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Letter to the Editor: Capillary Leak Syndrome in a Patient With Septicemia and Granulocyte-Colony-Stimulating Factor (G-CSF)-Induced Accelerated Granulopoiesis

To the Editor: A capillary leak syndrome is a potentially life-threatening event [1,2]. It has been repeatedly reported in cancer patients with septicemia who have received treatment with hematopoietic growth factors such as granulocyte-macrophage-colony-stimulating factor (GM-CSF) [3–5] or interleukin-4 (IL-4) [6]. We here report on an exceptional observation of a cancer patient in whom a capillary leak syndrome developed together with septicemia and an accelerated granulopoiesis which previously was stimulated by granulocyte-colony–stimulating factor (G-CSF).

The patient, a 15-year-old boy with mediastinal granulocytic sarcoma, had severe chemotherapy-induced bone marrow aplasia and received G-CSF (6 μg/kg/day) until the white blood count returned to normal (WBC 4.3 G/liter). Thirty-six hours after cessation of G-CSF he presented with a clinical situation suggesting septicemia (body temperature of >40°C, elevated acute phase proteins), and empirical antimicrobial treatment was started. Within 12 hours his clinical course was complicated by anuria, generalized edema, and severe hypotension (RR 60/30 mm Hg). Laboratory investigation revealed azotemia (creatinine 3.27 mg/dl, blood urea nitrogen 24 mg/dl), hypoproteinemia (41.7 g/liter), and electrolyte disturbances (sodium 132 mmol/liter, potassium 2.7 mmol/liter, chloride 91 mmol/liter). Together with the finding of a markedly decreased central venous pressure (−3 cm H_2O) a capillary leak syndrome was diagnosed. Vigorous fluid therapy (14 liters of cristalline solutions within 24 hours, i.e., 280 ml/kg/day) was required to achieve and maintain a positive central venous pressure and to stabilize serum electrolytes and to re-establish urine output. Total weight gain within 24 hours was 11.5 kg (22% of the original body weight). After 2 days of this therapy, the patient stably maintained a normal intravascular volume and subsequently fully recovered. Further chemotherapy and an allogeneic bone marrow transplantation were tolerated without a recurrence of a fluid imbalance.

The interesting observation was a significant increase of circulating granulocytes when the capillary leak syndrome became evident. Within the initial 12 hours of the onset of fever, the white blood count increased from 5.8 G/liter to 7.1 G/liter, with the absolute neutrophil count increasing from 3.8 G/liter to 6.9 G/liter. Bands and more immature forms were predominant and showed a marked toxic granulation. We suspect this rapid increase of peripheral activated granulocytes to be a potential trigger of the capillary leak syndrome [6]. A similar observation of a capillary leak syndrome being linked timewise to a rapid increase of peripheral granulocytes induced by G-CSF has recently been described after high-dose chemotherapy [7] and after bone marrow transplantation [8]. In the present case the sequence of events, i.e., the capillary leak syndrome developing after the cessation of the G-CSF treatment, argues against a direct effect of G-CSF on the capillary endothelium. Yet, a hypothesis proposed for a link between GM-CSF and a capillary leak syndrome might be also applicable for G-CSF. GM-CSF was demonstrated to induce a phenomenon of "endothelial sticking" by granulocytes [9]. This phenomenon together with a disturbance of inflammatory cytokines, as in septicemia, would promote the capillary leak. Some evidence [10] suggests that G-CSF, similarly to GM-CSF, enhances the expression of adhesion molecules of granulocytes, e.g., CD11b. Therefore, in this particular case with overt septicemia the accelerated release of activated granulocytes into circulation—a potential result of the previous action of G-CSF—might have been triggering the capillary leak.

Although extremely rare, the significance of a capillary leak syndrome arises from the fact that vigorous fluid therapy, despite generalized edema and impaired renal function, is essential to compensate for the intravascular fluid deficit and maintain the function of vital organs. The experience made in this case supports the view [6,8] that a capillary leak syndrome may occur in any situation of highly stimulated granulopoesis. Thus, awareness of this complication in the use of any hematopoietic growth factor is warranted.

