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Radio chemotherapy for Squamous Cell Carcinoma of Hypopharynx in One Patient with Ehler Danlos Disease

Berenice Collineau[1*], Laetitia Padovani[1], Nicolas Fahkry[2], Marie-Aleth Richard[2], Tiffany Busa[2], Isabelle Pougnet[1]

Abstract

Head and neck squamous cell carcinomas are frequent, in most cases developed in a context of alcohol and tobacco consumption. Therapeutic options for localized head and neck carcinomas are surgery, if possible, and radiotherapy with or without chemotherapy. Ehler-Danlos syndrome is a rare group of disease, clinically and genetically heterogeneous, characterized by connective tissue fragility. Management of adverse event during radiotherapy remains a challenge, especially for people known to have connective tissue disorder. Here, we report a case of a man suffering from periodontal Ehler Danlos syndrome, treated with concomitant radiochemotherapy, with adapted radiotherapy regimen, for hypopharyngeal squamous cell carcinoma.

Keywords: Radiotherapy; Hypopharynx cancer; Ehler-Danlos syndrome; Safety

Introduction

Ehler Danlos syndromes (EDS) represent a group of hereditary diseases belonging to connective tissue diseases. EDS is a rare syndrome (frequency estimated at 1 in 5000 in the general population), clinically and genetically heterogeneous, with predominantly autosomal dominant transmission. This syndrome is characterized by connective tissue involvement with common clinical features: joint hypermobility, hyperextensible skin and tissue fragility. Mutations in collagen genes or enzymes involved in collagen modification have been identified for most subtypes. The 2017 international classification of EDS describes 13 subtypes, according to clinical characteristics, even if the definitive diagnosis is based on the presence of a genetic variant. Classic EDS (cEDS) combines skin and joint involvement. More than 90% of patients with cEDS have a heterozygous mutation in one of the genes encoding type V and type I collagen (COL5A1 and COL5A2) [1,2].

Periodontal Ehler danlos syndrome (pEDS) is a rare disease, of autosomal dominant inheritance, caused by pathogenic variants in the C1R (90%) and C1S (10%) genes, encoding for C1r and C1s subunits of the first component of the classical complement pathway. The major criteria of pEDS that can suggest the diagnosis correspond to: early periodontitis (in childhood or adolescence), permanent tooth loss due to loss of gingival attachment, pre-tibial hyperpigmentation, and 1st degree family history with clinical criteria for EDS. The other suggestive signs may partly be joint hypermobility, skin fragility including abnormal scars and easy bruising, hernias. The presence of gingival attachment loss is considered pathognomonic for pEDS, leading to destructive inflammation of the dental anchor system and premature loss of teeth. Rare but severe vascular complications such as life-threatening arterial ruptures have been reported [1,3].

Affiliation:

[1]Department of Radiotherapy, Assistance Publique des Hôpitaux de Marseille, 80 Rue Brochier, 13005 Marseille, France

[2]Assistance Publique des Hôpitaux de Marseille, 80 Rue Brochier, 13005 Marseille, France

***Corresponding Author**
Berenice Collineau, Department of Radiotherapy, Assistance Publique des Hôpitaux de Marseille, 80 Rue Brochier, 13005 Marseille, France.

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Head and neck squamous cell carcinomas (HNSCC) and more particularly cancers of the pharynx are developed in most cases in a context of alcohol and tobacco consumption. According to the AJCC 2017 classification, treatment of inoperable localized cancers is based on radiotherapy, whether or not associated with chemotherapy or EGFR inhibitors [4-6]. Intensity-modulated conformal radiotherapy (IMRT) has become the standard irradiation technique in recent years, with classically delivered dose of 70 Gy [7,8].

