Case Report

Life-threatening pneumonia caused by human cytomegalovirus and *Mycoplasma pneumoniae* coinfection in a young, immunocompetent patient

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A young, previously healthy and immunocompetent patient was transferred to our hospital to recover a suspected *Ascaris* worm from his gall bladder. Although the diagnosis of *Ascaris* infection could not be confirmed, the patient suffered from cholecystitis. To our surprise, the respiratory situation of the patient deteriorated within 24 h under antibiotic therapy and he had to be transferred to the intensive care unit for mechanical respiration. Human cytomegalovirus (HCMV) was isolated directly from a bronchoalveolar lavage (BAL) sample, and *Mycoplasma pneumoniae* DNA was detected by PCR in an enrichment culture of the same BAL sample. Serology for HCMV and *M. pneumoniae* clearly supported a primary/post-primary infection for both agents (IgM detection, increase of IgG titres and, in the case of HCMV, a low avidity index of only 22%). Therefore, we assumed that a rare HCMV and *M. pneumoniae* coinfection was the aetiology of the fulminant pneumonia. Under broad antibiotic and antiviral treatment, the situation of the patient improved only very slowly.

Received 4 December 2009

Accepted 7 May 2010

Case report

A 27-year-old male patient was transferred to our hospital from a tertiary hospital with the suspected diagnosis of an *Ascaris* worm in the gall bladder, which had been seen by an ultrasound examination. We were asked to recover the worm via endoscopic retrograde cholangiopancreatography.

The patient had returned from a 40-week round-the-world trip, which took him to Brazil, Chile, Asia, New Zealand and Australia, 5 months previously. One month before admitting himself into the hospital because of fever of up to 40 °C, general malaise, joint ache and epigastric pain, he had returned from a 2 week trip to Mexico. He had never experienced this combination of symptoms before, which started only days previously. Tests for malaria were performed instantly and ruled out *Plasmodium* infection. Except for two sports injuries, his medical record was clear. He did not take any regular medications. He did not take

drugs, he did not smoke and his alcohol consumption was very moderate. The physical examination of the patient was completely normal.

Rather than detecting a worm in the gall bladder, we saw signs of a cholecystitis in the ultrasound examination. The wall of the gall bladder was swollen to 14 mm. The liver and spleen were enlarged; however, no signs of intra- or extrahepatic cholestasis were seen. Initial thoracic radiography did not show pleural effusions or pneumonia-like infiltrates.

Because of the fever and the signs of a cholecystitis, we started antibiotic treatment with ceftriaxone and metronidazole. Under this initial antibiotic regime, the patient's temperature did not decrease. The clinical status of the patient deteriorated rapidly 24 h later. Within hours, he became respiratory insufficient with a pulse oximeter oxygen saturation of 64% (under 8 l oxygen), and developed a tachycardia and cold sweats. While we were not able to identify the focus of the fever, his respiratory situation (breathing frequency of 40 min⁻¹) deteriorated further. Consequently, we had to transfer him to the medical intensive care unit, being subsequently forced to

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Abbreviation: BAL, bronchoalveolar lavage.

intubate him. Initially, the respiratory situation under mechanical ventilation turned out to be difficult: comparably large pressure values were needed to inflate the alveoli. Over the course of the next 4 days, the respirator pressure could be slowly reduced. Under a broad antibiotic and antiviral treatment with linezolid, moxifloxacin, meropenem and ganciclovir for 14 days (ganciclovir for 21 days), the condition of the patient improved only slowly. After staying at the medical intensive care unit for 10 days because of the respiratory assistance, he was transferred back to the normal ward. There the respiratory condition and the general fitness of the patient continued to improve only slowly. In a follow-up examination 3 weeks after discharge, the patient felt better, was still weak, but recovering further.

Liver enzymes were elevated from the start of the hospital stay. Bilirubin was initially 6.8 mg dl^{-1} (elevated), alanine aminotransferase was slightly elevated at 93 U l^{-1} , γ -glutamyltransferase was 75 U l^{-1} and the C-reactive protein level was 20 mg dl^{-1} (highly elevated; reference value $<0.5 \text{ mg dl}^{-1}$). In the course of the hospital stay, the highest value reached for bilirubin was 9.8 mg dl^{-1} (4 days after admission), for alanine aminotransferase was 328 U l^{-1} (9 days after admission) and for γ -glutamyltransferase

was 1001 U l^{-1} (18 days after admission). No eosinophilia was seen. These values were significantly lower when the patient visited our clinic on a scheduled follow up about 2 months later (Table 1).

