Ann Surg Oncol (2013) 20:3919–3926
DOI 10.1245/s10434-013-3099-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Hemophagocytic Syndrome: An Unusual and Underestimated Complication of Cytoreduction Surgery with Heated Intraperitoneal Oxaliplatin

Lilian Schwarz, MD[1], Valerie Bridoux, PhD[1], Benoit Veber, PhD[2], Eric Oksenhendler, PhD[3], Vincent Royon, MD[4], Francis Michot, PhD[1], and Jean-Jacques Tuech, MD, PhD[1]

[1]Department of Digestive Surgery, Hôpital Charles Nicolle, Rouen Cedex, France; [2]Surgical Intensive Care Unit, Hôpital Charles Nicolle, Rouen Cedex, France; [3]Department of Clinical Immunology, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, University Paris Diderot, Paris, France; [4]Department of Anaesthesiology, Hôpital Charles Nicolle, Rouen Cedex, France

ABSTRACT

Background. Hyperthermic intraperitoneal chemotherapy (HIPEC) improves the survival of select patients with peritoneal carcinomatosis. Hemophagocytic syndrome (HS) is a rare and potentially fatal disease. We describe our experience with five patients who developed HS following oxaliplatin HIPEC and propose a management procedure.

Methods. Hyperthermic intraperitoneal chemotherapy was performed using the open-abdomen technique (43 °C) with oxaliplatin (460 mg/m^2) for 30 min. If thrombocytopenia occurred from days 5 to 14, heparin-induced thrombocytopenia was evaluated. For thrombocytopenia with unknown etiology, we performed a bone marrow analysis (BMA). A BMA indicating HS stimulated an extensive infectious disease workup. Herein, we describe "reactive septic HS" and HS of unknown origin.

Results. We documented five patients with HS as a result of severe thrombocytopenia. Underlying infections were present in two patients who were treated with antibiotics and survived. For the remaining three patients, we found no underlying etiology of HS; multidisciplinary staff adapted the clinical management daily. Two patients died on postoperative days 40 and 29. The third patient survived after several operations and treatment with the VAC abdominal dressing system.

Conclusions. We present these cases to ensure that physicians are aware of the symptoms of HS after HIPEC, which are important for initiating immediate life-saving therapy. This condition is a diagnostic and therapeutic emergency. When HS complicates HIPEC, aggressive, early medical, and surgical management is required. However, the optimal management has not been defined.

First Received: 29 April 2013;
Published Online: 10 July 2013

J.-J. Tuech, MD, PhD
e-mail: jean-jacques.tuech@chu-rouen.fr

Complete cytoreduction surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) is a new standard of treatment for select patients with peritoneal tumor seeding.[1–4] It is an aggressive surgical approach with morbidity and mortality rates of 12–52 and 0.9–5.8 %, respectively.[5] These outcomes are similar to those of major gastrointestinal surgeries.[6] Infectious and hematological complications can occur after HIPEC, and the severe hematological complication rate can reach 48 %.[7] Severe thrombocytopenia may play a role in postoperative hemorrhage.[8,9]

In our experience, 5 patients developed hemophagocytic syndrome (HS), which induced thrombocytopenia after HIPEC. HS is a rare and potentially fatal disease. We report our experience and propose a procedure for the medical and surgical management of HS.

MATERIALS AND METHODS

Treatment

The peritoneal cancer index (PCI) was used to score the extent of peritoneal involvement.[10] CRS aimed to remove all evidence of tumor.[11] HIPEC was performed by the

open-abdomen technique at 43 °C with oxaliplatin (460 mg/m^2) for 30 min. All patients received a similar concentration of the drug.[12] The SunChip (Gamidatech, Eaubonne, France) was used. We administered intravenous leucovorin and 5-FU 1 h before HIPEC. The completeness of cytoreduction (CCR) was classified following surgery.[10] Patients received antibiotics every 2 h during surgery.

Postoperative Follow-up

Postoperatively, patients were admitted to the intensive care unit (ICU). No antibiotics were routinely administered after surgery. Fractionated heparin was used as prophylaxis. A laboratory evaluation including a complete blood count (CBC) and metabolic panel was performed 2× per day during the first 3 days and then daily for 7 days.

