

## CASE REPORT

## Genetic predisposition resulting in sinusoidal obstruction syndrome in a patient with resected sigmoid cancer on adjuvant oxaliplatin

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**SUMMARY**

A Chinese man who had undergone a curative high anterior resection for sigmoid cancer was administered XELOX (capecitabine and oxaliplatin) as postoperative adjuvant chemotherapy. He subsequently developed sinusoidal obstruction syndrome (SOS) that resolved on discontinuation of XELOX treatment. Genetic evaluation determined that he had the *GSTT1*-null and *GSTM1*-null genotype, known to be an independent risk factor for developing oxaliplatin-induced SOS.

**BACKGROUND**

This is the first reported case of oxaliplatin-induced sinusoidal obstruction syndrome (SOS) among the Chinese. Subsequent genetic testing revealed that this patient had the *GSTT1*-null and *GSTM1*-null genotype, known to be an independent risk factor for developing oxaliplatin-induced SOS.<sup>1</sup>

There is no known difference in the frequency of *GSTM1*-null genotype between patients of Chinese and non-Chinese ethnicities.<sup>1-9</sup> Interestingly, however, is the reported prevalence of *GSTT1*-null genotype being slightly higher in people of Chinese (45–50%) compared to those of non-Chinese (6–26%) origin. It is unclear if this translates to differences in risk of SOS in different ethnic groups. Our report highlights the association of a genetic predisposition for SOS and will hopefully increase clinicians' vigilance for this possibility in oxaliplatin-treated patients. Our finding, if validated, could potentially enable us to formulate a plausible genetic risk profile, together with other risk factors, to predict a patient's risk of developing SOS, before starting oxaliplatin-based chemotherapy. The choice of chemotherapy could thereafter be adjusted based on the patient's unique risk profile, or closer monitoring (if necessary, discontinuation) could be given, should oxaliplatin still be the choice of drug administered.

**CASE PRESENTATION**

A 56-year-old man of ethnic Chinese descent initially presented to his primary care physician, in June 2014, with per-rectal bleeding for 2 months. He had no significant medical history, no family history of colorectal cancer, no known drug allergies, denied any previous intake of alcohol, smoking and herbal agents, and was unemployed. Colonoscopy with biopsy showed moderately differentiated adenocarcinoma of the rectosigmoid. CT did not show metastases. Blood test of liver function was normal. The

patient underwent a high anterior resection of the sigmoid tumour. Histology confirmed adenocarcinoma with involvement of 1 of 16 regional lymph nodes. After surgery, the patient was given adjuvant chemotherapy using a combination of the XELOX regimen, comprising oral capecitabine 1000 mg/m<sup>2</sup> two times per day on days 1–14, plus intravenous oxaliplatin 130 mg/m<sup>2</sup> on day 1. The first cycle was uneventful but, 20 days after the second cycle of oxaliplatin, he presented to the clinic with a 1-day duration of acute abdominal distension. Clinically, he had facial swelling, generalised ascites and bilateral lower limb oedema. He was not taking any medications, other than dexamethasone as an antiemetic on the first 2 days of chemotherapy.

**INVESTIGATIONS**

Liver function test showed mild elevation of liver enzymes and hypoalbuminaemia (table 1). Urea and electrolytes were normal.

Haemoglobin count was 13.2 g/dL and serial white cell counts were not raised (on admission:  $5.2 \times 10^9/L$ ; before discharge:  $4.24 \times 10^9/L$ ).

Serum carcinoembryonic antigen was 3.2 µg/L, from the previous 2.1 µg/L at postoperation follow-up.

As nephrotic syndrome was considered, 24 h urine protein (0.18 g/day) and urine protein:creatinine ratio (0.13) were normal. Total cholesterol was 3.33 mmol/L.

Serological tests for hepatitis B and C viruses were negative.

CT of the chest/abdomen/pelvis showed moderate ascites, heterogeneous liver parenchyma and periportal oedema (possibly representing hepatic venous congestion) with no liver metastases. There were no features of superior or inferior vena cava obstruction. Ultrasound of the hepatic vein revealed no evidence of veno-occlusive disease.

