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Efficacy of intravenous cyclosporine in a case of cytophagic histiocytic panniculitis complicated by haemophagocytic syndrome after visceral leishmania infection

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ABSTRACT

Cytophagic histiocytic panniculitis (CHP) is a rare panniculitis characterised by systemic features, due to histiocytic infiltration along with haemophagocytosis, which may also appear in bone marrow, spleen, lymph nodes, and liver. Haemophagocytic lymphohistiocytosis (HLH) is a group of autoinflammatory disorders, which include macrophage activation syndrome, sometimes observed in the course of systemic autoimmune diseases, such as juvenile chronic polyarthritis, systemic lupus erythematosus or vasculitis, and infection-associated haemophagocytic syndrome; if not promptly recognised and treated, HLH can be fatal. Visceral leishmaniasis (VL) is a systemic disease caused by different forms of Leishmania spp., an intracellular protozoa. VL is endemic in tropical countries such as in the Middle East and the Mediterranean. The typical clinical and laboratory features are fever, hepatosplenomegaly, hypergammaglobulinaemia and pancytopenia. The features of VL may mimic some haematologic diseases.

We report a case of cytophagic histiocytic panniculitis and HLH, triggered by a previous visceral leishmania infection. Cyclosporine was quickly effective in this case, after failure of high-dose glucocorticoids, anakinra and etoposide.

Case report

In November 2013, a 22-year-old man from Bangladesh referred to the Emergency Room for headache, neck stiffness and persistent low-grade fever: a computed tomography (CT) of the head was negative and the patient was discharged with a diagnosis of tension headache.

One month later, he was admitted to the Infectious Disease Clinic for fever with shivering associated to productive cough and severe fatigue. He reported 18 kg weight loss during the previous two months, but no night sweats or itching. The patient presented an increase in size of multiple superficial lymph nodes and a painless skin lesion measured approximately 5x7 cm on the hip, like a palpable mass infiltrating the underlying deep layers.

Blood tests showed marked leucopoenia (WBC 1800/μl), mild anaemia (Hb 11 g/dl), slightly increased inflammatory markers (CRP12.84 mg/l, procalcitonin 0.09 ng/ml), LDH 1351 UI/L, CPK 514 UI/l, ferritin 2502 ng/ml. Peripheral blood immunophenotyping showed B lymphocytes normally represented, a T cell reduction with normal CD4/CD8 ratio and a marked reduction of NK cell count.

A skin ultrasound suggested a diagnosis of cellulitis, as concerns the skin lesion. Thoracic CT scan showed a thin pleural effusion (8 mm) to the right pleura, a consensual thickening of the lung parenchyma, a diffuse thoracic-abdominal lymph node enlargement (diameter up to 1.5 cm) and splenomegaly (13 cm). Finally, 18-fluorodeoxyglucose positron emission tomography (18FDG/CT-PET) showed an intense inflammatory activity in the anterior part of the right breast and hip region (in the area corresponding to the skin lesion) with an intense inhomogeneous accumulation on the skin and subcutaneous tissues. At the bronchoscopy, purulent secretions were found, but all microbiological analyses were negative including Ziehl-Neelsen, *M. tuberculosis* culture, *P. carinii* and respiratory viruses polymerase chain reaction (PCR), bacteria and fungi cultures. Despite antibiotic treatment with piperacillin/tazobactam and levofloxacin, fever persisted (body temperature up to 40°C). Blood cultures were negative. Therefore, the ongoing antibiotic therapy with linezolid, meropenem and clindamycin was interrupted. Since *Leishmania spp.* amastigotes were observed on bone marrow aspirate (Fig. 1), amphotericin B lipid complex in two doses was administered with complete fever resolution, disappearance of the skin lesion, and normalisation of white blood cell count, LDH, CPK, ferritin serum levels and inflammatory markers.

Two months later, fever reappeared and the patient was re-admitted to the Infectious Disease Clinic. New swollen painless skin lesions were observed on the left arm and on the other hip. A thorax and abdomen CT did not shown any new or specific lesions. Blood tests showed mild leucopoenia (WBC 2520/

