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Case Report
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Severe *Cytomegalovirus* Primo-Infection with Secondary Hemophagocytic Lymphohistiocytosis: Consider Underlying Immunodeficiency

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Abstract

Introduction: *Cytomegalovirus* (CMV) infections are common and usually mild, however in immunocompromised patients CMV infection can cause severe disease. Hemophagocytic Lymphohistiocytosis (HLH) is a syndrome of excessive immune activation, which can appear secondary to severe infection. Hairy Cell Leukemia (HCL) is an indolent B-cell neoplasm which frequently presents with immunodeficiency due to cytopenia's. This case report is the first describing this presentation of HCL and thereby it emphasizes the need for recognition of immune-incompetence and investigation of underlying conditions.

Case Report: We report a 34-year-old female patient who was initially admitted with symptoms of fever, coughing and dyspnea on exertion. Laboratory results showed an elevated CRP-level; thrombocytopenia and leukopenia. CMV IgG and IgM were positive which was confirmed by PCR-testing. After six days, she remained subfebrile and laboratory abnormalities persisted. Serum ferritin was determined which was >10.000 ug/L. The diagnosis of secondary HLH was considered and antiviral therapy was initiated. Bone marrow biopsy was performed in which the diagnosis of HLH was confirmed, however this also revealed HCL.

Conclusion: Severe course of CMV infection, or other opportunistic infections, might be the first sign of immunodeficiency and thereby indicate an underlying hematological condition in a formerly healthy patient.

Keywords: *Cytomegalovirus*; Immunodeficiency; Hemophagocytic lymphohistiocytosis; Hairy cell leukemia

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Introduction

Cytomegalovirus (CMV) infections are common and usually give mild symptoms in immunocompetent patients, consisting mainly of a sore throat, lymphadenopathy and fever.

However, in immunocompromised patients (i.e., AIDS patients, solid organ transplant-/hematopoietic stem cell recipients) CMV-infection, or more commonly reactivation, can cause severe disease with devastating organ damage. Therefore, antiviral medication is used in these patients for both prophylactic and therapeutic purposes [1].

Hemophagocytic Lymphohistiocytosis (HLH) is a syndrome of excessive immune activation, which can appear either idiopathic or secondary to, most likely, infections or malignancies. The massive immune cell activation can potentially lead to severe organ injuries causing a life-threatening condition [2]. Early recognition is essential for reducing both morbidity and mortality. HLH should be considered in case of the triad of fever, cytopenia's and splenomegaly. Mild initial symptoms may deteriorate remarkably rapid. Since there exists no test to certainly confirm the diagnosis of HLH, and no delay in treatment would be justified, treatment must be started in case of suspicion based on the international HLH-criteria (Table 1) [3].

Hairy Cell Leukemia (HCL) is an indolent B-cell neoplasm which usually presents with cytopenia's, especially monocytopenia, and splenomegaly. Hepatomegaly and lymphadenopathy are seen less frequently. Twenty-five percent of patients is asymptomatic and are diagnosed due to

incidental splenomegaly or pancytopenia. Patients are usually middle-aged at presentation and complaints, if present, often only consist of weakness and fatigue [4]. Pancytopenia causes these patients to be anemic and at increased risk for bleeding and severe infections [5].

We hereby present a young female patient who was initially admitted with a CMV infection, then developed a secondary HLH and finally was diagnosed with HCL through bone marrow biopsy. This case report is the first describing this presentation of HCL and thereby it emphasizes the need for recognition of immune-incompetence and investigation of underlying conditions.

Case Presentation

Patient information

A 34-year-old female presented at our Emergency Department (ED) (day 0) with complaints of spiking fever, malaise, headache, coughing with white-colored sputum, nausea, occasional night sweats, thoracic pain and dyspnea on exertion for nine days. She had no past medical history. Two days earlier, her general practitioner had started her on oral amoxicillin for a suspected pneumonia. There was no hemoptysis, no collapse, no contact with any animals, no sauna or swimming pool visit and no travel history besides a holiday to Spain and France three weeks earlier. She had been fully vaccinated against COVID-19.

