Lessons learned from chemotherapeutic and immunosuppressant induced Hepatitis B reactivation - a case series

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SUMMARY

This case series is to create awareness among clinicians on the importance of Hepatitis B screening prior to administration of chemotherapeutic agents and immunosuppressant in preventing Hepatitis B reactivation (HBVr). We also highlight the importance of identifying patients who are at risk of HBVr and when to initiate antiviral prophylaxis based on the current evidence-based guidelines. The case series consists of four patients seen in Hospital Selayang, Malaysia who developed fulminant liver failure secondary to chemotherapeutic agents or immunosuppressant induced HBVr. HBVr is likely to be of increasing clinical significance as potent immunosuppressive regimens are used more widely across all medical specialties. Clinicians should be made aware of the potential risk of patients developing fulminant liver failure following HBVr and its association with high morbidity and mortality. In the era of inexpensive Hepatitis B blood screening tests and safe potent antivirals, there is now a paradigm shift to make the test compulsory to screen all patient prior to initiation of chemotherapeutic agents or immunosuppressive therapy. Antiviral prophylaxis may be offered to more patients who are at risk of HBVr and the duration of both prophylaxis and subsequent monitoring may be extended until 6 to 18 months following completion of treatment.

KEYWORDS:
Hepatitis B reactivation, Chemotherapeutic induced Hepatitis B, Immunosuppressant induced Hepatitis B, Acute liver failure, Fulminant liver failure

INTRODUCTION

Hepatitis B virus (HBV) infection is a worldwide disease associated with significant morbidity and mortality. After acute infection, HBV infection can persist in about 1-2% of immunocompetent hosts.[1] In Malaysia, the incidence of hepatitis B was reported to have increased from 2.26 per 100,000 in 2010 to 12.65 per 100,000 population in 2015.[1] Most hepatitis B patients diagnosed now were born in the pre-vaccination era, with approximately 45% to 50% of them aged between 20 to 40 years.[1] Chemotherapeutic and immunosuppressant induced Hepatitis B reactivation (HBVr) is a life threatening complication leading to discontinuation of the required definitive treatment, fulminant hepatitis with severe acute liver failure and death. We present a case series of four patients who were seen in Hospital Selayang, Malaysia to illustrate the lessons learned.

CASE REPORTS

Case 1

A 35-year-old Malay gentleman who was diagnosed with Nasopharyngeal Carcinoma stage IVB (T3N3aM0) and who underwent 3 cycles of neo-adjuvant chemotherapy, given Cisplatin and 5-florouracil (Table I). Subsequently, was planned for his first fraction of radiotherapy but was noted to be deeply jaundiced with deranged liver enzymes. Hepatitis screening was done and his HBsAg came back as reactive. Of note, he had a strong family history of Hepatitis B, but he had never been screened before. He was admitted for close monitoring and initiation of anti-viral therapy.

Clinically he was jaundiced with no signs of hepatic encephalopathy and no stigmata of chronic liver disease. His vital signs were stable and systemic examination were unremarkable. Blood tests were as shown in Table II. Ultrasound Abdomen showed normal liver size with coarse echotexture and irregular margin. No splenic varices or ascites were present.

He was started on oral Tenofovir 300mg daily and transferred to our Liver centre. On day 13 of his admission, he decompensated further whereby he developed ascites and subsequently Grade I hepatic encephalopathy. At this point he was diagnosed to have acute on chronic liver failure (ACLF) Grade I with AARC score of 7. He was treated aggressively with ACLF management which included corrections of his electrolytes, fluid management, IV human albumin, IV N-Acetyl Cysteine and broad-spectrum antibiotic. Initially he responded well and had reversal of his encephalopathy after 2 days. However, his prolonged hospitalisation had led to septicaemia, and he succumbed subsequently.

Case 2

A 27-year-old Chinese lady with underlying vertically transmitted Chronic Hepatitis B (CHB) diagnosed at birth and diagnosed with Myasthenia Gravis aged 25. She was a treatment naïve Hepatitis B carrier with baseline HBV DNA of 24 IU/ml. She was a non-smoker, teetotaler with no history of drug abuse. She was single and not sexually active.

