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Preliminary report

Type II hypersensitivity reactions after oxaliplatin rechallenge can be life threatening

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ABSTRACT

Background: Rechallenge with oxaliplatin is common in the treatment of colorectal cancer and increases the risk of a detrimental oxaliplatin-induced immune reaction. Allergic reactions to oxaliplatin may be partially avoided by desensitization protocols involving immune suppressive drugs, slow administration and gradually increasing chemotherapeutic doses. However, non-IgE-mediated immunopathologic reactions to oxaliplatin remain challenging and may be potentially life-threatening.

Case presentation: Here we report two potentially fatal cases of type II hypersensitivity to oxaliplatin in metastatic colorectal cancer patients. Both patients manifested with severe thrombocytopenia, intravascular haemolysis, and acute kidney injury 4–6 h after oxaliplatin administration in a rechallenge setting. Serology revealed that the reactive entity for immune haemolysis was an IgG oxaliplatin-induced antibody. The course of anti-cancer treatment and severe adverse event after oxaliplatin rechallenge including diagnostic dilemma and the results of detailed routine clinical chemistry and hematology testing are described. Extended immunohaematology/serology testing revealed that the oxaliplatin-induced IgG antibody was present in the circulation prior to the onset of hypersensitivity, persisted for months and elicited cross-reactivity with other platinum agents.

Conclusion: Development of type II hypersensitivity reaction manifesting as a sudden onset of severe thrombocytopenia and immune haemolysis must be considered in patients treated with oxaliplatin, especially those on long-term therapy or when rechallenged. Step-wise diagnosis involves clinical presentation, detection of haemolysis in patient's blood and/or urine, evaluation of platelet count, and direct anti-globulin Coombs test.

1. Background

Platinum derivates have been in use in anti-cancer treatment since the late 1970s. With its broad spectrum effect, cisplatin is still in clinical use; however, the less toxic derivates carboplatin and oxaliplatin have replaced cisplatin for many indications. Thus, the platinum salts have been used widely and much clinical experience has been gained including the management of side effects. Immunopathologic reactions to platinum agents are mainly caused by type I IgE-mediated or type IV T-cell-mediated hypersensitivity [1]. Type I allergic reactions to platinum derivates are not rare, occurring for cisplatin in 5 to 20% of cases, for carboplatin in 9 to 27% of cases and for oxaliplatin in 10 to 19% of

Abbreviations: Ab, Antibody; ADAMTS13, A Disintegrin And Metalloproteinase with a ThromboSpondin type 1 motif, member 13; AIHA, Autoimmune Haemolytic Anemia; AHG, Antihuman Globulin; AKI, Acute Kidney Injury; ALT, Alanine Aminotransferase; aPTT, Activated Partial Thromboplastin Time; AST, Aspartate aminotransferase; CRP, C-reactive Protein; CT, Computer Tomography; DAT, Direct Antiglobulin Test; eGFR, Estimated Glomerular Filtration Rate; FOLFIRI, Chemotherapy regimen, FOL - folinic acid, F - 5-fluorouracil, IRI - irinotecan; FOLFOX, Chemotherapy regimen, FOL - folinic acid, F - 5-fluorouracil, OX - oxaliplatin; FU/FA, Chemotherapy regimen, FU -5-fluorouracil, FA - folinic acid; GGT, Gamma-glutamyltransferase; Hgb, Haemoglobin; HUS, Haemolytic Uremic Syndrome; IAT, Indirect Antiglobulin Test; ICU, Intensive Care Unit; IPF, Immature Platelet Fraction; ITP, Idiopathic thrombocytopenic purpura; LDH, Lactate Dehydrogenase; MAHA, Microangiopathic Haemolytic Anemia; mCRC, Metastatic Colorectal Carcinoma; MCV, Mean Corpuscular Volume; NRBC, Nucleated Red Blood Cell; PET, Positron Emission Tomography; PT, Prothrombin Time; RBC, Red Blood Cell; SOFA score, Sequential organ failure assessment score; TMA, Thrombotic Microangiopathy; TT, Thrombin Time; TTP, Thrombotic Thrombocytopenic Purpura; XELOX, Chemotherapy regimen, XEL - capecitabin (Xeloda®), OX – oxaliplatin

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cases [1,2]. Additionally, type II and type III reactions have been involved in oxaliplatin hypersensitivity [1]. Oxaliplatin-induced immune syndrome involving immune haemolytic anemia and immune thrombocytopenia occurs more frequently with long-term exposure and with an earlier occurrence when oxaliplatin is administered as a rechallenge [3–5].