Hematological Monitoring

We conducted laboratory tests for: CBC, liver enzymes, renal function, B_{12} levels, folic acid levels, LDH, fibrin degradation products, fibrinogen, erythrocyte sedimentation rate, and peripheral blood smear. If the platelet count dropped between days 5 and 14, heparin-induced thrombocytopenia was evaluated.

If the thrombocytopenia etiology was unclear, bone marrow analysis (BMA) was recommended. When the results were uninformative and persistent hematologic disorders were present, BMA was repeated. If hemophagocytosis was observed, HS was suspected. The HS diagnostic criteria were revised in 2004 (Table 1).[13] The minimal diagnostic requirements included: CBC, liver enzymes, bilirubin, triglycerides, ferritin, and a coagulation profile, including fibrinogen.

TABLE 1 Clinical and laboratory criteria for reactive hemophagocytic syndrome; 5 of the 8 criteria are needed to confirm the diagnosis

1.	Fever
2.	Splenomegaly
3.	Cytopenia
	Hb < 9 g/dL
	Pl < 100 × 10^9/L
	Neutrophils < 1 × 10^9/L
4.	Hypertriglyceridemia and/or hypofibrinogenemia
	Fasting triglycerides > 3 mmol/L
	Fibrinogen < 1.5 g/L
5.	Ferritin > 500 mg/L
6.	sCD25 > 2400 U/mL
7.	Decreased or absent NK-cell activity
8.	Hemophagocytosis in bone marrow analysis

Adapted from Ref.[13]

An extensive workup was performed to exclude a sepsis-related cause. Focal infections were diagnosed using clinical, microbiological, and radiological findings. After an HS diagnosis was established, the multidisciplinary staff adapted the management daily according to medical and hematological test results.

Platelet toxicity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events: grade III, 25,000–49,999/mm^3; grade IV, <25,000/mm^3.[14] "Reactive septic HS" was defined as HS secondary to bacterial infection. HS of unknown origin was termed "post-HIPEC HS."

RESULTS

Of the 98 patients who underwent CRS + HIPEC between March 2006 and June 2012, 5 patients developed HS. An underlying infection was present in 2 patients (reactive septic HS); the remaining 3 were diagnosed as having post-HIPEC HS. HS was confirmed in all 5 patients. A repeat BMA was required for 1 patient. Normocellular or hypercellular bone marrow was associated with characteristic histiocytes and erythrocyte and platelet phagocytosis (hemophagocytosis) (Tables 2, 3). The clinical features and laboratory findings are shown in Table 1. Platelet counts were evaluated over time, and grade III and IV platelet toxicity was observed (Fig. 1).

Clinical Outcome

Two Patients Presented Reactive Septic HS On postoperative day (POD) 4, patient 4 (October 2010) exhibited respiratory deterioration and septic shock. The bacteriological analysis revealed that a polymicrobial pulmonary infection was responsible for the clinical presentation, and broad-spectrum antibiotics were administered. The evolution was favorable until POD 12, when hemorrhagic and septic shock appeared with an initial abdominal presentation. The platelet level was ~40,000/mm^3.

Emergency laparotomy revealed parietal arterial bleeding. Culture of an intra-abdominal hematoma demonstrated *Enterococcus faecalis* and anaerobic Gram-positive bacilli. We reintroduced vasopressor drugs to treat the hemodynamic instability and extended the antibiotic therapy.

Thrombocytopenia (18,000/mm^3) and anemia (Hb 7.4 g/dL) resistant to transfusion persisted after 2 weeks in the ICU, despite the elimination of heparin-induced thrombocytopenia and the cause of the deficiency. BMA was performed on POD 16, and hemophagocytosis was extensively observed. The clinical evolution was favorable after 34 days in the ICU, during which multiple iterative platelet and red blood cell transfusions and prolonged antibiotic therapy were administered.

