Management of children and adolescents with gray zone lymphoma: A case series

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Abstract
Background: Data on management of gray zone lymphoma (GZL) in children and adolescents are scarce.
Procedure: This retrospective study assessed clinical characteristics and outcome in six Austrian patients with GZL less than 18 years of age (male-to-female ratio: 1:1; median age: 15.8 years).
Results: Two patients each had a classical Hodgkin lymphoma (cHL)-like and composite GZL subtype, and one patient each had a large B-cell non-Hodgkin lymphoma (LBCL)-like and sequential GZL subtype. All had advanced disease with mediastinal and extranodal involvement. Five patients received an LBCL- and one patient a cHL-directed polychemotherapy ± radiotherapy. Out of the former patients, three survived, including two who relapsed and underwent high-dose chemotherapy with autologous stem cell rescue. The latter patient survived.
Conclusions: GZL remains a diagnostic and therapeutic challenge, necessitating the development of novel treatment concepts performed in a prospective setting.

KEYWORDS
checkpoint inhibitors, gray zone lymphoma, outcome, relapse, treatment
1 | INTRODUCTION

Mediastinal and nonmediastinal gray zone lymphoma (GZL) is rare in childhood and adolescence, representing a B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma (DLBCL), especially primary mediastinal large B-cell lymphoma (PMLBCL), and classical Hodgkin lymphoma (cHL, nodular-sclerosis subtype).1-9 Both entities may appear simultaneously in one sample (cHL-like, LBCL-like, and composite GZL subtype) or recur sequentially as one of either entity.9 Therefore, GZL constitutes a “missing link” along a continuum between the two conditions.2,3,5,6,8 It has been postulated that GZL, cHL, and PMLBCL originate from a common precursor, i.e., a thymic B-lymphocyte, and that epigenetic alterations may lead to malignant transformation in either direction.6,8 The B-phenotype of the tumor cells may show positivity for CD20, CD30, MUM1, PAX5, CD79a, BOB1, OCT2, and BCL-6, whereas the T-phenotype may show positivity for CD5, CD30, MUM1, PAX5, and CD4.4,5,7,8 Genetic alterations involving the 9p24.1 locus (PD-L1/L2, JAK2) are found in more than half of the patients with GZL, and Epstein-Barr virus (EBV) is observed in about one quarter of the patients.4,5,7,9 GZL shows a male predominance,3,5,7,8,11,12 usually involves the mediastinum,2,3,5,7,8 and appears to have a higher tendency toward primary resistance, relapse, as well as toward inferior outcome as compared with PMLBCL or nodular-sclerosis cHL per se.3,4,7-9,12

Given the rarity of the disease and the fact that cHL and PMLBCL may occur simultaneously as a composite disease or sequentially but are usually treated differently, standardized therapeutic concepts are lacking, especially in pediatrics.3,4,6,8 Rituximab-based B-cell non-Hodgkin lymphoma (B-NHL)-directed regimens such as DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) appear to be preferable for first-line treatment.3,4,8,12 Furthermore, at least in the adult setting, GZLs more often undergo consolidation with involved-field irradiation.3,8 In case of relapse, high-dose (HD) chemotherapies such as HD-BEAM (BCNU, etoposide, ARA-C, melphalan) followed by autologous stem cell rescue (ASCR) have been reported to be associated with a superior outcome.4,8,12 In refractory disease, the additional use of novel therapeutic approaches—including the anti-CD30 monoclonal conjugated antibody brentuximab vedotin or PD-1 blockade with, e.g., pembrolizumab—has shown promising results in adult series.4,8,10,12,13 Finally, allogeneic hematopoietic stem cell transplantation (HSCT) may be another option for consolidation therapy.4,8

Due to its rarity, data concerning clinical course, treatment, and outcome of pediatric GZL are scarce. Herein, we describe the characteristics, treatment, and fate of six adolescents with GZL diagnosed in Austria within a period of >10 years.

2 | PATIENTS AND METHODS

2.1 | Patients

From March 1, 2004, to November 30, 2019, 174 pediatric patients with mature B-cell neoplasms were registered in Austria. Out of these 174 patients, six adolescents (3.4%) were diagnosed and treated with GZL (male, n = 3; female, n = 3). The median age at primary diagnosis was 15.8 years (range, 14.0-17.6 years). Clinical characteristics, pathology, immunohistochemistry, therapy, and outcome are shown in Tables 1 to 3. Four of six patients are alive in remission with a median follow-up of 8.7 years (range, 2.3-12.5 years) after initial diagnosis (last update: August 1, 2019).

