Unresectable and chemoresistant conjunctival squamous cell carcinoma on xeroderma pigmentosum treated by salvage radiation therapy: A case report and a review of the literature

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Keywords: Xeroderma pigmentosum, Squamous cell carcinoma, Radiation therapy, Chemoresistance.

Key clinical message

Radiotherapy is a very effective modality and its place should be reconsidered in the management of cancers in patients with xeroderma pigmentosum.

INTRODUCTION

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease characterized by a defect in DNA repair manifested essentially by extreme sensitivity to ultraviolet (UV) radiation, hence its name of photodermatosis [1,2]. Its vital prognosis is particularly conditioned by the appearance of cancers, essentially of the skin and ocular surfaces, requiring early and appropriate treatment [1, 2]. Among the therapeutic modalities, radiation therapy (RT) has had, until now, only a small place, as it is suspected to be potentially deleterious in these patients by its DNA damaging mechanism [1,2].

In this manuscript, we will report on the clinical history of a little girl with XP treated with standard-dose RT for an un-resectable, chemo-resistant squamous cell carcinoma (SCC) of the right ocular conjunctiva. In addition, we will review the literature on the association of XP and RT, focusing on the tolerance to ionizing radiation (IR).

CASE DESCRIPTION

A 10-year-old girl, third of five children, born of consanguineous parents, was referred to our department for the management of a painful right ocular mass, occurring in a field of XP. The same symptomatology was found in her younger sibling who also developed a conjunctival mass of the right lower eyelid.

At the age of two, the parents noticed a photophobia, multiple sunburns after brief sun exposure, and the presence of hyperpigmented and hypopigmented spots on the face, neck, and arms. At the age of seven, she developed a conjunctival mass on the lower right palpebral surface, which buds, ulcerates and finally becomes

so hemorrhagic that the patient consults in August 2020. She presented in a good general condition with an Easter Cooperative Oncology Group (ECOG) Performance Status (PS) of 1, a height of 125 cm and a weight of 23 kg. The initial clinical evaluation revealed an ulcerating and bulging12-cm right orbital mass, very hemorrhagic, infiltrating the homolateral nostril wing as well as the contralateral wing which appeared ulcero-necrotic (fig.1). There were no suspected cervical lymph nodes. Contralateral conjunctival hyperhemia as well as areas of cutaneous hyper- and hypopigmentedwere noted on the face, neck, entire chest and upper limbs. The orbito-cerebral computed tomography (CT) scan performed on August 8th, 2020 showed a 87mm right palpebral mass whose epicenter appeared to be the lower eyelid (fig.2). The mass invaded the masseter muscles, the infraorbital soft tissues and the eyeball which appeared outside the orbital cavity; there was a lysis of the zygomatic bone and the beginning of an extension into the infratemporal fossa. A biopsy revealed a poorly differentiated and invasive SCC. A thoraco-abdomino-pelvic CT scan revealed no secondary lesions. The tumor was therefore classified T4dN0M0 [3]. Given the extent of the tumor, the multidisciplinary tumor board (MDT) decided to start neoadjuvant chemotherapy, followed by a loco-regional treatment [surgery and/or concurrent chemo radiotherapy (CCRT)] depending on the response. After a pre-therapeutic assessment without any particularities, chemotherapy based on Cisplatin and 5Fluoro-Uracile (CDDP-5FU), at a rate of 6 courses every 3 weeks was implemented. The first cycle was administered on August 31th, 2020. After the third cycle, the patient developed a grade 3 anemia and neutropenia, requiring postponement of the fourth cycle. After management of this haematological toxicity, the 4th cycle was administered on November 11th, 2020. However, this time she developed a grade 3 acute renal failure with a glomerular filtration rate (GFR) of 15 ml/min/1.73m2 (versus GFR of 85.8/ml/min/1.73m2 on Nov. 1, 2020), which necessitated discontinuation of the chemotherapy. Clinically, only a stabilization of the tumor was seen. In view of this poor response, the reluctance

