LEISHMANIASIS – AN UNUSUAL CAUSE OF SPLENOMEGALY IN ROMANIA

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(Abstract): Leishmaniasis is a parasitic infection caused by protozoans classified as Leishmania species. Romania is not considered an endemic country and there are only few reports of sporadic cases in the last 100 years. However, studies suggest that the disease is spreading north. We present the case of a 44 year old female that presented with asthenia, perspiration, vertigo, weight loss and menometrorrhagias in small to medium quantity. Clinical exam revealed the presence of splenomegaly and her blood tests indicated she had pancitopenia; differential diagnosis included myeloproliferative or lymphoproliferative disorders, infections that evolve with spleen enlargement, autoimmune-related splenomegaly and hepatic - all tests were negative. She refused the bone marrow aspiration. Three months later, her condition worsened and the menometrorrhagias became more severe. Bone marrow aspiration revealed the presence of numerous intra and extracellular Leishmania spp. amastigotes. A detailed anamnesis showed that she had worked for six months in Italy as a care-giver nine months ago. She was transferred to Bucharest where she received optimal treatment. However, due to the continuous bleeding, the evolution was unfavourable. This is an alarm sign for physicians that should take into account the fact that, due to population migration and global warming, tropical infectious diseases are becoming more and more common. The signs and symptoms, as well as the treatment in leishmaniasis are reviewed, as well as a brief history of leishmaniasis in Romania. Keywords: VISCERAL LEISHMANIASIS, SPLENOMEGALY, TROPICAL DISEASES

Leishmaniasis is a parasitic infection caused by protozoans classified as Leishmania species, of the trypanosomatidae family. Transmission can occur after the bite of a phlebotomine sand fly (1) whose hosts are either animals (dogs or rodents), either humans, depending on geographical area (humans are more often hosts in hyperendemic areas).

The World Health Organization recognizes four forms of leishmaniasis, the occurrence of which depends on parasite
species and the reactivity of the immune system of the patient: cutaneous leishmaniasis (often self-healing and the most common form), diffuse cutaneous leishmaniasis (especially in immunocompromised patients), mucocutaneous leishmaniasis and visceral leishmaniasis (VL) (also known as "kala azar") - the most severe form, fatal if left untreated (2).

Over 90% of confirmed leishmaniasis infections are from India, Bangladesh, southern Sudan, Nepal and North-East Brazil (3); some Mediterranean countries such as Italy, Greece, Cyprus, France are considered endemic, as well as other European countries such as Portugal. Romania is not considered an endemic country and there are only few reports of sporadic cases in the last 100 years. However, studies suggest that the disease is spreading north because of several risk factors such as climate, population migration, (4) pet import (dogs as reservoir for the disease - leishmaniasis has up to 25% seroprevalence in domestic dogs in endemic countries) and adaptability of the vector to new environmental conditions (1, 2).

**CASE REPORT**

We present the case of a 44 year old female that was admitted to the Haematology department for asthenia, perspirations, vertigo, weight loss (7-8 kg in the last three months) and menometrorrhagias in small to medium quantity. The bleeding had appeared one week prior to admission, whereas all the other symptoms had appeared three months ago. She had a history of uterine fibroma, diagnosed 9 years ago, and treated conservatively. She was a stay-at-home mother, did not smoke or drink, and she lived in a spacious rural household.

Clinical examination revealed only a massive splenomegaly (10 cm below the costal margin). She was pale and dehydrated but had no fever. Rectal examination showed no signs of active bleeding.

Differential diagnosis was centred on splenomegaly and included: 1. myeloproliferative or lymphoproliferative disorders (syndrome?); 2. infections that evolve with spleen enlargement (such as hepatitis, HIV, mononucleosis); 3. autoimmune-related splenomegaly (encountered in lupus and rheumatoid arthritis); 4. hepatic disorders (cirrhosis); 5. idiopathic splenomegaly (exclusion diagnosis).

Blood tests revealed the presence of pancytopenia, with hipochrome normocytic anaemia (Hb = 5.1 g/dl); her platelets were 50,000/mm³ and white blood cell count was 1790/mm³, with a normal distribution and mature polymorphous lymphocytes that had morphological signs of activation (possibly due to a viral infection), thus eliminating myeloproliferative or lymphoproliferative disorders.