Several protocols of administration aiming at platinum desensitization have been developed [6] and predictive markers for allergy are sought [7]. Generally, platinum desensitization protocols based on gradual reintroduction of small amounts of drug antigen while escalating to the full dose, on prolonged infusion and on premedication with corticosteroids and antagonists of histamine receptors have been implemented into clinical practice to avoid or to minimize the occurrence of type I hypersensitivity [1,8]. Nevertheless, type II (IgG or IgM mediated) [9] and type III hypersensitivity reactions to oxaliplatin, manifesting as Evan's syndrome with haemolysis and/or thrombocytopenia [9], and chronic urticaria, joint pain, and proteinuria [10], respectively, remain challenging.

Two cases of severe complications presented as acute haemolysis and thrombocytopenia with acute kidney injury after oxaliplatin rechallenge are reported. Here we show routine and extended diagnostic testing that was performed in these cases and discuss early diagnosis of this type of adverse event.

2. Case presentation

2.1. Case report 1: clinical course

A female patient, born in 1965, was diagnosed with a rectal adenocarcinoma grade 2, *KRAS* wild type and *BRAF* wild type, with multiple liver metastases in Nov 2012. After 6 cycles of the 1st line chemotherapy FOLFOX/Panitumumab, the patient reached a partial response with liver metastases still unresectable. After 8 cycles oxaliplatin was discontinued due to increasing neurotoxicity with treatment continuing until Dec 2013 for a total 13 months when complete radiological response (PET/CT) was achieved. In Apr 2014, the liver metastases progressed and based on previous excellent effect of oxaliplatin, rechallenge with FOLFOX/Panitumumab was commenced. During a rechallenge, oxaliplatin was omitted after 6 cycles due to increasing neurotoxicity and the patient again achieved a partial response in the liver disease in Sep 2014. In Nov 2014, she underwent right-sided liver resection followed by 4 cycles of FOLFOX/Panitumumab with oxaliplatin in 2 of these cycles until Feb 2015 when oxaliplatin was put on hold due to a mild hypersensitivity reaction presenting as an itch and flush, from which time the patient continued on FU/FA de Gramont/Panitumumab. In Apr 2015, treatment was discontinued with no PET/CT signs of an active disease. In March 2016, the patient underwent stereotactic irradiation of a solitary progressing liver metastasis, followed by 2nd-line chemotherapy with FOLFIRI/Panitumumab until Jan 2017. Due to disease progression in supraclavicular and mediastinal lymph nodes and the fact that the patient had never progressed on oxaliplatin, she was rechallenged with XELOX in May 2017. Due to the patient's previous hypersensitivity reaction, oxaliplatin was administered according to a desensitization protocol with enhanced premedication, escalating dose and prolonged infusion time [11]. Administration of the 2nd cycle of XELOX was complicated by a sudden drop in platelet count, elevated liver function tests and a clinical picture of haematuria occurring 4 h after oxaliplatin infusion. The patient was immediately transferred to an intensive care unit for further investigation and treatment. Laboratory tests revealed ongoing haemolysis and a further drop in platelet count. Consequently, the patient developed acute kidney injury with low urinary output and a sudden drop in creatinine clearance resulting from massive haemolysis with a haemoglobinuria. A direct Coombs anti-globulin test was positive, showing an involvement of immune-mediated haemolysis. Therefore, a provisional diagnosis of acute oxaliplatin-induced Evan's syndrome with haemolytic anemia with a thrombocytopenia was considered, with a differential diagnosis of secondary thrombotic thrombocytopenic purpura/drug-induced haemolytic-uremic syndrome/microangiopathic haemolytic anemia. The patient was started on methylprednisolone 125 mg, fluids and furosemide to maintain urine output, and was administered 5 units of fresh frozen plasma (from day 2 to 6 after oxaliplatin) and 1 unit of platelet concentrate on day 5 to stop the haematuria. The patient's renal functions were rapidly deteriorating; therefore, haemodialysis was begun on day 3 with 5 sessions performed. Laboratory test for thrombotic thrombocytopenic purpura (TTP) - anti-ADAMTS13 Ab, and idiopathic thrombocytopenic purpura (ITP) - antiplatelet antibodies, came back negative which supported a final diagnosis of an acute drug-induced haemolytic anemia with thrombocytopenia (Evan's syndrome). Six days later, the patient improved and was transferred from the ICU back to a medical oncology ward. The total hospitalization time after the 2nd cycle of XELOX desensitization was 33 days. The patient remained on a tapering dose of corticosteroids (Prednisolone reduced by 5 mg per week) for a total of 5 months. Due to this event, her chemotherapy was switched to Irinotecan monotherapy until disease progression in June 2018 and further switched to Trifluridine/Tipiracil, with both regimens well tolerated. In Jan 2019, 86 months from the initial diagnosis of metastatic colorectal carcinoma (mCRC), the patient is still on Trifluridine/Tipiracil with a stable disease.