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Table I: Summary of patient's demographic, treatment, risks of HBVr and mortality outcome

Case	1	2	3	4
Age	35	27	52	61
Gender	Male	Female	Female	Female
Ethnicity	Malay	Chinese	Malay	Chinese
Co-morbidity	Nasopharyngeal carcinoma	Myasthenia gravis	Invasive breast Icarcinoma	Non hodgkin lymphoma
Known Hepatitis B	No	Yes	No	No
Family history of Hepatitis B	Yes	Yes	Yes	Yes
Chemotherapeutic Agents or Immunosuppressant received	Cisplatin 5-florouracil	High dose Corticosteroid	5-fluorouracil Epirubicin Cyclophosphamide	Rituximab Cyclophosphamide Doxorubicin Vincristine Prednisolone
Risk of HBVr	Moderate	High	High	High
Mortality at Day 90 from onset of jaundice	Deceased	Deceased	Alive (Palliative Care)	Deceased

Her myasthenic crisis was treated with plasma exchange and high dose corticosteroid. Initially she was prescribed with intravenous hydrocortisone 100mg 8 hourly and then it was changed to oral prednisolone at 1mg/kg/day. She was discharged well on tapering dose of oral prednisolone, oral Mycophenolate Mofetil 1g twice daily and oral pyridostigmine 60mg 6 hourly.

She presented 6 months later with 3-day history of jaundice, coagulopathy, and markedly elevated transaminases. Blood tests were compatible with acute flare of Hepatitis B (Table II). On day 5 of admission, she clinically deteriorated and developed Grade I hepatic encephalopathy. She was transferred to our liver center for further management and an emergency liver transplant work out was activated. Her AARC score was 10 at Day 0 with Grade II ACLF. Her condition continued to worsen despite optimal care and treatment. Unfortunately, she finally succumbed due to multi-organ failure while awaiting a cadaveric liver transplant.

Case 3

This was a 52- year-old Malay lady with underlying toxic multi-nodular goiter post radioactive iodine therapy. She had defaulted her thyroid hormone replacement therapy having been asymptomatic despite biochemically being hypothyroid with TSH 7.28mU/L and FT4 7.0 pmol/L. She was diagnosed to have Left breast invasive carcinoma Stage IV (T2N0M1) with bilateral lung nodules suggestive of metastasis. Histopathology examination revealed positive estrogen and progesterone receptors with negative C-erb-B2 receptor. She was started on 6 cycles of neo-adjuvant chemotherapy containing 5-fluorouracil, Epirubicin and Cyclophosphamide. During her admission for the 6th cycle of chemotherapy, she was noted to be jaundiced and was scheduled for repeat of her blood tests.

She was called in for admission when her blood tests showed features of acute flare of Hepatitis B. She was not known to have Hepatitis B before but had a very strong family history of Hepatitis B. She was initiated on anti-viral therapy, oral Tenofovir 300mg daily but continued to be further decompensated throughout the first month of therapy with refractory ascites which responded poorly to diuretics and regular peritoneal paracentesis.

Further assessment by our multi-disciplinary team, we decided that she was no longer a candidate for surgical intervention for a left breast mastectomy and axillary clearance nor chemotherapy. She finally opted for palliative care and currently having limited mobility with dependent basic activity of daily livings.

Case 4

A 61-year-old Chinese lady with history of previous Hepatitis B infection, her last HBsAg taken more than 10 years ago during her insurance medical check-up was non-reactive. Her father had Chronic Hepatitis B hence giving a strong family history. She had history of prolonged cough and treated as steroid dependent pneumonitis. Computed tomography (CT) imaging of her lungs showed right middle lobe consolidation; a core biopsy was done, and histopathology examination revealed the diagnosis of Extra Nodal Marginal Zone Lymphoma, a subtype of non-Hodgkin Lymphoma (stage IV).

In view of the site of interest and her performance status, she was subjected to 6 cycles of induction chemotherapy with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisolone (R-CHOP regime). She had excellent metabolic response and attained complete metabolic remission at the end of her treatment. Subsequently, she received further consolidation chemotherapy of Rituximab but unfortunately then she developed HBVr.

A week following her second dose of Rituximab, she presented with symptoms of jaundice, tea colored urine, lethargy, nausea, abdominal distention and reduced oral intake. Clinically she was afebrile, deeply jaundiced with no evidence of hepatomegaly or splenomegaly. Ultrasound abdomen showed normal liver size with smooth margin and relatively hypoechoeic liver parenchyma with prominent periportal echoes consistent with inflammation. Blood investigations revealed HBV DNA of 142,196,020 IU/ml and both reactive HBsAg and HBeAg. She was started on T. Entecavir 0.5mg daily but went into fulminant liver failure and ACLF shortly after and finally succumbed.