**DIFFERENTIAL DIAGNOSIS**

Our working diagnosis was oxaliplatin-induced SOS; differential diagnoses were liver metastases, nephrotic syndrome, viral hepatitis and sepsis.

Clinically, the onset of acute SOS is within 1–3 weeks of exposure to the offending medication. Patients present with signs of portal hypertension (ascites, oedema and varices), weight gain and abdominal pain. Jaundice is generally mild or absent, but may develop if the injury is severe. Blood tests typically show hepatic transaminase



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**Table 1** Patient's liver function test results

Time of measurement	Aspartate aminotransferase (IU/L)	Alanine aminotransferase (IU/L)	Alkaline phosphatase (IU/L)	$\gamma$ -Glutamyl transferase (IU/L)	Total bilirubin ( $\mu$ mol/L)	Total protein (g/L)	Albumin (g/L)
Preoperation	25	33	101 $\uparrow$	53	6 $\downarrow$	76	45
Postoperation; before #1 XELOX	20	20	98	NM	5 $\downarrow$	74	43
After #1 XELOX before #2 XELOX	43 $\uparrow$	33	91	NM	10	74	45
After #2 XELOX (at time of admission for ascites)	33	55	99	NM	17	52 $\downarrow$	28 $\downarrow$
During admission							
Day 2	51 $\uparrow$	47	108 $\uparrow$	64	14	55 $\downarrow$	29 $\downarrow$
Day 3	47 $\uparrow$	41	118 $\uparrow$	66	11	57 $\downarrow$	30 $\downarrow$
Day 4	53 $\uparrow$	44	125 $\uparrow$	NM	11	61 $\downarrow$	31 $\downarrow$
Day 8	65 $\uparrow$	45	121 $\uparrow$	NM	13	67 $\downarrow$	35 $\downarrow$
Day 9	48 $\uparrow$	36	109 $\uparrow$	74	11	62 $\downarrow$	33 $\downarrow$
At follow-up (6 days postdischarge)	36	28	130 $\uparrow$	NM	10	69	37 $\downarrow$

NM, not measured.

elevations following a hepatocellular pattern and mild or minimal alkaline phosphatase (ALP) increase.

Our patient developed facial swelling and ascites with bilateral lower limb oedema 20 days after the second course of XELOX was administered. His aspartate aminotransferase (AST), alanine aminotransferase (ALT) and ALP were only mildly raised, and total bilirubin was normal.

Liver ultrasound can suggest SOS by demonstrating hepatomegaly, ascites and liver texture changes suggestive of congestion, and can help exclude acute Budd-Chiari syndrome and portal vein thrombosis by demonstrating patency of hepatic and portal veins. Our patient's ultrasound hepatic vein was not suggestive of veno-occlusive disease, but CT scan showed heterogeneous liver parenchyma and periportal oedema, possibly representing hepatic venous congestion.

Malignant infiltration of the liver was excluded by the absence of liver metastases on CT scan. Nephrotic syndrome was excluded by normal 24 h urine protein, urine protein:creatinine ratio and total cholesterol. Viral hepatitis was unlikely as serological tests for hepatitis B and C viruses were negative. Normal white cell counts and absence of fever ruled out sepsis.

Our patient was treated symptomatically with oral frusemide. Subsequently, he was not given further oxaliplatin, and had no further episodes of ascites. The acute onset of his symptoms and their resolution on discontinuation of oxaliplatin raised the clinical suspicion of oxaliplatin-induced SOS.

## TREATMENT

The patient's ascites and oedema subsided after a short course of oral frusemide.

At follow-up 1 week later, he was well, with no liver tenderness, and no longer had ascites and limb swelling. Blood test showed that AST and ALT had normalised.

He was advised against further exposure to oxaliplatin, and did not have recurrence of symptoms.

## OUTCOME AND FOLLOW-UP

The patient was offered genetic testing to identify genotypic predisposition to oxaliplatin-induced SOS.