2.2. Case report 1: laboratory findings

Four hours after XELOX desentization, laboratory tests revealed significant increases in liver enzyme levels (GGT, AST, ALT), unconjugated bilirubin, circulating/free haemoglobin (Hgb) in plasma, lactate dehydrogenase (LDH) and urea, and a significant drop of both estimated glomerular filtration rate (eGFR) and platelet number (Table 1, Fig. E1a–c). Haptoglobin concentration was depleted. Proteinuria and haematuria were present. Levels of free haemoglobin, LDH, bilirubin, liver transaminases and GGT peaked next day morning (day 2) (Table 1, Fig. E1a). Laboratory signs of impairment of renal function peaked on day 3 with eGFR 0.1 (mL/min/1.73 m^2) with recovery starting on day 14 and reaching satisfactory renal function on day 160 (Table 1, Fig. E1c). Thrombocytopenia (6×10^9/L platelets) on day 1 after oxaliplatin exposure started to recover and reached normal levels on day 10 (Table 1, Fig. E1b). Haemoglobin level gradually decreased from 130 g/L at baseline to 69 g/L on day 10, with recovery from anemia in the following month (Table 1, Fig. E1b). The number of lymphocytes dropped to a grade 3 lymphopenia on day 1 and then gradually increased, peaking on day 6 (Fig. E1d). The blood smear on day 2 showed a toxic granulation, vacuolization, Döhle bodies and left shift in neutrophils; anisocytosis of RBC with teardrop cells, an insignificant number (0.3%) of schistocytes and occasional NRBCs. An increased (2–3.5%) number of schistocytes (keratocytes, helmet cells, microspherocytes) was observed in blood smears over the following days out to day 16 (Fig. E1e). Coagulation tests revealed a prolonged prothrombin time (PT-ratio 1.93), activated partial thromboplastin time (aPTT-ratio 1.27) and thrombin time (TT 28.5 s), as well as a reduced level of fibrinogen (1.4 g/L) and antithrombin (70.5%) on day 2 and normalized on day 3 except a prolonged TT and high D-dimer with an initial concentration of 147.90 mg FEU/L persisting for another week. On day 2, an anti-IgG specific direct agglutination test (DAT) was positive (2+), whereas indirect antiglobulin test (IAT; anti-RBCs Ab screen) and anti-ADAMTS13 autoantibodies were negative.

2.3. Case report 2: clinical course

A male patient, born 1957, was diagnosed with a rectal cancer with liver metastasis in Jun 2017. Following diagnosis, the patient underwent left-sided colostomy to prevent an imminent bowel obstruction and started the 1st-line chemotherapy FOLFOX/Bevacizumab,

Table 1
Dynamics of selected blood and urine parameters in the course of onset and management of oxaliplatin-related adverse event in Case 1.

	BL[1]	D1	D2	D3	D4	D5	D12	D35	D113
plasma Hgb (mg/L)	30	290	360	50	20	30	30	40	20
LDH (μkat/L)	3.4	16.0	24.7	22.2	15.8	12.0	5.3	5.0	5.7
bilirubin (μmol/L)	21	115	181	119	79	50	13	20	14
creatinine (μmol/L)	68	137	246	386	542	648	604	127	91
urea (mmol/L)	2.5	7.1	12.7	20.4	33.4	42.7	40	13.5	3.7
AST (μkat/L)	0.45	5.68	6.35	3.58	1.34	0.6	0.31	0.51	0.67
CRP (mg/L)	3.8	13.1	74.9	NA	49.8	27.8	4.0	2.7	NA
Hgb (g/L)	130	131	111	105	91	86	83	118	120
Platelets (x 10^9/L)	236	6	26	34	36	43	235	322	379
Urine Hgb	NA	3+	3+	3+	3+	3+	1+	NA	NA
Urine bilirubin	NA	1+	neg	neg	neg	neg	neg	NA	NA
Urine protein	NA	3+	2+	2+	1+	trace	trace	NA	NA

