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Epstein-Barr virus-associated thymic lymphoepithelial carcinoma in a child

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ABSTRACT

Thymic lymphoepithelial carcinoma is a rare neoplasm in children, with histological features similar to those of nasopharyngeal carcinoma and a frequent association with the Epstein-Barr virus (EBV). Diagnosis is challenging due to clinical and imaging overlaps with lymphomas and mediastinal germ cell tumors.

We present the case of a 12-year-old patient with a mediastinal mass, supraclavicular lymphadenopathy, and pulmonary metastases, histologically diagnosed as EBV-positive thymic lymphoepithelial carcinoma. He received chemotherapy with cisplatin and gemcitabine, immunotherapy with pembrolizumab, and radiation therapy, and achieved complete remission. The literature reports few pediatric cases, with a poor prognosis and a median survival of less than 24 months. However, the addition of anti-PD-1 immunotherapy in EBV-positive tumors appears to offer clinical benefit.

This case highlights the importance of a multidisciplinary approach and the potential benefits of combination therapies, including immunotherapy, in EBV-positive mediastinal tumors in children.

Keywords: *thymic carcinoma; Epstein-Barr virus; pediatrics; immunotherapy.*

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INTRODUCTION

Thymic lymphoepithelial carcinoma is a rare neoplasm of the thymic epithelium characterized by an undifferentiated histological pattern and a prominent lymphoplasmacytic infiltrate. Previously termed lymphoepithelioma-like carcinoma, the World Health Organization classified it as lymphoepithelial carcinoma in 2021.[1] It is rare in both adults and children; in pediatrics, very few cases have been reported in the literature, and it most commonly presents in the second decade of life.[2]

This condition is associated with the Epstein-Barr virus (EBV), which plays an oncogenic role in various epithelial tumors. Histologically, it corresponds to the extranasopharyngeal counterpart of EBV-associated nasopharyngeal carcinoma and shares similar morphological characteristics. Oncogenesis is related to viral latency and the expression of proteins such as LMP1 (latent membrane protein 1), which promote cell proliferation and immune evasion.[3,4]

Patients typically present with rapidly growing mediastinal masses and nonspecific symptoms such as cough, shortness of breath, weight loss, or fever.[5] It is more common in men and is usually diagnosed at advanced stages, with frequent metastases to lymph nodes, the lung, liver, and bone.[6,7] The differential diagnosis includes mediastinal lymphomas, germ cell tumors, NUT carcinoma (NUTM1-positive), and sarcomas. Positivity for Epstein-Barr encoded RNA *in situ* hybridization (EBER-ISH) in tumor tissue is a key diagnostic marker.[8,9]

Conventional treatment is based on platinum-based chemotherapy and radiation therapy. However, outcomes in advanced disease are limited, with a median survival of approximately 22 months from diagnosis and an approximate 5-year survival rate of 34%.[2,4] In recent years, immunotherapy with PD-1 (programmed death-1) inhibitors has emerged as a promising option, given the high expression of PD-L1 (programmed death-ligand 1) in EBV-positive tumors.[4,5,8-10]

CLINICAL CASE

A 12-year-old male patient with no significant past medical history presented with a dry cough that had persisted for two months, fatigue, and weight loss of 4 kg. On physical examination, a 3 × 3 cm, firm, and slightly tender supraclavicular lymph node was noted on the left side.