Acute (up to 90 days after the end of radiotherapy) and late side effects of head and neck area irradiation are frequent, poorly tolerated and can lead to serious complications. More than 90% of patients treated with concomitant radiochemotherapy develop acute toxicity, of which around 77 to 80% are grade 3-4. About 30% of patients develop delayed toxicity at 5 years, of which about 12 to 25% are grade 3-4. Main acute side effects are mucositis, radioepidermatitis, xerostomia, dysphagia and odynophagia, but toxicity can also affect the vessels or cause laryngeal oedema. They alter the quality of life, within 60% of cases, the establishment of enteral nutrition for the duration of the treatment, related to treatment- induced dysphagia or mucositis. Late side effects may include hypothyroidism, xerostomia, skin fibrosis, trismus or more rarely osteoradionecrosis [6,9,10]. In this article, we present a case of a man with hypopharyngeal squamous cell carcinoma, suffering from Ehler Danlos syndrome, treated with concomitant radio chemotherapy.

Case Report

Mr X is a 62-year-old man with periodontal Ehler Danlos syndrome with an alteration of the C1R gene (c.926G > T, p.(Cys309Phe)). His main symptoms of EDS are arthralgia, periodontal disease with total edentulism, healing disorders and in particular chronic venous ulcers of the lower limbs. In a context of chronic alcohol and tobacco intoxication and faced with a voluminous cervical lymphadenopathy, this patient was diagnosed with squamous cell carcinoma of the right piriform sinus after endoscopy in June 2021 [Figure 1].

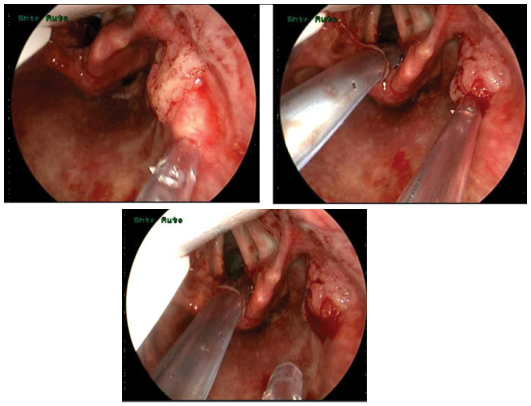

Figure 1: Initial endoscopy with visualization of the tumor (June 2021).

The initial CT scan found multiple bilateral cervical lymphadenopathy, including a large capsular rupture in right sector III, partially invading the right jugular vein [Figures 2 and 3]. The lesion was classified as T1 N3b M0, initially operable (according to the AJCC 8th edition).

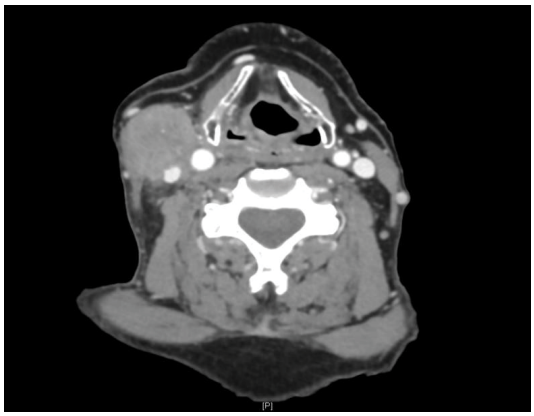

Figure 2: Initial CT scan with visualization of the lymph node sheathing the internal jugular vein.

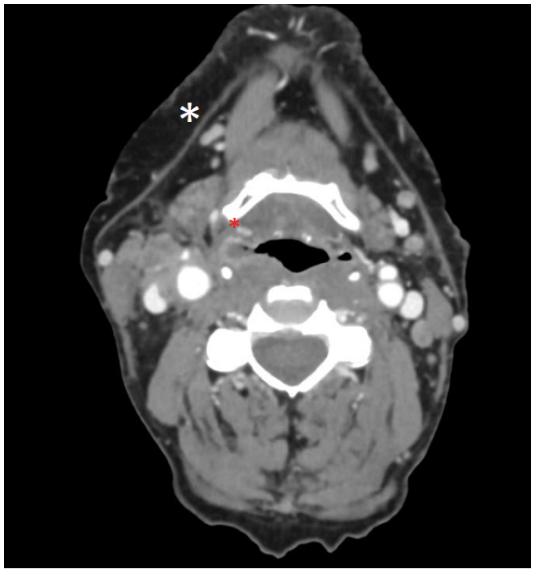

Figure 3: Initial CT scan with visualization of the right piriform sinus tumor.

