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Case Report

The First Case of Systemic Mastocytosis in a Xeroderma Pigmentosum Patient: An Association or a Coincidence?

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Abstract

Xeroderma Pigmentosum is a rare, autosomal recessive genodermatosis, characterized by an extreme photosensitivity as a consequence of a defect in nucleotide excision repair enzymes. Clinical manifestations are triggered by hypersensitivity to ultraviolet radiations, which results in multiple skin cancerous lesions. Few reports of extra cutaneous tumors in xeroderma pigmentosum patients included gastric cancer, bronchopulmonary cancer, colorectal cancer, astrocytoma, nephroblastoma, osteosarcoma and leukemia. Systemic mastocytosis is a rare disorder characterised by organ infiltration by neoplastic mast cells. The link between xeroderma pigmentosum and systemic mastocytosis is unclear and no case of association has been reported. Herein, we present the first tunisian case with a focus on the physiopathological similarities.

Keywords: Xeroderma Pigmentosum; Systemic Mastocytosis; Mast Cell; Genetics; C-KIT

Abbreviations

XP: Xeroderma Pigmentosum; SM: Systemic Mastocytosis; MITF: Microphthalmia-Associated Transcription Factor; STAT3: Signal Transducer and Activator of Transcription 3

Introduction

XP is a rare, autosomal recessive genodermatosis, characterized by an extreme photosensitivity as a consequence of a defect in nucleotide excision repair enzymes [1]. SM has never been described in XP patients. Herein, we present the first tunisian case with a focus on the physiopathological similarities.

Case Report

A 33-year-old male patient with an antecedent of XP (Figure 1) presented with a 3-month-history of abdominal pain, diarrhea, and vomiting. His brother had the same disorder, and developed multiple lesions of cutaneous melanoma. Our patient was operated several times for palpebral squamous cell carcinoma. He was also diagnosed with type 1 diabetes. Physical examination showed painless lymphadenopathy in the cervical, axillary and inguinal regions with hepatosplenomegaly. Blood analysis revealed the following results: White blood cell count, 1800/µL (normal range,

4500 11000/µL), hemoglobin, 9 g/dl (normal range, 14.0 - 17.5 g/dl), platelet count, 30 x 10^3/µl (normal range, 150 350 x 10^3/µL), Aspartate aminotransferase (AST), 127 UI/L (normal range, 10 - 30 U/L), γ-Glutamyltransferase (GGT), 111 U/L (normal range, 2-30 U/L), Alkaline phosphatase (ALP), 296 U/L (normal range, 30-120 U/L). The bone marrow biopsy showed a mast cell infiltration representing 35% of the hematopoeitic population (Figure 2a and 2b). Immunohistochemical staining was positive for CD117 and CD25 in mast cells (Figure 2c and 2d). A computed tomography scans revealed multiple lymph nodes with several hepatic, splenic and osteolytic bone lesions. The Serum tryptase level was at 125 µg/L (normal range < 13,5 µg/L). These findings were consistent with the diagnosis of agressive SM. We could not analyse the D816V mutation of *C-KIT* in our genetic laboratory. However, the genetic analysis did not reveal the D820V mutation. The patient received oral Imatinib but he unfortunately died after a 2-month follow up.

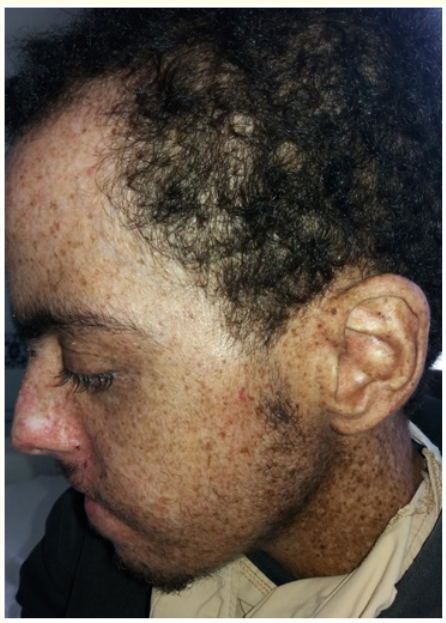

Figure 1: Clinical image. Multiples lentigines and hypopigmented macules on the face.

