# MALIGNANT THYROID TERATOMA AND XERODERMA PIGMENTOSUM: REPORT OF A RARE ASSOCIATION

# TÉRATOME MALIN DE LA THYROÏDE ET XERODERMA PIGMENTOSUM: A PROPOS D'UNE ASSOCIATION RARE

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## ABSTRACT

**Introduction**: Primary malignant thyroid teratoma (PMTT) is an exceedingly rare and aggressive germ cell tumour, primarily affecting adults. Its association with xeroderma pigmentosum (XP), a genetic disorder characterised by defective DNA repair, has never been documented. We report the first clinical observation of this lethal association and discuss the therapeutic dilemma it poses.

**Case Report**: A 17-year-old girl, known to have XP, presented with a rapidly enlarging, suspicious thyroid nodule. While initial cytological and radiological findings were misleadingly suggestive of benignity, the clinical progression was highly aggressive. The patient underwent total thyroidectomy with left mediastino-recurrent lymph node dissection. Final histopathology confirmed a PMTT with a primitive neuroectodermal component and regional lymph node metastasis. Cisplatin-based chemotherapy was initiated, but the clinical course was rapidly complicated by severe multi-organ toxicity. This systemic failure, directly linked to the DNA repair defect of the XP phenotype, led to a fatal outcome.

**Conclusion**: This unique case underscores the extreme diagnostic challenges of PMTT and the profound therapeutic impasse encountered in XP patients. The inherent hypersensitivity to DNA-damaging agents in XP individuals renders standard aggressive oncological protocols nearly impossible to implement, and calls for a critical reflection on personalised, low-toxicity treatment alternatives for this vulnerable population.

**Keywords**: Teratoma; Thyroid Neoplasms; Xeroderma Pigmentosum; Cisplatin; Drug-Related Side Effects and Adverse Reactions.

## RÉSUMÉ

**Introduction**: Le tératome malin primitif de la thyroïde (TMPT) est une tumeur germinale exceptionnellement rare et agressive, survenant principalement chez l'adulte. Son association au xeroderma pigmentosum (XP), maladie génétique caractérisée par un défaut de réparation de l'ADN, n'a jamais été rapportée. Nous rapportons la première observation clinique de cette association létale et discutons le dilemme thérapeutique qu'elle pose.

**Observation**: Une jeune fille de 17 ans, suivie pour un XP, a consulté pour un nodule thyroïdien suspect, rapidement évolutif. Alors que les données cytologiques et radiologiques initiales étaient faussement rassurantes, l'évolution clinique a été très agressive. La patiente a bénéficié d'une thyroïdectomie totale avec curage récurrentiel et médiastinal supérieur gauche. L'examen anatomopathologique définitif a confirmé un TMPT comportant un contingent neuroectodermique primitif, avec métastases ganglionnaires régionales. Une chimiothérapie à base de cisplatine a été instaurée, mais l'évolution a été rapidement marquée par une toxicité multiviscérale sévère. Cette défaillance systémique, directement liée au défaut de réparation de l'ADN du phénotype XP, a conduit à une issue fatale.

**Conclusion**: Cette observation unique souligne les difficultés diagnostiques majeures du TMPT et l'impasse thérapeutique profonde rencontrée chez les patients atteints de XP. L'hypersensibilité constitutionnelle de ces patients aux agents génotoxiques rend l'application des protocoles oncologiques agressifs standards quasi impossible et impose une réflexion critique sur des alternatives thérapeutiques personnalisées et peu toxiques pour cette population vulnérable.

**Mots-clés**: Tératome; Tumeurs de la thyroïde; Xeroderma pigmentosum; Cisplatine; Effets secondaires indésirables des médicaments.

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## INTRODUCTION

Primary malignant thyroid teratomas (PMTT) are extremely rare neoplasms. Fewer than 40 cases have been reported in the literature since the first case described by Buckwalter et al. in 1954 [1]. Teratomas are prevalent in the paediatric population and are mostly benign, with only a small proportion developing in extragonadal regions (approximately 5%) [2]. Head and neck tumours account for 5% of all germ cell tumours, benign and malignant, and for 6% of all teratomas [3, 4]. The most prevalent sites in the head and neck are the soft tissues of the neck, a subgroup of which involves the thyroid gland [5]. Given the uncommon nature of this tumour, no established guidelines for its management are currently available [2].

Xeroderma pigmentosum (XP) is an uncommon inherited autosomal recessive DNA repair disorder, caused by an impairment in nucleotide excision repair (NER). It has a significant incidence in countries with a high degree of consanguinity [6, 7]. Young XP individuals with inherited mutations in the XPC gene have been found to have multiple thyroid nodules and thyroid carcinomas in several studies of XP patients from North Africa [6]. To our knowledge, no PMTT has been reported in this population. The objective of this report is to describe an unusual association of primary malignant thyroid teratoma in an XP patient, and to discuss its clinical and pathological presentation and its therapeutic management. This work has been reported in line with the SCARE 2023 criteria [8].

