LETTER TO THE EDITOR
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Primary Gastric Extranodal NK/T Cell Lymphoma with T Cell Phenotype: A Very Rare EBV-Related Locally Involved Aggressive T Cell Lymphoma Case and the Therapeutic Effects of COVID-19 Infection

Derya Koyun[1], Seher Yüksel[2], Muhit Özcan[1], Işınsu Kuzu[2], Sinem Civriz Bozdağ[1]
[1]Ankara University Faculty of Medicine, Department of Hematology, Ankara, Türkiye
[2]Ankara University Faculty of Medicine, Department of Pathology, Ankara, Türkiye

Derya Koyun, M.D., Ankara University Faculty of Medicine, Department of Hematology, Ankara, Türkiye
dr.deryakoyun@hotmail.com

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To the Editor,
Extranodal NK/T cell lymphoma (ENKTL) is a rare subtype of non-Hodgkin's lymphoma often linked to Epstein-Barr virus (EBV) and has an unfavorable prognosis (1). Chronic active Epstein-Barr virus (CAEBV) is an important diagnostic consideration in differential diagnosis. By the 2022 version of the World Health Organisation classification, CAEBV is regarded as a lymphoproliferative disease of T or NK cells infected with EBV (2). This report of an ENKTL could provide critical insight into the manifestation, diagnostic challenges, and management of a scarce condition.
A 56-year-old woman presented with a 7-month complaint of persistent abdominal pain, progressive weight loss, and recurrent night sweats requiring further diagnostic evaluation. Increased gastric and proximal wall thickness and multiple small mesenteric lymph nodes were seen on computed tomography (Figure 1A-B). The endoscopic biopsy demonstrated active gastritis and ulceration, accompanied by an increased number of atypical cytotoxic T cells expressing CD4 and CD30 but no CD56 expression. EBER in situ hybridization confirmed EBV in the biopsy, with a plasma EBV DNA load of 378 copies/mL. The pathological interpretation was consistent with an EBV-associated NK/T cell lymphoproliferative disease. With limited mucosal involvement, phenotypic characteristics, and relation to EBV infection, the biopsies were considered gastrointestinal CAEBV, referring to described Japanese series (3).
The patient was started on a treatment schedule previously described by Sawada et al. (4). Her symptoms and plasma EBV load were significantly reduced with an initial conditioning regimen that included steroids (0.5 mg/kg/day), cyclosporine (3mg/kg/day), and etoposide (150mg/m2/week), followed by mini-CHOP (cyclophosphamide, doxorubicin, vincristine, and methylprednisolone). However, after the first cycle of mini-CHOP, the plasma EBV load increased again. At the end of the first cycle, she was diagnosed with COVID-19, and her EBV viral load was utterly negative. The second treatment cycle could be started with a delay of 15 days as soon as PCR negativity was achieved. Following the second treatment cycle, the patient's symptoms recurred, and a biopsy was repeated.
Pathological examination revealed necrosis, ulceration, and severe transmural infiltration of pleomorphic neoplastic lymphoid cells with mild eosinophilic to clear cytoplasms. Immunohistochemistry staining showed that tumor cells were positive for CD3, CD4, CD30, TCR B, and granzyme B with atypical T cell infiltration and clonal TCR gene rearrangement but negative for CD20 (Figure 1D). Pathologic findings demonstrated EBV-associated T/NK cell lymphoma with a T cell phenotype negative with CD56 more distinctive. TCR beta was clonal with molecular analysis, which supports the EBV-associated primary gastric NKTL with T cell phenotype. Following the initial phase of treatment, the patient was administered a DDGP regimen consisting of cisplatin, dexamethasone, gemcitabine, and pegaspargase. The initial cycle resulted in EBV-DNA negativity, accompanied by favorable tolerability. After the third cycle of treatment, the patient passed away due to complications arising from sepsis and multiple organ dysfunction (Figure 1C).
Distinguishing between Crohn's, intestinal tuberculosis, CAEBV, and ENKTL is challenging (3,5,6). The situation may be caused in certain gastrointestinal NKT cases, with CAEBV initially being suspected. Difficulties in diagnosing our case included the phenotypic diversity of the neoplastic NK/T cells, the limitation of the small endoscopic biopsy samples, and gastric localization. This case was unique because it had a T-cell rather than NK-cell phenotype.

Although information on the treatment of ENKTL is limited, asparaginase-containing regimens are promising (7,8). Our case is the second reported of ENKTL with spontaneous remission during COVID-19, followed by relapse post-infection resolution (9). Research revealed that NK cells express angiotensin-converting enzyme 2 (ACE2), the target receptor of COVID-19. The interaction between COVID-19 and ACE2 may induce high NKG2A expression and impair NK cell functionality. Overproducing pro-inflammatory cytokines in COVID-19 may also have an oncolytic effect with apoptosis. In our case, the EBV viral load (a pivotal marker for ENKTL) fell significantly during COVID-19.

On the other hand, SARS-CoV-2 infection has reactivated the immune system through cytokine storm-induced inflammation. As a result, T lymphocyte activity resumed, targeting and destroying tumor cells (10). Genetically engineered SARS-CoV-2 is expected to demonstrate antitumor efficacy in the ENKTL.

