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CASE REPORT

Hyperinfection by *Strongyloides stercoralis* probably associated with Rituximab in a patient with mantle cell lymphoma and hyper eosinophilia

Hiperinfección por *Strongyloides stercoralis* probablemente asociada con Rituximab en una paciente con linfoma e hipereosinofilia

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SUMMARY

The first report to our knowledge, of hyperinfection by *Strongyloides stercoralis* (HS) and hypereosinophilia, associated to immune suppression by Rituximab (the only drug received for the last one year and 10 months), in a patient with mantle-cell lymphoma (MCL), is presented. The patient has a 3-year history of MCL, and developed two accesses of HS during 2008, including meningitis, pneumonia and presence of larvae of *S. stercoralis* in the lungs. We had a unique chance to look at cytotoxicity of filariform larvae in the expectoration after Ivermectin treatment, showing immobilization and death of larvae, associated with eosinophils attached to the cuticle of the parasite.

Keywords: *Strongyloides stercoralis;* Hyperinfection; Rituximab; Eosinophilia; Lung dissemination; Lymphoma; Mantle-cell lymphoma.

RESUMEN

Se presenta el primer reporte, hasta donde tengamos información, de hiperinfección por *Strongyloides stercoralis* (HS) e hipereosinofilia asociados a inmunosupresión por Rituximab (el único medicamento recibido durante 1 año y 10 meses), en un paciente con linfoma de células del manto (LCM). La paciente tuvo una historia de 3 años con LCM, y desarrolló 2 accesos de HS durante el 2008, incluyendo meningitis, neumonía y presencia de larvas de *S. stercoralis* en los pulmones. Se tuvo la oportunidad única de observar la citotoxicidad contra las larvas filariformes en la expectoración, luego del tratamiento con Ivermectina, mostrando la inmovilización y muerte de las larvas, asociada a la presencia de eosinófilos adheridos a la cutícula del parásito.

INTRODUCTION

Hyperinfection by *Strongyloides stercoralis* (HS) is a well known clinical and parasitological event, in which the parasitic infection, usually limited to the intestinal wall of the upper small intestine, causing few or no symptoms, can spread to other areas of the gastro intestinal tract and to other organs; the latter is sometimes referred to as disseminated strongyloidiasis (DS)[14,15,16]. This situation is triggered by immune deficiency. Relevant causes of immune deficiencies associated with hyperinfection by *S. stercoralis* are malignancies such as lymphoma[7,16], leukaemia[14], immunosuppression with drugs, among which steroids are of major importance[14,15,16], organ and tissue transplants[5,19]. In a high percentage of all these situations, treatment with immunosuppressive drugs, particularly steroids, seems to be important[6]. Steroids are known to suppress eosinophilia and lymphocyte activation[4,14]. Other important causes include coinfection with the human T cell lymphotropic virus type-1 (HTLV-1)[9,26], hypogammaglobulinemia and malnutrition[14]. Coinfection with HIV has also been implicated, although the views are somewhat conflicting and the accepted view is that there are no solid criteria to establish a relationship between HIV infection and HS[14,16]. The death rate from HS,

particularly in the DS form, can be as high as 60-86% [7,13]. Although Ivermectin at one or two doses per day is the drug of choice for *S. stercoralis* infection, the dosing for HS or DS does not appear to have been worked out yet, as it has not for Thiabendazole, an effective drug, but with side effects, or Albendazole, a much less effective drug[14].

In this paper we report a case of hyperinfection by *S. stercoralis* with hyper-eosinophilia and respiratory distress, in a patient with non-Hodgkin's mantle cell lymphoma (MCL) receiving only Rituximab (anti-CD20 monoclonal antibody) as maintenance treatment, not associated to HTLV-1 infection, clinically cured with Ivermectin, and in which eosinophil cytotoxicity against larval stages in the lung could be documented.

