Atypical Clinical Presentation of Xeroderma Pigmentosum in a Patient Harboring a Novel Missense Mutation in the XPC Gene: The Importance of Clinical Suspicion

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Introduction

Xeroderma pigmentosum (XP) is a rare genodermatosis caused by abnormal DNA repair. XP complementation group C (XPC) is the most frequent type in Mediterranean countries. We describe a case with a novel mutation in the XPC gene. Case: A healthy Caucasian male patient was diagnosed with multiple primary melanomas. Digital follow-up and molecular studies were carried out. Results: During digital follow-up 8 more additional melanomas were diagnosed. Molecular studies did not identify mutations in CDKN2A, CDK4 or MITF genes. Two heterozygous mutations in the XPC gene were detected: c.2287delC (p.Leu763Cysfs*4) frameshift and c.2212A>G (p Thr738Ala) missense mutations. Conclusion: The p Thr738-Ala missense mutation has not been previously described. Missense mutations in the XPC gene may allow partial functionality that could explain this unusual late onset XP. Atypical clinical presentation of XPC could be misdiagnosed when genetic aberrations allow partial DNA repair capacity.

Key Words
Dermoscopy · Genodermatoses · Melanoma · Xeroderma pigmentosum · Confocal reflectance microscopy

Abstract

Background: Xeroderma pigmentosum (XP) is a genodermatosis caused by abnormal DNA repair. XP complementation group C (XPC) is the most frequent type in Mediterranean countries. We describe a case with a novel mutation in the XPC gene. Case: A healthy Caucasian male patient was diagnosed with multiple primary melanomas. Digital follow-up and molecular studies were carried out. Results: During digital follow-up 8 more additional melanomas were diagnosed. Molecular studies did not identify mutations in CDKN2A, CDK4 or MITF genes. Two heterozygous mutations in the XPC gene were detected: c.2287delC (p.Leu763Cysfs*4) frameshift and c.2212A>G (p Thr738Ala) missense mutations. Conclusion: The p Thr738-Ala missense mutation has not been previously described. Missense mutations in the XPC gene may allow partial functionality that could explain this unusual late onset XP. Atypical clinical presentation of XPC could be misdiagnosed when genetic aberrations allow partial DNA repair capacity.
cancers and progressive neurodegeneration [4].

We report the case of a Caucasian adult male who was diagnosed with XP at the age of 42 after removal of multiple primary melanomas but no carcinomas. A novel missense mutation in XPC in addition to another well-known frameshift has been identified as responsible for the disease.

**Case Report**

A Caucasian male, with neither relevant personal medical nor family history, was referred due to sporadic cutaneous melanoma on the forehead in July 2010 at the age of 38. It was a superficial spreading melanoma (SSM), Breslow 1.8 mm, with no ulceration. Physical examination revealed brown hair and eyes, Fitzpatrick's phototype III, and skin photoaging on sun-exposed areas with significant pigmentary changes such as actinic lentigos (fig. 1a). No neurological alterations, ocular surface changes or sun sensitivity were detected, the patient having been an outdoor worker without sun protection since his youth.

Wide margin excision was performed, and sentinel lymph node dissection was shown to be negative for metastasis. Another suspicious melanocytic lesion on his trunk was detected at the first clinical examination and confirmed as another SSM (Breslow 0.46 mm).

The patient was included in the high-risk surveillance program of a referral Melanoma Center, consisting of digital follow-up with total body photography and digitalized dermoscopy, and genetic counseling of multiple primary melanomas [5–8].

Several atypical melanocytic lesions were detected during the first 18 months of digital follow-up. Clinical, dermoscopic and in vivo confocal reflectance microscopy images of all these lesions were similar.

**Fig. 1.** Melanoma. **a** Clinical image. Note skin photoaging on the back where one of the suspicious lesions was detected (arrow). **b** Dermoscopic image of this lesion showed an asymmetric and polychromic melanocytic lesion, with irregular distribution of pigment, a wide area of peppering suggestive of regression, with a keratotic crust at the center. **c** A confocal image (500 × 500 μm) confirmed the melanoma suspicion since it showed an atypical honeycombed epidermal pattern, with atypical large dendritic cells. The pathology reported an in situ melanoma, lentigo maligna type.
Regression features on dermoscopy on the sun-damaged skin were the only relevant finding. After performing in vivo confocal reflectance microscopy, atypical dendritic pagetoid cells led to remove 3 more melanomas, which were: lentigo maligna melanoma type (LMM) with desmoplastic component on the scalp, Breslow 2.45 mm, in situ SSM on the back (fig. 1–3) and in situ LMM on the face.

