








### Tiroid Ewing Sarkomu ve Levotiroksinin Rektal Uygulaması

#### Thyroid Ewing Sarcoma and Rectal Administration of Levothyroxine

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#### ÖZ

Tiroid nöroendokrin tümörlerinin ayırıcı tanısı çok farklı hastalık gruplarını içerir. Özellikle kalsitonin negatif olgularda diğer nöroendokrin tümörler ayırıcı tanıya dahil edilmelidir. Ewing sarkomu tiroid dokusundaki nadir tümörlerden biridir ve özellikle kalsitonin negatif olgularda tiroidin nöroendokrin tümörlerinin ayırıcı tanıları arasında yer alması açısından önemlidir. Biz burada nadir görülen bir Tiroid Ewing sarkomu olgusunu ve tiroid hormon replasmanına yönelik başarılı rektal levotiroksin uygulamasını sunmayı amaçladık.

**Anahtar Kelimeler:** Tiroid Ewing, rektal levotiroksin, sarkom

#### ABSTRACT

The differential diagnosis of thyroid neuroendocrine tumors includes very different disease groups. Especially in calcitonin negative cases, other neuroendocrine tumors should be included in the differential diagnosis. Ewing sarcoma is one of the rare tumors in the thyroid tissue, and it is important in terms of being among the differential diagnoses of neuroendocrine tumors of the thyroid, especially in calcitonin negative cases. Here, we aimed to present a rare case of Thyroid Ewing's sarcoma and successful rectal levothyroxine administration for thyroid hormone replacement.

**Keywords:** Thyroid Ewing, rectal levothyroxine, sarcoma

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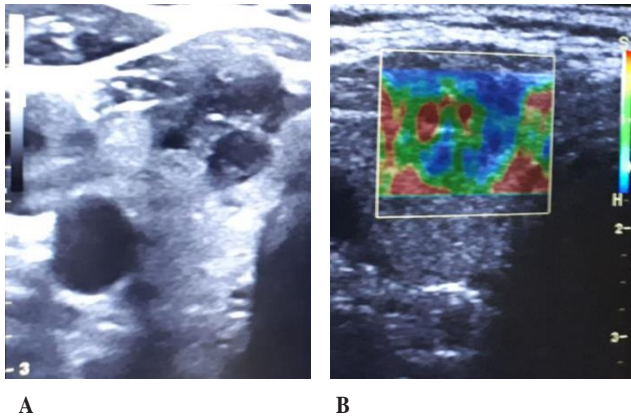
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## INTRODUCTION

Ewing sarcoma was first described by James Ewing in 1921. Tefft et al. first described extrasosseous Ewing's sarcoma in a patient in 1969 (1). Ewing sarcoma is a tumor frequently seen in children and bones. It may show involvement outside the bone at a rate of 20% (2). Extrasosseous Ewing sarcomas usually present clinically as a painless, rapidly growing mass in the paravertebral area, chest wall, and retroperitoneal area during or after adolescence. In the thyroid, sarcomas have a rate of less than 1% among thyroid cancers (3-4). In the literature, if resistant hypothyroidism persists despite oral therapy, it has been suggested to try different administration routes. These include gels and capsules due to a longer gastrointestinal transit time, or intravenous and rectal forms where absorption is not possible (5). There are few publications reporting the rectal use of levothyroxine. The results showed that the bioavailability of levothyroxine is lower compared to rectal administration. However, it has been suggested that ideal T4 levels can be maintained by increasing the dose. Increase in LT4 dose in rectal administration is not certain, especially in human (6). In this case, we aimed to present a case of thyroid Ewing sarcoma, a rare extraskeletal involvement of Ewing's sarcoma, and successful rectal levothyroxine administration applied in the follow-up.

