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Pediatric EBV positive Mucocutaneous Ulceration in stomach a rare entity

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Corresponding Author:	MEHMET ALAKAYA Mersin University Faculty of Medicine Mersin, TURKEY
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Mersin University Faculty of Medicine
Corresponding Author's Secondary Institution:	
First Author:	MEHMET ALAKAYA
First Author Secondary Information:	
Order of Authors:	MEHMET ALAKAYA
	Begumhan Demir GUNDOGAN
	Ali Ertug ARSLANKOYLU
	Yasemin Yuyucu KARABULUT
	Nalan AKYUREK
	Asuman Nur KARHAN
	Yusuf USTA
	Elvan Caglar CITAK
Order of Authors Secondary Information:	
Manuscript Region of Origin:	TURKEY
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Correction Note

Dear Editor and Reviewer, first of all thank you for evaluating this case report. Your suggestions made me very happy.

I completed the revision of the article in line with the suggestion of the dear Reviewer.

I've explained them one by one below

Yours sincerely

1- In the section of Introduction, Kulinski et al. The sentence is added using the reference of their work. Reference number 5

2- The sentence "*A possible explanation is that our patient also had AT and therefore was not able to properly control EBV infection*." was added to the Discussion section. Reference given. Number 5

3- *"Our case in a small child with AT is the first case of EBV MCU detected in the stomach in a pediatric series*." The sentence was added.

4- All wrong words have been corrected. Changed to Epstein.

5- Reference number 5 added. Other reference numbers have been changed due to this change.

Pediatric EBV Positive Mucocutaneous Ulceration in Stomach a Rare Entity

Mehmet Alakaya, MD,* Begumhan Gundogan, MD,† Ali Ertuğ Arslanköylü, MD,* Yasemin Yuyucu Karabulut, MD,‡ Nalan Akyurek, MD,§ Asuman Nur Karhan, MD,¶ Yusuf Usta, MD,¶ and Elvan Caglar Citak, MD,†

*Mersin University Faculty of Medicine Department of Pediatric Intensıve Care Unıt

†Mersin University Faculty of Medicine Department of Pediatric Oncology

‡Mersin University Faculty of Medicine Department of Pathology

§Gazi University Faculty of Medicine Department of Pathology

¶Mersin University Faculty of Medicine Department of Pediatric Gastroenterology

Correspondence to: MEHMET ALAKAYA, MD

Asst. Professor of Pediatric Intensıve Care Unıt, Mersin University Faculty of Medicine Department of Pediatric Intensıve Care Unıt, Mersin, TURKEY

e-mail address: drmehmetalakaya@mersin.edu.tr

Telephone Number: 0 505 938 4578

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No financial resources

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Introduction

Epstein Barr virus (EBV), also known as human herpesvirus 4 is a linear double-stranded DNA virus. It spreads through the oropharyngeal tract and can also be found in genital secretions. EBV more often infects B-cells and epithelial cells. It enters B-cells over CD21 and to epithelial cells that do not contain CD21 over the host's B1 integrins. (1) Asymptomatic primary lytic infection period begins in pursuit of the entry of EBV into the cell. It passes on to the latent period by forming a circular nucleic episome within the infected cell. (2) EBV-infected B-cells remain latent in lymphoid follicles for a lifetime. (3) Cells that have not entered the latent period are controlled by memory B-cell with CD4 lymphocytes. During conversion into plasma lymphocyte, EBV episome is made linear, and the lytic period begins, and new EBV virions are formed. This control is provided by CD8 lymphocytes and

Natural Killer cells in immunocompetent individuals. In immunocompromised individuals, this lytic cycle cannot be achieved; EBV-related lymphoproliferative diseases occur. Most of the EBV-associated lymphoproliferative diseases are classified under the category of mature B-cell neoplasms. After the revision in 2016, the world health organization has defined a new Lymphoproliferative disease group named EBV positive mucocutaneous ulceration (EBVMCU) in the lymphoid neoplasm classification. (4)

Ataxia Telangiectasia (AT) is an immunodeficiency situated in the DNA repair defect group and seen as a result of a mutation in the ATM gene. ATM protein encoded by the ATM gene assists cell division and DNA repair. ATM mutations cause the ATM protein to be reduced or not fully produced such that ultimately, cells cannot repair DNA strand breaks and cancerous changes occur over time. AT patients display a pattern of anti-EBV antibodies suggestive of poorly controlled EBV replication. (5) The severe course of EBV-related infections in patients with AT can be explained by this situation.

EBVMCU is more often seen in immunocompromised individuals. It is extremely rare in pediatric patients. When examining the places of involvement, it is most common in the oral mucosa and skin. Although the gastrointestinal tract is the third most common, gastric involvement was identified in only 1 adult patient in the literature. In line with our knowledge, our patient is the second but the first pediatric patient in terms of EBVMCU with gastric involvement in this respect. There may be different approaches in EBVMCU treatment. This conservative follow-up, reducing the drug dose if the patient is receiving immunosuppressant therapy, immune-mediated drugs effective on EBV in chemotherapy, and new treatment strategies.

