Received Date : 25-Apr-2016

Revised Date : 11-Sep-2016

Accepted Date : 03-Oct-2016

Article type : Case Report

Pregnancy as driver for melanoma

G. Richtig[1,2,3], L. Byrom[4,5], R. Kupsa[1], H. Schaider[2], R. Hofmann-Wellenhof[1], I.H. Wolf[1], H.P. Soyer[2,6], E. Richtig[1]

[1]Department of Dermatology, Medical University of Graz, Graz, Austria
Auenbruggerplatz 8, 8036 Graz, Austria
[2]Dermatology Research Centre, The University of Queensland, School of Medicine, Translational Research Institute, Brisbane, Queensland, Australia
Level 5, 37 Kent St, Translational Research Institute (TRI), Woolloongabba, QLD 4102, Australia
[3]Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Graz, Austria
Universitätsplatz 4, 8010 Graz, Austria
[4]Translational Research Institute, UQ Diamantina Institute, The University of Queensland, Woolloongabba, Queensland, Australia
Level 7, 37 Kent St, Translational Research Institute (TRI), Woolloongabba, QLD 4102, Australia
[5]Experimental Dermatology Group, UQ Centre for Clinical Research, The University of Queensland, Herston, Queensland, Australia
The University of Queensland Centre for Clinical Research, Royal Brisbane Hospital Building 71/918, Brisbane, Queensland 4029, Australia
[6]Department of Dermatology, Princess Alexandra Hospital, Brisbane, Queensland, Australia
199 Ipswich Road, Woolloongabba QLD 4102, Australia

Corresponding author: Erika Richtig, MD

Department of Dermatology, Medical University of Graz, Auenbruggerplatz 8, 8036 Graz, Austria

Telephone number: +4331638512371

Fax number: +4331638512466

Email address: erika.richtig@medunigraz.at

What's already known about this topic?

Naevi are known to change in colour and size during pregnancy and melanoma is the most common type of cancer in pregnant women.

What does this study add?

The clinical features, dermoscopic images and histopathological appearance of two slowly growing melanomas detected by sequential digital dermoscopy imaging during pregnancy are reported.

Abstract

Whether or not pregnancy favours the occurrence and growth of melanoma is a source of controversy in the literature. Several case reports have shown dramatic courses of diseases in pregnancy. We present a case of a 36-year-old woman with multiple naevi with one melanoma detected in 2009 in the first trimester and a second primary melanoma in 2010 in the third trimester of her pregnancy. Both lesions have been present for at least 5 years and have been interpreted as dysplastic naevi. Because of their growth during pregnancy they were removed. No metastatic disease has been found between 2010 and early 2016. This case shows the difficulty of detecting melanomas in pregnancy, particularly when they mimic dysplastic naevi in women with multiple naevi, who are at higher risk. Therefore, we suggest that pregnant women with numerous naevi should be precautious of any changes of their naevi in size, shape and colour. Every suspicious lesion should be either excised or documented/monitored carefully, e.g. with sequential digital dermoscopy imaging.

Background

Melanoma incidence is rising worldwide and causes the majority of skin cancer related deaths.[1] Besides the well-known risk factors of skin type, positive family history and genetic background there is ongoing discussion about whether or not pregnancy is a driver for the occurrence and growth of melanoma. In the 1950s several authors published cases of pregnant women with extraordinarily aggressive disease courses.[2,3] However, studies investigating the role of oestrogen and progesterone did not find any influence on the growth of melanoma.[4] In addition, older studies could not show an increased risk of death for women developing a melanoma in pregnancy.

This case gives a unique insight in the changes of two lesions in pregnancy.

