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Case Report

Valsartan Induced Melanoma?! First Description in Medical Literature!

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Abstract

BACKGROUND: Drug-induced carcinogenesis is a matter of huge popularity and the subject of in-depth research over the last few years. According to the literature, dopamine agonists and acetylsalicylic acid fall into the list of drugs likely to potentiate the development of cutaneous melanoma. However, according to recent data, widely used angiotensin receptor blockers (ARBs) for the treatment of arterial hypertension, also carry a risk of malignancy development. The content of probable carcinogens, such as NDMA or NDEA in the drug valsartan (ARBs), causes the product to be withdrawn from the market. Recent experimental data suggest that another angiotensin receptor blocker-losartan also stimulates cell adhesion and melanoma cell invasion.

CASE REPORT: We present a 70-year-old patient who has been on systemic therapy with a combined drug of amlodipine and valsartan since 2008 and only valsartan from 2015. Three years after the first intake of valsartan (2011), the patient developed a pigment lesion on the right arm. Approximately 2.5 years after doubling the dose of valsartan, the patient observed a progression in the size of the lesion, which was the cause of the dermatological examination and hospitalisation for surgical removal. The melanocytic lesion was removed by radical excision and a surgical field of 0.5 cm in all directions, followed by histological verification, which found the presence of cutaneous melanoma with a tumour thickness of 3 mm. A re-excision was planned with an additional surgical field of 1.5 cm in all directions combined with parallel removal of a draining lymph node.

CONCLUSION: The case is indicative of two things: 1) the possible triggering of melanoma within the systemic treatment with valsartan; and 2) the necessity for optimization of melanoma surgery within the one-step melanoma surgery, which in this case would result in a single surgical excision of the primary lesion, with an operational security field of 2 cm in all directions, along with the removal of a draining lymph node.

Introduction

Numerous data suggest that malignant melanoma may be drug-induced, and various mechanisms are likely to potentiate directly or indirectly carcinogenesis [1], [2], [3], [4], [5]. According to the number of publications in patients with schizophrenia and Parkinson's, the risk of melanoma is probably determined by blood levels of dopamine [1], [2]. Induction of malignant melanoma by acetylsalicylic acid has also been the subject of studies, and it is currently thought that men taking Aspirin on a daily basis are at an increased risk of developing melanoma [3]. According to the latest in vitro data, valsartan and losartan may also potentiate carcinogenesis [4], [5].

We describe a first official case of possible valsartan-induced melanoma following administration of an angiotensin receptor blocker- valsartan, produced by a company still on the market and not on the list of withdrawn products.

Case Report

We present a 70-year-old man, skin phototype II, no history of excessive exposure to UV light and no history of malignancy in the family. The patient suffers from arterial hypertension, which he controls through medication. The systemic cardiologic therapy started with a combined drug of amlodipine and valsartan (10/160 mg), once daily (1-0-0), from 2008 to 2018. Due to unsatisfactory control of

hypertension in 2015 additional valsartan (160mg) has been added to the therapy (0-0-1), which the patient is still receiving at the time of hospitalisation (2018). Three years after the first intake of amlodipine and valsartan (10/160 mg) (2011), the patient developed a pigment lesion on the right arm. Clinically and dermatoscopic (according to anamnestic data and the examinations conducted at that time) there was no evidence of cutaneous melanoma, and surgical treatment was not recommended. However, in 2015, the dose of valsartan was duplicated. Two and a half years later (2018), the patient observed gradual change in the size of the lesion, discomfort, small bleeding, and sensitivity in the area of the lesion.

Reason for hospitalisation of the patient is the progressive increase in the size of the lesion and bleeding observed from its surface over the last few days (Figure 1A). During the dermatological examination, in the area of the right arm, we found the presence of a melanocytic lesion with an uneven surface, a nodular component, uneven borders and partly a bleeding surface, clinically suspect to malignant melanoma (Figure 1A). The lesion was removed by elliptical excision, with an operative safety margin of 0.5 cm in all directions (Figure 1B and 1C). The surgical defect was closed by a single interrupted sutures (Figure 1D). The subsequent histological study showed that it is superficial nodular malignant melanoma, Clark's level III, Breslow's thickness- 3 mm, high mitotic activity and ulceration; abundant lymphocytic stromal reaction; resection lines-no infiltration.

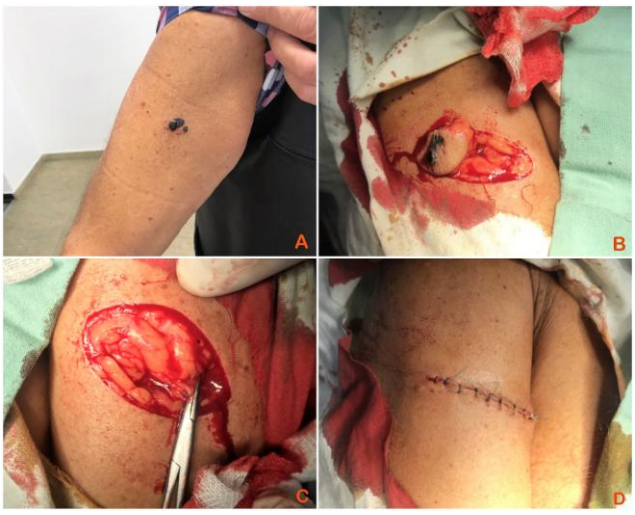

Figure 1: A) Clinical view of the melanocytic lesion with black colour, nodular component and partially bleeding surface; B) Intraoperative finding of the lesion removed by elliptical excision; C) Intraoperative finding of ligation of the blood vessels; D) Postoperative clinical picture of surgical defect closed by single interrupted sutures

Staging showed that it was a malignant melanoma stage IIB (T3bN0M0). The follow-up screening and the PET scan conducted detected the presence of a pathologically enlarged lymph node in the right axilla (suspected for metastatic), with dimensions 6/10 mm. Lymphatic scintigraphy was conducted, which confirmed the findings from the Pet Scan. A re-excision was performed with an operative safety margin of 1.5 cm in all directions, combined with removal of a draining lymph node and axillary lymphadenectomy on the right axilla. A single metastatic lymph node was established histologically; therefore the stage was defined as IIIC (T3bN1M0). A plan was prepared for 1) monthly control review, 2) monthly immunotherapy (vaccines) and 3) abdominal ultrasound at 6 months and once a year (in the winter) X-ray of the lung.

