

Activity of Metformin in Selected Malignant Tumours in Women



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Abstract

Acanthosis nigricans is a fairly common skin pigmentation disorder in obese people. This lesion may be a sign of a more serious health problem such as metabolic syndrome and some of the malignancy. Over the past several decades, while obesity and metabolic syndrome were a growing health problem across the developed countries, we need to be more cautious and alert about these lesions in routine clinical practice at internal medicine clinics. This case highlights the importance of AN on the lip corners where AN is rarely located.

Keywords : Unusual presentation; Acanthosis Nigricans; Obesity

Introduction

Obesity, type 2 diabetes and malignant tumours are a major global health problem of the 21st century. Metformin, widely used in diabetics and patients with malignant tumours, reduces respective morbidity and mortality due to these diseases. This applies equally well to cancers of the breast, ovary and endometrium. One of the mechanisms of metformin action involves the activation of LK β 1/AMPK pathway and inhibition of the mTOR pathway. Another involves the inhibition of cancer stem cells.

Obesity is a global health problem in the 21st century. According to WHO, in 2014, 2.1 billion people over the age of 21 were classed as overweight or obese (BMI \geq 25 and BMI \geq 30, respectively). Obesity is linked to an increased incidence of type 2 diabetes, the most widespread disease of contemporary civilization. Obesity and type 2 diabetes are associated with a growing incidence of malignant tumours of various locations, including breast cancer, ovarian cancer and endometrial cancer [1-6].

For more than 50 years metformin, the biguanide drug originating from *Medicago sativa* has been applied in the treatment of type 2 diabetes. Metformin reduces morbidity and mortality linked to various tumours (oesophageal cancer, colorectal cancer, cancers of the liver and pancreas), as well as malignant tumours in women. No such an effect was observed when diabetes was treated with insulin or sulphonylurea derivatives.

Meta-analysis of electronic data bases, including over 65 thousand patients with type 2 diabetes and malignant tumours, demonstrated that the use of metformin reduced morbidity by 31% and mortality by 34% as compared to treatment with antidiabetics [7-11]. Obesity and diabetes represent documented risk factors in the development of breast cancer in peri- and post-menopausal women. Studies conducted in women with type 2 diabetes demonstrated a protective effect of metformin against the development of breast cancer. In women treated with metformin, a higher frequency of cells positive for progesterone receptors (PgR) was found. A reduced frequency of triple-negative cancers, tumours characterised by high aggressiveness and poor prognosis, was also noted. It was found that metformin, in addition to neoadjuvant chemotherapy significantly elevated the proportion of complete pathological responses. The antineoplastic effect of metformin may provide a supplementary treatment to conventional therapeutic option [11-14].

Ovarian cancer

The application of metformin in patients with type 2 diabetes was demonstrated to significantly reduce the risk of ovarian cancer development. Observational results demonstrated a significant increase in progression free survival (PFS) and overall survival (OS) in women treated with the conventional therapy of cytostatic drugs together with metformin due to diabetes. Metformin increased the percentage of 5-year survival (67%) in

patients treated due to ovarian cancer in comparison to women without diabetes who underwent chemotherapy only [15-18].

Endometrial cancer

Numerous studies demonstrated the link between the development of endometrial cancer, diabetes and obesity. Meta analysis of electronic data bases, including 760,000 patients suffering from type 2 diabetes, demonstrated reduced morbidity resulting from endometrial cancer by 13% in women treated with metformin. This statistically significant reduction was not seen in patients with type 2 diabetes treated with other antidiabetics. It was found that metformin reduced mortality in women with endometrial cancer, including those with additional diseases [19-22].

The mechanism of metformin action is complex and includes numerous distinct interaction pathways, such as:

- A. Activation of LKβ1/AMPK pathway: the activation of AMPK pathway by metformin develops with the mediation of LKβ1K liver kinase resulting in the inhibition of mTOR pathway
- B. Direct inhibition of mTOR, independent of AMPK and LKβ1
- C. Reduced concentration of circulating insulin, inducing cell divisions and affecting the P13K pathway, linked to anti-apoptotic signalling
- D. Promotion of autophagy
- E. Activation of immune system
- F. A reduction of cyclin D₁ activity, a decrease in anti-apoptotic Bcl-2 and Bcl-x proteins and an increase in concentration of pro-apoptotic Bax
- G. Inhibition of cancer stem cell (CSC) activity, linked to a resistance to chemotherapy, radiotherapy, to progression of the disease and metastases.

Apart from the antidiabetic value of metformin, the additional anticancer activity of this drug provides a reason for further clinical studies [23-30].

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