CASE REPORT

CD4-positive lymphoepithelial-like carcinoma: Report of unusual case

Luaay Aziz, Raya Saab[1], Toufic Eid[2], Mousa A. Al-Abbadi[3]

Department of Ent and Head and Neck Surgery, Healthpoint Hospital, Abu Dhabi, United Arab Emirates, Departments of [1]Pediatrics and Adolescent Medicine and [2]Radiation Oncology, American University of Beirut, Beirut, Lebanon, [3]Department of Pathology and Laboratory Medicine, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates

Access this article online

Website: www.avicennajmed.com

DOI: 10.4103/ajm.AJM_135_17

Quick Response Code:

ABSTRACT

We are reporting an unusual case of lymphoepithelial-like carcinoma (LELC) in an 8-year-old female patient where the tumor cells showed unusual CD4 expression. The lesion was found in the left submandibular neck region, in the vicinity of the submandibular gland. The salivary gland was not infiltrated by the tumor, and the tumor exhibited a classic LELC with single and clusters of tumor cells surrounded by many hematolymphoid cells. The tumor cells revealed strong positivity for Epstein–Bar virus as confirmed by the EBER: Epstein-Barr Virus in situ hybridization (EBER-ISH) method of staining. Interestingly, the tumor cells expressed membranous immunostaining for the T-helper lymphocyte antibody (CD4) in addition to pan-cytokeratin. A brief discussion about this unusual finding is offered. The patient was treated as a case of Epstein–Bar virus-associated nasopharyngeal carcinoma with excellent response.

Key words: CD4, Epstein–Bar virus, lymphoepithelial-like carcinoma, nasopharyngeal carcinoma

INTRODUCTION

Masses and swelling in the head and neck are common presentation in children as well as adults. Many of these are due to lesions involving the lymph nodes. Lymphadenopathy in children is commonly caused by infection, but few cases can be due to benign or malignant diseases.

Lymphoepithelial like carcinoma (LELC) are usually defined as any carcinoma outside the nasopharynx without evidence of definite line of cellular differentiation commonly with associated non-neoplastic lymphoplasmacytic cell infiltrate. The histological morphology is similar to nasopharyngeal carcinoma (NPC) of the non-keratinizing undifferentiated type. Unlike NPC, not all cases of LELC are associated with the presence of Epstein-Barr virus. The most common location for LELC are salivary glands, however other locations such as oropharynx, sinunasal tract and larynx have been reported.

After obtaining the appropriate internal review board approvals and patient family consent, we present extremely unusual case of lymph node enlargement in the left side neck of an 8-year-old female patient were the morphologic histopathological examination showed LELC in a lymph node with no known primary after thorough clinical, intraoperative and imaging evaluation. Moreover, the epithelial tumor cells expressed the common T-helper cell surface marker CD4, which we believe to be the first observation in the literature.[1,2]

CASE REPORT

An 8-year old girl presented with a history of left-sided submandibular swelling of 1-week duration. There was

Address for correspondence: Dr. Mousa A. Al-Abbadi, Department of Pathology and Laboratory Medicine, Sheikh Khalifa Medical City, Abu Dhabi, United Arab Emirates.
E-mail: alabbadima@yahoo.com, ma.alabbadi@ju.edu.jo

Cite this article as: Aziz L, Saab R, Eid T, Al-Abbadi MA. CD4-positive lymphoepithelial-like carcinoma: Report of unusual case. Avicenna J Med 2018;8:58-62.

no reported fever, loss of weight or appetite, or any other generalized symptoms. There was no throat pain or difficulty in swallowing. She was started on broad-spectrum antibiotic treatment with no improvement, and the swelling increased in size. Computed tomography (CT) scan was done outside our institution and showed a large cystic mass lesion in the submandibular area. She had an open drainage procedure as an outpatient on the assumption of an abscess. The family was told that the drainage was successful and no further information was given to the family regarding microbial culture results.

She then presented to our outpatient clinic for further investigation since the mass did not change in size. On examination, she had a large submandibular mass measuring 5 cm × 5 cm which was slightly tender on palpation; she had no evidence of fever or tachycardia.