Discussion

Valsartan belongs to a group of medicines called angiotensin receptor blockers (ARBs) that are widely used to treat arterial hypertension [4]. According to randomised controlled trials, this group of blockers is associated with an increased risk of developing cancer, but the individual risk of any drug in this group is not yet known [4]. Lately, research has been increasing on the role of the renin-angiotensin system, and more specifically angiotensin II type 1 and type 2 receptors in the regulation of cell proliferation, angiogenesis and tumour progression [4]. As malignancy, malignant melanoma also falls within the scope of studies about the likelihood of being induced by ARBs [5]. The alleged carcinogenic effect of valsartan is first announced by the US manufacturer, Prinston Pharmaceuticals Inc., which in June 2018 informed the Food and Drug Administration (FDA) that it stopped the production of valsartan-containing products because it detected traces of N-nitrosodimethylamine (NDMA) in the active pharmaceutical ingredient of valsartan (API) provided by a Chinese manufacturer (Zhejiang Huahai Pharmaceutical Co) [6]. NDMA is classified as a chemical that belongs to the family of potent carcinogens and is used for the production of rocket fuel, softeners and other products [7]. According to the US Department of Health and Human Services, exposure to high doses of NDMA may cause liver damage, and NDMA is a likely human carcinogen [8]. Animal studies have shown that NDMA can cause tumours in the liver, kidneys and the respiratory tract, making it potentially harmful for humans as well [8]. Subsequently, the European and American health services have expanded the withdrawal of valsartan after detection of NDMA in medicines manufactured by a second Chinese pharmaceutical manufacturer (Zhejiang Tianyu Pharmaceuticals of Taizhou) and by a manufacturer in India (Hetero Labs Limited, Camber Pharmaceuticals) [9]. Although the FDA declares that not all drugs containing the NDMA ingredient are potentially dangerous, several companies voluntarily withdraw their products with valsartan (Major Pharmaceuticals, Solco Healthcare and Teva

Pharmaceuticals Industries, as well as valsartan/hydrochlorothiazide from Solco and Teva) [10]. In September 2018, information on a second potential carcinogen in the product valsartan-N-nitrosodiethylamine (NDEA) was published [11]. An important publication from 2018 explains the possible mechanism by which angiotensin receptor blockers (ARBs), particularly losartan, are involved in the pathogenesis of development of malignant melanoma [5]. It postulates that losartan inhibits the activity of NHE1 (Na+/H+ exchanger isoform 1) and migration of human melanoma cells (MV3), but at the same time stimulates MV3 cell adhesion and invasion [5].

The case presented by us poses several interesting questions: the newly discovered melanocytic lesion occurred 3 years after the first intake of valsartan, as in the last 2-3 years (2015-2018), the patient observed an increase in its size, which coincides with the introduction of a second product containing valsartan (of the same pharmaceutical company). The inevitable association that occurs is that the progression of melanoma and the likelihood of developing metastases may be dose-dependent [12]. In fact, according to the FDA, on a daily intake of the highest dose of valsartan (320 mg) throughout 4 years, 1/8000 patients are likely to develop cancer, which, according to the FDA, is sufficient reason to withdraw products (containing NDMA) [12]. An open question remains whether the cause lies in NDMA, NDEA or other carcinogens? Or the generic itself?

According to officially shared data from EMA (European Medicines Agency, within our electronic correspondence), there are already 9 reported cases of melanoma in patients taking valsartan, but none of them is officially disclosed. Interestingly, these cases are most likely of valsartan contaminated with NDMA (?) Or drugs that are in the FDA's prohibited lists? While missing detailed EMA data, we present a case with valsartan intake, produced in Germany! A product that is still on the market and does not fall into the list of withdrawn products (produced by a company belonging to the top 10 pharmaceutical giants). This means that the carcinogenic effect may not only be related to the presence or contamination with NDMA but may come directly from the generic substance of valsartan (?) [5)] as well as from the presence of a potential another carcinogen [11]. It should not be excluded that the onset of melanoma and the systemic administration of valsartan may be just a mere coincidence.

It should be noted that older patients, especially men over 65, are at increased risk of developing melanoma [13]. Also, it is believed that 50 years of age and older men are more often diagnosed with melanomas with a thickness ≥ 2.0 mm and that with increasing age, more frequently arise de novo melanomas [13]. Shared information is not an indictment to the respective manufacturer, but contains important clinical observations and analyses based on experimental data in the world literature, as well as from the previously recorded cases of melanomas in patients receiving valsartan -data shared by EMA.

In conclusion, this case reaches important conclusions, indicating that the systemic intake of valsartan may trigger the development of malignant melanoma and the likelihood of its progression being directly proportional to the dose. One step melanoma surgery, in this case, would be a good therapeutic solution providing removal of the lesion in one surgical session along with the removal of a draining lymph node.

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