TABLE 2 Patient-related oncological and surgical data

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	59	68	48	54	63
Sex (M/W)	W	M	W	M	M
CRS with HIPEC indication	Colon adenocarcinoma	PMP	PMP	Colon adenocarcinoma	Colon adenocarcinoma
Previous oxaliplatin-based chemotherapy	No	No	No	No	No
Surgical resection	Peritonectomy Partial gastrectomy Cholecystectomy Bilateral ovariectomy Omentectomy	Peritonectomy Omentectomy Right hemicolectomy	Peritonectomy Omentectomy Cholecystectomy Posterior pelvectomy Right hemicolectomy	Peritonectomy Omentectomy Low rectal resection Right hemicolectomy	Peritonectomy Omentectomy Cholecystectomy Sigmoidectomy Small bowel resection Splenectomy Prostatectomy
PCI	2	17	16	13	4
CCR	0	0	0	0	0
HIPEC drug schedule	Oxaliplatin	Oxaliplatin	Oxaliplatin	Oxaliplatin	Oxaliplatin
Operative duration (h)	5.7	9	8.5	8	9.5

On POD 5, patient 5 (November 2011) exhibited isolated thrombocytopenia (48,000/mm^3). BMA confirmed hemophagocytosis. A perioperative bacteriological analysis of the abdominal cavity rinsing liquid after HIPEC was positive for *Pseudomonas aeruginosa*. Despite the introduction of adapted antibiotic therapy, the patient progressed to septic shock. Radiological investigations found no etiology, but repeated blood cultures identified multi-drug-resistant *Enterobacter cloacae*. Hemorrhage was not observed. Repeated platelet transfusions and prolonged adapted antibiotic therapy were administered. The clinical evolution was favorable after 34 days in the ICU.

Three Patients Presented Post-HIPEC HS For patient 1 (November 2006), the first 48 h postoperative in the ICU were uneventful. On POD 4, the patient progressed to hemorrhagic shock associated with severe thrombocytopenia (18,000/mm^3). Abdominopelvic CT indicated diffuse peritoneal effusion with subcapsular liver hematoma. Emergency laparotomy was performed, and diffuse bleeding was observed and treated with packing. Depacking was performed 3 days after optimization of the coagulation parameters.

After 1 week in the ICU, severe thrombocytopenia resistant to iterative platelet and red blood cell transfusions persisted. An initial BMA was performed on POD 7, without diagnosis. On POD 10, a second BMA revealed hemophagocytosis. On POD 12, fever and multiorgan failure were observed, and laparotomy was performed. Intraoperative bacteriological sampling isolated two multi-drug-resistant bacteria: *Enterococcus faecium* and coagulase-negative *Staphylococcus*. After 15 days of sepsis stabilization and persistent refractory thrombocytopenia (34×10^9/L), the patient was reoperated for a bleeding anastomotic ulcer following the failure of endoscopic treatment on POD 39. After laparotomy, the multiorgan failure worsened with the onset of acute respiratory distress syndrome and severe intra-alveolar bleeding; the patient died on POD 40.

Patient 2 (October 2007) presented with hemodynamic impairment and renal failure during the postoperative follow-up in the ICU. On POD 5, severe thrombocytopenia was observed (19,000/mm^3), which clinically manifested as repeated moderate hemoptysis. BMA revealed hemophagocytosis on POD 7.

Intravenous immunoglobulin and platelet transfusion were used unsuccessfully. On POD 8, because of prolonged isolated fever, severe thrombocytopenia (4,000/mm^3), and anemia (Hb 7.9 g/dL), thoraco-abdominal CT was performed. A subcapsular liver hematoma was observed and was associated with intra-abdominal effusion. Blood products were transfused with unsatisfactory results. After an initial clinical improvement, the patient progressed to septic shock on POD 17, and radiological exploration demonstrated intra-abdominal effusion, with multiple intra-abdominal collections corresponding to hematomas. Because of the unfavorable clinical evolution, severe thrombocytopenia, progression to multiorgan dysfunction, and high risk of laparotomy due to the delay from the initial operation, supportive care was provided, and the patient died on POD 23.