Peripheral whole blood was obtained from the patient and healthy volunteers, with informed written consent. This study was approved by the SingHealth Institutional Review Board (CIRB Ref: 2011/826/B).

Genomic DNA was extracted from peripheral whole blood by standard column purification using Blood and Cell Culture kit (Qiagen, Hilden, Germany) according to manufacturer's protocol. Purified DNA was quantified on Nanodrop2000 (Thermo Scientific, USA).

Seminested PCR for *GSTM1* and *GSTT1* genes was performed on purified genomic DNA from the patient, with  $\beta$ -globin as an internal control, as previously described. Briefly, a 219–290 bp product was first amplified from 40–50 ng genomic DNA using Platinum *Taq* polymerase (Life Technologies, Carlsbad, California, USA) on a Geneamp 9700 Thermocycler (Applied Biosystems). The first PCR product was then diluted 100 times and subsequently used as a template for the second PCR. The same cycling conditions were used for both PCR cycles: initial activation at 95°C for 10 min; followed by 35 cycles of 95°C for 30 s, 55°C for 30 s and 72°C for 1 min; and final extension at 72°C for 10 min. Primers used were as listed by Vreuls *et al.*<sup>1</sup> Gel electrophoresis on 1% agarose with SYBR Safe (Life Technologies), with 2  $\mu$ l of total reaction volume was used to visualise the PCR products. For positive control, PCR on genomic DNA from a healthy volunteer with no colorectal disease was concurrently performed.

The seminested technique was adopted for its more accurate ability to amplify long DNA, as the fragment to be amplified had 219–290 bp. The primer sequences of both, first and second PCR, are listed in table 2.<sup>1</sup> Subsequently, electrophoretic analysis was performed, visualising the amplified product by SYBR Safe in a 1% agarose gel. As one of the primers is located in the deleted sequence, this technique enabled us to identify the homozygous null genotype.

The primers designed by Vreuls *et al.*,<sup>1</sup> or *GSTM1* and *GSTT1*, respectively, were such that one primer of the pair was located in the deleted sequence of the null genotypes. There was no product from the seminested PCR of *GSTM1* and *GSTT1* genes in the patient (figure 1), indicating that he had a homozygous null genotype for these two alleles.

## DISCUSSION

Oxaliplatin-based chemotherapeutic regimens such as FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) and XELOX (capecitabine and oxaliplatin) are commonly used in patients with colorectal cancer as adjuvant systemic chemotherapy postresection. While these drugs have demonstrated efficacy, they have also been associated with various degrees of hepatotoxicity.

**Table 2** Primer sequences of *GSTM1* and *GSTT1* genotype<sup>1</sup>

Primer designation	Sequences	Product length (bp)
<i>GSTM1</i>		
First amplification		
Forward	5'-GAACTCCCTGAAAAGCTAAAGC-3'	219
Reverse	5'-GTTGGGCTCAAATATACGGTGG-3'	
Second amplification		
Forward	5'-CAGAGTTTCTGGGAAGCGG-3'	191
Reverse	Idem first amplification	
<i>GSTT1</i>		
First amplification		
Forward	5'-TTCCTTACTGGTCTCACATCTC-3'	290
Reverse	5'-AAGACTTGGCAGCCAGACC-3'	
Second amplification		
Forward	Idem first amplification	249
Reverse	5'-TACAGACTGGGGATGGATGG-3'	
<i>β-globin</i>		
First amplification		
Forward	5'-GAAGAGCCAAGGACAGGTAC-3'	268
Reverse	5'-CAACTTCATCCAGTTCACC-3'	
Second amplification		
Forward	5'-GGCTGGGCATAAAAGTCAGG-3'	162
Reverse	Idem first amplification	

*GSTM1*, glutathione S-transferase μ; *GSTT1*, glutathione S-transferase enzyme θ.

