

# A Very Rare Case – Hairy Cell Leukemia in Patient with Sarcoidosis

Extrémně vzácný případ trichocelulární leukemie u pacientky se sarkoidózou

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## Summary

Although the coexistence of hairy cell leukemia with sarcoidosis has been reported in a few cases in the literature, in our case the patient had been diagnosed and followed about 10 years with sarcoidosis and massive splenomegaly. It has been demonstrated that T helper 1 cells exist in organs influenced by sarcoidosis. These cells produce IL-2 and IFN-γ and induce a nonspecific inflammatory response and granuloma formation. Also these cytokines may play a role in the development of hairy cell leukemia.

## Key words

hairy cell leukemia – sarcoidosis – massive splenomegaly

## Souhrn

I když koexistence trichocelulární leukemie se sarkoidózou byla již v literatuře publikována, byla v našem případě pacientka primárně diagnostikována a sledována pro sarkoidózu a masivní splenomegalii kolem 10 let. Bylo prokázáno, že pomocné T lymfocyty se vyskytují v orgánech ovlivněných sarkoidózou. Tyto buňky produkují IL-2 a IFN-γ a indukují nespecifickou závažnou reakci a tvorbu granulomů. Tyto cytokiny mohou také hrát roli ve vývoji trichocelulární leukemie.

## Klíčová slova

trichocelulární leukemie – sarkoidóza – masivní splenomegalie

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## Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown etiology that affects individuals worldwide and is characterized pathologically by the presence of noncaseating granulomas in involved organs. It typically affects young adults. It has been estimated that the lifetime risk of sarcoidosis in caucasian population is 0.85% [1].

Hairy cell leukemia (HCL) is an uncommon chronic B cell lymphoproliferative disorder, representing about 2% of all leukemias, and the median age at onset is 52; there is a strong male predominance of about four to one [2].

In the present case study, we report a 67-year-old female who had been diagnosed earlier as having sarcoidosis and was treated with corticosteroid therapy during 10–12 years. Afterwards, she was confirmed to have HCL. The diagnosis of HCL was established based on a combination of morphologic and immunophenotypic findings.

## Case report

A 67-year-old female was referred to our hospital in 2008 with a previous diagnosis of sarcoidosis and a history of long-term use of oral and parenteral corticosteroids for symptomatic treatment. At the time of presentation, she complained of dyspnea, progressive weakness, fatigue, photosensitivity and sensation of dry mouth developing a week after an upper respiratory tract infection. Constitutional symptoms such as weight loss, fever or night sweats were not present.

She had telangiectasias on her face, and her conjunctivae were pale and slightly icteric. Abdominal examination revealed hepatomegaly of 2 cm below the right subcostal margin and massive enlargement of the spleen, extending to the pelvic brim. Other physical findings, including respiratory, cardiovascular and digital rectal examinations were unremarkable and enlargement of lymph nodes was not noticed.

A complete blood count at admission revealed hemoglobin (Hb) level of 65 g/L, hematocrit (Hct) of 0.193, white blood cell (WBC) count of  $3.1 \times 10^9/L$  and platelet (Plt) count of  $112 \times 10^9/L$ . The erythro-

cyte indices and differential leukocyte counts were normal. Routine biochip blood urea nitrogen (9.51 mmol/L, normal: 2.50–7.34), indirect hyperbilirubinemia (17.1  $\mu\text{mol/L}$  mg/dL, normal: 3.42–13.68), increased serum transaminase concentrations (62 U/L, normal: 0–35) and markedly elevated levels of lactate dehydrogenase (2,048 U/L, normal: 220–450) were found. Results of both direct and indirect Coombs tests were positive. Routine urine examination revealed the presence of proteinuria. The other biochemical results, including erythrocyte sedimentation rate, were all within normal limits and the stool guaiac test was negative. The serological tests for various infectious agents (HBsAg, anti-HCV, anti-HIV 1 + 2, Parvovirus B19 Ig G/M antibody levels, TORCH titers) were found to be negative. Ig G, A, M levels were within normal limits. ANA, anti SS-A (anti-Ro) and anti SS-B (anti-La) antibodies were not detected. Serum protein electrophoresis was normal. Evaluation of the peripheral blood smear showed 36% neutrophils, 48% lymphocytes, 15% monocytes, and 1% metamyelocytes with anisocytosis, poikilocytosis, numerous pencil cells, a few fragmented red blood cells and spherocytes, and a normal distribution of platelets. Bone marrow aspiration revealed a slightly hypercellular marrow with megaloblastic changes in all lineages and a myeloid-erythroid ratio of 0.5.

