Coronavirus disease 2019 three months after hematopoietic stem cell transplant: a pediatric case report.

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Abstract

Pediatric cases represent a small part of COVID-19 cases reported worldwide and children seem to be mostly asymptomatic. The specific risks for patients in pediatric oncology wards are not well known yet. We describe here a pediatric hematopoietic stem cell transplant recipient infected by SARS-CoV-2. Despite being at high potential risk of a severe form of COVID-19 the patient we report only presented a rhinitis. She developed anti-SARS-CoV-2 IgM at D14 and IgG at D56 only and had a positive RT-PCR after 42 days. So far, it seems that in this fragile population COVID-19 is largely pauci-symptomatic.

Introduction

Pediatric cases represent a small part (from 1% to 5%) of COVID-19 cases reported worldwide[1]. This is mainly linked to the fact that infected children present asymptomatic or pauci-symptomatic forms and therefore aren't tested/counted, and/or are less infected given perhaps the lower expression level of ACE2 in their nasal mucosa[2]. Moreover severe forms and deaths are rare in pediatrics[1].

As of now the global register of pediatric oncology patients of St Jude's Hospital in partnership with the international society of paediatric oncology (SIOP) lists 137 cases of COVID-19 in 22 different countries[3]. We know that patients with malignancies under treatment or not are a fragile immunosuppressed population more susceptible to viral infections and more likely to present severe forms. Very little data is available on pediatric oncology patients with COVID-19 and the specific risks for patients in pediatric oncology wards are not well known yet. So far no concerning reports have emerged from countries that have been facing the COVID-19 epidemic such as China, Spain, Italy and US [4–7].Only France reported five severe forms on 33 infected patients nationaly[8].

In this report, we describe the complete clinical course and follow-up data of a pediatric patient infected with SARS-CoV-2 three months after having underwent Hematopoietic Stem Cell Transplant (HSCT) for acute myeloid leukemia.

Case report

The patient was a 17-year-old girl who underwent HSCT in Strasbourg University Hospitals, France on January 7, 2020 for an acute myeloid leukemia subtype M5 according to the French-British-American (FAB) classification diagnosed on October 1, 2019. She was treated initially in the MyeChild protocol (high-risk group) and developed following a severe sepsis in context of aplasia a mild dilated cardiomyopathy with left ventricle ejection fraction around 50% treated by Angiotensin-converting-enzymes (ACE) inhibitors. She had HSCT after consolidation course (first complete remission) with an intrafamilial donor. The conditioning regimen was Fludarabine, Busulfan; Ciclosporine was introduced for the Graft-versus-Host disease (GVHD)

prevention. One notable event during HSCT was a cutaneous and digestive GVHD grade III treated by corticosteroids. Bone marrow aspirations realized at D30, D60 and D90 showed cytological remission as well as a complete donor chimerism.

On March 24, 2020 (Day 0), the patient was tested for SARS-CoV-2 due to multiple suspect cases in the family: before lockdown measures one of her brother's classmates was tested positive, then the brother and both parents showed fever, anosmia and chest pain, and finally the patient's uncle developed a severe form of the disease. The patient presented only a rhinitis without fever, nor respiratory signs. Real-time PCR SARS-CoV-2 was positive on nasopharyngeal swab specimens (Institut Pasteur, Paris, France; WHO technical guidance). The assay targets two regions of the viral RNA-dependent RNA polymerase (RdRp) gene, and the threshold limit of detection was 10 copies per reaction. No other viral reactivation or infection (CMV, EBV, adenovirus) occurred.