TABLE 3 Postoperative and hematological characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Period of onset of thrombocytopenia (days)	4	7	5	6	7
Cause of HS	Post-HIPEC	Post-HIPEC	Post-HIPEC	Reactive septic	Reactive septic
Clinical manifestations at the onset of HPS					
Fever	+	+	+	+	+
Hepatomegaly	−	+	−	−	+
Splenomegaly	+	+	+	+	+
Jaundice	−	+	−	−	+
Skin rash	−	−	+	−	−
Laboratory findings at the onset of HPS					
WBCs (μL)	1880	950	1510	1040	1880
Neutrophils (μL)	1711	513	1072	874	1621
Hb (g/dL)	9.6	7.8	7.2	8.9	9.8
Plt ($\times 10^5$/mL)	18	4	25	36	27
LDH > 2 × upper limit	+	+	+	+	+
Ferritin > 1,000 ng/mL	+	NA	+	+	+
FDP > 10 μg/mL	+	+	+	+	+
Fibrinogen < 1.5 g/L	+	+	+	+	+
Bone marrow findings					
Cellularity	N	N	H	N	H
Histiocytes ($10 < N < 30$ %)	0.57	0.36	0.49	0.34	0.41
Histiocytes with ingested nuclei	+	+	+	+	+
Treatment for HS					
Antibiotic drugs	+	+	+	+	+
?-globulin	−	+	−	−	−
Clinical outcome					
Remission	−	−	+	+	+
Death	+	+	−	−	−

WBC white blood cell count, *Hb* hemoglobin level, *Plt* platelet count, *LDH* lactate dehydrogenase level, *FDP* fibrin degradation product level, *mPSL*, methylprednisolone, *G-CSF* granulocyte colony-stimulating factor

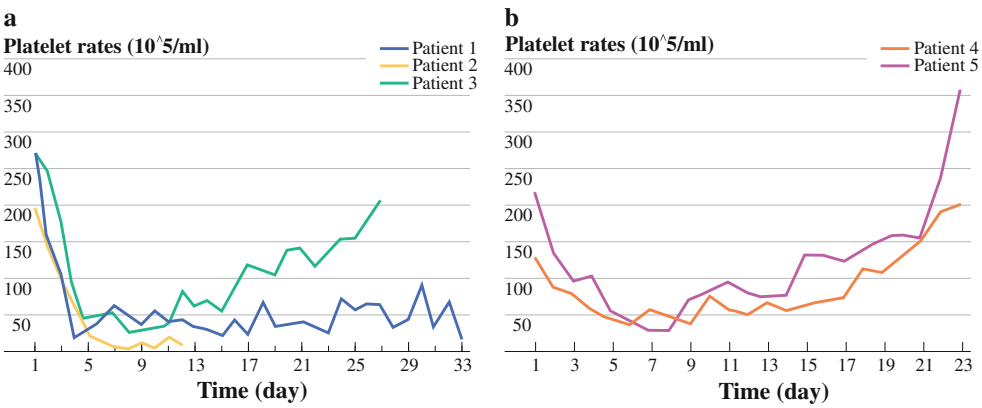

FIG. 1 Platelet curves. **a** Post-HIPEC HS. **b** Septic HS

On POD 5, patient 3 (October 2011) exhibited sudden arterial hypotension, with bleeding through the abdominal drain, and biologically severe thrombocytopenia (25,000/mm^3) and anemia (Hb 7.2 g/dL). BMA revealed HS. Laparotomy identified hemoperitoneum with diffuse intra-abdominal bleeding. Packing was performed. Two laparotomies were performed with packing because of persistent bleeding on PODs 7 and 9. Based on our previous experience and the high risk of repeated laparotomy and untreatable abdominal sepsis, the VAC abdominal

dressing system was used on POD 9. Intra-abdominal fluid samples were cultured during each VAC application, which led to adapted antibiotic therapy through POD 51. Platelet and coagulation indices were supported with blood product and platelet transfusions. Normalization of the platelet count was observed on POD 16. On POD 34, a definitive abdominal closure was performed, without sepsis recurrence. The clinical evolution was favorable after 54 days in the ICU.

DISCUSSION

Thrombocytopenia is a frequent toxic complication of systemic oxaliplatin therapy in up to 70 % of patients.[15] The reported incidence of grade III or IV platelet toxicity following CRS with heated intraperitoneal oxaliplatin is <10 %.[16,17] Although myelosuppression is recognized as the main cause of oxaliplatin-related thrombocytopenia during systemic treatment, the mechanism following HIPEC remains unclear. Elias et al.[8], in a pharmacokinetic study of increasingly hypotonic solutions of heated intraperitoneal oxaliplatin, reported a high incidence of unexplained postoperative peritoneal bleeding and unusually severe thrombocytopenia. Of 8 patients in the hypotonic solution group, 4 developed severe thrombocytopenia with peritoneal bleeding on POD 4. These presentations are similar to our idiopathic HS patients. However, Elias did not report BMA results. These cases of thrombocytopenia occurred too early to be related to bone marrow toxicity. Elias suggested that thrombocytopenia could be secondary to immunoallergic toxicity.[8]