Genetic molecular studies of a blood sample did not identify mutations in CDKN2A, CDK4 or MITF genes (only mutation p.Glu318Lys was tested); however, 2 heterozygous mutations in the XPC gene (NM_004628.4) were detected: a well-known pathogenic one (c.2287delC, p.Leu763Cysfs*4) and a missense mutation (c.2212A>G, p.Thr738Ala), the latter not described to date [9, 10] (fig. 4).

During the next 12 months, 5 additional melanomas were removed: 2 microinvasive SSMs on the back, both Breslow 0.3 mm, and 1 in situ SSM and 2 in situ LMM on the back and face, respectively. To date, no carcinoma has been detected; however, the desmoplastic invasive LMM on the scalp has recurred despite the correct wide excision. Only periodical blood sample analysis and locoregional lymph node ultrasonography are being performed. Neither visceral metastatic nor relapse disease of the 10 melanomas have been detected, and no adjuvant therapies have been given after 44 months of follow-up. The patient only uses physical and topical sun protection.

**Fig. 2.** Melanoma. **a** Dermoscopy presented an asymmetric melanocytic lesion with brownish structureless areas and atypical pigment on follicle openings and regression features as well. **b** Clinical image of the upper back, showing photodamaged skin and another previous melanoma scar.

**Fig. 3.** In vivo reflectance confocal microscopy (a) and histopathological (b) images of the lesion from figure 2. The image of 500 × 500 μm shows an atypical honeycombed pattern with multiple dendritic and roundish pagetoid cells. Note the correlation with the histopathological image, with the proliferation of atypical dendritic melanocytes (arrow) at the dermal-epidermal junction. Hematoxylin-eosin. ×400.
Discussion

The natural history of XP leads to skin atrophy and marked early photoaging, such as hypopigmented and hyperpigmented lesions, telangiectasias, lentigines, actinic keratosis and finally skin cancer (nonmelanoma and melanoma) development. The early onset of these skin features, with or without photosensitivity and sunburns, usually allows the diagnosis of XP in childhood.

We report an adult patient with an atypical diagnosis of XP, since he presented multiple melanomas (up to 10) prior to other skin features. He was supposed to be a healthy active outdoor worker who had not developed any carcinoma or actinic keratosis until 38 years of age.

Both his Mediterranean phenotype and his lentigos on sun-exposed areas could have been considered common findings in outdoor workers if multiple melanomas had not been detected. Epidemiological studies have demonstrated a positive, statistically significant and relevant association between occupational ultraviolet radiation and skin cancer risk. It is estimated that there is on average a 100% higher risk of developing squamous cell carcinomas compared to the general population; further studies are needed on other skin cancers such as multiple melanomas [11]. In our case, the occupational sun damage on its own was not enough to explain the development of 5 melanomas at the age of 42.

As usual in multiple primary melanomas, genetic studies were performed and mutations in high susceptibility loci (CDKN2A, CDK4 and MITF) were ruled out. At this point the XPC gene was investigated as well. Sequencing allowed the identification of a well-known mutation in the XPC gene (c.2287delC) and a mutation not previously described (p.Thr738Ala). The p.Thr738Ala...
was absent in the Ensembl project database (http://www.ensembl.org/), and it was predicted to be pathogenic by different bioinformatic prediction tools: disease causing by MutationTaster with a score of 0.99 (http://www.mutationtaster.org/), probably damaging by PolyPhen-2 with a score of 1.0 (http://genetics.bwh.harvard.edu/pph2/) and deleterious by the Protein Variation Effect Analyzer (PROVEAN, http://provean.jcvi.org/index.php), with a score of −4.130. Missense changes have been supposed to allow a partial function of the protein [10, 12].

To the best of our knowledge, only 1 report of XP diagnosed in adulthood has been described in the literature: a Caucasian French lady diagnosed with XPC at the age of 83, being the longest surviving XP patient. In this case 6 basal cell carcinomas and 10 melanomas occurred before the diagnosis of XP. Another missense mutation in XPC was detected as well, and the authors defend the possibility of ‘mild’ or incomplete forms of XP if a partial DNA repair is conserved [12].

In our case, we can hypothesize that the combination of his mixed genotype with the continuous sun exposure led to this unusual, but not ‘minor’, clinical presentation with 10 melanomas and no carcinoma. Further investigations could be of great interest to improve the knowledge of the role of the XPC gene and melanomagenesis in chronic sun-exposed areas.

It is important to highlight the efficiency of digital follow-up of high-risk patients in early detection and removal of malignant lesions and, as in our case, the aid of confocal microscopy to reduce even more the number needed to treat, as it has been recently demonstrated [13, 14]. Moreover, we highlight the importance of detection of early multiple melanomas to increase the suspicion of genetic background susceptibility. Proper family counseling and preventive strategies are the only opportunity to improve the outcome for XP patients.

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References