Clinical findings

During physical examination, breathing was found to be shallow and accelerated (20 times per minute) yet with proper oxygen saturation (SO_2 95%). The blood pressure measured 115/76 mmHg with a heart rate of 93 beats per minute. No cardiac or pulmonic abnormalities were detected.

Muscle tenderness was palpated on her back right-sided of the vertebrae.

Diagnostic assessment and therapeutic interventions

A chest X-ray revealed little bilateral pleural fluid. COVID-19 PCR was negative. The electrocardiogram was normal. Laboratory examination revealed multiple abnormalities (Table 2).

The CRP-level was elevated (272 mg/L) and the complete blood count showed thrombocytopenia and leukopenia. Renal function and electrolytes were normal. Liver enzymes were elevated, most likely due to either infection or use of amoxicillin. The patient was suspected of having an infection, most likely pneumonia, and was admitted for further diagnostics and treatment. Amoxicillin was switched to intravenous ceftriaxone.

The first day after admission (day 1) the diagnosis of pneumonia was questioned due to clinical deterioration despite treatment for almost 24 h with ceftriaxone and previous treatment with amoxicillin. Doxycycline was added to the ceftriaxone for antimicrobial coverage of atypical microorganisms and a CT-scan of chest and abdomen was performed to search for the focus of infection (Figure 1). This CT-scan revealed multiple abnormalities: Bilateral pleural fluid with compression atelectasis of the lower lung fields; ascites; hepatosplenomegaly and periportal edema. Due to the abdominal ascites and abdominal tenderness, the gynecologist was consulted for possible Pelvic Inflammatory Disease (PID), which was subsequently excluded based on negative cervical culture and negative PCR-tests for sexual transmittable diseases (Table 3). Multiple infectious disease tests were performed (Table 3). On day 5, the serological profiles of both EBV and CMV revealed positive IgM and IgG antibodies. However, the presence of high titers of EBV EBNA IgG and relatively low CMV IgG levels pointed towards an acute CMV infection with cross reactive EBV IgM antibodies. To distinguish a possible acute EBV from CMV infection, qualitative detection by PCR technique of EBV and CMV RNA was performed. The results showed negative EBV and positive CMV RNA confirming acute CMV infection. A pleural punctate was performed of the pleural fluid which also revealed a positive CMV PCR. Antibiotic treatment was then discontinued.

On day 6 the patient remained febrile and leukopenia and mild thrombocytopenia persisted (Table 2).

Serum ferritin level was determined which turned out to be >10.000 ug/L. Due to the combination of ongoing spiking fevers, cytopenia, highly elevated ferritin level and hepatosplenomegaly, the diagnosis of HLH was considered, which can develop secondary

Table 1: HLH-2004 diagnostic criteria [5].

The diagnosis of HLH can be established if criterion 1 or 2 is fulfilled.
1. A molecular diagnosis consistent with HLH
2. Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood)
Hemoglobin <90 g/L (hemoglobin <100 g/L in infants <4 wk)
Thrombocytes <100 × 10^9/L
Neutrophils <1.0 × 10^9/L
Hypertriglyceridemia and/or hypofibrinogenemia
Fasting triglycerides ≥ 3.0 mmol/L (i.e., ≥ 265 mg/dL)
Fibrinogen ≤ 1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy.
Low or no NK cell activity (according to local laboratory reference)
Ferritin ≥ 500 µg/L
sCD25 (i.e., soluble IL-2 receptor) ≥ 2400 U/mL

Table 2: Relevant laboratory results during admission.