CASE DESCRIPTION

The patient was a 59-year-old Venezuelan-born female, with a 3-year history of MCL in clinical remission, after receiving Rituximab-Hyper-CVAD, high dose Methotrexate and ARA-C for five cycles (October 2005-April 2006), and maintenance with Rituximab alone for one year and 10 months before admission. She was admitted to hospital on the 6th of February 2008 with a diagnosis of meningitis caused by a coagulase-negative *Staphylococcus* (apparently *S. warneri)*, which was resolved with intravenous Vancomycin. However, fever and mild respiratory symptoms persisted. Three weeks later she was readmitted because of abdominal pain, diarrhea, persistent productive cough, fever and periodical symptoms of intestinal pseudo-obstruction. Fecal examination showed abundant larvae of *S. stercoralis.* Examination of expectoration samples revealed abundant filariform larvae of *S. stercoralis* (about 40 larvae/50µL sputum). *Klebsiella pneumoniae* and *Candida albicans* were isolated from expectoration. Deterioration of health prompted admission to the Intensive Care Unit. Treatment included Cefotaxime 14 days, Fluconazole seven days**,** and Ivermectin (200 µg/kg/day for two days), with improvement of the symptoms. New examination of the patient at day 7 after Ivermectin treatment showed diffuse abdominal pain and no visceromegalies, edema in both legs, dry, desquamate and itchy skin, fever and cough still persistent with white expectoration, the feces were solid. A second 2-day course of Ivermectin was repeated, with improvement of respiratory symptoms. Direct and agar culture of expectoration and fecal examination samples using the concentration method of Baermann, carried out at 30 and 52 days after 2nd Ivermectin treatment, did not show larvae of *S. stercoralis*. Four months after first admission (25 June 2008), she again had pneumonia due to *K. pneumoniae* and was treated with Ceftazidine with clinical improvement, but high blood cell count (32,500/mm^3) and eosinophilia (22,425/mm^3) prompted examination of feces and expectoration, showing rabditiform larvae of *S. stercoralis* in both samples. She was previously medicated by others with Albendazole 400 mg/day for five days with no success, and later by us with Ivermectin 200 µg/kg/day for five days. Examination of feces (Direct, Baermann and agar plate[23]) and expectoration (Direct and agar plate) 12 days and two months after completion of treatment did not evidence the presence of larvae of *S. stercoralis.*

Background history: Lymphoma was diagnosed in April 2005 by biopsy of cervical lymph node. Chemotherapy-immunotherapy treatment Hyper-CVAD included three monthly cycles of Cyclophosphamide, Doxorubicin, Vincristine and dexamethasone, alternated with three monthly cycles of Methotrexate and Cytarabine, with Rituximab before each cycle[22]. Cycles of chemotherapy lasted until April 2006, after which only Rituximab bi-monthly was administered: in 2007 she received five doses, and in 2008 (up to August) four doses. She had frequent cough, diagnosed as bronchitis and findings of the chest tomography and x-ray were reported as interstitial bilateral infiltrates. Abdominal pain and diarrhea were reported since the beginning of chemotherapy for lymphoma, three years before admission. *S. stercoralis* infection was diagnosed in feces first time after last cycle of chemotherapy, and thereafter treated several times including a course of 1200 mg/day for three days with one day's rest for four cycles, without complete success. Six months before admission, she was treated at our Clinic of Parasitology with a single 200 µg/kg dose of Ivermectin because of a diagnosis of strongyloidiasis infection. Gastrointestinal bleeding and hematuria associated to pancytopenia post chemotherapy was observed in February 2006. Upper endoscopy in March 2006 showed chronic gastritis and granular duodenitis. The patient has been a permanent city dweller for the last 34 years, with no rural contacts. The expected time of infection by *S. stercoralis,* according to prolonged rural contacts with limited sanitation, appears to be 49-58 and/or 34-43 years previously.

Laboratory

Relevant laboratory tests available since August 2007: Haemoglobin between 10 and 14 gr/dL, white blood cell counts between 9,000 and 34,700/mm^3, eosinophils between 1,344 and 22,425/mm^3. Total proteins, albumin, globulins (range of normal values in mg/dL) around the time of first pneumonia: 5.3 (6.3-8.5), 3.4 (3.5-5.1), 1.9 (2.5-3.0) and two months after pneumonia: 5.7 (6.4-8.9), 4.4 (3.1-5.0), 0.1 (0.9-1.8) respectively. Immunoglobulins: IgG 212 (700-1600 mg/mL), IgM 16 (40-230 mg/dL), IgE 7.5 (< 48 IU/mL) and IgA 46.3 (70-400 mg/dL). Cerebral-spinal fluid examination at the time of meningitis showed signs of bacterial infection, and the culture showed gram positive *Staphylococcus***.** Cultures of expectoration at the time of first and second pneumonia infections showed *Klebsiella pneumoniae* and *Candida albicans*. Anti-core HBV was positive. *S. stercoralis* larvae in feces first time in April 2006, and thereafter several times diagnosed and incompletely treated until apparently successfully treated with Ivermectin (August 2007) six months before meningitis; again diagnosed at the time of first and second pneumonia infections. *S. stercoralis* larvae were observed in expectoration at time of first and second pneumonia infections. Culture of left external otitis secretion (May 2008) showed abundant growth of coagulase-negative *Staphylococcus* sp. HIV and HTLV I-II tests (carried out twice) were negative.

