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CASE REPORT

Case Report: Severe non-immune mediated haemolytic anaemia associated with acute hepatitis B and E co-infection in a patient with normal G6PD levels [version 1; peer review: 1 not approved]

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V1 First published: 06 Oct 2015, 4:1002
<https://doi.org/10.12688/f1000research.7086.1>

Latest published: 06 Oct 2015, 4:1002
<https://doi.org/10.12688/f1000research.7086.1>

Abstract

Severe non-immune mediated haemolytic anaemia (HA) rarely occurs in acute viral hepatitis, unless patients have underlying red cell enzyme abnormalities or pre-existing liver disease. We report such a case and provide a summary of other available cases to date.

Overall, young and fit patients suffering from acute viral hepatitis seem to be affected. Several viral subtypes have been associated, although we report the first hepatitis B and E co-infection case. It seems to occur when patients are recovering from hepatitis and the disease course is variable. The degree of anaemia is always severe, and is inevitably associated with increased morbidity and mortality.

Several theories exist with regard to its aetiology, including the disruption of erythrocyte metabolism. Although its optimal treatment strategies remain unclear, some evidence suggests a possible role for steroid therapy.

Keywords

viral hepatitis , anemia , hemolytic , hemolysis , glucose phosphate dehydrogenase deficiency

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1

version 1

06 Oct 2015

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Any reports and responses or comments on the article can be found at the end of the article.

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Competing interests: No competing interests were disclosed.

Grant information: The author(s) declared that no grants were involved in supporting this work.

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How to cite this article: Wang M, Yap F and Joynt G. **Case Report: Severe non-immune mediated haemolytic anaemia associated with acute hepatitis B and E co-infection in a patient with normal G6PD levels [version 1; peer review: 1 not approved]**

F1000Research 2015, 4:1002 <https://doi.org/10.12688/f1000research.7086.1>

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Background

Although mild haemolysis is a well known phenomenon associated with acute viral hepatitis and occurs in approximately 4% of affected patients¹, severe non-immune mediated haemolytic anaemia (HA) is rare and is usually associated with underlying red cell enzyme abnormalities^{2,3} or pre-existing liver diseases^{4,5}. We report a case of severe non-immune mediated haemolytic anaemia associated with acute viral hepatitis in the absence of any underlying enzyme or hepatic abnormalities. Only 7 other such cases have been found in the current literature, and their summaries will be provided and discussed.

Case report

A 48 year old Chinese male manual worker was admitted on 4th February with acute right-upper-quadrant abdominal pain for 5 days, preceded by flu like illness. He had no past history of liver

disease, anaemia or bleeding disorders. He reported recent consumption of raw seafood and unprotected sexual activities with sex workers, but denied any history of alcohol abuse or recreational drug use. He was not on any regular medications. Clinical examination revealed fever, deep jaundice and right-upper-quadrant tenderness with no signs of chronic liver disease or hepatic encephalopathy. His blood tests showed a severe hepatitis picture (Table 1) including a total bilirubin of 291 $\mu\text{mol/L}$ and alanine transaminase (ALT) of 8320 IU/L. He tested positive for hepatitis B surface antigen (HBsAg), IgM antibody to hepatitis B core antigen (anti-HBc IgM) and IgM antibody to hepatitis E virus (anti-HEV IgM). His real-time polymerase chain reaction (PCR) quantification for hepatitis B virus was 4.34 log IU/ml, thus confirming the diagnosis of acute viral hepatitis B and E co-infection. His haemoglobin (Hb) level was 13.3 g/dl and dropped to 12 g/dl initially, which suggested possible mild haemolysis. His international normalised ratio (INR) was

Table 1. Patient's blood results throughout the clinical course.

	04-Feb (day 1)	05-Feb (day 2)	06-Feb (day 3)	07-Feb (day 4)	08-Feb (day 5)	09-Feb (day 6)	10-Feb (day 7)	11-Feb (day 8)	12-Feb (day 9)
HB (g/dl)	13.3		↓10.8	↓8.9	↓4.9	↓10.2	↓8.8	↓8.4	↓10.4
MCV (fL)	96.6		96.1	↑97	↑101	95.7	83.5	85.9	89.3
WCC ($\times 10^9/\text{L}$)	10.4		↑23.3	↑41.8	↑57	↑41.1	↑24.6	↑23	10.1
Reticulocytes ($\times 10^9/\text{L}$)					↑201.1				
LDH (IU/L)			↑990	↑2493					
Na (mmol/L)	138		135	137	135				139
K (mmol/L)	↑5.1		↑5.2	↑5.1	HAEMOLYSED				4.1
U (mmol/L)	5.6		7	↑16.5	↑38.7				CVWH
Cr ($\mu\text{mol/L}$)	75		31	61	↑553				CVWH
Bilirubin ($\mu\text{mol/L}$)	↑291	↑378	↑730	↑1132		↑960			↑468
ALT (IU/L)	↑8320	↑5631	↑3330	↑2182		↑879			↑573
ALP (IU/L)	↑111	↑107	↑114	↑125		↑107			↑164
Total protein (g/L)	70								↓49
Albumin (g/L)	44								↓27
INR	↑1.5	1.2				1.37			↑1.83
aPTT (s)	33.8	30.7				34.2			↑45
pH	7.48								↓6.96
Base excess (mmol/L)	2								↓-21

1.5 on presentation which was also expected in severe acute hepatitis. He was empirically treated with entacevir, 0.5 mg once a day from day 1 to day 9 following admission, and vitamin K replacement, 10 mg twice a day for two days. In addition, his ceruloplasmin levels were normal, and paracetamol and salicylate were not detectable.