Unusual cases of immune-mediated severe thrombocytopenia and bleeding symptoms have been described in patients treated with intravenous oxaliplatin.[18–20] Drug-dependent antibodies can be formed after exposure to oxaliplatin and react with thrombocytes. The most common oxaliplatin-induced antiplatelet antibodies act against glycoprotein IIb/IIIa.[21] In our series, drug-dependent platelet antibodies were not evaluated. Interestingly, none of our patients were previously exposed to oxaliplatin.

However, an immunoallergic reaction cannot explain all hematological complications after CRS and HIPEC. The CHIPOVAC study was designed to evaluate the morbidity of HIPEC using oxaliplatin for advanced ovarian carcinoma.[9] The trial was prematurely closed because of an unacceptably high reoperation rate for peritoneal hemorrhage (9 of 31 patients, 29 %). A total of 13 emergency laparotomies were performed on 9 patients for intra-abdominal bleeding from POD 3–12. The median platelet level for these 9 patients was 88,500/mm^3 (54,000–191,000/mm^3). The delay of hemorrhage occurrence was comparable to that observed in our patients, but the platelet level was lower in our series. No BMA results were provided.

Among the etiologies of thrombocytopenia of undetermined origin, HS is a rare and potentially fatal disease. Two different types of HS have been described: genetic (primary) and acquired (secondary). Genetic HS was not the subject of this study. Classically, the etiologies of acquired HS include immunologic activation, systemic infection (viruses, bacteria, and protozoa), autoimmune disorders, medication, and underlying malignancy.[22] We believe that acquired HS could be caused by the combination of aggressive treatments for carcinomatosis (CRS, intraperitoneal oxaliplatin, and hyperthermia).

Hemophagocytic syndrome may be caused by excessive concentrations of inflammatory cytokines and organ infiltration by activated lymphocytes and histiocytes.[23,24] Hypercytokinemia promotes the activation of T-lymphocytes, macrophages, and histiocytes, leading to induction of the activated cytokine network, including interferon gamma (INF-γ), various interleukins (ILs) (IL-12, IL-18, IL-6, and IL-1) and tumor necrosis factor-alpha (TNF-α).

IL-1 and IL-6 induce fever. High levels of TNF-α and INF-γ and hemophagocytosis lead to pancytopenia. TNF-α inhibits lipoprotein lipase, leading to elevated triglyceride levels. Activated macrophages secrete ferritin and plasminogen activator, which increase plasmin levels and induce hyperfibrinolysis. Organ infiltration by activated lymphocytes and histiocytes leads to hepatosplenomegaly and increased liver enzymes and bilirubin.

Uncontrolled hyperinflammation can lead to neutropenia, bacterial and fungal infections, and multiorgan failure, and the survival rate is <50 %.[13] The risk increases after CRS because of the risk of postoperative bleeding favored by thrombocytopenia, leading to hematoma development, which promotes bacterial growth. To our knowledge, post-HIPEC HS has not been reported.

Challenged by severe and acute thrombocytopenia after CRS and HIPEC, surgeons and anesthesiologists must consider a diagnosis of HS and appraise the patient's medical situation immediately. The diagnostic criteria have been revised (Table 1).[13] The minimal diagnostic requirements include a CBC, liver enzymes, bilirubin, triglycerides, ferritin, and a coagulation profile, including fibrinogen. Patients should also undergo BMA; repeat examinations may be required because hemophagocytosis is often initially absent.

Treatment for HS must be established immediately because early therapeutic intervention may improve prognosis. However, there is no consensus or recommendation regarding treatment because of the rarity of this syndrome and patient heterogeneity.

We describe two types of HS following HIPEC in this article. Similar management must be initially performed in the ICU, and the fluid and electrolyte balance must be optimized. Organ failure is treated with specific

supplementation. Coagulation disorders may require adapted therapy and repeat transfusions of blood cell products. Patients should be screened for underlying infections.