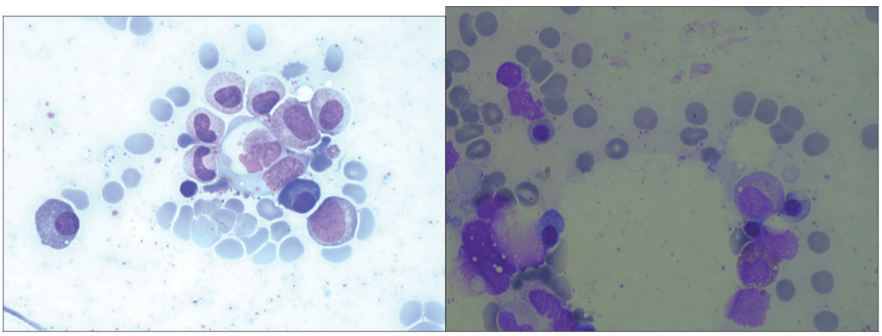

Fig. 1. Bone marrow biopsy showing few *Leishmania* amastigotes.

mm^3), increase of serum LDH (1530 IU/l), PCR (73 mg/l), ferritin (1471 ng/ml) and liver enzymes (AST 114 IU/l, ALT 179 IU/l). On admission, the patient was very sick, with fever (38,9°C), and intense fatigue. Four blood culture sets were performed and all were negative. A skin biopsy was performed and the histological examination was suggestive for active chronic panniculitis (Fig. 3–6). A new bone marrow biopsy showed histological findings consistent with reactive hyperplasia of bone marrow associated with a histiocytic granulomatous infiltrate. Based on this pathological finding, an anti-tuberculosis (TB) therapy was started. However, the patient continued to present fever (maximum 40.3°C). Then, a clinical diagnosis of panniculitis associated with haemophagocytic syndrome was done, based on the clinical picture and blood tests, characterised by pancytopenia, hyperferritinemia and increases of the liver enzymes. A second punch biopsy on the left arm showed macrophage phagocytosis of nuclear debris, red blood cells and white blood cells in a framework compatible with cytophagic histiocytic panniculitis associated with deep dermal vasculitis. Thus, high-doses of glucocorticoids (methylprednisolone 1 g for three days, followed by 40 mg twice daily) in combination with anakinra (Kineret® 100 mg/die) were started; since the TB infection was not clearly ruled out, anti-TB therapy was continued. One week later, since fever was not disappeared, cyclosporine 150 mg/die intravenously was added to the ongoing drugs. However, the concomitant administration of rifampicin did not allow reaching adequate plasma levels of cyclosporine (pre-dosing concentration undetectable, post-dosing concentration 74.50 ng/ml; after 5 days pre-dosing concentration 25.60 ng/ml). Thus, since the fever and skin lesions persisted, the immunosuppressive therapy was changed by suspending anakinra and introducing etoposide in combination with cyclosporine and methylprednisolone 1 mg/kg/day, while continuing anti-tuberculosis treatment. Since no clinical improvement was seen and cyclosporine plasma levels were still under the therapeutic threshold (29.90 ng/ml), empirical anti-tuberculosis therapy was finally suspended. After the interruption of rifampicin, the plasma levels of cyclosporine started to increase (302 ng/ml). Simultaneously, an initial deflection of the fever curve, soon followed by persistent disappearance of the fever, healing of skin lesions, and a general improvement were observed (Fig. 2). Also, resolution of HLH was recorded, with increase in white blood cell count and normalisation of liver enzymes, LDH and ferritin serum levels (Table I). Glucocorticoids were tapered to low doses in the following three weeks.

Seven month after the discharge, the disease was in clinical remission, and a repeated 18FDG/CT-PET was almost completely negative. Cyclosporine was ongoing orally at the dose of 250 mg/day (range between 250–300 ng/ml). Glucocorticoids were tapering to very low-doses and finally suspended.

Discussion

Cytophagic histiocytic panniculitis (CHP) is a very rare panniculitis that is associated with systemic features like fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, hypertriglyceridemia, and coagulopathy. It is characterised by infiltration of subcutaneous adipose tissue by benign-appearing cytophagic macrophages (1). The skin lesions show adipose tissue lymphocytic and histiocytic infiltration along with haemophagocytosis, which may also appear in bone marrow, spleen, lymph nodes, and liver. Patients may have a rapidly fatal disease course, or a longer disease course with intermittent remissions and exacerbations for many years prior to death, or a non-fatal acute or intermittent course responsive to treatment. Treatment of CHP includes: glucocorticoids in combination with cyclosporine, combined chemotherapeutic medications and most recently, anakinra, an interleukin-1 receptor antagonist (2).

