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RESEARCH ARTICLE

XERODERMAPIGMENTOSUM: EPIDEMIOLOGICAL, CLINICAL AND THERAPEUTIC ASPECTS

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Abstract

Xeroderma Pigmentosum (XP) is a rare and disabling genetic dermatosis that was first described in 1874. It is characterized by photo-induced cutaneous alterations, often associated with ocular lesions and sometimes with neurological involvement. The transmission of XP is on an autosomal recessive mode, and it is relatively frequent in countries with high consanguinity rates and large family sizes, such as those in the Maghreb region. This study aims to present an epidemiological, clinical, and histological profile of XP patients treated in the plastic surgery department in southern Morocco, reflecting the region's epidemiological reality and specifying the modalities of oncologic and reparative surgical treatment.

Introduction:-

XerodermaPigmentosum (XP) is a rare and disabling genetic dermatosis that was first described in 1874. It is characterized by photo-induced cutaneous alterations, often associated with ocular lesions and sometimes with neurological involvement. The transmission of XP is on an autosomal recessive mode, and it is relatively frequent in countries with high consanguinity rates and large family sizes, such as those in the Maghreb region. The condition's clinical heterogeneity, tumorigenic risks, and poor prognosis require regular monitoring and multidisciplinary care. The identification of a DNA repair deficit in XP cells in 1968 opened up a new area of research. The disease's clinical heterogeneity responds to mutations in seven different genes (classified as XPA to XPG) necessary for the nucleotide excision repair system, as well as the variant form of the efficient system. While there is no cure for XP, early diagnosis is crucial for starting photoprotection measures to prevent or delay the appearance of cutaneous and ocular neoplasms. Treatment mainly focuses on the prevention and the surgery of severe tumors, often repeated and disfiguring, using various plastic surgery techniques.

This study aims to present an epidemiological, clinical, and histological profile of XP patients treated in the plastic surgery department in southern Morocco, reflecting the region's epidemiological reality and specifying the modalities of oncologic and reparative surgical treatment.

Patients and Methods:-

This is a retrospective study conducted at the Plastic, Aesthetic, and Burns Surgery Department of Mohammed VI University Hospital of Marrakech from October 2007 to October 2018. The study included 28 patients treated for XerodermaPigmentosum (XP) and recruited through referral letters. All patients were hospitalized during this period, with 22.2% being multi-hospitalized in the same department. The diagnosis of XP was made based on epidemiological data and clinical context suggestive of XP, including a family history of consanguinity, previous

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cases in the family, onset of symptoms during sun exposure, cutaneous photosensitivity and photophobia, poikilodermic skin condition, cutaneous-mucosal tumors, ocular and neurological involvement. The data used in this study were obtained from the medical records of the 28 XP patients and were documented in a predefined data collection form.

Results:-

The epidemiological profile of the patients is as follows:

1. Annual distribution: The frequency of XP cases varied during the years studied, with the highest frequency recorded in 2016 and no cases recorded between 2008 and 2010.
2. Frequency: On average, two XP patients were admitted to the plastic, aesthetic and burns surgery department of CHU MOHAMED IV in Marrakech per year.
3. Age: The mean age of onset of first cutaneous signs was 1.41 years (range: 1 month-2 years), the mean age of onset of the first tumor was 8.7 years (range: 3 years-22 years), and the mean age of consultation was 7.72 years (range: 3 years-16 years) (Table I).

CASE NO.	age of 1st symptoms	age of 1st tumor	age of diagnosis	Ageof consultation	Clinicalform
1	1.5	-	1.5		INTERMEDIATE
2	1	-	1		INTERMEDIATE
3	1	6	1	6	GRAVE
4	1	10	1	10	GRAVE
5	1 month	3	1 month	3	GRAVE
6	1	11	1	11	INTERMEDIATE
7	2	6	2	7	GRAVE
8	2	8	2	6	GRAVE
9	3 months	3	2	3	GRAVE
10	2	14	14	14	INTERMEDIATE
11	2	12	2	12	VARIANT
12	1	6	1	6	GRAVE
13	1	16	1		INTERMEDIATE
14	1	16	1		INTERMEDIATE
15	2	4.5	4.5	4	GRAVE
16	2	5	2	5	GRAVE
17	1	3.9	1	4	GRAVE
18	1	8	1	6	GRAVE
19	1	18	1		INTERMEDIATE
20	2	10.10	2	10	INTERMEDIATE
21	2	8	2	8	GRAVE
22	6 months	4	6 months	4	GRAVE
23	2	7	2	7	GRAVE
24	2	4	2	4	GRAVE
25	2	22	2		VARIANT
26	2	16	2	16	INTERMEDIATE
27	2	13	2	13	INTERMEDIATE