Report of a Case

A 36-year-old woman with more than 100 naevi, who was 15 weeks pregnant in her first pregnancy, recognized a naevus on her right inframammary region had changed colour (Figure 1E to 1F). As she had been having regular skin examinations including sequential digital dermoscopy imaging because of her dysplastic naevus syndrome, she presented herself at the Department of Dermatology, Medical University of Graz in November 2009. No family history of melanoma was recorded, but the patient had a family history of breast cancer. Clinical examination showed an irregular pigmented flat plaque with different brownish colours and a white centre. Dermoscopic evaluation revealed that the naevus had a newly grown atypical pattern represented by enlargement, signs of regression, and loss in symmetry (Figure 1F) compared to the digital dermoscopic images taken at the last visit in April 2009 (Figure 1E). Diagnostic total excision of the suspicious lesion was performed and the diagnosis of melanoma was confirmed by histopathology (Breslow index, < 0.5 mm; mitotic index, < 1/mm^2; pT1a AJCC 2009; BRAF^{V600E}). At this examination, all other atypical naevi had similar clinical and dermoscopic features as in April 2009. At a follow-up appointment in April 2010 (37 weeks of pregnancy), another naevus on the posterior of her left foot had slightly changed in size, clinical and dermoscopic appearance compared to digital dermoscopy images taken in April 2009 (Figure 1K). Total excision was performed and histopathology, confirmed a second invasive melanoma (Breslow index < 0.5 mm; mitotic index < 1/mm^2; pT1a AJCC 2009; BRAF^{wt}). Histopathology for both melanomas showed no signs of an associated naevus. In May 2010 at gestation week 42, a healthy infant was born. In the five years since, the patient has been under close observation by our Department and has shown neither disease progression nor further melanomas.

Discussion

Pregnancy associated malignant melanoma (PAMM) is the most common cancer during pregnancy with an incidence of 5 to 10 per 100.000 pregnancies.[5] A meta-analysis by Byrom et al. could show that PAMM has a poorer prognosis compared to non-pregnancy associated melanomas with a pooled hazard ratio of 1.56.[6] A recent study conducted by Tellez et al. could further show a 5-fold increase in mortality and a 7-fold increase in metastasis in PAMM compared to non-PAMM.[7] However, the underlying mechanisms by which pregnancy influences melanoma and melanocytic nevi are still under investigation and several factors may favour the emergence and growth of melanoma during pregnancy.

Pregnancy-associated proteins such as oestrogen and progesterone are up-regulated in pregnancy to maintain and support the growth of the foetus, and the occurrence of PAMM might be due to these proteins. It has been shown that several of these proteins have a proliferative effect, but due to the multiplicity of upregulated pregnancy-related proteins it is difficult to identify the hormone(s) responsible for this phenomenon.[8,9]

Another possible mechanism is the reduced cellular immunity of pregnant women, which prevents the immune system of the mother attacking the foetus. Melanoma is a known immune system sensitive tumour, so pregnancy-associated immunosuppression may favour melanoma growth.[10]

Finally Khosrotehrani et al. demonstrated in a mouse model that pregnancy induces lymphangiogenesis in melanoma.[11] They also showed that pregnant mice had a significantly higher tumour volume compared to non-pregnant mice and in line with these results, the pregnant mice had also a significantly lower survival. A similar effect in humans might put pregnant women at higher risk of developing metastatic disease at earlier stages of their diseases. However Byrom et al. investigated the role of a subsequent pregnancy after previously treated non-pregnancy associated melanoma.[12] Interestingly the authors could not find any significant influence on melanoma outcome which suggests that pregnancy after the diagnosis and treatment of melanoma does not put women at a higher risk for recurrence or mortality.

During pregnancy a change in the colour of naevi is common due to hormonal influences, whereas an enlargement of naevi is mostly related to anatomic areas with physiological skin expansion.[13]

In our patient, two slowly growing melanomas hidden by multiple dysplastic naevi and appearing as dysplastic naevi, showed changes after the onset of pregnancy. As evidenced by sequential digital dermoscopy imaging the rapid change in the first melanoma is more prominent than the subtle change in the second melanoma, and one might speculate that was due to pregnancy-related hormonal changes and the down-regulation of cellular immunity. However, this would not explain the fact there

were differences in the clinical appearance of the two melanomas. Perhaps the BRAF status of each melanoma has played a crucial role.

We suggest that women with a higher risk of melanoma – e.g. more than 50 naevi or numerous dysplastic naevi - should be precautious of any changes of their naevi in size, shape and colour during pregnancy. The assessment of naevi in pregnancy is particularly challenging as many naevi, particularly on the abdomen and breasts, show changes in pigmentation and symmetrical growth in size. Sequential digital dermoscopy imaging as demonstrated in our case might be of help to assist dermatologists to meet this challenge. According to the database reprotox[14] Lidocaine as well as Bupivacaine can be used for local excisions during pregnancy, if necessary.

