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Porphyrias Associated with Malignant Tumors: Results of Treatment with Ionizing Irradiation

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Key Words
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Summary
Background: Porphyrin metabolism disorders, known as porphyria, represent inherited or acquired diseases. The development of porphyria due to light sensibility occurs especially with exposure to wavelengths in the range of 300–700 nm. Skin reactions and neurovisceral dysfunctions are known side effects of ionizing irradiation. It can be postulated that during or after ionizing irradiation treatment of patients affected with tumor and porphyria, severe side effects might appear, in contrast to patients without porphyria. This paper describes the treatment of 2 patients affected with tumor and concomitant porphyria. ***Patients:*** One female patient suffering from intermittent porphyria and breast cancer and one male patient suffering from porphyria cutanea tarda and bladder cancer were treated with ionizing irradiation (electrons and photons). No abnormalities nor any severe general or local side effects could be observed. ***Conclusion:*** Radiation therapy is not a 'stimulating' factor in activating porphyria symptoms.

Zusammenfassung
Hintergrund: Angeborene und erworbene Störungen des Porphyrinstoffwechsels sind als «Porphyria» bekannt und durch eine Empfindlichkeit gegenüber Licht mit Wellenlängen zwischen 300 und 700 nm gekennzeichnet. Bekannte Nebenwirkungen der Strahlentherapie sind Hautreaktionen sowie neuroviszerale Dysfunktionen. Man kann annehmen, dass es bei der Behandlung von Patienten mit Porphyrie und Tumorkrankheiten zum Auftreten schwerer Nebenwirkungen kommen wird, im Gegensatz zu Patienten ohne Porphyrie. Über die aktuellen Behandlungsergebnisse zweier Patienten mit malignen Tumoren bei gleichzeitig bestehender Porphyrie wird berichtet. ***Patienten:*** Eine Patientin mit akuter intermittierender Porphyrie und Mammakarzinom sowie ein Patient mit Porphyria cutanea tarda und Blasenkarzinom wurden mit ionisierender Strahlung (Elektronen und Photonen) behandelt. Es wurden weder außergewöhnliche Reaktionen noch stark ausgeprägte allgemeine oder lokale Nebenwirkungen verzeichnet. ***Schlussfolgerung:*** Die Strahlentherapie wirkt nicht als «Auslöser» für die Aktivierung einer bestehenden Porphyrie.

Introduction

Porphyria is characterized by porphyrin accumulation. Porphyrias are inherited or acquired disorders of specific enzymes in the heme biosynthetic pathway. These kinds of disorders are classified as either hepatic or erythropoietic, depending on the primary site of the overproduction and accumulation of the porphyrin precursor or porphyrin [1]. Porphyrins are the one important class of photosensitizers definitely synthesized internally by the body. In 'cutaneous porphyria' the presence of abnormal quantities of porphyrins in the skin results in acute or chronic photosensitivity. Today it is known that human porphyria is due to specific inherited defects, each representing a partial deficiency of one of the seven enzymes beyond ALA synthesis, and they are characterized by typical excretion patterns. Biochemical studies of the different porphyrins and precursors in urine, blood, and stool will allow the accurate diagnosis of each porphyria. The current classification defines the acute and non-acute types of porphyria, based on the main clinical presentation, which also considers their possible skin photosensitivity [2]. In 6–8 types of porphyria, the primary clinical manifestation is represented by skin photosensitization.

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Two types of porphyrias (acute intermittent porphyria and plumboporphyria) are non-cutaneous (there is no skin photosensitivity), but are stated with other clinical manifestations such as nausea, vomiting, abdominal pain and anxiety [2].
Porphyrin disorders other than porphyria may be found in a number of other diseases, particularly anemia and hepatobiliary disorders or in disorders caused by drugs or chemicals, either because the biosynthesis of heme is impaired or because the mechanisms of porphyrin excretion are abnormal [1, 2]. Acquired porphyrin disorders may be found in anemia, in hepatobiliary disorders, benign and malignant hepatic tumors, in intoxication or as paraneoplastic syndrome [3]. They often exhibit skin photosensibility [3].
The activation of the porphyrins is by means of contact with light, especially of wavelengths between 350 and 700 nm.
Ionizing radiation is effected by electromagnetic waves between 1 pm up to few nanometers. Ionizing irradiation is appreciated in healing, as palliative and also as adjuvant therapy. Side effects such as various skin reactions, e.g., skin inflammation, edema, ulcer, and neurovisceral dysfunction are well known.
Because of the skin sensitivity with porphyria, and because of the possible occurrence of side effects such as skin reactions or neurovisceral dysfunction after ionizing irradiation, it can be postulated that patients affected with tumor and porphyria tend to have more severe side effects than patients without porphyria.