## CASE REPORT

A 17-year-old girl with a history of XP and of several cutaneous head tumours was referred to our ENT department for a rapidly expanding midline neck mass. She also had a history of secondary hyperparathyroidism caused by hypovitaminosis D, which had been effectively managed with substitutive treatment. No family history of XP or of other neoplasms was found.

Physical examination revealed a 3 cm hard swelling with a palpable lower edge in the anterior lower left region of the neck, mobile on swallowing. No cervical nodes were found. Skin examination revealed several hypertrophic scars, from previous resections, and freckle-like pigmentations. A hard, well-defined nodular lesion was present at the tip of the tongue. A worrisome pigmented lesion was seen on the upper eyelid (Figure 1). The remainder of the physical examination was unremarkable.



**Figure 1**. Postoperative photograph of the patient showing the characteristic skin of xeroderma pigmentosum: multiple hyperpigmented, freckle-like lesions, and a nodular lesion at the tip of the tongue.

Serum calcium, sodium, potassium and chloride, urinalysis, blood count, parathyroid hormone, chest X-ray and electrocardiogram were all normal.

Neck ultrasound revealed a multinodular goitre predominating in the left lobe. The largest nodule measured 36 mm, and all nodules scored 3 according to the EU-TIRADS classification. No cervical nodes were observed. Fine needle aspiration (FNA) of the thyroid nodule was reported as benign. Excisional biopsy of the eyelid lesion revealed a 3 mm basal cell carcinoma with clear margins, and excisional biopsy of the tip of the tongue showed a haemangioma.

Surgery was performed. Exploratory Kocher cervicotomy revealed an independent nodule at level VI and a multinodular thyroid gland. A total thyroidectomy and a left mediastino-recurrent lymph node dissection were carried out. This option had been decided upon preoperatively, given the patient's predisposition to tumour development and the predominantly solid nature of all nodules.

Frozen section examination showed a torn left lobe filled by a cystic lesion containing a glossy greyish-white substance. The right lobe was colloid and multinodular. Final microscopic analysis revealed a poorly circumscribed proliferation within the left lobe, made up of several components, including squamous, rhabdomyoblastic and immature neural elements with pseudo-rosettes within a myxoid stroma (Figures 2 and 3). The nuclei of the tumour cells exhibited marked atypia. Mitoses were counted at 13 per 2 mm². Comedonecrosis and tumour thrombi were seen.

Immunohistochemistry showed that the neuroblastic component stained positively for synaptophysin and chromogranin A, the rhabdomyoblastic component for desmin and myogenin, and the epithelial component for pancytokeratin. All excised cervical lymph nodes were invaded by the immature neural component (8N+/8N). The final diagnosis was a grade 3 malignant immature teratoma of the thyroid gland with central lymph node metastases, classified pT3 N1a Mx.

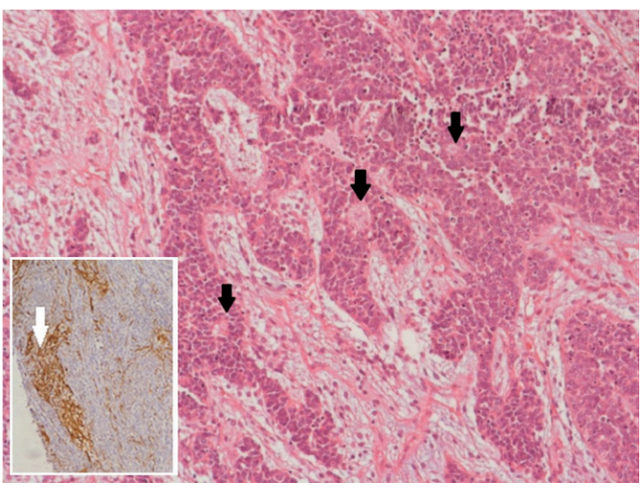


**Figure 2**. Immature teratoma: immature neural elements forming pseudo-rosettes (black arrows). Haematoxylin and eosin, x100. Inset (lower left): synaptophysin is positive in this component (white arrow). Immunohistochemistry, x100.

