

Irbesartan Induced Cutaneous Melanoma! Second Case in the Medical Literature!

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Abstract

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BACKGROUND: Drug-induced melanoma is a topic, concept or "reality" becoming more and more popular as the list of drugs considered as potential inducers of cutaneous melanoma is constantly growing. Interesting and current at the moment is the question/dilemma of "Irbesartan induced melanomas" and "Valsartan induced melanomas"! The following questions are without answers: 1) the general risk which angiotensin receptor blockers contain for potentiating the carcinogenesis and cancer development (as a whole); 2) available officialized data for withdrawal from the market of products with valsartan and irbesartan due to detected potential carcinogens-NDMA/NDEA, and 3) the missing official information on the most likely forms of cancer potentiated by these drugs. That is precisely why many questions remain open, and the inevitable assumption arises for the key, although according to some conspiratorial role of so-called "pharmaceutical giants" in the concept of drug-induced malignancies.

CASE REPORT: We present a 72-year-old man with arterial hypertension in connection with which he is taking Irbesartan 300 mg (1-0-0), Amlodipine 5 mg (0-0-1) and Moxonidine 0.2 mg (0-0-1). The patient reported the presence of pigment lesion in the head area, which dates from many years and 3 years ago it was at the size of the nail plate on the index finger. Irbesartan therapy dates from 1.5-2 years, and according to the patient 1.5-2 years after the start of irbesartan therapy, the lesion grew sixfold, accompanied by sensitivity and discomfort in the area. Clinically and dermatoscopically the lesion had data on superficial spreading cutaneous melanoma. Tumour thickness ≤ 1 mm was measured preoperatively by ultrasound. The so-called one-step melanoma surgery (OSMS) was performed, and the lesion was removed by elliptical excision with an operative surgical margin of 1 cm in all directions within one operative session. The subsequent histological study (and screening staging) found that it was a superficial spreading melanoma stage IA (T1bN0M0).

CONCLUSION: Possible, but unlikely, in our opinion, is that the intake of angiotensin receptor blockers (in particular irbesartan), and the progression of benign precursor lesions to malignant do not have a direct relationship. The growing number of data in the literature for drug-induced melanoma and massive withdrawal of products with valsartan and irbesartan due to the content of probable carcinogens speaks, however in favour of the opposite, namely that it is more likely to speak about established dependence than of a sporadic association. Drug-induced melanoma-rather a reality than a myth.

Introduction

In September 2018, NEJM-Journal Watch/New England Journal of Medicine shared information for revealed content of two potential carcinogens-NDMA and NDEA in the drug valsartan [1], [2]. It can be said that spreading drugs containing one or more carcinogens... becomes modern [1], [2]. Or just a trend? Normal and should not impress us! [1], [2], [3], [4], [5], [6], [7]. Interesting is also the fact that high-grade NEJMs formalise information for carcinogens in medications. However, it does not tell what type of cancer is observed at, during or after

their use [1], [2]. We specifically refer to the group of angiotensin receptor blockers [1], [2].

Case report

We present a 72-year-old man with arterial hypertension controlled through medication with Irbesartan 300 mg (1-0-0), Amlodipine 5 mg (0-0-1) and Moxonidine 0.2 mg (0-0-1). The treatment with Irbesartan dates from 1.5-2 years. The patient was hospitalised for surgical removal of a pigment lesion in

the head area. According to the patient's data, the lesion dates from several years, and 3 years ago it was at the size of a nail plate on the index finger. One and a half to two years after the start of irbesartan therapy, the patient observed a sixfold increase in the size of the lesion, sensitivity and discomfort, which is the reason for his presentation at the hospital of the Ministry of Interior and the attendant surgical removal. During the dermatological examination in the area of regio parietalis dextra, a melanocytic formation with irregular shape, dark brown to black colour, uneven distribution of pigment and presence of regression zones, clinically and dermatoscopically suspected for superficial spreading melanoma was visualised (Figure a and b). Tumour thickness ≤ 1 mm was measured preoperatively by ultrasound. The so-called one-step melanoma surgery was performed, and the lesion was removed by elliptical excision with an