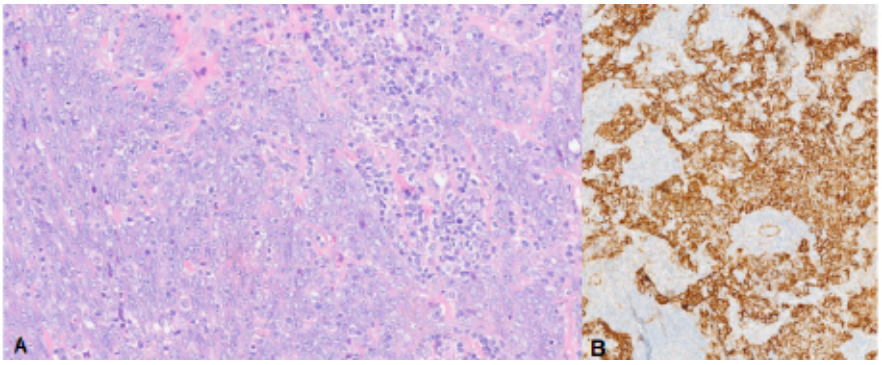
A chest X-ray revealed mediastinal widening, which was confirmed by computed tomography (CT) as a heterogeneous mediastinal mass with pulmonary nodules suggestive of metastasis, as well as mediastinal and left supraclavicular lymphadenopathy.

Laboratory tests revealed leukocytosis with neutrophilia, elevated lactate dehydrogenase levels, and an increased erythrocyte sedimentation rate. The tumor markers human β-chorionic gonadotropin (β-HCG) and alpha-fetoprotein were negative. Positive IgG antibodies to EBV were detected.

The histopathological and immunohistochemical findings from the lymph node biopsy are shown in *Figures 1A-B*, and *2A-B*.

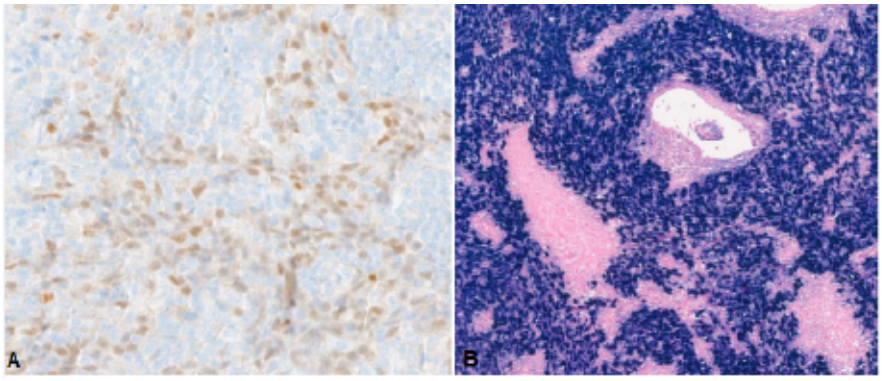
On immunohistochemical analysis, the tumor cells were positive for pancytokeratin, p40, p63 (focal), and CD117 (diffuse). CD5 highlighted intermingled T lymphocytes. Both

Figure 1. Anatomopathology



Biopsy of cervical lymphadenopathy: involvement by sheets, nests, and anastomosing strands of carcinomatous cells, accompanied by abundant lymphocytes, both in the fibrous stroma and intermingled with the neoplastic cells, H-E 10× (A). Immunohistochemistry showing positivity for pan-keratin (AE1AE3) in the epithelial tumor cells (B).

Figure 2. Anatomopathology



The epithelial tumor cells also expressed p40 (A) and KIT (CD117) by immunohistochemistry. In situ hybridization highlights tumor cells that are positive for the small EBV-encoded RNA (EBER) (B).

CD117 and CD5 are frequently expressed in thymic carcinomas (75-85%) and rarely in thymomas (<5%), making them useful in the differential diagnosis between these neoplasms. EBER-ISH was positive in 100% of tumor cells. Molecular analysis for NUTM1 (nuclear protein in testis, midline carcinoma family member 1) rearrangement was negative.

Based on the morphological and immunophenotypic findings, a diagnosis of thymic lymphoepithelial carcinoma was established, stage IVb according to the TNM classification of the American Joint Committee on Cancer (8th edition).[11]

A positron emission tomography-computed tomography (PET-CT) scan was performed, revealing hypermetabolic supradiaphragmatic lymph nodes, a large mediastinal mass, a single hypermetabolic liver lesion, hypermetabolic nodules in the right lung, and suspicious ipsilateral pleural thickening (*Figure 3*).