Cytotoxicity of Strongyloides stercoralis larvae: Expectoration samples provided a unique chance to look at filariform larval destruction. At day of diagnosis, larvae were all alive and moved vigorously. Two days after first 2-day doses of Ivermectin about 2/3 of the larvae were immobilized or with difficult movements, and surrounded by a cloud of cells (Fig. 1a). Most of the free cells and cells attached to the larval cuticle were eosinophils and some eosinophilic material could be detected at the parasite surface (Fig. 1b). By day 5 post Ivermectin, most larvae were dead or with little movements and surrounded by eosinophils.

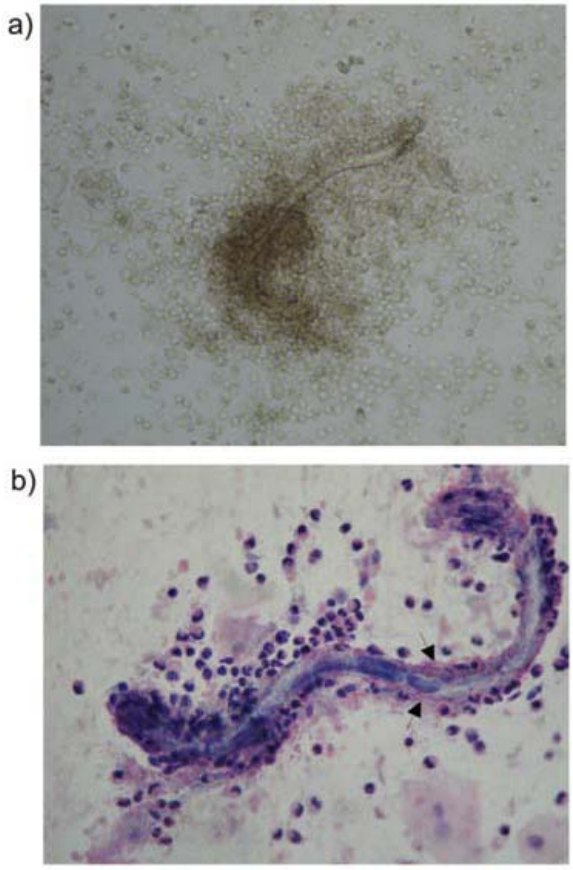

Fig. 1 - *In vivo* eosinophil-mediated cytotoxicity against filariform larvae of *Strongyloides stercoralis* in the expectoration, taken at the first pneumonia episode, two days after Ivermectin treatment. a) Fresh sample of expectoration showing a live stunted larvae surrounded by a cloud of cells (x100). b) Wright staining of expectoration smear of the same material as a), showing almost exclusively eosinophils surrounding or attached to a live stunted larvae, and eosinophilic material (↑) in the surface of the parasite (x400)

White blood cell counts, Rituximab and Strongyloides stercoralis hyperinfection accesses: Figure 2 shows the total and differential white blood cells (WBC) counts that could be recovered from December 2007 to July 2008. WBC counts were usually above normal throughout this period. Three peaks of eosinophilia were detected: the 1st coinciding with diagnosis of meningitis, the 2nd at the time of the first HS, and the 3rd coincided with a 2nd diagnosis of HS. Treatment of HS with Ivermectin and antibiotics resulted in clinical cure and a reduction in WBC counts. Lymphocyte counts were unremarkably constant throughout the period of observation. Rituximab applications did not appear to be associated to detectable changes in WBC counts.

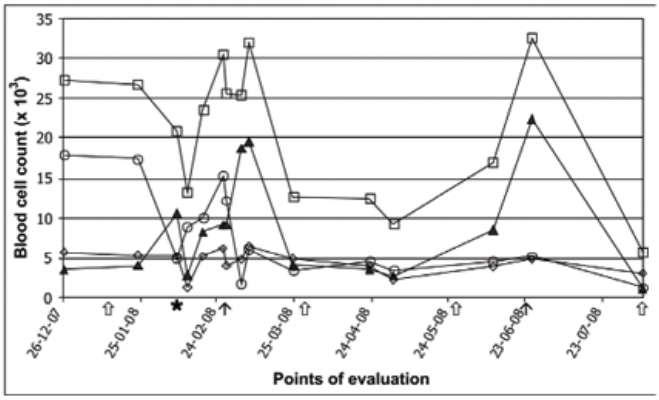

Fig. 2 - Total and differential white blood cell counts that could be collected from the patient between 26th December 2007 and 7th August 2008 and the following events: (⇧) Rituximab applications, (★) meningitis and (↑) episodes of hyperinfection of *Strongyloides stercoralis* detected in the intestine and lungs. (□) Total number of white blood cells, (○) Neutrophils, (▲) eosinophils, (◇) lymphocytes