2.2 | Methods

The analysis included all Austrian patients less than 18 years of age with nationally centrally reviewed histopathology of GZL at each time point of the disease course when tumor sampling was performed. According to the WHO classification of 2009, the description of the histological material revealed GZL in six cases. In all patients, diagnosis of GZL had been made in the course of their disease, including one patient with initial diagnosis before 2009, described as unclassifiable B-cell lymphoma with features of both DLBCL and cHL. All cases were reevaluated and retrospectively further classified into one of four subgroups (cHL-like, LBCL-like, composite, and sequential GZL), as previously proposed.14 Patient data collected included demographics and information on disease (lymphoma subtype, immunohistochemistry, age, gender, sites of involvement, stage of disease, and pretherapeutic leukocyte count and lactate dehydrogenase level), treatment (chemotherapy, radiotherapy, autologous HSCT), and outcome (date of progression/relapse, last follow-up, and death). Staging procedures have been described elsewhere.15,16 All patients were treated after informed consent from the patient, patient’s parents, or legal guardian had been obtained. Treatment studies were conducted according to the Declaration of Helsinki, and data collection was approved by the respective ethics committees.

3 | RESULTS

3.1 | Case 1

Fatigue in combination with a swollen neck and face resulting from superior vena cava obstruction led to the admission of a 17-year-old female. A mediastinal bulk with pleural and pericardial effusions and involvement of cervical, supraclavicular, and abdominal lymph nodes (LN; stage III) was detected. Supraclavicular lymph node biopsy revealed a composite GZL (LBCL + cHL). The LBCL component showed a diffuse infiltration of large blasts with round, slightly cleaved nuclei, and distinct nucleoli. Most of the tumor cells showed an eosinophilic cytoplasm. Intermingled clear cells could be found beside many mitoses. Blasts were positive for CD20, CD30, and PAX5 and negative for CD15 (Table 2). The cHL component showed typical Hodgkin and Reed/Sternberg (HRS) cells dispersed in an inflammatory background with eosinophilic granulocytes, plasma cells, macrophages, and small pleomorphic lymphocytes as well as obvious multifocal sclerosis. Cells of this component were positive for CD20, CD30, PAX5, and CD15. Chemotherapy was administered according to the B-NHL BFM
TABLE 1  Clinical and laboratory characteristics of the six patients with GZL at primary diagnosis

| Pt. | Age (years) | Gender | B-symptoms | WBC (10e9/L) | LDH (U/L) | Mediastinum | Cervical/ supraclavicular LN | Abdominal LN | Extramedullary involvement | Stagea |
|-----|-------------|--------|------------|--------------|-----------|-------------|-----------------------------|-------------|-----------------------------|--------|
| 1   | 17.6        | f      | No         | 19.800       | 310       | Yes         | Yes                         | Yes         | Pleura, PE                 | III    |
| 2   | 17.3        | m      | Yes        | 19.250       | 697       | Yes         | No                          | No          | No                          | III    |
| 3   | 15.0        | m      | No         | 9.300        | 273       | Yes         | Yes                         | No          | Pleura, PE, chest wall    | II-A-E |
| 4   | 14.0        | f      | No         | 7.700        | 205       | Yes         | Yes                         | No          | Lung, liver, pancreas     | III    |
| 5   | 16.2        | m      | No         | 13.210       | 252       | Yes         | Yes                         | Yes         | No                          | III    |
| 6   | 15.5        | f      | Yes        | 8.420        | 564       | Yes         | Yes                         | No          | Lung, pleura, PE          | III    |

Abbreviations: f, female; LDH, lactate dehydrogenase; m, male; PE, pericardial effusion; Pt., patient; WBC, leukocyte count.
aStage of disease was given according to the St. Jude's staging system for patients 1, 2, 4-6 and according to Ann Arbor for patient 3 (cHL-directed first-line treatment).

