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Virology Question and Answer Scheme (VIROQAS)

Acute respiratory distress in a neutropenic febrile patient after hematopoietic cell transplantation

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Case presentation

A 46-year-old male underwent hematopoietic cell transplantation (HCT) (day 0) from a 9/10 matched unrelated bone marrow donor, for an acute myeloid leukemia (AML). The conditioning regimen consisted of a non-myeloablative chemotherapy with clofarabine at 40 mg/m^2 (from day −6 to day −2), treosulfan at 14 g/m^2 (from day −6 to day −4), antithymocyte globulin at 2.5 mg/kg (from day −4 to day −2) and rituximab at 200 mg/m^2 on day −1. The immunosuppressive regimen included cyclosporine and methotrexate (on day +1, +3, +6 post-transplantation, 15 mg/m^2, 10 mg/m^2, 10 mg/m^2, respectively).

Routine pre-transplantation serological analyses revealed a CMV-seronegative donor to a CMV-seropositive recipient mismatch (D−/R+), whereas, both donor and recipient were *Toxoplasma gondii*-seropositive (D+/R+). Trimethoprim–sulfamethoxazole (TMP–SMZ) (160 mg/800 mg bid from day −7 to day −1) was administered as prophylaxis for *Pneumocystis jiroveci* infection, and gancyclovir (5 mg/kg iv d) as prophylaxis for CMV infection. There were no major complications and engraftment was documented on day +23 without any sign or symptom of graft-versus-host disease (GVHD). On day +35 full donor single tandem repeat (STR) and human leukocyte antigen (HLA) chimerism were established.

On day +42, the patient developed fever (>38 °C). Complete blood count revealed leukocyte count of 700 cells/mm^3, platelets 123,000/mm^3, hemoglobin 8.3 g/dL, C-reactive protein (CRP) of 41.2 mg/L, and an elevated lactate dehydrogenase (LDH) of 916 U/L (Table 1). On day +41, a reactivation of CMV (1411 copies/ml) was detected in plasma by quantitative real-time polymerase chain reaction (real-time PCR). On day +42, a preemptive antiviral treatment with foscarnet (90 mg/kg iv bid) was promptly initiated, together with empirical piperacillin/tazobactam (4.5 g iv qid) at first, then changed to meropenem (1 g iv tid). Chest radiograph was negative, as were all blood samples sent for cultures. The patient then developed severe liver dysfunction with hyperbilirubinemia and abnormal values of transaminases (>2 times normal value) and LDH (>10 times normal values) (Table 1). On day +49, CMV DNA increased up to 61,532 copies/ml, despite the addition of gancyclovir (5 mg/kg iv d) to foscarnet. No decrease of the body temperature was registered and serial blood and urine cultures

Abbreviations: HCT, hematopoietic cell transplantation; allo-HCT, allogeneic-hematopoietic cell transplantation; ARDS, acute respiratory distress syndrome; CMV, cytomegalovirus; PCR, polymerase chain reaction; BAL, bronchoalveolar lavage; OIs, opportunistic infections; AML, acute myeloid leukemia; TMP–SMZ, trimethoprim–sulfamethoxazole; GVHD, graft versus host disease; STR, single tandem repeat; HLA, human leukocyte antigen; LDH, lactate dehydrogenase; CRP, C-reactive protein; CT, computerized tomography.

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Table 1
Main laboratory and clinical findings.

	Days post allo-HCT								
	+42	+43	+44	+45	+46	+47	+48	+49	+50
CRP (mg/L)	41.2	35.7	100.8	147.3	186.3	138.7	259.8	261.5	329
WBC (10^9/L)	0.7	0.6	0.5	0.4	0.4	0.3	0.2	0.2	0.2
PLT (10^9/L)	123	113	113	113	80	81	68	30	36
Hb (g/dL)	8.3	7.2	8.6	7.6	9.6	10	9.1	9.1	7.3
LDH (U/L)	916	711	1028	872	1019	1516	1819	2092	2974
Clinical notes	[b]			[b]			[b]		[a]

CRP: c-reactive protein; WBC: white blood cells; PLT: platelets; Hb: hemoglobin; LDH: lactate dehydrogenase; allo-HCT: allogeneic hematopoietic cell transplantation.
[a] Severe respiratory distress, needing mechanical ventilation.
[b] Blood culture negative after 5 days.

