Fatal herpes simplex virus hepatitis following neoadjuvant chemoradiotherapy and anterior resection for rectal cancer

DP Toomey, AS Dhadda, LA Sanni, JP Cooke, JE Hartley

Hull and East Yorkshire Hospitals NHS Trust, UK

ABSTRACT

We describe the case of a young patient who contracted fatal herpes simplex virus hepatitis following neoadjuvant chemoradiotherapy and anterior resection for rectal cancer. The rarity and non-specific presentation of this treatable disease, which masqueraded as the sequelae of postoperative sepsis, resulted in a diagnosis following death. Features that should prompt inclusion of herpes simplex virus hepatitis in the differential diagnoses are suggested and the case is a reminder of how neoadjuvant therapy may subtly alter a patient's immunocompetency.

KEYWORDS

Radiotherapy – Rectal cancer – Hepatitis

Accepted 22 January 2014; published online XXX

CORRESPONDENCE TO

Des Toomey, E: toomey.des@gmail.com

Case History

A 47-year-old man was diagnosed with a T3N2M0 adenocarcinoma of the upper rectum. He had no significant past history, smoked four cigarettes per day and consumed five units of alcohol per week. Magnetic resonance imaging determined that the circumferential resection margin was threatened and long-course chemoradiotherapy (45Gy in 25 fractions with concurrent capecitabine) was recommended by the multidisciplinary team. He tolerated the treatment with minimal clinical toxicity. Routine blood testing on completion of radiotherapy demonstrated mild, asymptomatic leucopenia, neutropenia and lymphopenia that had mostly resolved when measured again at his preoperative assessment (Table 1). He underwent an uncomplicated high anterior resection with stapled colorectal anastomosis and a defunctioning loop ileostomy after a nine-week interval.

The patient's initial postoperative clinical course was normal other than a mild lymphopenia (Table 1) and low grade pyrexia (37.5°C). On postoperative day 6, he had a persistent ileus and elevated C-reactive protein (CRP). Intravenous co-amoxiclav was administered for wound cellulitis and pyrexia (38.2°C). On day 8, computed tomography (CT) revealed a 5cm collection adjacent to the anastomosis. Examination under anaesthesia that day confirmed a partial (posterior 25% circumference) anastomotic dehiscence with viable proximal colon and a small collection, which was drained through the defect.

The patient was managed non-operatively with nutritional support (parenteral nutrition in view of the ileus) and

antibiotics were changed to piperacillin/tazobactam. He appeared well over the following days although he did complain of abdominal pain. Alanine transaminase (ALT) levels were rising (Table 1) but this was initially attributed to parenteral nutrition and sepsis. The white cell count was depressed owing to ongoing lymphopenia but the neutrophil count remained normal and he was on piperacillin/tazobactam. On day 11, mild biochemical jaundice developed.

On day 12, the patient became clinically very unwell with increasing right-sided abdominal pain, progressive lactic acidosis, hypoglycaemia and deteriorating liver function tests (Table 1). Repeat CT showed no new findings but an enlarged liver was noted. Concern persisted over post-operative sepsis or bowel ischaemia and a laparotomy was performed. The liver was found to be markedly engorged and 'salmon pink', consistent with an acute liver injury. The hepatic artery was pulsatile and the portal vein patent on CT. A liver biopsy was taken. The presacral collection was irrigated again.

Over the next 48 hours, the patient deteriorated despite intensive support and antibiotic therapy. Liver function test results, protein and coagulation levels deteriorated, as did platelet count. A peripheral blood culture was positive for *Streptococcus faecium*. Following discussions with the hepatology team and the regional hepatobiliary unit, a diagnosis of fulminant hepatic failure was made, presumed secondary to septicaemia from bowel organisms. Toxicology was negative and viral hepatic screen results were awaited. The patient continued to deteriorate despite aggressive support and passed away on day 14.

Table 1 Blood test results in the postoperative period

Time	WCC	Neutro	Lympho	CRP	Bilirubin	ALT	ALP	Alb	
Normal range	4–11 x 10 ⁹ /l	2–7.7 x 10 ⁹ /l	0.8–3.4 x 10 ⁹ /l	<8 mg/l	7–23 µmol/l	5–45 iu/l	30–125 iu/l	36–48 g/l	
Initial	5.9	3.7	1.59		9	19	82	41	
NeoAd	2.4	1.38	0.57		10	34	76	39	
Pre-op	3.4	2.12	0.83		12	21	65	39	
Day 1	10.3	9.38	0.42	179	18	24	51	32	
Day 2	10.7	9.48	0.50	296	23	23	61	31	
Day 3	9.6	8.47	0.26	326	15	23	65	29	
Day 4	5.0	4.27	0.43		23	33	97	27	
Day 5	3.2	2.69	0.27	294	19	32	101	25	
Day 6	3.4	2.85	0.21	301	16	50	94	24	
Day 7	3.9	3.5	0.19	323	14	60	86	22	
Day 8	EUA/TPN	5.0	4.69	0.18	365	14	99	103	19
Day 9		3.2	2.89	0.15	14	178	102	20	
Day 10		3.2	2.82	0.12	338	17	449	206	19
Day 11		2.2	1.9	0.18	307	29	1165	384	18
Day 12	Liver Bx	3.6	3.18	0.28	299	42	2270	485	16
Day 13		8.9	10.26	0.16	258	48	2478	461	24
Day 14		14.2	13.64	0.91	65	64	1556	1337	21