of moving on to a second line chemotherapy due to the alteration of her renal function, and the non-resectability of the tumour, the MDT recommended radical RT. The local examination performed during the RT consultation revealed the right orbital mass, which was still 12 cm long, associated with the ulcerated lesion of the nostrils but without cervical adenopathies, in a little girl in good general condition with an ECOG PS of 1 and without neurological disorders. The dosimetric CT scan was performed on December 15th, 2020 and a dose of 59.4 Gy was prescribed on the tumor. The dosimetry performed allowed for optimal coverage of the mass (Fig. 3); the dosimetric constraints at the level of the organs at risk were also respected, evidently while scarifying the right ocular system. From January 13th, 2021 to February 26th, 2021, she received a total dose of 59.4 Gy in 33 fractions of 1.8 Gy per fraction. Tolerance to radiotherapy was good despite XP's terrain with a grade 2 dermatitis and a grade 2 mucositis of the oral cavity, which evolved well under local and systemic treatment. Clinically, the therapeutic response was reflected by a virtual disappearance of the pain and a 30 to 40% decrease in tumor mass. Knowing the delayed effect of RT, we expect an increase in therapeutic response in the coming weeks. Unfortunately, she was lost to follow-up 3 months after the end of the RT, due to social taboo on the disease.

DISCUSSION / REVISION OF THE LITERATURE

XP is a rare autosomal recessive genetic disorder, affecting on average 1 in 1,000,000 children worldwide, with a much higher prevalence in certain countries with communities where consanguinity is common (Japan, Middle East, Maghreb) [4, 5]. It is observed on all continents and in all racial groups, and affects both males and females, diagnosed at an average age of 12 years (range 1 month – 85 year) [1].

XP was first described in 1874 by Moritz Kaposi, a Hungarian dermatologist, and is essentially characterized by an increased sensitivity to ultraviolet (UV) radiation, hence its name photodermatosis [1]. It is actually a group of diseases

characterized by a defect of DNA repair mechanisms, particularly the Nucleotide Excision Repair (NER) pathway, involving the mutation of certain genes and proteins [1, 2]. Depending on the mutated gene and the defective protein, eight complementation groups have been identified, from XP-A to XP-G, and the variant group XP-V [1, 2]. Molecular genetic tests can be performed to identify the mutated gene and consequently the complementation group to which the patient belongs.

The clinical diagnosis is quite easy, marked by skin manifestations occurring from the first months of life, in the form of hypersensitivity to the sunlight with burns in photo-exposed areas, found in 63% of cases by Bradford in his study of 106 patients with XP [2]. Ocular symptoms, particularly in the form of early-onset photophobia, were also present, as well as progressive neurological degeneration, described in 24% of cases by Bradford [1, 2]. Finally, an increased susceptibility to skin and ocular surface cancers [basal cell carcinoma (BCC), SCC and melanoma)] is present with a 2.000 to 10.000 times higher risk compared to the general population [2]. Indeed, Kraemer reported skin cancers in 45% of patients, 97% of them on the face and neck, and Bradford reported a patient who developed 284 histologically documented BCCs, 12 SCCs and 24 melanomas [1, 2]. This cluster of arguments generally allows for the diagnosis of XP, but not for the type of complementation, even if there are some clinical differences depending on the mutated gene. Indeed, patients suffering from the XP-A or XP-D form generally present extreme sensitivity to UV radiation with important neurological disorders, whereas those suffering from the XP-E form present relatively mild symptoms and no neurological disorders, but will have more tendency, together with those of the XP-E form, to develop skin cancers [2].

RT for cancers of the skin and ocular surfaces

The vital prognosis is strongly conditioned by the almost inevitable occurrence of cancers of the skin and ocular surfaces [1]. Indeed, cancers represent the first

cause of death in these patients, requiring early and adapted management [1, 2]. This early diagnosis and management is sometimes difficult in certain cultures with a huge taboo on XP. Among the different therapeutic options, surgical treatment should always be considered as first line when feasible. Other treatment modalities must be discussed on a case-by-case basis in the MDT. RT, being a loco-regional treatment, could be an alternative to surgery, if not an adjuvant to surgery. However, given the physiopathology of XP and the fact that the main target of ionizing radiation (IR) is DNA, this RT has often been considered as potentially deleterious/contra-indicated for these patients.