TABLE 2  Histopathology and immunohistochemistry of the six patients with GZL at primary diagnosis

| Pt. | Histopathology | CD20 | CD30 | CD15 | PAX5 | CD79a | BCL6 | CD10 | EBER |
|-----|----------------|------|------|------|------|-------|------|------|------|
| 1   | GZL (composite) | ++/+ | ++/+ | +/−  | ++/+ | ++++  | −/−  | nd   | nd   |
| 2   | GZL (cHL-like) | +/+  | +++/+| ++++ | +/−  | +/+/++| −/−  | nd   | nd   |
| 3   | GZL (cHL-like) | +/++ | ++/− | +/++ | +/−  | +/++  | −/−  | nd   | nd   |
| 4   | GZL (composite)a | ++/+ | ++/+ | ++/+ | +/−  | −+++ | −/−  | −+++ | −/−  |
| 5   | GZL (LBCL-like) | +/++ | ++/+ | +/−  | −/−  | nd   | −/−  | −/−  | −/−  |
| 6   | PMLBCL         | +++  | +  | −    | +++  | ++++  | −    | −    | −    |

Symbols in front of the slash refer to the cHL component, and symbols after the slash refer to the LBCL component. +, < 50% positive; ++, 50%-80% positive; ++++, > 80% positive; −, negative.

Abbreviations: cHL, classical Hodgkin lymphoma; GZL, gray zone lymphoma; LBCL, large B-cell lymphoma; nd, not done; PMLBCL, primary mediastinal large B-cell lymphoma; Pt., patient.
aTwo separate samples from different sites with cHL and PMBCL each.

TABLE 3  Treatment, outcome and follow-up of the six patients with GZL

| Pt. | First-line therapy | Response | Duration | Relapse/ progression | Second-line therapy | Response | Duration to last FU |
|-----|--------------------|----------|----------|----------------------|---------------------|----------|-------------------|
| 1   | B-NHL BFM 04 (PMLBCL)a + RT (36 Gy) | CR       | 0.4 y    | cHL NS               | cHL-likeb + R, HD-BEAM + ASCR + RT (IF + boost) | CR       | 10.4 y            |
| 2   | B-NHL BFM 04 (DLBCL)c | PD     | na       | cHL NS               | cHL-likec + R       | DOD      | na                |
| 3   | EuroNet-PHL C1: TG2e + RT (19.8 Gy) | CR       | 8.9 y    | −                    | na                  | na       | 9.1 y             |
| 4   | 6x DA-EPOCH-R      | CR       | 3.9 y    | cHL NS               | 2x IEP + 2x COPDAC + 2x bortezomib, HD-BEAM + ASCR | CR       | 3.5 y             |
| 5   | 6x DA-EPOCH-R      | CR       | 1.8 y    | −                    | na                  | na       | 2.0 y             |
| 6   | 6x DA-EPOCH-R      | PD       | na       | GZL (cHL-like)       | R-ICE + 2x BeGEV + 3x COPDAC + 3x bortezomib | DOD      | na                |

Abbreviations: ASCR, autologous stem cell rescue; BFM, Berlin-Frankfurt-Münster; cHL NS, classical Hodgkin lymphoma nodular-sclerosing subtype; CR, complete remission; DLBCL, diffuse large B-cell lymphoma; DOD, dead of disease; DXM, dexamethasone; FU, follow-up; GZL, gray zone lymphoma; HD, high-dose; HLH, hemophagocytic lymphohistiocytosis; IF, involved-field; na, not applicable; NHL, non-Hodgkin lymphoma; PD, progressive disease; PHL, pediatric Hodgkin lymphoma; PMLBCL, primary mediastinal large B-cell lymphoma; Pt., patient; R, rituximab; RT, radiotherapy; TG, therapy group; y, years.

aPre-phase /A24/B24/CC/AA24/BB24/CC/BB24.
bOEPA/2x IEP/ABVD/OPPA/DXM-BEAM/2x R-COP (for definition of the blocks, refer to the main text).
cPre-phase/AA24/CC/BB24/AA24/CC.
d6x Rituximab/DXM/2x OEPA/COPP/6x gemcitabine + vinorelbine/2x IPP (for definition of the blocks, refer to the main text).
e2x OEPA/2x COPDAC (for definition of the blocks, refer to the main text).
3.2 | Case 2