SOS is often associated with oxaliplatin. It has also been described in association with drugs such as azathioprine, 6-mercaptopurine, 6-thioguanine, busulfan, cyclophosphamide, doxorubicin, etoposide, etc.<sup>10</sup>

Rubbia-Brandt *et al*<sup>11</sup> found that 34 of 43 (78%) patients treated with oxaliplatin developed hepatic sinusoidal dilation. SOS is characterised by sinusoidal dilation and congestion, centrilobular vein fibrosis and obstruction, perisinusoidal fibrosis, necrosis of pericentral hepatocytes, parenchymal extinction lesions, hepatocyte plate disruption and nodular regenerative hyperplasia.<sup>10 12–16</sup>

Oxaliplatin and other platinum compounds lead to the generation of reactive oxygen species that can deplete glutathione

from sinusoidal endothelial cells (SECs).<sup>17 18</sup> The toxic injury to these SECs causes damage to the sinusoidal wall, hence marked sinusoidal dilation and extravasation of erythrocytes into the Disse's spaces through the endothelial lining's discontinuities. Moreover, collagen matrix deposits in perisinusoidal spaces and terminal hepatic venules because of the activation of hepatic stellate cells.<sup>11 13</sup> As a result, there is circulatory compromise of centrilobular hepatocytes, fibrosis and obstruction of liver blood flow.

A number of other surgical series supported the findings of Rubbia-Brandt *et al*. Mehta *et al*<sup>19</sup> demonstrated that 61% of 70 patients receiving regimens containing oxaliplatin developed sinusoidal dilation. Three other studies found that 9.7%–23% of patients treated with oxaliplatin developed grade 2–3 sinusoidal dilation.<sup>12 20 21</sup> Kweekel *et al*<sup>22</sup> summarised a case series reporting an association between oxaliplatin and sinusoidal dilation (table 3).

A diagnosis of SOS can often be made based on clinical symptoms and signs, and routine laboratory tests. Liver histology is diagnostic but not always practical, due to chemotherapy-induced thrombocytopenia and neutropaenia. Transjugular liver biopsy and concurrent measurement of the hepatic venous pressure gradient can also be used for accurate diagnosis and grading for severity, based on degree of portal hypertension.

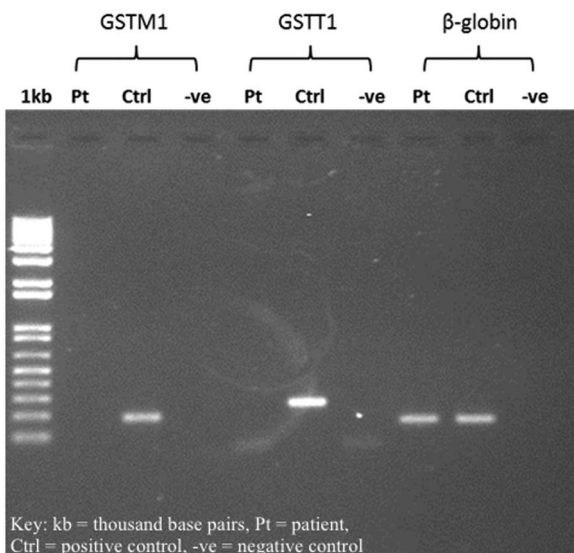
Monitoring for symptoms and signs of SOS for early recognition is perhaps most crucial in patients who receive oxaliplatin-based chemotherapy. Management of SOS is aimed at avoiding further injury by stopping oxaliplatin, providing support for complications such as pain and hypotension, and maintaining intravascular volume and renal perfusion while limiting third-space fluid accumulation.<sup>23 24</sup> Correcting electrolyte and acid-base imbalance and pulmonary failure, and managing infectious complications, are also essential.

Prevention of SOS is best achieved by keeping SOS in consideration, and thereafter withholding oxaliplatin or at least closely monitoring for signs and symptoms, if using oxaliplatin.