At that time the patient was still treated by prednisolone (0,4mg/kg/d) for her digestive GVHD, ciclosporine (4mg/kg/d), ACE inhibitors (0,12mg/kg/d), preventive anti-infectious treatment by sulfamethoxazole-trimethoprime, posaconazole, phenoxymethylpenicilline and valaciclovir. Cell blood count (CBC) showed an average hematological reconstitution with 3.5 $x10^9$/l white blood cell including 2.2 $x10^9$/l neutrophils, and a preexisting lymphopenia at 0.43 $x10^9$/l, hemoglobin 96 g/l and 53 $x10^9$/l platelets **(Table 1).** All laboratory analyses between March 24 and May 19, 2020, are shown in Table 1. The patient had a perfusion of intravenous immunoglobulin (IVIg, PRIVIGEN®) on March 10 and April 9 (D16), 2020 for the immune deficiency secondary to the HSCT. Immunophenotyping **(Table 1)** showed that she was cytopenic on every lineage (B, T and NK). Cytokines (IL-6, IL-8, IL-10) were within normal range. Chest computed tomography (CT) on March 31, revealed scattered ground glass opacities in the right lower lobe close to the pleura compatible with COVID-19, and one month later a fibrosis aspect as observed **(Figure1)** , reported as a usual evolution of COVID-19[9].

The SARS-CoV-2 real-time PCR on her nasopharyngeal swab was still positive 21 days and 42 days after the initial positive test, while negative on May 19 (D56). Serology tests were performed on serum samples collected at day 7, day 14 and day 56 after the first positive RT-PCR, with 2 different techniques : immunochromatographic lateral flow assay (Biosynex COVID-19 BSS® (Biosynex, Switzerland, Fribourg)), and ELISA to detect IgA and IgG (Euroimmun IgA, IgG, Lübeck, Germany). She developed neither IgA, IgM nor IgG on day 7. IgA remained negative, at day 14 and day 56. IgM were detected at day 14 only and remain weakly positive at day 56 and IgG were positive at day 56 only. The patient was hospitalized on April 7, 2020 for 4 days for an episode of dehydration with renal failure due to an increase of digestive GVHD signs (vomiting and diarrhea). She responded favorably with IV fluids and an increase of prednisolone. Beside this hospitalization unlinked to COVID-19 and the initial rhinitis, she didn't develop any signs of the disease and is so far doing well.

Discussion

40 patients followed in our onco-hematology department (Strasbourg University Hospital) were tested by SARS-CoV-2 RT-PCR since March 1, 2020, with six being positive. All of them were asymptomatic or presented a mild disease and none of them needed a specific treatment and/or being hospitalized. The patient we report about is the most immunosuppressed of our infected patients being an HSCT recipient and the only one presenting pulmonary lesions on chest CT scan. Despite being at high potential risk of a severe form of COVID-19 due to the post-allograft immunosuppression, mild dilated cardiomyopathy, GVHD, corticosteroids therapy, severe lymphopenia and despite the pulmonary images found on chest CT scan the patient we report only presented a rhinitis.

There are now several studies describing the kinetics of anti-SARS-CoV-2 IgM and IgG detection, most reporting that IgM are detectable as soon as 5-14 days after first clinical symptoms[10,11]. However, symptom severity may also affect the rate of seropositivity. A delayed or absent humoral response against SARS-CoV-2 has been reported in some patients [12] and may result in negative serology results[13]. Surprisingly, despite her immunosuppressed condition and her mild symptoms she developed an immune response with IgM produced

at D14 which is consistent with what can be found in the literature for immunocompetent patients [14]. IgG only appeared at day 56. Furthermore, the virus was said to remain detectable for up to three weeks [15], but our patient still had a weak positive RT-PCR after 42 days.

Very few data is available on children with cancer but it seems that in this fragile population COVID-19 is largely pauci-symptomatic. In any event, clinical management in this population is a challenge for the clinician because oncologic treatment is essential and cannot be postponed. It creates a number of difficulties regarding the follow-up organization of those infected patients needing weekly consultations.

References

1. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. *Acta Paediatr* . Published online April 14, 2020.

2. Bunyavanich S, Do A, Vicencio A. Nasal Gene Expression of Angiotensin-Converting Enzyme 2 in Children and Adults. *JAMA* . Published online May 20, 2020.