CHP can be also complicated by haemophagocytic syndrome or haemophagocytic lymphohistiocytosis (HLH), which is a severe histiocytic disorder characterised by a dysfunctional, uncontrolled immune response leading to activation and proliferation of macrophages (3). HLH is frequently underdiagnosed, fatal, and required prolonged immunochemotherapy consisting of combination therapy with etoposide, dexamethasone and cyclosporine (4). HLH can be primary (genetic) or secondary (acquired), associated with numerous conditions such as neoplastic, infectious, autoimmune or hereditary diseases. Secondary haemophagocytic syndrome has been frequently associated with intracellular pathogens that typically induce type 1 T-helper immune responses (5). The triggering agents in haemophagocytic syndrome are usually viruses of the herpes group, in particular Epstein-Barr and cytomegalovirus, *M. tuberculosis*, or parasite like *leishmania* (5).

In our case, leishmania infection preceded the onset of CHP. In fact, during the first admission, clinical recovery occurred after treatment with only amphotericin B. *Leishmania spp* is an intracellular protozoa, which can cause a systemic disease, called visceral leishmaniasis (VL). VL is endemic in tropical countries such as in the Middle East and the Mediterranean. The typical clinical and laboratory features are fever, hepatosplenomegaly, hypergam-

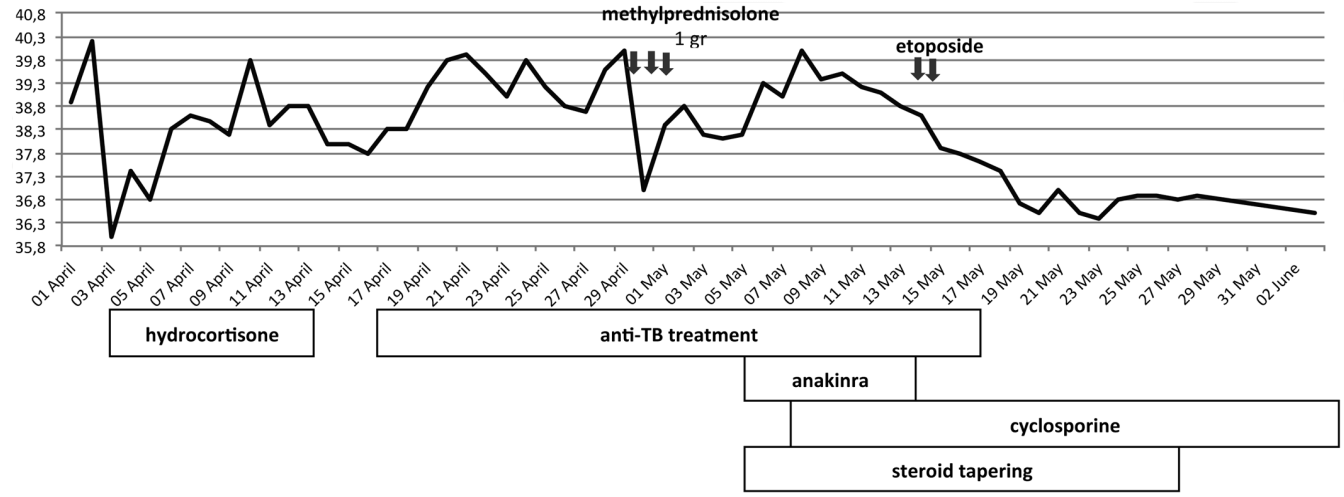

Fig. 2. Trend of the fever curve and its relationship with treatments employed.

maglobulin and pancytopenia. The features of VL may mimic some haematologic diseases (6), and, interestingly, VL also shares some clinical features with HLH. Notably, leishmania can infect also the skin, leading to superficial and deep perivascular infiltration with or without granuloma formation (7). However, cutaneous leishmaniasis can also cause panniculitis, both septal and lobular (7). In our patient, leishmania bodies were carefully searched in two repeated skin biopsies during the second admission, but without a positive result. Thus, panniculitis secondary to an active cutaneous infection by *Leishmania* was definitively ruled out, and CHP has been hypothesised as triggered by previous leishmania infection. Interestingly, this is the first report describing a leishmania infection followed by CHP.

In order to facilitate the diagnosis of HLH, the Histiocyte Society had developed a set of diagnostic criteria (8). The case herein described matched 5 of the 7 diagnostic parameters proposed. Peculiar histopathologic finding in HLH is a prominent and diffuse accumulation of lymphocytes and mature macrophages that occasionally exhibit haemophagocytosis (8). This pattern could be present in bone marrow, spleen, lymph nodes, liver, skin, lungs, and subcutaneous tissue. In the bone marrow, haemophagocytosis of mature and immature haematopoietic cells is characteristic, although a microscopic visualisation of haemophagocytosis does not necessarily need to be present to establish a definite diagnosis (8).Thus, our patient presented a CHP associated with HLH.