Very few cases concerning the use of RT for malignant neoplasia occurring in XP have been reported. In 1992, Salob et al. reported the case of a Pakistani young girl, who was diagnosed with XP-C at the age of 10 and confirmed by a significant 9% reduction in nucleotide excision repair (NER) in fibroblasts from biopsy specimens [6]. She had also developed a SCC of the right ocular conjunctiva and localized skin cancers of the face, all of which were successfully treated either by surgery or by application of 5-fluorouracil (5-FU) cream. However, at the age of 14, she presented with an angiosarcoma of the scalp treated by surgery followed by adjuvant RT, which had to be stopped early at a total dose of 38 Gy, i.e. 19 fractions of 02 Gy, because of poor tolerance [7]. Indeed, the treatment was marked by an acute grade 3 dermatitis associated with an osteonecrosis of the external table of the skull opposite the irradiated region, lesions which never completely healed. She also presented a chronic toxicity, i.e. 2 years after RT, in the form of a progressive cerebral edema leading to her death [7, 8].

More recently, in 2013 Sahai et al reported the case of a 10-year-old boy with XP who developed multiple BCC lesions of the face and scalp, for which he had hypofractionated RT totaling 48 Gy in 16 fractions, 36 Gy in 12 fractions, and 20 Gy in 5 fractions [11]. Tolerance was excellent with at most a grade 1 dermatitis,

and the response was good marked by a quasi-total to total regression of the lesions [11].

The incidence of non-cutaneous cancers in patients with XP is difficult to assess, however it seems that the brain is one of the preferential internal locations [1]. In 1999, Giglia et al reported on the case of a boy with XP-C diagnosed at the age of 4, who developed a thalamic anaplastic astrocytoma at the age of 7 [9]. He underwent subtotal resection with a 30 mm residue on postoperative magnetic resonance imaging (MRI), indicating chemotherapy with BCNU, Etoposide and Cisplatin, followed by RT with a standard total dose of 54 Gy [9]. Tolerance during treatment was good with stable neurological status. The response 2 months after the end of radiotherapy was marked by a total disappearance of the thalamic mass [9]. However, 1 month later there was a rapid deterioration of his neurological state with on the control MRI a multifocal tumor progression, leading to his death 6 months later [9].

In 1998, DiGiovanna et al reported the case of a 21-year-old patient with XP-C, whose disease history began at the age of 2, with a progression marked by the occurrence of multiple cutaneous tumours surgically resected [10]. He was subsequently included, at the age of 17 years, in a clinical trial evaluating the efficacy of oral isotretinoin in the prevention of skin cancers [10]. During the therapeutic window where isotretinoin was stopped, he presented a neurological symptomatology with tumor infiltration of the medulla on MRI. Histopathological examination after biopsies showed a grade II diffuse fibrillary astrocytoma [10]. As the tumor was not resectable, RT was performed at a total dose of 50.4 Gy [10]. Tolerance to the treatment was good with at most an acute grade 2 dermatitis without other associated signs, which allowed the author to conclude that "patients with XP can tolerate therapeutic doses of IR" [10]. Furthermore, this RT resulted in a complete tumor response after 02 years that persisted for at least 09 years [10]. This clinical case is most similar to ours. Indeed, our patient benefited from

standard dose RT with a good clinical tolerance marked at the most by a grade 2 dermatitis as for the DiGiovanna patient. Moreover, this RT allowed us to obtain a nice response, i.e. a reduction of more than 30% of the mass objectified at 1 month after the end of the RT. In the case described by DiGiovanna et al, the irradiated tumor was still persistent up to 8 months after RT and only started to regress well afterwards [10].

Re-irradiation

Even re-irradiation has been attempted, with first Wei et al reporting in 2010 the case of a 17- year-old patient with XP who had had 5 years earlier adjuvant RT at a total dose of 59.4 Gy in 33 fractions of right hemiface and hemi neck for a SCC [12]. Following the appearance of cervical and intra-parotid lymph node metastases, a new tumor resection associated with a right cervical neck dissection was performed [12]. Adjuvant re-irradiation was performed on the right hemi neck and the left submandibular area at a total dose of 54 Gy in 30 fractions. Tolerance was marked by grade 3 mucositis and grade 1 dermatitis, both evolving well under local treatment [12]. Eighteen months after the end of treatment, he had no sequelae and no recurrence [12].

