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RESEARCH ARTICLE

RADIATION-INDUCED PAPILLARY THYROID CARCINOMA IN A PEDIATRIC BRAIN TUMOR SURVIVOR

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Abstract

Secondary malignant neoplasms are a rare but feared late complication of pediatric cancers. Radiation therapy is a well-established risk factor for the development of thyroid tumors, particularly in children, whose thyroid gland is sensitive to the carcinogenic effects of ionizing radiation.This is the case of a 16-year-old female patient who was diagnosed at the age of 5 with a medulloblastoma of the posterior cranial fossa, which was surgically treated and irradiated. Ten years later, a cervical mass developed, leading to the diagnosis of papillary thyroid carcinoma (PTC) with lymph node involvement. Pulmonary nodules/micronodules were identified,consistent with hematogenous di ssemination. The patient received two doses of radioactive iodine therapy, in the context of an elevated postoperative thyroglobulin level. Follow-up chest CT revealed progression of a suspicious right lower lobe pulmonary micronodule, while whole-body scintigraphy showed multiple iodine-avid foci.This case highlights the need for long-term surveillance in pediatric cancer survivors due to the elevated risk of radiationinduced secondary thyroid malignancies.

Introduction:-

The incidence of papillary thyroid carcinoma (PTC) in individuals under 20 years of age is estimated at 0.46 per 100,000 person-years (95% CI: 0.33–0.59) (1). Recent studies (2) have examined both genetic susceptibility and therapeutic exposures as key contributors to the risk of secondary malignant neoplasms, which remain among the most feared complications in pediatric oncology. Radiotherapy plays a major role in the development of secondary malignant neoplasms, particularly following treatment for a primary malignancy.The thyroid gland, highly sensitive to radiation, is distinctively susceptible to damage caused by radiation. Even low doses of radiation in childhood can lead to a range of endocrine complications, including hypothyroidism, hyperthyroidism, or secondary thyroid cancer.A systematic review of the literature (21 studies; >100,000 patients) found that 20 out of 21 studies reported an increased risk of thyroid cancer following childhood radiotherapy (3). This evidence underscores the importance of systematic screening and long-term surveillance in pediatric populations exposed to radiation. Such measures are critical to ensure early detection of thyroid malignancies and enable timely and appropriate management.

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This report aims to illustrate these challenges through the case of a 16-year-old girl who developed metastatic papillary thyroid carcinoma eleven years after receiving craniospinal radiotherapy for medulloblastoma. Informed consent for publication was obtained from the patient.

Case Report:

We report the case of a 16-year-old female patient with a history of posterior fossa medulloblastoma treated at the age of 5 with surgery and radiotherapy (21 sessions totaling 55.8 Grays), with complete remission achieved. She was admitted to our department for evaluation and management of a cervical mass. There was no family history of thyroid cancer. Clinical examination revealed a right-dominant goiter with ipsilateral jugulocarotid lymphadenopathy (Image 1) and a short stature (-4DS).Cervical ultrasound identified a suspicious subcapsular nodule in the right lobe (23×25 mm, TIRADS 4), along with additional nodules of lower suspicion (TIRADS 2 and 3). A right lateral cervical mass (30×29 mm) raised concern for thyroidal or lymph node origin, while the left lobe showed benign cystic lesions. Cervical CT revealed large heterogeneous nodular lesions with cystic components in the right thyroid lobe, extending to the ipsilateral supraclavicular and jugulocarotid regions. An enlarged, contrast-enhancing jugulocarotid lymph node (short axis29 mm) was noted. Multiple pulmonary nodules and micronodules, the largest being 5 mm in the right lower lobe, suggested hematogenous spread.

Microbiopsy of the lateral cervical mass suggested a non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP), without definitive criteria for papillary carcinoma and no lymph node tissue identified.
The patient underwent total thyroidectomy with resection of the right recurrent laryngeal nerve due to tumor invasion. Intraoperative findings prompted cervical lymph node dissection (levels II-III-IV) and bilateral mediastinal lymphadenectomy.Histopathological analysis revealed a tumor proliferation in the right lobe, organized in papillary and follicular structures. Capsular invasion was present, without necrosis or vascular emboli. The remaining thyroid parenchyma exhibited multinodular hyperplasia. Metastatic lymph nodes with capsular rupture were present. The patient was staged as pT1bN1bMx, warranting a 50 mCi radioactive iodine therapy.

On whole-body scintigraphy, multiple iodine-avid foci were observed in the cervical region, consistent with residual thyroid tissue, as well as in both lung fields, corresponding on CT slices to pulmonary nodules suggestive of secondary lesions. Follow-up imaging showed no ultrasound-detectable residual thyroid tissue or lateral cervical lymphadenopathy. Thoraco-abdomino-pelvic CT revealed an empty thyroid bed with no contrast enhancement, complete regression of previously described cervical lymphadenopathy, and overall stability of the remaining findings. The patient subsequently received a second course of radioactive iodine therapy. Given the metastatic nature of the disease and the high risk of recurrence, the patient was placed on suppressive levothyroxine therapy, aiming for a TSH level below 0.1 mIU/L to minimize the risk of tumor stimulation.A genetic study was proposed to the patient but could not be performed due to limited resources.

