PREDNIMUSTINE-INDUCED MYOCLONUS—A REPORT OF THREE CASES

Prednimustine is a prednisolone ester of chlorambucil, specifically developed for treating tumors containing glucocorticoid receptors. It has been used in Europe for the treatment of several malignant diseases, including chronic lymphoid leukemia, non-Hodgkin's lymphomas, Hodgkin's disease, ovarian cancer, and breast cancer. The main side-effects of the drug are leukopenia, thrombocytopenia, cushingoid changes, nausea, vomiting, occasional and mild alopecia and skin rashes. At high doses, some psychiatric manifestations, such as euphoria and confusion, have been reported and ascribed to the prednisolone component of the drug (1) but no other types of neurologic toxicity have been described so far (2). This paper reports on three ovarian cancer patients who developed myoclonus during prednimustine treatment. To our knowledge no myoclonus associated with prednisone therapy has been reported previously.

Case 1. A 66-year-old woman was found to have FIGO stage III-C ovarian cancer at laparotomy. Bulky abdominal disease was left after primary surgery. She received 6 courses of i.v. PAC consisting of cisplatin (100 mg/m^2), cyclophosphamide (500 mg/m^2) and doxorubicin (50 mg/m^2) every 3 weeks, and achieved partial response. At the end of PAC chemotherapy, blood cell counts and biochemistry were normal except for a serum creatinine of 17 mg/l and a serum magnesium of 15 mg/l (normal values in our laboratory: 17.5 to 25 mg/l). Subsequently, she received second-line chemotherapy with oral prednimustine (120 mg/m^2/day × 5 days every 3 weeks). During the fourth and fifth days of the first course of prednimustine she developed several repeated episodes of uncontrolled twiching and jerking movements in arms and legs during day-time, lasting from some minutes up to two hours. The patient was conscious during the myoclonic jerks and completely recovered without any treatment after the prednimustine intake was stopped. A CT scan of the brain done immediately after the first course of prednimustine was completely normal. EEG was not recorded. Serum bicarbonate, calcium, potassium, sodium and glucose were normal, but the magnesium serum level was below the normal limits (= 14.8 mg/l). Three weeks after the first course of prednimustine treatment, she received a second course and again presented myoclonus in arms and legs, which disappered with i.v. diazepam (5 mg). During the following 3 course of prednimustine, she received prophylactic diazepam (5 mg p.o. every 12 h) and did not develop any further neuromuscular symptoms.

Case 2. A 71-year-old woman with FIGO stage III-C ovarian carcinoma received 7 courses of i.v. PAC chemotherapy (cisplatin 80 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2, every 3 weeks). She achieved a clinically complete response, but at second-look laparotomy, a persistent tumor in the pelvic cavity was found. At that time, the patient presented persistent hypomagnesemia (14 mg/l) due to cisplatin treatment. Afterwards, she received second-line treatment with oral prednimustine (120 mg/m^2/day for 5 days every 3 weeks). On the fourth and fifth days of the first prednimustine course she developed episodes of multifocal myoclonic movements in face, trunk, arms and legs during day-time, lastnig from some minutes to three hours. The patient was conscious during the jerks. EEG and CT scan of the brain were not performed. Serum electrolytes were normal, except for a magnesium level of 15.2 mg/l. The myoclonus disappeared after completion of the prednimustine treatment. During the following two courses of prednimustine, the patient received prophylactic oral diazepam (5 mg every 8 h) and did not present any further neuromuscular symptoms.

Case 3. A 60-year-old female was diagnosed as having FIGO stage III-B ovarian cancer at primary surgery. She received 7 courses of i.v. PAC chemotherapy, consisting of cisplatin (80 mg/m^2), cyclophosphamide (500 mg/m^2) and doxorubicin (50 mg/m^2) every 3 weeks. At second-look laparotomy, a complete resolution of all macroscopic tumor was found. Random peritoneal biopsies were also negative for tumoral cells. Ten months later, she relapsed and second-line treatment with oral prednimustine (120 mg/m^2/day for 5 days every 3 weeks) was started. At the beginning of prednimustine treatment, serum creatinine, calcium, potassium, sodium, and glucose were normal, but the magnesium serum level was 16.2 mg/l. During the third day of the first course of prednimustine treatment, she developed both intention myo-clonus and myoclonus at rest in the trunk and face. The patient was conscious during the myoclonic episodes. She received 5 mg of i.v. diazepam, with complete resolution of the neuromuscular signs. EEG and CT scan of the brain were not performed. On the second and third courses of prednimustine, she received prophylactic diazepam (5 mg p.o. every 12 h) and she did not present any further neuromuscular side-effects.

Discussion. To the best of our knowledge, the above described patients are the first cases of myoclonus associated with prednimustine treatment reported in medical literature. The causal association between the treatment with prednimustine and the observed myoclonus seems obvious, based on Karch and Lasagna's algorithm (3): a) there were appropriate time intervals between drug intake and event in all cases; b) the reactions disappeared after the end of treatment in cases 1 and 2 and relapsed on reintroduction of therapy without prophylactic antidote in case 1; and c) the neuromuscular events were not explained by the clinical state of the patients or other concomitant therapy. All patients recovered without any neurologic sequelae and they had no evidence of brain metastases. In addition, myoclonus has been described both in children (4) and adults (5) during treatment with the parent compound, chlorambucil. In fact, in one study when ^{14}C-labelled prednimustine was given by oral route, no intact prednimustine was detected in the plasma, although up to 60% of the labelled drug was absorbed (6). Prednimustine seems to be completely broken down in chlorambucil and prednisolone during absorption through the intestinal wall or during its first passage through the liver. Chlorambucil, therefore, seems to be the main cause of the therapeutic and toxic effects of prednimustine. We found three cases of prednimustine-induced myoclonus among 17 advanced ovarian cancer patients treated at our institution with oral prednimustine after failure of conventional cisplatin-containing chemotherapy. The high prevalence of prednimustine-induced myoclonus in our series (c. 18%) is quite surprising, since there have been no previous reports about this symptom in medical literature. The hypomagnesemia found in all our patients, due to previous treatment with cisplatin, could have contributed to the development of the neuromuscular symptoms. On the other hand, it is interesting to note that diazepam was very efficacious in controlling the myoclonic symptoms. All patients achieved complete protection from myoclonus in subsequent courses of therapy when oral diazepam was added to prednimustine.