operative safety margin of 1 cm in all directions within one operative session (Figure c and d). Due to the impossibility of closing the defect in its middle part, the decision was made to be performed advancement flap, and the skin flap was mobilised from the proximal part of the skull in the distal direction (Figure d). The wound edges were adapted and sewn with single interrupted sutures. The subsequent histological study found that it was a superficial spreading melanoma, Clark II level, Breslow's thickness of 1 mm, without ulceration. The staging was performed which established melanoma stage IA (T1bN0M0). The postoperatively established tumor thickness of 1 mm does not require re-excision, i.e. the required safety margin was respected within one surgical intervention. Due to this fact, the patient was left for clinical observation and a perfect cosmetic result was observed (Figure e).

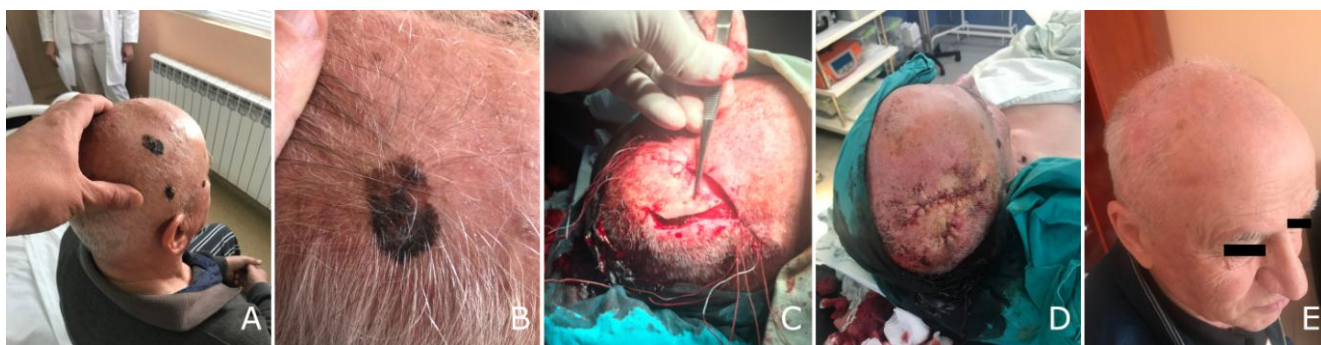


Figure 1: A), B) Clinical view of a melanocytic formation with irregular shape in the right parietal region, presence of regression zones, clinically and dermatoscopically suspected for melanoma; C) Elliptical excision of the lesion with 1 cm operational safety margin in all directions and performing of modified advancement flap; D) Postoperative clinical status of surgical defect closed by single interrupted sutures; E) Clinical view of perfect cosmetic outcome

Discussion

The latest and newest literature data speak in favour of the concept that the definition of drug-induced melanoma exists and becomes significance [8], [9], [10], [11] increasingly. Numerous data in the literature show that drugs for the treatment of schizophrenia and Parkinson's, for example, by various mechanisms affect melanogenesis and are capable of leading to a possible imbalance, ensuring respectively on the one hand 1) protection from melanoma development or 2) eventual progression to the last [11], [12], [13], [14], [15]. Interestingly, however, these are drugs for which there is no published or reported evidence of carcinogenic content [11], [12], [13], [14], [15]. But the latter are not stopped from production and application? Antihypertensive angiotensin receptor blockers are associated with an increased risk of not only melanomas development, but also other skin tumors [10]. With the case we presented, we ask two important questions: 1) are the so-called "pharmaceutical giants", with their produced and distributed drugs, in the root of potentiating

carcinogenesis and the development of de novo malignant lesions? and 2) are, the so called "Pharmaceutical companies", able to distribute the same drugs that, within existing precursor formations (normal or dysplastic nevi), potentiate their progression to malignant?