Here, we would like to present an 11-year-old boy patient diagnosed with EBVMCU in the stomach followed up due to AT, and who was started on Brentixumab Vedotin (BV) treatment, successfully treated and still in remission.

Case

Upon detecting telangiectasia in the eyes and oculomotor apraxia on physical examination in the center where he applied due to difficulty in walking, frequent falls, and speech disorder he encountered when he was 3.5 years old, the genetic examination was performed with the pre-diagnosis of ataxia-telangiectasia. The diagnosis was confirmed upon detecting NM_000051.3 pY 2036 homozygous mutation in the ATM (11q22) gene. The patient, who was followed up in the immunology department, was started on human immunoglobulin treatment every 3 weeks. In the physical examination performed due to swelling in the right neck six months before his last hospitalization, painless LAP of 2x1 cm in size was detected, and USG revealed lymphadenopathy in the right anterior cervical chain, the largest of which was 25 mm in the left anterior cervical, and 12 mm in size ovoid. Oral antibiotic treatment was started in the patient, and lymph nodes were determined to be a regression in size with treatment.

At age eleven, patient hospitalized due to abdominal pain and difficulty swallowing. An upper gastrointestinal (GI) endoscopy was performed and a large ulcerous lesion with fibrinous base extending to both antrum and corpus of the stomach was observed. Smaller ulcerative lesions were also observed around the major lesion. Gastric mucosa adjacent to lesion was edematous and fragile. Biopsy taken from this area. (Figure 1) Lower gastrointestinal endoscopy was normal. The patient, who had respiratory failure and pleural effusion and developed septic shock, was taken to the intensive care unit and started to be followed up. Empirical antibiotherapy was started for the patient.

Physical examination in the pediatric intensive care unit, the patient was conscious, somnolence, and body temperature were high (38.7 ° C). Blood pressure was appropriate for his age (110/70 mmHg) after arterial fluid resuscitation. He was tachypneic (32/min), dyspneic, his saturation was 84 in the presence of oxygen, and left lung lower zone ventilation

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Atypical CD 30 positive cells were found in the endoscopic biopsy of the patient. It was evaluated as primary gastric Hodgkin Lymphoma. Since the incidence of primary gastric lymphoma is very low, due to diagnostic suspicion, conducted a biopsy on the lymph node from the neck area with PET involvement. The biopsy was evaluated as necrosis and scattered histiocytes, and reactive lymphadenitis and a biopsy on the patient again. It was not detected the difference in appearance on endoscopy. Upon detecting polymorphic, large atypical cells CD 30 (+), CD 20 (+), EBER positive cells in the second biopsy taken, the patient was diagnosed with EBVMCU. (Figure 2)

EBV PCR was detected as positive, and EBV DNA was detected as 4890 copies/ml. Due to the immunohistochemically CD30, positive cells were more prominent, BV (Anti CD-30) treatment was started at 1.8mg/kg/dose. It was observed that the lesion completely regressed in the endoscopy performed after a total of 6 cures of treatment and there was no finding in favor of EBVMCU in the biopsy taken. (Figure 3) After the end of treatment's 2 month the control upper GI endoscopy showed a complete recovery. (Figure 4) The patient is still followed-up in remission.

DISCUSSION

EBVMCU was identified after the classification in 2016. (4) It is in the group of lymphoproliferative diseases. The first comprehensive study describing this lymphoproliferative disease was published by Dojcinov in 2010, and the study included 26 patients with advanced age-related immunosuppression or drug-induced immunosuppression. These patients were self-limiting patients with mucosal or cutaneous ulcers, commonly involving the oropharynx, gastrointestinal tract, or skin. (6) EBVMCU is more often seen in immunocompromised patients and patients with a history of drug use causing immunodeficiency. While Dojcinov et al., in their series, determined the median age of the patients in immunosuppressive drug users (iatrogenic) to be 69 years, this median was 80 years in patients without a history of drug use. It was observed that these patients used Methotrexate, Azathioprine, and Cyclosporine A as immunosuppressive agents. (6) Although our patient did not use immunosuppressant drugs, he had AT disease that caused immunodeficiency. Except for immunoglobulin support, he did not have regular use of medication. Accordingly, detailed patient history is very important in patients diagnosed with EBVMCU. The patient's underlying disease and drug use should be investigated in detail.