DISCUSSION

The definition of HBV reactivation (HBVr) varies between guidelines, but the basic concept is the same. Individuals with

Table II: Summary of blood investigations trend and AARC scores of all 4 cases

Case 1	**Chronology of results**						
Day(s) of jaundice	1	7	19	23	26	35	41
Day(s) after anti-viral treatment		1	13	17	20	29	35
Day(s) of ACLF							
AARC* Score (Grade)			**Day 0 7 (I)**	**Day 4 8 (II)**	**Day 7 10 (II)**		
Total Bilirubin (umol/L)	18.6	166.9	630	446	491	630	707
INR		2.2	4.6	4.0	3.7	4.8	9.0
Lactate (mmol/L)			0.96	0.64	1.69		
Creatinine (umol/L)		49	47	54	60	54	52
Hepatic encephalopathy (Grade)	Nil	Nil	Grade II	Nil	Nil	Grade III	Nil
HBV DNA (IU/ml)							
Log		68,542 4.84					
Case 2							
Day(s) of jaundice	3	4	6	11	14	16	19
Day(s) after anti-viral treatment		1	3	8	11	13	16
Day(s) of ACLF							
AARC Score (Grade)			**Day 0 10 (II)**	**Day 4 10 (II)**	**Day 7 11 (III)**		
Total Bilirubin (umol/L)	193	305	408	483	471	438	-
INR		5.78	4.8	4.1	3.8	5.3	8.4
Lactate (mmol/L)			1.84	1.96	2.7	8.01	4.26
Creatinine (umol/L)	54	43	40	48	41	29	109
Hepatic encephalopathy (Grade)	Nil	Nil	Grade II	Nil	Nil	Grade III	Grade IV
HBV DNA (IU/ml)							
Log (log10)				7,055 3.85			
Case 3							
Day(s) of jaundice	3	5	30	34	38	43	91
Day(s) after anti-viral treatment		1	26	30	34	39	87
Day(s) of ACLF							
AARC Score (Grade)				**Day 0 8 (II)**	**Day 4 8 (II)**	**Day 4 8 (II)**	
Total Bilirubin (umol/L)	347	446.9	421.2	333	370	386	240
INR	1.9	1.7	1.9	1.8	1.9	2.1	2.4
Lactate (mmol/L)				1.82	1.14	1.37	
Creatinine (umol/L)				56	68	139	78
Hepatic encephalopathy (Grade)	Nil	Nil	Nil	Nil	Nil	Nil	Nil
HBV DNA (IU/ml)							
Log (log10)		40,900,000 -		4,299 3.63			
Case 4							
Day(s) of jaundice	7	15	20	24	27	28	33
Day(s) after anti-viral treatment	1	9	14	18	21	22	27
Day(s) of ACLF							
AARC Score (Grade)			**Day 0 11 (III)**	**Day 4 11 (III)**	**Day 7 9 (II)**		
Total Bilirubin (umol/L)	46.9	230.9	367.8	477	475	595	509
INR	1.5		5.0	7.3	9.1	10.3	7.5
Lactate (mmol/L)	2.31		2.22	6.28	1.27		
Creatinine (umol/L)	35	46	64	58	59	151	199
Hepatic encephalopathy (Grade)	Nil	Nil	Grade I	Nil	Nil	Grade III	Grade IV
HBV DNA (IU/ml)							
Log (log10)	142,196,020 10		257,934 5.41				

*AARC: APASL ACLS Research Consortium

Table III: Risk of Hepatitis B reactivation stratified by immunosuppressive regimen

