Hemolytic-uremic syndrome caused by gemcitabine

The hemolytic-uremic syndrome (HUS) is a rare coagulation disorder, similar to thrombotic thrombocytopenic purpura, and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. It occurs preferentially in patients with gastric, colorectal and breast carcinoma, and sometimes as a fatal complication of bone marrow transplantation. HUS occasionally appeared after chemotherapy, particularly when mitomycin, cisplatin or bleomycin was used [1].

To our knowledge, only two case reports of HUS, caused by gemcitabine (2',2'-difluorodeoxycytidine), a novel synthetic pyrimidine nucleoside analogue, have been published [2, 3]. We report a patient with an advanced non-small cell lung carcinoma who was treated with gemcitabine before HUS developed.

In August 1997, a 55-year-old male patient was admitted because of pain in his right lumbar region. A large-cell pulmonary carcinoma in the right lower lobe was diagnosed and staged cT2N2M1, because of a right adrenal mass. After informed consent, the patient was included in a chemotherapy study for advanced NSCLC, and randomized to i.v. gemcitabine (Gemzar, Eli Lilly), which was given at a dose of 1,000 mg/m² on days 1, 8 and 15, repeated every 28 days. After two cycles, stable disease was noted. During the following two courses, the patient developed moderate edema of his legs and a bilateral pleural effusion, probably caused by a 'capillary leak syndrome', in the absence of manifest heart, liver or renal disease. Because of these side-effects, the patient was withdrawn from the study. Second-line chemotherapy with carboplatin (AUC 5, i.v., day 1) and vindesine (3 mg/m², i.v., days 1 and 15), repeated every 28 days, was initiated. A second cycle of carboplatin-vindesine was delayed one week, because of thrombocytopenia (grade 1). Six days later, the patient was readmitted because of severe dyspnea with tachypnea, tachycardia, and arterial hypertension (190/100 mmHg). Bilateral pleural effusion, cardiomegaly and the known infiltrate in the right lower lobe were seen radiographically. Laboratory analysis revealed a hemolytic anemia (hemoglobin 8.6 g/dl, normal 14-18; decreased haptoglobin; elevated lactate dehydrogenase 2,152 U/ml, normal 240-480; negative direct Coombs; excess of haptoglobin; elevated lactate dehydrogenase 2,152 U/ml, normal 240-480; negative direct Coombs; excess of fragmentocytes on peripheral blood smear; normal coagulation tests), thrombocytopenia (73 × 10⁹/l, normal 150-450), and renal failure (serum creatinine 2.14 mg/ml, normal 0.7-1.35; microscopic hematuria). Since therapy for HUS (fresh frozen plasma) failed, merely palliative treatment was further given and chemotherapy definitely abandoned. The patient died nine months after diagnosing NSCLC, and two months after HUS appeared.

In this case, the diagnosis of HUS is substantiated by clinical, radiologic and laboratory examinations. Because of the absence of neurologic symptoms and fever, thrombotic thrombocytopenic purpura is less likely. Regarding the cause of HUS, a correlation with previously given gemcitabine is proposed by exclusion. Intercurring infections were ruled out. No immunosuppressants were ever given, in fact, the patient was treated only with low-dose oral methylprednisolone, furosemide, inhaled steroids and bronchodilators before his admission. HUS is occasionally observed in untreated metastatic adenocarcinomas, but rarely occurs in chemonaive NSCLC patients. Before treatment, no evidence for HUS was present in our patient. As for HUS-inducing antineoplastic agents, a few reports about carboplatin or vindesine and HUS were found in a literature review, but, in every report, combined chemotherapy regimens were mentioned. For vindesine, these combined regimens mostly included mitomycin, an agent well-known to induce HUS. Also carboplatin was always given in high-dose chemotherapy regimens, requiring peripheral blood stem cell support, when HUS appeared as an adverse event [4]. Regarding the time of occurrence of HUS in our patient, it is well known that HUS may appear many weeks or even months after chemotherapy delivery [1]. However, it can not be completely excluded that, in our case, the effects or side-effects of the gemcitabine, carboplatin and vindesine combination were finally pathogenic for the development of HUS. So, in addition to two recently published and very similar cases [2, 3], we also want to propose that gemcitabine, though being overall a well-tolerated and mildly-toxic chemotherapeutic agent, be thought of as a possible causal agent for HUS.

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References


Aggressive bowel lymphoma in a patient with intestinal lymphangiectasia and widespread viral warts

Complication of an intestinal lymphangiectasia by a subsequent malignant lymphoma is a rare but known phenomenon. Until now six patients have been described [1-5], five of whom developed extra-nodal lymphomas (in stomach, breast, and thigh, and two in bowel), and one a nodal lymphoma in the...