Echographic imaging confirmed the clinical suspicion of splenomegaly, with a 135 mm - spleen, but revealed no other pathological findings (echographically normal liver); hepatic tests (ALAT, ASAT) were within normal range, thus eliminating cirrhosis as a possible aetiology.

Markers for autoimmune diseases - rheumatoid factor, anti-cyclic citrullinated peptide antibodies, antinuclear antibodies and anti double-stranded DNA antibodies were negative, thus eliminating autoimmune-related splenomegaly. HIV testing, HbS antigen, anti-HCV antibodies, Cytomegalovirus antibodies and anti-toxoplasmosis antibodies were absent as well, with IgM, IgA and IgG values within normal limits, thus eliminating the most
common infections that evolve with spleen enlargement.

In order to further investigate the pancytopenia, other blood tests were performed: bilirubin (both fractions were only slightly increased) and reticulocyte count (increased); these results, correlated with the fact that the anaemia was microcitic, lead to the conclusion that the main mechanism by which it had appeared had been blood loss. Gynaecological consult confirmed the presence of a fibroma with no active bleeding at the time of the consult. Although the patients’ stool tested positive for occult gastrointestinal bleed, both endoscopy and colonoscopy were negative for signs of active bleeding. Coagulation tests were performed - all within normal range. A bone marrow aspiration was suggested, but the patient refused the investigation.

The splenomegaly was considered to be reactive due to the presence of the activated lymphocytes in the formula. Leucopenia and thrombocytopenia were interpreted in the context of a medullar aplasia. Anaemia was interpreted as having a mixed etiology - medullar aplasia, hypersplenism, menometrorrhagias. The patient received blood transfusions and dietary supplements for the correction of anaemia. She was discharged with haematological parameters that had much improved, and she was prescribed dietary supplements (iron, folic acid, vitamin C).

Three-months follow-up examination revealed an increase in the dimensions of the spleen (175 mm), hepatomegaly and important gynaecological bleeding. Blood tests revealed the persistence of pancytopenia with a neutrophil count of 380 elements/mm³ and elevated ferritin level. Due to her important bleeding, the patient was transferred to the Gynaecology department, where haemostatic uterine curettage was performed.

After surgery, she returned to the Haematology department. A bone marrow aspiration was suggested once more and this time the patient consented. The results showed the presence of numerous intra and extracellular *Leishmania spp.* amastigotes (fig. 1). A detailed anamnesis showed that she had worked for six months in Italy as a care-giver nine months ago.

**Fig. 1.** Microscopic aspect of *Leishmania spp.* amastigotes from bone marrow aspiration
The patient was transferred to the "Victor Babes" Hospital of Infectious Diseases, where treatment with liposomal Amphotericin B was initiated. Metrorrhagia persisted (due to her uterine fibroma) and a second surgery was performed after which the bleeding continued; although best supportive care was given, the patient had an unfavourable outcome.

**DISCUSSION**

The purpose of this case presentation is to attract attention to the necessity of including tropical diseases in the differential diagnosis of difficult cases that do not respond to standard therapy. Considering the marked increase in population migration, the clinician must take into account imported infectious diseases. A meticulous anamnesis is essential in such situations, and it may help narrow the spectrum of etiological microorganisms and parasites, thus limiting the amount of tests required for a positive diagnosis.

*Leishmania infection in Romania*

The first report of a leishmaniasis case dates to 1912. No other cases were reported until 1954, when an outbreak of visceral leishmaniasis was reported in the Oltenia region. One other case was reported in 1991 (5). However, in the last 25 years, more and more leishmaniasis cases have been diagnosed in Romania - 14 cases of visceral leishmaniasis reported between 2000 and 2010. All patients had recently travelled to Mediterranean countries (6-8), as did our patient, who had travelled one year prior to her first hospital admission to Italy.

*Signs and symptoms in VL*

A descriptive study on 71 VL patients diagnosed in an African hospital indicated that the most frequent symptoms were fever, abdominal pain, loss of appetite, weight loss, epistaxis, diarrhoea, cough and joint pains (10). Similar rates are reported on an Italian population - all children and 90% of the adults were febrile at presentation (1).

Most common signs in VL include splenomegaly (60-97%), hepatomegaly (50-60%), lymphadenopathy (20%), ascites and lower limb oedema (around 10%) (1, 3, 10-11). The most common clinical presentation consists in fever associated with hepatosplenomegaly (1); some authors have identified a "classical triad" of signs, symptoms and laboratory findings in VL that consist in fever, splenomegaly and pancytopenia (9).