We present a case of EBV-associated primary gastric ENKTL with a T-cell phenotype misdiagnosed as CAEBV. Further studies are needed to explore the potential of SARS-CoV-2 as an oncolytic agent.

References

1. Kim SJ, Jung HA, Chuang SS, et al. Asia Lymphoma Study Group. Extranodal natural killer/T-cell lymphoma involving the gastrointestinal tract: analysis of clinical features and outcomes from the Asia Lymphoma Study Group. J Hematol Oncol. 2013;6:86.

2. Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: Lymphoid Neoplasms. Leukemia. 2022;36(7):1720-1748.

3. Aihara Y, Moriya K, Shimozato N, et al. Chronic active EBV infection in refractory enteritis with longitudinal ulcers with a cobblestone appearance: an autopsied case report. BMC Gastroenterol. 2021;21(1):6.

4. Sawada A, Inoue M, Kawa K. How we treat chronic active Epstein-Barr virus infection. Int J Hematol. 2017;105(4):406–418.

5. Chen H, Zhang Y, Jiang Z. A case report of NK-cell lymphoproliferative disease with a wide involvement of digestive tract develop into Epstein–Barr virus associated NK/T cell lymphoma in an immunocompetent patient. Medicine 2016;95:3176.

6. Lookzadeh S, Pourabdollah TM, Jamaati H, Rezaei M, Marashian M. Primary gastrointestinal involvement in a case of extranodal-extranasal natural killer T cell lymphoma. Tanaffos. 2020;19:74–8.

7. Zhao Q, Fan S, Chang Y et al. Clinical efficacy of DDGP in the initial treatment of advanced stage extranodal NK/T-cell lymphoma and its correlation with Epstein-Barr virus. Cancer Management and Research 2019;11: 3555–3564.

8. Jeong SH. Extranodal NK/T cell lymphoma. Blood Res. 2020;55:63–71.

9. Pasin F, Calveri MM, Pizzarelli G, et al. Oncolytic effect of SARS-CoV2 in a patient with NK lymphoma. Acta Bio Medica. 2020; 91(3):e2020047.

10. Barkhordar M, Rostami FT, Yaghmaie M, et al. Spontaneous Complete Remission of Acute Myeloid Leukemia in the Absence of Disease-Modifying Therapy following Severe Pulmonary Involvement by Coronavirus Infectious Disease-19. Case Rep Hematol. 2022;2022:2603607.

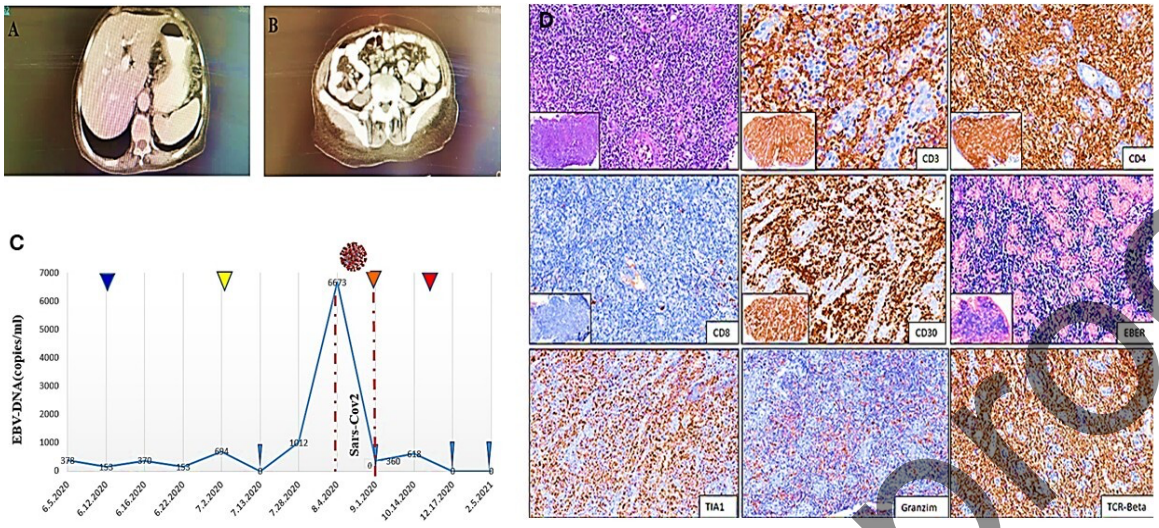

Figure 1. (A) Abdominal computed tomography imaging diffuse gastric wall thickening, **(B)** Multiple lymphadenopathies in the mesentery. **(C)** Plasma Epstein-Barr Virus (EBV)-DNA (copies/mL) ( ) Steroid, cyclosporin, and etoposide, ( ) first cycle mini-CHOP (cyclophosphamide, doxorubicin, vincristine, methylprednisolone) ( ) second cycle mini-CHOP, ( ) DDGP (cisplatin, dexamethasone, gemcitabine, pegaspargase). **(D)** Immunohistochemical characteristics of tumor cells. Immunohistochemical stainings of a cluster of differentiation CD3, CD4, CD8, CD30, EBER, T-cell restricted intracellular antigen 1 (TIA1), Granzim, and TCR.