Then, in 2011, Schaffer et al reported the case of 2 boys with XP and SCCs of the skins treated by surgical resection and adjuvant RT without significant toxicity [13]. The first boy presented at the age of 13 years a locally advanced SCC of the left cheek, surgically resected and then irradiated to a total dose of 67 Gy in 38 fractions, with good tolerance [13]. He presented a tumor recurrence in the irradiated area, which was treated by surgery and re-irradiation 2 years after the first RT, this time with a dose of 54 Gy in 30 fractions, still with good tolerance [13].

Research on radio-sensitivity

One hypothesis to explain the above described differences in radiosensitivity may be the different subgroups. However, case reports and preclinical studies have not yet succeeded in demonstrating one.

In table 1, which lists the main clinical cases reported, seven out of the 17 cases belonged to the XP-C, for the other 10, the group was not specified; 3 cases had a grade 3 toxicity or more, including 1 from XP-C group and 2 from unspecified groups.

In Arlette's preclinical study [14], the 33 XP lines were distributed as described in table 2. The line that showed hyper-radiosensitivity belonged to the XP-C complementation group. Two other lines were slightly more sensitive than normal (groups G and D), but no clear relationship between group and radiosensitivity could be found.

More particularly, in 2008 Arlette et al published the results of their studies conducted on a large cohort of XP fibroblast lines [14]. For this purpose, they assessed their radio-sensitivity by comparing the cell survival after irradiation with a Cobalt 60 source of 33 XP fibroblast lines versus 53 normal fibroblast lines, 8 fibroblast lines of Ataxia telangiectasia (A-T), 7 fibroblast lines of Cockayne syndrome (CS) and 4 fibroblast lines combining XP and CS [14]. In general, XP fibroblasts did not appear more radiosensitive than normal cells, as well as cell lines combining XP and CS [14]. On the other hand, and not surprisingly, A-T fibroblasts were extremely radiosensitive [14]. However, among the XP cells subgroup analysis found one line (XP14BR) which was extremely radiosensitive like A-T cells, and two lines (XP3BR and XPJCLO) which were slightly more radiosensitive than normal cells [14]. Moreover, Arlette et al, using gene transfer techniques, had shown that this hyper-radiosensitivity noted with the XP14BR line was not related to the XP-C mutation but rather to the presence of another

gene [8]. Finally, it is important to note that this XP14BR line comes from the fibroblast culture of the previously described young Pakistani girl who had an adjuvant RT for an angiosarcoma of the scalp with an acute toxicity requiring the stop of her treatment and a chronic toxicity which led to her death [7]. The 2 other radiosensitive lines (XP3BR and XPJCLO) were from patients who had never had RT, not allowing to establish a link between cellular radiosensitivity and clinical radiosensitivity [14]. In the absence of hyper-radiosensitivity of fibroblasts from XP patients, it becomes difficult or impossible to correlate with clinical radiosensitivity. This is all the more true since the DNA damage caused by IR essentially involves the base excision repair (BER) and non-homologous end joining (NHEJ) repair pathways, whereas it is the NER pathway that is defective in XP [7,13,14]. However, most authors agree on the need to be cautious before initiating RT in XP patients [7, 13, 14]. This precautionary principle was applied by Schaffer, who tried 5 sessions of 0.2 Gy on her 13-year-old patient before delivering 67 Gy [13].

CONCLUSION

Xeroderma pigmentosum is a rare genetic disease whose vital prognosis is conditioned by the occurrence of cancers. Its physiopathology, characterized by a defect in DNA repair, has always led to a restraint of the use of RT in the management of the associated cancers, a restraint which until now has not been clearly founded. Therefore, the place of RT in these patients could/should be reconsidered. Nevertheless, this RT will have to be done with caution and evaluated on an individual base. While waiting for more profound research to confirm or refute this restraint, is each evidence, even a single case report, of interest.

Author contribution

Study design: MM, DVG.

Data collection: MM, PMG.

Data analysis and interpretation: MM, DVG.

Writing of the manuscript: MM, DVG.

Revision of the manuscript: All authors.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

None.

Acknowledgments

We thank editors and the anonymous reviewers for their insightful comments and great help to improve this work.

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Fig.1: ulcerating and bulging12-cm right orbital mass at the initial clinical evaluation.