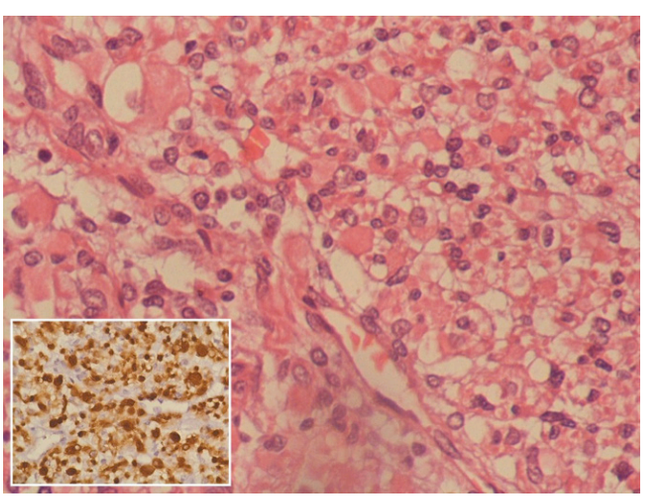


**Figure 3.** Immature teratoma: proliferation of rhabdomyoblasts. Haematoxylin and eosin, x400. Inset (lower left): desmin is positive (white arrow). Immunohistochemistry, x400.

The staging CT scan revealed lymph node metastases with a mass effect on the left jugular vein. After a multidisciplinary team meeting, chemotherapy according to the VIP protocol (cisplatin, etoposide and ifosfamide) was decided upon. Following a pretherapeutic assessment, treatment was started two months after surgery. Evaluation by CT scan after the second cycle showed a complete response.

Unfortunately, several complications emerged after the third cycle. Seven days later, the patient developed pancytopenia, with a haemoglobin level of 5.4 g/dL, epistaxis and acute renal failure requiring several haemofiltration sessions and blood transfusions. She then developed posterior reversible encephalopathy syndrome (PRES), with headache, vomiting and convulsive status epilepticus comprising five seizures. PRES was confirmed by magnetic resonance imaging. She was discharged after one month to continue haemofiltration in another department, and subsequently died from severe anaemia refractory to repeated transfusions. Overall survival was 8 months.

## DISCUSSION

Teratomas are believed to arise from totipotent cells and can form anywhere in the body. Although they typically develop in the testes or ovaries, 2% to 5% may arise in extragonadal sites [9]. According to the World Health Organization classification of tumours of endocrine organs, thyroid teratomas must contain material derived from all three embryonal layers, and must contain immature neural tissue to be categorised as malignant [10]. They frequently give rise to systemic metastases, regional infiltrative growth and disease-related mortality in older children and adults [4, 10].

Although all preoperative investigations in the present case favoured a benign lesion, our patient was at high risk of developing a primary malignant tumour because of her XP. Tunisia, Algeria and Morocco have one of the highest rates of XP worldwide (>1/50,000), related to an elevated allelic frequency of a founder XPC mutation in populations with high rates of consanguinity [7].

The most common clinical presentation of PMTT is an asymptomatic progressive enlargement of the neck; depending on the size and location of the tumour, patients may also present with substantial airway obstruction [2]. This neck swelling may be accompanied by lymphadenopathy or distant metastases, which mostly affect the lungs and the bones [2].

Preoperative diagnosis of PMTT is difficult. Preoperative ultrasound often reveals a well-defined heterogeneous lesion with solid and cystic components, which is the typical appearance of PMTT; ultrasound has a sensitivity of 41% and a specificity of 92%. CT and MRI of the neck may be useful preoperatively, providing a better imaging assessment [2, 4].

Fine needle aspiration cytology (FNAC) is often inconclusive or inaccurate in thyroid teratoma. We were unable to make a preoperative diagnosis because our patient's cytology report was benign, corresponding to Bethesda category II. In a systematic review of articles published between January 2000 and September 2020, only one patient was diagnosed with PMTT before surgery, despite the use of multiple preoperative investigations such as ultrasound and FNA [2]. Thyroid teratomas appear exceedingly difficult to diagnose on FNAC because of their cytomorphological heterogeneity, even when a small biopsy specimen is used, and because of the cytomorphological overlap with neuroblastoma or with medullary carcinoma showing neuroblastoma-like areas [3, 9].

Histologically, malignant teratoma shows a preponderance of primitive neuroepithelium in conjunction with another component [3]. Immature neuroepithelium is the essential feature that defines malignancy in operative specimens [1, 2]. Our findings match those reported in the literature, since the neuroepithelial tissue was predominant and correlated with the aggressiveness of the disease. Although thyroid teratomas are broadly classified as germ cell tumours, their histogenesis and molecular underpinnings remain poorly understood, regardless of grade [10].

Frozen section diagnosis of teratoma may be difficult, given the need to identify the three different germ cell layers, which may require special staining in poorly differentiated cases [3]. Immunohistochemistry can help validate neuronal differentiation and reveal ectodermal or mesodermal features [2]. In our case, immunohistochemistry confirmed the presence of immature neural tissue, documented by positivity for both synaptophysin and chromogranin A, in addition to the presence of parallel components. Published research reports that primitive spindle cell components with rhabdomyoblastic differentiation are regularly seen in PMTT; this was demonstrated in our case by desmin and myogenin positivity [10].