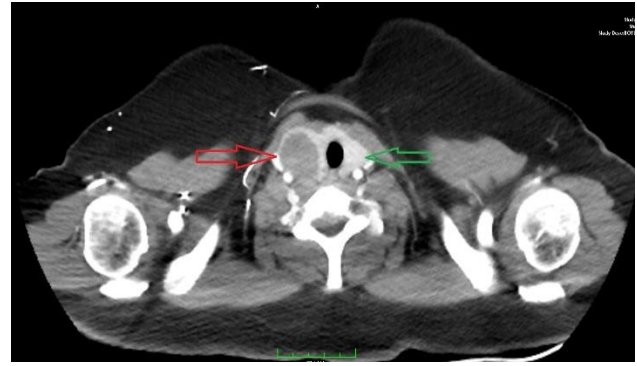
## CASE REPORT

A 19-year-old female patient presented with a painless, palpable swelling in the neck that had been going on for 15 days. In laboratory examinations, the patient was euthyroid and antithyroid peroxidase antibody was negative. In the thyroid ultrasonography, nodule with irregular borders, 35 mm in size in hypoechoic structure (TIRADS-4) in right lobe and 9 mm in size in the left lobe (Figure 1).



**Figure 1.** A: 35 mm hypoechoic nodule with irregular borders in right thyroid lobe. B: Elastographic image of the nodule (blue color = lower stiffness, red color = higher stiffness)

Fine-needle aspiration biopsy of the nodular thyroid in the right lobe was performed. The pathology result showed malignant cytological findings and Ki-67 proliferation index was reported as %30-40. In addition, the cytomorphological and immunohistochemical findings were suspicious for small blue round cell neoplasms. In computed tomography; It was observed that there was a 92x42 mm mass lesion obliterating the right pyriform sinus, starting from the right thyroid lobe and extending to the level of the oropharynx (Figure 2).

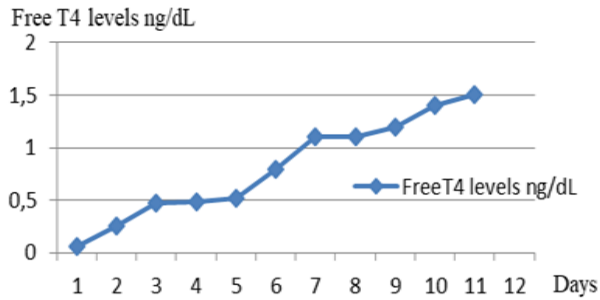


**Figure 2.** Red arrow: Malign thyroid nodule appearance, green arrow: thyroid tissue. Red Arrow suspicious thyroid nodule in the right lobe of thyroid. Green Arrow Normal left thyroid lobe.

Total thyroidectomy and mass excision were performed with surgery. Pathology result was reported as undifferentiated small round blue cell tumor. In immunohistochemical studies; diffuse nuclear positive with NKX2.2, diffuse nuclear positive with FLI-1, diffuse membranous positive with CD99 and positivity with ERG were found. EWSR1 rearrangement positivity and accompanying immunohistochemical positivity also supported the EWSR1-ERG fusion positivity seen in Ewing sarcoma, and the patient was diagnosed with Ewing sarcoma.

After the operation, radiotherapy was planned for the patient by taking the opinion of medical oncology and radiation oncology. Total parenteral nutrition was started because oral intake was completely blocked due to swelling and edema in the neck of the patient after radiotherapy. Total parenteral nutrition therapy was given to the patient who had no oral intake. Percutaneous endoscopic gastrostomy was planned since total parenteral nutrition therapy treatment lasted 10 days. Meanwhile, since the patient could not receive levothyroxine replacement, TSH was found to be 40 mU/l. Since the patient's oral nutrition is completely closed; rectal levothyroxine replacement was considered for the patient, since intravenous thyroxine is not available in our country and its supply from abroad will take more than 2 weeks.