[1] BL, baseline prior to the adverse event. NA, not available.

remaining on this treatment until Nov 2017 for 5 cycles in total, resulting in a partial response in the liver. The patient underwent pelvic irradiation to keep local disease under control, a left hemihepathectomy in Jan 2018 and a Hartman resection of the primary tumour in Mar 2018. The final histology showed lymph-node positive disease (2 nodes out of 14); therefore, the patient was a candidate for post-op chemotherapy with FOLFOX that began in Apr 2018. However, the 2nd cycle of chemotherapy was complicated by a sudden rise in temperature immediately following oxaliplatin infusion, with laboratory markers of severe infection such as elevated CRP and procalcitonin, and a significant drop in platelet count as well as an increased level of creatinine and increased liver function tests (Table 2). Under a provisional diagnosis of sepsis, the patient was transferred to the ICU. Unexpectedly, the clinical presentation was somewhat different from what his laboratory results would suggest. Blood pressure as well as heart rate were within normal limits and there were no changes in quick SOFA sepsis score. Although clinical presentation was not supporting sepsis, the patient was started on antibiotics (Piperacillin/Tazobactam + Metronidazole), fluids and microbiological screening was performed. The drop in platelets was thought to be a result of possible sepsis as well as prolonged coagulation times, and 2 units of platelets were administered. The patient was thoroughly examined for potential sources of sepsis; lung X-ray was negative, CT of abdomen and pelvis was negative and surgical consult was negative. The patient was in good clinical condition, contrasting with the massively increased acute phase/sepsis laboratory parameters including procalcitonin plasma concentration. With laboratory findings of haemolysis and positive direct Coombs anti-globulin test, the provisional diagnosis of sepsis was changed to an acute drug-induced haemolytic anemia with thrombocytopenia. Splenomegaly was excluded by ultrasound. The patient was started on corticosteroids (methylprednisolone 80 mg, equal to 100 mg of prednisolone) and fresh frozen plasma as treatment for potential drug-induced HUS/TTP. Microbiological screening was negative except for coagulase-negative staphylococci contamination of the patient's i.v. port which was without clinical relevance. Antibiotics were discontinued on day 3. With steroid treatment, the patient began to improve rapidly, with renal function as well as liver function tests, procalcitonin and C-reactive protein (CRP) dropping back to normal. The patient was discharged from the ICU on tapering doses of Prednisolone. The total hospitalization time after the oxaliplatin-related adverse event was 19 days. Due to this event, further chemotherapy was put on hold. Second-line treatment with FOLFIRI was started after disease progression and was well tolerated. After further progression, the patient is now on 3rd-line monotherapy with Panitumumab.

2.4. Case 2: laboratory findings

On day 1, blood tests revealed signs of red blood cell lysis such as elevation of LDH, free haemoglobin and hyperbilirubinemia that peaked on day 3 and then dropped within a couple days (Table 2, Fig. E2a). Plasma haptoglobin was depleted. Laboratory signs of impairment of renal functions occurred on day 1 with eGFR 0.46 mL/min/1.73m^2, persisted the next 7 days, and recovered with an eGFR above 1.0 mL/min/1.73m^2 and normal levels of urea on day 16 (Table 2, Fig. E2c). Proteinuria, hematuria and bilirubinuria were present (Table 2). Loss of proteins peaked on day 4 with total plasma protein 52 g/L and albumin 23 g/L. Levels of acute phase proteins peaked on day 1 with CRP 97 mg/L and procalcitonin > 100 microg/L and dropped gradually within the following week. The levels of liver enzymes were not substantially affected. Haemoglobin level dropped on day 7 and recovered during the following month (Table 2, Fig. E2b). Thrombocytopenia peaked on day 3 and returned to normal on day 12 (Table 2, Fig. E2b). A rapid recovery of platelet number on day 13 was preceded by an elevated (30%) fraction of immature platelets (IPF). The number of lymphocytes dropped to grade 3 lymphopenia on day 1 and then gradually increased to mild lymphocytosis on day 8 (Fig. E2d). Blood smears from day 2 to day 10 showed toxic granulation, vacuolization and Döhle bodies in neutrophils and a prevalence of schistocytes (17–24%) (Fig. E2e); from day 4, the presence of reactive lymphocytes and lymphocytes with plasmocytoid morphology was observed (Fig. E2f). Likewise, the white blood cell scattergram revealed the presence of atypical plasmocytoid lymphocytes and flow cytometry showed activation of T-cells and B-cells (Fig. E2f–h). Erythrocytic mean corpuscular volume (MCV) decreased compared to baseline up to day 6 due to presence of a substantial amount of fragmented red blood cells, with macrocytosis occurring on day 35. Reticulocytosis occurred on day 10. Coagulation tests were mildly prolonged (PT, aPTT, TT), levels of fibrinogen and antithrombin mildly reduced, and D-dimer elevated up to