Examination of the throat revealed normal tonsils and no lesions could be found in the oral cavity. No abnormalities could be found in the nasopharynx or hypopharyngeal area.

Laboratory examination showed leukocytosis with a white blood cell count of 24,000 with 70% neutrophils, 20% lymphocytes, and 7% monocytes. The C-reactive protein was mildly elevated at 83 mg/L. Levels of serum lactate dehydrogenase and uric acid were normal.

Neck ultrasound and CT scan [Figure 1] showed a necrotic mass lesion in the left submandibular region, measuring 5.6 cm × 5.2 cm × 5.2 cm, suggestive of an abscess with associated adjacent reactive appearing lymph nodes.

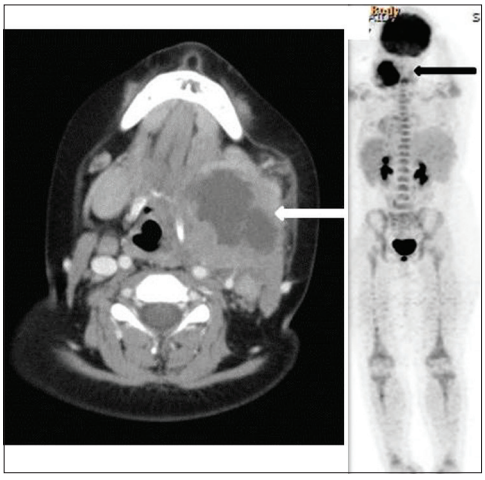

Figure 1: Left image: Computed tomography scan of the neck, transverse section, showing a necrotic mass lesion in the left submandibular region measuring 56 × 52 × 52 mm suggestive of an abscess (arrow) with associated adjacent reactive appearing lymph nodes. Right image: Positron emission tomography scan showing the large left submandibular tumor with intense positivity

The patient was admitted and was started on intravenous clindamycin and oral augmentin and dexamethasone. The next day, she underwent an open drainage on the assumption of an organizing abscess. During the procedure and on opening the mass, we found an inflamed firm tissue surrounding the wall of a cystic cavity which was attached to the submandibular gland. The salivary gland appeared normal in size but with extensive adhesions to the cystic wall mass. The cystic cavity revealed a serous fluid with no obvious pus. The tissue was found to have extensive adhesions where dissection was difficult. However, multiple representative biopsies were taken on an attempt for a complete excision including the removal of the attached submandibular gland. The tissue was sent for histopathological examination and culture. She was discharged on oral antibiotics and advised to come back after 1 week as an outpatient follow-up.

However, she was readmitted 3 days later with fever and serous discharge from the surgical wound. Laboratory parameters on the second admission revealed leukocytosis and increased inflammatory parameters. By ultrasound examination, there was a mass lesion at the left submandibular location measuring 4 cm × 3 cm × 5 cm with complex mixed echogenicity.

Computerized axial tomography scan revealed a large submandibular collection and nearby multiple enlarged small lymph nodes. The right submandibular gland appeared normal. Chest X-ray was within normal limits.

Basic immune workup for immunodeficiency was negative. The immune status screening showed mumps viral IgM, which was reported as positive IgM but with low levels of detection, Epstein–Bar virus (EBV) IgG was positive, and quantitative EBV polymerase chain reaction analysis showed 6500 copies/ml. Cytomegalovirus IgG was positive, but IgM was negative. Toxoplasma IgG and IgM were both negative. C3 and C4 serum levels were elevated. Bartonella antibodies were also negative. She was restarted

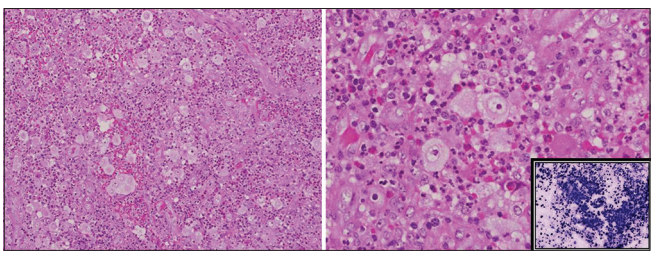

Figure 2: Medium- (left) and high-power (right) view of the routine histological section showing single and clusters of large atypical cells with abundant cytoplasm, large nucleus, and prominent nucleoli (H and E). The inset is the Epstein–Bar virus stain by the EBER ISH method revealing strong reactivity