On the first day, 500 mcg of levothyroxine was dissolved in 500 cc physiological saline and administered rectally as a high enema. Basal free T4 and 2, 4, 6 hours free T4 levels were checked. When there was not enough increase on the first day, the same procedure was applied with 1000 mcg on the second day. Since there was no increase in the free T4 level at this dose, the same procedure was started with 2000 mcg. At this dose, the free T4 level of the patient started to increase on the 7th and 8th days, and this procedure was repeated until the 12th day. (Figure 3).



**Figure 3.** The chart represents the detailed patient response (T4 level) to various preparations and doses of levothyroxine (LT4). Days 1–3: LT4 500 µg/day. Days 4–6: LT 1000 µg/day. Days 7–12: rectal LT 2000 µg/day.

## DISCUSSION

Ewing sarcoma/primitive neuroectodermal tumors belong to the group of small round cell tumors. These tumors are usually found in the skeletal system in the pediatric age group. Ewing sarcomas originating from non-osseous thyroid are very rare and there are few cases in the literature. Diagnosis is made by clinical, radiological and histopathological findings. Clinically, it may present with a fast-growing, painless, swelling neck mass(7). As in our case, the patient presented with a painless, palpable swelling mass in the neck. When a nodule was detected in the thyroid, it was observed that the mass enlarged both on physical examination and ultrasonographically when he applied for the pathology result after fine needle aspiration biopsy procedure. In a study evaluating the radiological images of patients with extraosseous Ewing sarcoma in the literature; It has been reported that the masses are hypoechoic and contain pseudocapsules on ultrasonography, and they show low attenuation with heterogeneous contrast enhancement on computed tomography(8). Computed tomography performed in our case also showed that the mass was heterogeneous and showed low attenuation likewise in the literature. Ewing's sarcoma with extraosseous involvement is one of the high-risk tumors in terms of local recurrence and distant metastasis. Age and surgical treatment are important factors in terms of prognosis(9). We believe that the younger age of our patient and the fact that the mass was surgically removed almost completely contributed to the cure. In the patient who developed local recurrence after surgery, the tumor was reduced by radiotherapy, and then chemotherapy was started. In the patient who developed local recurrence after surgical removal of the tumor, complete obstruction of the esophagus developed due to both the effect of the mass and the edema secondary to radiotherapy during radiotherapy. The patient began to be unable to take solid and liquid foods. Unfortunately, liquid form levothyroxine could not be supplied. Rectal levothyroxine treatment was started after 10 days of closure of oral intake, since the PEG procedure would be performed under anesthesia and thyroid replacement was required. When the patient's freeT4 levels increased with high-dose levothyroxine treatment in the form of high enemas, the procedure was successfully performed. Rectal administration of levothyroxine is based on the administration of high-dose drug, ranging from 31.25 µg/kg to 62.5 µg/kg, on animal models(10). In a study in which the efficacy and bioavailability of the LT4 suppository form compared to the oral form

were evaluated in humans; It has been emphasized that the suppository form has lower efficacy and bioavailability and that it should be given twice as much as oral in hypothyroidism(6-11). In our case, a much higher dose of LT4 had to be used to reach the effective dose. Although there are studies in animals, there is no dose range for rectal administration of levothyroxine in humans; We applied to around 40 µg/kg for 7-10 days. On the 7th day increase in free T4 was observed and invasive procedure could be performed. As in our patient, rectal levothyroxine administration is important in terms of being a safe and effective method of administration in such cases where oral and parenteral drug administration is not possible.

In conclusion Ewing's sarcoma in the thyroid is one of the rare malignant tumors of the thyroid, and few cases have been reported in the literature. EWSR1 rearrangement positivity and accompanying immunohistochemical ERG positivity, which is one of the variants of Ewing sarcoma, which we detected in our case, is a very rare condition. We could not perform oral thyroid hormone replacement in our patient, the experience of rectal levothyroxine administration, which has been applied in a limited number of cases in the literature, may be a treatment alternative for patients who do not have oral intake.

**Informed Consent:** Consent was obtained from all participants in this study.

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