Reactive Septic HS

Similar to what was found by previous reports, the incidence of hemophagocytosis in thrombopenic patients with severe sepsis was 52–64 %.[25,26] Multiorgan dysfunction and infection are independent risk factors of hemophagocytosis, although 60–70 % of septic reactive HS cases will regress with adapted antibiotic therapy and control of organ failure.[25,27] For the most serious patients with multiple organ failure, specific immune and cytotoxic treatment should be discussed.

Post-HIPEC HS

In our study, the origin of HS was a component of CRS and oxaliplatin HIPEC. Thus, treatment of the baseline origin of HS was impossible. Treatment aims to reduce the inflammatory response and control cell proliferation, using immunomodulatory or immunosuppressive cytotoxic products. Cytokine control plays a key role in HS treatment. Steroids and other immunosuppressants have

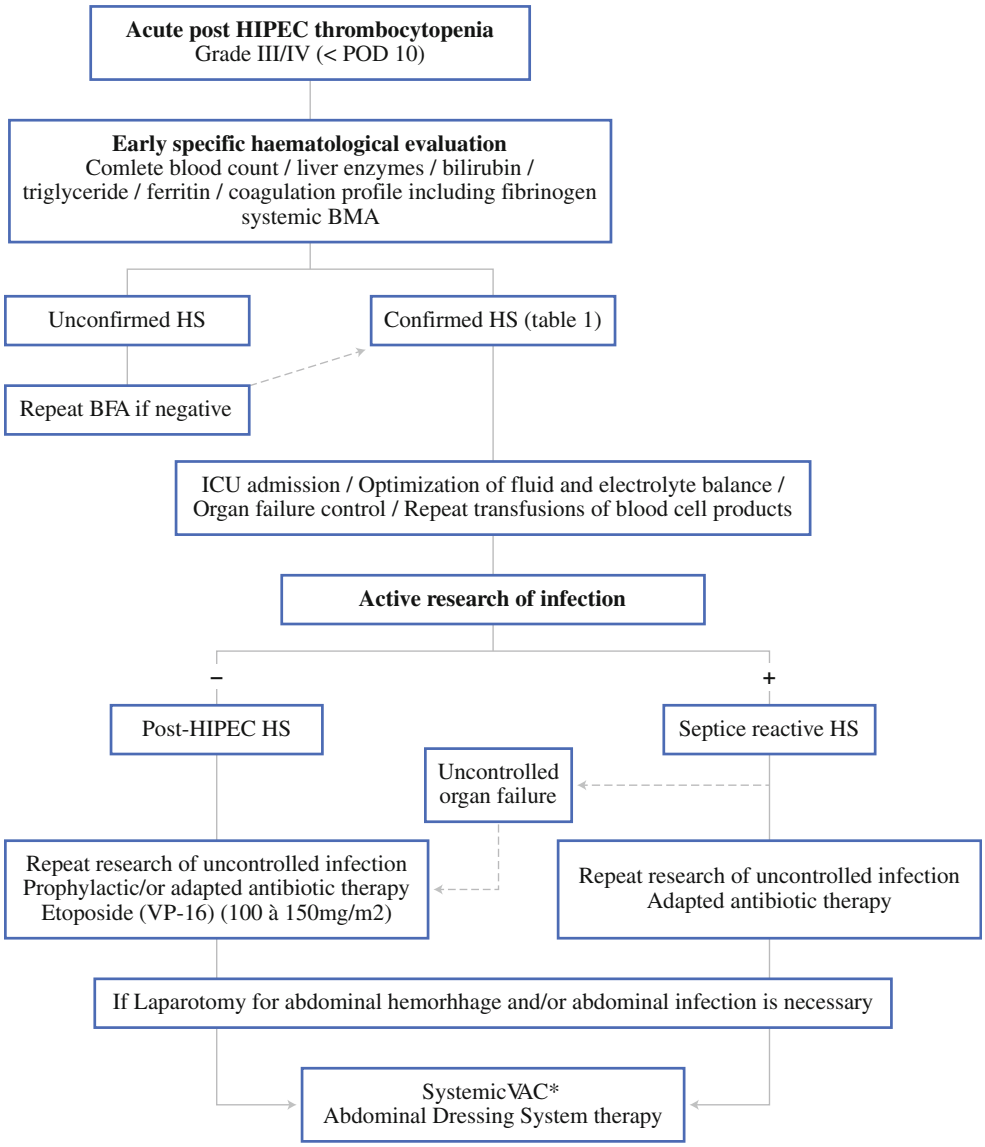

FIG. 2 Proposal of algorithm for the "de principe" management of HS after CRS with HIPEC. *BMA* bone marrow analysis, *HS* hemophagocytic syndrome, *POD* postoperative day

conventionally been applied to suppress the inflammatory response, combined with baseline disease treatment. These treatments are cytotoxic to lymphocytes and inhibit cytokine production and dendritic cell differentiation.[13,22,27–29]