EBVMCU usually presents with a solitary lesion. 17% of the cases in the literature are multifocal. Generally, lesions occur on the skin (29%), oral mucosa (52%) or gastrointestinal tract (19% - 40% colon, 30% esophagus, 20% rectum and 10% terminal ileum). (7) Although it is quite rare in the stomach, it was first shown by EBVMCU Gabsi et al. in a 62-year-old male in the stomach, and to our knowledge, no other case of gastric involvement was reported. (8) The youngest case with EBVMCU is a patient with 5-month skin involvement in the literature. (9) Still, in another study report, a 16-year-old male patient was diagnosed with CHARGE syndrome (coloboma, heart defect, atresia of the nasal choanae, retardation of growth, genital and ear abnormalities, and deafness) and EBVMCU with nasopharyngeal

mucosal involvement. (10) In line with our knowledge, our patient is important because it is the first case of EBVMCU in the stomach in children. A possible explanation is that our patient also had AT and therefore was not able to properly control EBV infection. (5)

EBVMCU are polymorph infiltrates that may histopathologically contain histiocytes, eosinophils, plasma cells, large pleomorphic immunoblasts similar to Hodgkin reed stenberg (HRS) cells, numerous medium-sized T cells, apoptotic bodies, as well as well-defined ulcers that may include vascular invasions and necrosis. Large pleomorphic blast cells and HRS-like cells express CD20, CD30, CD15, PAX5, OCT2, MUM1, BOB1, EBER, CD45. In 33% of cases, a decrease or absence of CD20 expression is observed. These large atypical cells are positive for EBV's latent membrane protein-1 (LMP-1). (11-12) In consequence of gastric endoscopic biopsy performed before the treatment of our patient, polymorphic, lymphocyte-containing, histiocytes, Hodgkin-like cells, and immunoblasts were present. The diagnosis was made by detecting CD20, CD30, and EBER positivity in atypical large cells. (Figure 2A,2A1,2A2,2A3)

Although EBVMCU does not have treatment instructions and guidelines, the treatment regimen, which is generally common in adult patients, is conservative. In the use of immunosuppressant drugs, discontinuation or dose reduction is recommended. Studies conducted were determined that complete remission is achieved in the range of 2-12 weeks in 2/3 of EBVMCU cases using immunosuppressive drugs. However, the median duration is 4 weeks with only drug dose reduction. Rarely, progression and relapse were observed. (7-13) However, some studies have shown that 36% of patients diagnosed with EBVMCU are administered aggressive treatment, although it is a self-limiting diagnosis and that Rituximab or drugs can increase immunological control EBV are used in these treatments. There are also cases where chemotherapy protocols are applied. (14-15-16) Nevertheless, the factors that contribute to a treatment strategy's decision to be applied and the prognosis prediction have

not been clarified yet. We preferred our patient to be hospitalized in the intensive care unit due to the underlying immune deficiency and anti CD30 monoclonal antibody BV, one of the new targeted treatment regimens, because of the patient's CD30 positivity. BV targets CD30 overproduced from Hodgkin and Reed Sternberg cells and large cell lymphoma malignant cells. This drug is highly effective in a wide range of CD30 positive lymphomas such as classical Hodgkin lymphoma, anaplastic large cell lymphoma, T cell lymphoma, and diffuse large B cell lymphoma. BV binds to CD 30 on the cell surface. Vedotin is transported to the nucleus cells, joining the cell cycle, disrupting the cycle and causing apoptosis. Pediatric experience confirms adult patient data. In the study of Locatelli et al., it has been shown that single-agent brentuximab vedotin treatment is effective in pediatric patients with poor prognosis Hodgkin lymphoma and systemic anaplastic large cell lymphoma. (17-18-19-20) There are also studies applying BV in EBVMCU treatment. Thomas Pincez et al. in their study have demonstrated the effectiveness of BV therapy in a patient who was diagnosed with EBV positive Burkitt Lymphoma at the age of 11 and who was diagnosed with primary colon originated EBVMCU as a result of examinations performed for persistent fever, diarrhea, and weight loss during follow-up. It was found that the disease regressed after the first week, and the EBVMCU did not recur after the treatment. (21) Still, in the same study, BV was used in a case diagnosed with AT in childhood. This 16 years old patient was applied with dysphagia, anorexia, and a severe eating disorder. In his/her examination, severe palatine ulcer and cervical lymphadenopathy were detected. In his/her biopsy, according to the lymphoproliferative patient classification, it was diagnosed as monomorphic non-germinal center B-cell. Complete response was received from 3 months of BV treatment. (21)

There is no data in the literature regarding the treatment of primary gastric-derived EBVMCU. BV treatment was administered to our patient at 1.8 mg/kg/dose every 3 weeks.

Complete remission was achieved after a total of 6 cures of treatment. The patient was sent to the palliative care center with oxygen support.

Conclusion

Consequently, mucocutaneous ulcers should be kept in mind when immunocompromised children present with gastrointestinal symptoms. Solely after our knowledge increases, the most appropriate treatment will be determined in these patients according to the underlying disease. Although EBVMCU is very rare in childhood, weight loss in immunosuppressive patients should not be overlooked in children with nutritional problems. Our case in a small child with AT is the first case of EBVMCU detected in the stomach in a pediatric series. We think that appropriate treatment modalities will be determined by the increase of our knowledge about this disease.