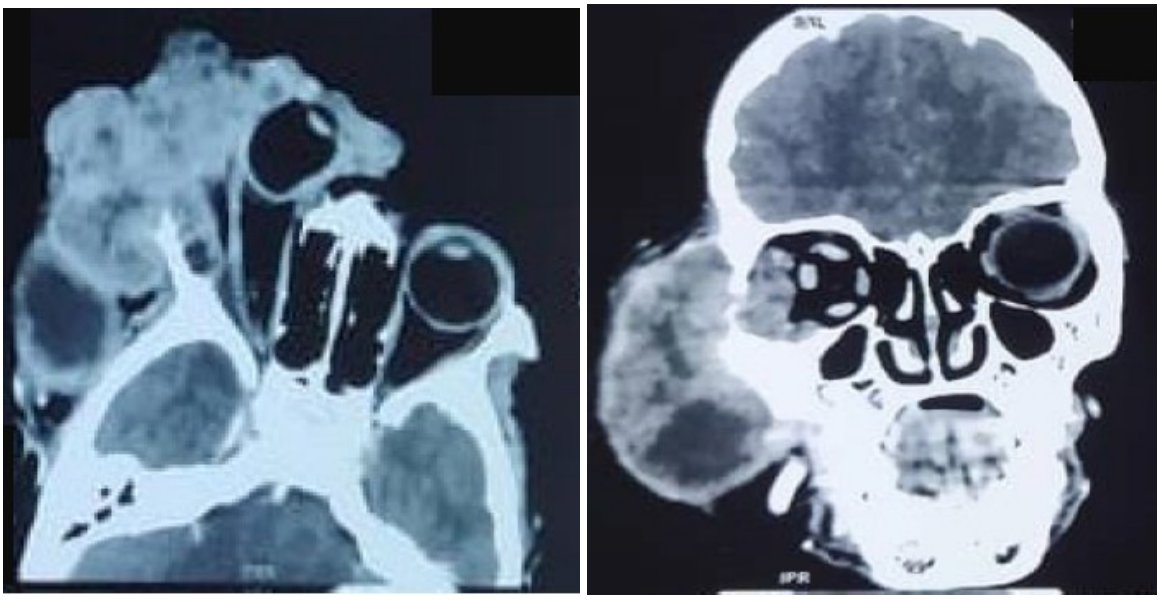

Fig.2: Right orbital mass invading the masseter muscles, the infraorbital soft tissues, lysing the zygomatic bone and infiltrating the infratemporal fossa on the axial et frontal orbito-cerebral CT scan.

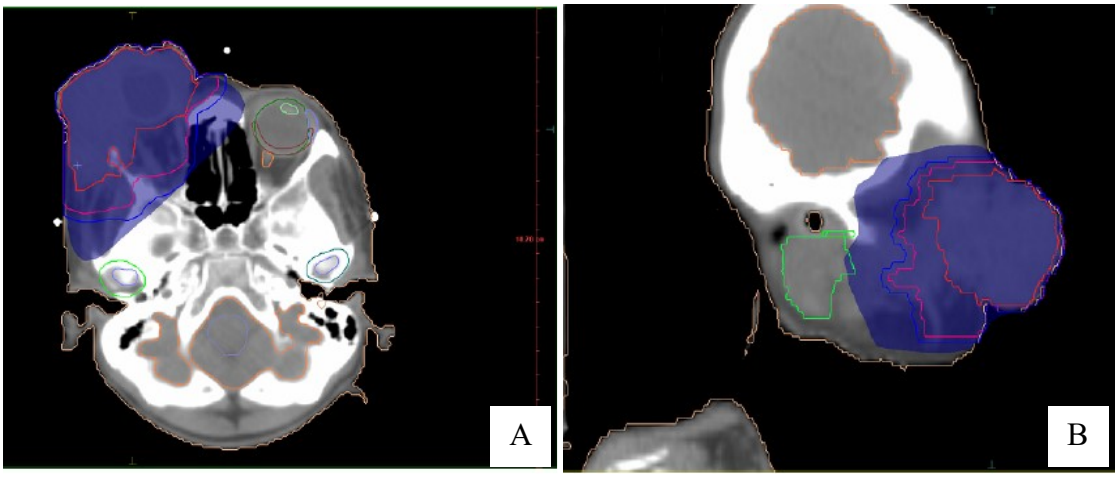

Fig.3: Dose color wash from a transversal (A) and a sagittal (B) planning CT scan

Fig.4: one month after RT