	HBsAg positive	HBsAg negative, anti-HBc positive
Low Risk < 1%	• Traditional immunosuppressive agents (e.g.: azathioprine, methotrexate) • Intra-articular corticosteroids • Any dose of oral corticosteroids daily for <1 week	• Traditional immunosuppressive agents (e.g.: azathioprine, methotrexate) • Intra-articular corticosteroids • Low-dose corticosteroids for ≥4 weeks (e.g.: prednisolone <10 mg or equivalent) • Any dose of oral corticosteroids daily for <1 week
Moderate Risk 1-10%	• Less potent TNF-α inhibitors (e.g. etanercept) • Cytokine or integrin inhibitors (e.g. abatacept, natalizumab) • Tyrosine kinase inhibitors (e.g. imatinib, nilotinib) • Immunophilin inhibitors, including cyclosporine • Proteasome inhibitors (e.g.: bortezomib) • Histone deacetylase inhibitors • Low dose corticosteroids for duration of ≥4 weeks (e.g.: prednisolone <10mg daily or equivalent) • Systemic chemotherapy	• TNF-α inhibitors (e.g., etanercept, adalimumab, infliximab) ☒ • Cytokine or integrin inhibitors (e.g., abatacept, natalizumab) • Tyrosine kinase inhibitors (e.g. imatinib, nilotinib) • Moderate to high dose corticosteroids daily for ≥4 weeks Moderate dose (e.g.: prednisolone 10-20mg daily or equivalent) or high-dose (e.g.: prednisolone >20 mg daily or equivalent) • Anthracycline derivatives (e.g., doxorubicin, epirubicin) • Immunophilin inhibitors, including cyclosporine • Proteasome inhibitors (e.g.: bortezomib) • Histone deacetylase inhibitors • Systematic chemotherapy, including HCC
High Risk > 10%	• B-cell depleting agents (e.g.: rituximab) • Anthracycline derivatives (e.g.: doxorubicin, epirubicin) • Moderate to high dose corticosteroids daily for ≥4 weeks Moderate dose (e.g.: prednisolone 10-20mg daily or equivalent) or high-dose (e.g.: prednisolone >20 mg daily or equivalent) • Potent TNF-α inhibitors, (e.g.: adalimumab, infliximab) • Local treatment for HCC (e.g.: TACE)	• B-cell depleting agents (e.g.: rituximab)

Note: Anti-HBc = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBVr = hepatitis B virus reactivation; HCC = hepatocellular carcinoma; TACE = trans arterial chemoembolization; TNF = tumour necrosis factor
Source referenced from [4].

CHB (HBsAg positive for at least 6 months and measurable HBV DNA in the blood) and previously infected but serologically cleared HBV infection (HBsAg negative, anti-HBV-core antibody (anti-HBc) positive) are both susceptible to HBVr. In patients with CHB, reactivation is defined by a rise in HBV DNA above baseline.[2] In patients with previous HBV, reactivation is defined by either the appearance of HBV DNA in the blood or conversion to the reactive HBsAg state.[2] The latter process is known as reverse seroconversion.

Advancement in the treatment of inflammatory and malignant diseases have led to the upsurge use of chemotherapeutic and immunosuppressant as the treatment of a wide range of medical specialties. These advancements in treatment options have been met with the challenge of increased risk of HBVr. It is important to recognize that HBVr in this clinical setting is potentially preventable. Therefore, screening (Figure 1) and identifying patients at risk of HBVr as well as institution of prophylactic antiviral therapy prior to initiation of immunosuppression is essential.[2] HBsAg and anti-HBc (total or immunoglobulin G) testing should be performed in all patients before initiation of any chemotherapeutic agents or immunosuppressant.

The subsequent step after screening is risk stratification based on virological status and chemotherapeutic or immunosuppressant regimen. The magnitude of risk of HBVr is associated with the HBV serological status of the individuals (Figure 1) and the potency and duration of immunosuppression (Table III). Patients with CHB have a higher risk than patients with previous HBV.[3,4,5] Hematopoietic stem cell transplant recipients (HSCT) and B cell–depleting therapies (e.g., rituximab) confer the highest risk among chemotherapeutic regimens.[5] The American Gastroenterological Association (AGA) suggests that anthracyclines (e.g., doxorubicin) and moderate-dose corticosteroids (≥10 mg of daily prednisone or equivalent for ≥4 weeks) confer higher risk than other immunosuppressant agents.[3,6]

The final step in preventing HBV reactivation is tailoring management based on risk stratification. For patients with CHB, prophylactic antiviral therapy should be administered for at least a week before the initiation of chemotherapeutic agents or immunosuppressive therapy, regardless of baseline serum HBV-DNA level.[7] First line nucleoside analogue (NA) for example Entecavir or Tenofovir was preferred over other