The authors declare no conflict of interest

No financial resources

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Figure Legends

Figure 1- Large ulcerous lesion in antrum and corpus of the stomach

Figure 2- Endoscopic biopsy results (2A- The infiltrate is polymorphous, containing lymphocytes, histiocytes, immunoblasts, and Hodgkin-like cells. (HE, original magnification x200), Large atypical cells were positive for CD20 (2A1), CD30 (2A2) and EBER (2A3); (original magnification: a-c x200)

Figure 3- The restricted image of the ulcerative lesion with a healed mucosal appearance

Figure 4- Healed gastric mucosa

Figure 1

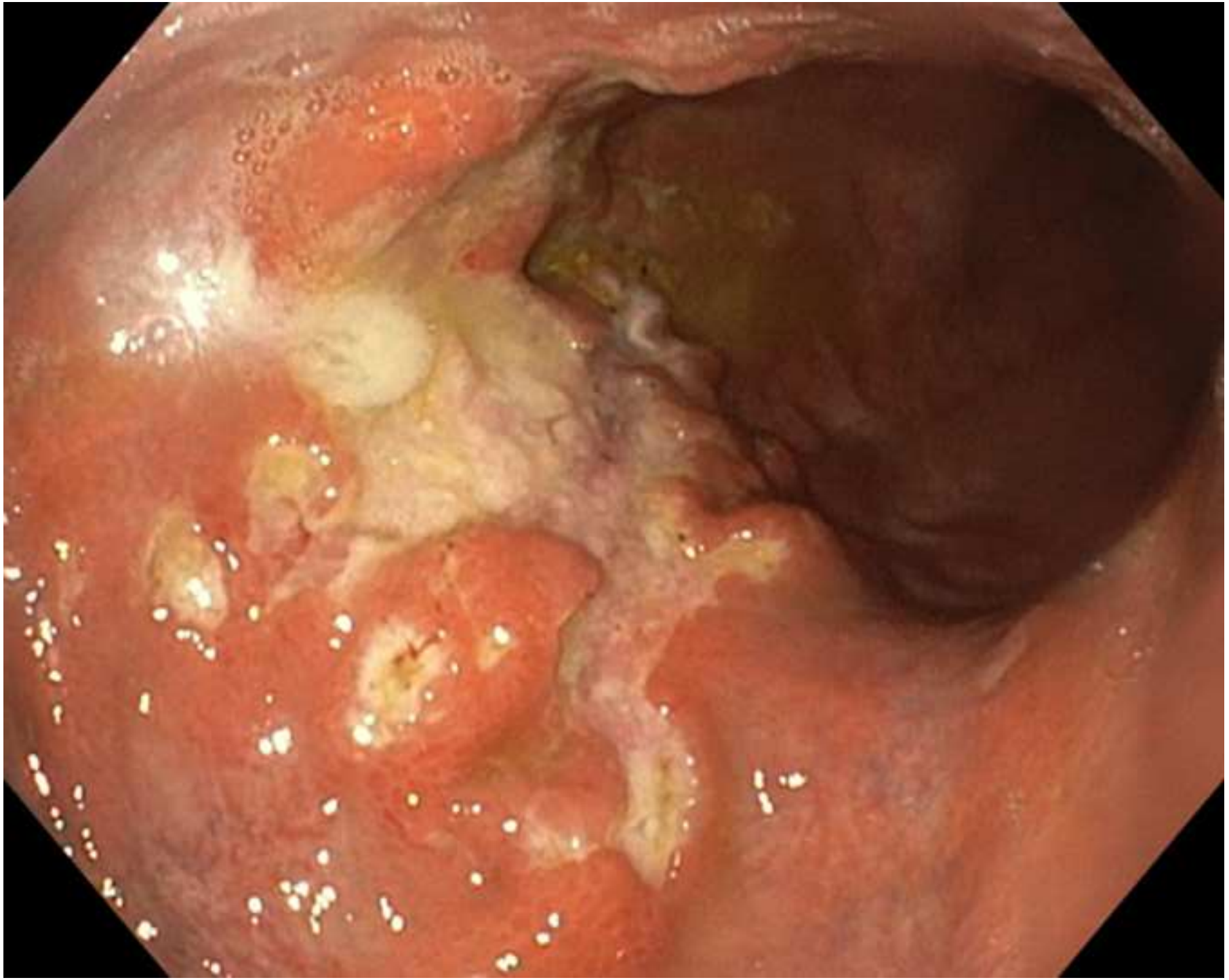

Figure 2

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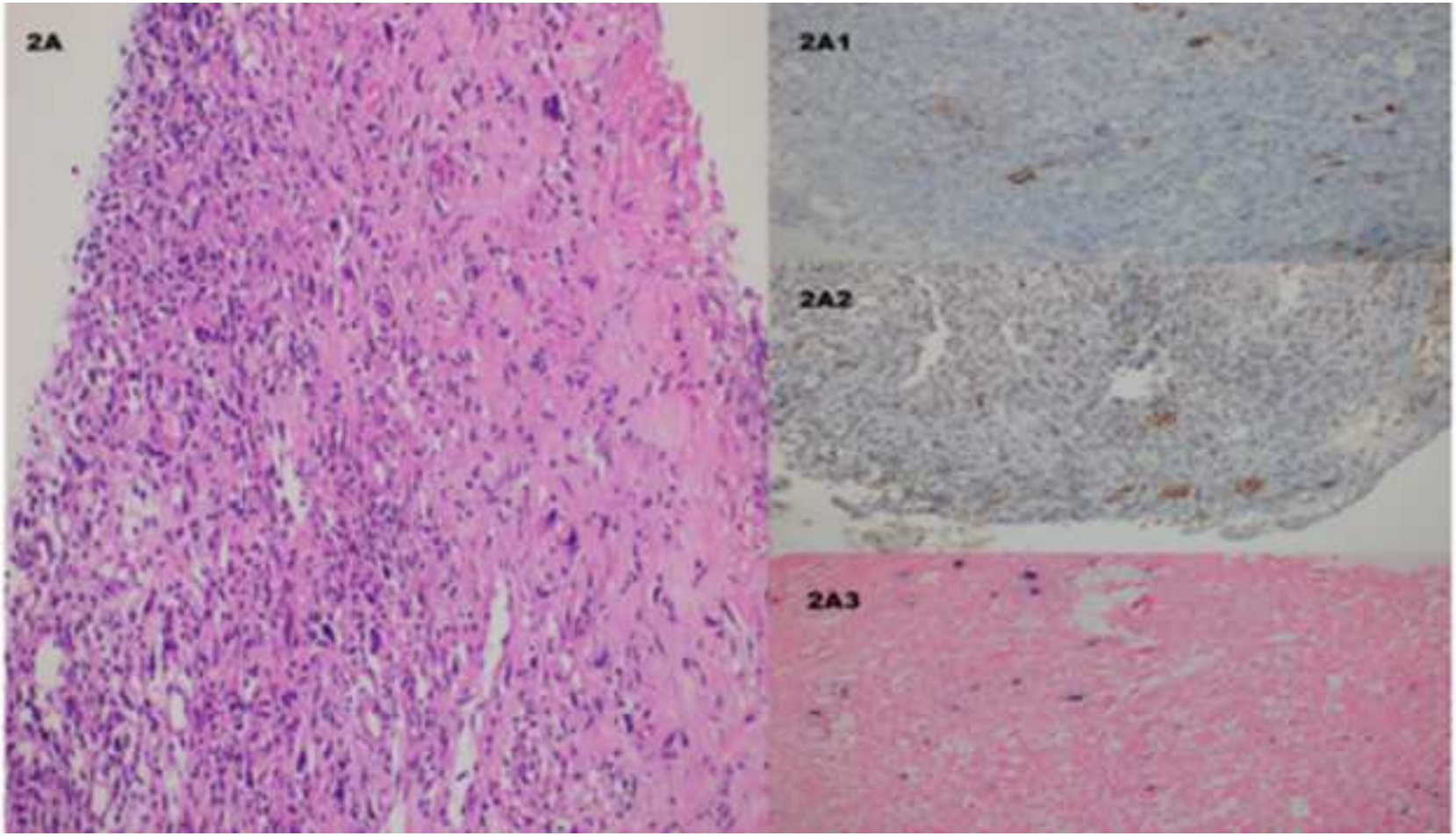