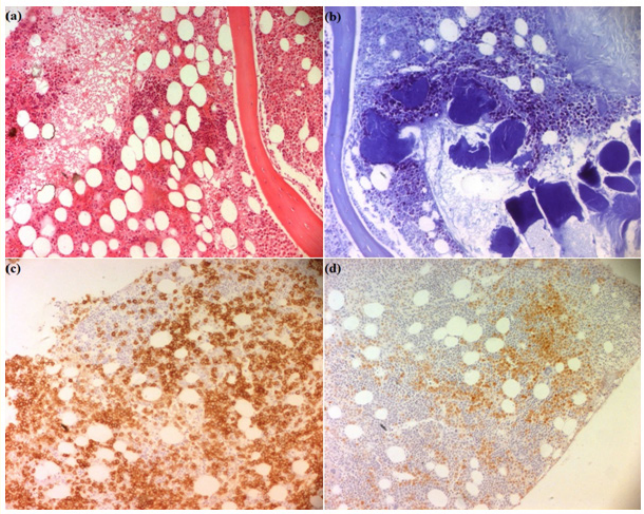

Figure 2: Bone marrow histological examination. (a) Interstitial and paratrabecular mast cell aggregate (haematotoxylin and eosin stain, original magnification×200). (b) Paratrabecular mast cells with purple granules (May-Grünwald Giemsa stain, original magnificationx200). (c) Positive immunostaining for CD117 (immunohistochemistry stain, original magnificationx200). (d) Positive immunostaining for CD25 (immunohistochemistry stain, original magnificationx200)

Discussion

XP is not uncommon in Tunisia where consanguineous marriages are traditional. Clinical manifestations are triggered by hypersensitivity to ultraviolet radiations (UVR), which results in multiple skin cancerous lesions [1,2]. Few reports of extra cutaneous tumors in XP patients included gastric cancer, bronchopulmonary cancer, colorectal cancer, astrocytoma, nephroblastoma, osteosarcoma and leukemia [2]. SM is a rare disorder characterised by organ infiltration by neoplastic mast cells [3]. The link between XP and SM is unclear and no case of association has been reported. However, The physiopathology of SM is dominated by the activating D816V mutation of the C-KIT mast cell membrane receptor that codes for a tyrosine kinase receptor protein (CD117) [3,4]. The C-KIT is also a melanocyte membrane receptor that harbors the D820V muta-

tion, which is well described in cutaneous melanomas appearing in sun-damaged skin [5]. Moreover, few reports in the literature have shown a higher risk of melanoma in patients with SM.

In fact, recent findings shed light on certain similarities between this two disorders, including expression of the transcription factors MITF and STAT3, besides dependence on C-KIT receptor [6]. A study conducted in Japan by Bito., *et al*. on XP patients' skin concluded that UVR induces STAT3 activation through reactive oxygen species and DNA damage [7]. Another study performed by Seoane., *et al*. in Germany, Switzerland and the United States demonstrated that the MITF directly controls general transcription and UVR-induced nucleotide excision repair, which is defected in XP patients [8].

In our case, the occurrence of SM may be entirely coincidental. On the other hand, all like cutaneous melanoma, XP condition may have predisposed to its development via hypersensitivity to UVR and DNA damage, resulting in *C-KIT* D816V mutation, as well as STAT3 and MITF pathways dysfunction. All these findings incite us to think about the possible physiopathological implications connecting XP and SM, in particular the role of UVR in the genesis of SM.

Conclusion

This case emphasizes the possible association between XP and SM which may be helpful to understand the biology of these two ambiguous disorders.

Conflict of Interest

None.

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