The mass withdrawal of products with valsartan and subsequently irbesartan (due to found content of potential carcinogens-NDMA and NDEA) by various drug companies, puts a number of "troubling questions", namely: First, "Based on what grounds or data companies have decided to check their products for carcinogens?" and secondly, "Do these" giants "have data for development or existing risk for the development of tumor formations (or already existing ones) within a possible reception of the indicated medications (currently unofficial)?" [1], [2], [3], [4], [5], [6], [7]. Only the answer to these questions can explain the rapid withdrawal of different products from different pharmaceutical companies. The rationale in the media and medical space at the moment for "potential carcinogenic risk" is not enough!

The following question remains open: 1) whether, for medications that currently have unclear

pro-carcinogenic action (???), there are data that the incidence of melanoma is increased? And (2) why drugs with a proven carcinogenic effect are withdrawn without explanation at the moment what forms of cancer are found within their application [1], [2], [3], [4], [5], [6], [7]. The facts are the least disturbing. And such data surely exists! This indirectly speaks that pharmaceutical companies in all likelihood have databases for the frequency of a particular type of cancer that occurred within or after the application of a particular drug? However, such data should be formalised at the moment. Namely-that such facts (as shared by us) could hardly be confessed by companies that, for example, pay 370 million dollars to the US court and keep the direction of their domestic policy only for "inner consumption" or far from the media noise [16].

The other contradictory issue, statement, or point of view should be the following: Is it possible for certain pharmaceutical companies to distribute products with carcinogenic substances, while at the same time the company/is in question offer/s a wide range of medications for the treatment of melanomas and other advanced cancers? Although conspiratorial, the answer is categorical: Yes! Companies that withdraw certain medications or for which there is evidence of association with cutaneous melanomas, at the same time are engaged in the treatment of the latter! And are among the top 10 pharmaceutical companies! One superficial analysis of the data shows that this is a reality. And it can be verified in all media.

Interestingly, the case described is the second formalised by us regarding the relationship between irbesartan and melanoma. We presented a patient with a precursor melanocytic lesion, initially identified as a melanocytic nevus, which changes its size six times and progressed to melanoma, the latter occurring 1.5-2 years after systemic intake of irbesartan. A sporadic association may be available, but we think it is less likely.

In conclusion, the probability, in the presence of precursor lesions, the intake of irbesartan to trigger their development towards melanoma, is completely real. This is confirmed by the presented by us (so far) two different patients with arterial hypertension, controlled with irbesartan, manufactured by various pharmaceutical companies. This indirectly speaks in favour of the notion that the primary substance, not possibly NDMA/NDEA contamination, is the basis for potentiation of carcinogenesis? The possible, but highly unlikely hypothesis that the melanoma development in adults is simply associated with the intake of angiotensin receptor blockers is not excluded.

References

1. Herman A. Another Potential Carcinogen Found in Valsartan. NEJM Journal Watch, September 17, 2018. Retrieved from

<https://www.jwatch.org/fw114583/2018/09/17/another-potential-carcinogen-found-valsartan>

2. Kelley J. Valsartan-Containing Heart Drugs Recalled Due to Possible Cancer Risk. NEJM Journal Watch, July 16, 2018. Retrieved from <https://www.jwatch.org/fw114368/2018/07/16/valsartan-containing-heart-drugs-recalled-due-possible>

3. D'Arrigo T. FDA states as valsartan recalls grow. AphA, September 4, 2018. Retrieved from <https://www.pharmacist.com/article/fda-issues-statement-valsartan-recalls-grow>

4. Christensen J. FDA expands recall of blood pressure drug valsartan due to cancer concern. CNN, August 10, 2018. Retrieved from <https://edition.cnn.com/2018/08/08/health/valsartan-recall-fda-expanded/index.html>

5. Wendling P. More Drug Makers Tagged as Valsartan Recall Grows. WebMD, August 13, 2018. Retrieved from <https://www.webmd.com/heart-disease/news/20180813/more-drug-makers-tagged-as-valsartan-recall-grows>