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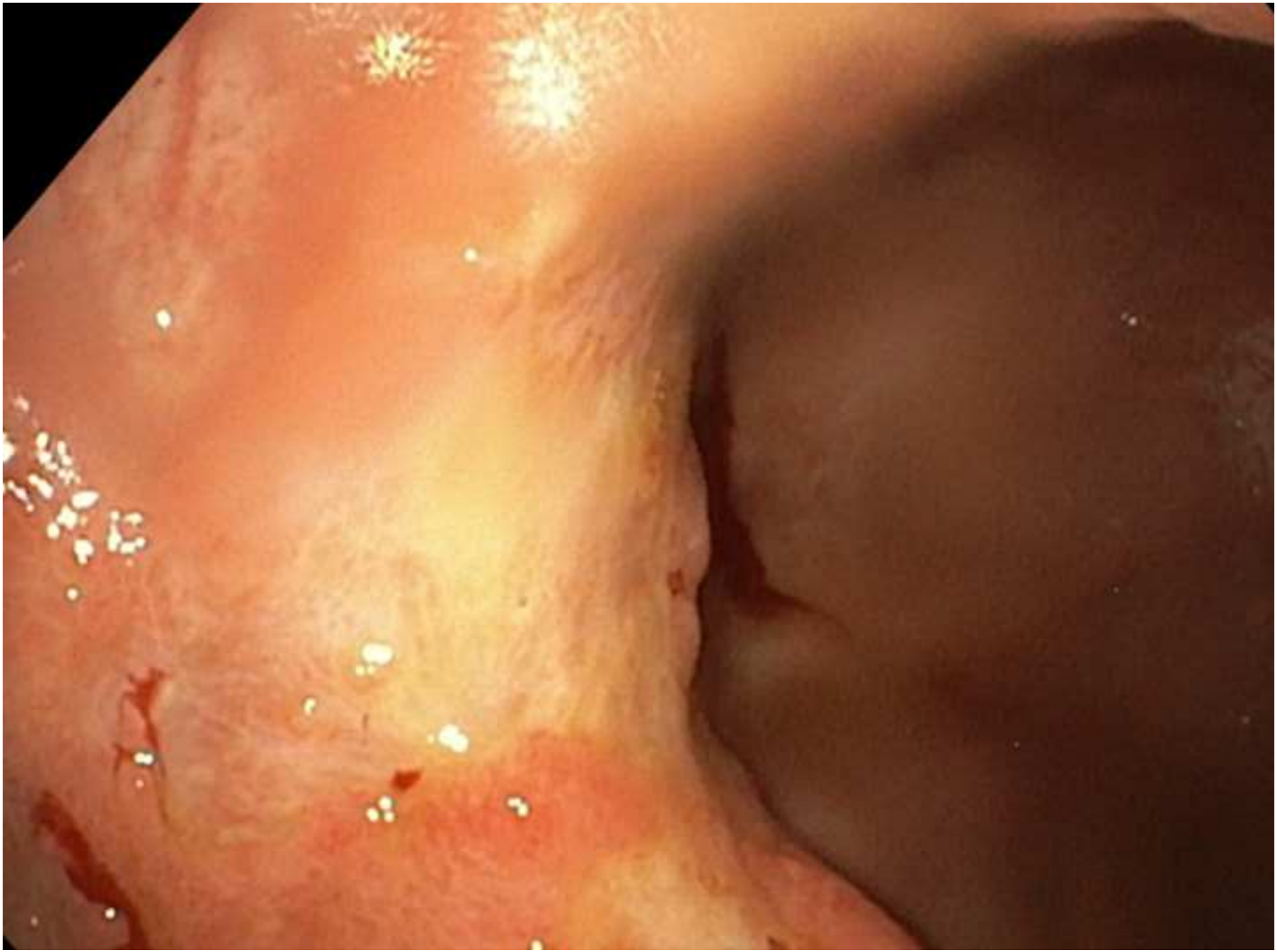

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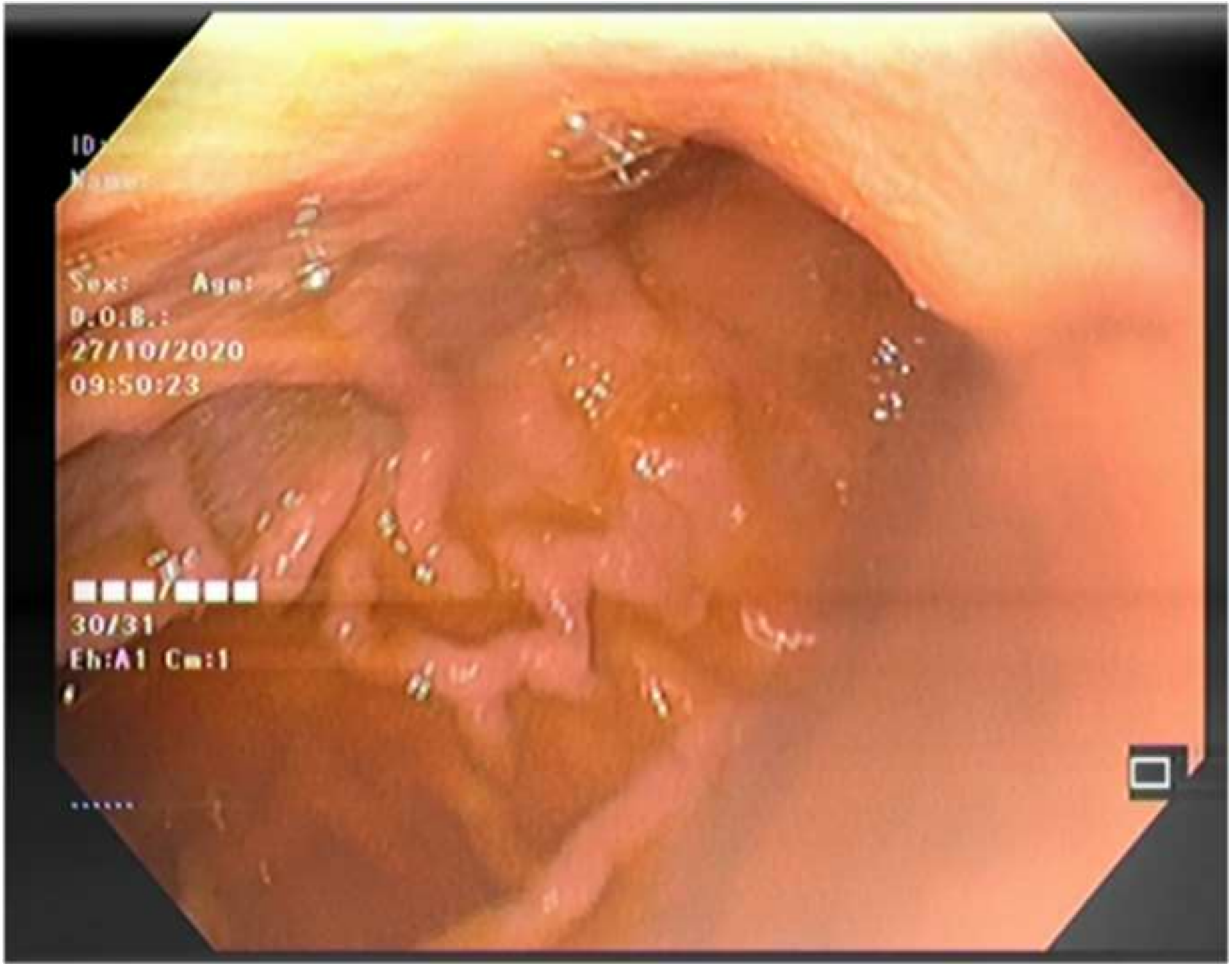