3. https://global.stjude.org/en-us/global-covid-19-observatory-and-resource-center-for-childhood-cancer/registry.html.

4. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. *N Engl J Med* . Published online March 18, 2020.

5. Rojas T de, Perez-Martinez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. *Pediatric Blood & Cancer* . n/a(n/a):e28397.

6. Balduzzi A, Brivio E, Rovelli A, et al. Lessons after the early management of the COVID-19 outbreak in a pediatric transplant and hemato-oncology center embedded within a COVID-19 dedicated hospital in Lombardia, Italy. Estote parati. *Bone Marrow Transplant* . Published online April 20, 2020:1-6.

7. Boulad F, Kamboj M, Bouvier N, Mauguen A, Kung AL. COVID-19 in Children With Cancer in New York City. *JAMA Oncol* . Published online May 13, 2020.

8. Andre N, Rouger-Gaudichon J, Brethon B, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: High risk of severe forms? *Pediatric Blood & Cancer* . n/a(n/a):e28392.

9. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study.*Lancet Infect Dis* . Published online February 24, 2020.

10. Guo L, Ren L, Yang S, et al. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). *Clin Infect Dis* . Published online March 21, 2020.

11. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *Clin Infect Dis* . Published online March 28, 2020.

12. Zhao J, Liao X, Wang H, et al. Early virus clearance and delayed antibody response in a case of COVID-19 with a history of co-infection with HIV-1 and HCV. *Clin Infect Dis* . Published online April 9, 2020.

13. Yongchen Z, Shen H, Wang X, et al. Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients. *Emerg Microbes Infect* . 2020;9(1):833-836.

14. Vabret N, Britton GJ, Gruber C, et al. Immunology of COVID-19: current state of the science. *Immunity* . Published online May 2020:S1074761320301837.

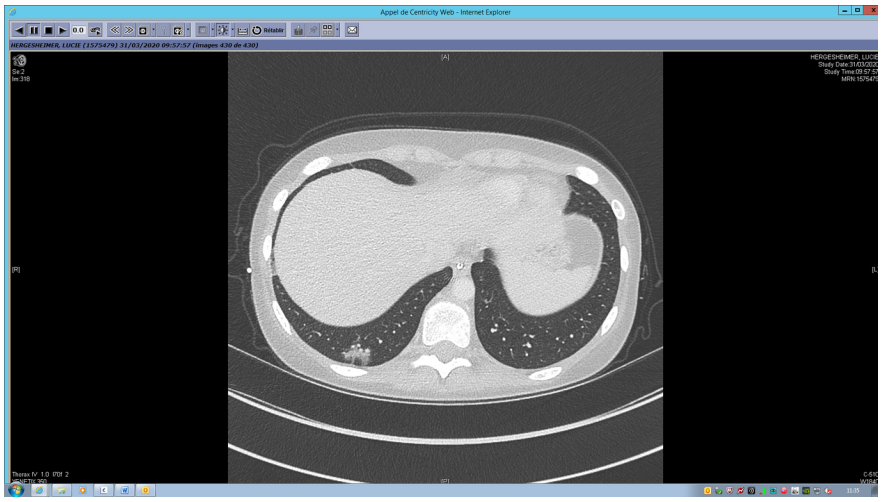
15. To KK-W, Tsang OT-Y, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study.*The Lancet Infectious Diseases* . 2020;20(5):565-574.