Day	0	1	6	8	10	12	Reference value
CRP (mg/L)	272	288	195	72	33	14	<10
ESR (mm/h)			66	59	74	91	<20
Hemoglobin (g/dL)	12.1	11.8	11.8	9.3	9.8	10.6	11.3-14.8
Hematocrit (L/L)	0.36	0.34	0.35	0.28	0.3	0.33	0.32-0.44
Erythrocytes (× 10^{12}/L)			3.6	2.9	3.0	3.4	3.7-5.0
MCV (fL)	96	96	97	97	99	97	82-98
Thrombocytes (× 10^9/L)	132	138	149	148	219	325	150-350
Leukocytes (× 10^9/L)	2	1.5	1.6	1.5	1.9	2.8	3.0-10.0
Basophils (× 10^9/L)	0.0	0.0			0.0		<0.1
Eosinophils (× 10^9/L)	0.1	0.0			0.0		<0.3
Neutrophils (× 10^9/L)	1.3	0.9	0.6		1.3	1.1	1.3-5.7
Lymphocytes (× 10^9/L)	0.6	0.6			0.5		0.8-3.7
Monocytes (× 10^9/L)	0.0	0.0			0.0		0.2-0.9
Reticulocytes (× 10^9/L)			18	18	37	81	10-70
Haptoglobin (g/L)			2.73	2.34	2.44	2.49	0.30-2.00
Ferritin (ug/L)			>10000	5419	2713	1468	20-150
APTT (sec)			37	34	31		22-34
PT (sec)			11.9	12.1	11.7		9.5-12.5
Fibrinogen (g/L)				1.4		2.3	1.8-3.5
Creatinine (umol/L)	60	58	52	48	50	47	44-80
Bilirubin (umol/L)	8	8	13	10	10	10	<17
Alkaline phosphatase (U/L)	285	304	326	248	218	205	<98
g-GT (U/L)	217	267	486	403	341	278	<38
ALAT (U/L)	102	100	130	110	152	144	<34
ASAT (U/L)	109	121	374			117	<31
LDH (U/L)	314	348	629	433	348	294	<247
Albumin (g/L)			24	23	26	31	35-45
Triglycerides (mmol/L)				3.2		3.7	<2.2

to CMV infection. Therefore, CMV treatment with ganciclovir was started intravenously on day 9, which was switched to oral valganciclovir on day 11. Antiviral therapy was continued for a total duration of 14 days. A bone marrow biopsy was performed on day 10 to confirm the diagnosis of HLH and to evaluate other potential underlying (hematological) disease. Furthermore, despite an already negative PCR on peripheral blood, leishmaniasis could hereby definitely be excluded as possible (additional) cause since this can cause a similar disease course yet requires significantly different treatment [6].

Bone marrow aspirate revealed many macrophages showing phagocytosis of multiple hematopoietic cells, which confirmed the diagnosis HLH (Figure 2a, 2b). Furthermore, some lymphocytes appeared 'hairy', suggesting a hairy cell leukemia (Figure 2c, 2d). No Leishmania parasites were seen.

Flowcytometric analysis of the bone marrow aspirate showed a small, normal polyclonal B-lymphocyte population (1% of the leukocytes) and an abnormal sIg Lambda light chain restricted B-cell population with immunophenotypic marker expression characteristic for hairy cell leukemia (CD19+/ strong CD20+/ CD5-/ CD10+/ CD11c+/ CD23-/ CD25+/ CD43- / CD79b+/ CD103+/ LAIR1 (CD305)+/ CD200+/ light scattering pattern matching larger and complex cells) (Figure 3). The CD10 expression is atypical but is reported in 10% to 15% of HCL patients [7].

Follow-up and outcomes

From day 11 on, two days after starting antiviral treatment, the patient remained free of fever and recovered steadily, and so she was discharged on day 14. The weeks after admission her complete blood count fully recovered except for ongoing monocytopenia (Table 2). Additional lymphocyte subset count revealed decreased B-cells (0.03 × 10^9/L), whereas T-cells were normal (CD4+ 0.56 × 10^9/L; CD8+ 0.88 × 10^9/L). Rise of the CMV IgG titer one month after initial testing from 52.1 U/ml to 94.2 U/ml confirmed a primo-CMV infection. Since the HCL probably indirectly caused the severe course of the CMV infection, which indicated some sort of immunodeficiency, treatment for the HCL was considered.

