



Case report

Adenovirus related lymphohistiocytic hemophagocytosis: Case report and literature review



G. Mellon^{a,*}, B. Henry^{a,b}, O. Aoun^c, D. Boutolleau^{b,d}, A. Laparra^a, J. Mayaux^e,
M. Sanson^{b,f}, E. Caumes^{a,b}

^a Service des maladies infectieuses et tropicales, Groupe Hospitalier Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

^b Sorbonne Universités, UPMC Univ Paris 06, France

^c Antenne Médicale de Colmar, Centre Médical des armées de Strasbourg, 2 rue des Belges BP, 30446, Colmar, France

^d Service de virologie, Groupe Hospitalier Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

^e Service de pneumologie et réanimation médicale, Groupe Hospitalier Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

^f Service de neurologie 2, Groupe Hospitalier Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013 Paris, France

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ABSTRACT

Introduction: Adenoviral infection is a classic cause of lymphohistiocytic hemophagocytosis (LH) in bone marrow transplantation but is rare outside this setting.

Case report: A 31-year-old female, with a history of treated mesencephalic astrocytoma, was hospitalized for fever, pancytopenia, elevated liver enzymes, hyperferritinemia and hypertriglyceridemia. Adenovirus viral load in blood was 7.3×10^9 copies/mL. Bone marrow aspirate examination confirmed LH. The patient recovered without specific LH or adenovirus-directed treatment.

Conclusion: Adenovirus-related LH, common in bone marrow transplant recipients, should also be considered in patients with chemotherapy in solid tumors.

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1. Why this case is important

Human adenovirus (HAdV) is most often responsible for benign infections in immunocompetent patients. However, in immunocompromised patients, it can cause severe, sometimes life-threatening diseases, such as pneumonia, hepatitis, pancreatitis, encephalitis and disseminated disease.

Four cases of adenovirus-related lymphohistiocytic hemophagocytosis (LH) have been previously reported in adult non-stem cell transplant recipients.

2. Case description

A 31-year-old female was admitted to our unit on July 1st, 2013, with a history of acute fever ($> 38.5^\circ\text{C}$), which begun on June 21th, unresponsive to amoxicillin/clavulanate and ciprofloxacin therapy. She had a relevant history of grade III mesencephalic astrocytoma, diagnosed in June 2012. Full remission occurred after two cycles of temozolomide followed by five cycles of lomustine (last cycle was performed June 3rd), leaving her with a right-

sided hemi-hyperesthesia, sparing face. No hospitalization was reported between June 3rd and June 21st. Upon admission, physical examination revealed a 39°C fever, splenomegaly and unchanged neurological findings.

Laboratory investigations showed pancytopenia (haemoglobin: 8.5 g/dL, leukocytes: $930/\text{mm}^3$ with 650 neutrophils/ mm^3 and 240 lymphocytes/ mm^3 , platelets: $16,000/\text{mm}^3$) associated with elevated liver enzymes (ALAT: 122 IU – normal value (N) < 26 ; ASAT: 120 IU – N < 27), hypertriglyceridemia (3.22 g/L – N < 1.35), hyperferritinemia (1070 $\mu\text{g/L}$ – N < 300), and elevated lactate dehydrogenase (617 UI – N < 390). Bone marrow aspiration ruled out malignant infiltration, leishmaniasis and histoplasmosis, but confirmed the LH diagnosis.

Adenovirus quantitative real time PCR was positive in whole blood (7.3×10^9 copies/mL) and stool (1.3×10^5 copies/mL). Investigations for other infectious agents classically responsible for LH were negative. HAdV DNA extraction from blood and stool specimens was performed on the QIA Symphony SP instrument using the QIA Symphony DNA Midi Kit (Qiagen GmbH, Hilden, Germany). On the other hand, DNA amplification was performed on the Light-Cycler 480 system (Roche Diagnostics, Meylan, France) using a laboratory-developed real-time PCR assay, as previously reported [1]. This assay, adapted from the initial protocol described by Heim et al. [2], is based on the amplification of the conserved hexon gene

* Corresponding author.

E-mail address: guillaume.mellon@aphp.fr (G. Mellon).

Table 1
Adenovirus related lymphohistiocytic hemophagocytosis: clinical and biological features, treatment and outcome of published cases.