28	1	11	1	11	INTERMEDIATE

Table I:- Distribution of patients by age of first symptoms, age of diagnosis and age of first tumor.

4. Gender: The study included 12 female cases (44%) and 16 male cases (56%), with a sex ratio of 1.33.
5. Origin: Fourteen patients were of urban origin, while 12 were of rural origin. The majority of patients were from Marrakech and its surrounding regions.
6. Education: The majority of patients (17 cases) were not educated, while only one case was educated (the hours and level of education are not mentioned in the data).
7. Socioeconomic level: Most cases (21 patients) were of low socioeconomic status.
8. The medical history: 72% of cases (20 cases) had a history of consanguinity, with 1st-degree consanguinity in 9 cases, and 2nd or 3rd-degree consanguinity in the others. 43% of patients (12 cases) had a family history of similar cases. Most patients were exposed to the sun. All patients used sun protection, such as sunscreen, hats, and sunglasses, with 8 patients wearing anti-UV suits.

All 28 patients had skin manifestations such as photosensitivity and various types of skin tumors (Table II). In addition, 15% of the patients had freckles, 5% had dry skin, and 3% had poikiloderma, hypopigmentation lesions, and actinic keratosis. The patients also had 205 skin and mucosal tumors, which were operated on

Table II:- Distribution of tumors in patients.

Patient'sNumber	Number of surgical procedures	Number of tumors/procedure	Total number of tumors
1	1	3	3
2	1	2	2
3	1	3	3
4	1	1	1
5	1	1	1
6	1	1	1
7	1	1	1
8	1	7	7
9	5	Procedure 1:5–procedure 2:5–procedure 3:2–procedure 4:3–procedure 4:3	18
10	3	procedure1:11-procedure 2:5–procedure3:3	19
11	2	Procedure 1:16–procedure 2:7	23
12	1	8	8
13	1	5	5
14	1	4	4
15	2	Procedure 1:4–procedure2:3	7
16	1	7	7
17	2	procedure1:7–procedure 2:5	12
18	1	9	9
19	1	7	7
20	3	procedure1:6–procedure 2:5–procedure 3:1	12
21	1	8	8
22	1	12	12

23	1	9	9
24	1	1	1
25	1	13	13
26	1	3	3
27	1	2	2
28	1	7	7

The tumors were found on different parts of the body, with a predominance on the face. Some patients also had palpable cervical lymphadenopathy, and a few had ophthalmological symptoms, such as photophobia and variable severity of ophthalmological involvement. No neurological involvement was detected during the clinical examination. The majority of patients had a severe form of the disease.

The histological nature of skin and mucosal tumors was reported in 86.8% of cases. The average age of appearance of the first skin tumor, regardless of histological type, was 8.7 years, with an age range from 3 to 22 years. Malignant tumors were dominated by well and moderately differentiated and invasive squamous cell carcinomas, accounting for 52% of cases. This was followed by basal cell carcinomas at 27% and melanomas at 2%. Among benign tumors, keratoacanthomas accounted for 2% of cases, and there were also 4% of preneoplastic lesions, specifically actinic keratosis.