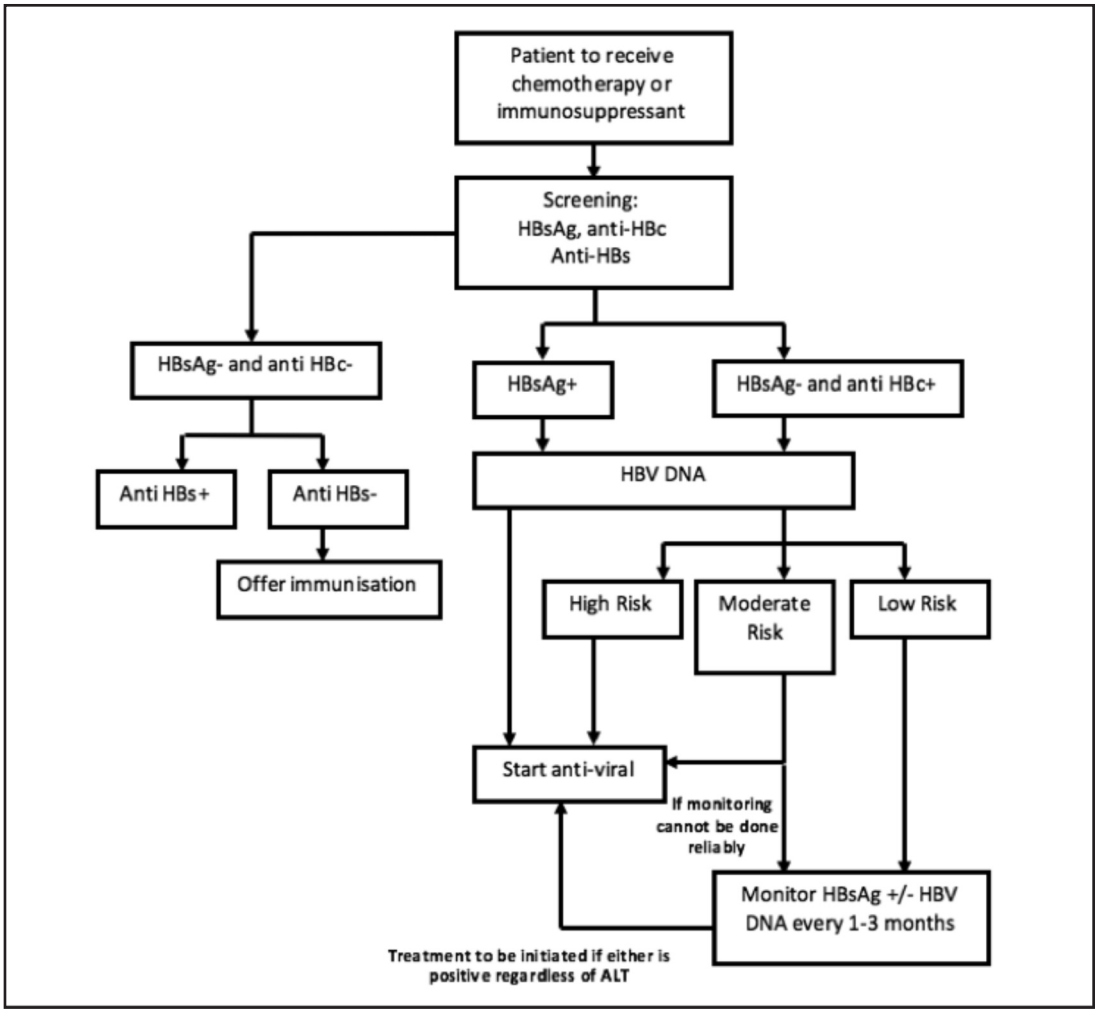

Fig. 1: Screening algorithm for management of patients who are planned to receive chemotherapy or immunosuppressant and are at risk of Hepatitis B reactivation.

NAs because of their higher potency and high resistance barrier, as multiple meta-analyses have shown reduction in reactivation, hepatitis, mortality, and anticancer therapy interruption.[6,7]

Antiviral prophylaxis should be continued well after cessation of immunosuppression, generally 12 to 18 months if high-potency therapies are used, particularly for patients who undergo HSCT or received B cell–depleting therapies[7] and 6 to 12 months for other agents.[3,5] Once prophylaxis treatment is withdrawn, it is recommend for clinicians to continue biochemical monitoring as there were large percentage of reactivation cases occurring after antiviral withdrawal. However, for patients receiving chronic immunosuppression, for example transplantation and biological therapy, much less is known about the optimal duration of prophylaxis that is needed.

CONCLUSION

Hepatitis B reactivation is preventable if patients who are at risk are appropriately identified through screening and triaged to an appropriate treatment strategy. This case series highlights the importance of HBV screening in patients who are planned for chemotherapeutic or immunosuppressive therapy. We suggest that there is more work to be done to improve HBV screening rates and education on preventing Hepatitis B virus reactivation.

CONSENT TO PARTICIPATE

This study was registered under National Medical Research Register (NMRR ID: 20-2546-57421) dated 27th November 2020 and the patients gave written informed consent for the use of the data in this publication.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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