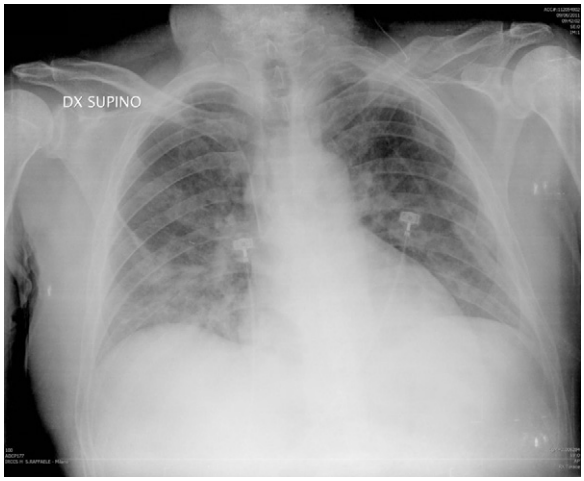

Fig. 1. Chest X-ray. Interstitial pneumonia with patchy consolidation.

were persistently negative for bacteria and fungi. Real-time PCR analysis, performed on plasma for enteroviruses, HSV-7, HSV-8, VZV, and EBV, were all negative.

On day +50, the patient developed a respiratory distress, requiring mechanical ventilation. A chest radiograph showed an interstitial pneumonia with patchy consolidation, interpreted as CMV pneumonia (Fig. 1). Chest CT scan showed lung inflammation at the right apex, with probable evolution toward ARDS, whereas brain CT scan was negative. A bronchoalveolar lavage (BAL) was negative for culturable bacterial or fungal species, *P. jiroveci*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* or any acid-alcohol resistant bacteria.

Acute pulmonary distress related to CMV reactivation was considered in this case.

What is your most likely clinical diagnosis?

What other test would you perform?

Clinical resolution

The patient died on day +51, and it was not possible to perform an autopsy. *Post-mortem* real-time PCR amplification on BAL fluid taken on day +50 was performed, evidencing high load of *T. gondii* DNA (Fig. 2). The same assay was performed on serially stored frozen plasma samples, evidencing increasing loads of *T. gondii* DNA starting from day +37. A similar trend was also observed for CMV. Neither *T. gondii* nor CMV was detectable before allo-HCT or in the early pre-engraftment phase (Fig. 2).

What is the incidence of *Toxoplasma gondii* reactivation after HCT?

What is the importance of *Toxoplasma gondii* screening after HCT?

Definitions for toxoplasmosis after HCT – reconsidering the proposed criteria?

How post-HCT *T. gondii* screening should be performed?

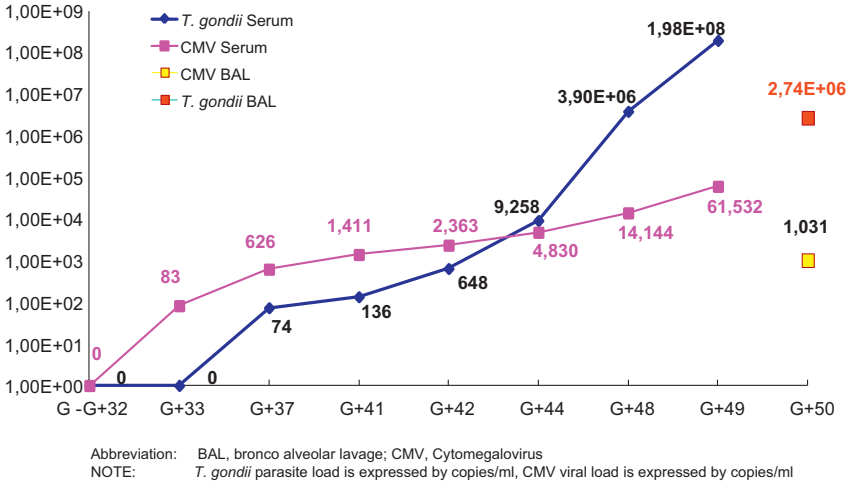

Fig. 2. Quantitative real-time PCR results in peripheral plasma and BAL samples. *Abbreviations*: BAL: bronchoalveolar lavage; CMV: cytomegalovirus. *Note*: *T. gondii* parasite load is expressed by copies/ml and CMV viral load is expressed by copies/ml.

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