High resolution computed chest tomography demonstrated bilateral micro and macro nodular infiltrates with lower lobe predominance, findings suggestive of sarcoidosis. Abdominal ultrasonography and contrast-enhanced abdominopelvic computed tomography displayed an enlarged liver and spleen (19 cm and 30 cm in maximum diameter, resp.) and increased echogenicity of the liver parenchyma (Grade 2–3). DEXA scan of the lumbar spine and right hip showed low bone mineral density with a total T score of –4.6 and 1.5, resp. Tc-99m MDP whole-body bone scintigraphy revealed increased activity at the 12<sup>th</sup> thoracic vertebra, which was compatible with a fracture line.

During hospitalization, the patient was treated with supportive care with

multiple blood transfusions, received Pneumococcal, Meningococcal, and Haemophilus influenzae type B vaccinations and underwent a splenectomy for massive splenomegaly and hypersplenism. She was also started on prednisolone at a dose of 48 mg/day, calcium and vitamin D supplements and once-weekly bisphosphonate therapy to reduce the risk of bone loss and fractures. Over the next 18 months, the dose of prednisolone was slowly tapered to a maintenance dose.

In December 2009, she returned with generalized weakness, severe fatigue, night sweats and fever. The patient's blood cell count at her second admission showed the following values: Hb: 91 g/L, Hct: 0.277, WBC:  $60 \times 10^9/L$ , Plt:  $128 \times 10^9/L$ . Erythrocyte indices (MCV, MCH, and MCHC) were within the normal ranges, and the differential leukocyte count consisted of 64.1% lymphocytes, 30.5% monocytes, 5.0% neutrophils and 0.4% basophils. The reticulocyte count was 5.2%. Her peripheral blood and bone marrow smear showed atypical lymphocytes displaying cytoplasmic projections which were positive for tartrate-resistant acid phosphatase (TRAP). Immunophenotypic analysis of peripheral blood revealed neoplastic lymphoid cells brightly positive for CD11c, CD20, CD22, CD23, CD79b (cytoplasm), HLA DR, and slightly positive for CD5, CD10, CD18, CD25, CD79a (surface) and CD103, which was consistent with HCL. The diagnosis of HCL was further confirmed by immunohistochemical staining of bone marrow biopsy. Cytogenetic analysis revealed karyotype of 47, XX, +16 in 18% of metaphases.

When the diagnosis of HCL was established, she received a single cycle of cladribine (0.1 mg/kg per day by continuous infusion for seven days). In present day, our patient is in a good physical condition, and all laboratory findings including blood count are completely normal.

## Discussion

HCL is an uncommon malignancy, representing about 2% of all leukemias, with approximately 600 to 800 new cases diagnosed each year in the United Sta-

tes [1]. Clinical manifestations, morphology and immunophenotype are helpful for diagnosing this disorder [3]. An absolute monocytopenia is a characteristic feature of HCL. The demonstration of TRAP activity is a useful complementary tool for the diagnosis of HCL [4]. Immunological markers demonstrate a mature B cell phenotype with expression of CD11c and often CD103, DBA44.

Two previous reports of accompanying HCL and sarcoidosis were noted in a patient with 12 years' diagnosis of sarcoidosis with newly occurring HCL on the follow-up [5] and another one with a concurrent diagnosis [6].

Previous reports supposed that T lymphocyte defects were responsible for B cell proliferation into both HCL and sarcoidosis. In sarcoidosis, T cells recognize antigens and take part in amplification of local cellular immune responses which is achieved by the expression of various cytokine mediators. It has been demonstrated that T helper 1 cells exist in organs influenced by sarcoidosis. These cells produce IL-2 and IFN- $\gamma$  and induce a nonspecific inflammatory response and granuloma formation [7]. Recent studies have shown the

role of these cytokines in the development of HCL. Moreover, hairy cell activation includes expression of the autoregulated IL-2 receptor (the CD25 surface antigen represents the  $\alpha$ -chain) [8]. So, the change in the cellular microenvironment by the sarcoidosis-defective T cells may contribute to development of HCL.

Although the cause of oligoclonal T cell proliferation in HCL has not yet been explained, it is similar to sarcoidosis. Sarcoidosis patients have a wide variety of oligoclonal T cells, and this represents response to different epitopes [7]. This makes one think that some epitopes triggering the inflammatory changes in sarcoidosis may contribute to hairy cell activation as exogenous stimuli.

It may be considered that development of sarcoidosis could be a result caused by HCL although one of the referenced case studies describes a temporal pattern of the two diseases. Some antigens restricted to hairy cells, such as CD11c and CD103, are associated with activation of lymphoid and non-lymphoid cell types [9].

In our case, the diagnosis of HCL was further confirmed by immunohisto-

chemical staining of bone marrow biopsy. Whether it is only a co-incidence or there is a causal relationship between HCL and sarcoidosis, merits further investigation.

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