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CASE REPORT

Basal Cell Carcinoma development after use of Metformin - Potential role of Nitrosamines as Enhancing Factors

Desenvolvimento de Carcinoma Baso Celualr após o uso de Metformina – Potencial papel das Nitrosaminas como Fatores Favorecedores

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Abstract

The potential or actual contamination of widely distributed medications with nitrosamines is currently a serious problem. Medications, such as ranitidine, metformin, rifampicin, hydrochlorothiazide, angiotensin-converting enzyme (ACE) inhibitors, and sartans, used as monotherapy or in combination with other drug classes, practically contain ingredients potentiating tumor generation and tumor progression. The dilemma with the ˝increased availability˝ of nitrosamines concerns the subsequent development not only of single but also of multiple skin tumors, sometimes even in combination with other tumor types. The development, in particular, of keratinocyte tumors after administering drugs such as sartans, hydrochlorothiazide and ACE inhibitors has been described repeatedly over the past 7 years. Data on these types of tumors have been officially published not only in a number of large-scale european and american retrospective analyzes but also in the form of dozens of case studies with a retrospective/prospective nature. We describe the case of a patient who developed a basal cell carcinoma (BCC) of the chin, which enlarged significantly after taking potentially nitrosamine-contaminated metformin. The role of nitrosamines as a possible key factor in tumor development is discussed.

Keywords: Basal cell carcinoma. Drug-enhanced carcinogenesis. Metformin. Nitrosamines. Skin cancer. Valsartan.

Resumo

A contaminação potencial ou real de medicamentos amplamente distribuídos com nitrosaminas é atualmente um grave problema. Medicamentos como ranitidina, metformina, rifampicina, hidroclorotiazida, inibidores da ECA, sartans, usados em monoterapia ou em combinação com outras classes de medicamentos, contêm estes ingredientes que potencializam a geração e progressão tumoral. O dilema com o ˝aumento da disponibilidade das nitrosaminas diz respeito ao desenvolvimento subsequente não apenas de tumores de pele, mas também às vezes em combinação com outros tipos de tumores. O desenvolvimento, em particular, de tumores de queratinociticos aproximadamente após o mesmo período de tempo dentro da administração de fármacos como sartans, hidroclorotiazida e inibidores da ECA, não deve ser considerado surpreendente e foi descrito repetidamente nos últimos 7 anos. Os dados sobre esses tipos de tumores foram publicados oficialmente não apenas em várias análises retrospetivas europeias e americanas em larga escala, mas também na forma de dezenas de

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estudos de caso com natureza retrospetiva/prospetiva. Descrevemos o caso de um paciente que desenvolveu um carcinoma basocelular do mento que sofreu crescimento significativo após tomar metformina potencialmente contaminada com nitrosamina. Discute-se o papel das nitrosaminas como possível fator chave no desenvolvimento do tumor.

Palavras-chave: Nitrosaminas. Cancro de pele. Carcinoma basocelular. Carcinogénese mediada por fármacos. Metformina. Valsartan.

Introduction

The global problem of nitrosamines enhancing carcinogenesis has gained increasing importance in recent years[1]. In the scientific literature, there are additional new data on the contamination of commonly used medications by the presence of certain mutagens/carcinogens, also known as nitrosamines[2]. To all intents and purposes, metformin turns out to be one of this so-called ˝problematic drugs[3]˝

The amount of data in the medical literature postulates that both potential and actual contamination with nitrosamines is directly related to the development and progression of both melanocytic[4,5] and keratinocytic skin tumors[6,7], but in fact, not only[8].

Case report

A 61-year-old male (Fitzpatrick skin type 2) reported to the Dermatology Department with a growing cutaneous lesion on the face that was present for 20-25 years (as confirmed by the patient's picture ID card) but started growing progressively after initiating therapy in 2015. As the lesion wasn't considered cancerous or at risk for developing cancer, it was therefore left untreated. The patient denied a previous history of sunburns, allergies or any form of skin cancer in the family. Since 2015 he has been diagnosed with diabetes mellitus, hypercholesterolemia and hypertriglyceridemia. Systemic medications prescribed for type 2 diabetes were metformin hydrochloride 500 mg three times a day (2015-2017), dapagliflozin/metformin hydrochloride 5 mg/1000 mg twice daily (2017-2021) and glimepiride 4 mg twice daily in combination with metformin hydrochloride 1000 mg/day (2021-22). In 2015, after starting therapy, the lesion changed its shape, form and consistency over a short period of time and slowly progressed until the patient came for a dermatological evaluation in 2022.

Laboratory tests showed the following relevant abnormalities: glucose levels 8.77 mmol/L (normal 2.8-6.1 mmol/L), total cholesterol 5.54 mmol/L (normal < 5.17 mmol/L), HDL-cholesterol 1.09 mmol/L (normal for men > 1.45 mmol/L), LDL-cholesterol 4.20 mmol/L (normal < 3.36 mmol/L), VLDL-cholesterol 0.89 mmol/L (normal < 0.65 mmol/L), triglycerides 1.95 mmol/L (normal < 1.71 mmol/L), C-reactive protein (CRP) 8.36 mg/l (normal < 5 mg/L).