	Our case	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Authors [reference]	–	[3]	[4]	[5]	[6]	[7]	[8]
Year	–	1990	2002	2003	2005	2011	2014
Patient (gender and age)	Female, 31 yo ^a	Female, 6 yo ^a	Female, 12 yo ^a	Male, 2 yo ^a	Male, 51 yo ^a	Male, 15 months	Male, 11 months
Comorbidity	Chemotherapy (astrocytoma)	Autologous stem cell transplantation	None	None	Allogeneic stem cells transplantation	None	None
Clinical presentation	Hepatitis	Pneumonia Hepatitis	Pneumonia	Pneumonia Gastro-enteritis	Pyelonephritis Hemorrhagic cystitis	Pneumonia	Pneumonia
<i>Clinical examination</i>							
Fever	yes	yes	yes	yes	n/a ^b	yes	yes
Hepatomegaly	no	no	yes	yes	n/a ^b	yes	yes
Splenomegaly	yes	no	no	yes	n/a ^b	no	yes
Lymphadenopathies	no	no	yes	no	n/a ^b	no	no
Neurological signs	no	no	no	yes	n/a ^b	no	yes
Respiratory signs	no	yes	yes	yes	n/a ^b	yes	yes
Cutaneous signs	no	no	yes (purpura)	no	n/a ^b	no	no
<i>Biological features</i>							
Anemia	yes	yes	no	yes	n/a ^b	yes	yes
Leucopenia	yes	yes	no	yes	n/a ^b	yes	no
Thrombopenia	yes	yes	yes	no	n/a ^b	yes	yes
Hypofibrinemia	no	yes	yes	no	n/a ^b	no	no
Elevated liver enzymes	yes	yes	yes	yes	n/a ^b	yes	yes
Specific treatment	None	IV Ig	Cyclosporin A dexamethasone	IV Ig	Ribavirin	None	IV Ig
Outcome	Recovered	Deceased	Recovered	Recovered	Recovered	Recovered	Recovered

^a years old.^b not available.

of HAdVs, and, therefore, does not allow HAdV typing. HAdV DNA quantification was achieved by the use of a standard curve generated from 10-fold serial dilutions of Adenovirus quantified DNA control (tebu-bio, Le Perray-en-Yvelines, France).

In the absence of organ specific symptoms of adenovirus infection and acute organ failure, cidofovir or ribavirin antiviral molecules, or immune targeted therapy such as steroids, etoposide or intravenous polyvalent immunoglobulins were not given. Clinical course improved progressively with resolution of fever within four days. The patient was discharged after a three-week hospitalization. The lymphocyte account at recovery was 940/mm³ and adenovirus quantitative real time PCR was controlled (1.2×10^5 copies/mL in whole blood and 1.9×10^3 copies/mL in stool).

3. Other similar and contrasting cases in the literature

To our knowledge, six cases of HAdV-associated LH have previously been reported [3–8]. Most reported cases occurred in young patients, five in children, and one in a 51-year-old man. Their characteristics are presented in Table 1.

Moreover, among HAdV-associated LH reported in the literature, two were associated with hematopoietic cell stem transplantation [3,6] and four occurred in immunocompetent patients [4,5,7,8]. In contrast, in the present case, LH occurred after chemotherapy.

On the other hand, our patient recovered without any specific treatment, while most patients of cases reported in literature received a treatment [3–6,8].

4. Discussion

To our knowledge, this is the first solid-organ tumor-related case of HAdV-associated LH reported so far in an adult patient.

LH is due to proliferation and activation of macrophages in response to a cytokine storm. Activated macrophages produce pro-inflammatory cytokines (IL-1, IL-6, TNF- α) which trigger CD8⁺ T-lymphocytes activation, thus maintaining an amplification loop responsible for a hyper-inflammatory state [9,10]. LH is a rare but underestimated disease, and affects all ages, with a male predominance [11]. Mortality is mainly related to the underlying disease [11].

The diagnosis of LH is based on specific clinical and biological features [12]. Risdall et al. made the first description of reactive LH in 1979 [13]. The presence of hemophagocytosis on cytological or histological examination is not sufficient for this diagnosis. Current diagnosis criteria are summarized in Table 2 [14].

Two etiological groups of LH are classically described. The first one, corresponding to primary LH, is a group of genetic diseases affecting the immune system, which are mostly diagnosed during childhood. It includes familial hemophagocytic lymphohistiocytosis, Duncan and Purtilo syndrome (X-linked lymphoproliferative syndrome), Chediak-Higashi and Griscelli syndromes. These syndromes are often triggered by an intercurrent infectious process.

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