Even if the relationship of CHP and HLH is still debated, many, if not all, patients affected with CHP may have HLH, as occurred in our case. In fact, HLH appeared a complication of CHP in this case, as well as HLH can complicate the course of haematologic malignancies or many inflammatory systemic diseases, such as Still's disease, systemic connective tissue diseases, or systemic vasculitis. Fatal haemophagocytic syndrome may be often associated with both benign and malignant subcutaneous panniculitis (9). Notably, vasculitis features were also described in the skin biopsy of our patient (Fig. 3). Panniculitis with vasculitis is rare and set in a systemic infectious or autoimmune/dysreactive background (10), as herein observed.

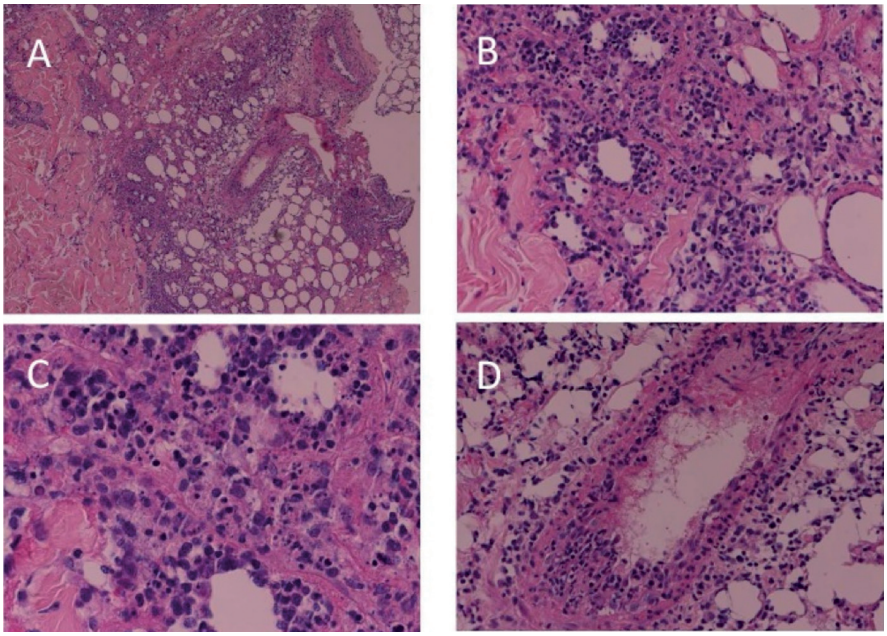

Fig. 3. Skin biopsy by haematoxylin-eosin staining showing parakeratosis and epidermal spongiosis, perivascular exudative and granulomatous inflammation in deep dermal layers. Dense fibrosis into derma layer; at hypodermic level, pattern of lobular panniculitis, with nuclear debris, erythrocyte and leukocyte phagocytosis by macrophages. **3A.** Lobular panniculitis (H&E, 10x magnification). **3B.** Focal necrosis and leukocyte infiltration (H&E, 20x magnification). Fig. **3C.** Histiocytic cytophagocytosis (H&E, 40x, magnification). Fig. **3D.** Venular subcutaneous vasculitis (H&E, 20x, magnification).

Table I. Laboratory changes before and after the introduction of cyclosporine.

Date	WBC (10^3/µl)	Hb (g/dl)	PLT (x10^3/µl)	AST (IU/l)	ALT (IU/l)	LDH (IU/l)	Ferritin (ng/ml)	CRP (mg/l)
14 April	2350	8.8	159	115	76	978		13
17 April	2180	9.8	165	117	89	934	1494	5
24 April	1920	9	183	85	78	844		39
29 April	2680	9.6	158	122	81	1062	2095	
03 May	2010	8.6	103	81	100	793	1324	6
			Cyclosporine introduction					
08 May	1180	7.4	95	65	67	841	1614	40
13 May	920	8.9	98	54	48	882	1900	41
17 May	1320	8.3	118	42	40	744	1861	15
22 May	2970	8.9	154	45	51	735	1610	5
26 May	2020	9.1	174	21	26	690	568	2
03 June	5200	10.7	320	23	20	614	275	0

WBC: white blood cell; Hb: haemoglobin; PLT: platelets; AST: aspartate aminotransferases; alanine aminotransferases; CRP: C-reactive protein.

Furthermore, in the present case, since the TB infection could not definitively rule out, the use of etoposide as first-line therapy for HLH did not seem feasible, while anakinra appeared safer in this context, based on the experience coming from its use in rheumatoid arthritis (11). However, only a transient response due to high doses of glucocorticoids was initially observed, thus cyclosporine was subsequently added. Importantly, cyclosporine was quickly effective in this case by recovering from fever and healing of the skin lesions, only when its plasma concentration became into the therapeutic range, after rifampicin suspension (Fig. 1).

