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Xeroderma Pigmentosum and Acute Lymphoblastic Leukemia: A Case Report

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Abstract

Background: Xeroderma pigmentosum (XP) is a group of rare diseases resulting in most cases from a dysfunction of nucleotide excision repair (NER). It is characterized by extreme hypersensitivity to ultraviolet rays and predisposes to malignant skin tumors that can appear as early as childhood. XP is rarely associated with internal neoplasms such as acute lymphoblastic leukemia. **Case Report:** A 5-year-old Moroccan Girl, a xeroderma pigmentosum patient, was diagnosed with acute lymphoblastic leukemia with a complex karyotype. The hemogram revealed a non-regenerative pancytopenia. Peripheral blood smear confirmed pancytopenia and revealed the presence of 70% blast cells. Bone marrow aspiration revealed infiltration by 94% granular morphological blast cells with a lymphoid aspect. Immunophenotyping of blasts was in favor of ALL type B. The patient was treated with chemotherapy according to the Protocol for Acute Lymphocytic Leukemia for 32 months. End-of-chemotherapy explorations were without anomaly. The patient declared a complete remission 2 years ago. **Conclusion:** The management of these patients remains a challenge. Studies focusing on xeroderma pigmentosum patients developing hematological malignancies are necessary to better understand the most appropriate strategies and precautions for this specific case.

Subject Areas

Hematology, Medical Genetics, Oncology, Pediatrics

Keywords

Xeroderma Pigmentosum, Acute Lymphoblastic Leukemia, Bone Marrow, Complex Karyotype, Chemotherapy

1. Introduction

Xeroderma pigmentosum (XP) is a group of rare diseases characterized in most cases by dysfunction of nucleotide excision repair (NER), resulting in increased sensitivity to UV radiation in affected individuals [1]. It was first described in 1874 by dermatologist Moriz Kaposi based on a series of four patients with fine, dry skin presenting wrinkles, checkerboard pigmentation, small vessel dilatations, skin contraction, and the development of skin tumors [2].

XP has been found on all continents and in all racial groups. By autosomal recessive inheritance, males and females are equally affected. A more recent survey in Western Europe suggests around 2.3 live births per million. Anecdotally, the incidence in North Africa and the Middle East, where consanguinity is high, is significantly higher [3].

Diagnosis is based on the presence, from birth, of an acute and prolonged reaction to sunburn at all exposed sites, eye anomalies, abnormally early lentiginosis in sun-exposed areas, or the appearance of skin cancers at an early age. Clinical diagnosis is confirmed by cellular tests for defective DNA repair [1]. Eight responsible proteins have been identified to date, enabling XP to be divided into clinically heterogeneous complementation groups [4]. In Morocco, molecular epidemiology studies have shown that two mutations predominate in our population. These are the recurrent c.1643_1644delTG mutations in the XPC gene, followed by the c.682C > T mutation in the XPA gene [5].

Several studies in the literature have shown that individuals carrying XP polymorphisms have an increased risk of developing acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) [6]. We present here an interesting case of XP associated with acute lymphocytic leukemia.

2. Case Report

A 5-year-old girl was born of a consanguineous marriage (first degree), one of two siblings. The patient has been diagnosed with xeroderma pigmentosum since the age of 2 years. Since childhood, she has presented several dermatological symptoms, photosensitivity, and erythematous-squamous plaques with pigmented macules were observed on sun-exposed zones. During the evolution of her disease, the patient developed squamous cell carcinoma (SCC) in situ of the nose and infiltrating SCC of the lower lip, both of which were treated surgically.

The patient was admitted to our department for a bone marrow failure syndrome with hemorrhagic manifestations (epistaxis and skin ecchymosis) and manifestations of an anemic syndrome consisting of asthenia and fatigue evolving 3 weeks before her admission.

Clinical examination revealed a patient with general deterioration, stable respiratory function, tachycardia at 120 beats/minute, apyretic. Dermatological examination revealed skin lesions including multiple lentigines and papular/ulcerated lesions suggestive of skin tumors, gingival hypertrophy, hepatomegaly, and splenomegaly, with no adenopathy. Cardiac auscultation and neu-

rological examination were normal (Figure 1).

The hemogram (Table 1) revealed non regenerative pancytopenia (white blood cell count 3750/µl, neutrophil count 750/µl, hemoglobin 3.9 g/dl, and platelets 20,000/µl). The reticulocyte count was 12,500/µl. Peripheral blood smear confirmed pancytopenia and revealed the presence of 70% blast cells. Bone marrow aspiration revealed infiltration by 94% granular morphological blast cells with a lymphoid aspect. Immunophenotyping of blasts was in favor of ALL type B. Cytospin was negative. Chromosome banding analysis showed a complex karyotype with numerous chromosomal aberrations, including a hyperdiploid clone with 52 chromosomes, trisomy 3 and 9, and tetrasomy 14 and 21. Viral serologies were negative, and hemostasis and liver function tests were correct. Electrocardiography was unremarkable, with good ejection fraction. Abdominal ultrasound confirmed hepatosplenomegaly. Chest X-ray was normal.

The diagnosis of standard-type acute lymphocytic leukemia was retained. The patient was treated with chemotherapy according to the Protocol for Acute Lymphocytic Leukemia for 32 months. End-of-chemotherapy explorations were without anomaly. The patient declared a complete remission 2 years ago.