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Letter to the Editor: Response to Successful Management of a Child With Asparaginase-Induced Hemorrhagic Pancreatitis

To the Editor: The case described by Lamelas et al. is certainly similar to the case we published [1]. Although their patient did well without the use of octreotide and with supportive care, including the use of broad-spectrum antibiotics, this type of outcome appears to be more the exception than the rule. Asparaginase-induced hemorrhagic pancreatitis is a serious complication of chemotherapy and may be associated with significant morbidity and mortality. Although mortality from l-asparaginase-induced hemorrhagic pancreatitis has not been reported as a single entity, the mortality rates of necrotizing, hemorrhagic pancreatitis have been published and range from 10% to 86% [2–6], with a published mortality rate for children of 86% [3].

The intent in presenting our case was to make clinicians aware of a new, possibly beneficial therapy for the treatment of patients with this potentially deadly complication. It is important to note that a single case report does not prove the efficacy of a particular therapeutic approach, just as a report of a positive outcome when the therapy is not employed does not prove lack of efficacy. Our hope is that the reported positive outcome will spur interest in the further study of octreotide in the management of asparaginase-induced hemorrhagic pancreatitis in a double-blind, placebo-controlled trial. Only by using this method can this question be answered unequivocally.

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Letter to the Editor: Cutaneous Toxicity Following Administration of Dactinomycin

To the Editor: We read with interest, the papers by Coppes et al. [1] and by Kanwar et al. [2], reporting cutaneous toxicity following treatment with dactinomycin. Because both the incidence and the mechanism by which dactinomycin causes cutaneous toxicity are unknown, it was suggested to report on other patients in order to increase our knowledge of this entity [1]. After reading these reports, and knowing how important dactinomycin treatment is in some childhood tumors, we were uncertain whether treatment with the drug should be continued under these circumstances. Our experience with a similar patient is reported so that relevant guidelines can be developed.

We recently observed similar skin lesions in a 4-year-old child who was treated for a Wilms tumor stage 4 with unfavourable histology. Vincristine (1.5 mg/m^2 weekly for 11 weeks and then 4 weekly), dactinomycin (1.5 mg/m^2 4 weekly), and doxorubicin (30 mg/m^2 4 weekly) were used. Shortly after the start of chemotherapy, the child developed bilateral symmetrical lesions in the neck, the axillary and inguinal regions, the abdomen, and the upper and lower legs. These consisted of spotted and maculopapular exanthemata with evolution to irregular pigmentation and central desquamation. On the palms and soles, circumscribed areas of erythema with desquamation were observed. There was no itching or any other complaint. On biopsy, only normal architecture of the epidermis, dermis, and subcutaneous tissue was observed. The epidermis showed marked orthokeratosis. In the dermis there was a discrete perivascular infiltration with lymphocytes and histiocytes; some of the histiocytes contained melanin pigment. We also observed extravasation of erythrocytes. The deeper parts of the dermis showed an increased interstitial cellularity comprising lymphocytes and eosinophils. The subcutaneous fat was without abnormalities. As the treatment with dactinomycin was considered essential for this child with stage 4 Wilms tumor with unfavourable histology, we decided to continue the treatment under the protection of antihistamines and corticosteroids. Nevertheless, after the next course, the child developed a warm itching rash on the elbows and knees, and the palms and soles were scaly. These were treated with local corticosteroids. During the next 2 months, all lesions gradually disappeared despite continuation of the dactinomycin. Currently the chemotherapy is tolerated without any problem.

The pathophysiology of the skin toxicity is not yet known. On biopsy, we only found nonspecific features. The pigment-loaded macrophages suggest prior damage of the epidermis due to interface dermatitis. We consider the skin reaction as a toxic/drug-induced reaction, rather than an allergic phenomenon such as lymphomatoid contact dermatitis. In the latter, endogenous antigens are presented by macrophages in the skin, and a bandlike infiltrate of lymphocytes is seen [3]. The eosinophils and lymphocytes, probably responsible for the itchy rashes, and the pigment-loaded macrophages, presumably related to the hyperpigmentation, can all be targets for treatment with corticosteroids in combination with antihistamines.