DISCUSSION

Strongyloidiasis HS has a long lasting history of association with lymphoma, although it appears that it is more a consequence of the immunosuppressive treatment of this malignancy, particularly the use of steroids**.** The first diagnosis of strongyloidiasis in our patient was made after the last cycle of chemotherapy-immunotherapy of mantle cell lymphoma. Thereafter, she was diagnosed of strongyloidiasis several times before admission and treated with Albendazole, without eradication of the parasite. The cycles of chemotherapy-immunotherapy with Rituximab-Hyper-CVAD included the corticosteroid dexamethasone, known to be associated

with HS, and could explain the first exacerbations of the parasite infection. However, the actual relapses of HS do not appear to be related to steroid treatment since the cycles of chemotherapy-immunotherapy were concluded one year and 10 months before admission. Since the only immunosuppressive drug she has been receiving thereafter (and is still receiving) is Rituximab, a relationship between HS and this drug could be postulated.

Rituximab is a chimeric murine/human monoclonal antibody anti-CD20, an antigen present in B lymphocytes and in most B cells of non-Hodgkin's lymphoma. *In vitro* evidence shows that Rituximab works with the human immune system to induce B-cell lysis through an antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity and stimulates apoptosis[2]. It can also induce neutropenia[18]. There are reports in which Rituximab alone or its addition to standard chemotherapy schedules for lymphoma has increased the risk of life-threatening infections, either opportunistic or not, such as bacterial, fungal, protozoan, viral and viral reactivations[3]. However, it appears that infections are more frequent in HIV-associated B-cell lymphoma. To our knowledge, ours appears to be the first report of a helminth opportunistic infection that could be related to a B-cell immunosuppressant agent. Rituximab also induces a reduction in immunoglobulin levels particularly IgG[12] and IgM[8]. It has been shown that B-cells and IgM are relevant in immunity against *S. stercoralis*, and probably prevent the parasite spreading[1,10].

Eosinopenia, or at least absence of eosinophilia, is associated with most conditions in which immunodeficiency leads to *S. stercoralis* hyperinfection and consequently to high lethality[6,13]. On the other hand, patients with strongyloidiasis and hyper eosinophilia appear to survive longer[6,20] and may have few symptoms in spite of immune suppression[25]. Our case is unusual in the fact that hyper-eosinophilia has been constant throughout eight months of observation. Eosinophilia has been considered a good prognosis factor in cases of HS [14,25], a contention which is reinforced by the survival of this patient to meningitis and pneumonia, both highly lethal complications in HS. This may lead to think that hyper-eosinophilia and larval destruction by an antibody-dependent eosinophil-mediated cytotoxicity, after Ivermectin initial damage to the parasite, may have been a major cause for survival and quick health recovery of this patient. This in spite of low serum levels of total immunoglobulins subclasses detected in this patient. However, some specific IgE response against parasite antigens could be detected in her serum (not shown in this paper).

Eosinophils are major effector cells of cytotoxicity against larval stages of parasitic helminths[11]. If eosinophils are not available in sufficient quantities, cytotoxicity may not be efficient, once treatment has been administered. It appears that in this immunosuppressed patient, there may be a potentiation between the drug and the eosinophil damage to the parasite, as it has been observed experimentally in filarial infections with Ivermectin[21] or Diethylcarbamazine[17].

Failure of Ivermectin treatment is another point to consider. The patient had been unsuccessfully treated with frequent and prolonged doses of Albendazole. Eventually, as Ivermectin became available to this patient, she received several schemes with therapeutic failures, until a continuous five dose per day scheme was administered, with successful disappearance of larvae in feces and sputum. The only condition we have found in the literature related to drug failure in strongyloidiasis treated with Albendazole, Thiabendazole or Ivermectin, is coinfection with the HTLV-1 virus[26]. Our patient does not appear to be coinfected with HTLV-1 and other explanations like immune suppression by Rituximab or insufficient Ivermectin doses should be sought.

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