However, there were no clinical signs or laboratory abnormalities suggesting a hepatobiliary disease before ATRA treatment. In conclusion, ATRA has proven to be an effective agent for inducing a complete hematological remission in a young patient with APL, but serious temporary and persisting side-effects prevented an early consolidation chemotherapy. The later necessary relapse therapies had only little influence on the serological signs of the hepatobiliary disorder.

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TUMOUR-INDUCED HYPERCALCAEMIA, RESISTANT TO SYSTEMIC ANTI-HYPERCALCAEMIC AND CHEMO-ENDOCRINE TREATMENTS, BUT RESPONDING TO RADIOTHERAPY IN A BREAST CANCER PATIENT

Tumour-induced hypercalcaemia (TIH) in breast cancer (BC) patients is commonly associated with advanced disease, in particular with bone metastases (1–3). The underlying mechanism includes local and/or distant production of osteoclast activating factors (4, 5), although direct bone destruction by malignant cells cannot be excluded (6). Treatment of choice in acute TIH includes hydration followed by the use of bisphosphonates (7, 8), dissodium pamidronate (*aminohydroxypropylidene diphosphonate*, APD) being the most effective (8–11).Most of the patients respond to the application of APD 60–90 mg, in either a single or divided doses. Calcitonin can be added in life-threatening cases, to accelerate the serum calcium decrease. Long-term control of TIH could be achieved by the effective treatment of the underlying malignancy, primarily by the use of systemic therapy (12). Recurrent TIH is often associated with disease relapse, or with continuing bone destruction (13). It is reasonable to believe that removal of all tumour lesions, or otherwise achieved disease control, will also enable long-term control of TIH, the reports of which are extremely rare. The present case report concerns the long-term control of TIH, induced by an irradiation-caused disease remission, in an advanced BC patient with TIH. The prior unusual complete regression of distant metastases to systemic chemotherapy, combined with the lack of local response, made the palliative breast irradiation the main, or 'radical' treatment of the sole tumour lesion. The very good local response to radiotherapy (complete clinical regression, although not histologically confirmed), was followed by systemic effects, described as follows.

Case report. A 58-year-old perimenopausal female patient, was admitted in November 1994, to the Institute for Oncology and Radiology of Serbia. Physical examination revealed a large, inoperable tumour mass, including whole left breast, with skin infiltration and multiple ulcerations, but without lymph-node involvement. Abdominal echotomography revealed solitary liver metastasis in the right lobe, but no other distant metastases were detected. Bone scintigraphy was also normal, without any focal healing. The patient was otherwise well, with no relevant past medical or family history, complaining only of anorexia, vomiting and constipation during the last several days. Laboratory findings, including liver function tests, were in the normal range, except for mild hyperglycaemia, increased serum creatinine to more than three times the normal level, and increased serum calcium level (Ca^{++}) to 3.84 mmol/l (corrected value for total protein level 3.44). The incisional breast biopsy revealed a lobular breast cancer, histological grade 2. Steroid receptors were not determined.

After two days of intravenous (i.v.) hydration (with solutions of 0.9% NaCl and 5% glucose, 2 000 ml and 1 000 ml per day respectively), only a slight decrease in Ca^{++} and creatinine levels was noted. The APD (Aredia^{R}, Ciba Geigy) was applied, 15 mg daily in a slow i.v. infusion of 125 ml 0.9% NaCl, total dose 60 mg APD. Oral hypoglycaemics were also prescribed. The serum Ca^{++} normalized on the 6th day of the treatment. Since the serum creatinine remained slightly increased, the hydration was continued. On the 11th day from the start of APD treatment, chemotherapy with CAF regimen was initiated (cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2 and 5-fluorouracil 500 mg/m^2, i.v. on day 1, at 21-day intervals). Then the castration by irradiation was performed with TD of 12 Gy, in 4 fractions, using a linear accelerator. On the last day of ovarian irradiation

(i.e. 14th day from the APD treatment), the recurrent TIH occurred. Since Ca^{++} increased during the re-infusional therapy, the patient was given one single dose of APD 60 mg. Five days later, Ca^{++} normalized. The second course of CAF chemotherapy was applied. After 2 weeks, a new relapse of TIH occurred, with no response to hydration, and the second retreatment with APD was performed with 90 mg, divided into daily doses of 15 mg. Only a slight decrease in Ca^{++} level was noted during the next 4 days, and then the Ca^{++} again increased. Eight days after the last APD dose, Ca^{++} continued to increase and the patient was treated with calcitonin (Miacalcic nasal spray, 200 IU per day on alternate days) for the next 6 days. No response was obtained. Liver echotomography revealed the complete regression of liver metastasis. On the contrary, the tumour mass in the left breast progressed slowly from the beginning of the treatment, signs of inflammation developed, accompanied by deeper and more enlarged ulcerations. No other distant tumour involvement was detected. The findings, therefore, led us to conclude that the breast tumour mass was responsible for the maintenance of TIH, which prompted us to perform the palliative irradiation of the left breast. This was started during the Miacalcic support treatment. Four days later the serum Ca^{++} level increased for the first time to over 4.0 mmol/l, the calcitonin treatment was discontinued, and dexamethasone was introduced, 4 mg i.m., twice daily, until the end of radiotherapy. Total dose of irradiation was 30 Gy, delivered in 6 fractions, for 12 days, on 60 Co using two opposed tangential fields (TDF 72.5). The serum Ca^{++} reached its highest level in the middle of the radiotherapy treatment (4.68 mmol/l, corrected for total proteins 4.38), being followed by transient neurological symptoms (somnolence, confusion), oliguria and constipation, after which a gradual decrease in Ca^{++} occurred. Two days after the end of radiotherapy, all symptoms had disappeared, and the normocalcaemia was achieved, remaining during the next 10 months of follow-up.