Immature and malignant teratomas consisting mostly of neural tissue must be distinguished histologically from extraskeletal Ewing sarcoma, primitive neuroectodermal tumours, small cell carcinoma, malignant lymphoma and other malignant small cell tumours. In these cases, the identification of additional tissue elements, of the immature or malignant neural tissue, and confirmation by an immunohistochemical panel are crucial for the diagnosis of teratoma [1]. A differential diagnosis with other malignancies therefore needs to be considered whenever the tumour is composed of immature and additional malignant components with areas of mesenchymal and neural tissue.

Regarding the molecular features of PMTT, numerous published studies have revealed gene alterations linked to these uncommon tumours, and several publications have documented a somatic DICER1 mutation, which may play a critical role in malignant transformation [2, 4]. DICER1 had previously been linked to well-differentiated thyroid carcinomas and to multinodular hyperplasia, but these data show a previously unknown role for recurrent DICER1 mutations in primitive thyroid malignancies. This is why malignant thyroid teratomas have been proposed as a clinicopathological category separate from thyroid gland teratomas [4].

There are no established therapeutic guidelines for PMTT, owing to the rarity of the tumour. Adjuvant therapy, which may involve radiotherapy, chemotherapy or both, has been administered in most reported cases after complete surgical excision [1-3, 5]. Benign teratomas have a good prognosis after surgical removal, whereas PMTT has a substantially lower survival rate, often less than one year [5, 10]. In terms of surgical management, total thyroidectomy with central neck dissection appears to be the best course of action. Lateral neck dissection should be performed in the event of macroscopic invasion or of lymphadenopathy detected by palpation or by ultrasound [5].

The effectiveness of external radiotherapy and of radioiodine treatment in improving survival has not been demonstrated [1, 2, 5]. By contrast, aggressive adjuvant chemotherapy, particularly cisplatin-based regimens, has been widely used in patients with immature PMTT and has led to improved long-term outcomes in several studies [2]. The drugs used in PMTT are similar to those commonly prescribed for germ cell tumours; they typically include the bleomycin, etoposide and cisplatin protocol, either alone or in combination with additional agents intended to treat the sarcomatous component [10]. In the present case we used a VIP protocol combining cisplatin, etoposide and ifosfamide, with a good tumour response but lethal adverse effects. The haematotoxic adverse effects of these drugs limit both their dose and their efficacy.

Chemotherapy can be hazardous in XP patients, killing too many normal cells because of their defective DNA repair. Seven patients in the French XP cohort died after receiving chemotherapy, and several XP patients have been reported to have died from cisplatin-related toxicity, including myelosuppression and multi-organ failure [7]. These observations suggest that, when chemotherapy is required, it may be advisable to use less harmful agents that do not damage DNA where possible, or at least to significantly reduce the doses used [7].

Even after extensive surgery, chemotherapy and radiotherapy, PMTT usually shows an aggressive clinical course and a short survival of approximately eight months, the longest postoperative survival recorded being 22 months. The response to radiotherapy and to chemotherapy is temporary, and local recurrence as well as cervical and pulmonary metastases are frequent [10]. The relatively high recurrence rates and the short time to recurrence after the first operation mirror the considerable aggressiveness of these rare tumours, and cancer-related death occurred in almost one third of the cases included in the largest published review [2].

For the first three years, patients should have regular follow-up with ultrasound, CT or MRI, or PET imaging. Tumour markers such as alpha-fetoprotein and beta-hCG should be measured during follow-up visits, since malignant germ cell components may produce these markers and thus signal recurrence [1]. In the present case, none of these markers was assessed. Our young patient died from the adverse effects of chemotherapy, 8 months after diagnosis.

## CONCLUSION

The prognosis of primary malignant thyroid teratoma remains poor and is primarily determined by the patient's age, by the tumour size at presentation and by the histological degree of immaturity. While aggressive

multimodal therapy is generally recommended to improve outcomes, this case demonstrates that such optimal treatment can be lethal in the context of xeroderma pigmentosum.

Because of the constitutional defect in DNA repair, standard genotoxic chemotherapy protocols must be carefully reconsidered in XP patients in order to avoid fatal systemic toxicity. This unique association underscores the necessity of early thyroid screening in this vulnerable population and highlights the urgent need for research into targeted, less invasive therapeutic alternatives. Further studies are required to elucidate the potential pathogenic links between XP and the emergence of rare internal malignancies such as PMTT.

**Ethical considerations** The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the institution where the patient was managed. Written informed consent was obtained from the patient's parents for the publication of this case report and of the accompanying identifiable images (Figure 1).

## Conflict of interest

The authors declare that there is no conflict of interest with respect to the research, the authorship or the publication of this article. There are no financial or personal relationships with other people or organisations that could inappropriately influence this work.

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