Image 1: Goiter with right-lobe predominance

Discussion:-

The estimated prevalence of thyroid nodules in children and adolescents ranges from 0.5% to 2% (4). Papillary carcinoma is the most common form of pediatric thyroid cancer, with a peak incidence around age 15 and a female predominance (69 to 79% of cases) (5). Thyroid irradiation is the primary risk factor, as observed in our patient. A pooled analysis of 16,757 childhood cancer survivors identified 187 cases of thyroid cancer, demonstrating a relative risk of 13.7 for an approximate thyroid dose of 10 Gy (6).Furthermore, hypothyroidism is a frequent complication of radiotherapy for head and neck cancers, occurring in 15 to 50% of cases (7), with a peak risk at 2–3 years and potentially emerging up to 25 years after irradiation. This risk is dose-dependent (50% at 33 Gy) and is influenced by the patient's age and sex, warranting lifelong monitoring (8).Exposure to cervical, mediastinal, craniospinal, or whole-body irradiation during childhood significantly increases the risk of thyroid carcinoma, following a linear dose–response relationship that plateaus between 10 and 30 Gy, then declines at higher doses due to cytotoxic effects (6). The thyroid is highly radiosensitive, with a latency period of 5 to 10 years, potentially extending up to 50 years (10). Notably, even low doses of 0.05–0.1 Gy during childhood are linked to a markedly elevated long-term risk of thyroid cancer (9).

Radiation exposure induces DNA damage in thyroid follicular cells, both directly and via persistent oxidative stress through reactive oxygen species (ROS) (10), thereby promoting genomic instability. This mechanism underlies the high frequency of gene rearrangements such as RET/PTC3, which are especially prevalent in radiation-induced pediatric papillary thyroid carcinomas (11).Radiation-induced thyroid cancers, particularly in children, present distinct histopathological features, often with solid or follicular growth patterns, papillary nuclear features, and frequent multifocality. Post-radiation tissue also exhibits fibrosis, nuclear atypia, and architectural disorganization, which can complicate the histological distinction between benign lesions, NIFTP, and invasive papillary carcinoma. These findings highlight the need for expert pathological review in irradiated thyroid tissue. (12)

From a molecular perspective, identifying diagnostic (to clarify indeterminate cytology) and prognostic (to detect mutations associated with risk of recurrence or metastatic potential) biomarkers is essential in thyroid oncology for targeted therapies, BRAF or RET inhibitors in advanced, persistent, or radioiodine-refractory cases. Molecular testing typically includes detection of BRAF and RAS mutations, Ret/PTC and PPARγ/Pax8 rearrangements, and the quantification of specific microRNAs, to help predict prognosis in papillary carcinomas (13) and support a more personalized approach to care. These cancers are strongly associated with RET/PTC rearrangements, while BRAF V600E mutations are rare in the context of irradiation (11). A germline genetic predisposition may contribute to both childhood and thyroid cancers. DICER1 syndrome, a hereditary disorder, increases the risk of multiple neoplasms, particularly in the thyroid, brain, and pleuropulmonary system. However, its role in thyroid tumorigenesis remains insufficiently explored.

All patients irradiated in childhood involving the thyroid should be monitored for thyroid cancer. Two surveillance strategies are recommended: ultrasound imaging in response to palpable abnormalities, or routine ultrasound screening every 2 to 5 years. Annual thyroid palpation is advised, with follow-up beginning 5 to 8 years after irradiation (14). Fine-needle aspiration (FNA) is recommended in the presence of suspicious ultrasound features, regardless of nodule size.Children exhibit higher rates of cervical lymph node metastases, distant, mostly pulmonary metastases present as diffuse micronodular lesions, and recurrences occur more frequently compared to adults (15). Despite more advanced disease at diagnosis, children have a better prognosis, with low mortality and disease stabilization following I-131 therapy (16). Long-term survival exceeds 90%, despite relatively frequent lymph node recurrences (21-29%) (17), which are typically manageable with surgery and radioactive iodine. Most occur within the first five years, but late recurrences—up to 40 years post-exposure—have been reported (18), emphasizing the need for lifelong surveillance

The European Thyroid Association recommends (16) total thyroidectomy in children with radiation-induced differentiated thyroid carcinoma, given the high risk of bilateral and multifocal disease and the need to minimize recurrence. A lateral neck dissection is recommended when lymph node metastasis is confirmed. Central neck dissection is indicated in cases where malignant cytology is accompanied by extrathyroidal invasion or loco-regional spread. Prophylactic dissection may be considered depending on tumor size, multifocality, and surgical expertise.
Iodine-131 therapy is indicated for persistent, unresectable loco-regional or nodal disease, as well as known or suspected iodine-avid distant metastases. A structural and biochemical response to initial I-131 treatment may occur within 15–18 months (19); therefore, a minimum interval of 12-months is recommended before any additional treatment, although this should be individualized based on clinical response.

Our patient developed metastatic papillary thyroid carcinoma 11 years after craniospinal radiotherapy for medulloblastoma, with a total dose of 55.8 Gy**.** This presentation aligns with known latency and dose–response patterns of radiation-induced thyroid cancer. The presence of cervical and pulmonary metastases reflects the aggressive but typical behavior of pediatric post-radiation PTC. Initial biopsy suggested NIFTP, but surgical pathology revealed capsular invasion and nodal metastases, confirming malignancy and illustrating diagnostic challenges in irradiated tissues. The patient underwent total thyroidectomy, received two courses of radioactive iodine therapy, and was started on TSH-suppressive levothyroxine.

Conclusion:-

This case illustrates the long-term risks associated with pediatric oncology treatments, particularly radiation therapy, in the development of secondary neoplasms. It highlights the heightened sensitivity to the carcinogenic effects of ionizing radiation and emphasizes the importance of a multidisciplinary approach involving oncologists, endocrinologists, radiologists, and psychological support. Prolonged surveillance is crucial for the early detection of such complications and for optimizing patient care. However, this case also reveals the current lack of specific clinical guidelines for the long-term follow-up of radiation-exposed pediatric patients, underscoring the need for evidence-based protocols. It thus serves as a reminder of the need to balance therapeutic efficacy with the minimization of long-term adverse effects in the treatment of pediatric cancers.

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