The paraclinical profile of the patients was focused on the search for anemia, the histological nature of the tumor, or its extension assessment. Two patients showed iron-deficiency anemia in their blood tests. Radiological examinations included chest X-rays, cervical lymph node ultrasounds, ocular ultrasound, thoraco-abdomino-pelvic CT scans, and facial and cerebral CT and MRI scans. No genetic tests were performed. Biopsies were performed on all patients, with seven receiving partial skin biopsies due to the large size of their tumors, and the remaining patients receiving surgical excision with a 2 mm margin. The results showed various findings, including inflammatory cervical lymph nodes, thyroid nodules, orbital and nasal lesions, and tumors of the parts of the face and scalp. Most of the examinations showed normal results.

The therapeutic management of skin tumors, focused on preventive measures and surgical treatments. Preventive measures recommended include topical and clothing photoprotection. All patients received surgical treatment under general anesthesia, which consisted of tumor excision with lateral margins ranging from 0.5cm to 3cm depending on the histological type of the tumor. In some cases, deeper excision was necessary, involving subcutaneous tissue, muscles, cartilage, and bone. Lymph node dissection was only performed in one patient with poorly differentiated squamous cell carcinoma and cervical lymphadenopathy.

Reconstruction of the surgical defect was either immediate or delayed, and various techniques were used, including directed healing, direct suture closure, skin grafts, and flaps. Three cases also underwent prophylactic excision and skin grafting. No chemotherapy or radiotherapy was indicated in this series

As for the follow-up and progression of XP and its treatment.

1. Postoperative follow-up :

The patients were treated in the postoperative period with antibiotics such as amoxicillin clavulanic acid 1g 3 times daily and analgesics, notably acetaminophen codeine 1 tablet 3 times daily. They also benefited from anti-inflammatory dressings made of vaseline and fucidin to promote healing of wounds until pathology results are recovered, as we vitamin therapy and iron supplements

2. Evolution :

Ten cases experienced recurrence and new lesions on the face and body, one case had complete healing of the face, and eight experienced blindness due to ocular invasion. Another case developed hypo-pigmented skin and an unsightly patch in the grafted area, one case resumed therapy while 15 cases were lost to follow-up.

Discussion:-

Xerodermapigmentosum is a cosmopolitan disease [1], affecting all races. Some authors suggest that it is rare in the Black race [2, 3], but despite all data obtained exclusively in hospital settings, there are no definitive and comprehensive studies that can affirm with certainty that XP is relatively rarer in Black populations. Additionally,

there is a recruitment bias as only complicated cases seek medical consultation. The role of melanin photoprotection in delaying the diagnosis of the disease in this race is also not well understood. However, the prohibition of consanguineous marriage in some Black African tribes may partly explain its rarity [4].

The worldwide distribution of XP is peculiar; it is rare in Europe and the United States with an estimated prevalence of 1/250,000 [5, 8], and less rare in Japan where the prevalence reaches 1/22,000 [5, 12], and particularly in some Middle Eastern and North African countries where the prevalence is, for example, estimated at 1/10,000 in Tunisia [5, 7, 13]; favored by consanguineous marriages and large families [5, 11, 7, 12].

In Morocco, in a study conducted at the Hassan II University Hospital in Fez in 2013, XP represented 0.7% of hospitalizations and 0.14% of all consultations in the dermatology department of the Hassan II University Hospital in Fez [14]. In our study, the average number of admissions was two patients per year in the plastic surgery and burn unit of the Med V University Hospital in Marrakech. This frequency shows that XP is relatively rare. A national study is necessary to have an idea of the real frequency of this disease in our context.

The frequency of the different XP groups is unequal: 80% of patients are classic XP, of which 90% are XP A, C, and D; and 10% are B, E, F, and G; 20% of XP patients are XP variant [6]. Their worldwide distribution is heterogeneous with a predominance of certain forms depending on the regions: group C is most frequently reported in Mediterranean countries [15, 16] and in Europe (60% of XP cases in France are XPC), groups A and F in Japan (XPA represents 40% of all cases in Japan), and groups C and D represent respectively 20% and 30% in the United States, while group A is very rare [6].