Table 2
Dynamics of selected blood and urine parameters in the course of onset and management oxaliplatin-related adverse event in Case 2.

	BL[1]	D1	D2	D3	D4	D5	D12	D35	D109
Plasma Hgb (mg/L)	20	210	450	590	90	50	20	20	30
LDH (μkat/L)	3.6	16.1	17.6	26.8	27.4	19.5	10.0	4.0	3.5
bilirubin (μmol/L)	6	35	49	51	33	22	8	7	5
creatinine (μmol/L)	56	217	189	161	193	236	125	72	69
urea (mmol/L)	4.8	16.4	15.6	12.4	19.2	22.5	11.4	9.4	6.6
AST (μkat/L)	0.33	1.04	1.04	1.42	1.23	NA	0.4	0.37	0.31
CRP (mg/L)	3.1	91.4	68.9	37.6	21.2	NA	4.0	3.4	2.9
procalcitonin (μg/L)	NA	> 100	98.12	53.95	39.71	22.33	NA	NA	NA
Hgb (g/L)	116	102	87	102	99	91	84	122	135
Platelets (x 10^9/L)	164	23	24	2	4	64	180	173	216
Urine Hgb	NA	3+	NA	NA	3+	3+	1+	NA	NA
Urine bilirubin	NA	1+	NA	NA	neg	neg	neg	NA	NA
Urine protein	NA	3+	NA	NA	3+	3+	neg	NA	NA

[1] BL, baseline prior to the adverse event. NA, not available.