Patients and Methods

Two patients, a 48-year-old female and a 70-year-old male, have been examined. Since 1991, the woman suffered from intermittent porphyria subclassified as acute intermittent porphyria without significant skin manifestation. Since 1996, she also suffered from the classical signs of this kind of porphyria showing especially neurological manifestations with motoric polyneuropathia, abdominal pain, and kidney insufficiency. In March 1996, cancer in the left breast was diagnosed (pT2pN0pM0). After mastectomy no other adjuvant treatment was adopted, because hormone therapy such as Tamoxifen treatment can stimulate acute hepatic porphyria. In November 1996, a recurrence surgery was performed on the left chest wall without complete microscopic resection (R1 resection). From January 1997 to March 1997 we proceeded with a locoregional radiation treatment (50 Gy + 10 Gy boost) using photons and electrons. In 1998 the patient returned to our department because of cerebral and mediastinal metastases, which were treated with a total fractionated treatment dose of 46 and 50 Gy, respectively. The patient died from metastases 4 months later. During the irradiation treatment the patient had dialysis three times per week because of kidney insufficiency. Coproporphyrin and uroporphyrin I and III in plasma were controlled before and after dialysis.
The second patient (male) suffered from porphyria cutanea tarda since 1990. In 1993, bladder cancer surgery with construction of an ileo-neobladder was performed. In 1997, recurrence surgery became necessary with construction of a preternatural anus. After the operation the patient was treated with the linear accelerator using photons to a total fractionated dose of 45 Gy and 9 Gy boost. The uroporphyrin level was measured before and after irradiation in urine specimens. Both patients were controlled clinically daily during the irradiation course. Clinical follow-up was performed in the following 6 weeks and then every 3 months after treatment. The monitoring consisted in skin control of the irradiation field, tumor screening (laboratory, computed tomography, and urologic evaluation of general status).

Results

The 2 patients did not show any severe skin side effects such as inflammation or ulcers. The manifested acute side effects remained in the normal range for patients treated with ionizing irradiation. The patient with breast cancer showed only a slight erythema in the boost field and no other acute, subacute or chronic side effects by irradiation within the follow-up period of 16 months after the first irradiation. The patient with bladder cancer developed a light skin erythema in the anal region as well as diarrhea at the end ot the irradiation period. The following controls did not show subacute or chronic side effects resulting from irradiation within the follow-up period of 24 months. The control before, during and at the end of irradiation of coproporphyrin and uroporphyrin I and III in the plasma of the patient with acute intermittent porphyria showed the following levels: coproporphyrin 0.3–0.4 μg/dl (ref. 0–0.2 μg/dl), uroporphyrin I 11–17 μg/dl, uroporphyrin III 6.3–10.8 μg/dl (ref. 0–0.2 μg/dl), with a higher level before the dialysis and a relative low level immediately after the dialysis.
A fractionated 24-hour urine specimen collected from the 2nd patient before and at the end of the irradiation showed a markedly elevated uroporphyrin level of 735 μg / total volume (ref.: 3–25 μg / total volume), with only slight differences of values before and after treatment.

Discussion

A variety of changes in normal tissues are induced by ionizing irradiation, depending on the total dose, the fractionation schedule (day and time), and the tissue volume to be treated [4]. After the application of therapeutic doses of ionizing irradiation, cell death occurs at the time of mitosis [5]. The time to develop tissue injury critically depends on the turnover time and differentiation kinetics of the involved tissue. The time dependency of this process is reflected by using the terms ‘acute’, ‘subacute’, and ‘late’ effects. These terms are used to describe the response of normal tissue to ionizing radiation [4].
The accumulation of porphyrins yields a high skin sensitivity to light, especially for wavelengths between 300 and 700 nm [1]. Neuropathy and neurovisceral dysfunction are characteristic in case of acute intermittent porphyria. This light sensitivity is the main reason for symptoms such as red skin, edema, and ulcer. These symptoms also occur after irradiation treatments, too. Therefore, it is to be expected that patients affected with porphyria can have severe skin side effects in comparison to patients without porphyria after ionizing irradiation treatments.
Furthermore, there may be a connection between porphyria and tumor. An abnormality of heme synthesis linked to carcinogenesis initiation which increases the subsequent mutation rate in the affected clone or the increase of intracellular ROS (reactive oxygen species) during porphyria is an important source of mutagenesis [2, 6]. The patient with bladder cancer was operated 4 months after irradiation due to hepatocellular tumor.
The scarce literature regarding the treatment of tumor patients with concomitant porphyria by irradiation therapy showed no

evidence of severe side effects [7, 8]. The information includes 4 patients with porphyria cutanea tarda [7] and 1 patient with variegata porphyria [8].

The wavelength of the ionizing radiation applied during irradiation treatment of our patients was ca. 1 pm for electrons and ca. 3 pm for photons, in other words, far beyond the activation wavelength of porphyrins (350–700 nm).

Based on the scarce literature and our 2 case reports, we can presume that for patients suffering from tumor with concomitant porphyria who are treated with radiation therapy, the probability of side effects will not differ from that of patients with only tumor.

Before treatment, the irradiated skin area needs to be examined carefully to avoid severe skin damage in already existing lesions.

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