ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 11, pp.60542-60545, November, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

A CHALLENGING CASE OF NON-MALIGNANT FEVER AND PANCYTOPENIA

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ARTICLE INFO

Article History:
Received 29th August, 2017
Received in revised form
12th September, 2017
Accepted 21st October, 2017
Published online 30th November, 2017

Key words:

Pancytopenia,
Visceral Leishmania,
Lymphocytic hemophagocytosis.

ABSTRACT

Visceral leishmania, known as Kala Azar, is a rare but increasing disease especially in Lebanon. The protozoan parasite proliferates in the reticulo-histiocyte system producing a large spectrum of different symptoms that can mimic other diseases like malignancies. HL-Hemophagocytic lymphohistiocytosis is a possible complication that can rapidly deteriorate the patient clinical situation and make the diagnosis even more difficult. We report a challenging case of fever and pancytopenia in an otherwise well looking Lebanese 3 years old girl.

Citation: Grace Akoury, Valeria Modica Alameddine, Nada Khoury, Rawane Dagher, Pauline Abou Jaoude, Mode AlOjaimi, Rayan Ghyie and Marie Claude Fadous Khalife. 2017. "A Challenging case of non-malignant fever and pancytopenia", *International Journal of Current Research*, 9, (11), 60542-60545.

INTRODUCTION

Pediatric hemophagocytic lymphohistiocytosis (HLH) is a life threatening syndrome where an uncontrolled activation and proliferation of T cells and macrophages occur (Zied GAifer *et al.,* 2016). An immediate initiation of treatment is necessary. The unspecific symptoms and the variable clinical presentations make the diagnosis very difficult leading to an increased risk of mortality (Iwona Malinowska, 2014). A secondary HS can be triggered by infections that require an appropriate specific treatment. If the prompt recognition of HLH is very difficult, the diagnosis of visceral leishmania is even a mirage. We present a case of a child with persistent fever, pancytopenia and hepatosplenomegaly.

Clinical case

A previously healthy three years old Lebanese girl born to consanguineous parents presented to the emergency department of our university hospital for fever of 6 weeks duration refractory to multiple antibiotic therapy. The girl had a high-grade fever starting 6 weeks ago, every 6 to 8 hours, responsive to antipyretics, with decrease PO intake and abdominal distension as by parents.

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Past medical history positive for recurrent antibiotic therapy with no improvement and one Packed Red Blood Cell transfusion 2 weeks before presentation because of anemia. On physical exam, the child was moderately pale, playful and had normal facial features. Less than the 5th percentile for height (83cm) and weight (10, 6 kg). Her pulse and blood pressure were normal . She also had a normal pulmonary and cardio-vascular exam. Her abdomen was soft, distended with mild hepatomegaly and splenomegaly of 6 cm below costal margin. No pathologic lymph nodes were found. Congenital cutaneous hyper pigmented lesions on the arms, abdomen and legs were noted Neurologic exam and psychomotor development were normal for the age.

CBC and Blood film inspection revealed moderate anemia (8.8 gr/dL, MCV 79,8 fL, RGC 3.5 10^6/uL) leukopenia (3,77. 10^3/uL), moderate neutropenia (0.505 K/uL) and mild thrombocytopenia (125 .10^3 /uL) with high inflammatory markers (CRP 69.8 mg/L ,ESR 100 ,PCT 3,8 ng/mL). Normal liver enzymes and liver function tests. Normal C3 and C4 but positive ANA antibodies (1/160), lupus anticoagulant antibodies and anti β2 microglobuline antibodies positive, ANTI dsDNA , pANCA and cANCA negative. Viral serology (EBV, CMV, Parvovirus) Negative; mycoplasma titers negative, Wright and widal negative, toxoplasma IgM was

positive (2.58 Index), PPD negative. Blood cultures were negative, first urine catheterized culture positive for E.Coli ESBL. Abdominal ultrasound was positive for a mild hepatomegaly and splenomegaly (16 cm), left uretropelvic junction abnormality with dilation of 1, 8 cm (>1,5). Cardiac ultrasound done in order to r/o endocarditis was negative. The girl was started on Imipenem antibiotic for treatment of resistant urinary tract infection without improvement. Repeated blood tests (Table 1) showed progressive pancytopenia (Hb 6 gr/dL, ANC 0.278 K/uL, PLT 55 10^3/uL) and high reticulocytes count (5.19 %), LDH (1353 U/L), positive direct coombs and normal haptoglobin (2, 9 g/L). No deficits in folic acid and vitamin B12 were noted. Normal coagulation studies.

fibrinogen (4 gr/L). The high level of Triglycerides (387 mg/dL) and ferritin along with the presence of pancytopenia, hepatosplenomegaly, increasing hepatic liver enzymes (AST 274 U/L, ALT 118U/L) and fever matched the criteria of hemophagocytic lymphohistiocytosis. Bone marrow biopsy was done and corticosteroids started with no improvement.