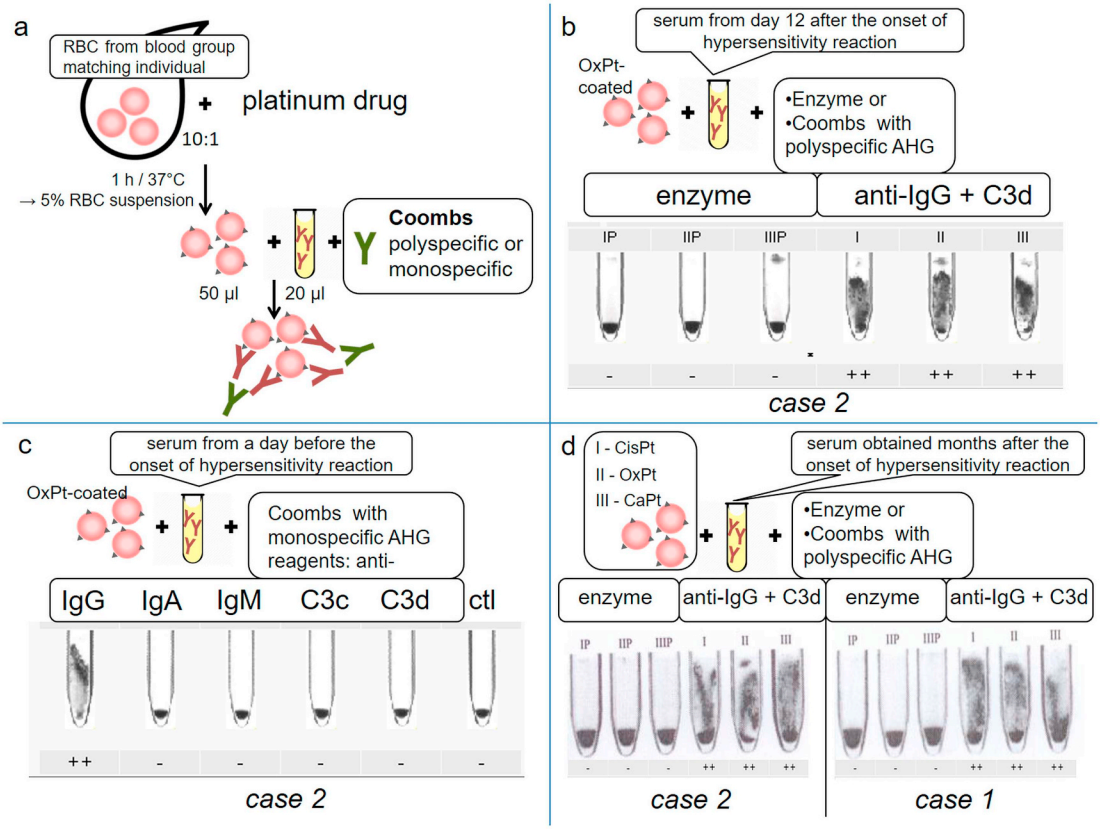

Fig. 1. Coombs testing of the oxaliplatin-induced antibodies.
(a) Schematic description of Coombs testing of patients' serum and platinum-coated RBCs and Coombs testing performed in b–d. Blood-group matching RBCs for coating were randomly selected. Oxaliplatin (Teva, 5 mg/ml), Cisplatin (Ebewe, 1 mg/ml), Carboplatin (Accord, 10 mg/ml). (b) Positive reaction of the case 2 serum from day 12 and oxaliplatin-coated RBCs in the AHG test but not enzyme test (performed in triplicates) in ID-Card (BIO-RAD, Id-n°: 50581). (c) Reaction of the case 2 serum from the day preceding the hypersensitivity reaction, and oxaliplatin-coated RBCs in monospecific AHG reagents in ID-Card (BIO-RAD, Id-n°: 50830). (d) Positive reaction of the case 2 and case 1 serum obtained 6 and 12 months, respectively, after the onset of hypersensitivity and cisplatin (CisPt, I), oxaliplatin (OxPt, II), or carboplatin (CaPt, III)-coated RBCs in the AHG test but not enzyme test (BIO-RAD, Id-n°: 50581).

36.6 mg FEU/L on days 1 and 2. Anti-ADAMTS13 autoantibodies were measured on day 4 and were negative. Type I hypersensitivity was excluded by a negative skin prick test with oxaliplatin and a negative *in vitro* flow cytometric evaluation of basophil activation by oxaliplatin, both performed on day 12, and by the clinical presentation of the adverse event. Polyspecific DAT was positive (2+), IAT (anti-RBCs Ab screen) was negative. Patient serum obtained on day 12 revealed positive reactions with both i) the patient's RBCs (1+) and ii) oxaliplatin-coated RBCs (2+) in polyspecific AHG test (Fig. 1a,b). Moreover, the patient's serum, obtained the day before the 2nd cycle of rechallenged FOLFOX and analyzed retrospectively, revealed a positive reaction (2+) with oxaliplatin-coated RBCs in a monospecific anti-IgG Coombs test (Fig. 1c). Additionally, we performed Coombs test with RBCs coated with oxaliplatin, carboplatin or cisplatin and serum obtained 6 months after hypersensitivity reaction in case 2 and 12 months in case 1 and showed long-term presence of antibodies against RBCs coated with all examined platinum preparations.