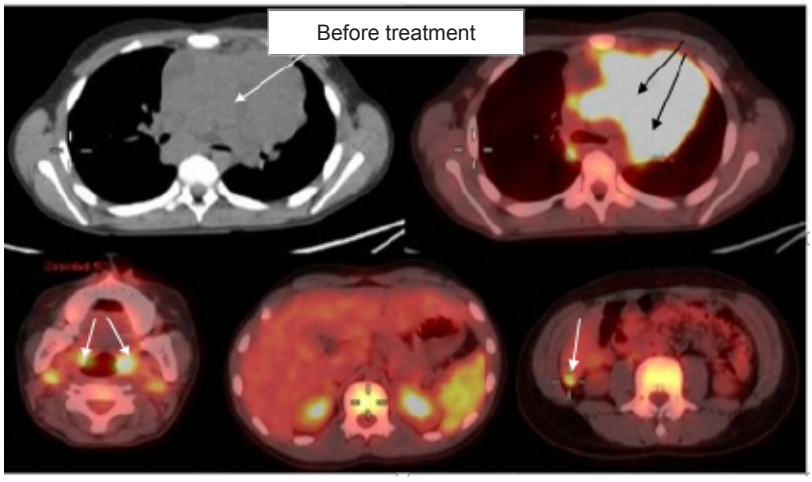
The bone marrow biopsy showed no evidence of tumor involvement.

The treatment regimen consisted of chemotherapy and immunotherapy with cisplatin (80 mg/m^2, day 1) and gemcitabine (1000 mg/m^2, days 1 and 8) for 8 cycles, along with pembrolizumab (200 mg) for 4 cycles, repeated every 3 weeks.

After three cycles, PET-CT showed a partial response, with regression of liver lesions.

After completion of treatment, only a single residual hypermetabolic supraclavicular lymph node remained, with resolution of the

Figure 3. Pre-treatment positron emission tomography



PET-CT performed at diagnosis showed hypermetabolic supradiaphragmatic lymph nodes, a large mediastinal mass, and a single hypermetabolic liver lesion.

pulmonary and hepatic lesions. Mediastinal and supraclavicular radiation therapy (50 Gy) was administered.

Seventeen months after diagnosis, the patient remains in complete remission, with a PET-CT scan showing no uptake (*Figure 4*).

DISCUSSION

Epithelial tumors of the thymus, which include thymomas and thymic carcinomas, are rare neoplasms and account for only 0.2-1.5% of malignancies, of which thymic carcinomas constitute approximately 20%.[11]

Lymphoepithelial carcinoma in children presents with clinical features consistent with those of our patient, who presented with a dry cough, asthenia, and weight loss. CT scanning revealed a heterogeneous mediastinal mass with pulmonary nodules, lymphadenopathy, and a hepatic lesion, consistent with stage IVb (TNM, 8th edition). The histology and immunophenotype were consistent: undifferentiated epithelial neoplasm with abundant lymphoplasmacytic infiltrate and positivity for pancytokeratin, p40, CD117, and EBER-ISH in 100% of tumor cells.