Since the aetiology of the illness was unclear and the patient had travelled extensively, we performed a wide range of bacteriological and virological tests as well as a number of tests for parasites on a cultural and serological basis. The blood, stool and urine cultures and serologies were all negative. Apart from positive results for *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and human cytomegalovirus (HCMV), all other virological tests turned out to be negative, including serology for human T-lymphotropic virus 1 and 2, human immunodeficiency virus (HIV) and hepatitis A and B viruses, and PCR for adenovirus, Epstein-Barr virus and human herpesvirus 6. Since the IgM titre for cytomegalovirus was highly positive, we consequently added ganciclovir to the treatment. However, HCMV pp65 antigenaemia was negative.

We performed a whole body CT scan, which did not show the typical picture of a pulmonary HCMV infection. Rather it showed the picture of eosinophilic syndrome (Fig. 1). In

Table 1. Time-course of the laboratory chemistry as well as of the HCMV and *M. pneumoniae* serology

P, Pleural effusion; S, serum; R, throat wash. Bold type indicates the highest values obtained.

	Day in clinic													
	-3	-2	1	2	3	4	5	7	9	11	12	15	18	47
Leukocytes ($\times 10^3 \text{ } \mu\text{l}^{-1}$)	15.4	14.4	11.6	15.5	18.9	32.0	27.2	15.3	17.2	17.8	12.4	8.4	8.4	4.9
Bilirubin (mg dl^{-1})	2.7	7.7	6.8	7.1	7.3	9.8	9.7	6.9	5.0	4.1	3.5	2.9	2.7	1.4
Alanine aminotransferase (U l^{-1})	227	80	93	72	63	129	136	127	328	199	134	157		42
γ -Glutamyltransferase (U l^{-1})	106	104	75	50	44	65	68	184	774	546	388	621	1001	484
C-reactive protein (mg dl^{-1})	0.7	1.6	20.5	20.9	22.3	24.8	23.5	12.5	4.4	6.9	7.4	1.7		0
Bacteriology (<i>M. pneumoniae</i>)														
IgM	Neg		Neg							Neg				14
IgG			95							120				90
IgG/A (blot)			Susp							Pos				
IgM (blot)			Pos							Pos				
Enrichment DNA					Pos (BAL)									
					Neg (BAL)									
Virology (HCMV)														
IgG	6				78					26				37
IgM	Pos				Pos					Pos				Pos
Culture					Neg (P) pos (BAL)									
DNA				Neg (S)	Pos (BAL)		Neg (S)			Neg (BAL)		Neg (R)		Neg (S)
pp65				Neg				Neg			Neg

Fig. 1. Initial CT scan of the lung of the patient showing the infiltrates on both sides of the lung.

contrast to the initial radiological picture, substantial pleural effusions were seen in both lungs. The liver was slightly enlarged and the gall bladder wall was swollen. In the bronchoscopy, the typical picture of a tracheobronchitis was seen.

HCMV DNA was directly amplified from a BAL sample, and isolated on human fibroblast cell cultures. However, HCMV DNA was not amplified from a pleural effusion. Subsequently, *M. pneumoniae* DNA was detected by PCR after enrichment culture of the BAL sample. Diagnosis of a recently acquired or acute *M. pneumoniae* infection was supported by the detection of high titres of agglutinating antibodies (MPPA 1:640) as well as by the detection of IgM antibodies and slightly rising IgG titres. Although the serology for *C. pneumoniae* was also positive, we believe that the patient had been exposed to chlamydia in the past

because titres of *C. pneumoniae* remained at a similar level during the course of the hospital stay.

In a control CT scan of the thorax, done 1 week after the first scan, an increase of the density of the lung parenchyma in the apical lung and a positive broncho-pneumogram were seen. These pictures suggested a capillary leak. In a third CT scan another 2 days later, the fibrotic rearrangement had increased. Additional examinations were performed to exclude the possibility of an immune defect or malignancy: the bone marrow biopsy showed in all cell lines substantial haematopoiesis and a significant activation of granulopoiesis. No hints of a systemic disease or infiltrates or a malignant lymphoma were found. Also the immune status of the patient was normal.

Before the patient left the hospital, we performed another abdominal ultrasound. The morphology of the gall bladder was completely normal; no intra- or extrahepatic cholestasis was seen. No HCMV DNA was detectable in leukocytes and plasma of the IgG-positive patient. The transaminases decreased further, the value for the bilirubin was almost back to normal, and the γ -glutamyltransferase was still elevated. The HIV screening test was repeated and was negative.