On the following few days his ALT improved and INR normalised (Table 1). But while these parameters and his clinical status were improving, his Hb level was noted to drop to 10.8 g/dl on day 3 following admission, then to 8.9 g/dl on day 4 and finally to a nadir of 4.9 g/dl on day 5. This was accompanied by a rapid increase in total bilirubin levels, which peaked at 1132 µmol/L with an indirect bilirubin level of 461.7 µmol/L. Severe haemolysis was suspected and confirmed on further blood tests: haptoglobin of < 0.2 g/l (normal range: 0.30 to 2.00 g/l), lactate dehydrogenase of (LDH) 2493 IU/L (normal range: 106–218 IU/L), and reticulocytes of $201.1 \times 10^9/L$. His peripheral blood film showed polychromasia, which was compatible with haemolysis, with no evidence of sickle cell morphology or hereditary spherocytosis. Furthermore, he had a normal glucose-6-phosphate dehydrogenase (G6PD) level. His direct Coombs test was negative with a normal cold agglutinin titre, thus confirming non-autoimmune haemolytic anaemia. He was treated with folate, 5 mg once a day from day 5 to day 9 following admission. In addition, his bone marrow aspirate excluded any haematological malignancies and his raised WCC of $57 \times 10^9/L$ was thought to be a significant leukemoid reaction in response to the haemolysis. Unfortunately, his condition was further complicated by acute renal failure (Table 1) and severe chest sepsis, requiring continuous venous venous haemofiltration (CVVH) at 3 litres ultrafiltration per hour, high dose terlipressin at 1 mg every 6 hours and noradrenaline at the range of 0 to 1.2 mcg/kg/min to target mean arterial pressure of 65 mmHg, as well as intravenous tazocin at the dose of 4.5 g three times a day. All supportive were continued until day 9 following admission. The acute severe haemolysis resolved as quickly as it occurred, after transfusing a total of 5 units of whole blood between day 5 and day 8 following admission, his Hb level stabilised (Hb 10.4 g/dl on day 9 following admission) and LFTs much improved (Table 1).

Unfortunately, the patient deteriorated again on the evening of day 9. He developed increasing abdominal distension, melaena and severe metabolic acidosis (pH 6.96, BE -21). An urgent abdominal computerized tomography (CT) scan showed intramural gas and diminished mucosal enhancement of segments of large bowel with pneumoperitoneum, suggestive of perforated large bowel, likely secondary to intestinal ischaemia attributed to sepsis and vasopressors. An urgent laparotomy and subtotal colectomy was performed, and the intra-operative findings confirmed ischaemic bowel and intestinal perforation. However, the patient failed to improve and finally succumbed on day 10.

Discussion

The authors found seven other case reports of severe non-immune mediated haemolytic anaemia in patients with acute viral hepatitis, having normal G6PD levels and no previous liver disease (Table 2)^{4–8}. Of the 4 cases in which the virus subtype was known, A, B and E subtypes were all involved. All the patients were young, aged between 11 and 48, with good past health. They all dropped their Hb levels significantly to below 8 g/dl, with one case reaching a nadir of 3.99 g/dl. In the majority of cases, the haemolysis presented when the patient was showing improvement from hepatitis, either clinically or evidenced by the dropping in their liver parenchymal enzyme levels. All the patients received blood transfusion and five patients received steroids, four of whom were thought to have responded. In all cases, the haemolysis was associated with a suboptimal clinical outcome, of which six patients had a prolonged hospital stay with a median duration of around 30 days. The remaining one succumbed.

Our patient was co-infected with hepatitis B and E, most likely due to his sexual activity with a sex worker and consumption of raw seafood respectively, and severe haemolysis associated with this type of co-infection has not been reported in the literature before. The co-infection might have contributed to the poor outcome of this patient. Additionally, our patient's haemolysis developed over a few days and resolved as rapidly as it developed, as the transfusion of 5 units of whole blood alone was sufficient to stabilize the Hb level (Table 1). Haemolysis with such a rapid rate of onset and resolution has not been observed in other cases.

The mechanism for non-immune mediated haemolytic anaemia in acute viral hepatitis is not clear. One theory suggests that partially oxidative metabolites that decrease erythrocyte-reduced glutathione are released in acute viral hepatitis, and this decreased level of reduced glutathione impairs the integrity of erythrocytes^{1,2}. Some data suggest that haemolysis is caused by an extracorporeal factor including the virus itself^{9–11}. Other theories include endogenous hepatotoxic substances, splenomegaly and alteration of red cell osmotic fragility as potential causes of haemolysis^{2,4}.