The patient was monitored in the outpatient-clinic, where therapy versus wait-and-see policies were discussed. After shared decision making it was eventually decided to withhold therapy and monitor closely with an outpatient-clinic visit and laboratory tests every three months.

Table 3: Microbiology and immunology results during admission.

MICROBIOLOGY
Pharyngeal swap
Negative PCR-tests: SARS-CoV-2, Influenza A, Influenza B, RSV, Parainfluenzavirus-1/2/3, *Rhinovirus*, *Human metapneumovirus*, *Coxiella burnetii*, *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydia psittaci*
Blood
Cultures: no growth
Hepatitis A: IgM <0.100 (neg); Total <0.100 (pos*)
Hepatitis B: HBsAg (iU/mL) <0.030 (neg); anti-HBs (mIU/mL) 766 (pos); anti-HBcore 1.22 (neg)
Hepatitis E: HBeAg (U/mL) <0.0100 (neg); anti-HBe 2.13 (neg); IgM 4.51**; IgG 2.31**; PCR neg
HIV: RNA (copies/mL): <100 (neg)
EBV: VCA IgM >160 U/mL (pos); VCA IgG 187 U/mL (pos); EBNA IgG 410 U/mL (pos); PCR: neg
CMV: IgM >140 U/mL (pos); IgG 52.1 U/mL (pos); PCR (iU/mL) 352305 (pos)
Leishmania: PCR neg; agglutinative weakly pos***
Pleural fluid
Gram preparation: no growth****
EBV PCR: neg
CMV PCR: pos
M. tuberculosis complex PCR: neg
Urine
Pneumococcal Ag and Legionella Ag: neg
Cervical swap
Cultures: no growth
Negative PCR tests: *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, *Trichomonas vaginalis*
IMMUNOLOGY (blood)
ANA (ratio): 0.4 (neg)
Anti-dsDNA (iU/mL): 4 (neg)
sIL-2 receptor (pg/mL): >10000 (elevated)
sIL-2 receptor titration (pg/mL): >50000 (elevated)

*Either vaccination or previous infection.
**possibly recent infection with hepatitis E however due to a negative HEV PCR a false-positive HEV IgM is more likely with a previous HEV infection (thus no current one).
***weakly positive reaction in rk39 test, which indicates possible antibodies for Leishmania but also false-positive reaction is possible. Bone marrow diagnostics would be required (and were performed resulting negative).
****no observed micro-organisms and/or acid-fast stains.