3. Discussion and conclusions

We have described 2 cases of potentially fatal complications caused by oxaliplatin-induced acute haemolytic anemia with thrombocytopenia and an acute kidney injury in metastatic colorectal cancer patients. In both cases, a coagulation cascade was activated, demonstrated by prolonged coagulation times as well as an increased level of D-dimer and therefore TTP/drug-induced HUS/microangiopathic haemolytic anemia (MAHA) were included in the initial differential diagnosis. Results from testing for anti-ADAMTS13 autoantibodies came back within normal limits, thus making diagnosis of TTP less likely. Both patients tested negative for anti-platelet antibodies. However, the detection of anti-platelet antibodies is of uncertain diagnostic value for drug-induced immune thrombocytopenia [12]. On the other hand, both patients tested positive for a direct anti-globulin Coombs test, supporting the diagnosis of oxaliplatin-induced immune-mediated haemolytic anemia. Both patients were started on corticosteroids as soon as a suspicion for immune-mediated haemolysis was raised. Besides that, fresh frozen plasma was administered, both to maintain coagulation factors within normal limits and as a basic treatment for TTP/atypical HUS, although a suspicion of the latter was rather minor. In both patients, corticosteroids showed an immediate effect on haemolysis both clinically and in laboratory tests. Similar clinical symptoms and laboratory findings could have been caused by microangiopathic haemolytic anemia, especially in patients with advanced cancer; however, the acute onset of symptoms and immediate effect of corticosteroid treatment ruled out MAHA.

The first symptoms in case 1 were jaundice and haemoglobinuria, which were originally thought to be a result of both liver injury and thrombocytopenia. The patient in case 2 presented initially with symptoms of systemic inflammatory response syndrome with low platelets. Subsequently both patients developed a detectible level of acute kidney injury (AKI) which required treatment with haemodialysis in case 1. Cases of fatal renal failure as the result of acute drug-induced immune haemolytic anemia have been reported [13,14]. The AKI in both patients was predominantly caused by the nephrotoxic action of haemoglobin protein complexes, heme proteins and heme resulting from haemolysis [15]. It is of note that in case 2, the procalcitonin level

of > 100 μg/L on day 1 contributed to a provisional diagnosis of sepsis not supported by the clinical status of the patient. A substantial elevation of procalcitonin (frequently above > 10 μg/L) in non-septic patients with acute kidney injury has been recently published [16], possibly connecting a massive inflammatory response to the pathogenesis of AKI. Further, the laboratory tests confirmed haemolytic anemia secondary to oxaliplatin administration. Typical laboratory findings of RBC lysis, but not of sepsis, such as hyperbilirubinemia, elevated free haemoglobin level and substantially elevated LDH, were observed in both patients and suggested intravascular haemolysis. In real-life practise, however, it may be difficult to distinguish an artificial haemolysis caused by an improper blood draw from an intravascular haemolysis, as both events would result in free heamoglobin and LDH elevation. However, since free haemoglobin is removed from the circulation under conditions of intravascular heamolysis, its elevation in plasma is lower than expected in artificial haemolysis conditions, where we expect that haemolysis quantified as an increment of 100 mg/L of circulating haemoglobin will result in a corresponding increase in LDH equal to 0.2 μkat/L [17]. Thus, in both patients, a massive increase in LDH with disproportionally mild increase in free haemoglobin level was suggestive of intravascular haemolysis, as subsequently confirmed by the depleted haptoglobin.

Pathophysiologically, the triggers of these severe adverse events were oxaliplatin-induced immunopathology reactions. Both patients experienced their hypersensitivity reactions following the 2nd cycle of oxaliplatin rechallenge that was administered 27 months in case 1 and 6 months in case 2 after the first administration of oxaliplatin. The first patient (case 1) had a history of mild hypersensitivity reaction to oxaliplatin and so the drug had been administered in a desensitization manner without any typical IgE-related symptoms. However, the course of adverse events and anti-IgG positive DAT suggested development of type II hypersensitivity to oxaliplatin. Case 1 resembles a previously published clinical case of combined hypersensitivity, since type I anaphylaxis preceding type II haemolytic anemia and thrombocytopenia has been reported for administration of carboplatin in a desensitization regimen [18]. In the latter In case 2, the hypersensitivity symptoms occurred unpredictably. The development of immunopathologic reaction was accompanied by the activation of neutrophils, T- and B-cells, and by the presence of plasmocytoid cells in peripheral blood. Extended examination by skin prick test and basophil activation test in this patient excluded IgE-mediated hypersensitivity to oxaliplatin. On day 12, the patient's serum revealed a mild positive reaction with the patient's RBC in the AHG test phase, suggesting the presence of oxaliplatin-triggered antigen on the RBC membrane sometime after the last exposure to oxaliplatin. Importantly, an IgG-specific reaction of the patient's serum from the day before the 2nd cycle of rechallenged FOLFOX and oxaliplatin-coated RBCs defined the source of type II hypersensitivity reaction and confirmed that the immunopathologic IgG antibodies were present in the patient's circulation prior to the rapid onset of the oxaliplatin-induced adverse event and were likely produced upon the 1st cycle of rechallenged FOLFOX. In IgG-mediated AIHA, we would expect predominantly extravascular haemolysis by macrophages, with RBC destruction and sequestration occurring mainly in the liver and the spleen. IgG, however, is also capable of fixing complement which enhances its haemolytic ability and thereby enables haemolysis in the intravascular space, potentially stimulating coagulation and fibrinolysis [19]. Here we also showed that oxaliplatin-induced antibodies remained in the circulation for many months after the onset of hypersensitivity reaction making repeated treatment with oxaliplatin impossible. Moreover, we proved that these persistent antibodies elicited cross-reactivity with other platinum drugs, namely cisplatin and carboplatin. Importantly, this is to our knowledge the first report on IgG cross-reactivity to platinum drugs. Thus patients sensitized to oxaliplatin may be at risk when exposed to other platinum agents not only in terms of IgE-mediated allergic reactions [20,21] but also in terms of IgG-mediated type II hypersensitivity. Taken together, for our two cases of Evan's syndrome after oxaliplatin rechallenge, we conclude that the reactive entity was an IgG drug-dependent antibody that was present in the circulation prior to the onset of hypersensitivity to oxaliplatin, persisted for months and elicited cross-reactivity with other platinum agents.