In our experience, it is not necessary to stop dactinomycin, which is an important drug in the treatment of some tumors. The cutaneous toxicity can be controlled by the addition of corticosteroids and antihistamines.

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Letter to the Editor: Recurrence of SIADH After a High-Dose Regimen of Thiotepa, Carboplatin, and Etoposide Phosphate

To the Editor: The side effect of hyponatremia as consequence of a syndrome of inappropriate secretion of antidiuretic hormone (SIADH) was reported for chemotherapeutic regimens containing cyclophosphamide [1], ifosfamide [2], vincristine [1], vinblastine [1], cisplatin [1], and melphalan [1]. In addition, regimens containing etoposide and cyclophosphamide [3] have led to the occurrence of SIADH, which was attributed to cyclophosphamide. For the new prodrug etoposide phosphate [4], this side effect has not been published before.

We therefore report on the repeated life-threatening episodes of hyponatremia in a 3-year and 5-month-old girl with a tumor of the pineal gland. She was treated with a high-dose regimen of thiotepa, carboplatin, and etoposide phosphate followed by an autologous peripheral stem cell rescue. The regimen consisted of a 2-h infusion of 200 mg/m^2 per day thiotepa on days −7 to −5, a 24-h infusion of carboplatin 400 mg/m^2 per day on days −6 to −4, and a 72-h infusion of etoposide phosphate 400 mg/m^2 per day on days −6 to −4.

On day –5 of chemotherapy, the girl presented a sudden generalized convulsion. The serum sodium concentration prior to therapy was 137 mmol/l; at the time of seizure it was noted to be 123 mmol/l. Serum creatinine was normal before, during, and after therapy (0.4 mg/dl, creatinine clearance 100 ml/min 1.73 m^2). There were no signs of infection, blood glucose as well as potassium, calcium, and magnesium levels were within the normal range. There was no clinical evidence of fluid depletion. The fluid administration was 140 ml/kg per day with a sodium supplementation of 10 mmol/kg per day. The seizure was self-limiting and the girl's mental status returned to normal during correction of the hyponatremia. 12 h later the serum sodium concentration was 133 mmol/l. The course of carboplatin and etoposide phosphate treatment was continued, and 24 h later, 36 h after the first event, the serum sodium concentration dropped to 119 mmol/l. The girl's consciousness deteriorated, and chemotherapy was discontinued. By restriction of fluids to 80 ml/kg per day and increasing the sodium supplementation, the serum sodium concentration returned to normal within 12 h. A cerebral CT scan revealed no evidence of tumor progression or signs of elevated intracranial pressure. Repeat electroencephalograms before and after therapy showed no abnormalities, and no abnormalities of kidney, adrenal, or thyroid function were detected. The blood pressure as well as the acid–base status were normal. During the episodes of hyponatremia, the serum osmolality was low, with 250 mosmol/kg H_2O and the urine osmolality high with 500 mosmol/kg H_2O. The fractional excretion of sodium was high with 4% (normal, less than 1%), and the urinary sodium concentration was 213 mmol/l.

The constellation of low serum sodium and high urinary sodium indicates SIADH, presumably initiated by the administration of etoposide phosphate. SIADH may also be due to the concurrently-administered carboplatin. Preceding chemotherapy, however, in this child included etoposide as well as carboplatin and resulted in no episodes of hyponatremia. No reports have been published before this showing carboplatin- or thiotepa-induced SIADH. Carboplatin may induce hyponatremia due to its nephrotoxic potential, but not in the setting of SIADH [5]. Since this girl had received carboplatin repetitively without toxic side effects, we conclude that etoposide phosphate was the causative agent of SIADH in our patient.

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