Bone marrow biopsy result showed leishmaniasis, negative culture (Figure 2).

Patient received liposomal amphotericin B therapy and improved clinically and biologically in 72 hrs.

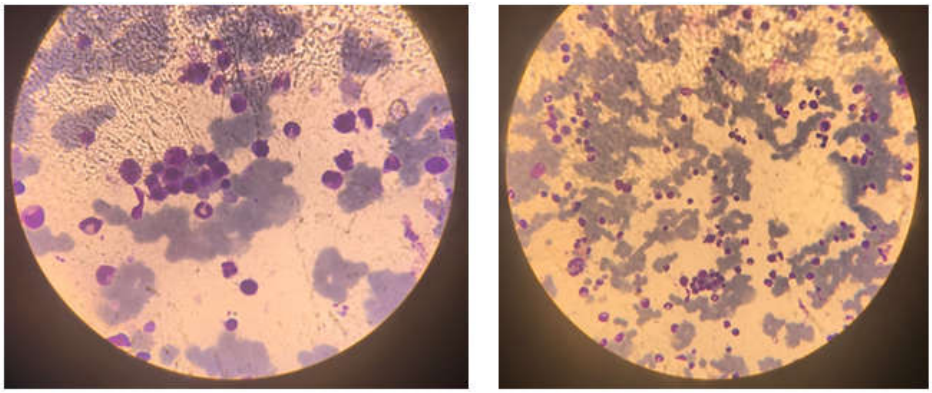

Figure 1. Bone marrow aspirate

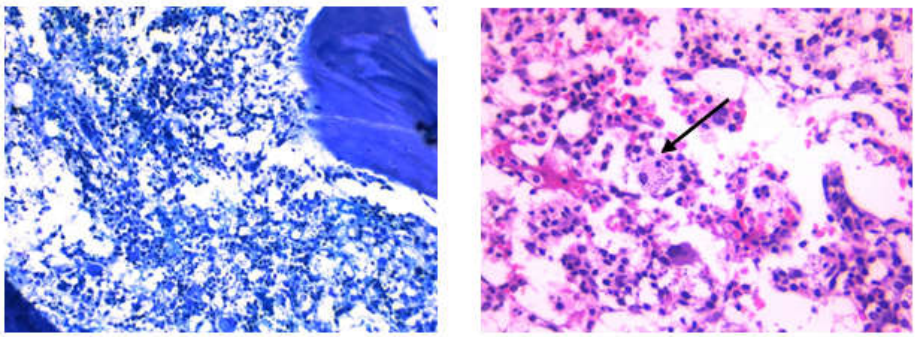

Figure 2. Bone marrow biopsy

Table 1: Laboratory results

Test	Day 1	Day 15 (day 1 of therapy)	Normal value
Red blood cell count (RBC)	3.58x10^6	3.4x10^6/uL	4.5-6.5 x 10^6/uL
Hemoglobin (Hb)	8.84g/dL	8.2 g/dL (post transfusion)	11.5-12.5 g/dL
Mean corpuscular volume (MCV)	79.8fl	78.6 fL	75-80 fL
White blood cell count (WBC)	3.7x10^3/mm^3	1.7x10^3/mm^3	4-10x10^3/mm^3
Platelet count	125 000	55 000	150x10^3-350x10^3
ANC	0.505 K/uL	0.278	2.00-6.90
Direct coombs test	Positive	Positive	
Indirect coombs test	Negative	Negative	
Lactic dehydrogenase (LDH)	369U/L	1353 U/L	110-295 U/L
AST	70 U/L	274 U/L,	13-35 U/L
ALT	29 U/L	118U/L	5-45 U/L
Ferritin	>2000 ng/mL	40.000 ng/mL	15-200ng/mL
CRP	69.8 mg/L	161 mg/L	0-5 mg/L
ESR	100	125	

Bone marrow aspirate and total body scan were negative for malignancy (Figure 1).

Inflammatory markers increased (ESR 125, CRP 161 mg/L) with extremely high level of ferritin (40 000ng/mL) but normal

DISCUSSION

We discussed a case of a child who presented with persistent fever, pancytopenia and hepatosplenomegaly in the context of

resistant urinary tract infection in an otherwise well looking baby. After the resolution of the urinary tract infection, no improvement in the symptoms of the baby were seen.Malignancy, viral illness and autoimmune diseases were ruled out after extensive laboratories and radiological exams.Extreme elevation of inflammatory proteins associated with persistent fever, pancytopenia, hypertriglyceridemia and hepatosplenomegaly were suspicious for HLH. While corticosteroids for HLH were started, visceral Leishmania was finally diagnosed after a bone marrow biopsy. Antimicrobial therapy was started and the child quickly recovered.