As the mixed response to chemotherapy was already noted, the same regimen was continued with acceptable toxicity. The first sign of clinical response to radiotherapy was observed 16 days later, initially manifested in the ulcerations becoming more dry. The full response was obtained after 2 months: with the enlarged breast becoming almost normal in size and consistency, and complete healing of all ulcerations, with multiple scars remaining on the skin. Ten months after the termination of radiotherapy, the primary tumour is still in clinical remission. The patient's overall condition is good, the only pathological findings being a continuous slightly increased serum creatinine level (about 140 μmol/l), and mild diabetes. Chemotherapy was discontinued after 12 cycles and a maintenance therapy with tamoxifen was recommended.

Discussion. It is not known why tumour lesions, i.e. tumour cells start producing TIH-causing factors. However, empirical observations demonstrated that TIH in BC is commonly associated with advanced disease (3, 14). TIH is often seen in terminal cases, and can sometimes even be the cause of terminal disease. On the contrary, serious TIH is rare in early BC, and in the NED stage of the disease. Our own experience (Nešković-Konstantinović et al., unpublished data), revealed few cases of mild, chronic or occasional hypercalcaemia in stages I–II BC, or in NED stage, and not a single serious TIH case. This leads to the conclusion that not only the presence of evolutive tumour lesions, clinically overt or occult, are required to produce TIH, but also that tumour growth needs to be aggressive, possibly autonomous. Once the disease is disseminated, it is impossible to conclude whether all tumour lesions/cells are equally capable of producing TIH, or whether only a certain subpopulation of cells, or perhaps even certain locations of metastases are responsible for TIH. It has never been clearly demonstrated that the primary tumour can cause TIH.

This clinical case is unusual from several points of view. It confirmed that a primary breast tumour, although locally advanced, can produce TIH-causing factors, since even though the liver metastases had completely regressed, the TIH was found to have worsened. Another unusual feature is that the lesion, causing TIH, was located outside the bones. In current literature, TIH developing in the absence of bone metastases is usually designated as humorally mediated, the parathyroid-hormone related protein (PTHrP) being, at least partially, responsible for its pathogenesis (7). However, it seems that two types of TIH, bone metastatic and humorally mediated, could not simply be distinguished according to the underlying factors, or pathogenic mechanism (7, 12). In any event, it would have been of interest to determine the levels of PTHrP in our patient, but this was not possible.

Furthermore, it was shown that TIH with no response to systemic chemotherapy, to APD retreatment, and to calcitonin (in second relapse), could respond to local radiotherapy. In fact, we observed earlier that palliative irradiation of involved bones could contribute to the control of TIH (3), but the bone irradiation was never applied as a sole treatment, or to all known tumour lesions: it was always combined with the new endocrine or chemotherapeutic regimens. In the present case, the possible influence of systemic chemotherapy or, even more, of castration should be discussed. These treatments were performed about 2.5 months before the definite normocalcaemia achievement, a period of time sufficient for the assessment of response to chemotherapy. Concerning the castration, as endocrine treatment, its contribution to the overall result was questionable, because of the patient's age and perimenopausal status. A delayed response to castration could, however, not be entirely excluded. Moreover, the clinical appearance, with distant liver metatases, did not suggest an endocrine dependency. The use of calcitonin and the last application of APD, prior to radiotherapy, could not be responsible for the long-term control of TIH, because of the known duration of their effect and the lack of the immediate response (12, 15). Concerning the use of dexamethasone during the course of radiotherapy, some kind of interaction, changing the pattern of the tumour growth was possible. It is also well known that dexamethasone can influence TIH, but the duration of this effect is usually short (7). Thus, we conclude that the overall clinical response of breast tumour, as well as the response of TIH was likely to be an exclusive effect of radiotherapy. Finally, another unusual feature should be pointed out: the clinical response to the irradiation was preceded by the calcaemia normalization, suggesting that a slow-responsive tumour changed its biological properties early.

In conclusion, our case report shows that good control of overall disease is not only necessary, but even essential for the long-term control of TIH. It also emphasizes that successful radiotherapy is able to turn off the production of TIH-causing factors, even before the clinically assessable response; this biochemical/biological feature may have a role in an early prediction of the clinical response to radiotherapy.

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