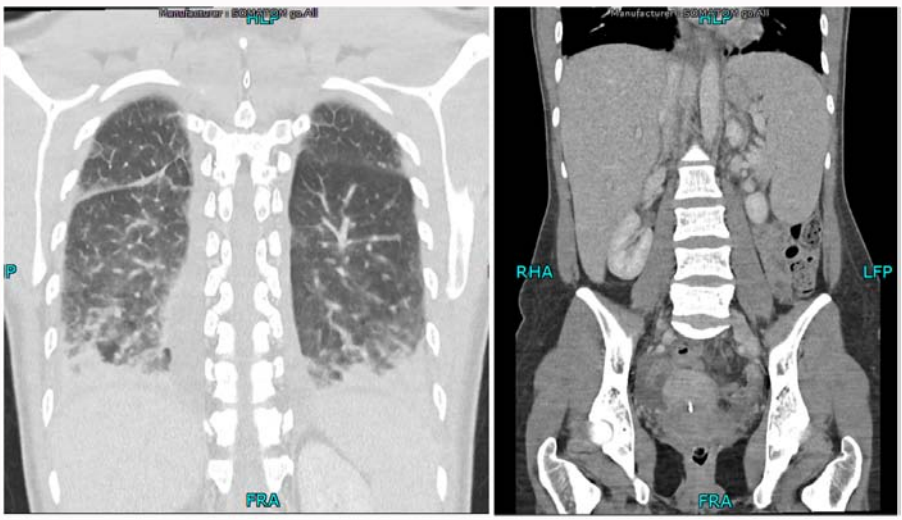

Figure 1: CT imaging of thorax and abdomen. Left: bilateral pleural effusion. Right: Hepatosplenomegaly.

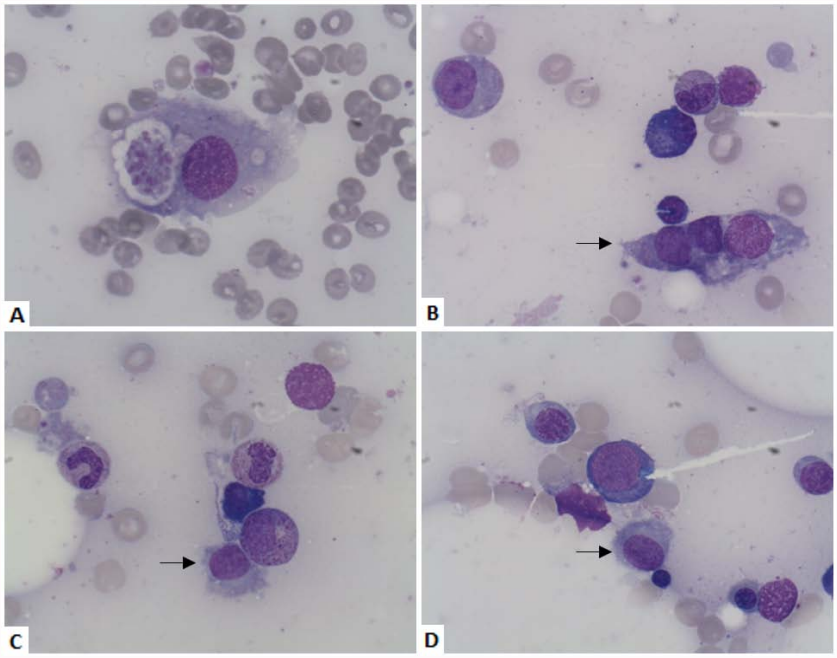

Figure 2: a) Bone marrow macrophage showing phagocytosis of thrombocytes. B) Bone marrow macrophage showing phagocytosis of two other cells (arrow). c, d) Bone marrow smear showing Hairy cells (arrows).