Discussion

Primary HCMV infection occurs most frequently during breastfeeding (Hamprecht *et al.*, 2001) and childhood as well as at a young adult age (Rafailidis *et al.*, 2008), and the virus persists for life in the host, generally in the latent stage. Reactivation of HCMV from latency is well known in patients with HIV infection and in recipients of stem cells or organ transplants. These immunocompromised patients are at high risk of developing HCMV disease with significant morbidity and mortality rates. In contrast, infections in HIV-negative persons not receiving immunosuppressive drugs are usually asymptomatic. Only about 10% of acquired infections are symptomatic, leading to further diagnostic procedures. HCMV can cause mono-

Fig. 2. Recombinant HCMV immunoblot assay of serum from the patient 4 days after admission. HCMV IgG and IgM reactivity against different CMV recombinant phospho- [p150 and p65 (tegument proteins)] and glycoprotein (gB1 and gB2) specific antigens is shown in the recomBLOT CMV IgG/IgM assay (Mikrogen). The IgG avidity assay (lane 2) shows a distinct reduction of the intensity against three relevant boxed antigens [immediate early antigen (IE 1), p150 and recombinant CM2]. The reduction equals roughly about 50% of the initial staining intensity and represents low to intermediate HCMV IgG avidity. gB reactivity is still very weak.

nucleosis-like symptoms with fever, fatigue, pharyngitis, adenopathy and hepatitis (van der Meer *et al.*, 1996). Recently, HCMV infections in critically ill, non-immunosuppressed patients with sepsis have been described. In a prospective clinical study performed in our clinic, we saw 36 % of anti-HCMV IgG seropositive patients in our intensive care unit developing an active HCMV infection despite absence of immunosuppression. The mortality in these patients seemed to be higher (55 %) and the duration of the intensive care treatment was significantly longer (30 vs 23 days) (Heininger *et al.*, 2000, 2001). In addition, HCMV pneumonia has been described in sickle cell patients (Haddad *et al.*, 1984).

M. pneumoniae is one of the most common causes of atypical pneumonia in collected series from the US and other parts of the world (Bartlett & Mundy, 1995). Many infections are mild to asymptomatic; however, fatal outcomes have been described (Ou *et al.*, 2008). The onset of the illness is gradual and is usually heralded by headache, malaise and low-grade fever (Clyde, 1993). Symptoms and signs of *M. pneumoniae* infection may be divided into those due to respiratory tract or to extrapulmonary disease. Most patients with respiratory infection do not develop pneumonia. However, in our case, the presence of *M. pneumoniae* might have influenced recent HCMV infection leading to early viral reactivation and pneumonia (Hamprrecht *et al.*, 2005).

After HCMV IgM detection was reported, we started treatment with ganciclovir. The IgG titre of HCMV peaked a few days after admittance (78 AU l^{-1}) and a recombinant CMV immunoblot assay was performed. There, the IgG avidity assay showed a distinct reduction of intensity of relevant antigens, representing low to intermediate CMV IgG avidity (Fig. 2). Additionally, the recombinant IgG immunoblot showed only minimal reactivity to the viral gB1 and gB2 antigens, which underlines that the primary HCMV infection had been acquired about 3 months previously (Schoppel *et al.*, 1997). The low avidity index of HCMV of 22 %, as was determined by another laboratory, supported our results. Moreover, the patient was HCMV negative when tested as a blood donor 6 months previously. Thus we hypothesize that the patient suffered from a post-primary HCMV infection, which was complicated by a coinfection with *M. pneumoniae*. Whether or not *M. pneumoniae* acted only as a 'bystander' and/or caused a 'superinfection' remains unclear. Since initial antibiotic treatment did not prevent the serious clinical course of the disease and *M. pneumoniae* infections are rather slow in their onset, we do not believe that *M. pneumoniae* was the single aetiology of the severe pneumonia. Furthermore, we suspect that the cholecystitis and hepatitis were also caused by HCMV, although a liver biopsy was not performed. It is also possible that *M. pneumoniae* caused or contributed to the aetiology of hepatitis (Cunha, 2003; Gröllich *et al.*, 2003; Romero-Gómez *et al.*, 2006).

In conclusion, we initially received the patient to recover a suspected *Ascaris* worm via endoscopic retrograde cholangiopancreatography and ended up with almost losing the patient. We believe that HCMV and *M. pneumoniae* together have caused this fulminant and almost lethal development of the disease because it is unlikely that either of the two agents alone would have caused fulminant pneumonia in an immunocompetent young adult.

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