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Atypical CD 30 positive cells were found in the endoscopic biopsy of the patient. It was evaluated as primary gastric Hodgkin Lymphoma. Since the incidence of primary gastric lymphoma is very low, due to diagnostic suspicion, conducted a biopsy on the lymph node from

the neck area with PET involvement. The biopsy was evaluated as necrosis and scattered histiocytes, and reactive lymphadenitis and a biopsy on the patient again. It was not detected the difference in appearance on endoscopy. Upon detecting polymorphic, large atypical cells CD 30 (+), CD 20 (+), EBER positive cells in the second biopsy taken, the patient was diagnosed with EBVMCU. (Figure 2)

EBV PCR was detected as positive, and EBV DNA was detected as 4890 copies/ml. Due to the immunohistochemically CD30, positive cells were more prominent, BV (Anti CD-30) treatment was started at 1.8mg/kg/dose. It was observed that the lesion completely regressed in the endoscopy performed after a total of 6 cures of treatment and there was no finding in favor of EBVMCU in the biopsy taken. (Figure 3) After the end of treatment's 2 month the control upper GI endoscopy showed a complete recovery. (Figure 4) The patient is still followed-up in remission.

DISCUSSION

EBVMCU was identified after the classification in 2016. (4) It is in the group of lymphoproliferative diseases. The first comprehensive study describing this lymphoproliferative disease was published by Dojcinov in 2010, and the study included 26 patients with advanced age-related immunosuppression or drug-induced immunosuppression. These patients were self-limiting patients with mucosal or cutaneous ulcers, commonly involving the oropharynx, gastrointestinal tract, or skin. (6) EBVMCU is more often seen in immunocompromised patients and patients with a history of drug use causing immunodeficiency. While Dojcinov et al., in their series, determined the median age of the patients in immunosuppressive drug users (iatrogenic) to be 69 years, this median was 80 years in patients without a history of drug use. It was observed that these patients used Methotrexate, Azathioprine, and Cyclosporine A as immunosuppressive agents. (6) Although our patient did not use immunosuppressant drugs, he had AT disease that caused immunodeficiency. Except

for immunoglobulin support, he did not have regular use of medication. Accordingly, detailed patient history is very important in patients diagnosed with EBVMCU. The patient's underlying disease and drug use should be investigated in detail.

EBVMCU usually presents with a solitary lesion. 17% of the cases in the literature are multifocal. Generally, lesions occur on the skin (29%), oral mucosa (52%) or gastrointestinal tract (19% - 40% colon, 30% esophagus, 20% rectum and 10% terminal ileum). (7) Although it is quite rare in the stomach, it was first shown by EBVMCU Gabsi et al. in a 62-year-old male in the stomach, and to our knowledge, no other case of gastric involvement was reported. (8) The youngest case with EBVMCU is a patient with 5-month skin involvement in the literature. (9) Still, in another study report, a 16-year-old male patient was diagnosed with CHARGE syndrome (coloboma, heart defect, atresia of the nasal choanae, retardation of growth, genital and ear abnormalities, and deafness) and EBVMCU with nasopharyngeal mucosal involvement. (10) In line with our knowledge, our patient is important because it is the first case of EBVMCU in the stomach in children. A possible explanation is that our patient also had AT and therefore was not able to properly control EBV infection. (5)