WCC = white cell count; Neutro = neutrophil count; Lympho = lymphocyte count; CRP = C-reactive protein; ALT = alanine transaminase; ALP = alkaline phosphatase; Alb = albumin; Initial = before any treatment; NeoAd = end of neoadjuvant therapy; Pre-op = preoperative assessment; EUA = examination under anaesthesia; TPN = total parenteral nutrition; Liver Bx = laparotomy and open liver biopsy

Results received following the patient's death demonstrated previous exposure to hepatitis A and B but no active infection. Hepatitis C and human immunodeficiency virus serology were negative. Final histology of the liver biopsy reported a large proportion of liver cells with evidence of nuclear inclusion with glassy nuclei suggesting herpes virus inclusion. Immunohistochemistry for herpes simplex virus (HSV) was extensively positive within the

nuclei and cytoplasm, in keeping with HSV associated liver necrosis (Fig 1).

Discussion

First described in 1969, HSV hepatitis is a rare condition that is mostly confined to third trimester pregnant women and immunocompromised patients. There are only a

Figure 1 Liver biopsy showing hepatic necrosis (A) with herpes simplex virus inclusion bodies (B) and strongly positive immunohistochemistry for herpes simplex virus (C)

handful of case reports in non-pregnant, immunocompetent people.¹ Owing to its rarity and non-specific presentation, its diagnosis follows death in 67% of pregnant patients and 74% of non-pregnant patients. When untreated, the mortality rate is 90% but Norvell *et al* have demonstrated that early treatment with acyclovir can decrease death or liver transplant rates from 88% to 51%.² Such early treatment is difficult to achieve as the diagnosis is only suspected prior to receiving the histopathology report in 23% of cases.^{2,5}

In this case, HSV hepatitis presented in the postoperative patient and was masked by low grade bacterial sepsis. The patient was presumed to be immunocompetent. However, it is likely that neoadjuvant chemoradiotherapy had affected the systemic immune system, in particular lymphocyte production. Grimm *et al* have previously reported a fulminant case of HSV hepatitis in a patient undergoing chemoradiotherapy for oesophageal cancer.⁴ Our case differs in that there was a ten-week interval between treatment and infection in a seemingly well patient.

Although myelosuppression is rare during treatment with capecitabine, the blood tests following radiotherapy showed a lymphopenia, suggesting a degree of immunological compromise, but this largely recovered before surgery. We hypothesise that the stress of surgery and then postoperative sepsis unmasked a chemoradiotherapy induced tendency to lymphopenia, leaving the patient susceptible to viral infection or reactivation.

Conclusions

It is disturbing how this (admittedly rare) complication of colorectal surgery masqueraded as the effects of bacterial sepsis and parenteral nutrition. We suggest that the triad of neoadjuvant therapy, lymphopenia and rising ALT should prompt the inclusion of viral hepatitis in the differential diagnoses at an early stage, even with positive bacterial blood cultures. Empirical antiviral therapy would be justified when there is a high clinical suspicion or progression to fulminant hepatitis is threatened.⁵

References

1. Lakhan SE, Harle L. Fatal fulminant herpes simplex hepatitis secondary to tongue piercing in an immunocompetent adult: a case report. *J Med Case Rep* 2008; **2**: 356.
2. Norvell JP, Blei AT, Jovanovic BD, Levitsky J. Herpes simplex virus hepatitis: an analysis of the published literature and institutional cases. *Liver Transpl* 2007; **13**: 1,428–1,434.
3. Velasco M, Llamas E, Guijarro-Rojas M, Ruiz-Yagüe M. Fulminant herpes hepatitis in a healthy adult: a treatable disorder? *J Clin Gastroenterol* 1999; **28**: 386–389.
4. Grimm B, Padberg B, Ruhstaller T *et al*. Fatal herpes simplex virus hepatitis in a patient with esophageal cancer under radiochemotherapy. *Onkologie* 2008; **31**: 620–622.
5. Peters DJ, Greene WH, Ruggiero F, McGarrity TJ. Herpes simplex-induced fulminant hepatitis in adults: a call for empiric therapy. *Dig Dis Sci* 2000; **45**: 2,399–2,404.