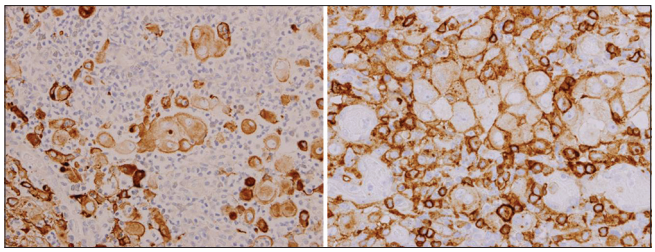

Figure 3: Immunohistochemical stains showed immunoreactivity for pan-cytokeratin AE1/3 (left) and the same cells were also immunoreactive for CD4 (right). The CD4 stain is membranous and is obviously lining the large atypical tumor cells in addition to the surrounding reactive T-lymphocytes. The details of this close used are SP35, Rabbit monoclonal antibody, Ventana Medical Systems, Inc. Tucson, AZ, USA

on intravenous antibiotics, ceftriaxone, and clindamycin but developed allergy to the latter; therefore, it was replaced by augmentin.

Histopathologic findings

The histological examination revealed intensely inflamed soft-tissue fragments with mixed inflammatory cell infiltrate composed of neutrophils, plasma cells, lymphocytes, and histiocytes. However, occasional large atypical cells were seen scattered in between these tissue fragments. These atypical cells were large, polygonal, and epithelioid with abundant cytoplasm and large nucleus. The cells contained large and prominent eosinophilic nucleoli in addition to occasional mitoses [Figure 2]. Immunohistochemical stains revealed immunoreactivity of these large cells for pan-cytokeratin (AE1/3) but negativity for CD68 and most lymphoid markers (CD3, CD5, CD20, CD8, CD23, and CD45) except strong membranous staining for CD4 [Figure 3]. Two different clones of CD4 were tested; the first clone is SP35, Rabbit monoclonal antibody, Ventana Medical Systems, Inc. Tucson, AZ, USA, while the second clone is 4B12 from Dako, Santa Clara, CA, USA. Both clones showed immunoreactivity; stronger on the Ventana clone. All positive and negative controls were appropriate.

Viral *in situ* hybridization staining for EBV by the EBER method showed strong nuclear staining [Figure 2 inset]. A diagnosis of EBV-positive lymphoepithelial-like carcinoma (LELC) in the submandibular region was rendered.

Based on the final pathologic diagnosis, the family was advised to have examination of the child under general anesthesia for endoscopy and biopsy from the nasopharynx, but they refused.

Based on multidisciplinary team's discussion, it was recommended to have multimodality oncological treatment which is not available at our institution. Therefore, the patient was referred to the American University of Beirut Medical Center where advanced care for such cases would be available.

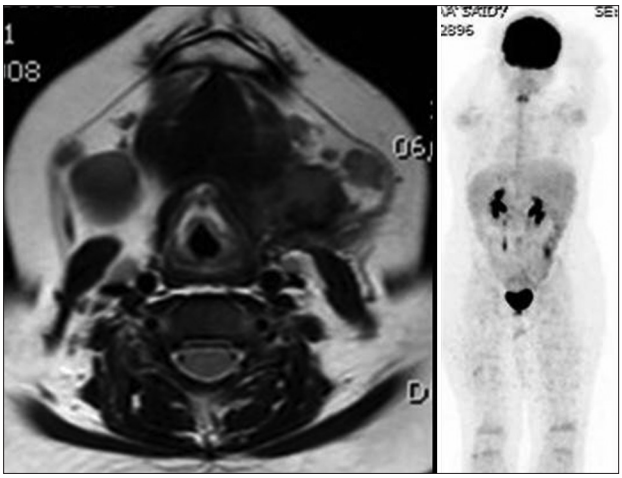

Figure 4: Left image: follow-up magnetic resonance imaging scan of the neck showing almost complete resolution of the mass after treatment. Right image: follow-up posttreatment positron emission tomography scan demonstrating complete resolution of the tumor