Genetic expression profiling performed by Brandt *et al* in 2011 revealed that, compared with controls, in oxaliplatin-induced SOS livers, gene expression analysis showed that upregulated genes included those involved in acute phase response (notably interleukin 6), coagulation system (*Serpine1*, *THBD* and *VWF*), hepatic fibrosis/hepatic stellate cell activation (*COL3a1*, *COL3a2*, *PDGF-A*, *TIMP1*, and *MMP2*), oxidative stress (*JUN*, *SOD2*), angiogenesis (*VEGF-C*) and hypoxic factors (*HIF1A*). The most significant increase was observed in *CCL20* mRNA.<sup>25</sup>

At present, the only known and validated germline predisposition gene associated with SOS is with *GSTM1*.<sup>1</sup> Inactivation of the platinum compound by glutathione and other antioxidants helps prevent against toxicity.<sup>22 26 27</sup> Glutathione and platinum form an adduct that leads to detoxification of oxaliplatin. This adduct formation is catalysed by glutathione S-transferase enzyme (GST).<sup>22</sup> Several subclasses of GST are known; θ (*GSTT*), μ (*GSTM*), α (*GSTA*), π (*GSTP*) and ω (*GSTO*), each with their own polymorphism.<sup>28</sup> *GSTT* and *GSTM* have null genotypes—*GSTT1*-null and *GSTM1*-null. The null genotypes result in no enzymatic GST function hence decreased adduct formation between glutathione and platinum, hence decreased defence mechanism against oxaliplatin.<sup>22 27</sup> A patient may therefore be susceptible to SOS if there are deficiencies in the detoxification process.<sup>11 29</sup>

Consideration for genetic testing was made for our patient as SOS seemed the most likely diagnosis to account for the acute



**Figure 1** Gel electrophoresis results.

**Table 3** A summary of case series reporting the association between oxaliplatin and sinusoidal dilation

Study	Number of patients	Sinusoidal dilation	Greater morbidity	Greater mortality
Vauthey <i>et al</i> <sup>20</sup>	79	15 of 79 patients (19%)	No	No
Mehta <i>et al</i> <sup>19</sup>	70	43 of 70 patients (61%)	No	No
Aloia <i>et al</i>	52	10 of 52 patients (19%)	Yes*	No
Kandutsch <i>et al</i> <sup>12</sup>	47	11 of 47 patients (23%)	No	No
Rubbia-Brandt <i>et al</i> <sup>25</sup>	43	34 of 43 patients (78%)	Not available	Not available
Pawlik <i>et al</i> <sup>21</sup>	31	3 of 31 patients (10%)	No	No
Nakano <i>et al</i> <sup>16</sup>	90	38 of 90 patients (42%)	Yes	No

\*Aloia *et al* found a non-statistically significant trend towards increased morbidity.

onset of his ascites and lower limb swelling after the second cycle of XELOX, and the fact that his symptoms did not reappear after XELOX was stopped. He was found to have the *GSTT1*-null and *GSTM1*-null genotype. This finding could potentially allow us, in association with other risk factors, to conceive a plausible genetic risk profile predicting whether a patient is at risk of developing SOS, before starting oxaliplatin, and subsequently might result in discontinuation of oxaliplatin on an individual patient basis. Further prospective research will be helpful to evaluate this.

### Learning points

- ▶ In patients who need oxaliplatin-based chemotherapy, monitoring for signs and symptoms of sinusoidal obstruction syndrome (SOS) after the administration of oxaliplatin is crucial for prompt management should the need arise: discontinuing oxaliplatin and supportive management.
- ▶ Prevention of SOS is best achieved by keeping SOS in consideration.
- ▶ Our patient with oxaliplatin-induced SOS was found to have the *GSTT1*-null and *GSTM1*-null genotype, the latter of which has been found to be an independent risk factor for oxaliplatin-induced SOS.<sup>1</sup>
- ▶ Genetic testing can be useful in predicting a patient's risk of developing oxaliplatin-induced SOS before starting oxaliplatin, and hence can enable suitable adjustments to the cumulative amount of oxaliplatin treatment given. Further research is necessary to develop this possibility.

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**Contributors** SXX and SHC performed the experiments and collated data. JN provided scientific oversight and designed the study.

**Competing interests** None declared.

**Patient consent** Obtained.

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