In our series, all 28 XP patients diagnosed were admitted to the plastic surgery and burn department for surgical procedures of cutaneous and mucosal tumor lesions. The average age of first cutaneous signs was 1.41 years (1 month-2 years) and the average age of onset of the first tumor was 8.7 years (3 years-22 years). The average age of consultation was 7.72 years (3 years-16 years). The age of onset of the first tumors varied between 2 months and 20 years with an average of 8 years, except in XP variant cases where they can appear later (up to 40 years in some cases). Thus, this age limit depends not only on the complementation group but also on the tumor histological type; indeed, basal cell and squamous cell carcinomas are the first to appear (most often before 10 years) followed by melanomas that appear later (around 17 years). [9, 10].

XP is an autosomal disease, therefore both sexes have the same risk of having XP. In our series, the sex ratio is similar to that of the literature, with a male predominance.

In our series, as well as in the literature, there is no ethnic predisposition for XP. (6) The majority of our patients come from urban areas (53%), unlike the IBN ROCHD series where most were from rural areas (85%) (7), which should make it easier for them to access healthcare. 75% of our patients come from a low socioeconomic background, similar to the IBN ROCHD series where all patients came from families with a disadvantaged socioeconomic status: rural habitat (85%), distance from healthcare facilities (80%). The consanguinity and large family size are factors that increase the chance of an AR disease, such as XP, to manifest; they are characteristic of Maghreb countries including Morocco. (6, 11) The presence of a similar XP case in the family is a risk factor that allows doctors to easily and early diagnose the disease; this risk factor is present in 43% of our cases, whereas in the IBN Rochd series, it is 15% (7), which can be explained by the limited number of cases in our series. In sunny Maghreb countries, especially in Morocco, sun protection for children is difficult to obtain, which seems to play a role in the early onset of tumors. In Tunisia, photoprotection was almost absent in 1980, but it has significantly improved since the 2000s; as a result, medical management has shifted from aggressive tumor destruction to a less aggressive conservative treatment. This has considerably improved the survival and quality of life of these patients. (7)

XP is a condition that combines cutaneous and ocular manifestations of hypersensitivity to sunlight, and sometimes neurological involvement, resulting in a characteristic clinical picture. The age of onset and intensity of symptoms can vary greatly due to genetic heterogeneity and environmental factors [5]. Diagnosis is usually straightforward when the patient presents with advanced complications, but can be difficult in the absence of a suggestive family history. Symptoms typically start to appear between 6 months and 2 years of age, with a mean age of onset of 1.15 years [7]. Repeat episodes of severe sunburn, unusually persistent erythema in photoexposed areas, and a family history of the disease should raise suspicion of XP.

The positive diagnosis of cutaneous carcinomas is based on clinical examination and confirmed by anatomopathological examination, which allows for an accurate diagnosis, quality control of excision, and appropriate management. Cutaneous-mucosal tumors of all histological types were reported in 86.8% of cases (19 cases). If effective photoprotection is not introduced early, the accumulation of unrepaired DNA lesions induced by UV radiation can lead to the appearance of various benign tumors, actinic keratoses, and especially malignant tumors characterized by high frequency, multiplicity, and early onset, which can occur as early as childhood and significantly shorten life expectancy [17, 18]. In our series, the mean age of onset of the first cutaneous tumor of any histological type was 8.7 years, with an age range from 3 to 22 years. The age of onset of the first tumors varies depending on the clinical form of XP but remains very early, averaging 8 years, which is 50 years earlier than in the general population [7]. The mean age of onset of the first tumor in the IBN ROCHD series was 7.7 years [7].

Conclusion:-

Xerodermapigmentosum (XP) is a rare autosomal recessive disease characterized by heterogeneous clinical and cellular manifestations, including dermatological and ocular symptoms with a high risk of skin and mucosal neoplasia, and sometimes neurological involvement. The disease is often diagnosed late and is prevalent in regions with high consanguinity and sunny climates. Early and comprehensive medical and social management is crucial for reducing morbidity and mortality. Surgery is the preferred treatment for XP tumors, but it is difficult and may require multiple surgical procedures. Preventive measures, including awareness, genetic counseling, photoprotection, and early diagnosis, are essential. Despite these measures, XP patients often have a nocturnal and shortened life.

Conflict of interest statement

All authors declare that they do not have any conflict of interest in this publication.

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