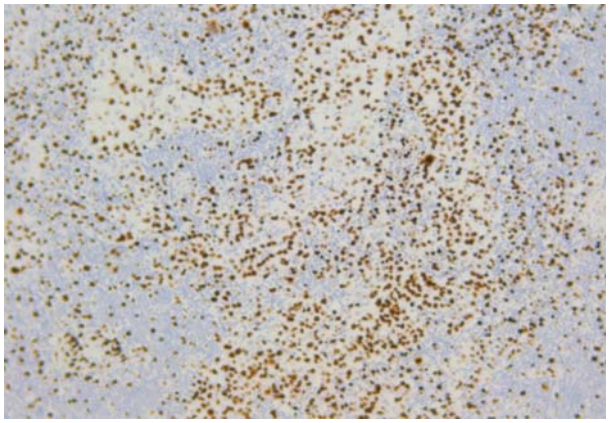

Fig. 2. Immunohistochemical markers – CD68/+/, S100/+/

acerbation: deepening of the anemic syndrome (Hb-78x10^9/l), increasing leukocytosis (Leu-46.52x10^9/l) and occurrence of thrombocytopenia (Plt-85x10^9/l). They persisted, with apparent tendency of exacerbation of the febrile-intoxication syndrome, generalized lymphadenomegaly and hepatosplenomegaly. Ascites, hypoalbuminemia and peripheral edema became present. The patient's state was deteriorating progressively. An increased percentage of monocyte population was determined in the peripheral blood and bone marrow (Fig. 3 and Fig. 4).

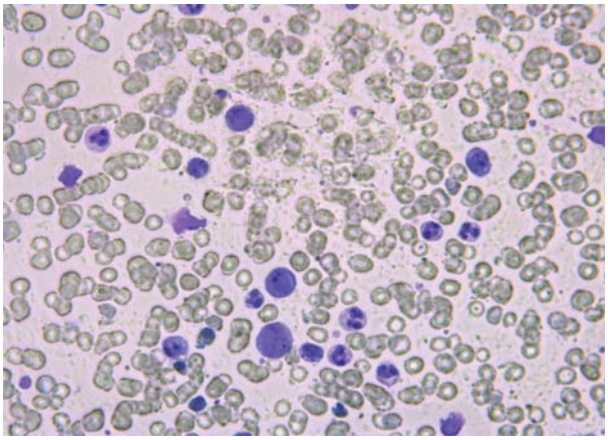

Fig. 3. Photomicrograph showing a high proportion of monocyte in peripheral blood smear (The monocyte has a pale, greyish-blue vacuolated cytoplasm)

Based on clinical laboratory data, it was suggested the transformation of disease into malignant histiocytosis should be considered. Treatment was performed according to a protocol R-CHOP but there was no therapeutic response. A few days later, a fatal outcome was registered for the patient.

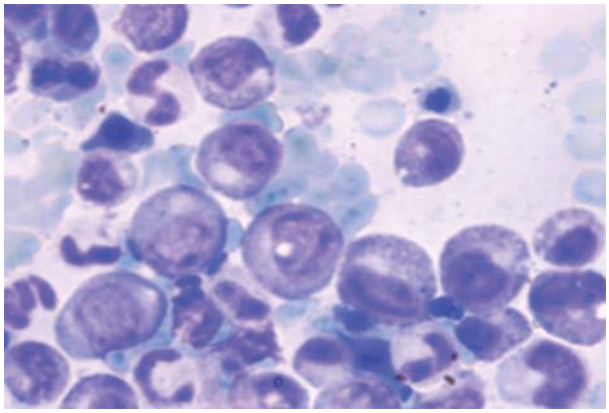

Fig. 4. Bone marrow examination (bone marrow aspiration). The bone marrow is hypercellular and shows myeloid preponderance and left shift with increased number of immature monocytic precursors

DISCUSSION

RDD is a benign disease of histiocytes, which represents real challenge in regard to clinical and pathological diagnosis. In the case described, undeniable evidence is present for the presence of classical, clinical, morphological and immunohistochemical image of sinus histiocytosis. Usually, histiocytes in RDD differ morphologically from those in Langerhans cell histiocytosis or in interdigitating dendritic cells. Immunohistochemical examination is sufficient in order to differentiate morphologically difficult cases. Unlike Langerhans cell histiocytosis, where mutation BRAFV600E can be found, in RDD – this mutation is not present (21, 22). This fact can be used for a differentiation of both diseases in extremely rare cases where the morphological and immunohistochemical examinations are uncertain.

In the literature, there are single cases describing the progressive development or transformation of RDD into a malignant process. Prognostic significance of this phenomenon is of particular importance and calls for adopting an individual approach for therapeutic behavior with the patient. According to literary data, the following forms of transformation can be discussed: 1) in about 27% of the cases, RDD can transform into a malignant process (Non-Hodgkin lymphoma, acute lymphoblastic leukemia); 2) histological changes such as SHML (sinus histiocytosis with massive lymphadenomegaly) are found in the lymph nodes of patients with autoimmune lymphoproliferative syndrome (ALPS), most often connected with mutations in the gene, which codes the TNFRSF6 Fas antigen. This shows that 1/3 of the cases of SHML are connected with disruption of apoptosis (18, 23).

The case reported by us confirms the data specified above. This reminds us that the differential diagnosis of hematological diseases, depending on clinical manifestation, can include many different possibilities irrespective of the patient‘s age.

CONCLUSION

Sinus histiocytosis with massive lymphadenomegaly, also known as Rosai-Dorfman-Destombes disease, usually surprises clinicians. It is interesting due to its rare occurrence in clinical practice, absence of pathognomonic symptoms and unclear evolution.

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