In medical oncology practice, rechallenge with platinum agents is an alluring option, especially in patients where all other standard drugs had been used and the patient is still in a good shape and willing to undergo further treatment [22,23]. Accordingly, oxaliplatin in Case 1 patient was kept until serious complications with Evan's syndrome developed. The rationale behind rechallenging oxaliplatin was an excellent effect and the fact that she had never progressed on it. The previous minor allergic reaction was considered not serious. Moreover, we have learned both from clinical experience and the literature that rechallenge with oxaliplatin is accompanied by frequent allergic reactions [1] that may be managed using a desensitization protocol [6]. Nevertheless, the oxaliplatin-driven non-type I hypersensitivity immune reactions are especially worrisome because we have limited tools to predict and prevent them. They are unlikely to be prevented by desensitization protocols and may be overlooked or confused with other acute conditions. The onset can be sudden, immediately following infusion; thus, patients treated with oxaliplatin, especially those on long-term therapy or when rechallenged, should be watched carefully [4]. Patients with unusual symptoms and/or laboratory tests following oxaliplatin infusion must be tested in stepwise manner to exclude immune-mediated life-threatening conditions including haemolytic anemia with thrombocytopenia and systemic inflammatory response syndrome, both potentially resulting in multiple organ failure. To reveal immediate features of haemolysis after oxaliplatin administration, a urine dipstick for haemoglubinuria or biochemical tests for haemolysis, such as LDH levels with free haemoglobin concentration, should be considered. If these features of heamolysis are present, haptoglobin level needs to be evaluated to confirm the presence of intravascular haemolysis. Further, complete blood count would reveal the status of thrombocytopenia. Finally, immediate accessibility to direct anti-globulin Coombs test DAT results (within 1–2 h) would support correct diagnoses and potentially save patients' lives. Future studies may reveal whether actively testing for drug-dependent antibodies among patients on long-term/rechallenged oxaliplatin therapy can predict increased risk of oxaliplatin-induced AIHA [24].

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Declarations

Ethics approval and consent to participate.

The study was performed in compliance with the Declaration of Helsinki and informed consent was obtained from both patients.

Consent for publication

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Authors' contributions

JV diagnosed and treated the patients at ICU, conceived the study, co-designed immunohaematology/serology testing, contributed to data interpretation, drafted and approved the manuscript. ST treated the patients at the medical oncology ward, contributed to the diagnosis, contributed to data interpretation, drafted and approved the manuscript. IK treated the patients at the outpatient oncology ward, contributed to data interpretation, drafted and approved the manuscript. LF performed haemalogy and flow cytometry analysis, contributed to figure preparation, drafted and approved the manuscript. JN performed skin prick testing, contributed to data analysis and interpretation, drafted and approved the manuscript. LZ-D performed laboratory data collection, co-designed immunohaematology/serology testing, contributed to figure preparation, contributed to data analysis and interpretation, drafted and finalized the manuscript.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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