LETTER TO THE EDITOR

Mitotane-induced febrile pancytopenia: a first case report in paraneoplastic Cushing's syndrome

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Mitotane (o,p'DDD) is an antineoplastic agent with selective inhibitory action on adrenal cortex activity. It is used in the treatment of inoperable adrenocortical tumors and in some patients with Cushing's syndrome (1). To date, no hematological adverse effects have been reported except for exceptional cases of mild neutropenia (2). We report a first case of febrile pancytopenia after mitotane therapy for paraneoplastic Cushing's syndrome.

A 58-year-old woman was hospitalized for acute severe Cushing's syndrome with facial erythrosis, buffalo-neck, obesity (body mass index >35), hypertension (blood pressure >200/100 mmHg) and diabetes mellitus (glycemia >3 g/l). Urinary cortisol was higher than 1200 µg/day. Examination revealed a poorly differentiated carcinoid tumor (chromogranin A+) of the middle gut with lymphatic dissemination, and two liver metastases which secreted corticotropin. A neoadjuvant therapy with mitotane (3 g/day) was initiated. Seven days after mitotane introduction, the patient presented fever (>39 °C) and chills. Clinical examination showed right basal pneumonia. Hematological evaluation disclosed pancytopenia: hemoglobin 79 g/l, neutrophil blood cells $1.3 \times 10^9/l$ and platelets $40 \times 10^9/l$. Laboratory tests revealed an inflammation (C Reactive protein >220 mg/l) and blood cultures were positive for *Klebsiella pneumoniae*. Other pertinent laboratory data, including liver and renal function tests results, serology for virus infection (HIV, hepatitis B and C, B19 parvovirus), and serum levels of vitamin B₁₂ and folic acid were normal. Bone marrow examination showed a hypocellular picture, suggestive of drug-induced bone marrow suppression. The patient was treated with cefotaxim 3 g/day and ciprofloxacin 1000 mg/day (mitotane treatment was withdrawn). Hematological abnormalities resolved on the 12th day of hospitalization. Excluding other causes, mitotane-associated pancytopenia was considered (3). The

patient was treated with octreotide (300 µg/day s.c. for 20 days) and radical surgery was then carried out.

Almost all patients given mitotane experience anorexia, nausea and vomiting and about 40% suffer some central toxicity with dizziness, sedation, lethargy and vertigo (1). Rare cases of adrenal insufficiency are described. To our knowledge, febrile pancytopenia has not been described as a side effect of mitotane (chemically derived from chlorobenzene). The case we describe had unquestionable pancytopenia (fulfilled the criteria proposed by Benichou and Solal-Celigny (3)) and severe *Klebsiella pneumoniae* sepsis. The mechanism of mitotane-induced pancytopenia is unknown (cumulative toxicity or idiosyncratic reaction?), but our case suggested toxicity.

We recommend that mitotane be considered as a potential cause of pancytopenia. Careful clinical and hematological monitoring should be performed. We propose that the drug should be withdrawn immediately if there is a suspicion of blood disorders.

References

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