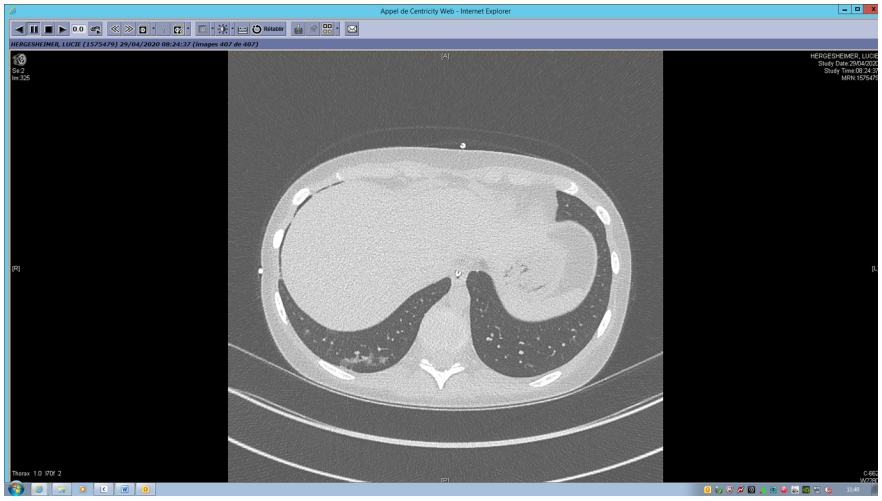
	03/24/2020 (D0)	03/31/2020 (D7)	04/07/2020 (D14)	04/14/2020 (D21)	04/21/2020 (D28)	05/05/2020 (D42)	05/19/2020 (D56)
Cell Blood Count							
Leucocytes (3.9-10.5, 10^9/l)	**3.02**	**3.50**	5.32	7.09	4.07	4.69	4.95
PNN (1.8-7.9, 10^9/l)	2.12	2.20	2.45	3.59	2.56	2.68	3.19
Lymphocytes (1.0-4.0, 10^9/l)	**0.36**	**0.43**	**0.9**	**0.86**	**0.53**	**0.67**	**0.51**
Hb (12.0-16.0, g/dl)	**9.3**	**9.6**	**9.9**	**11.8**	**10.2**	**10.1**	**9.9**
Platelets (150-400, 109/l)	**36**	**53**	**70**	**81**	**80**	**122**	**124**
Immunoglobulins							
IgG (7.2-14.7, g/l)	9.53	**8.02**	**6.73**		7.83	**6.71**	**8.95**
IgA (1.1-3.6, g/l)	**<0.26**	**<0.26**	**<0.26**		**<0.26**	**<0.26**	**<0.28**
IgM (0.48-3.1, g/l)	**0.21**	**0.21**	**0.25**		**0.37**	**0.29**	**0.26**
T cells count							
CD2+ Cells (1100-1700, 10^6/l)	**295** (79.8%)	**328 (87.1%)**	**665** (89.3%)		**506** (87.6%)	**569** (87.8%)	**412 (72.4%)**
CD3+ Cells (1100-1700, 10^6/l)	**226** (62.5%)	**264 (69.2%)**	**548** (68.2%)		**396** (66.9%)	**424** (65.7%)	**362 (62.7%)**
CD3+/CD4+ Cells (700-1100, 10^6/l)	**136** (36.8%)	**148 (39.2%)**	**309** (41.4%)		**232** (39.6%)	**237** (36.5%)	**209 (36.7%)**
CD3+/CD8+ Cells (500-900, 10^6/l)	**85** (22.9%)	**96 (25.6%)**	**175** (23.5%)		**142** (24.2%)	**163** (25.3%)	**125 (22%)**
CD4/CD8 ratio	1.6	1.5	1.8		1.6	1.4	1.7