A 17-year-old male presented with cough and B-symptoms. Histopathology (lung biopsy) revealed a cHL-like GZL involving the mediastinum and both lungs (stage III). Tissue was infiltrated by many HRS as well as lacunar cells, surrounded by an inflammatory background and multifocal necroses. In addition, components of a DLBCL, consisting of blasts with round nuclei and multiple nucleoli, were present. Immunohistochemistry showed the cHL component to be positive for CD30, CD15, and PAX5, slightly positive for CD20, and negative for CD79a as well as BCL6. The LBCL component showed positivity for CD20, CD30, and PAX5, being negative for CD15, CD79a, and BCL6. The patient received chemotherapy according to the B-NHL BFM 04 protocol for DLBCL. Restaging at the end of therapy demonstrated progressive disease, which was histopathologically (lung biopsy) shown to be a nodular-sclerosing cHL (CD15, CD30, and PAX5 positive, CD20 inconsistently positive, BCL6 negative). Second-line treatment consisted of cHL-like therapy with intermittent DXM, 2× OEPA (vincristine, etoposide, prednisone, and adriamycin), 1× COPP (cyclophosphamide, vincristine, procarbazine, and prednisone) + rituximab, 6× gemcitabine and vinorelbine, and 2× IPP (ifosfamide, prednisone, and cisplatin) due to several further progressions, with a fatal outcome 1.4 years after initial diagnosis.

3.3 | Case 3

Dyspnea led to the diagnosis of a mediastinal tumor mass expanding to the infra-/supraclavicular and hilar LN in a 15-year-old male. Extra-nodal involvement included the chest wall and pericardial and pleural effusions (Ann Arbor stage II-A-E). Lung biopsy confirmed diagnosis of a CD20-, CD30-, CD15-, and PAX5-positive cHL-like GZL. Within the histologic picture of nodular-sclerosing Hodgkin lymphoma with characteristic HRS cells and eosinophils, several foci of patchy blast infiltrates were found. The patient received cHL-like treatment according to the EuroNet-Pediatric HL-C1 protocol (treatment group 2) with involved-field radiotherapy (19.8 Gy) leading to a CCR for 9.1 years.

3.4 | Case 4

A 14-year-old female was admitted with cough, thoracic pain, and tachycardia. Diagnosis of composite GZL (two separate samples with PMLBCL and cHL each) with mediastinal, cervical, infraclavicular, and pulmonary as well as hepatic and pancreatic involvement was histologically confirmed (stage III): the lung biopsy revealed a PMLBCL with dense sheets of blasts with round or slightly cleaved nuclei and prominent nucleoli. Many of the blasts showed a clear cytoplasm, many others had an abundant, eosinophilic cytoplasm. The blasts infiltrated lung tissue as well as intercostal musculature and were positive for CD20, PAX5, CD79a, BCL6, CD10, and, to some extent, CD30. A concomitant mediastinal LN biopsy revealed infiltration with a cHL, nodular-sclerosing subtype: within sclerotic areas, characteristic HRS cells as well as lacunar cells were distributed within the tissue containing eosinophils, macrophages, small lymphocytes, and plasma cells. This component was CD30, PAX5, CD15, and CD20 positive. After 6× DA-EPOCH-R, CR was achieved. After four years, a mediastinal relapse of nodular-sclerosing cHL (CD20, CD30, PAX5, and CD15 positive) was detected. Second-line chemotherapy consisted of 2× IEP (ifosfamide, etoposide, and prednisone) and 2× COPDAC (cyclophosphamide, vincristine, prednisone, and dacarbazine) + brentuximab vedotin, followed by HD-BEAM with ASCR. The patient is in CCR for 3.5 years.

3.5 | Case 5

A 16-year-old male presented with increasing swelling of cervical and supraclavicular LN. Biopsy confirmed an LBCL-like GZL with mediastinal, cervical, supraclavicular, axillary, and lung involvement (stage III). The infiltrated tissue showed either patchy or confluent areas of large blasts with round or ovaloid, partially cleaved nuclei with multiple prominent nucleoli, and abundant and eosinophilic cytoplasm. Within the blast infiltrates, diffusely dispersed classical HRS cells could be detected, as well as the presence of sclerotic bands. By immunohistochemistry, the cHL component was positive for CD20, CD30, PAX5, and CD15, whereas the LBCL component was CD20, CD30, and, to some extent, CD15 positive, and negative for PAX5 and CD79a. The patient received 6× DA-EPOCH-R, resulting in CCR for two years.