In conclusion, prednimustine seems to be able to induce myoclonus in ovarian cancer patients previously treated with cisplatin. These patients should be informed about the possibility of developing myoclonus and should probably receive concomitant prophylactic treatment with oral diazepam, especially if they present hypomagnesemia.

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SIMULTANEOUS PULMONARY CARCINOMA IN TWINS—A CASE REPORT AND REVIEW OF THE LITERATURE

The biological mechanisms responsible for the malignant transformation of a cell and the development of malignant tumours remain largely unknown, even if some progress has been made owing to recent advances in cell and molecular genetics. Concerning risk factors for development of different tumours, epidemiological studies have given considerable knowledge. For lung cancer, smoking is thus known to be the predominant risk factor, explaining approximately 80% of the cases. However, lung cancer also occurs in non-smokers, and the occurrence in pairs of twins strongly suggests that the disease may also be caused by genetically determined changes. Having participated in the treatment of one twin of a pair of female non-smokers with lung cancer, we reviewed the literature on simultaneous cancer, particularly lung cancer, in twins but found only five reported such pairs with lung cancer (1–5). Here we present brief case reports on two twins, one of whom was treated by us, and comment on some possible factors involved.

Case 1. Previous to her lung cancer, this patient (BG), who was born in 1923, was in good health. She was a housewife but occasionally assisted her husband in his company. She had never smoked. In the summer 1983 she developed respiratory tract symptoms, and observed during one period blood in sputum. During the autumn she developed multiple small adenopathies in the right supraclavicular fossa and mild pain in the back and one hip. Left-sided parenchymal changes seen on chest x-rays during the summer were found to have progressed, giving reason to suspect cancer. She deteriorated and was admitted with severe back pain in November 1983. On admission she had lymph node metastases on the right side of the neck, which were extirpated and yielded a diagnosis of poorly differentiated large cell carcinoma with solid growth. Bronchoscopy confirmed left-sided lung cancer, and x-rays showed metastases in the spinal column. She received four courses of cisplatin and etoposide from December 1983 to March 1984, but subsequently manifested progression with pleural effusion and increase of the spinal metastases. In May and June 1984, the patient was given radiotherapy to the lumbar and lower thoracic spine, and in June 1984 she got a course of etoposide. Her condition subsequently deteriorated, however, and she died on July 19, 1984, with disseminated lung cancer. No autopsy was performed.

Case 2. PG, the twin sister of BG (case 1) had also been generally healthy before her cancer. She had never smoked, and her alcohol consumption was negligible. She ran her own textile shop. Upon learning of her sister's cancer, she consulted a physician although she was asymptomatic. Chest x-rays showed a $3 \times 3 \times 5$ cm apical right-sided lung tumour that was operated on December 21, 1983, with resection of the right upper lobe and wedge resection of the apical segment of the right lower lobe. Histology showed a $4.5 \times 4 \times 4$ cm tumour, classified at retrospective review as a well-to-moderately differentiated bronchioalveolar carcinoma, with hilar lymph node metastases. It was staged as T2 N1 M0. The patient was given postoperative radiotherapy to the mediastinum, a total dose of 60 Gy. She was recurrence-free until February 1992, when chest x-rays showed newly developed parenchymal changes in her left lung, which fine-needle aspiration cytology showed to be adenocarcinoma. She was operated (September 7, 1992) with lobectomy of the left upper lobe, histologic examination showed a 2.3×1.8 cm tumour assessed as being a well-differentiated bronchioalveolar large-cell carcinoma. The postoperative course was smooth, and she was discharged on September 14, 1992. Subsequent comparison of slides from 1983 to 1992 showed a similar picture of well-to-moderately differentiated adenocarcinoma of bronchioalveolar type.

Discussion. According to information obtained at history taking the two reported sisters were monozygotic twins, with the same blood group (A+). However, no other objective evidence of monozygosity was available. Both twins were non-smokers, and, as far as could be ascertained, none of them had been exposed to any other known environmental risk factors for lung cancer. They did not know of any other cancer in the family. In several respects they differed from other reported cases of lung cancer in twins (1–5). All these twin pairs were male, and as far as information was available the patients were smokers; both twins in one pair had been exposed to asbestos. Histological diagnosis was available for both twins in four pairs, and in these it was mutually consistent (anaplastic bronchial cancer in one pair, bronchio-alveolar carcinoma in one pair, and squamous cell carcinoma in two pairs). In the fifth pair, histological diagnosis (squamous cell carcinoma) was available for only one twin. In our twin pair the lung cancers were, according to retrospective review, definitely of different types. In case 1 it was a poorly differentiated large-cell carcinoma whereas in case 2 it was an adenocarcinoma of bronchio-alveolar type. The tumours in the right and left lungs of case 2, developing with an interval of 9 years, had quite similar histology. Bronchioalveolar carcinoma is a rather unusual form of lung cancer. Its occurrence is correlated to smoking (6), but similar to other adenocarcinomas this association is much less pronounced than