EBVMCU are polymorph infiltrates that may histopathologically contain histiocytes, eosinophils, plasma cells, large pleomorphic immunoblasts similar to Hodgkin reed stenberg (HRS) cells, numerous medium-sized T cells, apoptotic bodies, as well as well-defined ulcers that may include vascular invasions and necrosis. Large pleomorphic blast cells and HRS-like cells express CD20, CD30, CD15, PAX5, OCT2, MUM1, BOB1, EBER, CD45. In 33% of cases, a decrease or absence of CD20 expression is observed. These large atypical cells are positive for EBV's latent membrane protein-1 (LMP-1). (11-12) In consequence of gastric endoscopic biopsy performed before the treatment of our patient, polymorphic, lymphocyte-containing, histiocytes, Hodgkin-like cells, and immunoblasts were present. The diagnosis was

made by detecting CD20, CD30, and EBER positivity in atypical large cells. (Figure 2A,2A1,2A2,2A3)

Although EBVMCU does not have treatment instructions and guidelines, the treatment regimen, which is generally common in adult patients, is conservative. In the use of immunosuppressant drugs, discontinuation or dose reduction is recommended. Studies conducted were determined that complete remission is achieved in the range of 2-12 weeks in 2/3 of EBVMCU cases using immunosuppressive drugs. However, the median duration is 4 weeks with only drug dose reduction. Rarely, progression and relapse were observed. (7-13) However, some studies have shown that 36% of patients diagnosed with EBVMCU are administered aggressive treatment, although it is a self-limiting diagnosis and that Rituximab or drugs can increase immunological control EBV are used in these treatments. There are also cases where chemotherapy protocols are applied. (14-15-16) Nevertheless, the factors that contribute to a treatment strategy's decision to be applied and the prognosis prediction have not been clarified yet. We preferred our patient to be hospitalized in the intensive care unit due to the underlying immune deficiency and anti CD30 monoclonal antibody BV, one of the new targeted treatment regimens, because of the patient’s CD30 positivity. BV targets CD30 overproduced from Hodgkin and Reed Sternberg cells and large cell lymphoma malignant cells. This drug is highly effective in a wide range of CD30 positive lymphomas such as classical Hodgkin lymphoma, anaplastic large cell lymphoma, T cell lymphoma, and diffuse large B cell lymphoma. BV binds to CD 30 on the cell surface. Vedotin is transported to the nucleus cells, joining the cell cycle, disrupting the cycle and causing apoptosis. Pediatric experience confirms adult patient data. In the study of Locatelli et al., it has been shown that single-agent brentuximab vedotin treatment is effective in pediatric patients with poor prognosis Hodgkin lymphoma and systemic anaplastic large cell lymphoma. (17-18-19-20) There are also studies applying BV in EBVMCU treatment. Thomas Pincez et al. in their study have demonstrated

the effectiveness of BV therapy in a patient who was diagnosed with EBV positive Burkitt Lymphoma at the age of 11 and who was diagnosed with primary colon originated EBVMCU as a result of examinations performed for persistent fever, diarrhea, and weight loss during follow-up. It was found that the disease regressed after the first week, and the EBVMCU did not recur after the treatment. (21) Still, in the same study, BV was used in a case diagnosed with AT in childhood. This 16 years old patient was applied with dysphagia, anorexia, and a severe eating disorder. In his/her examination, severe palatine ulcer and cervical lymphadenopathy were detected. In his/her biopsy, according to the lymphoproliferative patient classification, it was diagnosed as monomorphic non-germinal center B-cell. Complete response was received from 3 months of BV treatment. (21)

There is no data in the literature regarding the treatment of primary gastric-derived EBVMCU. BV treatment was administered to our patient at 1.8 mg/kg/dose every 3 weeks. Complete remission was achieved after a total of 6 cures of treatment. The patient was sent to the palliative care center with oxygen support.

Conclusion

Consequently, mucocutaneous ulcers should be kept in mind when immunocompromised children present with gastrointestinal symptoms. Solely after our knowledge increases, the most appropriate treatment will be determined in these patients according to the underlying disease. Although EBVMCU is very rare in childhood, weight loss in immunosuppressive patients should not be overlooked in children with nutritional problems. Our case in a small child with AT is the first case of EBVMCU detected in the stomach in a pediatric series. We think that appropriate treatment modalities will be determined by the increase of our knowledge about this disease.

The authors declare no conflict of interest

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Figure Legends

Figure 1- Large ulcerous lesion in antrum and corpus of the stomach

Figure 2- Endoscopic biopsy results (2A- The infiltrate is polymorphous, containing lymphocytes, histiocytes, immunoblasts, and Hodgkin-like cells. (HE, original magnification x200), Large atypical cells were positive for CD20 (2A1), CD30 (2A2) and EBER (2A3); (original magnification: a-c x200)

Figure 3- The restricted image of the ulcerative lesion with a healed mucosal appearance

Figure 4- Healed gastric mucosa