During robot-assisted surgery, following the naso-tracheal intubation, the patient presented with significant epistaxis requiring packing, themselves responsible for significant ulceration of the mucosa of the posterior pharyngeal wall and tearing of tissues. Faced with these hemorrhagic complications, the surgery had to be interrupted.

A new multidisciplinary consultation meeting ruled on a therapeutic alternative by concomitant radio-chemotherapy in view of the patient's inoperability. Because of his history of periodontal Ehler danlos syndrome, which could lead to potentially greater side effects, the radiotherapy regimen

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was adapted. This planned to deliver a total dose of 60 Gy according to a split course and bi-fractionated scheme with the aim of promoting the repair of healthy tissue; inspired by the VOKES scheme used in re-irradiation in HNSCC [11].

The patient therefore benefited from 4 phases of 15 Gy in 10 fractions and in 5 days; with 1.5 Gy per fraction. Each phase was spaced 2 weeks apart. The concomitant chemotherapy was CISPLATIN (15 mg/m²) and 5 FU (175 mg/m²), delivered from D1 to D5 of each phase of radiotherapy. During radiotherapy, the patient presented with grade 1 dysphagia with liquid and semi-liquid food resulting in a loss of 4 kg. No cutaneo mucosal or vascular side effects were reported. The potentiation chemotherapy of the 4th series of radiotherapy was not performed given the doses of CISPLATIN already received and the risk of potential renal failure.

In November 2021, the first reassessment scan showed tumor and lymph node partial response. In addition, the patient recovered a solid diet and showed no more acute side effects from the radiotherapy. In March 2022, the next follow-up CT scan shows persistence of right sector III lymph nodes which present hypermetabolic activity on PET-CT. Close monitoring is decided. In May 2022, the CT scan confirms the presence of a recurrent lymphadenopathy in capsular rupture (Tx rN3b M0). An endoscopy with biopsies were then performed: no local tumor recurrence was demonstrated on the piriform sinus biopsies. In the lymphadenopathy, there was a recurrence of his squamous cell carcinoma with a CPS score of 5 [Figure 4].

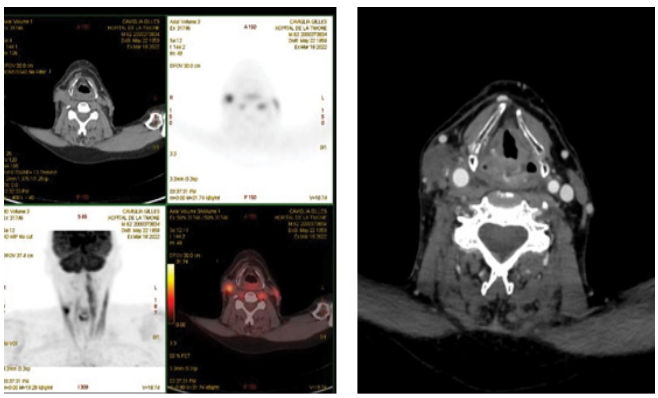

Figure 4: PET-CT and CT scan showing lymphadenopathy persistence (May 2022).

Because of the sheathing of the internal carotid artery, lymphadenopathy recurrence was inoperable. Immunotherapy with NIVOLUMAB is then started in June 2022.

During treatment, the appearance of pulmonary pseudonodules were noted, in a context of infectious pneumopathy, but persistent over time [Figure 5]. Lung biopsies found possibly immune-mediated lesions without malignant cells. Immunotherapy was then suspended in January 2023, because of pulmonary toxicity.