At admission, this classical triad was NOT present; the fact that our patient was afebrile at her first presentation augmented the difficulty of including leishmaniasis in the differential diagnosis; initially, there was no hepatomegaly (although it appeared at follow-up), no enlarged lymph nodes, no oedema and no bleeding other than the genital one interpreted in the context of the uterine fibroma. Laboratory findings were similar to other reported VL cases (12) - anaemia, leucopenia with relative lymphocytosis and thrombocytopenia.

*Delay in diagnosis in countries that are not endemic*

VL is frequently misdiagnosed, especially in non-endemic countries and by physicians that have not had a lot of experience with tropical diseases. Diagnosis is difficult due to the unspecific early phase and the fact that the parasite is largely sequestered in the spleen, liver and bone marrow - traumatic interventions are required for a positive diagnosis (9).

For instance, Brazil is one of the coun-
tries that have experienced an increase in VL cases over the last two decades, with more and more areas becoming endemic for this disease. In the 1980's, in urban Brazil, there was an increase in VL mortality rates due to the fact that physicians underestimated and failed to diagnose VL - it was encountered only in certain rural areas at the time and they had little to no experience with this disease (13).

Our patient was correctly diagnosed approximately 14 weeks after her first hospital admission. This delay lead to an unfavourable prognosis and was a consequence of several factors: incomplete anamnesis, impossibility to perform bone marrow aspiration and the concomitant fibroma that complicated the case and aggravated the prognosis.

**Particularities of the clinical case:**
- young immunocompetent female (HIV negative, no immunosuppressant medication); first anamnesis did not stress on her recent travels, so differential diagnosis did not include tropical diseases; first hospital admittance showed isolated splenomegaly (no associated hepatomegaly) and pancytopenia that could not be thoroughly investigated; associated fibroma as a source of continuous bleeding and confounder that lead to an unfavourable outcome.

**CONCLUSIONS**

This case report presents the management of a VL patient, with unfavourable outcome due not only to associated comorbidities, but also to delay in diagnosis and, consequently, treatment. Its purpose is to attract attention to the increase in incidence of this disease in particular and exotic diseases in general in non-endemic countries due to globalization and increasing migration; thus, they can no longer be excluded by Romanian physicians from the differential diagnosis. Such aetiologies should be suspected in patients that do not respond well to initial treatment, or that have travelled in the last three years to other countries.

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**REFERENCES**


NEWS

PERIODONTAL CHANGES IN PATIENTS UNDERGOING RADIOTHERAPY FOR HEAD AND NECK MALIGNANCY

The most common modalities used in head and neck cancer treatment are represented by surgical resection, radiotherapy and chemotherapy, used singly or in combination. Direct damage to the oral soft and hard tissue structures frequently occurs from radiotherapy and chemotherapy, and indirect damage may also arise from systemic toxicity. The prospective study conducted by a group of researchers from the department of Periodontics - Government Dental College, Calicut, India was designed to analyze the effect of radiotherapy on periodontal parameters in oncology patients prior to irradiation in the head and neck area, compared with 6 months following treatment. The statistical analysis was done using SPSS. The study sample consisted of 29 patients of head and neck malignancy (17 male and 12 female), of mean age 45.66 years. Only 22% of patients had various habits (eg. smoking, tobacco chewing, and alcohol consumption) and the majority of patients (27.59%) had tongue malignancy. All periodontal parameters represented by OHIS (the oral hygiene index Siller), CAL (clinical attachment level), GR (gingival recession), except PPD (probing pocket depth) were significantly increased after radiotherapy. When comparison was made between doses and fractions, only in mandible statistically significant difference were observed in gingival recession. Although there was no significant change probing pocket depth, there was increased gingival recession, clinical attachment level, and plaque index associated with radiotherapy. In this study, 61.5% cases of mandibular teeth and 34.4% cases of maxillary teeth showed attachment loss greater than 0.2 mm. In conclusion, all patients with head and neck malignancy should undergo an oral examination before the initiation of cancer therapy with adequate prophylaxis. (Ammajan RR, Joseph R, Rajeev R, Choudhary K, Vidhyadharan K. Assessment of periodontal changes in patients undergoing radiotherapy for head and neck malignancy: A hospital-based study. J Cancer Res Ther, 2013 ; 9 (4) : 630-637).

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