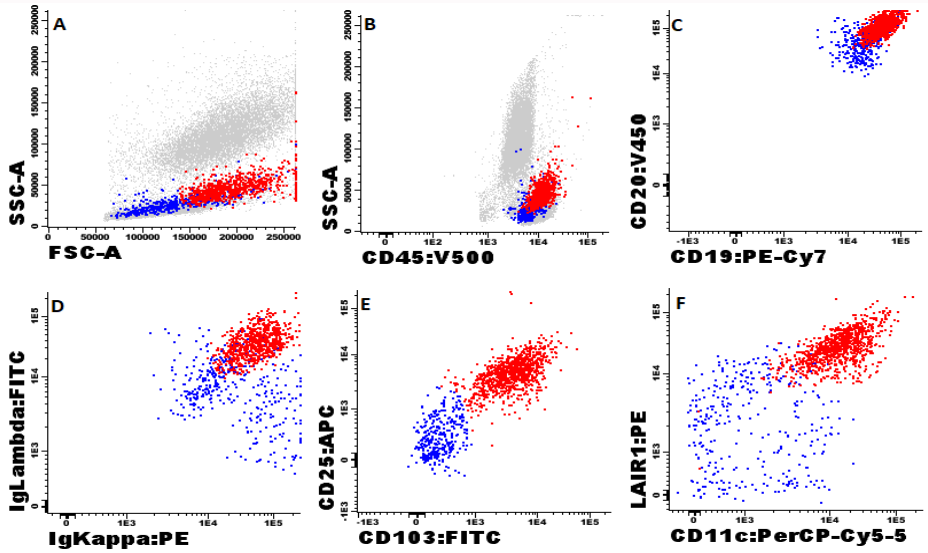

Figure 3: The HCL cell population is indicated with red dots, and residual normal B-lymphocytes (blue dots) and remaining leukocytes (grey dots) are also shown. Dot plot A shows the increased forward- and sideward light scatter characteristics of the HCL cells (larger and more complex cells) compared to normal B-lymphocytes. Plot C shows that both cell populations express mature B-lymphocyte markers CD19 and CD20. The clonal expansion of the HCL population is illustrated by the restricted lambda surface light chain expression versus polyclonal kappa/lambda expression in normal B-lymphocytes (plot D). Plot E and F show expression of CD103, CD25, CD11c and LAIR1, characteristic for HCL cells.

Discussion

Our patient was diagnosed with acute CMV infection resulting in secondary HLH and HCL as underlying, indirect cause of the severe course of the CMV infection. Diagnosis of HLH in our patient was complicated by the large overlap in symptoms of CMV and HLH such as splenomegaly, fever and cytopenia. Treatment with ganciclovir was initiated because of a high clinical suspicion of HLH based on the international HLH-criteria. However, as complete blood counts were already slightly recovering before initiation of the treatment, one could argue if the eventual recovery was either due to the treatment or the natural course of the CMV infection.

To the best of our knowledge, this is the first case report describing a CMV-induced HLH as first presentation of HCL. Both HLH and HCL are rare, yet individually both are associated with CMV [8-11]. CMV-induced HLH has been described in very few case reports [8-10], which all report an underlying immunodeficient status in their patient, such as HIV [8] or (treatment of) rheumatoid disease [9]. Disseminated CMV infection is associated with an immunosuppressed condition [3] and also specifically with HCL as is presented in a case report on CMV-pneumonitis with underlying

HCL from Awadallah et al. [11]. These findings emphasize the importance of considering immune-incompetence in case of CMV-induced HLH.

Treatment of HLH and, in case of secondary HLH, its underlying cause are mainly based on clinical status of the patient. In case of suspected HLH, identification of the HLH-trigger is essential.

However, if the patient is unstable, steroids (and in some cases intravenous immune globulin) must be initiated before evaluation of this trigger. Further treatment always depends on the underlying cause. For infections such as EBV or leishmaniasis, treatment might be indicated [5]. For CMV infection, treatment is usually only indicated in immunocompromised patients [12]. There is however no consensus on treatment indications in the immunocompetent population. Several case reports describe successful treatment of CMV in immunocompetent patients, yet the majority of these patients would most likely have recovered without intervention [13,14]. In our patient, treatment was initiated due to the secondary HLH, since HLH on itself is an indication for treatment of the underlying trigger.

Conclusion

Conclusively, some lessons can be learned from this case. (1) Clinicians must be aware of immune-incompetence in case of severe course of opportunistic infections, especially in formerly healthy patients. (2) Reconsidering an initial diagnosis in case of inconsistency between clinical symptoms and this initial diagnosis is extremely important. (3) Investigation of an underlying hematological condition is indicated in case of suspected immunodeficiency.

Authors' Contribution

MJ collected clinical data and wrote the first concept. JD added clinical data and interpretation for the infectiology data and RG did so for the hematologic data. JN and MH performed and interpreted laboratory diagnostic tests. All authors gave critical input and had substantial contribution to this manuscript. The work was then critically revised by all authors and finally approved. All authors are accountable for all aspects of this work.

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