Treatment and follow-up

Pretreatment positron emission tomography scan showed large left retromandibular and parapharyngeal mass 7 cm × 6 cm with Standardized Uptake Value of 17 causing mass effect on the oropharynx with deviation from midline to the right, with ipsilateral cervical lymphadenopathy [Figure 1]. The decision was made to treat this patient as a case of nasopharyngeal carcinoma (NPC) Stage IIB. She received induction chemotherapy (cisplatin 80 mg/m^2/dose and 5-fluorouracil 1 g/m^2/day × 4 days, both repeated every 3 weeks for a total of 3 cycles) as per the Children's Oncology Group protocol ARAR0331. She demonstrated a very good response after 3 cycles, with significant decrease in the size of the flourodeoxyglucose-avid conglomerate of soft-tissue masses/lymph nodes in the left submandibular region to 2.5 cm × 2 cm and resolution of their activity.

She then received concurrent chemoradiation with cisplatin 100 mg/m^2 every 3 weeks where two cycles were given during radiation therapy. The radiation dose was 45 Gy in 25 fractions to neck lymph nodes, followed by a boost of 16.2 Gy in 9 fractions to the tumor volume. The total tumor dose was 61.2 Gy in 34 fractions where the treatment was delivered using intensity modulated radiotherapy. At the end of treatment, imaging showed further decrease in the residual lesions [Figure 4].

DISCUSSION

Pediatric NPC is a rare tumor.[1,2] The incidence of this disease is relatively high in some countries such as Tunisia, Southern China, Mediterranean Basin, and Alaska.[3,4]

The most common etiological factor in childhood EBV-associated NPC is viral infection with EBV.[5]

In most of these patients, the initial presentation of NPC is cervical lymphadenopathy. Many studies showed that the majority of NPC in children usually present with advanced stage and regional metastasis.[6-11]

LELC is defined as any carcinoma outside the nasopharynx without evidence of specific cellular differentiation where the histology is similar to NPC nonkeratinizing undifferentiated type. LELCs may or may not be associated with EBV. Furthermore, these LELCs may show histologic similarities to other malignant neoplasms of specific sites in the head and neck creating challenges in the differential diagnosis, especially in small biopsy samples.[12]

The major salivary glands are among the most common organs to be involved by LELC in their different anatomical locations. The parotid gland is the most frequently involved; this is followed by the submandibular gland, and rarely, the sublingual and minor salivary glands. Most patients are in their middle age, and the usual presenting clinical symptom is swelling or mass in the neck which can be associated with pain. In some cases, the facial nerve may be affected with facial palsy. Associated cervical lymphadenopathy may occur in some of these cases.[13,14]

Our case is unusual for its location where the salivary gland was completely normal and for the young age of the patient. In addition, the CD4 immunostaining was extremely unusual. Indeed, and after reviewing the English language literature, this will qualify as the first case where the tumor cells of a LELC or even NPC are immunoreactive for CD4 antibodies. A few previous reports showed numerous reactive T-lymphocytes where many of these are T-helper cells (CD4 + ve) that are present in the vicinity of NPC and LELC. However, none of these studies indicated immunoreactivity for CD4 antibodies. Some of these indicated an intense reaction of different subsets of lymphocytes in the microenvironment of these tumors and few alluded to some sort of immunomodulation action and possible targeted therapy.[15-19] One may argue that these are actually background nonspecific immunostaining; however, we strongly believe that the membranous nature of the immunoreactivity for CD4 in our case appears to be genuine.