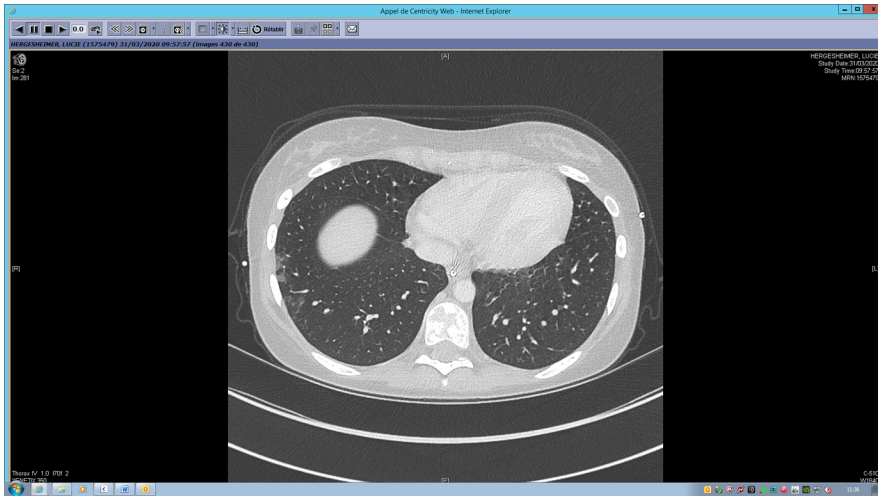
	03/24/2020 (D0)	03/31/2020 (D7)	04/07/2020 (D14)	04/14/2020 (D21)	04/21/2020 (D28)	05/05/2020 (D42)	05/19/2020 (D56)
B cells count							
CD19+ Cells (200-400, 10^6/l)	**1** (0.3%)	**3** (0.9%)	**2** (0.3%)		**4** (0.7%)	**3** (0.5%)	**4** (0.6%)
CD20+ Cells (200-400, 10^6/l)	**1** (0.3%)	**1** (0.2%)	**2** (0.3%)		**3** (0.5%)	**5** (0.7%)	**3** (0.6%)
NK cells count							
CD56+/CD3- Cells (200-400, 10^6/l)	**107** (30%)	99 (25.6%)	238 (30.8%)		**174** (29.8%)	207 (32%)	**178** (30.4%)
RT-PCR results	Positive			Positive		Positive	Négative
Cycle threshold (CT)	24,1			34		37,6	/
Viral load (copies/mL)	462843,2			33.7		20,2	/
SARS-CoV-2 serology results	SARS-CoV-2 serology results	SARS-CoV-2 serology results	SARS-CoV-2 serology results	SARS-CoV-2 serology results	SARS-CoV-2 serology results	SARS-CoV-2 serology results	SARS-CoV-2 serology results
IgM		Negative	**Positive** (w)				**Positive** (w)
IgA		Negative	Negative				Negative
IgG		Negative	Negative				**Positive** (w)

Table 1: biological and clinical data

(w) = weak







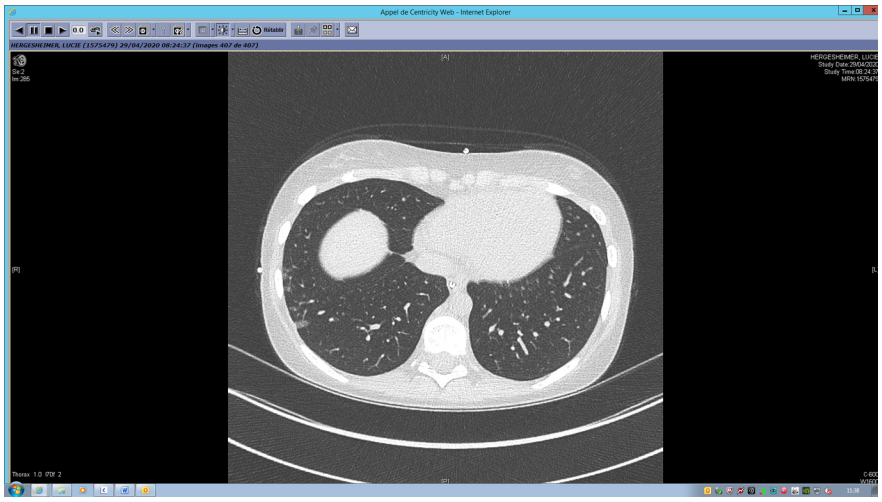


Figure 1: Chest CT on March 31 (D7) shows scattered ground glass opacities in the right lower lobe close to the pleura (panel A, panel C), and the reevaluation of chest CT on April 29 (D36) shows a slight resorption of ground glass opacities (panel B, panel D)

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