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Title: Severe liver failure due to Influenza A infection in a Hemodialysis Patient

Short Title: Severe liver failure in hemodialysis

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Abstract

Patients with influenza infection most commonly present with upper and occasionally lower respiratory tract symptoms. However, extrapulmonary presentations such as hepatitis are infrequently observed. We report a case of a hemodialysis patient with influenza A infection who presented with severe hepatitis and liver failure, while his respiratory symptoms were mild. It is important to recognize influenza infection as an unexplained cause of hepatitis and liver failure. In our case, liver failure resolved with supportive treatment.

Key words: infection, liver failure, extrapulmonary manifestation, hemodialysis

Introduction

Hemodialysis patients are prone to infections due to impaired immunity (1). Influenza infection is one of the common respiratory infections in hemodialysis patients and has a higher mortality than the general population (2). Respiratory symptoms, fever and malaise are the common clinical features but extrapulmonary manifestations may be present or occasionally become the predominant clinical presentations.

Case History

Our patient was a 67 year-old man with end-stage renal failure due to diabetic nephropathy. He received peritoneal dialysis for 6 years and was switched to hemodialysis in 2010 after an episode of

fungal peritonitis. He also had history of ischemic heart disease with coronary artery bypass performed in 2010 and an implantable cardioverter defibrillator inserted for inducible ventricular tachycardia in 2013. He presented with mild productive cough, malaise and fever for 2 days. His blood pressure was 110/60 mmHg. His oxygen saturation was 97% in room air. He had a low grade fever of 37.8°C. Complete blood picture revealed mild lymphopenia ($0.79 \times 10^9/L$) and thrombocytopenia ($95 \times 10^9/L$). Liver enzymes were markedly raised with hyperbilirubinemia and clotting profile showed prolonged prothrombin time and activated partial thromboplastin time (Table 1). His chest X-ray was clear. Nasopharyngeal aspirate was positive for influenza A by rapid viral antigen detection, with subsequent RNA sequencing confirming it to be the H3N2 subtype. Blood culture was negative. Serological markers for hepatitis A, B, C and E were negative. There was no evidence of systemic hypotension. He denied the use of herbal or any over-the-counter medications. Serum paracetamol level was undetectable. Computed tomography scan of the abdomen was unremarkable. He was given an empirical course of piperacillin/ tazobactam 2.25gm every 8 hours. Oseltamivir was not prescribed as his onset of symptoms was over 48 hours when the laboratory diagnosis of influenza A was made. He was monitored closely and received hemodialysis in the intensive care unit. His serum ammonia level was raised but he did not have any encephalopathy features clinically, nor did he have any other symptoms from complications of liver failure. His respiratory symptoms gradually improved. Liver function began to improve after day 5. He was discharged from hospital on day 16. His liver function and clotting profile gradually normalized after 4 weeks.

Discussion

This is, to the best of our knowledge, the first and the most severe case of seasonal influenza A H3N2 infection leading to hepatic failure in a hemodialysis patient without concomitant severe respiratory involvement. He made an uneventful recovery after 4 weeks. Influenza A infection is the most likely cause of hepatic failure as the patient had no hypotensive episodes, cardiac event, infective hepatitis or any exposure to hepatotoxic agents. Liver biopsy has not been performed as the patient had severe coagulopathy.

Influenza A is an *Orthomyxoviridae*. It is a negative –sense, single-stranded enveloped ribonucleic acid virus. The most common circulating strain of the winter influenza season of 2014-2015 in the Northern Hemisphere was the H3N2 strain (3) .

Influenza A virus not only attacks the respiratory tract but also leads to systemic involvement, either by direct viral infection or by triggering a systemic inflammatory response (4). These mechanisms were proposed through demonstration of influenza A virus infection in mouse models. Influenza A virus could spread to non-respiratory organs. Viral cultivation was shown in the thymus and heart muscle, and their RNA was detected in the liver and spleen, possibly spread by transient viremia (5).

Sanchez-Lanier et al. have found areas of microvesicular fatty metamorphosis and focal hepatic necrosis alongside influenza A particles in their mouse experiments (6). However, *Polakos et al.* suggested a different mechanism of influenza A induced liver injury by collateral damage. In their

mouse model, influenza A virus was absent in the liver but a significant proportion of influenza-specific CD8⁺ T cell was found. Together with activated Kupffer cells, they form an inflammatory focus, resulting in apoptosis of the T cells and hepatocytes (7). Reduction of anti-oxidant production (e.g. glutathione, Vitamin E) induced by influenza viral infection could also increase the risk of hepatic oxidative stress and hepatic damage (8).

Hepatitis or liver failure caused by influenza A virus have been recognized in patients with underlying cirrhosis (9), children (10), pregnant women (11) and immunocompromised individuals such as renal and liver transplant recipients (12, 13). The degree of hepatic damage is proposed to be determined by the magnitude of CD8⁺T cell immune response and the interaction with pre-existing antibodies to influenza. Inadequate antibodies to counteract the influenza infection may trigger CD8⁺ T cell response. Pre-existing influenza antibodies could trigger cross reactive CD8⁺ T cells memory, producing profound CD8⁺ T cell response and severe liver damage (7). In general, both T and B cell immune response are impaired in dialysis patients (14). Nonetheless, preferential T cell activation towards Th1 than Th2 cells occurs in hemodialysis patients. Through INF α , Th1 cells provide help to CD8⁺ cytotoxic T cells. The individual variability of T cell immune response remains to be elucidated. The bias towards Th1 activity in dialysis patients also explains their poor antibody response after influenza vaccination (15), which in turn make them prone to influenza infection. Previous reports have demonstrated that a timely prescription of oseltamivir may lead to a faster recovery of liver function and reduce morbidity and improve survival (16, 17). In our case, oseltamivir was not

prescribed due to the delay in presentation from symptom onset. Liver failure improved gradually with supportive treatment alone.

Conclusion

Influenza A infection could predominantly present as severe hepatitis and lead to liver failure in hemodialysis patients. Recognition of this extra-pulmonary presentation of influenza A is important as this may come alongside with mild or unrecognizable respiratory symptoms. Liver failure resolved with supportive treatment.

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Table 1. Laboratory parameters of our patient since admission.

	Reference range	Day 1	Day 2	Day 3	Day 5	Day 7	Day 15	Day 29
Albumin (g/L)	39-50	37	40	35	32	31	33	36
Total Bilirubin (umol/L)	4-23	13	55	79	103	87	64	25
ALP (U/L)	42-110	168	261	261	212	143	274	190
ALT (U/L)	8-58	1631	>3000	>3000	2314	913	161	43
AST (U/L)	15-38	2497	>3000	>3000	1760	339	85	51
NH3 (umol/L)	<33	9	-	44	38	-	-	-
APTT (seconds)	25.9-33.7	69.4	65.7	84.2	97.0	67.8	44.1	-
PT (seconds)	11.3-13.5	22.6	78.0	74.3	34.7	19.6	13.5	-

Abbreviations: ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transaminase; NH3, ammonia; APTT, activated partial thromboplastin time; PT, prothrombin time.