Visceral leishmania (VL) is almost an exclusively pediatric parasitosis caused by a protozoa frequently found in South Western Asia, Eastern Africa, Brazil and Mediterranean countries (Kira-Lee KOster, 2015). Leishmania is considered to be endemic in Lebanon (Ali Alawieh *et al.,* 2014) and especially in2013-2014 after the massive increase of Syrian refugees (The UN Refugee Agency, 2013). Records from the Epidemiological Surveillance Department and Lebanese Ministry of Public Health (ESDMOH) from January 2001 to March 2014 showed the presence of only two cases of visceral leishmania (Ali Alawieh, 2014) proving how rare this entity is even in endemic countries. The clinical manifestations of the disease tend to appear months till years after first exposure. Simultaneous infections can trigger the clinical manifestations of leishmania (Higel *et al.,* 2015). In our case, the child was at first diagnosed to have a resistant urinary tract infection associated with urinary tract malformations and a possible SIRS- systemic inflammatory response syndrome.

This finding further delayed the correct diagnosis. Unspecific symptoms (such as fever, weight loss, and lymphadenopathies) may occur, followed by more specific manifestations like pancytopenia and hepatosplenomegaly (Magill, 1993). All these nonspecific symptoms may be misleading (Lakhdar Idrissi *et al.,* 2007). Viral agents, toxic substances, malignancies and vitamin B12 deficiency can be considered as possible differential diagnoses (Magill *et al.,* 1993). In our case we described the presence of a high positive direct Coombs test and positive lupus anticoagulant antibodies, ANA antibodies and anti β microglobulinemia.The presence of autoantibodies can be explained by the exaggerated hypergammaglobulinemia secondary to polyclonal B cells activation (Higel *et al.,* 2015). Leishmania and HLH are two intrinsic connected entities. Visceral leishmania is a great mimicker of HLH and at the same time it can cause secondary HLH in 28% of the cases (http://journals.lww.com/pidj/abstract/2015/12000/hemophagocytic_syndrome_in_children_with_Visceral.7.aspx).

HLH is a life-threatening condition with an excessive immune response caused by activated cytotoxic T cells and macrophages (Higel *et al.,* 2015). Acquired HLH can be triggered by infections as with the leishmania protozoa. The acquired form appears to be less severe than the genetic syndrome but a prompt identification of the "triggers" is important to start an early effective treatment and to decrease the risk of toxic chemotherapy (Risdall, 1984). As we previously described, the child was diagnosed and treated as having HLH and Leishmania was confirmed only later. The diagnosis of HLH was supported by the presence of five of the known requested criteria (Henter *et al.,* 2004): fever, splenomegaly, peripheral blood cytopenia, hypertriglyceridemia, Ferritin>3000 ng/mL (Allen *et al.,* 2008). It is worth noting that HLH was especially suspected when extremely increasing levels of ferritin were demonstrated. Ferritin is a general marker of inflammation. When greater than 10,000ng/mL the differential diagnoses are limited to: sepsis, infection, iron overload, and HLH (Katie Sackett, 2016). The degree of ferritin elevation has been linked with poor prognosis (Bennett *et al.,* 2011. The clinically well looking child even with extremely high ferritin and persistent high fever is peculiar in our patient. Definitive diagnosis of VL needs a positive smear or tissue culture. Our initial bone marrow analysis failed to show the presence of Leishmania, and only the bone marrow biopsy demonstrated the diagnosis. As described by Kpster and Al. often the initial bone marrow puncture can be falsely interpreted as being normal (Kira-Lee *et al.,* 2015). The visualization of the amastigotes is usually found in macrophages only with a careful and prolonged examination (Chulay *et al.,* 1983). Other possible studies as molecular and serologic testing can be very helpful if negative or inconclusive histopathology or cultures(16), but they are not always available especially in developing countries.

Conclusions

Hemophagocytic syndrome can lead to an acute and life-threatening inflammatory reaction. A very early diagnosis is essential. If the cause of acquired forms of HS is not correctly treated, symptoms and the critical clinical condition can persist. The suspicion of VL could be very challenging also in endemic areas. Many factors can be implicated as: nonspecific symptoms, many differential diagnoses, unavailability of all laboratories tests especially in developing countries and difficult histologic diagnosis. The examination of histological findings could be falsely negative. A careful and rigorous analysis of the samples by an expert pathologist are the key for a successful diagnosis.

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