6. Howard J. Valsartan recall: 4 things patients should know. CNN, August 28, 2018. Retrieved from <https://edition.cnn.com/2018/07/19/health/valsartan-recall-explainer/index.html>

7. Brooks M. FDA Issues Alert on Irbesartan Due to Contamination. Medscape Medical News, November 01, 2018. Retrieved from <https://www.medscape.com/viewarticle/904270>

8. Sipahi I, Debanne S, Rowland D, Simon D, Fang J. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *Lancet Oncol.* 2010; 11(7):627-36. [https://doi.org/10.1016/S1470-2045\(10\)70106-6](https://doi.org/10.1016/S1470-2045(10)70106-6)

9. Tang H, Zhai S, Song Y, Han J. Use of Antihypertensive Drugs and Risk of Malignant Melanoma: A Meta-analysis of Observational Studies. *Drug Saf.* 2018; 41(2):161-169. <https://doi.org/10.1007/s40264-017-0599-x> PMID:28905299

10. Nardone B, Orrell K, Vakharia P, West D. Skin cancer associated with commonly prescribed drugs: tumor necrosis factor alpha inhibitors (TNF- α s), angiotensin-receptor blockers (ARBs), phosphodiesterase type 5 inhibitors (PDE5Is) and statins -weighing the evidence. *Expert Opin Drug Saf.* 2018; 17(2):139-147. <https://doi.org/10.1080/14740338.2018.1400530> PMID:29103328

11. Tchernev G, Lozev I, Temelkova I, Chernin S, Yungareva I. Schizophrenia as Potential Trigger for Melanoma Development and Progression! The Psycho-Neuro-Endocrine-Oncology (P.N.E.O) Network! Open Access Maced J Med Sci. 2018; 6(8):1442-1445. <https://doi.org/10.3889/oamjms.2018.276>

12. Krummel T, Neifeld JP, Taub N. Effects of dopamine agonists and antagonists on murine melanoma: correlation with dopamine binding activity. *Cancer.* 1982; 49(6):1178-84. [https://doi.org/10.1002/1097-0142\(19820315\)49:6<1178::AID-CNCR2820490619>3.0.CO;2-H](https://doi.org/10.1002/1097-0142(19820315)49:6<1178::AID-CNCR2820490619>3.0.CO;2-H)

13. Bertoni J, Arlette P, Fernandez H, Fitzer-Attas C, Frei K, Hassan N, Isaacson H, Lew F, Molho E, Ondo G, Phillips J, Singer C, Sutton P, Wolf J. Increased melanoma risk in Parkinson disease: a prospective clinicopathological study. *Arch Neurol.* 2010; 67(3):347-52. <https://doi.org/10.1001/archneurol.2010.1> PMID:20212233

14. Inzelberg R, Rabey JM, Melamed E, Djaldetti R, Reches A, Badarny S, Hassin-Baer S, Cohen O, Trau H, Aharon-Peretz J, Milo R, Schwartz M, Huberman M, Gilead L, Barchana M, Liphshiz I, Fitzer-Attas C, Giladi N. High prevalence of malignant melanoma in Israeli patients with Parkinson's disease. *J Neural Transm (Vienna).* 2011; 118(8):1199-207. <https://doi.org/10.1007/s00702-011-0580-2> PMID:21298300

15. Mortensen P. The occurrence of cancer in first admitted schizophrenic patients. *Schizophr Res.* 1994; 12(3):185-94. [https://doi.org/10.1016/0920-9964\(94\)90028-0](https://doi.org/10.1016/0920-9964(94)90028-0)

16. United States Department of Justice. Manhattan U.S. Attorney Announces \$370 Million Civil Fraud Settlement Against Novartis Pharmaceuticals For Kickback Scheme Involving High-Priced Prescription Drugs, Along With \$20 Million Forfeiture Of Proceeds From The Scheme. U.S. Attorney's Office, November 20, 2015. Retrieved from <https://www.medscape.com/viewarticle/904270>