CONCLUSION

We presented an unusual case of EBV-associated LELC in the vicinity of the submandibular gland region in a young patient where the tumor cells showed obvious immunoreactivity for CD4. We can only speculate that CD4 expression of these epithelial tumor cells is probably an aberrant expression and may occur. These findings should be taken into consideration to avoid any misinterpretation of CD4 expression in such rare cases.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Douglass EC, Pratt CB. Management of infrequent cancers of childhood. In: Pizzo PA, Poplack DG, editors. Principles and Practice of Pediatric Oncology. 3rd ed. Philadelphia: Lippincott-Raven; 1977. p. 977-81.
2. Wenig BM. Lymphoepithelial-like carcinomas of the head and neck. Semin Diagn Pathol 2015;32:74-86.
3. Ellouz R, Cammoun M, Attia RB, Bahi J. Nasopharyngeal carcinoma in children and adolescents in Tunisia: Clinical aspects and the paraneoplastic syndrome. IARC Sci Publ 1978;20:115-29.
4. Stiller CA. International variations in the incidence of childhood carcinomas. Cancer Epidemiol Biomarkers Prev 1994;3:305-10.
5. Wolf H, zur Hausen H, Becker V. EB viral genomes in epithelial nasopharyngeal carcinoma cells. Nat New Biol 1973;244:245-7.
6. Attia AB, Maalaj M, Ellouz R, Ayed FB. Results of radiotherapy and adjuvant chemotherapy in the treatment of nasopharyngeal cancer in young patients. A review of 28 cases. J Eur Radiother 1986;4:61-7.
7. Ayan I, Altun M. Nasopharyngeal carcinoma in children: Retrospective review of 50 patients. Int J Radiat Oncol Biol Phys 1996;35:485-92.
8. Pao WJ, Hustu HO, Douglass EC, Beckford NS, Kun LE. Pediatric nasopharyngeal carcinoma: Long term follow-up of 29 patients. Int J Radiat Oncol Biol Phys 1989;17:299-305.
9. Fernandez CH, Cangir A, Samaan NA, Rivera R. Nasopharyngeal carcinoma in children. Cancer 1976;37:2787-91.
10. Jenkin RD, Anderson JR, Jereb B, Thompson JC, Pyesmany A, Wara WM, *et al.* Nasopharyngeal carcinoma – A retrospective review of patients less than thirty years of age: A report of children's cancer study group. Cancer 1981;47:360-6.
11. Mertens R, Granzen B, Lassay L, Gademann G, Hess CF, Heimann G, *et al.* Nasopharyngeal carcinoma in childhood and adolescence: Concept and preliminary results of the cooperative GPOH study NPC-91. Gesellschaft für pädiatrische onkologie und hämatologie. Cancer 1997;80:951-9.
12. Wenig BM. Lymphoepithelial-like carcinomas of the head and neck. Semin Diagn Pathol 2015;32:74-86.
13. Ellis GL, Auclair PL. Lymphoepithelial carcinoma. In: Ellis GL, Auclair PL, editors. Tumors of Salivary Glands. AFIP Atlas of Tumor Pathology. Series 4; Fascicle 9. Silver Spring: ARP Press; 2008. p. 349-56.
14. Tsang WY, Kuo TT, Chan JK. Lymphoepithelial carcinoma. In: Barnes L,

Eveson JW, Reichart P, Sidransky D, editors. World Health Organization Classification of Tumours: Pathology & Genetics. Head and Neck Tumours. Lyon: IARC Press; 2017. p. 251-2.
15. Tao CJ, Chen YY, Jiang F, Feng XL, Jin QF, Jin T, *et al.* A prognostic model combining CD4/CD8 ratio and N stage predicts the risk of distant metastasis for patients with nasopharyngeal carcinoma treated by intensity modulated radiotherapy. Oncotarget 2016;7:46653-61.
16. Moss DJ, Lutzky VP. EBV-specific immune response: Early research and personal reminiscences. Curr Top Microbiol Immunol 2015;390:23-42.
17. Zheng Y, Parsonage G, Zhuang X, Machado LR, James CH, Salman A, *et al.* Human leukocyte antigen (HLA) A*1101-restricted epstein-barr virus-specific T-cell receptor gene transfer to target nasopharyngeal carcinoma. Cancer Immunol Res 2015;3:1138-47.
18. Mrizak D, Martin N, Barjon C, Jimenez-Pailhes AS, Mustapha R, Niki T, *et al.* Effect of nasopharyngeal carcinoma-derived exosomes on human regulatory T cells. J Natl Cancer Inst 2015;107:363.
19. Qin Y, Weng J, Lan G, Wei H, Huang B, Sun J, *et al.* Effect of p53 gene therapy on the local immunity and the efficacy of patients with nasopharyngeal carcinoma. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2012;26:980-3.