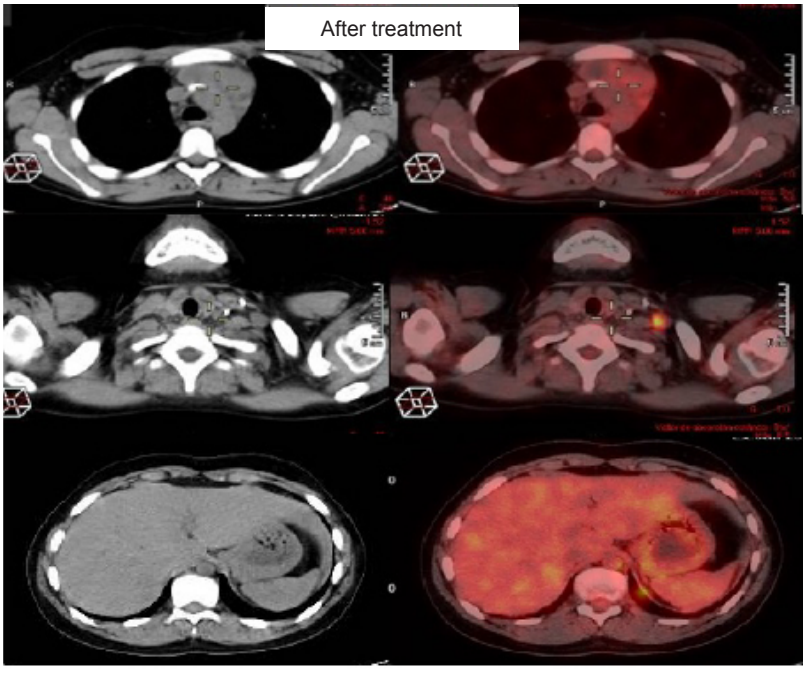
Negative results for germ cell tumor markers (β-HCG, alpha-fetoprotein) and NUTM1 ruled out alternative diagnoses, including germ cell tumors and NUT carcinoma. The advanced stage and metastatic spread are consistent with the aggressive nature of this tumor as described in the literature.

The optimal treatment for lymphoepithelial carcinoma remains unclear due to the small number of reported cases, particularly in the pediatric population. In patients with localized and potentially resectable disease, complete surgical resection is the initial treatment of choice. In contrast, for patients with clinically uncertain or unresectable tumors, neoadjuvant chemotherapy regimens, thoracic radiation therapy, or a combination of both modalities have been used. Patients with locally advanced disease typically receive multimodal treatment.[11]

The prognosis in childhood is poor, with a median survival of approximately 22 months and a 5-year survival rate of about 34%. Factors associated with a poorer prognosis include advanced disease at diagnosis, the presence of bone or liver metastases, and the inability to perform a complete surgical resection.[4,8]

In this context, conventional treatments based on platinum-based chemotherapy and radiation therapy have shown limited results.[11]

Figure 4. Post-treatment positron emission tomography



Post-treatment PET-CT scan following immunochemotherapy and radiation therapy showed a complete response.

In recent years, immunotherapy with immune checkpoint inhibitors has emerged as a therapeutic alternative. PD-1 is an inhibitory receptor expressed on activated T cells, while its ligand PD-L1 can be expressed on tumor cells and in the tumor microenvironment. The interaction between the two acts as an immune "checkpoint" that suppresses T-cell activation and promotes tumor evasion. In EBV-associated tumors, PD-L1 expression is typically elevated, providing a biological rationale for the use of PD-1/PD-L1 axis-blocking antibodies, such as pembrolizumab, which can restore the antitumor immune response. Although pediatric experience is still limited, published series in adults with EBV-associated nasopharyngeal carcinoma support the potential benefit of this immunotherapeutic strategy.[1,12,13] In a multicenter cohort of pediatric patients with lymphoepithelial carcinoma, the combination of PD-1 inhibitors with chemotherapy was associated with higher response rates and 1- and 2-year progression-free survival rates of 100% and 73%, respectively.[2] Consistently, a larger multicenter study demonstrated that patients with lymphoepithelial carcinoma who received immunotherapy had significantly longer overall survival than those who never received it (p <0.0001, hazard ratio 0.39, 95% CI: 0.25-0.63), underscoring its therapeutic value in advanced disease.[10]

In line with this emerging evidence, our patient received combination therapy consisting of chemotherapy and immunotherapy, followed by radiation therapy. This strategy achieved a sustained complete metabolic response, as evidenced by the resolution of lesions on PET-CT, and a complete remission 17 months after diagnosis. This favorable outcome contrasts with the historically poor prognosis described and suggests that incorporating immunotherapy into platinum-based regimens could improve outcomes in this tumor type, even in advanced stages.

Given the rarity of these cases, it is important to emphasize the need for discussion within multidisciplinary committees and consultation with experts to determine the appropriate course of treatment for these patients with such rare diagnoses. ■

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