Conclusions

In conclusion slowly growing melanomas may occur during pregnancy and therefore every change in a naevus – especially apart from usual symmetrical enlargement of naevi on the abdomen and the breasts – should be taken very serious since a delay in diagnosis might have a negative influence on the outcome.

References

1 Deeks ED. Nivolumab: a review of its use in patients with malignant melanoma. *Drugs* 2014; **74:**1233–1239.
2 Pack GT, Scharnagel IM. The prognosis for malignant melanoma in the pregnant woman. *Cancer* 1951; **4:**324–334.
3 Houghton AN, Flannery J, Viola MV. Malignant melanoma of the skin occurring during pregnancy. *Cancer* 1981; **48:**407–410.
4 Marzagalli M, Casati L, Moretti RM, et al. Estrogen Receptor β Agonists Differentially Affect the Growth of Human Melanoma Cell Lines. *PLoS ONE* 2015; **10:**e0134396.
5 Eibye S, Kjær SK, Mellemkjær L. Incidence of pregnancy-associated cancer in Denmark, 1977-2006. *Obstet Gynecol* 2013; **122:**608–617.
6 Byrom L, Olsen C, Knight L, et al. Increased mortality for pregnancy-associated melanoma: systematic review and meta-analysis. *J Eur Acad Dermatol Venereol* 2015; **29:**1457–1466.
7 Tellez A, Rueda S, Conic RZ, et al. Risk factors and outcomes of cutaneous melanoma in women less than 50 years of age. *J Am Acad Dermatol* 2016; **74:**731–738.
8 Giorgi V de, Gori A, Alfaioli B, et al. Influence of sex hormones on melanoma. *J. Clin. Oncol.* 2011; **29:**e94-5; author reply e96.
9 Prithviraj P, Anaka M, McKeown SJ, et al. Pregnancy Associated Plasma Protein-A links pregnancy and melanoma progression by promoting cellular migration and invasion. *Oncotarget* 2015.

10 Trowsdale J, Betz AG. Mother's little helpers: mechanisms of maternal-fetal tolerance. *Nat. Immunol.* 2006; **7:**241–246.
11 Khosrotehrani K, Nguyen Huu S, Prignon A, et al. Pregnancy promotes melanoma metastasis through enhanced lymphangiogenesis. *Am. J. Pathol.* 2011; **178:**1870–1880.
12 Byrom L, Olsen CM, Knight L, et al. Does pregnancy after a diagnosis of melanoma affect prognosis? Systematic review and meta-analysis. *Dermatol Surg* 2015; **41:**875–882.
13 Zampino MR, Corazza M, Costantino D, et al. Are melanocytic nevi influenced by pregnancy? A dermoscopic evaluation. *Dermatol Surg* 2006; **32:**1497–1504.
14 Garey J, Lavigne S, Lione A, et al. Reprotox. Available at: https://reprotox.org/ (last accessed 11 August 2016).

Figure 1. Development of the two lesions over a period of five years

The upper lesion showed subtle changes before pregnancy (Figure 1D-E) and pronounced atypical growth patterns with enlargement during pregnancy (Fig. 1F) leading to diagnostic excision. The lower lesion had a continual change in its growth pattern over four years (Figure 1G-K), with a significant enlargement during pregnancy (Figure 1L) leading to second diagnostic excision (MoleMax, Derma Medical Systems, Vienna, Austria, magnification x30).

Figure 2. HE staining of the first malignant melanoma (Magnification x4 (A), x10 (B) and x20 (C)).

Superficial melanoma. There are atypical melanocytes singly and in nests at the dermo-epidermal junction and throughout the epidermis. In addition, there are also few small nests of atypical melanocytes in the papillary dermis.

Figure 3. HE staining of the second malignant melanoma (Magnification x4 (A), x10 (B) and x20 (C)).

In situ part of the second melanoma: There is an increased number of atypical melanocytes singly and in small nests at the dermo-epidermal junction. Note there are also atypical melanocytes in the upper layers of the epidermis.