However, these drugs may aggravate or facilitate severe infections and increase surgical morbidity, including anastomotic leaks. Fearful of these complications and risks, these treatments were not used in our series.

After analyzing the available literature, etoposide appears to be the cornerstone of HS-specific treatment. Etoposide is highly active, with a cytotoxic compound selective for the monocytic lineage. As proof of its efficiency in the treatment of Epstein-Barr virus-associated HS, 1 study demonstrated that the early introduction of etoposide-based regimens was the only significant variable for survival, with a 14-fold higher relative risk of death for patients who did not receive etoposide or received it >4 weeks after diagnosis.[30] The administration of intravenous immunoglobulin or plasmapheresis was also proposed to treat HS secondary to severe infections, with a lack of evidence; however, some success has been recorded.[31]

In our experience, patients with HS required laparotomy and often relaparotomy. After HIPEC, laparotomy can be difficult, risky, and sometimes impossible (patient 2) if performed late in the course after the first procedure. If abdominal sepsis occurs and surgical treatment is not possible, the patient will die. To manage this course, we used a VAC abdominal dressing system in our last patient (Fig. 2), which allows aspiration of a large amount of fluid and facilitates iterative laparotomy. We believe that this approach should be recommended early in patients with HS when the risk for abdominal sepsis has been identified and discussed as a de principe management.

In conclusion, these 5 patients are presented to ensure physician awareness of HS after HIPEC with oxaliplatin. Reactive HS is a disease for which the incidence is likely underestimated after aggressive curative surgery, including CRS and HIPEC. Severe sepsis is 1 possible etiology, as is the direct toxicity of chemotherapy; the latter has not been proven. Awareness of HS symptoms is important to initiate prompt life-saving therapy. HS is a diagnostic and therapeutic emergency without a consensus recommendation for management. The evolution is often poor with high mortality. When HS complicates HIPEC, aggressive, early medical, and surgical management is required. Further study is required to determine the optimal treatment, which could be based on the proposed therapeutic algorithm (Fig. 2).

Ethical Standard The protocol was approved by the institutional review board.

REFERENCES

1. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol.* 2003;21:3737–43.
2. Glehen O, Kwiatkowski F, Sugarbaker PH, Elias D, Levine EA, De Simone M, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. *J Clin Oncol.* 2004;22:3284–92.
3. Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. *J Clin Oncol.* 2009;27:681–5.
4. Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol.* 2009;27:6237–42.
5. Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of morbidity and mortality. *Ann Surg.* 2009;249:900–7.
6. Winter JM, Cameron JL, Campbell KA, Arnold MA, Chang DC, Coleman J, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg.* 2006;10:1199–210; discussion 1210–1.
7. Elias D, Raynard B, Boige V, Laplanche A, Estphan G, Malka D, et al. Impact of the extent and duration of cytoreductive surgery on postoperative hematological toxicity after intraperitoneal chemohyperthermia for peritoneal carcinomatosis. *J Surg Oncol.* 2005;90:220–5.
8. Elias D, El Otmany A, Bonnay M, Paci A, Ducreux M, Antoun S, et al. Human pharmacokinetic study of heated intraperitoneal oxaliplatin in increasingly hypotonic solutions after complete resection of peritoneal carcinomatosis. *Oncology.* 2002;63:346–52.
9. Pomel C, Ferron G, Lorimier G, Rey A, Lhomme C, Classe JM, et al. Hyperthermic intra-peritoneal chemotherapy using oxaliplatin as consolidation therapy for advanced epithelial ovarian carcinoma: results of a phase II prospective multicentre trial. CHIPOVAC study. *Eur J Surg Oncol.* 2010;36:589–93.
10. Jacquet P, Sugarbaker PH. Current methodologies for clinical assessment of patients with peritoneal carcinomatosis. *J Exp Clin Cancer Res.* 1996;15:49–58.
11. Sugarbaker PH. Peritonectomy procedures. *Ann Surg.* 1995;221:29–42.
12. Elias D, Bonnay M, Puizillou JM, Antoun S, Demirdjian S, El OA, et al. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. *Ann Oncol.* 2002;13:267–72.
13. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48:124–31.
14. NCI. CTEP: NCI Guidance on CTC Terminology Applications. Bethesda, MD: National Cancer Institute. 2009. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed 1 March 2013.
15. Jardim DL, Rodrigues CA, Novis YA, Rocha VG, Hoff PM. Oxaliplatin-related thrombocytopenia. *Ann Oncol.* 2012;23:1937–42.
16. Votanopoulos K, Ihemelandu C, Shen P, Stewart J, Russell G, Levine EA. A comparison of hematologic toxicity profiles after