Dermatological examination showed a 4.5 cm ulcerated and infiltrated tumor lesion on the right lower facial area, at the level of the mandible (Fig. 1), with a deep central ulcer and elevated and uneven borders formed by pigmented and translucent nodules with telangiectasia, that was adherent to the deeper structures. Biopsy confirmed BCC.

Computed tomography scan of the head and neck showed a soft tissue tumor formation of about 80/17 mm with uneven outlines involving the skin and subcutaneous tissue at the level of the right mandible with no evidence of bone involvement. After contrast enhancement, the lesion significantly increased its density characteristic. No secondary or other focal pathological changes were seen in the brain parenchyma. A surgical approach, with a wide excision under local anesthesia, was recommended. The patient refused surgery, and radiation therapy is being considered.

Discussion

The role of nitrosamines has been discussed as a potential inducer of both melanocytic[9] and keratinocytic tumors[7]. In recent years, the regulatory authorities, in the face of EMA and FDA, have created new parameters/limits to help regulate/limit the availability of certain carcinogens/mutagens - nitrosamines, with the hope for maximum prevention for patients worldwide[10]. Nevertheless, because of the polymorbidity and the related multi-medication, the determination of the so-called acceptable daily intake doses for nitrosamines in a given drug gradually and increasingly loses its significance/relevance. Actually, the total concentration of nitrosamines taken by a given patient is most likely determined by the concentration or availability of nitrosamines in not one but several medications. The concomitant intake, for example, of thiazide diuretics with sartans, often turns out to have an additional risk in terms of developing skin cancer in combination with other forms of cancer[11,12], compared to monomedication with, for example, only a sartan[13].

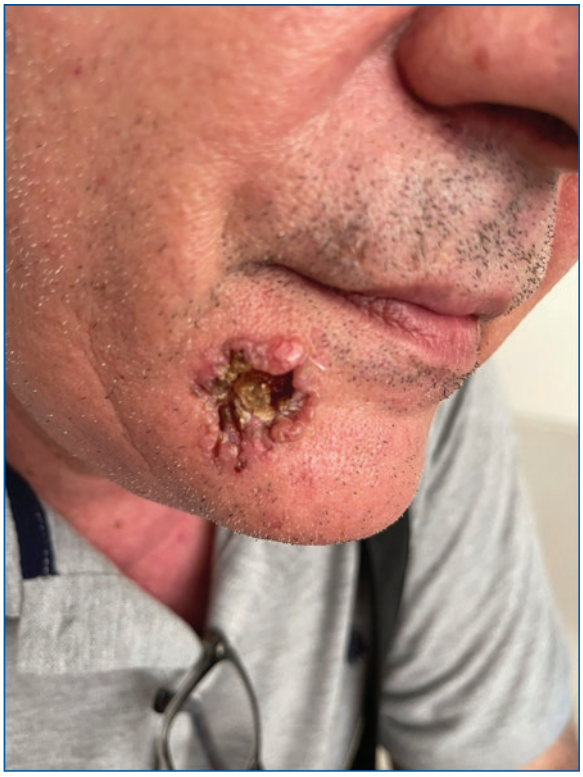

Figure 1. Large, ulcerated tumor lesion on the right lower facial area, at the level of the mandible, with 4-5 cm with elevated and uneven borders formed by some pigmented and translucent nodules with teleangiectasia typical of BCC, with deep ulceration in the middle with adherence to the deeper structures.

Therefore, the relationship between the intake of thiazide diuretics, metformin, rifampicin, or sartans, and the subsequent development of one or multiple cancers, should not be pathogenetically determined based on the individual action of each drug class, as mentioned substances have different mechanisms of action. A search for another pathogenetic inducer other than concepts such as "sporadicity" or "simple association" should then be looked after. This connection between the intake of these medications and the development of the same or relatively the same forms of cancer could be due to the availability of other substances or a contaminating substance that is available in many of the above-mentioned classes of drugs, particularly nitrosamines[14].

Keratinocyte tumors, such as basal cell and squamous cell carcinomas, were recently announced as a possible side effect of the treatment of hypertension with hydrochlorothiazide or with sartans/hydrochlorothiazide[15], well before companies such as Pfizer officially announced the presence of nitrosamine contamination in their products[16]. Therefore, side effects resulting from metformin contaminated with nitrosamines should also be analogous: both for the development of melanomas and keratinocytic skin tumors.

In the world literature, there is already data regarding the parallel administration of potentially contaminated metformin with sartans or metformin with sartans and hydrochlorothiazide, which led to the development of melanoma[5] or atypical fibroxanthoma in combination with prostate carcinoma[17].

The tumors that would arise as a result of such potential administration were similar to or analogous to the case presented, in which a previous skin lesion progressed into a large BCC in the chin area in a 61-year-old man after using potentially nitrosamine-contaminated metformin and other drugs seven years. In this case, we may suspect that nitrosamines in the drugs used might have enhanced BCC growth due to its known carcinogenic potential, but additional factors like ultraviolet exposure might also have contributed.

Key in terms of reasoning about the development of cancer after taking relevant medications should be, on the one hand[1], monitoring the dose-dependent time intervals in a larger group of patients and, on the other hand[2] regular control/identification regarding the type of the nitrosamines found in the batches of the medications. These two factors would contribute significantly to a further understanding of the real dimension of the effect of nitrosamines on enhanced cutaneous carcinogenesis.

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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