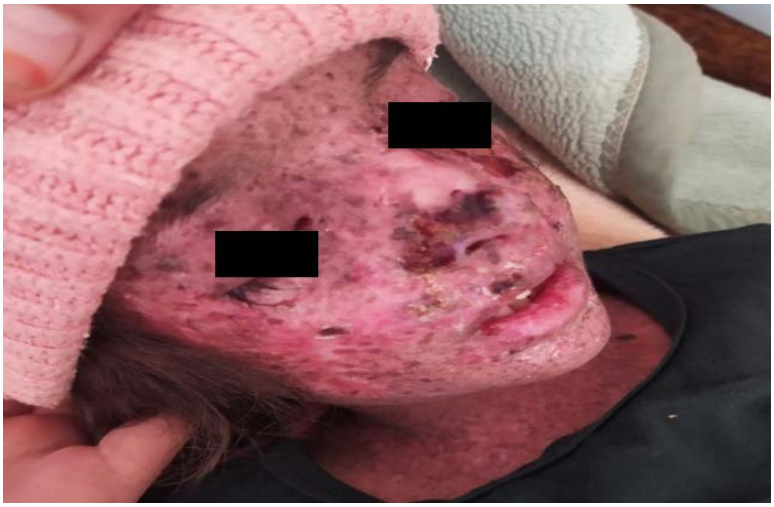

Figure 1. The appearance of the Dyschromia characteristic of xeroderma pigmentosum in photoexposed zones.

Table 1. The biological tests carried out on our patient.

Laboratory parameter	the values of the biological tests carried out on our patient	References
White blood cell (/µg)	3740	4000 - 10,000
Lymphocytes (/µg)	2500	2000 - 4000
Neutrophil (/µg)	750	1500 - 7000
Hemoglobin (g/dl)	3.9	12 - 16
Platelets (/µg)	20,000	150,000 - 450,000
Reticulocytes (/m^2)	12,500	80,000 - 120,000

3. Discussion

XP is a rare form of general dermatosis caused by defects in the excusable repair of DNA damaged by exposure to sunlight [7]. The incidence of XP seems to vary across the globe. The incidence reported in the US and Europe is 1/250,000 and in Japan and other countries at a higher frequency is 1/20,000 - 40,000 [1]. XP is transmitted autosomal recessively, which explains its high frequency in consanguineous marriages [7], especially in the Maghreb countries, including Morocco, which has a nuclear family structure and a high rate of consanguinity (15.25%). [8]. The age at presentation of xeroderma pigmentosum can vary widely, ranging from early infancy to adulthood. Some individuals may present with symptoms shortly after birth, while others may not develop symptoms until later in childhood or even adulthood [9].

XP exhibits genetic heterogeneity due to mutations in different genes involved in nucleotide excision repair pathways. These mutations lead to defects in repairing UV-induced DNA damage, which in turn increases the risk of skin cancer and other complications associated with XP. Genetic studies have described eight XP complementation groups (XP-A to G) caused by abnormal and defective nucleotide excision repair, corresponding to mutations in the genes encoding XPA, XPB, XPC, XPD, XPE, XPF, XPG, and dominant XP. The diverse clinical manifestations observed in XP patients are attributed to the specific mutations in these genes and the resulting impairment in DNA repair mechanisms. The severity of symptoms and the age at onset can vary among individuals depending on the complementation group and the extent of DNA repair deficiency [10].

The clinical presentation varies between severe and mild forms. The severe form is characterized by an early onset, generally before the age of one year, and the clinical presentation is associated with intense photophobia and cutaneous erythema. Malignant skin tumors appear in early childhood. Survival is rare. This form corresponds to Maghrebian XPC with the mutation "V548A fs XR72" [11]. The mild form is characterized by a less severe onset (age > 3 years), with erythema and photophobia being rare, and dyschromia not evident until 5 years of age; malignant skin tumors appear relatively late, around age 20 or more. It corresponds to XPF and XPV [12].

Few studies have been conducted on the distribution of genetic polymorphisms in the DNA repair gene XP and other members of various repair systems in hematological neoplasia, especially childhood ALL. The association of XP with internal neoplasms such as acute lymphocytic leukemia is not reported frequently, confirming both their infrequency and their incidence, which remains 10 - 20 times higher than in the general population [5]. In the present article, we report the case of a Moroccan patient suffering from XP who developed acute lymphocytic leukemia with a complex karyotype with a hyperdiploid clone with 52 chromosomes, trisomy 3 and 9, and tetrasomy 14 and 21. The multicenter study by Min Wen *et al.* found that polymorphisms significantly increased

the risk of developing childhood leukemia in the dominant (OR = 1.21, 95% CI [1.10 - 1.35], P ≤ 0.001) and heterozygous (OR = 1.22, 95% CI [1.09 - 1.36], P ≤ 0.001) models. [13]. The Tunisian study by Kais Douzi *et al.* analyzing the relationship between NER DNA repair gene polymorphisms and leukemia susceptibility in the Tunisian pediatric population showed that the XPC polymorphism could be involved in leukemia susceptibility [14].

For our patient, the difficulty in our case lies not only in the association of XP and leukemia but also in the complexity of the karyotype, which is a poor prognostic factor and may sometimes explain the poor tolerance of chemotherapy. On the other hand, the role of polymorphisms in the XP DNA repair gene in increasing the toxicity of chemotherapy has not been demonstrated.

4. Conclusion

The association of xeroderma pigmentosum and acute lymphoblastic leukemia in children is rarely reported in the literature. The management of these patients remains a challenge for the medical team. Studies with larger sample sizes and more detailed information on the risk factors of XP patients developing hematological malignancies are needed to better understand the most appropriate strategies and precautions for this specific case.

Conflicts of Interest

The authors declare no conflicts of interest.

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