3.6 | Case 6

A 15-year-old female was admitted with cough, swelling of cervical, and supraclavicular LN and B symptoms. Initial diagnosis revealed a PMLBCL. The LNs were densely infiltrated by blasts with round or slightly cleaved nuclei and several prominent nucleoli. Many of the blasts revealed a clear cytoplasm. Numerous mitoses as well as apoptosis were evident. The PMLBCL was CD20, PAX5, CD79a, and BCL-6 positive, partly positive for CD30, and negative for CD15, CD10, and EBER. It extended from the right cervical region to the diaphragm, with lung, pleural, and pericardial involvement (stage III). Restaging after 6× DA-EPOCH-R showed progression. Lymph node biopsy revealed a tissue infiltration by a cHL, nodular-sclerosing subtype, without areas of DLBCL (CD30, PAX5, CD15, and EBER positive; CD79a partially positive; CD20 negative). Therefore, diagnosis of sequential GZL was made. The patient received an individualized second-line treatment with 1× R-ICE, 3× COPDAC, and 2× BeGEV (bendamustine, gemcitabine, and vinorelbine) + brentuximab vedotin. Following further...
mediastinal and thoracic progression of histologically confirmed composite GZL (Figure 1). HD-BEAM with ASCR was conducted, and therapy completed with involved-field irradiation (30.6 Gy, hilar boost up to 45 Gy).

One year after initial diagnosis, the patient was readmitted with dyspnea, tachycardia, and fever. Besides new thoracic lesions and pleural effusions, reactivation of EBV led to hemophagocytic lymphohistiocytosis (HLH) with ferritin levels > 188,000 ng/mL. HLH-directed treatment with dexamethasone, etoposide, rituximab, and ruxolitinib was applied. Although HLH could be effectively controlled, staging and another biopsy revealed further progression of LBCL-like GZL on both sides of the diaphragm. Because of CD30 positivity, a triweekly brentuximab vedotin regimen was initiated. Given the retrospective confirmation of 9p24.1 amplification, PD-1 blockade with biweekly pembrolizumab was added, in order to prepare for eventual allogeneic HSCT.

Following initial partial remission, the patient experienced extensive progression with new abdominal bulks after three months. Because of additional presence of severe pembrolizumab-associated colitis, biopsy was conducted in assumption of pseudoprogression. However, histology reconfirmed GZL (EBER positive) with loss of B-cell markers such as CD19 and CD20. With regard to the initial 9p24.1 and FGFR-1 amplifications, the patient received ruxolitinib and ponatinib in addition to DXM, brentuximab vedotin, and bortezomib.

Two months later, staging showed further progression with multiple new lesions (including liver and bones) and reactivation of HLH (ferritin levels > 200,000 ng/mL) combined with immune-mediated colitis, prolonged pancytopenia, severe immunodeficiency, as well as kidney and heart failure. The patient finally died 1.7 years after initial diagnosis.

4 | DISCUSSION

Although the present analysis has been conducted retrospectively and patients were not treated according to a common strategy, this
comparatively large report on six pediatric patients with centrally reviewed GZL (two composite, two CHL-like, one LBCL-like, and one sequential subtype) covering a time period of >10 years allows several important insights in a rare disease. Our data show that pediatric patients with GZL are usually adolescents and almost always have an advanced disease stage with involvement of the mediastinum and extranodal sites (mainly the lungs, pleura, and pericardium). None of the patients had involvement of the bone marrow or central nervous system. Immunohistochemistry showed CD20, CD30, PAX5, and, at least to some extent, CD15 positivity in all six cases. This immunohistochemical pattern is in accordance with the definition of GZLs, which are defined by the WHO 2016 classification as a B-cell lymphoma, unclassifiable, with intermediate features of DLBCL and CHL.1-5,7,10,11,14

Initial diagnosis of GZL was already made in five cases, while one patient with sequential subtype had an initial diagnosis of PLBC. Overall, first-line treatment was B-NHL-directed in five of six cases, whereas one patient received CHL-directed initial therapy. Four of our six patients had well-responding diseases with CR following first-line treatment. In a case series of four pediatric patients, Baqari et al. described first CR in all their patients following NHL-directed treatment.11 Evens et al. reported superior results in GZL patients receiving rituximab-based B-NHL-directed first-line treatment (DA-EPOCH-R, with 62% CCR rates.3,4 However, although a CCR was achieved in two of our four patients with initial CR, relapse was observed in the other two patients as late as four years after first-line treatment. This not only is in line with the high relapse rates of 50% to 58% reported for both adults and children, but also underlines the importance of extended follow-up in patients with GZL.4,7 Both our patients recurred as CHL, received HD-BEAM with ASCR as part of their relapse treatment, and entered a second CR.