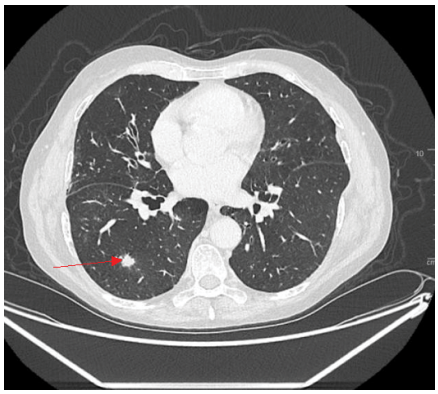

Figure 5: CT scan with pulmonary pseudonodule (December 2022).

After therapeutic abstention with close CT monitoring, no local or metastatic recurrence was noted, but the persistence of suspicious lymphadenopathy corresponding to the one described since March 2022 [Figure 6].

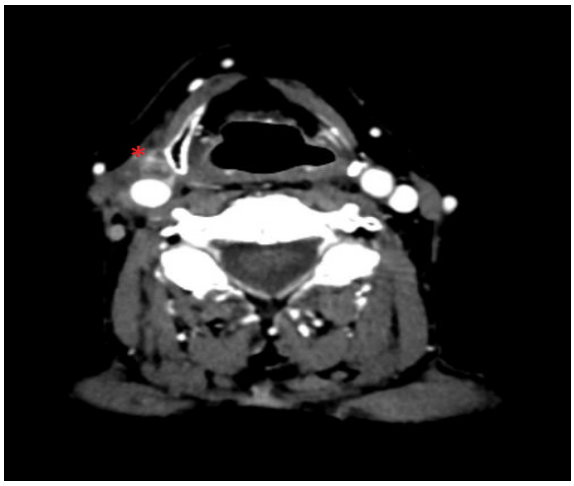

Figure 6: CT scan with persistence of suspicious lymphadenopathy (May 2023).

In May 2023, the patient presented with septic shock with a urinary starting point associated with multiple organ failure (hemodynamic, renal, hepatic, hematological with thrombocytopenia, spontaneous spleen fracture) which resulted in the patient's death.

Discussion

To our knowledge, only 2 case reports have been previously reported in the literature concerning the performance of radiotherapy in patients with Ehler Danlos syndrome, and none is about HNSCC. The first case report published in 1996, described the development of multiple aneurysms of the polygon of Willis within 7 months following cerebral radiotherapy in a 62-year-old patient [12].

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The second case report published in 2021 describes the performance of postoperative radiotherapy for a 62-year-old patient with EDS of the hypermobile subtype, suffering from breast cancer. Acute grade 2 skin toxicity was reported but no long-term complications from radiotherapy received, associated with tumor remission [13].

A meta-analysis was performed in response to the dogma that collagen diseases and inflammatory bowel diseases are contraindications to radiotherapy. This meta-analysis concerns patients who had radiotherapy alone, post-operatively, combined or not with chemotherapy, all locations combined. The results concerning collagen diseases show an acute toxicity rate including 1% of grade 3-4. Regarding delayed toxicity, the rate of grade 3-4 side effects was 6%. In this meta-analysis, only 25% of patients received radio-chemotherapy and no localization concerned the head and neck area [14].

In addition, there are other connective tissue diseases with clinical and pathophysiological similarities, of hereditary origin, mainly Marfan's disease. Two case reports have been published concerning radiotherapy in patients with Marfan's disease. The first case [15] described a 17-year-old woman with Marfan's disease who was treated for a frontal mixed glioma. She was treated with adjuvant radiotherapy at a dose of 50 Gy in 25 fractions. Tolerance during radiotherapy was correct and comparable with patients without Marfan's disease. Long after radiotherapy, the patient presented with complex partial epilepsy and clinical deterioration of her glioma, with no scanographic anomaly or cerebral radionecrosis in favor of radiotherapy toxicity. The second case [15] described a 65-year-old patient with Marfan's disease treated for favorable intermediate-risk prostate adenocarcinoma. He received radiotherapy using the IMRT technique (6 MV photons) with a delivered dose of 79.8 Gy in 42 fractions, with excellent tolerance during and after treatment.

Conclusion

Cervical radiotherapy treatment, at appropriate doses, seems to be feasible with good tolerance in patients with periodontal Ehler Danlos syndrome.

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