Conclusion

Severe non-immune mediated haemolytic anaemia occurs rarely in patients with acute viral hepatitis with no G6PD deficiency or pre-existing liver disease and is associated with suboptimal outcomes. Most patients are young with good health status and are affected when they have recovered or are recovering from hepatitis. The anaemia secondary to haemolysis is so far always severe and can predispose the patients to other organ dysfunctions. Several viral subtypes are associated, although the disease mechanism is unclear, despite several proposed theories. In terms of treatment, several patients are thought to have responded to steroids in addition to transfusion, indicating its potential therapeutic role.

Table 2. Summary of case reports of severe Coomb's negative haemolytic anaemia associated with acute viral hepatitis in patients with normal G6PD levels.

Author/ Year	Age	Sex	Ethnicity/ Nationality	Viral hepatitis subtype	Coomb's test	PMH/SH/ Medications	Presentation	WCC ($\times 10^9/L$)	Treatment	Outcome
Raffensperger EC, et al. 1958⁵	43	F	Caucasian American	Unknown	Negative	Diphtheria, sleeping pills	The patient was improving from the hepatitis. On day 26 she became increasingly jaundiced and feverish and Hb dropped to 3.99 g/dl.	14	Transfusion, IV and oral steroids	Recovered - discharged on day 54
Raffensperger EC, et al. 1958⁵	11	M	Caucasian American	Unknown	Negative	Nil	The patient was stable after initial presentation, but on day 6, experienced worsening jaundice and abdominal pain, and Hb dropped to 7.7 g/dl.	25.3	Transfusion, IV steroids	Recovered - discharged in 2 weeks
Hansbarger EA, et al. 1963⁴	16	M	Unknown	Unknown	Negative	Nil	The patient's initial presentation suggested appendicitis but he failed to improve after a pyoappendix was removed. He was subsequently found to have acute viral hepatitis complicated by severe haemolytic anaemia, with Hb dropping from 9.8 g/dl to 5.9 g/dl in 12 days, and later developed renal failure and coma.	>40	Transfusion, IV and IM steroids	Died on day 32
Hansbarger EA, et al. 1963⁴	14	M	African American	Unknown	Negative	Nil	Hb was 5 g/dl on presentation with acute viral hepatitis of one month duration previously.	15.1	Unspecified symptomatic treatment	Recovered - discharged in 3 months
Vanderhoof JA, et al. 1976⁶	17	F	Caucasian American	B	Negative	IV drug use	The patient was discharged after her hepatitis improved. But 3 days afterwards, she was re-admitted with increasing jaundice with Hct of 29% which dropped to 17.5% the following day.	5.4	Transfusion only	Recovered - discharged in 1 month
Ting PL, et al. 1984⁷	27	F	Chinese	B	Negative	Pregnant	The patient had an Hb 8.1 g/dl on presentation which dropped to 5.9 g/dl in the following 9 days, in the meantime, her AST and ALT improved.	Not available	Transfusion, oral steroids	Recovered - discharged on day 24
Ibe M, et al. 1997⁸	39	F	Unknown	A	Negative	Mild RA, steroids	The patient developed increasing jaundice after presentation. Her Hb dropped from normal level to 7.7 g/dl in 1 month.	5.2	Transfusion, oral steroids	Recovered - discharge date unknown estimated to be > 1 month
Our case 2012	48	M	Chinese	B and E	Negative	Foreign travel, sex with sex worker	Whilst the patient was improving from his hepatitis, his Hb dropped from 13.3 g/dl to 4.9 g/dl in 5 days. His haemolytic anaemia was associated with acute renal failure.	>40	Antiviral drug, transfusion	Died on day 10

Consent

Written informed consent for publication of their clinical details was obtained from the next of kin of the patient.

Author contributions

MXW prepared the first draft of the manuscript. FHYY and GMJ conceived the case report and guided MXW in preparing the first

draft of manuscript. All authors were involved in the revision of the draft manuscript and have agreed to the final content.

Competing interests

No competing interests were disclosed.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Reviewer Report 02 November 2015

<https://doi.org/10.5256/f1000research.7628.r10685>

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Rosario Notaro

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Michael Wang and co-Authors report a case of severe non-immune mediated hemolytic anemia occurred during an episode of acute E and B viral hepatitis in a patient that is not G6PD deficient.

Unfortunately the manuscript does not provide strong evidence that the patient is not G6PD deficient. In fact, the Authors have measured G6PD level (the level is not shown) only during the hemolytic episode when reticulocyte count was high ($201.1 \times 10^9/L$): it is well known that high reticulocyte count can mask the deficiency of G6PD. In order to prove that the patient is not G6PD deficient the Authors should show G6PD levels measured before the hemolytic episode or they should show that at DNA level the patient carried a G6PD mutation known to be associated with G6PD deficiency. In addition, a more extensive workout for inherited hemolytic anemia (pyruvate kinase deficiency, etc.) would be a good addition.

Minor Points

Abstract. The abstract reports no data about the actual clinical case.

Conclusion. This is a summary of the literature poorly related with the findings from the reported clinical case.

Table 1: Few abbreviations are not spelt out.

Competing Interests: No competing interests were disclosed.

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