The efficacy of cyclosporine supports the hypothesis that the granulomatous lesions of CHP and the secondary haemophagocytic syndrome are both T cell-dependent. This observation is consistent with the higher frequency of haemophagocytic syndrome in the course of T-cell lymphomas (12, 13). On the other hand, leishmania specific CD4 T cells release IFNγ limits parasite replication in patients with visceral leishmaniasis (14); also CD8+ T cells protect against *L. donovani* infection in healed visceral leishmaniasis individuals (15). Thus, in predisposed individuals, persistent abnormal activation of T cells after leishmania eradication might be implicated in the development of CHP and HLH.

In conclusion, leishmania is a possible trigger for CHP, and then, it should be sought in all cases of panniculitis. Cyclosporine appeared to be the treatment of choice in CHP, since it was effective after failure of high-doses of glucocorticoids, and anakinra. Treatment of CHP with cyclosporine was effective also on secondary HLH, which not responded to etoposide. Since CHP and HLH can be the clinical presentation of ongoing infections, and cyclosporine shows many interactions with antibiotic drugs, a deep work-up to rule out infections and, in particular TB infection, should be performed, in order to start cyclosporine without the risk of worsening possible concomitant infections, and in the absence of potentially interfering drugs.

References

1. ARONSON IK, WOROBEC SM: Cytophagic histiocytic panniculitis and hemophagocytic lymphohistiocytosis: an overview. *Dermatol Ther* 2010; 23: 389-402.
2. RAJASEKARAN S, KRUSE K, KOVEY K *et al*.: Therapeutic role of anakinra, an interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistiocytosis. *Pediatr Crit Care Med* 2014; 15: 401-8.
3. TROTTESTAM H, HORNE A, ARICÒ M *et al*.: Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. *Blood* 2011; 118: 4577-84.
4. ROSADO FG, KIM AS: Hemophagocytic lymphohistiocytosis: an update on diagnosis and pathogenesis. *Am J Clin Pathol* 2013; 139: 713-27.
5. ROUPHAEL NG, TALATI NJ, VAUGHAN C, CUNNINGHAM K, MOREIRA R, GOULD C: Infections associated with haemophagocytic syndrome. *Lancet Infect Dis* 2007; 7: 814-22.
6. MATZNER Y, BEHAR A, BEERI E, GUNDERS AE, HERSHKO C: Systemic leishmaniasis mimicking malignant histiocytosis. *Cancer* 1979; 43: 398-402.
7. SHARQUIE KE, HAMEED AF: Panniculitis is an important feature of cutaneous leishmaniasis pathology. *Case Rep Dermatol Med* 2012; 2012: 612434.
8. HENTER JI, HORNE A, ARICÓ M *et al*.: HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer* 2007; 48:124-31.
9. CRAIG AJ, CUALING H, THOMAS G, LAMERSON C, SMITH R: Cytophagic histiocytic panniculitis--a syndrome associated with benign and malignant panniculitis: case comparison and review of the literature. *J Am Acad Dermatol* 1998; 39: 721-36.
10. TER POORTEN MC, THIERS BH: Panniculitis. *Dermatol Clin* 2002; 20: 421-33, vi
11. FURST DE, KEYSTONE EC, FLEISCHMANN R *et al*.: Updated consensus statement on biological agents for the treatments of rheumatic diseases, 2009. *Ann Rheum Dis* 2010; 69: 2-29.
12. TZANNOU I, BALTA AM, BAKIRI M: Hemophagocytic syndrome associated with hematologic malignancies. *Hospital Chronicles* 2011; 6: 110-7.
13. MÉNARD F, BESSON C, RINCÉ P *et al*.: Hodgkin lymphoma-associated hemophagocytic syndrome: a disorder strongly correlated with Epstein-Barr virus. *Clin Infect Dis* 2008; 47:531-4.
14. KUMAR R, SINGH N, GAUTAM S *et al*.: Leishmania specific CD4 T cells release IFNγ that limits parasite replication in patients with visceral leishmaniasis. *PLoS Negl Trop Dis* 2014; 8.
15. KAUSHAL H, BRAS-GONÇALVES R, NEGI NS, LEMESRE JL, PAPIEROK G, SALOTRA P: Role of CD8(+) T cells in protection against Leishmania donovani infection in healed Visceral Leishmaniasis individuals. *BMC Infect Dis* 2014; 14: 653.