About one third of patients with GZL have primary refractory disease.3,4,9 Two of our six patients showed early progression, and all had a fatal outcome despite miscellaneous therapy. In a report of Wilson et al., all their five patients with primary refractory GZL died despite multimodal salvage treatment and allogeneic SCT, defining a subgroup with a very dismal prognosis.3 Robust CD15 positivity and advanced stage of disease were found to be poor prognostic markers.3,4 Because all our patients had advanced stage disease (according to St. Jude’s staging system) and all our cases showed CD15 positivity to some extent, we could not confirm the aforementioned findings.

One of our patients experienced multiple progressions in the setting of concomitant HLH despite multimodal treatment. Based upon recent reports, the patient’s situation drove our decision toward novel therapeutic modalities including checkpoint inhibition and the use of ruxolitinib.10,17,18 To our knowledge, we describe the first pediatric GZL patient receiving pembrolizumab. However, in contrast to the three successfully treated adult cases described by Melani et al.,10 PD-1 blockade had to be omitted in our patient upon reprogression with loss of 9p24.1 amplification and due to severe pembrolizumab-associated colitis. Under the rationale that 9p24.1 amplification is not only linked to PD-L1 expression, but also to JAK2 activation, we used ruxolitinib for both HLH and GZL treatment, and repeatedly observed transient disease stabilization.17,18 However, owing to the combination of multiple drugs, the contribution of single agents to transient disease stabilization in this setting remains unclear.

Despite multimodal treatment, we faced a refractory, histomorphologically, and genetically changing disease in a multimorbid patient. Changes of histomorphology and immunohistochemical patterns were consistently found in relapse biopsies of the other patients, identifying GZL as a highly variable tumor alongside a continuum between CHL on the one end and LBCL/PLLBCL on the other.

While underlining the remarkable diagnostic and therapeutic challenges harbored by GZL, we could not determine any prognostic factor from our case series, but drew the following conclusions: First, GZL shows a high tendency toward relapse/progression and may even recur after years. However, CCR can be achieved following first-line treatment and even following relapse therapy. Second, optimal first-line treatment remains unclear: NHL-directed front-line treatment led to CR in three patients. However, two of them relapsed as CHL. The one patient with primary HL-like treatment plus consolidation radiotherapy showed the longest first CR observed in our patients. Although classified as Ann Arbor stage II because of CHL-directed treatment, this patient would have also met the criteria for stage III lymphoma according to the St. Jude’s staging system. Although involved-field irradiation may be considered even within first-line therapy, complementary treatment catching both entities may probably be required for long-term remission.

Two of our six patients experienced early progression, which consistently proved to be fatal. Thus, novel therapeutic options, such as brentuximab vedotin, PD-1 blockade, JAK inhibition, or chimeric antigen receptor (CAR) T-cell therapy, should be considered early and, thus, their targets should be determined already at initial diagnosis allowing curative intents before the evolution of a highly aggressive disease precludes further therapeutic options. Due to the retrospective character of this case series, a systematic molecular analysis was not applicable, but should be included in future studies in order to explore the genetic nature and possible biomarkers as well as potential targets for treatment.

In conclusion, management of GZL remains a diagnostic and therapeutic challenge owing to the rarity, clinical heterogeneity, and highly aggressive character of the tumor, as well as the lack of standardized treatment concepts. Prospective studies evaluating novel therapy approaches are highly needed.

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AUTHOR CONTRIBUTIONS

AA and TP designed and planned the study; AA and TP wrote the manuscript; AA and TP collected and analyzed the data; CBS and ISK were in charge of the histopathological analyses; all other authors (GED, MT, KZ, HL, RL, MD, GM, and MB) as well as AA and TP recruited,
treated, and identified the patients. All authors read and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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