heated intraperitoneal chemotherapy with oxaliplatin and mitomycin C. *J Surg Res.* 2013;179:e133–9.
17. Sugarbaker PH, Alderman R, Edwards G, Marquardt CE, Gushchin V, Esquivel J, et al. Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy. *Ann Surg Oncol.* 2006;13:635–44.
18. Shao YY, Hong RL. Fatal thrombocytopenia after oxaliplatin-based chemotherapy. *Anticancer Res.* 2008;28:3115–7.
19. Curtis BR, Kaliszewski J, Marques MB, Saif MW, Nabelle L, Blank J, et al. Immune-mediated thrombocytopenia resulting from sensitivity to oxaliplatin. *Am J Hematol.* 2006;81:193–8.
20. Bautista MA, Stevens WT, Chen CS Curtis BR, Aster RH, Hsueh CT. Hypersensitivity reaction and acute immune-mediated thrombocytopenia from oxaliplatin: two case reports and a review of the literature. *J Hematol Oncol.* 2010;3:12.
21. Hoff PM, Saad ED, Costa F, Coutinho AK, Caponero R, Prolla G, et al. Literature review and practical aspects on the management of oxaliplatin-associated toxicity. *Clin Colorectal Cancer.* 2012;11:93–100.
22. Janka GE. Hemophagocytic syndromes. *Blood Rev.* 2007;21: 245–53.
23. Schneider EM, Lorenz I, Muller-Rosenberger M, Steinbach G, Kron M, Janka-Schaub GE. Hemophagocytic lymphohistiocytosis is associated with deficiencies of cellular cytolysis but normal expression of transcripts relevant to killer-cell-induced apoptosis. *Blood.* 2002;100:2891–8.
24. Henter JI, Elinder G, Soder O, Hansson M, Andersson B, Andersson U. Hypercytokinemia in familial hemophagocytic lymphohistiocytosis. *Blood.* 1991;78:2918–22.
25. Francois B, Trimoreau F, Vignon P, Fixe P, Praloran V, Gastinne H. Thrombocytopenia in the sepsis syndrome: role of hemophagocytosis and macrophage colony-stimulating factor. *Am J Med.* 1997;103:114–20.
26. Trimoreau F, Francois B, Desachy A, Besse A, Vignon P, Denizot Y. Platelet-activating factor acetylhydrolase and haemophagocytosis in the sepsis syndrome. *Mediat Inflamm.* 2000;9:197–200.
27. Fisman DN. Hemophagocytic syndromes and infection. *Emerg Infect Dis.* 2000;6:601–8.
28. Tsuda H. Hemophagocytic syndrome (HPS) in children and adults. *Int J Hematol.* 1997;65:215–26.
29. Imashuku S. Advances in the management of hemophagocytic lymphohistiocytosis. *Int J Hematol.* 2000;72:1–11.
30. Imashuku S, Kuriyama K, Teramura T, Ishii E, Kinugawa N, Kato M, et al. Requirement for etoposide in the treatment of Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. *J Clin Oncol.* 2001;19:2665–73.
31. Tateishi Y, Oda S, Sadahiro T, Nakamura M, Hirayama Y, Abe R, et al. Continuous hemodiafiltration in the treatment of reactive hemophagocytic syndrome refractory to medical therapy. *Transfus Apher Sci.* 2009;40:33–40.